RV 2016/2017

Risco vascular em 2016/2017

Síntese de publicações pelo Núcleo de Estudos de Prevenção e Risco Vascular da Sociedade Portuguesa de Medicina Interna

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RV 2016/2017

Introdução

O projeto RV 2016/2017 nasceu de uma vontade comum dos membros do Grupo de Estudos de Risco e Prevenção vascular da Sociedade Portuguesa de Medicina Interna.

Tem como objetivo ser uma fonte independente e credível de informação, revista e compilada por quem se dedica a cada um dos temas com paixão, de forma a que contribua para a atualização de conhecimentos abrangendo as diversas áreas do risco vascular.

Embora cada capítulo represente a visão particular dos seus autores, globalmente, o projeto pretende dar uma panorâmica única daquilo que melhor se fez na área do risco vascular. `

Sempre que possível, procuraremos salientar aquilo que de mais relevante se publicou em Portugal, pois devemos primeiro conhecer a nossa casa antes de correr mundo.

Esta (desejamos nós) é a primeira de muitas edições do projeto RV. Tem a aspiração de poder contribuir para a formação contínua na área cardiovascular, já que, apesar das melhorias registadas, a doença vascular continua a ser a maior causa de morte no nosso país.

Agradecemos a colaboração dos Núcleos de Estudos de Doença vascular Cerebral, de Insuficiência Cardíaca e de Diabetes, que participaram neste projecto.

Um agradecimento também aos laboratórios Menarini pelo apoio à edição.

Um forte abraço e até ao RV 2018

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RV Nutrição 2016/2017

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A doença vascular aterosclerótica pode ser considerada uma doença da civilização, pois, embora conhecida desde a Antiguidade, a sua prevalência tem evoluído paralelamente com o desenvolvimento das sociedades, sendo hoje a principal causa de morte no primeiro Mundo. E o que é que mudou com a evolução das sociedades? Para além do envelhecimento da população, fator de risco não modificável, mudaram fundamentalmente dois aspetos: a nutrição e a atividade física. Come-se de mais e mexe-se de menos, o que resulta em excesso de gordura corporal e perturbações metabólicas, as quais, como a insulino-resistência, a diabetes, a dislipidemia e a hipertensão arterial, são importantes fatores de risco de aterosclerose. Não admira pois que a investigação da relação da nutrição com a aterosclerose passe, em parte, por estas alterações metabólicas ligadas ao excesso de gordura corporal e suas causas.

A análise dos estudos na área da nutrição, é contudo, complexa, não só porque a interação entre os nutrientes provenientes dos diferentes alimentos não é linear, mas também porque a interação com o indivíduo e o seu estado fisiológico, bem como com as suas interações com o meio ambiente, podem influenciar o efeito dos alimentos na saúde, em geral, e na doença vascular aterosclerótica em particular. Será esta uma das razões para as disparidades encontradas entre muitos estudos, cujos resultados muitas vezes se contradizem. Tal como na Medicina em geral, mas na nutrição ainda com maior ênfase, as verdades absolutas não existem e, por isso, como nos tem mostrado o passado em relação a alguns alimentos, o que é verdade hoje pode não ser amanhã.

De entre os estudos selecionados a dieta mediterrânica tem lugar de destaque continuando a investigação a demonstrar a sua importância na prevenção da doença cardiovascular. Para além do mais este padrão alimentar parece trazer benefícios não apenas em relação a estas doenças mas também em relação a outras, como o cancro. De salientar, no entanto, que esta dieta já não é regularmente praticada nos países do Sul da Europa e, por outro lado, que a dieta mediterrânica, mais que uma mera ingestão de alimentos representa um padrão de vida onde os aspetos dietéticos se intrincam com um clima particular e com hábitos de atividade física e lazer próprios.

A gordura saturada continua em discussão, bem como o consumo de ovos e os ácidos gordos polinsaturados, mostrando assim que para além de muito já se saber, com certeza ainda muito mais haverá para investigar e aprender. Como alguns estudos aventam, o que durante muitos anos se pensou ser mau, nem sempre o será, e o que durante muito tempo se pensou ser protetor poderá não o ser, tudo dependendo do contexto das complexas interações entre os alimentos, o indivíduo e o meio ambiente.

Merece destaque o facto de um estudo mostrar o papel nocivo que os contaminantes dos alimentos, como os bifenilospoliclorados, podem ter no aumento do risco cardiovascular. Numa altura em que, para além da poluição ambiental, os fertilizantes, inseticidas, conservantes e outras substâncias são cada vez mais usados na produção e conservação dos alimentos, este será seguramente um tema de grande investigação futura.

De salientar também que os últimos estudos continuam a associar o álcool, o café e o chocolate ao risco cardiovascular. O excesso de álcool como promotor, o café como protetor e o chocolate como protetor em doses moderadas e como promotor em doses elevadas.

The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort

Praagman J, Beulens JWJ, Alssema M et al

Am J Clin Nutr 2016; 103:356–65

BACKGROUND: The association between saturated fatty acid (SFA) intake and ischemic heart disease (IHD) risk is debated.
OBJECTIVE: We sought to investigate whether dietary SFAs were associated with IHD risk and whether associations depended on1) the substituting macronutrient, 2) the carbon chain length of SFAs, and 3) the SFA food source.
DESIGN: Baseline (1993–1997) SFA intake was measured with a food frequency questionnaire among 35,597 participants from the European Prospective Investigation into Cancer and Nutrition–Netherlands cohort.IHD risks were estimated with multivariable Cox regression for the substitution of SFAs with other macronutrients and for higher intakes of total SFAs, individual SFAs, and SFAs from different food sources.
Results: During 12 y of follow-up, 1807 IHD events occurred. Total SFA intake was associated with a lower IHD risk (HR per 5% of energy: 0.83; 95% CI: 0.74, 0.93). Substituting SFAs with animal protein, cis monounsaturated fatty acids, polyunsaturated fatty acids(PUFAs), or carbohydrates was significantly associated with higher IHD risks (HR per 5% of energy: 1.27–1.37). Slightly lower IHD risks were observed for higher intakes of the sum of butyric (4:0) through capric (10:0) acid (HRSD: 0.93; 95% CI: 0.89, 0.99), myristic acid (14:0) (HRSD: 0.90; 95% CI: 0.83, 0.97), the sum of pentadecylic (15:0) and margaric (17:0) acid (HRSD: 0.91: 95% CI: 0.83, 0.99),and for SFAs from dairy sources, including butter (HRSD: 0.94; 95%CI: 0.90, 0.99), cheese (HRSD: 0.91; 95% CI: 0.86, 0.97), and milk and milk products (HRSD: 0.92; 95% CI: 0.86, 0.97).
CONCLUSIONS: In this Dutch population, higher SFA intake was not associated with higher IHD risks. The lower IHD risk observed did not depend on the substituting macronutrient but appeared to be driven mainly by the sums of butyric through capric acid, the sum of pentadecylic and margaric acid, myristic acid, and SFAs from dairy sources. Residual confounding by cholesterol-lowering therapy and trans fat or limited variation in SFA and PUFA intake may explain our findings. Analyses need to be repeated in populations with larger differences in SFA intake and different SFA food sources.

Comentário: este estudo não corrobora o que muitos outros mostraram, isto é, uma associação inequívoca entre o consumo de gordura saturada e doença coronária isquémica, permitindo voltar à discussão do tipo de gordura saturada e nomeadamente do peso relativo de cada um dos vários ácidos gordos saturados na doença aterosclerótica. Estes resultados estão de acordo com os estudos que mostram que alguns alimentos ainda que ricos em gordura saturada, como o queijo, parecem ser protetores contra a doença coronária isquémica.

Predictive role of the Mediterranean diet on mortality in individuals at low cardiovascular risk: a 12-year follow-up population-based cohort study

Bo S, Ponzo V, Goitre I, et al

J Transl Med 2016; 14:91-99

BACKGROUND: Adherence to the Mediterranean diet reduces the risk of all-cause and cardiovascular (CV) mortality and the incidence of CV events. However, most previous studies were performed in high-risk individuals. Our objective was to assess whether the adherence to the Mediterranean diet, evaluated by the MED score, was associated with all-cause and CV mortality and incidence of CV events in individuals at low CV risk from a population-based cohort, after a 12-year mean follow-up.

METHODS: A cohort of 1658 individuals completed a validated food-frequency questionnaire in 2001–2003. The MEDscore was calculated by a 0–9 scale. Anthropometric, laboratory measurements, and the vital status were collected at baseline and during 2014. The baseline CV risk was estimated by the Framingham risk score. Participants were divided into two groups: individuals at low risk (CV < 10) and individuals with CV risk ≥10.

Results: During a 12-year mean follow-up, 220 deaths, 84 due to CV diseases, and 125 incident CV events occurred. The adherence to the Mediterranean diet was low in 768 (score 0–2), medium in 685 (score 4–5) and high in 205(score >6) individuals. Values of BMI, waist circumference, fasting glucose and insulin significantly decreased from low to high diet adherence only in participants with CV risk ≥10. In a Cox-regression model, the hazard ratios (HRs) in low risk individuals per unit of MED score were: HR = 0.83 (95 % CI 0.72–0.96) for all-cause mortality, HR = 0.75 (95 % CI0.58–0.96) for CV mortality, and HR = 0.79 (95 % CI 0.65–0.97) for CV events, after multiple adjustments. In individuals with CV risk ≥10, the MED score predicted incident CV events (HR = 0.85; 95 % CI 0.72–0.99), while the associations with all-cause (HR = 1.02; 95 % CI 0.90–1.15) and CV mortality (0.94; 95 % CI 0.76–1.15) were not significant.

CONCLUSIONS: Greater adherence to the Mediterranean diet was associated with reduced fatal and non-fatal CV events, especially in individuals at low CV risk, thus suggesting the usefulness of promoting this nutritional pattern in particular in healthier individuals.

Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73)

Ramsden CE, Zamora D, Majchrzak-Hong S, et al

BMJ 2016;353: i1246

OBJECTIVE: To examine the traditional diet-heart hypothesis through recovery and analysis of previously unpublished data from the Minnesota Coronary Experiment (MCE) and to put findings in the context of existing diet-heart randomized controlled trials through a systematic review and meta-analysis.

Design: The MCE (1968-73) is a double blind randomized controlled trial designed to test whether replacement of saturated fat with vegetable oil rich in linoleic acid reduces coronary heart disease and death by lowering serum cholesterol. Recovered MCE unpublished documents and raw data were analyzed according to hypotheses prespecified by original investigators. Further, a systematic review and meta-analyses of randomized controlled trials that lowered serum cholesterol by providing vegetable oil rich in linoleic acid in place of saturated fat without confounding by concomitant interventions was conducted. Setting: One nursing home and six state mental hospitals in Minnesota, United States.

Participants: Unpublished documents with completed analyses for the randomized cohort of 9423 women and men aged 20-97; longitudinal data on serum cholesterol for the 2355 participants exposed to the study diets for a year or more; 149 completed autopsy files.

Interventions: Serum cholesterol lowering diet that replaced saturated fat with linoleic acid (from corn oil and corn oil polyunsaturated margarine). Control diet was high in saturated fat from animal fats, common margarines, and shortenings.

Main Outcome Measures: Death from all causes; association between changes in serum cholesterol and death; and coronary atherosclerosis and myocardial infarcts detected at autopsy.

Results: The intervention group had significant reduction in serum cholesterol compared with controls (mean change from baseline −13.8% *v* −1.0%; P<0.001). Kaplan Meier graphs showed no mortality benefit for the intervention group in the full randomized cohort or for any prespecified subgroup. There was a 22% higher risk of death for each 30 mg/dL (0.78 mmol/L) reduction in serum cholesterol in covariate adjusted Cox regression models (hazard ratio 1.22, 95% confidence interval 1.14 to 1.32; P<0.001). There was no of benefit in the intervention group for coronary atherosclerosis or myocardial infarcts. Systematic review identified five randomized controlled trials for inclusion (n=10 808). In meta analyses, these cholesterols lowering interventions showed no evidence of benefit on mortality from coronary heart disease (1.13, 0.83 to 1.54) or all cause mortality (1.07, 0.90 to 1.27).

Conclusions: Available evidence from randomized controlled trials shows that replacement of saturated fat in the diet with linoleic acid effectively lowers serum cholesterol but does not support the hypothesis that this translates to a lower risk of death from coronary heart disease or all causes. Findings from the Minnesota Coronary

Experiment add to growing evidence that incomplete publication has contributed to overestimation of the benefits of replacing saturated fat with vegetable oils rich in linoleic acid.

Comentário: mais um artigo que acentua a hipervalorização dada em certa altura à substituição da gordura saturada por gordura polinsaturada. De facto, está hoje cada vez mais claro que o problema não reside apenas na gordura saturada versus gordura polinsaturada, mas sim no tipo e proporção de ácidos gordos que compõem cada tipo de gordura. Por outro lado a próprio efeito deletério ou protetor de cada um dos ácidos gordos e do próprio colesterol dependem de muitos outros fatores, nutricionais e não nutricionais, dificultando assim recomendações rígidas. Foi esta inconsistência que levou recentemente a FDA a retirar a ênfase que desde há muitos anos vinha pondo na limitação da ingestão de gordura saturada e colesterol alimentar.

Associations of egg and cholesterol intakes with carotid intima-media thickness and risk of incident coronary artery disease according to apolipoprotein E phenotype in men: the Kuopio Ischaemic Heart Disease Risk Factor Study

Virtanen JK, Mursu J, Virtanen HE, et al

Am J Clin Nutr. 2016;103(4):999-1007

BACKGROUND: In general populations, the effects of dietary cholesterol on blood cholesterol concentrations are modest. However, the relation is stronger in those with an ε4 allele in the apolipoprotein E gene (APOE). There is little information on the association between cholesterol intake and the risk of coronary artery disease (CAD) among those with the ApoE4 phenotype.

OBJECTIVE: We investigated the associations of intakes of cholesterol and eggs, a major source of dietary cholesterol, with carotid intima-media thickness and the risk of incident CAD in middle-aged and older men from eastern Finland.

DESIGN: The study included 1032 men aged 42-60 y in 1984-1989 at the baseline examinations of the prospective, population-based Kuopio Ischaemic Heart Disease Risk Factor Study. Data on common carotid artery intima-media thickness (CCA-IMT) were available for 846 men. Dietary intakes were assessed with 4-d food records. Associations with incident CAD and baseline CCA-IMT were analyzed by using Cox regression and ANCOVA, respectively.

RESULTS: The ApoE4 phenotype was found in 32.5% of the men. During the average follow-up of 20.8 y, 230 CAD events occurred. Egg or cholesterol intakes were not associated with the risk of CAD. Each 1 additional egg (55 g)/d was associated with a multivariable-adjusted HR of 1.17 (95% CI: 0.85, 1.61) in the ApoE4 noncarriers and an HR of 0.93 (95% CI: 0.50, 1.72) in the ApoE4 carriers (P-interaction = 0.34). Each 100-mg/d higher cholesterol intake was associated with an HR of 1.04 (95% CI: 0.89, 1.22) in the ApoE4 noncarriers and an HR of 0.95 (95% CI: 0.73, 1.25) in the ApoE4 carriers (P-interaction = 0.81). Egg or cholesterol intakes were also not associated with increased CCA-IMT.

CONCLUSION: Egg or cholesterol intakes were not associated with increased CAD risk, even in ApoE4 carriers (i.e., in highly susceptible individuals).

Comentário: durante muitos anos foi aconselhado limitar o consumo de ovos devido à sua riqueza em colesterol, sem que, contudo, qualquer estudo tenha provado claramente uma associação entre o consumo de ovos e a doença vascular isquémica. Este estudo vem mostrar que não existe essa associação e que provavelmente a recomendação em relação ao consumo de ovos foi exagerada e não suportada cientificamente durante décadas. De facto, embora os ovos sejam ricos em colesterol, a existência de outros componentes do ovo com propriedades anti-ateroscleróticas poderão explicar o efeito não deletério associado à riqueza de colesterol.

Intake of whole grains is associated with lower risk of myocardial infarction: the Danish Diet, Cancer and Health Cohort

Helnæs A, Kyrø C, Andersen I, Lacoppidan S, Overvad K, Christensen J, Tjønneland A, Olsen A

Am J Clin Nutr. 2016;103(4):999-1007

BACKGROUND: High intake of whole grains has been associated with lower risk of coronary heart disease; however, the research that has been used to evaluate different effects of different whole-grain cereals (e.g., wheat, rye, and oats) has been sparse.

OBJECTIVE: We investigated the association between whole-grain intake in terms of total intake and intakes of different cereals and myocardial infarction.

DESIGN: This prospective study included 54,871 Danish adults aged 50-64 y, of whom 2329 individuals developed myocardial infarction (13.6 y of follow-up). Detailed information on daily intake of whole-grain products was available from a self-administered food-frequency questionnaire, and intakes of total whole grain and whole-grain species (wheat, rye, and oats) were estimated. The association between intake of whole grains and risk of myocardial infarction was examined with the use of a Cox proportional hazards model adjusted for potential confounders.

RESULTS: For both men and women with total whole-grain intake in the highest quartile, lower risks of myocardial infarction were shown [HRs: 0.75 (95% CI: 0.65, 0.86) and 0.73 (95% CI: 0.58, 0.91), respectively] than for individuals with intake in the lowest quartile. When the specific cereal species were considered, rye and oats, but not wheat, were associated with lower myocardial infarction risk in men. No significant associations were seen in women. For total whole-grain products, significantly lower myocardial infarction risks were seen with higher intakes in both men and women. Rye bread (in men and women) and oatmeal (in men) were associated with significantly lower risk of myocardial infarction, whereas no significant association was shown for whole-grain bread, crisp bread, and wheat.

CONCLUSION: In this study, we provide support for the hypothesis that whole-grain intake is related to lower risk of myocardial infarction and suggest that the cereals rye and oats might especially hold a beneficial effect.

Comentário: é um estudo interessante que vem comprovar o que já se sabia, isto é que os cereais integrais, para além de benefícios gerais a nível metabólico, cancro e outras doenças, têm também benefício para a saúde cardiovascular. Tal efeito está decerto associado à sua riqueza em fibra, minerais e vitaminas, os quais podem diminuir o risco cardiovascular por diversas vias, mas também ao efeito positivo que a fibra tem na diminuição do índice glicémico, particularmente no centeio e na aveia.

Dietary exposure to polychlorinated biphenyls and risk of myocardial infarction in men . A population-based prospective cohort study

Bergkvist C, Berglund M, Glynn A, Julin B, Wolk A, Åkesson A

Environ Int. 2016; 88:9-14

BACKGROUND: Major food contaminants such as polychlorinated biphenyls (PCBs) are proposed to play a role in the etiology of cardiovascular disease (CVD), but to date the impact of PCBs on cardiovascular health need to be explored.

METHODS AND RESULTS: We assessed the association between validated food frequency questionnaire-based estimates of dietary PCB exposure and risk of myocardial infarction, ascertained through register-linkage, among 36,759 men from the population-based Swedish Cohort of Men, free of cardiovascular disease, diabetes and cancer at baseline (1997). Relative risks were adjusted for known cardiovascular risk factors, long-chain omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) and methyl mercury exposure. During 12years of follow-up (433,243 person-years), we ascertained 3005 incident cases of myocardial infarction (654 fatal).

Compared with the lowest quintile of dietary PCB exposure (median 113ng/day), men in the highest quintile (median 436ng/day) had multivariable-adjusted relative risks of 1.74 (95% confidence interval [CI], 1.30-2.33; p-trend<0.001) for total and 1.97 (95% CI 1.42-2.75; p-trend<0.001) for non-fatal myocardial infarction. In mutually adjusted models, dietary PCB exposure was associated with an increased risk of myocardial in farction, while the intake of long-chain omega-3 fish fatty acids was associated with a decreased risk. We also observed an effect modification by adiposity on the association between of dietary PCB exposure and myocardial infarction, with higher risk among lean men (p value for interaction =0.03).

CONCLUSIONS: Exposure to PCBs via diet was associated with increased risk of myocardial infarction in men.

Dietary α-Linolenic Acid, Marine ω-3 Fatty Acids, and Mortality in a Population With High Fish Consumption: Findings From the PREvención con DIeta MEDiterránea (PREDIMED) Study

Sala-Vila A; Guasch-Ferre M, Hu FB, for the PREDIMED Investigators

J Am Heart Assoc 2016;5: e002543

BACKGROUND: Epidemiological evidence suggests a cardioprotective role of α-linolenic acid (ALA), a plant-derived ω-3 fatty acid. It is unclear whether ALA is beneficial in a background of high marine ω-3 fatty acids (long-chain n-3 polyunsaturated fatty acids) intake. In persons at high cardiovascular risk from Spain, a country in which fish consumption is customarily high, we investigated whether meeting the International Society for the Study of Fatty Acids and Lipids recommendation for dietary ALA (0.7% of total energy) at baseline was related to all-cause and cardiovascular disease mortality. We also examined the effect of meeting the society's recommendation for long-chain n-3 polyunsaturated fatty acids (≥500 mg/day).

METHODS AND RESULTS: We longitudinally evaluated 7202 participants in the PREvención con DIeta MEDiterránea (PREDIMED) trial. Multivariable-adjusted Cox regression models were fitted to estimate hazard ratios. ALA intake correlated to walnut consumption (r=0.94). During a 5.9-y follow-up, 431 deaths occurred (104 cardiovascular disease, 55 coronary heart disease, 32 sudden cardiac death, 25stroke). The hazard ratios for meeting ALA recommendation (n=1615, 22.4%) were 0.72 (95% CI 0.56–0.92) for all-cause mortality and 0.95(95% CI 0.58–1.57) for fatal cardiovascular disease. The hazard ratios for meeting the recommendation for long-chain n-3 polyunsaturated fatty acids (n=5452, 75.7%) were 0.84 (95% CI 0.67–1.05) for all-cause mortality, 0.61 (95% CI 0.39–0.96) for fatal cardiovascular disease, 0.54 (95% CI 0.29–0.99) for fatal coronary heart disease, and 0.49 (95% CI 0.22–1.01) for sudden cardiac death. The highest reduction in all-cause mortality occurred in participants meeting both recommendations (hazard ratio 0.63 [95% CI 0.45–0.87]).

CONCLUSIONS: In participants without prior cardiovascular disease and high fish consumption, dietary ALA, supplied mainly by walnuts and olive oil, relates inversely to all-cause mortality, whereas protection from cardiac mortality is limited to fish-derived long-chain n-3 polyunsaturated fatty acids.

Comparison of the DASH (Dietary Approaches to Stop Hypertension) diet and a higher-fat DASH diet on blood pressure and lipids and lipoproteins: a randomized controlled trial

Chiu S, Bergeron N, Williams PT, Bray GA, Sutherland B, Krauss RM

Am J Clin Nutr. 2016;103(2):341-7

BACKGROUND: The DASH (Dietary Approaches to Stop Hypertension) dietary pattern, which is high in fruit, vegetables, and low-fat dairy foods, significantly lowers blood pressure as well as low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol.

OBJECTIVE: The study was designed to test the effects of substituting full-fat for low-fat dairy foods in the DASH diet, with a corresponding increase in fat and a reduction in sugar intake, on blood pressure and plasma lipids and lipoproteins.

DESIGN: This was a 3-period randomized crossover trial in free-living healthy individuals who consumed in random order a control diet, a standard DASH diet, and a higher-fat, lower-carbohydrate modification of the DASH diet (HF-DASH diet) for 3 wk each, separated by 2-wk washout periods. Laboratory measurements, which included lipoprotein particle concentrations determined by ion mobility, were made at the end of each experimental diet.

RESULTS: Thirty-six participants completed all 3 dietary periods. Blood pressure was reduced similarly with the DASH and HF-DASH diets compared with the control diet. The HF-DASH diet significantly reduced triglycerides and large and medium very-low-density lipoprotein (VLDL) particle concentrations and increased LDL peak particle diameter compared with the DASH diet. The DASH diet, but not the HF-DASH diet, significantly reduced LDL cholesterol, HDL cholesterol, apolipoprotein A-I, intermediate-density lipoprotein and large LDL particles, and LDL peak diameter compared with the control diet.

CONCLUSIONS: The HF-DASH diet lowered blood pressure to the same extent as the DASH diet but also reduced plasma triglyceride and VLDL concentrations without significantly increasing LDL cholesterol. This trial was registered at clinicaltrials.gov as NCT01404897.

Alcohol Abuse and Cardiac Disease

Whitman IR, Agarwal V, Nah G et al

JACC 2017; 69, 1: 13-24 DOI: 10.1016/j.jacc.2016.10.048

BACKGROUND: Understanding the relationship between alcohol abuse, a common and theoretically modifiable condition, and the most common cause of death in the world, cardiovascular disease, may inform potential prevention strategies.

Objectives: The study sought to investigate the associations among alcohol abuse and atrial fibrillation (AF), myocardial infarction (MI), and congestive heart failure (CHF).

METHODS: Using the Healthcare Cost and Utilization Project database, we performed a longitudinal analysis of California residents ≥21 years of age who received ambulatory surgery, emergency, or inpatient medical care in California between 2005 and 2009. We determined the risk of an alcohol abuse diagnosis on incident AF, MI, and CHF. Patient characteristics modifying the associations and population-attributable risks were determined.

RESULTS: Among 14,727,591 patients, 268,084 (1.8%) had alcohol abuse. After multivariable adjustment, alcohol abuse was associated with an increased risk of incident AF (hazard ratio [HR]: 2.14; 95% confidence interval [CI]: 2.08 to 2.19; $p < 0.0001$), MI (HR: 1.45; 95% CI: 1.40 to 1.51; $p < 0.0001$), and CHF (HR: 2.34; 95% CI: 2.29 to 2.39; $p < 0.0001$). In interaction analyses, individuals without conventional risk factors for cardiovascular disease exhibited a disproportionately enhanced risk of each outcome. The population-attributable risk of alcohol abuse on each outcome was of similar magnitude to other well-recognized modifiable risk factors.

CONCLUSIONS: Alcohol abuse increased the risk of AF, MI, and CHF to a similar degree as other well-established risk factors. Those without traditional cardiovascular risk factors are disproportionately prone to these cardiac diseases in the setting of alcohol abuse. Thus, efforts to mitigate alcohol abuse might result in meaningful reductions of cardiovascular disease

Comentário: é um estudo que mostra claramente o efeito negativo do consumo excessivo de bebidas alcoólicas em três das mais frequentes patologias cardiovasculares da atualidade. Será de salientar o risco desproporcionado que os indivíduos com baixo risco cardiovascular apresentam, razão porque deverá passar a ser dada muito mais importância ao consumo excessivo de bebidas alcoólicas, mesmo naqueles que não apresentam outros fatores de risco cardiovascular. A tão conhecida curva em J associada ao consumo de bebidas alcoólicas fica aqui bem patente na sua parte negativa e agora não apenas relacionada com o enfarte do miocárdio, mas também com a fibrilhação auricular e com a insuficiência cardíaca.

Chocolate intake and incidence of heart failure: Findings from the Cohort of Swedish Men

Steinhaus DA, Mostofsky E, Levitan EB et al

Am Heart J 2017; 183:18-23

AIMS: The objective of this study was to evaluate the association of chocolate consumption and heart failure (HF) in a large population of Swedish men.

METHODS: We conducted a prospective cohort study of 31,917 men 45-79 years old with no history of myocardial infarction, diabetes, or HF at baseline who were participants in the population-based Cohort of Swedish Men study. Chocolate consumption was assessed through a self-administrated food frequency questionnaire. Participants were followed for HF hospitalization or mortality from January 1, 1998, to December 31, 2011, using record linkage to the Swedish inpatient and cause-of-death registries.

RESULTS: During 14 years of follow-up, 2,157 men were hospitalized (n = 1,901) or died from incident HF (n = 256). Compared with subjects who reported no chocolate intake, the multivariable-adjusted rate ratio of HF was 0.88 (95% CI 0.78-0.99) for those consuming 1-3 servings per month, 0.83 (95% CI 0.72-0.94) for those consuming 1-2 servings per week, 0.82 (95% CI 0.68-0.99) for those consuming 3-6 servings per week, and 1.10 (95% CI 0.84-1.45) for those consuming ≥1 serving per day (P for quadratic trend = .001).

CONCLUSIONS: In this large prospective cohort study, there was a J-shaped relationship between chocolate consumption and HF incidence. Moderate chocolate consumption was associated with a lower rate of HF hospitalization or death, but the protective association was not observed among individuals consuming ≥1 serving per day.

Comentário: desde há muito que o chocolate é tido eventual protetor contra as doenças cardiovasculares, embora os estudos nem sempre apontem no mesmo sentido. Tem esta inconsistência de resultados a ver com problemas metodológicos e também com o próprio grau de pureza do chocolate. Este estudo, dirigido à insuficiência cardíaca e não á doença coronária isquémica como acontece na maioria dos estudos sobre o assunto, vem também mostrar um novo dado que é a existência de uma curva em jota, mostrando que o consumo moderado tem efeito benéfico enquanto o consumo elevado tem efeito nefasto.

Association Between Dietary Factors and Mortality from Heart Disease, Stroke, and Type 2 Diabetes in the United States

Micha R, Peñalvo JL, Cudhea F et al

JAMA. 2017;317(9):912-924. doi:10.1001/jama.2017.0947

IMPORTANCE: In the United States, national associations of individual dietary factors with specific cardiometabolic diseases are not well established.

OBJECTIVE: To estimate associations of intake of 10 specific dietary factors with mortality due to heart disease, stroke, and type 2 diabetes (cardiometabolic mortality) among US adults.

DESIGN, SETTING, AND PARTICIPANTS: A comparative risk assessment model incorporated data and corresponding uncertainty on population demographics and dietary habits from National Health and Nutrition Examination Surveys (1999-2002: n = 8104; 2009-2012: n = 8516); estimated associations of diet and disease from meta-analyses of prospective studies and clinical trials with validity analyses to assess potential bias; and estimated disease-specific national mortality from the National Center for Health Statistics.

EXPOSURES: Consumption of 10 foods/nutrients associated with cardiometabolic diseases: fruits, vegetables, nuts/seeds, whole grains, unprocessed red meats, processed meats, sugar-sweetened beverages (SSBs), polyunsaturated fats, seafood omega-3 fats, and sodium.

MAIN OUTCOMES AND MEASURES: Estimated absolute and percentage mortality due to heart disease, stroke, and type 2 diabetes in 2012. Disease-specific and demographic-specific (age, sex, race, and education) mortality and trends between 2002 and 2012 were also evaluated.

RESULTS: In 2012, 702 308 cardiometabolic deaths occurred in US adults, including 506 100 from heart disease (371 266 coronary heart disease, 35 019 hypertensive heart disease, and 99 815 other cardiovascular disease), 128 294 from stroke (16 125 ischemic, 32 591 hemorrhagic, and 79 578 other), and 67 914 from type 2 diabetes. Of these, an estimated 318 656 (95% uncertainty interval [UI], 306 064-329 755; 45.4%) cardiometabolic deaths per year were associated with suboptimal intakes—48.6% (95% UI, 46.2%-50.9%) of cardiometabolic deaths in men and 41.8% (95% UI, 39.3%-44.2%) in women; 64.2% (95% UI, 60.6%-67.9%) at younger ages (25-34 years) and 35.7% (95% UI, 33.1%-38.1%) at older ages (≥75 years); 53.1% (95% UI, 51.6%-54.8%) among blacks, 50.0% (95% UI, 48.2%-51.8%) among Hispanics, and 42.8% (95% UI, 40.9%-44.5%) among whites; and 46.8% (95% UI, 44.9%-48.7%) among lower-, 45.7% (95% UI, 44.2%-47.4%) among medium-, and 39.1% (95% UI, 37.2%-41.2%) among higher-educated individuals. The largest numbers of estimated diet-related cardiometabolic deaths were related to high sodium (66 508 deaths in 2012; 9.5% of all cardiometabolic deaths), low nuts/seeds (59 374; 8.5%), high processed meats (57 766; 8.2%), low seafood omega-3 fats (54 626; 7.8%), low vegetables (53 410; 7.6%), low fruits (52 547; 7.5%), and high SSBs (51 694; 7.4%). Between 2002 and 2012, population-adjusted US cardiometabolic deaths per year decreased by 26.5%. The greatest decline was associated with insufficient

polyunsaturated fats (−20.8% relative change [95% UI, −18.5% to −22.8%]), nuts/seeds (−18.0% [95% UI, −14.6% to −21.0%]), and excess SSBs (−14.5% [95% UI, −12.0% to −16.9%]). The greatest increase was associated with unprocessed red meats (+14.4% [95% UI, 9.1%-19.5%]).

CONCLUSIONS: and Relevance: Dietary factors were estimated to be associated with a substantial proportion of deaths from heart disease, stroke, and type 2 diabetes. These results should help identify priorities, guide public health planning, and inform strategies to alter dietary habits and improve health.

Adherence to the Mediterranean diet during pregnancy and offspring adiposity and cardiometabolic traits in childhood

Chatzi L, Rifas-Shiman SL, Georgiou V, et al

Pediatr Obes. 2017 Aug;12 Suppl 1:47-56

BACKGROUND: In adults, adherence to the Mediterranean diet has been inversely associated with cardiovascular risk, but the extent to which diet in pregnancy is associated with offspring adiposity is unclear. We aimed to investigate the association between adherence to Mediterranean diet in pregnancy and offspring cardiometabolic traits in two pregnancy cohorts.

METHODS: We studied 997 mother-child pairs from Project Viva in Massachusetts, USA, and 569 pairs from the Rhea study in Crete, Greece. We estimated adherence to the Mediterranean diet with an a priori defined score (MDS) of nine foods and nutrients (0 to 9). We measured child weight, height, waist circumference, skin-fold thicknesses, blood pressure, and blood levels of lipids, c-reactive protein and adipokines in mid-childhood (median 7.7 years) in Viva, and in early childhood (median 4.2 years) in Rhea. We calculated cohort-specific effects and pooled effects estimates with random-effects models for cohort and child age.

RESULTS: In Project Viva, the mean (SD, standard deviation) MDS was 2.7 (1.6); in Rhea it was 3.8 (1.7). In the pooled analysis, for each 3-point increment in the MDS, offspring BMI z-score was lower by 0.14 units (95% CI, -0.15 to -0.13), waist circumference by 0.39 cm (95% CI, -0.64 to -0.14), and the sum of skin-fold thicknesses by 0.63 mm (95% CI, -0.98 to -0.28). We also observed lower offspring systolic (-1.03 mmHg; 95% CI, -1.65 to -0.42) and diastolic blood pressure (-0.57 mmHg; 95% CI, -0.98 to -0.16).

CONCLUSION: Greater adherence to Mediterranean diet during pregnancy may protect against excess offspring cardiometabolic risk.

Comentário: *estudo interessante que mostra não só o benefício da adesão à dieta mediterrânica, mas, essencialmente, que a prevenção cardiovascular se deve iniciar com as mães durante a gravidez.*

Coffee consumption after myocardial infarction and risk of cardiovascular mortality: a prospective analysis in the Alpha Omega Cohort

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Am J ClinNutr. 2017 Oct;106(4):1113-1120

BACKGROUND: Consumption of coffee, one of the most popular beverages around the world, has been associated with a lower risk of cardiovascular and all-cause mortality in population-based studies. However, little is known about these associations in patient populations.

OBJECTIVE: This prospective study aimed to examine the consumption of caffeinated and decaffeinated coffee in relation to cardiovascular disease (CVD) mortality, ischemic heart disease (IHD) mortality, and all-cause mortality in patients with a prior myocardial infarction (MI). Design: We included 4365 Dutch patients from the Alpha Omega Cohort who were aged 60-80 y (21% female) and had experienced an MI <10 y before study enrollment. At baseline (2002-2006), dietary data including coffee consumption over the past month was collected with a 203-item validated food-frequency questionnaire. Causes of death were monitored until 1 January 2013. HRs for mortality in categories of coffee consumption were obtained from multivariable Cox proportional hazard models, adjusting for lifestyle and dietary factors.

RESULTS: Most patients (96%) drank coffee, and the median total coffee intake was 375 mL/d (~3 cups/d). During a median follow-up of 7.1 y, a total of 945 deaths occurred, including 396 CVD-related and 266 IHD-related deaths. Coffee consumption was inversely associated with CVD mortality, with HRs of 0.69 (95% CI: 0.54, 0.89) for >2-4 cups/d and 0.72 (0.55, 0.95) for >4 cups/d, compared with 0-2 cups/d. Corresponding HRs were 0.77 (95% CI: 0.57, 1.05) and 0.68 (95% CI: 0.48, 0.95) for IHD mortality and 0.84 (95% CI: 0.71, 1.00) and 0.82 (95% CI: 0.68, 0.98) for all-cause mortality, respectively. Similar associations were found for decaffeinated coffee and for coffee with additives.

CONCLUSION: Drinking coffee, either caffeinated or decaffeinated, may lower the risk of CVD and IHD mortality in patients with a prior MI.

Comentário: o café é desde há muito apontado como protetor cardiovascular, havendo alguma discussão à volta da quantidade óptima, o que não é fácil de estabelecer pois a sensibilidade individual ao café é grande. Os benefícios advêm das substâncias antioxidantes presentes na bebida, embora a cafeína possa ter, segundo alguns estudos um papel deletério. Neste estudo conclui-se que o café descafeinado também tem efeito positivo, desvalorizando assim o papel da cafeína. Seria interessante evoluir para estudos bem desenhados em que fosse possível determinar o peso da cafeína, só por si, na doença cardiovascular.

RV Dislipidemias 2016/17

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Constituindo a doença vascular a principal causa de morte dos países desenvolvidos e a dislipidemia a principal responsável pelo risco atribuível populacional no que se refere à doença coronária e uma das principais relativamente ao acidente vascular cerebral isquémico, são em grande número os artigos relativos a esta temática nas revistas médicas, quer nas mais especializadas, como é o caso da Curr Opin Lipidol, do European Heart Journal e da Atherosclerosis quer nas generalistas como a NEJM, a JAMA e o BMJ. Procurámos selecionar nestas publicações referentes ao biénio 2016-2017, os artigos que nos pareceram mais interessantes relativamente às temáticas abordadas, quer pela inovação de conceitos, quer pelo aprofundamento e eventual confirmação de ideias já existentes, mas de grande atualidade. Iremos encontrar nas próximas páginas publicações que nos falam do colesterol incluído em todas as lipoproteínas contendo apoB e não só nas LDL como importante fator aterogénico, do papel das hipertrigliceridemias ligeiras a moderadas no risco vascular, não só pela redução dos níveis do C-HDL habitualmente associados, mas também pela sua correlação positiva com as partículas remanescentes ricas em colesterol. Também será abordado o papel cardioprotetor dos ácidos gordos ómega 3, particularmente ao reduzirem a lipogénese hepática e os níveis das VLDL remanescentes, a sua ação anti-inflamatória e anti-trombótica e anti-PCSK-9. Relativamente a novos hipolipemiantes os resultados do FOURIER vieram demonstrar não só a capacidade do evolocumab, em associação às estatinas, de reduzir significativamente e de uma forma segura os valores do C-LDL mas, mais importante, de reduzir igualmente de uma forma significativa a incidência dos eventos vasculares major. Tinha sido já demonstrado no estudo GLAGOV a sua capacidade para inibir o crescimento da placa carotídea e foi igualmente demonstrada a segurança do evolocumab em termos cognitivos. Outros novos fármacos através de diferentes mecanismos apresentam também como alvo terapêutico a proteína PCSK-9; é o caso do inclisiran. Outros fármacos hipolipemiantes estão a ser testados como sejam o ácido benpedoico, o gencabeno, o pemafibrato e o pradigast. Relativamente às hipertrigliceridemias a abordagem anti CIII poderá constituir-se numa eficaz terapêutica na redução destas lipoproteínas e dos seus remanescentes. Poderemos igualmente encontrar alguns trabalhos que se debruçaram sobre a redução do colesterol em indivíduos sem doença aterosclerótica clínica, de múltiplas etnias, com baixo ou intermédio risco vascular e sobre as estratégias de rastreio das dislipidemias em crianças e adolescentes. Referência também a uma publicação que demonstra a ainda baixa intensidade terapêutica na abordagem dos doentes com eventos coronários agudos, nomeadamente no que se refere às doses utilizadas das estatinas. Também a tão controversa e debatida relação entre os valores do CLDL e as capacidades cognitivas mereceu destaque na nossa revisão bibliográfica. Não poderíamos deixar de referir um artigo da Curr Opin Lipidol que se debruça sobre uma temática extremamente atual e que está já abrir novas vias terapêuticas em diversas áreas, nomeadamente nas que se referem ao controlo das dislipidemias e da doença vascular; trata-se do microbioma intestinal e da sua relação com os metabolismos lipídico, glucídico e a obesidade. Por último de referir os resultados do estudo REVEAL em que o anacetrapib reduziu significativamente o risco de eventos coronários major mas em que esta redução terá sido devida à redução dos valores do C-LDL e não ao extraordinário aumento do C-HDL. Será o *requiem* dos inibidores da CETP? Para a abordagem das dislipidemias segundo o estado da arte aconselhamos a consulta das "2016 ESC/EAS Guidelines for the Management of Dyslipidaemias", publicadas no European Heart Journal.

The central role of arterial retention of cholesterol rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity

Boren J, Williams KJ

Curr Opin Lipidol 2016 (5), 27:473–483

Purpose of review: Today, it is no longer a hypothesis, but an established fact, that increased plasma concentrations of cholesterol-rich apolipoprotein-B (apoB)-containing lipoproteins are causatively linked to atherosclerotic cardiovascular disease (ASCVD) and that lowering plasma LDL concentrations reduces cardiovascular events in humans. Here, we review evidence behind this assertion, with an emphasis on recent studies supporting the 'response-to-retention' model – namely, that the key initiating event in atherogenesis is the retention, or trapping, of cholesterol-rich apoB-containing lipoproteins within the arterial wall.

Recent findings: New clinical trials have shown that ezetimibe and anti-PCSK9 antibodies – both nonstatins – lower ASCVD events, and they do so to the same extent as would be expected from comparable plasma LDL lowering by a statin. These studies demonstrate beyond any doubt the causal role of apoB-containing lipoproteins in atherogenesis. In addition, recent laboratory experimentation and human Mendelian randomization studies have revealed novel information about the critical role of apoB-containing lipoproteins in atherogenesis. New information has also emerged on mechanisms for the accumulation in plasma of harmful cholesterol-rich and triglyceride-rich apoB-containing remnant lipoproteins in states of overnutrition. Like LDL, these harmful cholesterol-rich and triglyceride-rich apoB-containing remnant lipoprotein remnants become retained and modified within the arterial wall, causing atherosclerosis.

Summary: LDL and other cholesterol-rich, apoB-containing lipoproteins, once they become retained and modified within the arterial wall, cause atherosclerosis. This simple, robust pathophysiologic understanding may finally allow us to eradicate ASCVD, the leading killer in the world.

Comentários: sabe-se que o colesterol por si só, mesmo que junto à parede arterial, não causa aterosclerose. Atente-se no colesterol transportado pelos eritrócitos, que iguala em quantidade o transportado pelas LDL, sem propriedades aterogénicas. Apenas quando integrado nas lipoproteínas que contêm apoB, quer sejam as LDL, as IDL e/ou as remanescentes das quilomicra, adquire a capacidade de ultrapassar a barreira endotelial, mesmo que intacta e iniciar o processo aterogénico. Há uma relação entre os níveis das lipoproteínas contendo apoB e a permeabilidade endotelial. A redução dos níveis destas lipoproteínas através da terapêutica anti-sense teve como consequência uma redução da permeabilidade endotelial. Diversos proteoglicanos nomeadamente o biglicano, o perlecano e o versicano são essenciais para a retenção na parede arterial das lipoproteínas contendo apoB, não só as LDL e as IDL mas também as Lp pós-prandiais, iniciando o processo aterogénico.

The future of n-3 polyunsaturated fatty acid therapy

Davidson MH, Benes LB

Curr Opin Lipidol 2016, 27 (6):570–578

Purpose of review: this article focuses on the potential role by which a complex mixture of omega-3 fatty acids (OM3-FAs) may beneficially modify cardiovascular risk by modifying the cholesterol composition of atherogenic lipoproteins. This hypothesis is being tested in the STRENGTH trial, which is enrolling 13 000 patients on statins at high cardiovascular risk with hypertriglyceridemia and low HDL cholesterol (HDL-C) treated with an OM3-carboxylic acid.

Recent findings: complex mixtures of OM3-FAs containing predominately eicosapentanoic acid and docosahexanoic acid in combination with statins, lowers non-HDL by reducing triglyceride-rich lipoprotein cholesterol (TRL-C) while shifting small LDL cholesterol (LDL-C) to large LDL-C. Recent genomic and epidemiological studies have implicated TRL-C and small LDL-C as causal for cardiovascular disease. Therefore OM3-FAs containing both eicosapentanoic acid and docosahexanoic acid in combination with statins may beneficially modify the high residual risk for patients with hypertriglyceridemia and low HDL-C.

Summary: although outcome trials are underway, subgroup analyses of data from previous randomized controlled trials are suggestive of a reduction in coronary artery disease and atherosclerotic cardiovascular disease event rates with triglyceride and TRL-C lowering therapies, particularly if accompanied by low HDL-C. Although the limitations of such data are acknowledged, clinicians must make treatment decisions while awaiting more definitive results from well-designed large-scale randomized controlled trials.

Comentários: verifica-se uma mudança de paradigma relativamente ao potencial aterogénico das hipertrigliceridemias ligeiras a moderadas; para além dos níveis habitualmente reduzidos das HDL verfica-se uma associação das lipoproteínas remanescentes, ricas em colesterol e triglicerídeos, comprovadamente aterogénicas. Os ácidos gordos ómega 3, eicosapentanoico e docosahexanoico reduzem a lipogénese hepática e a concentração das VLDL e das suas remanescentes. Por outro lado, em associação às estatinas contrariam o aumento da síntese do ácido araquidónico induzido por estes últimos fármacos. Aguarda-se o resultado do STRENGTH trial, realizado em indivíduos de alto risco CV e com hipertrigliceridemia, em que se compara a associação de estatina com os ácidos gordos ómega 3 na redução de eventos. Outras propriedades atribuídas aos ácidos gordos ómega 3 são as ações anti-inflamatórias e anti-trombóticas, assim como contrariar o aumento do PCSK-9 induzido pelo fenofibrato.

Gut microbiome and lipid metabolism: from associations to mechanisms

Wang Z, Koonen D, Hofker M , Fub J

Curr Opin Lipidol 2016, 27 (3):216–224

Purpose of review: the gut microbiome has now been convincingly linked to human metabolic health but the underlying causality and mechanisms remain poorly understood. This review focuses on the recent progress in establishing the associations between gut microbiome species and lipid metabolism in humans and discusses how to move from association toward causality and mechanistic understanding, which is essential knowledge to bring the observed associations into clinical use.

Recent findings: recent population-based association studies have shown that the gut microbiota composition can explain a substantial proportion of the interindividual variation in blood triglycerides and HDL-cholesterol level and predict metabolic response to diet and drug. Faecal transplantation has suggested that this is a causal effect of microbiome on host metabolism, although the underlying mechanism remains largely unexplored.

Summary: the gut microbiome is transitioning from being a 'missing' organ to a potential target for therapeutic applications. Due to the complex interplay between the gut microbiome, the host genome, and diet, a systematic approach is required to pave the way for therapeutic development.

Comentários: evidência crescente tem demonstrado o papel exercido pelo microbioma intestinal na doença cardiometabólica e particularmente no metabolismo lipídico. A associação entre o microbioma intestinal e os níveis de triglicerídeos e do CHDL (é menos evidente a relação com o CLDL) foi demonstrada em estudos no rato e nos humanos. Também relativamente ao metabolismo glucídico e à obesidade, diversos fenótipos têm sido influenciados pela transplantação fecal. Relativamente aos mecanismos responsáveis por estas ações metabólicas do microbioma, parecem estar parcialmente dependentes dos ácido gordos de cadeia curta (AGCC), através da indução por estes de hormonas da saciedade - (GLP-1), peptídeo YY, e leptina, pela supressão da lipogénese hepática –cAMP / proteína quinase e pelo aumento do metabolismo oxidativo. Os AGCC podem igualmente induzir a neoglucogénese e a atividade simpática intestinais, melhorando a homeostase da glucose. Diversas terapêuticas interferem com o microbioma intestinal, desde a transplantação fecal, uso dos antibióticos, dos inibidores das bombas de protões e da metformina. A intervenção dietética constitui uma das armas mais eficazes para alterar favoravelmente o microbioma intestinal.

Adiponectin, lipids and atherosclerosis

Katsiki N, Mantzoros C, Mikhailidis DP

Curr Opin Lipidol. 2017 Aug;28(4):347-354

Purpose of review: adiponectin is an adipokine with anti-inflammatory, antioxidant, antiatherogenic, pro-angiogenic, vasoprotective and insulin-sensitizing properties. Several factors may influence adiponectin levels, such as genetic polymorphisms, obesity / body fat distribution, diet and exercise as well as cardiovascular risk factors such as sleep deprivation and smoking as well as medications. Adiponectin has been proposed as a potential prognostic biomarker and a therapeutic target in patients with cardiometabolic diseases.

Recent findings: this narrative review discusses the associations of adiponectin with obesity-related metabolic disorders (metabolic syndrome, nonalcoholic fatty liver disease, hyperuricaemia and type 2 diabetes mellitus). We also focus on the links between adiponectin and lipid disorders and with coronary heart disease and noncardiac vascular diseases (i.e. stroke, peripheral artery disease, carotid artery disease, atherosclerotic renal artery stenosis, abdominal aortic aneurysms and chronic kidney disease). Further, the effects of lifestyle interventions and drug therapy on adiponectin levels are briefly reviewed.

Summary: based on available data, adiponectin represents a multifaceted biomarker that may beneficially affect atherosclerosis, inflammation and insulin resistance pathways. However, there are conflicting results with regard to the associations between adiponectin levels and the prevalence and outcomes of cardiometabolic diseases. Further research on the potential clinical implications of adiponectin in the diagnosis and treatment of such diseases is needed.

Comentários: Esta adipoquina com propriedades antiinflamatórias, antioxidantes e anti-aterogénicas tem apresentado resultados algo contraditórios quando se estuda a sua relação com os fatores de risco vascular (FRV) e a doença vascular (DV). A maioria dos estudos tem demonstrado uma associação da adiponectina com elevados níveis de C-HDL e redução dos níveis do C-LDL e dos triglicerídeos, assim como uma associação negativa com a síndrome metabólica e a diabetes. No entanto, relativamente à prevalência da DV, cardíaca, cerebral e periférica os resultados são contraditórios. Alguns resultados mostram uma acção aparentemente protetora, evidenciando uma relação entre elevados níveis da adiponectina e a ocorrência da doença. Também a ação dos diversos fármacos sobre a adipoquina se destaca do expectável. Os ácidos gordos ómega 3 e a maioria das estatinas aumenta os seus níveis, exceto a rosuvastatina, enquanto a ezetimiba apresenta resultados equívocos. Estão em desenvolvimento alguns fármacos dirigidos para o aumento dos níveis / ação da adiponectina, como é o caso de diversos análogos do seu recetor. Em conclusão, carecem mais estudos para definitivamente esclarecer o papel desta adipoquina na doença vascular.

Clarifying complex inheritance: apolipoprotein C3 and atherosclerosis

Galton DJ

Curr Opin Lipidol. 2017 Aug;28(4):308-312

Purpose of review: To describe some steps in the progress in the molecular biology of a peptide, apolipoprotein C3; its gene mutations that render individuals susceptible or resistant to developing hyperlipidaemia and atherosclerosis.

Recent findings: Data that lead to the development of a new therapeutic agent volanesorsen.

Summary: The agent blocks the function of the mRNA of apolipoprotein C3 and successfully treats severe hypertriglyceridaemia in phase 3 trials (Ionis Pharmaceuticals)

Comentários: a apo C3 é uma proteína de 79 aminoácidos, sintetizada no fígado e no intestino e que se liga às lipoproteínas ricas em triglicerídeos, VLDL e quilomicra, inibindo a ação da lipoproteína lípase (LPL), e consequentemente o metabolismo destas lipoproteínas conduzindo ao aumento dos remanescentes das VLDL e quilomicra altamente aterogénicas. Existem três variantes (apo C3-0, apo C3-1 e apo C3-2), que se supõe terem diferentes ações sobre a LPL. Populações com alterações na síntese desta apoproteína conduzindo a uma redução dos seus níveis, apresentam uma redução da doença vascular.

Num estudo de fase dois, um oligonucleótido anti-mRNA da apo C3 reduziu os níveis desta apoproteína e dos triglicerídeos, sem efeitos secundários significativos. Os autores terminam sugerindo que o estudo genético com o objectivo de caracterizar a variante e a acção da apo C3 expressada, poderá constituir uma nova ferramenta de avaliação do risco vascular e que a apoC3 poderá ser um novo alvo da terapêutica hipolipidemiante.

Screening for Lipid Disorders in Children and Adolescents: US Preventive Services Task Force Recommendation Statement.

Bibbins-Domingo K, Grossman DC, Curry SJ, for the US Preventive Services Task Force

JAMA. 2016; 316(6):625-33

IMPORTANCE: Elevations in levels of total, low-density lipoprotein, and non-high-density lipoprotein cholesterol; lower levels of high-density lipoprotein cholesterol; and, to a lesser extent, elevated triglyceride levels are associated with risk of cardiovascular disease in adults.

OBJECTIVE: To update the 2007 US Preventive Services Task Force (USPSTF) recommendation on screening for lipid disorders in children, adolescents, and young adults.

EVIDENCE REVIEW: The USPSTF reviewed the evidence on screening for lipid disorders in children and adolescents 20 years or younger--1 review focused on screening for heterozygous familial hypercholesterolemia, and 1 review focused on screening for multifactorial dyslipidemia.

FINDINGS: Evidence on the quantitative difference in diagnostic yield between universal and selective screening approaches, the effectiveness and harms of long-term treatment and the harms of screening, and the association between changes in intermediate outcomes and improvements in adult cardiovascular health outcomes are limited. Therefore, the USPSTF concludes that the balance of benefits and harms cannot be determined.

CONCLUSIONS AND RECOMMENDATION: The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for lipid disorders in children and adolescents 20 years or younger.

Comentários: A hipercolesterolemia familiar não tratada, é uma causa bem demonstrada de doença cardiovascular prematura. Apesar de 7,8% dos adolescentes norte-americanos apresentarem c-LDL>130mg/dl e poderem sofrer desta doença, questões éticas e de viabilidade de execução impedem que existam estudos randomizados controlados com crianças/adolescentes com duração suficiente que permitam demonstrar diferenças estatisticamente significativas em duas estratégias terapêuticas distintas. Assim sendo, a Task Force, considerou não haver evidência disponível de momento para aferir a relação risco-benefício do rastreio da dislipidémia na população com idade inferior a 20 anos assim como da indicação para iniciar terapêutica farmacológica. Nesse sentido, este grupo decidiu não emitir nenhuma recomendação, deixando a cada clínico a decisão de rastrear o perfil lipídico ou não. Desta avaliação, foram excluídas as dislipidémias secundárias bem como a hipercolesterolemia familiar homozigótica.

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Yusuf S, Bosch J, Dagenais G, for the HOPE-3 Investigators

N Engl J Med 2016; 374:2021-2031

BACKGROUND Previous trials have shown that the use of statins to lower cholesterol reduces the risk of cardiovascular events among persons without cardiovascular disease. Those trials have involved persons with elevated lipid levels or inflammatory markers and involved mainly white persons. It is unclear whether the benefits of statins can be extended to an intermediate-risk, ethnically diverse population without cardiovascular disease.

METHODS In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants in 21 countries who did not have cardiovascular disease and were at intermediate risk to receive rosuvastatin at a dose of 10 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included revascularization, heart failure, and resuscitated cardiac arrest. The median follow-up was 5.6 years

RESULTS The overall mean low-density lipoprotein cholesterol level was 26.5% lower in the rosuvastatin group than in the placebo group. The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P=0.002). The results for the second coprimary outcome were consistent with the results for the first (occurring in 277 participants [4.4%] in the rosuvastatin group and in 363 participants [5.7%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001). The results were also consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% of the participants, vs. 3.1% in the placebo group; P=0.02) and muscle symptoms (in 5.8% of the participants, vs. 4.7% in the placebo group; P=0.005).

CONCLUSIONS Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)

Comentários: neste estudo, HOPE-3, realizado em pessoas de 21 países e de 6 continentes, com risco cardiovascular intermédio e com valores basais de CLDL normais (127 mg/dl) a utilização de baixas doses de Rosuvastatina, 10 mg/dia, conduziu a uma redução de um composto de morte por doença cardiovascular, EAM não fatal, AVC não fatal, necessidade de ressuscitação por paragem cardíaca e de revascularização e de insuficiência cardíaca. Os benefícios verificaram-se independentemente dos níveis basais de LDL e da tensão arterial, da proteína C-reativa, do risco vascular basal, da idade, do sexo ou do grupo étnico, incluindo a população chinesa e outros asiáticos.

Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up.

Vallejo-Vaz AJ, Robertson M, Catapano AL, Watts GF, Kastelein JJ, Packard CJ, Ford I, Ray KK

Circulation. 2017 Nov 14;136(20):1878-1891

BACKGROUND: Patients with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL are at a higher risk of atherosclerotic cardiovascular disease as a result of long-term exposure to markedly elevated LDL-C levels. Therefore, initiation of statin therapy is recommended for these individuals. However, there is a lack of randomized trial evidence supporting these recommendations in primary prevention. In the present analysis, we provide hitherto unpublished data on the cardiovascular effects of LDL-C lowering among a primary prevention population with LDL-C ≥190 mg/dL.

METHODS: We aimed to assess the benefits of LDL-C lowering on cardiovascular outcomes among individuals with primary elevations of LDL-C ≥190 mg/dL without preexisting vascular disease at baseline. We performed post hoc analyses from the WOSCOPS (West of Scotland Coronary Prevention Study) randomized, placebo-controlled trial, and observational post-trial long-term follow-up, after excluding individuals with evidence of vascular disease at baseline. WOSCOPS enrolled 6595 men aged 45 to 64 years, who were randomly assigned to pravastatin 40 mg/d or placebo. In the present analyses, 5529 participants without evidence of vascular disease were included, stratified by LDL-C levels into those with LDL-C <190 mg/dL (n=2969; mean LDL-C 178±6 mg/dL) and those with LDL-C ≥190 mg/dL (n=2560; mean LDL-C 206±12 mg/dL). The effect of pravastatin versus placebo on coronary heart disease and major adverse cardiovascular events were assessed over the 4.9-year randomized controlled trial phase and on mortality outcomes over a total of 20 years of follow-up.

RESULTS: Among 5529 individuals without vascular disease, pravastatin reduced the risk of coronary heart disease by 27% (P=0.002) and major adverse cardiovascular events by 25% (P=0.004) consistently among those with and without LDL-C ≥190 mg/dL (P-interaction >0.9). Among individuals with LDL-C ≥190 mg/dL, pravastatin reduced the risk of coronary heart disease by 27% (P=0.033) and major adverse cardiovascular events by 25% (P=0.037) during the initial trial phase and the risk of coronary heart disease death, cardiovascular death, and all-cause mortality by 28% (P=0.020), 25% (P=0.009), and 18% (P=0.004), respectively, over a total of 20 years of follow-up.

CONCLUSIONS: The present analyses provide robust novel evidence for the short- and long-term benefits of lowering LDL-C for the primary prevention of cardiovascular disease among individuals with primary elevations of LDL-C ≥190 mg/dL.

Comentário: embora seja facilmente aceite que doentes com elevados níveis de LDL-colesterol estão sob alto risco de doença cardiovascular, não existia até recentemente uma análise que demonstrasse a indicação para prevenção primária nesta população. Perante a impossibilidade ética de um estudo prospectivo para avaliação da indicação terapêutica das estatinas numa população com LDL-colesterol>190 mg/dl sem evidência de doença

vascular à luz da evidência científica actual, foi realizada uma análise retrospetiva do ensaio WOSCOPS (West of Scotland Coronary Prevention Study) em 5529 doentes, divididos em dois grupos pelo cut-off de LDL-colesterol de 190 mg/dl; o efeito da pravastatina foi avaliado ao final dos 4,9 anos e a mortalidade após 20 anos de follow-up. Verificou-se uma redução de doença coronária de 27% e efeitos adversos cardiovasculares major de 25% consistente nos 2 grupos; a mortalidade cardiovascular e em geral teve uma redução de 25% e 18% respetivamente após 20 anos de follow-up. Fica assim provado o benefício da terapêutica com estatina como prevenção primária nos doentes com LDL>190 mg/dl, que têm alto risco cardiovascular pela exposição prolongada a elevados níveis de partículas aterogénicas assim como naqueles com LDL>155 mg/dl, valor a partir do qual se provou redução da mortalidade sob terapêutica com estatina.

Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries– Findings from the EUROASPIRE IV survey.

Reiner Z, De Backer G, Fras Z, for the EUROASPIRE Investigators.

Atherosclerosis. 2016 Mar;246:243-50

OBJECTIVE: Since dyslipidaemia is one of the most important risk factors for coronary heart disease (CHD), lowering of LDL-cholesterol (LDL-C) causes significant reduction in morbidity and mortality, particularly in patients with established CHD. The aim of this survey was to assess how statins were prescribed in CHD patients at discharge after a coronary event from hospitals throughout Europe and how the intake of these drugs was reported by the patients when they were seen more than one year later in relationship with their achieved LDL-C levels.

METHODS: 6648 CHD patients' data from centres in 24 European countries were gathered using standardized methods. Lipid measurements were performed in one central laboratory. Patients were divided in three groups: high-intensity statin therapy, moderate or low intensity statin therapy and no statin therapy at all.

RESULTS: 90.4% CHD patients were on statin therapy at the time of discharge from the hospital which d ecreased to 86% one year later. Only 37.6% of these patients were prescribed a high-intensity statin at discharge which even decreased to 32.7% later. In only 6 countries (all of them high-income countries) the number of patients on a high-intensity statin therapy increased substantially after the hospital discharge. It is worrying that statin therapy was discontinued in 11.6% and that only 19.3% of all CHD patients achieved target values of LDL-C < 1.8 mmol/L at the time of interview.

CONCLUSIONS: Too many CHD patients with dyslipidaemia are still inadequately treated and most of these patients on statin therapy are not achieving the treatment targets. Therapeutic control of LDL-C is clearly related to the intensity of lipid lowering drug regimen after the CHD event indicating that a considerable potential still exists throughout Europe to reduce CHD mortality and morbidity rates through more efficient LDL-C lowering.

Comentários: apesar de claramente documentados os benefícios da terapêutica com estatinas nos doentes com doença coronária, o controlo da dislipidémia como fator de risco é sub-óptimo. A prescrição insuficiente dos fármacos hipolipidemiantes está bem evidenciada neste estudo, onde 9,6% dos doentes admitidos por doença coronária têm alta sem prescrição de uma estatina e apenas 37,6% com estatina de alta potência. Consequentemente o controlo do mesmo é insuficiente, onde menos de 30% dos doentes atingem os valores alvo desejáveis. Tornam-se curiosas as diferenças entre países europeus, com 23% dos doentes a não serem medicados num país desenvolvido como a Holanda, sendo o país que mais estatinas prescreveu o Chipre (63/64 doentes). Este tipo de publicações, são de extrema importância para nos fazer refletir n o trabalho diário e se estamos ou não em sintonia com as recomendações europeias.

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients

Nicholls, SJ, Puri R, Anderson T, Ballantyne CM for the GLAGOV Randomized Clinical Trial

JAMA 2016 Dec 13;316(22):2373-2384.

IMPORTANCE Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated. OBJECTIVE To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

DESIGN, SETTING,AND PARTICIPANTS The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography. INTERVENTIONS Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

MAIN OUTCOMES AND MEASURES The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.

RESULTS Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6mg/dL; difference, −56.5mg/dL [95%CI, −59.7 to −53.4]; P < .001). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, −1.0% [95%CI, −1.8%to −0.64%]; P < .001). The secondary efficacy parameter, normalized

TAV, decreased 0.9mm^3 with placebo and 5.8mm^3 with evolocumab (difference, −4.9mm^3 [95%CI, −7.3 to −2.5]; P < .001). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3%vs 47.3%; difference, 17.0% [95%CI, 10.4%to 23.6%]; P < .001 for PAV and 61.5% vs 48.9%; difference, 12.5% [95%CI, 5.9% to 19.2%]; P < .001 for TAV).

CONCLUSIONS AND RELEVANCE Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

Comentários: já havia sido demonstrado que a terapêutica com estatinas em alta dose leva à regressão da placa de ateroma quando se atingem valores de c-LDL inferiores a 70mg/dl. Este novo grupo de fármacos, os inibidores da PCSK9, tem demonstrado reduções muito consideráveis do c-LDL e com efeito aditivo, quando associado a estatinas. Neste estudo, a associação do Evolucumab a uma estatina mostrou mais uma vez uma eficácia n otável na redução do c-LDL. Em consequência disso, o end-point primário foi alcançado, demonstrando ainda que a mais intensa redução do c-LDL se associa a uma redução do volume da placa de ateroma coronário às 76 semanas de tratamento, em doentes com doença coronária prévia. Parece assim existir evidência que quanto mais baixo o c-LDL, melhor, pelo menos até valores de 36mg/dl.

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

Sabatine MS, Giugliano RP, Keech AC, for the FOURIER Steering Committee and Investigators

N Engl J Med. 2017 May 4;376(18):1713-1722

BACKGROUND: Evolocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin–kexin type 9 (PCSK9) and lowers low-density lipoprotein (LDL) cholesterol levels by approximately 60%. Whether it prevents cardiovascular events is uncertain.

METHODS: We conducted a randomized, double-blind, placebo-controlled trial involving 27,564 patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 70mg/dL or higher who were receiving statin therapy. Patients were randomly assigned to receive evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo as subcutaneous injections. The primary efficacy end point was the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke. The median duration of follow-up was 2.2 years.

RESULTS: At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol/L) to 30 mg per deciliter (0.78 mmol/L) (P<0.001). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; P<0.001) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). The results were consistent across key subgroups, including the sub- group of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol/L]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).

CONCLUSIONS: in our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol/L) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

Comentários: Este foi o ensaio de fase III mais antecipado do ano de 2017. Trata-se de um estudo de eficácia, em termos de redução de eventos cardiovasculares, do Evolocumab (inibidor da PCSK9) em associação a uma estatina. O tempo médio de seguimento foi curto em comparação com ensaios do mesmo âmbito (48 semanas), no entanto, a associação estatina/evolucumab demonstrou uma redução de eventos cardiovasculares em 15% sem ter conseguido atingir resultados estatisticamente significativos na redução da mortalidade cardiovascular. A eficácia na redução dos valores do C-LDL foi o esperado tendo em conta os ensaios prévios: reduções de 59% do valor basal do c-LDL. O evolucumab junta-se assim às estatinas e ao ezetimibe na evidência de redução de eventos cardiovasculares.

Higher Visit-to-Visit Low-Density Lipoprotein Cholesterol Variability Is Associated with Lower Cognitive Performance, Lower Cerebral Blood Flow, and Greater White Matter Hyperintensity Load in Older Subjects

Smit RA, Trompet S, Sabayan B, et al

Circulation. 2016 Jul 19;134(3):212-21

Background: recently, it was shown that intraindividual variation in low-density lipoprotein cholesterol (LDL-C) predicts both cerebrovascular and cardiovascular events. We aimed to examine whether this extends to cognitive function and examined possible pathways using a magnetic resonance imaging substudy.

Methods: we investigated the association between LDL-C variability and 4 cognitive domains at month 30 in 4428 participants of PROSPER (PROspective Study of Pravastatin in the Elderly at Risk). Additionally, we assessed the association of LDL-C variability with neuroimaging outcomes in a subset of 535 participants. LDL-C variability was defined as the intraindividual standard deviation over 4 postbaseline LDL-C measurements, and all analyses were adjusted for mean LDL-C levels and cardiovascular risk factors.

Results: higher LDL-C variability was associated with lower cognitive function in both the placebo and pravastatin treatment arms. Associations were present for selective attention (P=0.017 and P=0.11, respectively), processing speed (P=0.20 and P=0.029), and memory (immediate recall, P=0.002 and P=0.006; delayed recall, P=0.001 and P≤0.001). Furthermore, higher LDL-C variability was associated with lower cerebral blood flow in both trial arms (P=0.031 and P=0.050) and with greater white matter hyperintensity load in the pravastatin arm (P=0.046). No evidence was found for interaction between LDL-C variability and pravastatin treatment for both cognitive and magnetic resonance imaging outcomes.

Conclusions: we found that higher visit-to-visit variability in LDL-C, independently of mean LDL-C levels and statin treatment, is associated with lower cognitive performance, lower cerebral blood flow, and greater white matter hyperintensity load.

Comentários: foi descrita uma associação entre a maior variabilidade nos valores de C-LDL e pior performance cognitiva nos indivíduos mais idosos numa subanálise de um ensaio randomizado e prospetivo com pravastatina, no qual se incluíram 4428 indivíduos entre os 72 e os 82 anos com elevado risco de, ou com doença vascular conhecida. A variabilidade foi calculada a partir do desvio padrão aos 3, 6, 12 e 24 meses. A performance cognitiva avaliada foi menor em doentes com maior variabilidade no C-LDL, com ou sem terapêutica com estatinas em curso; nestes doentes com maior variabilidade foi também encontrada uma associação com menor fluxo cerebral total em ambos os grupos de doentes e de maior número de zonas hiperintensas na substância branca (apenas no grupo tratado com estatinas). A explicação apresentada prende-se com a possibilidade de a maior variação nos níveis de C-LDL causar maior disfunção endotelial ou instabilidade das placas de ateroma e eventos subclínicos. Mais estudos são necessários nesta área mas parece existir evidência de que nas idades mais avançadas, a grande variação do valor de c-LDL pode ser mais deletéria que benéfica, não havendo no entanto relação com os valores absolutos de c-LDL.

Cognitive Function in a Randomized Trial of Evolocumab

Giugliano RP, Mach F, Zavitz K , for the EBBINGHAUS Investigators

N Engl J Med 2017; 377:633-643

BACKGROUND: findings from clinical trials of proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors have led to concern that these drugs or the low levels of low-density lipoprotein (LDL) cholesterol that result from their use are associated with cognitive deficits.

METHODS: In a subgroup of patients from a randomized, placebo-controlled trial of evolocumab added to statin therapy, we prospectively assessed cognitive function using the Cambridge Neuropsychological Test Automated Battery. The primary end point was the score on the spatial working memory strategy index of executive function (scores range from 4 to 28, with lower scores indicating a more efficient use of strategy and planning). Secondary end points were the scores for working memory (scores range from 0 to 279, with lower scores indicating fewer errors), episodic memory (scores range from 0 to 70, with lower scores indicating fewer errors), and psychomotor speed (scores range from 100 to 5100 msec, with faster times representing better performance). Assessments of cognitive function were performed at baseline, week 24, yearly, and at the end of the trial. The primary analysis was a noninferiority comparison of the mean change from baseline in the score on the spatial working memory strategy index of executive function between the patients who received evolocumab and those who received placebo; the noninferiority margin was set at 20% of the standard deviation of the score in the placebo group.

RESULTS A total of 1204 patients were followed for a median of 19 months; the mean (±SD) change from baseline over time in the raw score for the spatial working memory strategy index of executive function (primary end point) was −0.21±2.62 in the evolocumab group and −0.29±2.81 in the placebo group (P<0.001 for noninferiority; P = 0.85 for superiority). There were no significant between-group differences in the secondary end points of scores for working memory (change in raw score, −0.52 in the evolocumab group and −0.93 in the placebo group), episodic memory (change in raw score, −1.53 and −1.53, respectively), or psychomotor speed (change in raw score, 5.2 msec and 0.9 msec, respectively). In an exploratory analysis, there were no associations between LDL cholesterol levels and cognitive changes.

CONCLUSIONS: In a randomized trial involving patients who received either evolocumab or placebo in addition to statin therapy, no significant between-group difference in cognitive function was observed over a median of 19 months.

Comentários: uma das controvérsias que mais tem alimentado a discussão referente à redução dos níveis de colesterol circulante, é a possível relação entre os seus baixos valores e a redução das capacidades cognitivas, inclusivamente com uma maior ocorrência de quadros demenciais. Estudos randomizados e controlados por placebo não demonstraram qualquer relação significativa entre a redução dos níveis da colesterolémia, a utilização das estatinas e as funções cognitivas. Fisiopatologicamente o nosso cérebro utiliza nas suas necessidades estruturais e funcionais, um tipo de lipoproteínas HDL, ricas em apo E, sintetizadas in situ e não as

lipoproteínas circulantes no plasma, indicando uma independência entre os níveis plasmáticos das lipoproteínas e a sua concentração cerebral.

Este trabalho, o EBBINGHAUS, trata-se de uma subanálise do FOURIER, em doentes sem antecedentes de qualquer patologia neurológica ou psiquiátrica em avaliação prévia à inclusão no estudo. Apesar dos baixos valores de C-LDL obtidos no grupo de doentes tratado com o inibidor da PCSK-9, não se verificaram quaisquer diferenças entre os dois grupos no que que se refere às funções cognitivas, nomeadamente nos scores spatial working memory strategy index of executive function, working memory, episodic memory e psychomotor speed. *Assim, mais uma vez se demonstrou a segurança da redução significativa dos níveis plasmáticos do colesterol no que diz respeito às funções neurológicas superiores.*

New oral agents for treating dyslipidemia

Gryn SE, Hegele RA

Curr Opin Lipidol 2016, 27 (6):579–584

Purpose of review: We provide an overview of orally administered lipid-lowering therapies under development.

Recent findings: Recent data support statins for intermediate risk primary prevention, and ezetimibe for high-risk secondary prevention. Novel agents in development include bempedoic acid and gemcabene, and work continues on one remaining cholesteryl ester transfer protein inhibitor, anacetrapib, to determine whether this class can reduce cardiovascular risk. Selective peroxisome proliferator-activated receptor modulators such as K-877 are under study to determine whether they have an advantage over older fibrates. Diacylglycerol transferase inhibitors such as pradigastat appear to have potent triglyceride-lowering effects, even for patients with familial chylomicronemia syndrome. Finally, novel v-3 preparations are available with significant triglyceride lowering, although their role in therapy remains unclear.

Summary: statins will remain the backbone of lipid-lowering therapy, although several novel oral agents are promising. The common theme across drugs in development is the demonstration of good lipid-lowering effect, although lacking cardiovascular outcomes data, which will likely be necessary before any of them, can be recommended or approved for widespread use.

Comentários: novos hipolipemiantes orais vão surgindo, capazes de - geralmente em associação com as estatinas - conseguir reduções adicionais do CLDL. Como exemplo temos, o ácido benpedoico com o seu mecanismo dual, redução do acetil-CoA por um lado (molécula precursora do colesterol), e aumento da AMPK por outro, (proteína cinase que controla enzimas envolvidas na biossíntese do colesterol e dos ácidos gordos). O gencabeno, que reduz o nível das LDL, dos triglicerídeos e aumenta as HDL aparentemente por redução da síntese e aumento da degradação das lipoproteínas ricas em triglicerídeos. O pemafibrato, um novo e mais potente agonista dos PPAR alfa, com efeitos mais marcantes nas diversas frações lipoproteicas comparativamente aos atuais fibratos. O pradigast inibe a enzima diacilglicerol aciltransferase, essencial na síntese e absorção das gorduras. No entanto associa-se a intoleráveis efeitos secundários gastrointestinais.

Effects of K-877, a novel selective PPARα modulator (SPPARMα), in dyslipidaemic patients: A randomized, double blind, active- and placebo-controlled, phase 2 trial

Ishibashi S, Yamashita S, Arai H, for the K-877-04 Study Group.

Atherosclerosis. 2016 Jun; 249:36-43.

BACKGROUND AND AIMS: to assess the efficacy and safety of K-877 (Pemafibrate), a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα) that possesses unique PPARα activity and selectivity, compared with placebo and fenofibrate in dyslipidaemic patients with high triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-C) levels.

METHODS AND RESULTS: this study was a double blind, placebo-controlled, parallel-group 12-week clinical trial. The study randomized 224 patients to K-877 0.025, 0.05, 0.1, 0.2 mg BID, fenofibrate 100 mg QD, or placebo (1:1:1:1:1:1) groups. Least squares mean percent changes from the baseline TG levels were -30.9%, -36.4%, -42.6%, -42.7% for the K-877 0.025, 0.05, 0.1, 0.2 mg BID respectively ($p < 0.001$), which were greater than that of the fenofibrate 100 mg QD (-29.7%, $p < 0.001$) group. Statistically significant improvements from the baseline HDL-C, very-low-density lipoprotein cholesterol, chylomicron cholesterol, remnant lipoprotein cholesterol, apolipoprotein (apo) B (apoB), and apoC-III were also observed in the K-877 groups. The incidence of adverse events (AEs) in the K-877 groups (32.4-56.8%) was comparable to those in placebo (47.2%) and fenofibrate 100 mg QD (56.8%); adverse drug reactions (ADRs) in the K-877 groups (2.7-5.4%) were less than those in placebo (8.3%) and fenofibrate 100 mg QD (10.8%) groups.

CONCLUSION: in dyslipidaemic patients with high TG and low HDL-C, K-877 improved TG, HDL-C, and other lipid parameters without increasing AEs or ADRs, compared to placebo and fenofibrate. K-877 can be expected to improve atherogenicity and to be a new beneficial treatment for dyslipidaemic patients.

Comentários: A terapêutica hipolipidemiante está em fase de grande investigação, situação compreensível, dado que a mortalidade cardiovascular é uma, se não a principal, causa de morte nos países desenvolvidos. Novos agentes têm sido testados com grande frequência, aguardando-se no entanto a sua entrada no mercado. A molécula K-877 é um fármaco em fase II de investigação clínica, que tem propriedades agonistas do receptor PPAR-alfa, consequentemente com efeitos predominantemente nos triglicéridos e na elevação do c-HDL. Este ensaio, mostra-nos efeitos contraditórios. Redução dos triglicéridos e elevação do C-HDL, numa proporção dose-dependente e com maior eficácia que a classe dos fibratos. No entanto, apresenta elevação do c-LDL, partícula com clara associação com eventos cardiovascular. Apesar de ser um estudo de fase II e consequentemente com um follow up curto, esta nova molécula não apresentou, efeitos adversos significativos. A investigação nesta área continua, aguardamos os resultados dos ensaios de fase III.

Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

Kausik R, M.D., Landmesser U, Leiter LA et al

N Engl J Med. 2017 Apr 13;376(15):1430-1440

BACKGROUND: In a previous study, a single injection of inclisiran, a chemically synthesized small interfering RNA designed to target PCSK9 messenger RNA, was found to produce sustained reductions in low-density lipoprotein (LDL) cholesterol levels over the course of 84 days in healthy volunteers. METHODS: We conducted a phase 2, multicenter, double-blind, placebo-controlled, multiple- ascending-dose trial of inclisiran administered as a subcutaneous injection in patients at high risk for cardiovascular disease who had elevated LDL cholesterol levels. Patients were randomly assigned to receive a single dose of placebo or 200, 300, or 500 mg of inclisiran or two doses (at days 1 and 90) of placebo or 100, 200, or 300 mg of inclisiran. The primary end point was the change from baseline in LDL cholesterol level at 180 days. Safety data were available through day 210, and data on LDL cholesterol and proprotein convertase subtilisin–kexin type 9 (PCSK9) levels were available through day 240. RESULTS: A total of 501 patients underwent randomization. Patients who received inclisiran had dose-dependent reductions in PCSK9 and LDL cholesterol levels. At day 180, the least-squares mean reductions in LDL cholesterol levels were 27.9 to 41.9% after a single dose of inclisiran and 35.5 to 52.6% after two doses (P<0.001 for all comparisons vs. placebo). The two-dose 300-mg inclisiran regimen produced the greatest reduction in LDL cholesterol levels: 48% of the patients who received the regimen had an LDL cholesterol level below 50 mg per deciliter (1.3 mmol/L) at day 180. At day 240, PCSK9 and LDL cholesterol levels remained significantly lower than at baseline in association with all inclisiran regimens. Serious adverse events occurred in 11% of the patients who received inclisiran and in 8% of the patients who received placebo. Injection-site reactions occurred in 5% of the patients who received injections of inclisiran.

CONCLUSIONS: In our trial, inclisiran was found to lower PCSK9 and LDL cholesterol levels among patients at high cardiovascular risk who had elevated LDL cholesterol levels. (Funded by the Medicines Company; ORION-1 ClinicalTrials.gov number, NCT02597127.)

Comentário: Este ensaio randomizado e duplamente cego de fase 2 veio dar seguimento aos resultados obtidos numa população saudável, utilizando um fármaco que consiste numa molécula capaz de interferir com o RNA mensageiro do gene do PCSK9 (Inclisiran) atuando num nível diferente dos inibidores desta molécula, mas aumentando igualmente a expressão do receptor do LDL na superfície da célula. Em 501 doentes distribuídos em diferentes grupos, foram testadas diferentes doses assim como intervalos de administração em doentes de elevado risco cardiovascular (com LDL>100 mg/dl ou >70mg/dl com evento cardiovascular prévio) sob dose máxima de estatina e sem terapêutica com inibidor da PCSK9; os resultados foram avaliados durante 12 meses. A redução alcançada do LDL foi dose dependente; a maior redução (52,6%) foi obtida no grupo em que foram administradas duas doses de 300 mg de Inclisiran separadas por 3 meses, resultado sobreponível ao alcançado com os inibidores da PCSK9 como seria expectável; esta redução manteve-se durante todo o período de monitorização. Ocorreram efeitos secundários graves em 11% dos pacientes que receberam o fármaco, em comparação com 8% no grupo placebo, que compreenderam síndrome gripal e elevações transitórias das transaminases; contudo, são necessários ensaios maiores para aferir a segurança do fármaco

Effects of Anacetrapib in Patients with Atherosclerotic Vascular Disease

The HPS3/TIMI55–REVEAL Collaborative Group

N Engl J Med. 2017 Sep 28;377(13):1217-1227

Background: patients with atherosclerotic vascular disease remain at high risk for cardiovascular events despite effective statin-based treatment of low-density lipoprotein (LDL) cholesterol levels. The inhibition of cholesteryl ester transfer protein (CETP) by anacetrapib reduces LDL cholesterol levels and increases high-density lipoprotein (HDL) cholesterol levels. However, trials of other CETP inhibitors have shown neutral or adverse effects on cardiovascular outcomes. METHODS: we conducted a randomized, double-blind, placebo-controlled trial involving 30,449 adults with atherosclerotic vascular disease who were receiving intensive atorvastatin therapy and who had a mean LDL cholesterol level of 61 mg per deciliter (1.58 mmol/L), a mean non-HDL cholesterol level of 92 mg per deciliter (2.38 mmol/L), and a mean HDL cholesterol level of 40 mg per deciliter (1.03 mmol/L). The patients were assigned to receive either 100 mg of anacetrapib once daily (15,225 patients) or matching placebo (15,224 patients). The primary outcome was the first major coronary event, a composite of coronary death, myocardial infarction, or coronary revascularization. RESULTS: during the median follow-up period of 4.1 years, the primary outcome occurred in significantly fewer patients in the anacetrapib group than in the placebo group (1640 of 15,225 patients [10.8%] vs. 1803 of 15,224 patients [11.8%]; rate ratio, 0.91; 95% confidence interval, 0.85 to 0.97; P=0.004). The relative difference in risk was similar across multiple prespecified subgroups. At the trial midpoint, the mean level of HDL cholesterol was higher by 43 mg per deciliter (1.12 mmol/L) in the anacetrapib group than in the placebo group (a relative difference of 104%), and the mean level of non-HDL cholesterol was lower by 17 mg per deciliter (0.44 mmol/L), a relative difference of −18%. There were no significant between-group differences in the risk of death, cancer, or other serious adverse events.

CONCLUSIONS: Among patients with atherosclerotic vascular disease who were receiving intensive statin therapy, the use of anacetrapib resulted in a lower incidence of major coronary events than the use of placebo. (Funded by Merck and others; Current Con- trolled Trials number, ISRCTN48678192; ClinicalTrials.gov number, NCT01252953; and EudraCT number, 2010-023467-18.)

Comentários: Após múltiplos trabalhos terem conduzido à exclusão do C-HDL como alvo terapêutico nas últimas recomendações, muita expectativa existia sobre a apresentação deste último estudo clínico com inibidores da CETP. A terapêutica com Anacetrapib levou a um incremento do C-HDL em 104% (mas também a uma redução de LDL de 18%); após mais de 4 anos de seguimento foi demonstrada uma redução de eventos cardiovasculares em 9% com significado estatístico. Esta redução deveu-se aos beneficio nos eventos coronários (EAM fatal ou não fatal e revascularização), não tendo havido efeito sobre o AVC isquémico. Os resultados estão relacionados com a redução dos valores de c-LDL, sem aparente relação com o incremento nos valores do c-HDL. Não houve efeitos secundários significativos, mas verificou-se uma acumulação progressiva do fármaco no tecido adiposo ao longo do estudo. Apesar dos resultados positivos, o patrocinador do ensaio suspendeu o processo de desenvolvimento desta molécula. Terá representado o fim do HDL como alvo terapêutico ?

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

Ridker PM, Everett BM, Thuren T, for the CANTOS Trial Group

N Engl J Med 2017; 377:1119-1131

BACKGROUND Experimental and clinical data suggest that reducing inflammation without affecting lipid levels may reduce the risk of cardiovascular disease. Yet, the inflammatory hypothesis of atherothrombosis has remained unproved.

METHODS: We conducted a randomized, double-blind trial of canakinumab, a therapeutic monoclonal antibody targeting interleukin-1β, involving 10,061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter. The trial compared three doses of canakinumab (50 mg, 150 mg, and 300 mg, administered subcutaneously every 3 months) with placebo. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

RESULTS: At 48 months, the median reduction from baseline in the high-sensitivity C-reactive protein level was 26 percentage points greater in the group that received the 50-mg dose of canakinumab, 37 percentage points greater in the 150-mg group, and 41 percentage points greater in the 300-mg group than in the placebo group. Canakinumab did not reduce lipid levels from baseline. At a median follow-up of 3.7 years, the incidence rate for the primary end point was 4.50 events per 100 person-years in the placebo group, 4.11 events per 100 person-years in the 50-mg group, 3.86 events per 100 person-years in the 150-mg group, and 3.90 events per 100 person-years in the 300-mg group. The hazard ratios as compared with placebo were as follows: in the 50-mg group, 0.93 (95% confidence interval [CI], 0.80 to 1.07; P = 0.30); in the 150-mg group, 0.85 (95% CI, 0.74 to 0.98; P = 0.021); and in the 300-mg group, 0.86 (95% CI, 0.75 to 0.99; P = 0.031). The 150-mg dose, but not the other doses, met the prespecified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point that additionally included hospitalization for unstable angina that led to urgent revascularization (hazard ratio vs. placebo, 0.83; 95% CI, 0.73 to 0.95; P = 0.005). Canakinumab was associated with a higher incidence of fatal infection than was placebo. There was no significant difference in all-cause mortality (hazard ratio for all canakinumab doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P = 0.31).

CONCLUSIONS: Antiinflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering.

Comentários: diversos estudos demonstraram uma associação positiva entre níveis elevados de marcadores inflamatórios, como a proteína-C-reativa (PCR) e a interleucina 6, e o risco vascular. Foi também já demonstrado que os efeitos vasculares benéficos das estatinas se ficaram a dever não só à redução do colesterol mas também dos níveis de inflamação. Até agora não existia evidência confirmada de que a redução dos níveis de inflamação sem concomitante redução das partículas lipídicas circulantes reduzisse o número de eventos vasculares. No estudo apresentado, indivíduos com antecedentes de enfarte agudo do miocárdio (EAM) e um nível de PCR superior ou igual a 2 mg/l foram medicados com diversas doses de canakinumab e, sem ter havido qualquer efeito nos

níveis das lipoproteínas plasmáticas, verificou-se que este anti-interleucina 1 beta reduziu significativamente o end point primário (composto de EAM não fatal, AVC isquémico não fatal e morte cardiovascular) em comparação com placebo. Estes resultados vieram reforçar o papel da inflamação no processo aterosclerótico, na doença que dele deriva e abrir novas perspetivas terapêuticas anti-aterogénicas para além dos fármacos hipolipemiantes.

U-shaped relationship of HDL and risk of infectious disease: two prospective population-based cohort studies.

Madsen CM, Varbo A, Tybjærg-Hansen A, Frikke-Schmidt R, Nordestgaard BG

Eur Heart J. 2017 Dec 8. doi: 10.1093/eurheartj/ehx665.

AIMS: preclinical evidence has indicated that HDL may play an important role in the immune system; however, very little is known about the role of HDL in the immune system in humans. We tested the hypothesis that low and high concentrations of HDL cholesterol are associated with risk of infectious disease in the general population.

METHODS AND RESULTS: we included 97 166 individuals from the Copenhagen General Population Study and 9387 from the Copenhagen City Heart Study with measurements of HDL cholesterol at baseline. The primary endpoint was any infectious disease requiring hospital admission, ascertained in the Danish health registries from baseline in 2003-13 or 1991-94 through 2014; 9% and 31% of individuals in the two studies experienced one or more infectious disease events. Using restricted cubic splines, there was a U-shaped association between concentrations of HDL cholesterol and risk of any infection. Following multifactorial adjustment, individuals with HDL cholesterol below 0.8 mmol/L (31 mg/dL) and above 2.6 mmol/L (100 mg/dL) had hazard ratios for any infection of 1.75 (95% confidence interval 1.31-2.34) and 1.43 (1.16-1.76), compared to those with HDL cholesterol of 2.2-2.3 mmol/L (85-95 mg/dL). In the Copenhagen City Heart Study, corresponding hazard ratios for any infection were 2.00 (1.16-3.43) and 1.13 (0.80-1.60).

CONCLUSION: low and high HDL cholesterol concentrations found in 21% and 8% of individuals were associated with higher risk of infectious disease in the general population. These findings do not necessarily indicate causality.

Comentário: esta análise retrospetiva, com todas as suas limitações, levanta a possibilidade de existir um papel do HDL-colesterol além do risco cardiovascular, nomeadamente nos mecanismos de imunidade. Os valores extremos de HDL-colesterol estão associados a maior risco de infeção com gravidade implicando internamento hospitalar, nomeadamente abaixo de 31 mg/dl e acima de 100 mg/dl, sendo maior o risco no grupo com baixo HDL. A faixa de valores de HDL-colesterol com menor risco infecioso é aquela entre os 85 e os 95 mg/dl. Estas conclusões derivam da análise de 2 estudos populacionais dinamarqueses, após ajuste multifactorial, contudo,

não existe necessariamente relação de causalidade assim como não foi avançado o possível mecanismo fisiopatológico para este facto. Fica assim aberto caminho para estudos prospetivos, nomeadamente para aferição se a terapêutica moduladora de c-HDL diminui o risco de infeções graves.

RV Hipertensão Arterial 2016/17

Vitória Cunha: Hospital Garcia de Orta

Fernando Martos Gonçalves: Hospital Beatriz Ângelo

A Hipertensão arterial (HTA) é o principal fator de risco para o desenvolvimento de doenças cardiovasculares, que são atualmente a primeira causa de morte nos países desenvolvidos. A HTA é uma patologia com elevada prevalência, afetando mais de um bilião de pessoas em todo o mundo segundo a OMS e mais de 40% da população portuguesa segundo o estudo PHYSA, e apesar do progresso farmacológico e tecnológico não se vislumbra ainda um controlo adequado.

A HTA continua a ser uma área de investimento científico importante, não só pelo peso que representa na morbi-mortalidade cardiovascular, mas também pelas inúmeras questões ainda por responder: desde mecanismos fisiopatológicos a objetivos terapêuticos, desde abordagens farmacológicas a novos devices para tratamento mais invasivo.

Em anos anteriores, estudos como o PHYSA e o SPRINT foram bases para mais questões, e 2016 pode não ter acabado com nomes tão sonantes, mas certamente acaba com maior conhecimento, mais desafios, mais pontos por decifrar, mais limitações para superar. Continuam a surgir fármacos, alvos terapêuticos, tratamentos não farmacológicos, e acima de tudo continuam a ser questionadas as ideias de sempre e ser almejadas abordagens mais eficazes. Ainda assim, também o ano de 2017 vem embalado naquilo que se pode chamar a Hipertensão na Era Pós-SPRINT, em particular com as tão criticadas guidelines americanas.

São publicados anualmente mais de 20000 artigos sobre hipertensão arterial. Num universo destes, é sempre difícil escolher as principais novidades de um ano, e esta seleção não deve deixar passar leituras mais desatentas de outros estudos interessantes, mas sim estimular a procura e atualização de conhecimentos por parte de todos. Optámos por estudos predominantemente clínicos e no pendor prático da sua aplicação, deixando para edições futuras os estudos mais moleculares ou de investigação genética. Não pela falta de importância, mas pela inevitável seleção limitada dos mesmos. O que apresentamos presentemente ajuda a rever alguns temas importantes e repensar algumas ideias pre-definidas na nossa abordagem diária. É fundamental que a procura de mais e melhor continue, e devemos abrir o espírito crítico e tentar descortinar a ciência na prática diária.

Boas leituras.

White-coat and masked hypertension as risk factors for progression to sustained hypertension: the Finn-Home study.

Sivén SS, Niiranen TJ, Kantola IM, Jula AM.

J Hypertens. 2016; 34(1):54-60.

OBJECTIVES: To assess the risk of progression from white-coat hypertension (WCHT) and masked hypertension (MHT) to sustained hypertension (SHT) in a nationwide unselected population sample.

METHODS: Both office and home blood pressure (BP), along with other cardiovascular risk factors, were measured in an unselected population sample of 944 participants in 2000 and 2011. We compared the risk of progression to SHT (office BP ≥140/90 mmHg and home BP ≥135/85 mmHg or start of treatment with antihypertensive medication) between 528 participants with normotension (office BP <140/90 mmHg and home BP <135/85 mmHg), 142 participants with WCHT (office BP ≥140/90 mmHg and home BP < 135/85 mmHg), and 63 participants with MHT (office BP < 140/90 mmHg and home BP ≥135/85 mmHg) at baseline. We used the χ test and a multivariable-adjusted log-binomial regression model to evaluate the association between baseline BP categories and incident SHT.

RESULTS: During an 11-year follow-up, the rate of progression to SHT increased from normotension (18%) to WCHT (52%) and MHT (73%), P < 0.0001. Progression to SHT became more likely with an increasing baseline home BP category (Ptrend < 0.0001). The multivariable-adjusted relative risks (95% confidence interval) for developing SHT, as compared with normotension, were 2.8 (2.2-3.6, P < 0.0001) for WCHT and 3.8 (2.9-5.0, P < 0.0001) for MHT.

CONCLUSIONS: Persons with WCHT and MHT have a three to four-fold risk for developing SHT than those with NT and could benefit from active follow-up and lifestyle counselling.

Comentário: este estudo foi selecionado porque a hipertensão da bata branca e a mascarada são dois conceitos fundamentais, mas nem sempre relembrados nos grandes estudos. Não são entidades clínicas ainda bem definidas, mas já se sabe que têm grande impacto no prognóstico cardiovascular a médio/longo prazo, embora o real impacto seja por vezes questionado. Foram avaliados 944 indivíduos seguidos durante 11 anos. A maioria dos estudos anteriores chegaram a conclusões semelhantes mas com menos dados, tinham amostras mais pequenas e follow-up mais curtos e apenas um tinha mais de 900 doentes e um seguimento a 8 anos mas abordando apenas a hipertensão da bata branca. Apenas Mancia et al tinham realizado um estudo de dimensão semelhante e com conclusões concordantes. As limitações do trabalho são aspetos difíceis de eliminar numa abordagem deste género. Este trabalho salienta-se pelo tempo de seguimento dos intervenientes, que dadas as questões ainda por esclarecer nestas áreas o torna sem dúvida mais uma ferramenta útil pelos resultados mais sólidos que nos traz. A conclusão de que a hipertensão da bata branca e a hipertensão mascarada não são benignos pode não ser uma novidade, mas a solidez deste trabalho permite que os clínicos façam um seguimento mais atento a este tipo de doentes, com avaliação do estilo de vida mais pormenorizado e provavelmente uma maior agressividade na abordagem terapêutica.

How to Screen for Non-Adherence to Antihypertensive Therapy

Gupta P, Patel P, Horne R et al

Curr. Hypertension Rep. 216; 18 (12): 89

The quality of assessment of non-adherence to treatment in hypertensive is poor. Within this review, we discuss the different methods used to assess adherence to blood pressure-lowering medications in hypertension patients. Subjective reports such as physicians' perceptions are inaccurate, and questionnaires completed by patients tend to over report adherence and show a low diagnostic specificity. Indirect objective methods such as pharmacy database records can be useful, but they are limited by the robustness of the recorded data. Electronic medication monitoring devices are accurate but usually track adherence to only a single medication and can be expensive. Overall, the fundamental issue with indirect objective measures is that they do not fully confirm ingestion of antihypertensive medications. Detection of antihypertensive medications in body fluids using liquid chromatography–tandem mass spectrometry is currently, in our view, the most robust and clinically useful method to assess nonadherence to blood-pressure-lowering treatment. It is particularly helpful in patients presenting with resistant, refractory or uncontrolled hypertension despite the optimal therapy. We recommend using this diagnostic strategy to detect nonadherence alongside a no-blame approach tailoring support to address the perceptions (e.g. beliefs about the illness and treatment) and practicalities (e.g. capability and resources) influencing motivation and ability to adhere.

Comentário: a prevalência da hipertensão resistente deixa este tema no topo das preocupações quando abordamos um doente, pois a escalada terapêutica acaba por ficar comprometida sem a correta avaliação da adesão ao tratamento. Apesar das dificuldades técnicas, esta revisão interessante remete-nos para o balanço entre testes dispendiosos e tempo até atingir o controlo tensional, quando este é adiado constantemente pelo não cumprimento da medicação prescrita. Será sem dúvida algo que deve ser ponderado nos custos hospitalares/ laboratoriais, mas se pensarmos que a não adesão terapêutica é causa do mau controlo numa elevadíssima percentagem de casos, e como tal, causa de AVCs e EAMs precoces e incapacitantes, talvez seja sensato ponderar o investimento em técnicas que nos permitam o diagnóstico destas situações mais precocemente. Evitar-se-iam assim mais consultas de seguimento a doentes não cumpridores, com medições constantes de valores de pressão arterial elevados, de discursos educadores para a saúde muitas vezes sem eco, e meses e anos a fio de mau controlo tensional com o errado rótulo de HTA resistente ou refratária, quando afinal bastaria talvez provar a não adesão e evitar internamentos para este efeito.

Poderá ser um documento relevante para mudar abordagens laboratoriais, e posteriormente sucessos terapêuticos. É uma revisão sólida e pormenorizada feita por uma equipa multidisciplinar credível, e sem dúvida um tema que deve ser explorado com alguma urgência. Artigos como este devem servir de apelo aos clínicos para não esquecer os falsos hipertensos mal controlados.

Recognition and Management of Resistant Hypertension

Braam B, Taler SJ, Rahman M et al

Clin J Am Soc Nephrol. 2016 Nov 28. doi: 10.2215/CJN.06180616

Despite improvements in hypertension awareness and treatment, 30%–60% of hypertensive patients do not achieve BP targets and subsequently remain at risk for target organ damage. This therapeutic gap is particularly important to nephrologists, who frequently encounter treatment-resistant hypertension in patients with CKD. Data are limited on how best to treat patients with CKD and resistant hypertension, because patients with CKD have historically been excluded from hypertension treatment trials. First, we propose a consistent definition of resistant hypertension as BP levels confirmed by both in-office and out-of-office measurements that exceed appropriate targets while the patient is receiving treatment with at least three antihypertensive medications, including a diuretic, at dosages optimized to provide maximum benefit in the absence of intolerable side effects. Second, we recommend that each patient undergo a standardized, stepwise evaluation to assess adherence to dietary and lifestyle modifications and antihypertensive medications to identify and reduce barriers and discontinue use of substances that may exacerbate hypertension. Patients in whom there is high clinical suspicion should be evaluated for potential secondary causes of hypertension. Evidence-based management of resistant hypertension is discussed with special considerations of the differences in approach to patients with and without CKD, including the specific roles of diuretics and mineralocorticoid receptor antagonists and the current place of emerging therapies, such as renal denervation and baroreceptor stimulation. We endorse use of such a systematic approach to improve recognition and care for this vulnerable patient group that is at high risk for future kidney and cardiovascular events

Comentário: apesar de haver várias revisões prévias acerca deste tema, é importante manter a atualização do conhecimento nesta área e os autores conseguiram consolidar informação importante com mais pormenores do que muitos trabalhos semelhantes anteriores. Exemplos são a abordagem feita às terapêuticas não farmacológicas, com especial ênfase dado à doença renal crónica que acaba por ser tão prevalente no hipertenso. O olhar de uma equipa predominantemente nefrologista tornam mais sólidos os conceitos da terapêutica na doença renal crónica, como o exemplo da própria avaliação da volémia para a escolha da classe farmacológica ou o ajuste fino da dosagem nesta base metabólica. São revisitadas as definições e a abordagem passo-a-passo do doente com hipertensão resistente. É interessante a sugestão que os autores fazem numa redefinição do conceito, introduzindo a individualização dos alvos-terapêuticos como a base do mesmo.

Role of Adding Spironolactone and Renal Denervation in True Resistant Hypertension: One-Year Outcomes of Randomized PRAGUE-15 Study.

Rosa J, Widimský P, et al

Hypertension. 2016 Feb;67(2):397-403.

This randomized multicenter study compared the relative efficacy of renal denervation (RDN) versus pharmacotherapy alone in patients with true resistant hypertension and assessed the effect of spironolactone addition. We present here the 12-month data. A total of 106 patients with true resistant hypertension were enrolled in this study: 52 patients were randomized to RDN and 54 patients to the spironolactone addition, with baseline systolic blood pressure of 159±17 and 155±17 mm Hg and average number of drugs 5.1 and 5.4, respectively. Twelve-month results are available in 101 patients. The intention-to-treat analysis found a comparable mean 24-hour systolic blood pressure decline of 6.4 mm Hg, P=0.001 in RDN versus 8.2 mm Hg, P=0.002 in the pharmacotherapy group. Per-protocol analysis revealed a significant difference of 24-hour systolic blood pressure decline between complete RDN (6.3 mm Hg, P=0.004) and the subgroup where spironolactone was added, and this continued within the 12 months (15 mm Hg, P= 0.003). Renal artery computed tomography angiograms before and after 1 year post-RDN did not reveal any relevant changes. This study shows that over a period of 12 months, RDN is safe, with no serious side effects and no major changes in the renal arteries. RDN in the settings of true resistant hypertension with confirmed compliance is not superior to intensified pharmacological treatment. Spironolactone addition (if tolerated) seems to be more effective in blood pressure reduction.

Comentário: a desnervação renal surgiu inicialmente como uma nova esperança no tratamento da HTA resistente, e durante algum tempo foi utilizada por muitos centros. Em 2014 acabou por abrandar o ritmo devido às limitadas evidências. Este trabalho veio reiterar as críticas que o próprio Symplicity HTN-3 fez ao antecessor Symplicity HTN-2. O PRAGUE-15 foi um estudo prospectivo, aberto, randomizado e realizado em 3 centros em Praga, e a terapêutica aplicada foi revista na medição da pressão arterial nas 24h, permitindo o crossover ao fim de 1 ano. Este seguimento a um ano só tinha ainda sido realizado com o Symplicity HTN-3. Foram incluídos 106 doentes hipertensos avaliados por MAPA, excluídos os doentes com não adesão terapêutica e com hipertensão secundária. Foram avaliados dois grupos: um submetido a desnervação renal e terapêutica farmacológica, e um grupo com terapêutica farmacológica intensiva incluindo espironolactona. Após a randomização os doentes submetidos a desnervação foram mantidos sob terapêutica médica durante um ano e os submetidos a terapêutica intensiva mantiveram a espironolactona. Foi interessante os investigadores terem continuado a comparação da abordagem farmacológica com a "tecnológica" desde o original PRAGUE-15, e apesar de tudo de terem esticado a junção de ambas ao fim de um ano e a sua sobreposição. O estudo vem no final reiterar a eficácia da espironolactona na hipertensão resistente e os mecanismos da mesma como fundamentais para a compreensão de uma grande percentagem destes casos. A redução da pressão arterial nas 24h foi significativa em ambos os grupos e a desnervação mostrou-se um procedimento seguro; no entanto, a espironolactona mostrou-se mais eficaz na redução da PA que a desnervação renal em doentes com exclusão de não adesão e com terapêutica médica optimizada.

Effects of blood pressure-lowering treatment. Prevention of heart failure and new-onset heart failure--meta-analyses of randomized trials.

Thomopoulos C, Parati G, Zanchetti A.

J. Hypertens. 2016 Mar;34(3):373-84; 384.

BACKGROUND AND OBJECTIVES: Relative effectiveness of blood pressure (BP)-lowering treatment on various outcomes was evaluated by meta-analyses restricted to randomized controlled trials (RCTs) measuring all major outcomes, and the question whether BP lowering and each class of antihypertensive agents prevent new-onset heart failure by meta-analyses limited to RCTs excluding baseline heart failure from randomization.

METHODS: Source of these meta-analyses are our databases of BP-lowering RCTs vs placebo or less-active treatment, and head-to-head comparisons of different antihypertensive classes. Risk ratios (RRs) and 95% confidence intervals of seven outcomes were calculated by a random-effects model. The relationships of outcome reductions to BP differences were investigated by meta-regressions.

RESULTS: First, 35 BP-lowering RCTs measured all outcomes, and heart failure [RR 0.63 (0.52-0.75)] and stroke [RR 0.58 (0.49-0.68)] were the outcomes most effectively prevented. Second, heart failure and stroke reductions were significantly related to SBP, DBP and pulse pressure reductions. Third, in 18 BP-lowering RCTs excluding baseline heart failure from recruitment, heart failure reduction ('new-onset' heart failure) [RR 0.58 (0.44-0.75)] was very similar to that in the entire set of RCTs. Fourth, in meta-analyses of head-to-head comparisons of different antihypertensive classes, calcium antagonists were inferior in preventing 'new-onset' heart failure [RR 1.16 (1.01-1.33)]. However, this inferiority disappeared when meta-analysis was limited to RCTs allowing concomitant use of diuretics, β-blockers or renin-angiotensin system blockers also in the calcium antagonist group [RR 0.96 (0.81-1.12)].

CONCLUSION: BP-lowering treatment effectively prevents 'new onset' heart failure. It is suggested that BP lowering by calcium antagonists is effective as BP lowering by other drugs in preventing 'new-onset' heart failure, unless the trial design creates an unbalance against calcium antagonists.

Comentário: neste trabalho, foram considerados estudos randomizados (de antihipertensores vs placebo ou outros fármacos menos eficazes) para avaliar o benefício da terapêutica antihipertensiva na prevenção de novos casos de Insuficiência cardíaca (IC). Analisando os dados, o tratamento antihipertensor evita novos casos de AVC e IC e esta prevenção está associada com a redução da PA (sistólica e diastólica) e da pressão de pulso. Nas meta-análises existentes que comparam os diferentes grupos de fármacos antihipertensores, os medicamentos menos eficazes são os antagonistas do cálcio. No entanto, ao associarem-se com outros fármacos, nomeadamente diuréticos, betabloqueantes ou modificadores do eixo renina-angiotensina-aldosterona, esta inferioridade desaparece.

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Lonn EM, Bosch J, et al for the HOPE-3 Investigators

N Engl J Med 2016; 374:2009-20.

BACKGROUND: Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.

METHODS: In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants at intermediate risk who did not have cardiovascular disease to receive either candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome additionally included resuscitated cardiac arrest, heart failure, and revascularization. The median follow-up was 5.6 years.

RESULTS: The mean blood pressure of the participants at baseline was 138.1/81.9 mm Hg; the decrease in blood pressure was 6.0/3.0 mm Hg greater in the active-treatment group than in the placebo group. The first coprimary outcome occurred in 260 participants (4.1%) in the active-treatment group and in 279 (4.4%) in the placebo group (hazard ratio, 0.93; 95% confidence interval [CI], 0.79 to 1.10; P=0.40); the second coprimary outcome occurred in 312 participants (4.9%) and 328 participants (5.2%), respectively (hazard ratio, 0.95; 95% CI, 0.81 to 1.11; P=0.51). In one of the three prespecified hypothesis-based subgroups, participants in the subgroup for the upper third of systolic blood pressure (>143.5 mm Hg) who were in the active-treatment group had significantly lower rates of the first and second coprimary outcomes than those in the placebo group; effects were neutral in the middle and lower thirds (P=0.02 and P=0.009, respectively, for trend in the two outcomes).

CONCLUSIONS: Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease.

Comentários: neste estudo multicêntrico, foram incluídos 12.705 doentes (ambos sexos, idade media 65 anos, PA media 138.1/81.9 mm Hg, 1/3 eram hipertensos) sem doença cardiovascular (DCV) e com risco cardiovascular (RCV) intermédio. Foram randomizados em 2 grupos: associação de Candesartan 16 mg + hidroclorotiazida 12.5 mg e um grupo placebo. Foram igualmente randomizados para Rosuvastatina 10 mg vs placebo. Após um follow-up de 5.6 anos, no grupo de tratamento a PA diminuiu 6.0/3.0 mm Hg.

Concluíram que para a globalidade dos doentes sem DCV e com RCV intermédio, o tratamento com um ARA II e uma tiazida em doses baixas não reduz a DCV. Apenas no subgrupo com PA sistólica mais elevada (PA média 154 mm Hg) os resultados foram positivos.

Estes resultados contrariam a impressão pós-SPRINT de que quanto mais baixa a PA melhor. De facto, poderá não ser assim em doentes com RCV baixo, idade media avançada e valores de PA sistólica menores de 145 mm Hg. Neste sentido, interessa recordar que os doentes do estudo SPRINT tinham maior RCV.

Por outro lado, nos doentes tratados com Rosuvastatina, houve uma redução dos eventos CV e não foi observada uma sinergia na associação com ARA II mais tiazida.

Este estudo tem algumas limitações: quase 50% dos doentes são asiáticos, o grande número de centros (228 centros de 21 países) pode retirar alguma homogeneidade e poucas medições de PA. Estes resultados poderão suportar/apoiar a polipílula (medicação com antihipertensores mais estatinas mais?) em prevenção primária. Neste contexto, interessa realçar o papel das medidas não farmacológicas no controlo da PA.

Effect of Intensive Blood-Pressure Treatment on Patient-Reported Outcomes

Berlowitz DR; Foy, CG, Kazis LE, for the SPRINT Research Group

N Engl J Med 2017; 377:733-44

BACKGROUND: The previously published results of the Systolic Blood Pressure Intervention Trial showed that among participants with hypertension and an increased cardiovascular risk, but without diabetes, the rates of cardiovascular events were lower among those who were assigned to a target systolic blood pressure of less than 120 mm Hg (intensive treatment) than among those who were assigned to a target of less than 140 mm Hg (standard treatment). Whether such intensive treatment affected patient-reported outcomes was uncertain; those results from the trial are reported here

METHODS: We randomly assigned 9361 participants with hypertension to a systolic blood-pressure target of less than 120 mm Hg or a target of less than 140 mm Hg. Patient-reported outcome measures included the scores on the Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Veterans RAND 12-Item Health Survey, the Patient Health Questionnaire 9-item depression scale (PHQ-9), patient-reported satisfaction with their blood-pressure care and blood-pressure medications, and adherence to blood-pressure medications. We compared the scores in the intensive-treatment group with those in the standard-treatment group among all participants and among participants stratified according to physical and cognitive function.

RESULTS: Participants who received intensive treatment received an average of one additional antihypertensive medication, and the systolic blood pressure was 14.8 mm Hg (95% confidence interval, 14.3 to 15.4) lower in the group that received intensive treatment than in the group that received standard treatment. Mean PCS, MCS, and PHQ-9 scores were relatively stable over a median of 3 years of follow-up, with no significant differences between the two treatment groups. No significant differences between the treatment groups were noted when participants were stratified according to baseline measures of physical or cognitive function. Satisfaction with blood-pressure care was high in both treatment groups, and we found no significant difference in adherence to blood-pressure medications.

CONCLUSIONS: Patient-reported outcomes among participants who received intensive treatment, which targeted a systolic blood pressure of less than 120 mm Hg, were similar to those among participants who received standard treatment, including among participants with decreased physical or cognitive function.

Comentário: é de salientar esta avaliação feita aos indivíduos estudados no SPRINT, no que respeita à auto-apreciação dos outcomes, da adesão terapêutica, da satisfação com o controlo da pressão arterial (PA), e mesmo relativamente ao estado físico e mental. Embora subjectiva e por auto-relato dos doentes, a apreciação positiva e significativamente melhor dos indivíduos sujeitos a redução mais intensiva da PA (<120mmHg) comparando com os indivíduos sujeitos a redução mais "modesta" da PA (<140mmHg), veio dar mais consistência à segurança da redução para valores de PA-alvo <120mmHg.

Sem dúvida salientou um importante aspecto que muitas vezes é base de crítica para o resultado do próprio SPRINT, dado que a inclusão de um indivíduo num ensaio clínico é muitas vezes considerado como factor para aumento da adesão terapêutica. Um doente que faz parte de um ensaio clínico tem "necessariamente" tem maior acompanhamento, e como tal geralmente mais motivação para a adesão terapêutica, arma comprovada no resultado final dos valores alvo de PA.

Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses

Brunström M, Carlberg B

BMJ 2016; 352: i717.

OBJECTIVE: To assess the effect of antihypertensive treatment on mortality and cardiovascular morbidity in people with diabetes mellitus, at different blood pressure levels.

DESIGN: Systematic review and meta-analyses of randomised controlled trials.

RESULTS: 49 trials, including 73 738 participants, were included in the meta-analyses. Most of the participants had type 2 diabetes. If baseline systolic blood pressure was greater than 150 mm Hg, antihypertensive treatment reduced the risk of all cause mortality (relative risk 0.89, 95% confidence interval 0.80 to 0.99), cardiovascular mortality (0.75, 0.57 to 0.99),myocardial infarction (0.74, 0.63 to 0.87), stroke (0.77, 0.65 to 0.91), and end stage renal disease (0.82, 0.71 to 0.94). If baseline systolic blood pressure was 140-150 mm Hg, additional treatment reduced the risk of all cause mortality (0.87, 0.78 to 0.98), myocardial infarction (0.84, 0.76 to 0.93), and heart failure (0.80, 0.66 to 0.97). If baseline systolic blood pressure was less than 140 mm Hg, however, further treatment increased the risk of cardiovascular mortality (1.15, 1.00 to 1.32), with a tendency towards an increased risk of all cause mortality (1.05, 0.95 to 1.16). Meta regression analyses showed a worse treatment effect with

lower baseline systolic blood pressures for cardiovascular mortality (1.15, 1.03 to 1.29 for each 10 mm Hg lower systolic blood pressure) and myocardial infarction (1.12, 1.03 to 1.22 for each 10 mm Hg lower systolic blood pressure). Patterns were similar for attained systolic blood pressure.

CONCLUSIONS: Antihypertensive treatment reduces the risk of mortality and cardiovascular morbidity in people with diabetes mellitus and a systolic blood pressure more than 140 mm Hg. If systolic blood pressure is less tha 140 mm Hg, however, further treatment is associated with na increased risk of cardiovascular death, with no observed benefit.

Comentário: as recomendações relativamente ao tratamento da HTA em diabéticos têm variado. Durante anos foram recomendados valores inferiores a 130/80 mmHg. Guidelines da ESH/ESC de 2013 estabeleceram o alvo de 140/85 mmHg, mas em 2016 a American Diabetes Association estabeleceu objetivos de 140/90 mmHg, referindo que em diabéticos jovens, com albuminúria ou outros fatores de risco cardiovascular o objetivo seria a sistólica inferior a 130 mmHg.

Neste estudo, uma meta análise de ensaios clínicos randomizados (48 estudos, 73.738 doentes), é analisado o efeito da terapêutica antihipertensora sobre a morbimortalidade cardiovascular de doentes com diabetes, considerando os valores no início do tratamento e os conseguidos com o tratamento.

As principais conclusões foram que tratamento é benéfico quando a sistólica é superior a 140 mmHg. Quando a PA sistólica inicial é inferior a 140 mmHg ou a PA sistólica pós-tratamento é inferior a 130 mmHg, o tratamento associa-se a aumento da mortalidade cardiovascular. A explicação poderá estar na maior rigidez arterial dos doentes com diabetes, e um compromisso da perfusão miocárdica, que será também dependente da PA sistólica. Independentemente das limitações deste estudo, os autores confirmam uma atitude prudente relativamente ao objetivo de controlo da PA em diabéticos.

Intensive versus Standard Blood Pressure Control in SPRINT Eligible Participants of the ACCORD-BP Trial

Buckley LF, Dixon DL, Wohlford GF et al

Diabetes Care 2017; 40 (2): 1733-38

OBJECTIVE: We sought to determine the effect of intensive blood pressure (BP) control on cardiovascular outcomes in participants with type 2 diabetes mellitus (T2DM) and additional risk factors for cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS: This study was a post hoc, multivariate, subgroup analysis of ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) participants. Participants were eligible for the analysis if they were in the standard glucose control arm of ACCORD-BP and also had the additional CVD risk factors required for SPRINT (Systolic Blood Pressure Intervention Trial) eligibility. We used a Cox proportional hazards regression model to compare the effect of intensive versus standard BP control on CVD outcomes. The "SPRINT-eligible" ACCORD-BP participants were pooled with SPRINT participants to determine whether the effects of intensive BP control interacted with T2DM.

RESULTS: The mean baseline Framingham 10-year CVD risk scores were 14.5% and 14.8%, respectively, in the intensive and standard BP control groups. The mean achieved systolic BP values were 120 and 134 mmHg in the intensive and standard BP control groups ($P < 0.001$). Intensive BP control reduced the composite of CVD death, nonfatal myocardial infarction (MI), nonfatal stroke, any revascularization, and heart failure (hazard ratio 0.79; 95% CI 0.65–0.96; $P = 0.02$). Intensive BP control also reduced CVD death, nonfatal MI, and nonfatal stroke (hazard ratio 0.69; 95% CI 0.51–0.93; $P = 0.01$). Treatment-related adverse events occurred more frequently in participants receiving intensive BP control (4.1% vs. 2.1%; $P=0.003$). The effect of intensive BP control on CVD outcomes did not differ between patients with and without T2DM ($P > 0.62$).

CONCLUSIONS: Intensive BP control reduced CVD outcomes in a cohort of participants with T2DM and additional CVD risk factors.

Comentário: um trabalho curioso, publicado por um grupo na Diabetes Care, em que aplicou os critérios de inclusão do SPRINT numa coorte do ACCORD-BP (grupo de tratamento menos intensivo para controlo da HbA1c) de forma a perceber até que ponto a população diabética, (excluída do estudo SPRINT), beneficiaria do mesmo tipo de redução agressiva de PA.

O estudo concluiu que o tratamento mais intensivo da PA reduziu os eventos cardiovasculares (CV), nomeadamente a morte por doença CV, o enfarte agudo do miocárdio não fatal, acidente vascular cerebral não fatal e insuficiência cardíaca nestes participantes do ACCORD-BP elegíveis para o SPRINT.

Parece interessante a forma como os autores encontraram de incluir uma das populações excluídas do SPRINT, e curioso terem pegado numa coorte de doentes de um estudo que mostrou resultados opostos ao SPRINT.

Demonstra um espírito crítico importante, mas acima de tudo uma procura de respostas às questões que tantos colocam, mesmo depois das evidências publicadas.

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial

Williamson JD, Supiano MA, Applegate WB et al

JAMA 2016 June 28, 315 (24): 2673-82

IMPORTANCE: The appropriate treatment target for systolic blood pressure (SBP) in older patients with hypertension remains uncertain.

OBJECTIVE: To evaluate the effects of intensive (<120 mm Hg) compared with standard (<140 mm Hg) SBP targets in persons aged 75 years or older with hypertension but without diabetes.

DESIGN, SETTING, AND PARTICIPANTS: A multicenter, randomized clinical trial of patients aged 75 years or older who participated in the Systolic Blood Pressure Intervention Trial (SPRINT). Recruitment began on October 20, 2010, and follow-up ended on August 20, 2015.

INTERVENTIONS: Participants were randomized to an SBP target of less than 120 mm Hg (intensive treatment group, n = 1317) or an SBP target of less than 140 mm Hg (standard treatment group, n = 1319).

MAIN OUTCOMES AND MEASURES: The primary cardiovascular disease outcome was a composite of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular causes. All-cause mortality was a secondary outcome.

RESULTS: Among 2636 participants (mean age, 79.9 years; 37.9% women), 2510 (95.2%) provided complete follow-up data. At a median follow-up of 3.14 years, there was a significantly lower rate of the primary composite outcome (102 events in the intensive treatment group vs 148 events in the standard treatment group; hazard ratio [HR], 0.66 [95% CI, 0.51-0.85]) and all-cause mortality (73 deaths vs 107 deaths, respectively; HR, 0.67 [95% CI, 0.49-0.91]). The o1verall rate of serious adverse events was not different between treatment groups (48.4% in the intensive treatment group vs 48.3% in the standard treatment group; HR, 0.99 [95% CI, 0.89-1.11]). Absolute rates of hypotension were 2.4% in the intensive treatment group vs 1.4% in the standard treatment group (HR, 1.71 [95% CI, 0.97-3.09]), 3.0% vs 2.4%, respectively, for syncope (HR, 1.23 [95% CI, 0.76-2.00]), 4.0% vs 2.7% for electrolyte abnormalities (HR, 1.51 [95% CI, 0.99-2.33]), 5.5% vs 4.0% for acute kidney injury (HR, 1.41 [95% CI, 0.98-2.04]), and 4.9% vs 5.5% for injurious falls (HR, 0.91 [95% CI, 0.65-1.29]).

CONCLUSIONS AND RELEVANCE: Among ambulatory adults aged 75 years or older, treating to an SBP target of less than 120 mm Hg compared with an SBP target of less than 140 mm Hg resulted in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause.

Comentários: estamos perante mais um estudo sobre a hipertensão arterial no idoso, feito com doentes do estudo SPRINT, analisando o subgrupo de doentes com idade superior a 75 anos. Foram randomizados 2636 doentes, com risco cardiovascular acrescido em 2 grupos: grupo de tratamento intensivo (conseguir PA sistólica inferior a 120 mm Hg) vs. grupo "standard" em que se pretendia uma PA sistólica inferior a 140 mm Hg.

Foi interrompido ao fim de 3,1 anos pelas diferenças encontradas, a favor do grupo de tratamento intensivo. Destacaríamos a menor mortalidade global e menos insuficiência cardíaca (IC); no entanto sem redução do

síndroma coronária aguda, incluindo EAM, nem de AVC nem da mortalidade cardiovascular. E sem aumento significativo dos efeitos adversos.

Estes resultados diferem de anteriores (ex. HYVET) e das guidelines existentes, algumas recentes, que estabelecem metas mais "prudentes". Desconhecendo qual o significado futuro destes resultados, queríamos apenas destacar algumas questões referentes ao estudo. Começaríamos pela metodologia da medição da PA não comparável com estudos prévios, com uso de dispositivos automáticos e sem a presença de observadores; doentes com menos comorbilidades que os da vida real (foram excluídos doentes diabéticos, com AVC prévio, IC, demência); também seria interessante a estratificação por grupos etários.

Finalmente, o evento CV que mais diminuiu foi a IC e não o AVC ou a doença coronária, como seria de esperar pela maior relação com o valor de PA sistólica. É bem possível que a medicação antihipertensiva usada tenha significado, pois no grupo intensivo utilizaram-se mais 50% de IECAs, ARAs e diuréticos e sabemos o seu papel no IC.

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.

Whelton PK, Carey RM, Aronow WS et al

J Am Coll Cardiol. Sep 2017, 23976; DOI: 10.1016/j.jacc.2017.07.745

Comentário: a maior novidade do ano parece ser sem dúvida a publicada pela Task Force do American College of Cardiology e American Heart Association: as Guidelines Americanas para a prevenção, detecção, avaliação e abordagem da Hipertensão arterial. O extenso documento que uniu 11 associações, trouxe como principal novidade o que parece ser o balanço entre os resultados do SPRINT e as palavras do JNC-8: a redefinição de HTA, com o diagnóstico estabelecido a partir de valores de PA 130/80mmHg. Desaparece assim a pré-hipertensão, com o argumento de que indivíduos com este valor já seriam de risco CV significativo, e como tal redefine-se o diagnóstico. Aumenta assim a prevalência de americanos e indivíduos em todo o mundo com HTA, embora não aumente propriamente o número de indivíduos a necessitar de tratamento, visto as guidelines considerarem que os indivíduos com HTA grau 1 sem doença CV estabelecida e com risco CV < 10% devem iniciar medidas gerais de mudança de estilo de vida e não terapêutica antihipertensora logo em primeira linha.

As guidelines trazem também como novidade a PA alvo, que passa a ser <130/80mmHg para todas as populações, excepto o facto de apenas definirem a PA sistólica nos "idosos" (>65 anos) como alvo de < 130mmHg, sem comentário acerca da diastólica e ressalvando a óbvia avaliação do estado geral e tolerabilidade farmacológica.

Este documento dá particular destaque à Automedição da PA (AMPA) e a Medição Ambulatória da PA (MAPA) como ferramentas essenciais não só no diagnóstico, mas também no seguimento regular dos doentes hipertensos. Descreve aliás muito pormenorizadamente os métodos, em especial da AMPA, focando o papel de educação do

doente neste sentido. Salienta também o papel da HTA mascarada, da HTA da bata branca e do efeito de bata branca, descrevendo as situações específicas em que estas devem ser investigadas/ excluídas.

As novas guidelines referem também uma ferramenta de cálculo de risco CV, uma estimativa de risco a 10 anos realizada online com recurso a dados demográficos, dados laboratoriais (colesterol) e valores de PA, e antecedentes, hábitos e terapêutica.

No que respeita à terapêutica, de destacar não só o facto de introduzirem à partida a terapêutica com dois fármacos de início na HTA grau 2 (embora sem grande ênfase nas associações fixas), mas em particular ao facto de retirarem categoricamente os betabloqueantes da terapêutica de primeira linha. São ainda referidos os ARA II como fármacos mais úteis na prevenção da recorrência da fibrilhação auricular. No que respeita às medidas de estilo de vida, são um capítulo muito salientado neste documento: a suplementação com potássio volta a ser recomendada (salvo excepções descritas), e para cada medida descrita foi incluído o impacto aproximado na redução dos valores da PA sistólica.

Para finalizar, as guidelines também introduzem alguma modernidade ao salientar o papel da telemedicina como estratégia útil na abordagem e seguimento do doente hipertenso, dos incentivos financeiros e estratégias de financiamento dos sistemas de saúde como ferramentas facilitadoras da adesão terapêutica e controlo da PA.

Qual será o caminho que as guidelines europeias irão seguir? Serão as definições também alteradas? Os alvos também redefinidos?

Diretrizes de 2017 para manejo da hipertensão arterial em cuidados primários nos países de língua portuguesa

Oliveira GM, Mendes M, Malachias MB, Morais J et al

Rev Port Cardiol 2017; 36:789-98

Resumo A meta da Organização Mundial da Saúde de reduzir a mortalidade por doenças crónicas não transmissíveis em 2% ao ano exige um enorme esforço por parte dos países. Esse grande desafio lançado pela Organização Mundial de Saúde requer uma ação política global e concertada através de medidas nas comunidades, com intervenções populacionais de cunho custo-efetivo para reduzir prevalência das doenças crónicas não transmissíveis e dos seus fatores de risco. A hipertensão arterial tem grande prevalência nas populações dos países de língua portuguesa e representa o principal fator de risco para complicações como acidente vascular cerebral, enfarte agudo do miocárdio e doença renal crónica, correspondendo em importância à dislipidemia e obesidade para as doenças ateroscleróticas. Ações conjuntas que visem à implementação de medidas de prevenção primária poderão reduzir os desfechos relacionados com a doença hipertensiva, especialmente acidente vascular cerebral e enfarte agudo do miocárdio. Torna-se necessário garantir a implementa¸cão dessas diretrizes para o tratamento da HTA no terreno, através de um processo continuado, que envolva fundamentalmente ações de educação, de mudança do estilo de vida e garantia de acesso aos medicamentos.

Comentário: considerando a grande prevalência da hipertensão arterial nos países de língua portuguesa e norteados pelos objectivos da Organização Mundial da Saúde de redução da mortalidade das doenças crónicas não transmissíveis, reuniram-se peritos de Portugal, Brasil, Angola, Moçambique, Cabo Verde, S. Tomé e Príncipe.

Publicaram um conjunto de recomendações para prevenção primaria, completas, considerando o diagnóstico, técnica de medição, a lesão de órgãos-alvo, estratificação de risco, medidas não farmacológicos/estilo de vida e tratamento, incluindo situações particulares como hipertensão secundária e gravidez.

Na classificação, são considerados os valores prévios à era "pós-SPRINT".

Evaluation Of Sodium And Potassium Intake In Subpopulations In A Representative Sampling Of The Adult Population Of Portugal

Polonia J, Martins L, Pinto F, Nazaré J

Journal of Hypertension 2016; 34:e421-e422

Objective: To evaluate the salt and potassium intake in subpopulations of a representative sample of the adult population of Portugal.

Design and method: A national hypertension survey (PHYSA) was done in 2012. Population studied was n = 3720 ageing 49+15yrs. Caucasians were 97.1%, 52.6% were female. From all, 2568 completed valid (by creatinuria) 24h urinary sampling for measuring sodium (UNa) and potassium (UK) daily excretion. Results: Hypertension prevalence was 42.2%. Average UNa was 183+65 mmol/d (10.7 g salt/d) and UK+ 77+27 mmol/d. In the population only in 4.4% the UNa was within the recommended < 100 mmol/d (i.e. 5.8 g salt/d) levels and only in 3.8% UK was > the recommended 100mmol/d. Also in 36.2% of the population UNa was > 200 mmol/d (> than double the recommended). UNa (mmol/d) was higher: in hypertensives, HTs (186 ± 65) vs normotensives (177 ± 65), p < .001, in male (184+66) vs female (176 ± 63) p < .001, in obese, (BMI > 30 Kg/m2 prevalence = 20.4%) (201 ± 48) vs non-obese same age (166 ± 61), p < .001, in diabetics - prevalence 10.4% (191 ± 45) vs nondiabetics with same age (174 ± 56) p < 0.001, in those with albuminuria (>30 mg/24h) (186 ± 51) vs normoalbuminuric (142 ± 44) p < .001, in those with ventricular hypertrophy (LVH) (198 ± 60) vs no LVH (142 ± 43), p < .001, and in hypertensives with previous cardiovascular events (188+39) vs no events same age (171+51 mmol/d), p < .001. Conclusions: Portuguese population shows high levels of salt and low levels of potassium intake. Higher salt intake associated with hypertension, obesity, diabetes, target organ damage and cardiovascular events.

Comentário: o estudo PHYSA publicado em 2014 é indiscutivelmente um marco para o conhecimento da hipertensão arterial em Portugal. A partir duma amostra representativa da população portuguesa, permitiu-nos

apurar a prevalência, o conhecimento, o tratamento e o controlo da hipertensão arterial. Foram ainda feitas colheitas de urina de 24 h para determinação de sódio e de potássio. Destas, foram validadas (pela creatinuria) 2568 amostras, concluindo-se que a população portuguesa tem uma ingesta excessiva da sódio e diminuída de potássio. Apenas 4.4% tinha um valor de sódio urinário dentro dos valores normais e de potássio eram 3.8%

A excreção de sódio urinário estava significativamente aumentada em hipertensos, obesos, diabéticos, homens, na presença de macroalbuminuria, de hipertrofia ventricular esquerda e em doentes com eventos cardiovasculares prévios. Impõe-se, pois, intervir na sociedade no sentido de reduzir a ingesta de sódio.

A salt-sensing kinase in T lymphocytes, SGK1, drives hypertension and hypertensive end-organ damage

Norlander AE, Saleh MA, Pandey AK et al

JCI Insight. 2017;2(13): e92801.

We previously showed that angiotensin II (Ang II) increases T cell production of IL-17A, and that mice deficient in IL-17A have blunted hypertension and attenuated renal and vascular dysfunction. It was recently shown that salt enhances IL-17A production from CD4+ T cells via a serum- and glucocorticoid-regulated kinase 1–dependent (SGK1-dependent) pathway. Thus, we tested the hypothesis that SGK1 signalling in T cells promotes hypertension and contributes to end-organ damage. We show that loss of T cell SGK1 results in a blunted hypertensive response to Ang II infusion by 25 mmHg. Importantly, renal and vascular inflammation is abrogated in these mice compared with control mice. Furthermore, mice lacking T cell SGK1 are protected from Ang II– induced endothelial dysfunction and renal injury. Loss of T cell SGK1 also blunts blood pressure and vascular inflammation in response to deoxycorticosterone acetate–salt (DOCA-salt) hypertension. Finally, we demonstrate that the Na+-K+-2Cl– cotransporter 1 (NKCC1) is upregulated in Th17 cells and is necessary for the salt-induced increase in SGK1 and the IL-23 receptor. These studies demonstrate that T cell SGK1 and NKCC1 may be novel therapeutic targets for the treatment of hypertension and identify a potentially new mechanism by which salt contributes to hypertension.

Salt-responsive gut commensal modulates TH17 axis and disease

Wilck N, Matus MG, Kearney SM, et al

Nature 2017 Nov 30;551(7682):585-589

A Western lifestyle with high salt consumption can lead to hypertension and cardiovascular disease. High salt may additionally drive autoimmunity by inducing T helper 17 (TH17) cells, which can also contribute to hypertension. Induction of TH17 cells depends on gut microbiota; however, the effect of salt on the gut microbiome is unknown. Here we show that high salt intake affects the gut microbiome in mice, particularly by depleting Lactobacillus murinus. Consequently, treatment of mice with L. murinus prevented salt-induced aggravation of actively induced experimental autoimmune encephalomyelitis and salt-sensitive hypertension by modulating TH17 cells. In line with these findings, a moderate high-salt challenge in a pilot study in humans reduced intestinal survival of Lactobacillus spp., increased TH17 cells and increased blood pressure. Our results connect high salt intake to the gut–immune axis and highlight the gut microbiome as a potential therapeutic target to counteract salt-sensitive conditions.

Comentário: houve ainda alguns estudos na área dos mecanismos fisiopatológicos que também são de salientar, pois para além de se basearem em temas que estão muito na moda – o primeiro pega na HTA como doença inflamatória e o segundo no tema do microbioma e microbiota –, podem ter impacto em novidades terapêuticas futuras. Vêm no seguimento de trabalhos prévios (em especial o da interleucina) e relembram a importância do estudo molecular ou fisiopatológico, e do que pode significar mesmo que a longo prazo.

De referir o estudo de Norlander publicado em Julho no Journal of Clinical Investigation, que demonstrou que uma kinase salt-sensing dos linfócitos T (SGK1) contribui para a HTA e para a lesão de órgão-alvo renal e vascular. Não só coloca a HTA no grupo de patologias com contributo fisiopatológico da inflamação, como identifica um potencial alvo terapêutico.

O segundo trabalho a referir é o de Wilck e colegas publicado na Nature, que se baseia no microbioma intestinal e no princípio do consumo de sal e seu impacto na HTA. Wilck demonstrou que o Lactobacillus spp está suprimido no microbioma intestinal dos indivíduos com elevado consumo de sal e pode ter impacto na fisiopatologia da HTA, e consequentemente também como alvo terapêutico.

Report of the National Heart, Lung, and Blood Institute Working Group on the Role of Microbiota in Blood Pressure Regulation. Current Status and Future Directions

Raizada MK, Joe B, Bryan NS et al

Hypertension. 2017; 70:479-485

...The Working Group (WG) reviewed existing and emerging scientific evidence connecting gut and oral microbiota to BP regulation. The WG was organized into 4 thematic sessions: (1) the link between microbiota and hypertension session included presentations on gut–brain axis and microbiota in animal models of hypertension and vascular dysfunction; (2) a session on the role of microbiota in human disease included CVD, kidney disease, and metabolic syndrome; (3) the oral microbiota session discussed the Human Oral Microbiome Database advances in metagenomic and metabolomic technologies and the role of nitrate in BP regulation; and (4) discussion on microbiota as a potential therapeutic target included dietary modifications, circadian regulation, and impact of chronic stress on the gut–brain axis...

Comentário: estão a surgir muitos trabalhos relacionando o microbiota com patologias crónicas (Diabetes mellitus, Obesidade, Doença renal crónica, Insuficiência cardíaca…) assim como com a hipertensão arterial. Parece, pois, interessante que o National Heart, Lung, and Blood Institute tenha reunido 16 peritos em diversa áreas para discutir este tópico.

Fica claro que, havendo evidência significativa que relaciona o microbiota com a regulação da pressão arterial, muito há por conhecer nesta área. No entanto, fica em aberto que a manipulação da microbiota intestinal poderá ser uma nova estratégia terapêutica para a hipertensão arterial

RV Diabetes 2016/17

Francisco Araújo

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Poucas áreas da saúde têm tido tanta repercussão nos media em Portugal nos últimos anos. Muito deste interesse tem a ver com a epidemia que a diabetes representa entre nós, com números que colocam Portugal na cauda da Europa. A prevalência em Portugal continua em crescendo, estimando-se que 13,3% da população (mais de um milhão de portugueses) tenha diabetes.

Por outro lado, existe muita informação disponível, com dados que são recolhidos de uma forma pouco usual entre nós, com rigor e constância ao longo de anos, permitindo-nos ter uma tremenda ferramenta de conhecimento. A sétima edição do Relatório Anual do Observatório Nacional da Diabetes em 2016 e o Plano Nacional da Diabetes em 2017, apesar de alguns dados positivos, registam um aumento dos internamentos associados à diabetes e da despesa com medicamentos.

Também a nível mundial a diabetes ganha uma relevância crescente. O interesse na investigação é enorme… Em 2016/17 o termo diabetes representou cerca de 40000 artigos/ano na PubMed. Compare-se com 10000 entradas no ano 2000 ou 24000 correspondências em 2010. Muitos dos avanços na terapêutica devem-se às imposições da agência reguladora americana - a FDA - que desde as dúvidas levantadas pela rosiglitazona, impôs estudos de segurança vascular para a aprovação de novos fármacos para a diabetes.

Sabemos que, quanto mais elevada a HbA1c maior o risco cardiovascular, mas a dificuldade tem estado em provar o contrário. Até há pouco tempo, não tinha sido demonstrado que o melhor controlo glicémico reduzisse eventos cardiovasculares, aquilo a que se chamou "paradoxo macrovascular". É verdade que uma terapêutica intensiva tinha mostrado redução das complicações microvasculares e que uma série de estudos recentes (TECOS, EXAMINE, ELIXA, ADVANCE, ORIGIN), tinha demonstrado a segurança cardiovascular com diferentes abordagens, mas faltava esse passo…

A procura de medicamentos que pudessem não só mostrar segurança, mas também a redução de eventos cardiovasculares, tornou-se o Santo Graal para a indústria farmacêutica. E se em 2015 o estudo EMPA-REG tinha sido uma pedrada no charco, 2016 foi um ano com resultados positivos nesta área, com a apresentação dos estudos LEADER e SUSTAIN6 com análogos da GLP1. Já em 2017 os estudos EXSCEL e CANVAS demonstraram contudo que devemos ter precaução no assumir que existem efeitos de classe com estas novas terapêuticas, no que confere à redução de risco CV (EXSCEL) e segurança (CANVAS).

Há várias teorias para explicar a diferença nos resultados dos estudos, e diversas e aliciantes hipóteses têm sido exploradas e serão abordadas nesta revisão do que melhor houve em 2016 e 2017.

The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell–Centric Classification Schema

Schwartz SS, Epstein S, Corkey BE, Grant S, Gavin III JR and Aguilar RB

Diabetes Care 2016; 39(2): 179-186

The current classification system presents challenges to the diagnosis and treatment of patients with diabetes mellitus (DM), in part due to its conflicting and confounding definitions of type 1 DM, type 2 DM, and latent autoimmune diabetes of adults (LADA). The current schema also lacks a foundation that readily incorporates advances in our understanding of the disease and its treatment. For appropriate and coherent therapy, we propose an alternate classification system. The β-cell–centric classification of DM is a new approach that obviates the inherent and unintended confusions of the current system. The β-cell–centric model presupposes that all DM originates from a final common denominator—the abnormal pancreatic β-cell. It recognizes that interactions between genetically predisposed β-cells with a number of factors, including insulin resistance, susceptibility to environmental influences, and immune dysregulation/inflammation, lead to the range of hyperglycemic phenotypes within the spectrum of DM. Individually or in concert, and often self-perpetuating, these factors contribute to β-cell stress, dysfunction, or loss through at least 11 distinct pathways. Available, yet underutilized, treatments provide rational choices for personalized therapies that target the individual mediating pathways of hyperglycemia at work in any given patient, without the risk of drug-related hypoglycemia or weight gain or imposing further burden on the β-cells. This article issues an urgent call for the review of the current DM classification system toward the consensus on a new, more useful system.

Comentários: no artigo é defendido que a classificação atual da diabetes, não reflete os doentes com fenótipo intermédio entre DM1 e DM2. Muitos doentes classificáveis como LADA são assumidos como tipo 2, gerando opções terapêuticas que poderão não ser as mais correctas. É proposto um modelo β- cêntrico, em que os mecanismos que medeiam a hiperglicemia têm a célula β como pano de fundo e em que esses mecanismos podem ser alvo de intervenção terapêutica individualizada.

A disfunção da célula β decorre da susceptibilidade genética individual, da insulinorresistência, de factores ambienciais e de mecanismos autoimunes / inflamatórios. Os autores propõem mais três mecanismos fisiopatológicos ao octeto sinistro (" the ominous octet") descrito por De Fronzo em 2009. A microbiota intestinal, a inflamação latente de baixo grau, e níveis de amilina reduzidos, integrariam o "onze atroz" ("the egregious eleven") e poderiam ser alvo de terapêuticas dirigidas. As incretinas por exemplo, têm demonstrado efeito anti-inflamatório, e reduzem a absorção aumentada de glucose no intestino delgado que ocorre pela diminuição dos níveis de amilina.

Association Between Socioeconomic Status and Mortality, Cardiovascular Disease, and Cancer in Patients With Type 2 Diabetes.

Rawshani A, Svensson AM, Zethelius B, Eliasson B, Rosengren A, Gudbjörnsdottir S.

JAMA Intern Med. 2016; 176(8):1146-54

Importance: The association between socioeconomic status and survival based on all-cause, cardiovascular (CV), diabetes-related, and cancer mortality in type 2 diabetes has not been examined in a setting of persons with equitable access to health care with adjustment for important confounders.

Objective: To determine whether income, educational level, marital status, and country of birth are independently associated with all-cause, CV, diabetes-related, and cancer mortality in persons with type 2 diabetes.

Design, Setting, and Participants: A study including all 217 364 individuals younger than 70 years with type 2 diabetes in the Sweden National Diabetes Register (January 1, 2003, to December 31, 2010) who were monitored through December 31, 2012, was conducted. A Cox proportional hazards regression model with up to 17 covariates was used for analysis. Main Outcomes and Measures: All-cause, CV, diabetes-related, and cancer mortality.

Results: Of the 217 364 persons included in the study, mean (SD) age was 58.3 (9.3) years and 130 839 of the population (60.2%) was male. There were a total of 19 105 all-cause deaths with 11 423 (59.8%), 6984 (36.6%), and 6438 (33.7%) CV, diabetes-related, or cancer deaths, respectively. Compared with being single, hazard ratios (HRs) for married individuals, determined using fully adjusted models, for all-cause, CV, and diabetes-related mortality were 0.73 (95% CI, 0.70-0.77), 0.67 (95% CI, 0.63-0.71), and 0.62 (95% CI, 0.57-0.67), respectively. Marital status was not associated with overall cancer mortality, but married men had a 33% lower risk of prostate cancer mortality compared with single men, with an HR of 0.67 (95% CI, 0.50-0.90). Comparison of HRs for the lowest vs highest income quintiles for all-cause, CV, diabetes-related, and cancer mortality were 1.71 (95% CI, 1.60-1.83), 1.87 (95% CI, 1.72-2.05), 1.80 (95% CI, 1.61-2.01), and 1.28 (95% CI, 1.14-1.44), respectively. Compared with native Swedes, HRs for all-cause, CV, diabetes-related, and cancer mortality for non-Western immigrants were 0.55 (95% CI, 0.48-0.63), 0.46 (95% CI, 0.38-0.56), 0.38 (95% CI, 0.29-0.49), and 0.72 (95% CI, 0.58-0.88), respectively, and these HRs were virtually unaffected by covariate adjustment. Hazard ratios for those with a college/university degree compared with 9 years or less of education were 0.85 (95% CI, 0.80-0.90), 0.84 (95% CI, 0.78-0.91), and 0.84 (95% CI, 0.76-0.93) for all-cause, CV, and cancer mortality, respectively.

Conclusions and Relevance: Independent of risk factors, access to health care, and use of health care, socioeconomic status is a powerful predictor of all-cause and CV mortality but was not as strong as a predictor of death from cancer.

Comentários: mesmo na população da Suécia em que o acesso aos cuidados de saúde é simples, universal e de qualidade acima da média, existem diferenças na causa de morte das pessoas com diabetes. Na morte de origem cardiovascular ou relacionada com a diabetes, há benefício para quem tem rendimentos mais altos (quase metade do risco), para quem tem mais educação e para quem tem companheiro(a). Esta redução de risco para os mais ricos, não se verificou na mortalidade por cancro, o que poderá implicar uma diferente etiopatogenia na doença

oncológica. O destino final (a morte), até na Suécia é igual para todos , apenas o "when" e o "how" poderão ser distintos.

É paradoxal que os imigrantes, sobretudo os provenientes de países mais pobres, tenham uma mortalidade mais baixa. Isto poderá traduzir o chamado "wealthy migrant effect", em que apenas os mais preparados, os mais fortes e saudáveis dos imigrantes conseguem emprego ou integrar-se nas sociedades para onde emigram.

Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomized controlled trial

Bolinder J, Antuna R., Geelhoed-Duijvestijn P, Kröger J, Weitgasser R

Lancet 2016; 388 (10057): 2254-2263

Background: Tight control of blood glucose in type 1 diabetes delays onset of macrovascular and microvascular diabetic complications; however, glucose levels need to be closely monitored to prevent hypoglycaemia. We aimed to assess whether a factory-calibrated, sensor-based, flash glucose-monitoring system compared with self-monitored glucose testing reduced exposure to hypoglycaemia in patients with type 1 diabetes.

Method: In this multicentre, prospective, non-masked, randomized controlled trial, we enrolled adult patients with well controlled type 1 diabetes (HbA1c ≤58 mmol/mol [7·5%]) from 23 European diabetes centres. After 2 weeks of all participants wearing the blinded sensor, those with readings for at least 50% of the period were randomly assigned (1:1) to flash sensor-based glucose monitoring (intervention group) or to self-monitoring of blood glucose with capillary strips (control group). Randomization was done centrally using the biased-coin minimization method dependent on study centre and type of insulin administration. Participants, investigators, and study staff were not masked to group allocation. The primary outcome was change in time in hypoglycaemia (<3·9 mmol/L [70 mg/dL]) between baseline and 6 months in the full analysis set (all participants randomized; excluding those who had a positive pregnancy test during the study).

Findings: Between Sept 4, 2014, and Feb 12, 2015, we enrolled 328 participants. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycaemia changed from 3·38 h/day at baseline to 2·03 h/day at 6 months (baseline adjusted mean change −1·39) in the intervention group, and from 3·44 h/day to 3·27 h/day in the control group (−0·14); with the between-group difference of −1·24 (SE 0·239; p<0·0001), equating to a 38% reduction in time in hypoglycaemia in the intervention group. No device-related hypoglycaemia or safety issues were reported. 13 adverse events were reported by ten participants related to the sensor—four of allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-

site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate). There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device.

Interpretation: Novel flash glucose testing reduced the time adults with well controlled type 1 diabetes spent in hypoglycaemia. Future studies are needed to assess the effectiveness of this technology in patients with less well controlled diabetes and in younger age groups.

Comentários: não é habitual serem publicados artigos em revistas de prestígio sobre sistemas de monitorização, nem os estudos costumam ter este desenho controlado e aleatorizado, comparando uma estratégia de auto-monitorização da glucose com uma nova tecnologia flash de determinação da glicemia intersticial. Este estudo poderá mudar a forma como seguimos e controlamos a diabetes tipo 1 (e também a tipo 2 que utilize regimes mais complexos ou intensos de insulina). Para já comparticipada para a diabetes tipo 1, o futuro dirá se não será aprovada a outros subgrupos de populações em que a hipoglicemia poderá ter repercussões mais graves, como em algumas profissões (pilotos, etc.), ou em doentes com elevado risco cardiovascular.

Neste estudo, a utilização deste novo dispositivo em doentes com DM1 resultou numa redução de 38% do tempo total em hipoglicemia e do número de episódios de hipoglicemia sobretudo no período noturno. Não houve diferença no controlo da diabetes (valores semelhantes de HBA1c no final do estudo). É necessário avaliar se a prática corrobora os resultados na vida real, longe de ambientes mais controlados, como aqueles que decorrem nestes estudos clínicos.

Genetic Predictors of Cardiovascular Mortality During Intensive Glycemic Control in Type 2 Diabetes: Findings from the ACCORD Clinical Trial

Shah HS, Gao H, Morieri ML, Skupien J, et al

Diabetes Care 2016 Nov; 39(11): 1915-1924.

OBJECTIVE To identify genetic determinants of increased cardiovascular mortality among subjects with type 2 diabetes who underwent intensive glycemic therapy in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.

RESEARCH DESIGN AND METHODS A total of 6.8 million common variants were analyzed for genome-wide association with cardiovascular mortality among 2,667 self-reported white subjects in the ACCORD intensive treatment arm. Significant loci were examined in the entire ACCORD white genetic dataset (n = 5,360) for their modulation of cardiovascular responses to glycemic treatment assignment and in a Joslin Clinic cohort (n = 422) for their interaction with long-term glycemic control on cardiovascular mortality.

RESULTS Two loci, at 10q26 and 5q13, attained genome-wide significance as determinants of cardiovascular mortality in the ACCORD intensive arm (P = 9.8 × 10–9 and P = 2 × 10–8, respectively). A genetic risk score (GRS) defined by the two variants was a significant modulator of cardiovascular mortality response to treatment assignment in the entire ACCORD white genetic dataset. Participants with GRS = 0 experienced a fourfold reduction in cardiovascular mortality in response to intensive treatment (hazard ratio [HR] 0.24 [95% CI 0.07–0.86]), those with GRS = 1 experienced no difference (HR 0.92 [95% CI 0.54–1.56]), and those with GRS ≥2 experienced a threefold increase (HR 3.08 [95% CI 1.82–5.21]). The modulatory effect of the GRS on the association between glycemic control and cardiovascular mortality was confirmed in the Joslin cohort (P = 0.029).

CONCLUSIONS Two genetic variants predict the cardiovascular effects of intensive glycemic control in ACCORD. Further studies are warranted to determine whether these findings can be translated into new strategies to prevent cardiovascular complications of diabetes.

Comentários: a variabilidade inter-individual ao efeito de um medicamento, pode à partida parecer imprevisível. Antes de iniciarmos um medicamento temos uma ideia genérica de qual o grau de resposta previsto e dos seus efeitos secundários, mas sabemos que existem características individuais que podem alterar essa previsão. Comorbilidades como a doença renal, o tipo de alimentação, as interações medicamentosas, enfim, há um sem número de fatores que podem alterar o expectável. E a genética? E se tivermos um método diagnóstico que nos permita decidir que a utilização de um medicamento ou de uma estratégia mais intensiva, pode no indivíduo A fazer bem e no B fazer mal?

Foi o que os autores deste artigo fizeram quando exploraram a hipótese de que, a presença destas variantes genéticas tornaria os doentes mais suscetíveis aos efeitos deletérios da hipoglicemia. Poderemos no futuro através de um teste genético, selecionar aqueles doentes que beneficiam, (ou que podem ser prejudicados), com uma terapêutica mais intensiva para o controlo glicémico como a que foi utilizada no ACCORD?

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Marso SP, Daniels GH, Brown-Frandsen K, for the LEADER Trial Investigators.

N Engl J Med 2016; 375:311-22

BACKGROUND: The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS: In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS: A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS: In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.)

Comentários: foi o primeiro estudo com análogos da GLP-1 a demonstrar redução de eventos cardiovasculares e o único até à data a demonstrar redução de mortalidade cardiovascular e total. O número de doentes necessários para tratar em três anos de modo a prevenir um evento foi de 66. Ao contrário dos resultados do estudo EMPA REG com o inibidor da SGLT2 empaglifozina, no estudo LEADER, a curva de separação de eventos surge mais tardiamente, e há redução de eventos cerebrovasculares e coronários, podendo significar um benefício por modificação do processo aterosclerótico.

O facto do estudo LEADER ter apresentado superioridade em relação ao placebo contrasta com resultados prévios com inibidores da DDP4 e com o estudo ELIXA com o lixisenatide, um agonista GLP1 de semi-vida mais curta. As

diferenças entre estes estudos poderão estar relacionadas com os próprios fármacos ou com a população estudada. No estudo LEADER o tempo de evolução médio da diabetes era de 12,8 anos e a HbA1c média era 8,7%, superior ao da maior parte dos outros estudos, mas comparável ao estudo SUSTAIN 6. No estudo LEADER a prevalência de doentes com doença cardiovascular estabelecida (72,4%) era inferior aos estudos com EXAMINE, TECOS e SAVOR com inibidores da DPP4 em que todos os doentes tinham doença CV estabelecida.

Do ponto de vista de segurança, no LEADER, existiu um aumento não significativo de complicações na retina versus placebo (RR 1,15; 95% CI 0,87-1,52). O fármaco mostrou-se seguro do ponto de vista de casos de insuficiência cardíaca (RR 0,87; 95% CI 0,73-1,05) e de eventos renais (RR 0,78; 95%CI 0,67-0,92).

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Marso SP, Bain SC, Consoli A, for the SUSTAIN-6 Investigators

N Engl J Med 2016; 375:1834-44

BACKGROUND: Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

METHODS: We randomly assigned 3297 patients with type 2 diabetes who were on a standardcare regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

RESULTS: At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P<0.001 for noninferiority). Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04). Rates of death from cardiovascular causes

were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.

CONCLUSIONS: In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide.

Comentários: apesar de não ter existido redução da mortalidade total ou cardiovascular como no estudo LEADER, este é o segundo ensaio clínico com agonistas da GLP1 a demonstrar redução de eventos cardiovasculares. Existem diferenças entre os estudos SUSTAIN6 e LEADER a nível do período de seguimento (2,1 vs 3,8 anos) e do tempo de evolução da diabetes (13,9 vs 12,8 anos). Era semelhante a HbA1c de base (8,7%) e tal como no LEADER, a curva de separação de eventos no estudo SUSTAIN ocorreu tardiamente (após um ano). Este facto, aliado à diminuição de EAM não fatal (sem significância estatística) e de AVC isquémico (menos 39%), faz-nos pensar que esta estratégia tem influência direta no processo aterosclerótico.

O aumento significativo de eventos na retina pode não ter relação com o próprio fármaco em particular, já que sabemos que correções rápidas da glicemia podem ter este tipo de complicações, como já demonstrado na diabetes tipo1 no DCCT. A maioria dos doentes que tiveram complicações na retina (mais de 80%) já tinham retinopatia prévia. Há benefício do fármaco a nível da nefropatia, o que afasta um efeito negativo comum a nível microvascular.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Wanner C, Inzucchi SE, Lachin JM for the EMPA-REG OUTCOME Investigators

N Eng J Med 2016; 375:323-334

BACKGROUND Diabetes confers an increased risk of adverse cardiovascular and renal events. In the EMPA-REG OUTCOME trial, empagliflozin, a sodium–glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. We wanted to determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial.

METHODS We randomly assigned patients with type 2 diabetes and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m2 of body-surface area to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.

RESULTS Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (hazard ratio in the empagliflozin group, 0.61; 95% confidence interval, 0.53 to 0.70; P<0.001). Doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. There was no significant between-group difference in the rate of incident albuminuria. The adverse-event profile of empagliflozin in patients with impaired kidney function at baseline was similar to that reported in the overall trial population.

CONCLUSIONS In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care.

Comentários: esta sub-análise do EMPA-REG mostrou uma redução de 39% nas complicações renais. A empaglifozina reduz a reabsorção de glucose no tubo contornado proximal, o que leva um mecanismo contrarregulador da atividade do sistema renina-angiotensina mediada pela mácula densa. É interessante perceber que apesar de uma queda inicial da taxa de filtração glomerular, a deterioração da função renal foi menor do que com o placebo. Será interessante ver se estes dados alteram as aprovações na Europa para a empaglifozina que sugerem não iniciar a medicação em doentes com clearance abaixo de 60 ml/min e suspender (naqueles já medicados) quando a clearance cai abaixo dos 45 ml/min.

Mantêm-se os cuidados no risco acrescido de depleção de volume em doentes medicados simultaneamente com diuréticos. Em 2017, o CANVAS demonstrou resultados positivos na progressão de albuminúria (RR 0,73) e de

outcomes renais (RR 0,60). A melhoria precoce (logo às 12 semanas) na excreção urinária de albumina e a reversibilidade do benefício apos a suspensão do fármaco fazem pensar que o mecanismo protetor é sobretudo hemodinâmico, por redução da pressão intraglomerular. Esta reversão não é, contudo, completa, sugerindo que há modificações estruturais benéficas com a utilização de iSGLT2.

CV Protection in the EMPA-REG OUTCOME Trial: A"Thrifty Substrate" Hypothesis

Ferrannini E, Mark M, Mayoux E

Diabetes Care 2016; 39(7):1108-14

The striking and unexpected relative risk reductions in cardiovascular (CV) mortality (38%), hospitalization for heart failure (35%), and death from any cause (32%) observed in the EMPA-REG OUTCOME trial using an inhibitor of sodium–glucose cotransporter 2 (SGLT2) in patients with type 2 diabetes and high CV risk have raised the possibility that mechanisms other than those observed in the trial - modest improvement in glycemic control, small decrease in body weight, and persistent reductions in blood pressure and uric acid level - may be at play. We hypothesize that under conditions of mild, persistent hyperketonemia, such as those that prevail during treatment with SGLT2 inhibitors, b-hydroxybutyrate is freely taken up by the heart (among other organs) and oxidized in preference to fatty acids. This fuel selection improves the transduction of oxygen consumption into work efficiency at the mitochondrial level. In addition, the hemoconcentration that typically follows SGLT2 inhibition enhances oxygen release to the tissues, thereby establishing a powerful synergy with the metabolic substrate shift. These mechanisms would cooperate with other SGLT2 inhibition–induced changes (chiefly, enhanced diuresis and reduced blood pressure) to achieve the degree of cardioprotection revealed in the EMPA-REG OUTCOME trial. This hypothesis opens up new lines of investigation into the pathogenesis and treatment of diabetic and nondiabetic heart disease.

Comentário: uma hipótese brilhante, mas ainda não definitiva sobre qual ou quais são os efeitos pleiotrópicos dos iSGLT2, que contribuem para o seu benefício clinico. A ideia de que os corpos cetónicos funcionam como um super-fuel, produzindo mais energia do que a fonte habitual no coração do doente com diabetes - os ácidos gordos e não a glicose como no coração saudável – provocou uma onda de novas hipóteses para justificar os resultados do EMPA REG.

Entre outras, não podemos esquecer por exemplo, o efeito glucorético e a redução do volume plasmático que os iSGLT2 provocam e que pode explicar o rápido benefício na redução de insuficiência cardíaca e morte súbita. E já aqui falámos dos efeitos de feed-back tubuloglomerular, com diminuição do hiperfiltrado glomerular e redução na progressão da doença renal.

Já em 2017, uma outra teoria incorpora o NHE3 (sodium-hidrogen-exchanger) que poderá ser um dos principais elementos com responsabilidade na reabsorção de sódio a nível renal. O NHE3 está presente nas células renais e cardíacas e é inibido pelos iSGLT2. Esta inibição a nível cardíaco pode levar uma melhoria do metabolismo mitocondrial e da função sistólica. (JAMA Cardiol. 2017 Sep 1;2(9):1025-1029).

O futuro trará mais certezas? Talvez…

Long-term Benefits of Intensive Glucose Control for Preventing End-Stage Kidney Disease: ADVANCE-ON

Wong MG, Perkovic V, Chalmers J et al, for the ADVANCE-ON Collaborative Group

Diabetes Care 2016; 39(5): 694-700.

OBJECTIVE: the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial reported that intensive glucose control prevents end-stage kidney disease (ESKD) in patients with type 2 diabetes, but uncertainty about the balance between risks and benefits exists. Here, we examine the long-term effects of intensive glucose control on risk of ESKD and other outcomes.

RESEARCH DESIGN AND METHODS: survivors, previously randomized to intensive or standard glucose control, were invited to participate in post-trial follow-up. ESKD, defined as the need for dialysis or kidney transplantation, or death due to kidney disease, was documented overall and by baseline CKD stage, along with hypoglycemic episodes, major cardiovascular events, and death from other causes.

RESULTS: a total of 8,494 ADVANCE participants were followed for a median of 5.4 additional years. In-trial HbA1c differences disappeared by the first post-trial visit. The in-trial reductions in the risk of ESKD (7 vs. 20 events, hazard ratio [HR] 0.35, P = 0.02) persisted after 9.9 years of overall follow-up (29 vs. 53 events, HR 0.54, P < 0.01). These effects were greater in earlier-stage CKD (P = 0.04) and at lower baseline systolic blood pressure levels (P = 0.01). The effects of glucose lowering on the risks of death, cardiovascular death, or major cardiovascular events did not differ by levels of kidney function (P > 0.26).

CONCLUSIONS: intensive glucose control was associated with a long-term reduction in ESKD, without evidence of any increased risk of cardiovascular events or death. These benefits were greater with preserved kidney function and with well-controlled blood pressure.

Comentários: muito se fala de memória metabólica e dos efeitos que uma estratégia terapêutica mais intensiva pode trazer a nível da doença microvascular. O seguimento a longo prazo permite que os estudos possam ganhar robustez. No ADVANCE, o número de casos de doença renal terminal que surgiram no período de aleatorização era pequeno; ao fim de dez anos de extensão no seguimento dos doentes, apesar de já não existirem diferenças no controlo glicémico entre os dois grupos, pôde-se constatar que o benefício a nível da progressão da doença renal se mantinha, com desenvolvimento de menos casos de DRC terminal. A análise por subgrupos permitiu ainda perceber que quem tinha mais benefício da estratégia intensiva eram os doentes com estádios menos graves da DRC e aqueles com melhor controlo da pressão arterial, o que está de acordo com as recomendações que nos sugerem que a estratégia terapêutica deve ser mais intensiva nas fases iniciais da doença.

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes

Schauer PR, Bhatt DL, Kirwan JP for the STAMPEDE Investigators

N Engl J Med 2017; 376:641-651

BACKGROUND Long-term results from randomized, controlled trials that compare medical therapy with surgical therapy in patients with type 2 diabetes are limited.

METHODS We assessed outcomes 5 years after 150 patients who had type 2 diabetes and a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 27 to 43 were randomly assigned to receive intensive medical therapy alone or intensive medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The primary outcome was a glycated hemoglobin level of 6.0% or less with or without the use of diabetes medications.

RESULTS Of the 150 patients who underwent randomization, 1 patient died during the 5-year follow-up period; 134 of the remaining 149 patients (90%) completed 5 years of follow-up. At baseline, the mean (±SD) age of the 134 patients was 49±8 years, 66% were women, the mean glycated hemoglobin level was 9.2±1.5%, and the mean BMI was 37±3.5. At 5 years, the criterion for the primary end point was met by 2 of 38 patients (5%) who received medical therapy alone, as compared with 14 of 49 patients (29%) who underwent gastric bypass (unadjusted P=0.01, adjusted P=0.03, P=0.08 in the intention-to-treat analysis) and 11 of 47 patients (23%) who underwent sleeve gastrectomy (unadjusted P=0.03, adjusted P=0.07, P=0.17 in the intention-to-treat analysis). Patients who underwent surgical procedures had a greater mean percentage reduction from baseline in glycated hemoglobin level than did patients who received medical therapy alone (2.1% vs. 0.3%, P=0.003). At 5 years, changes from baseline observed in the gastric-bypass and sleeve-gastrectomy groups were superior to the changes seen in the medical-therapy group with respect to body weight (−23%, −19%, and −5% in the gastric-bypass, sleeve-gastrectomy, and medical-therapy groups, respectively), triglyceride level (−40%, −29%, and −8%), high-density

lipoprotein cholesterol level (32%, 30%, and 7%), use of insulin (−35%, −34%, and −13%), and quality-of-life measures (general health score increases of 17, 16, and 0.3; scores on the RAND 36-Item Health Survey ranged from 0 to 100, with higher scores indicating better health) (P<0.05 for all comparisons). No major late surgical complications were reported except for one reoperation.

CONCLUSIONS Five-year outcome data showed that, among patients with type 2 diabetes and a BMI of 27 to 43, bariatric surgery plus intensive medical therapy was more effective than intensive medical therapy alone in decreasing, or in some cases resolving, hyperglycemia. (Funded by Ethicon Endo-Surgery and others; STAMPEDE ClinicalTrials.gov number, NCT00432809.)

Comentário: as recomendações da ADA para 2018 indicam que a cirurgia metabólica deve ser considerada em doentes com DM2 e IMC entre 30.0–34.9 kg/m^2, apesar da terapêutica médica optimizada incluindo insulina, se existir um mau controlo glicémico (grau de evidência B).

Para esta recomendação muito têm contribuído os sucessivos resultados do STAMPEDE, agora com a apresentação dos dados a 5 anos. Apesar de ser um estudo de apenas um centro (e de uma só equipa cirúrgica), há melhoria em vários fatores de risco CV (peso, hipertensão, perfil lipídico) e a redução de HBA1c demonstrou ser persistente ao longo dos 5 anos. Falta perceber se este estudo é generalizável a outros centros e se há benefício na redução de eventos clínicos e não apenas nos factores de risco vascular, com este tipo de abordagem.

Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs: The CVD-REAL Study

Kosiborod M, Cavender MA, Fu AZ, for the CVD-REAL Investigators and Study Group

Circulation. 2017; 136:249–259.

BACKGROUND: Reduction in cardiovascular death and hospitalization for heart failure (HHF) was recently reported with the sodium-glucose cotransporter-2 inhibitor (SGLT-2i) empagliflozin in patients with type 2 diabetes mellitus who have atherosclerotic cardiovascular disease. We compared HHF and death in patients newly initiated on any SGLT-2i versus other glucose-lowering drugs in 6 countries to determine if these benefits are seen in real-world practice and across SGLT-2i class.

METHODS: Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i

initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

RESULTS: After propensity matching, there were 309 056 patients newly initiated on either SGLT-2i or other glucose-lowering drugs (154 528 patients in each treatment group). Canagliflozin, dapagliflozin, and empagliflozin accounted for 53%, 42%, and 5% of the total exposure time in the SGLT-2i class, respectively. Baseline characteristics were balanced between the 2 groups. There were 961 HHF cases during 190 164 person-years follow-up (incidence rate, 0.51/100 person-years). Of 215 622 patients in the United States, Norway, Denmark, Sweden, and the United Kingdom, death occurred in 1334 (incidence rate, 0.87/100 person-years), and HHF or death in 1983 (incidence rate, 1.38/100 person-years). Use of SGLT-2i, versus other glucose lowering drugs, was associated with lower rates of HHF (hazard ratio, 0.61; 95% confidence interval, 0.51–0.73; P<0.001); death (hazard ratio, 0.49; 95% confidence interval, 0.41–0.57; P<0.001); and HHF or death (hazard ratio, 0.54; 95% confidence interval, 0.48–0.60; P<0.001) with no significant heterogeneity by country.

CONCLUSIONS: In this large multinational study, treatment with SGLT-2i versus other glucose-lowering drugs was associated with a lower risk of HHF and death, suggesting that the benefits seen with empagliflozin in a randomized trial may be a class effect applicable to a broad population of patients with type 2 diabetes mellitus in real-world practice.

Comentários: Nos últimos anos a "obrigatoriedade" do registo clinico eletrónico e as grandes bases de dados, permitiu que sejam realizados estudos observacionais de grande qualidade. É o caso do CVD REAL em que cerca de 1.400.000 doentes que iniciaram um fármaco hipoglicemiante, foram agrupados de modo a obter dois grupos com características basais semelhantes e estudar o que tinha sucedido àqueles que iniciavam um iSGLT2 vs outro fármaco hipoglicemiante. Chegou-se assim ao número de cerca de 300.000 doentes, com idade média 57 anos, 44% mulheres, a esmagadora maioria (87%) em prevenção primária.

O estudo teve um seguimento inferior a um ano (210-270 dias). Neste curto espaço de tempo houve uma diferença significativa na hospitalização por insuficiência cardíaca, mas é na redução da mortalidade global (o verdadeiro hard-end-point) em 51%, que os resultados impressionam...

Os resultados foram semelhantes nos doentes medicados com canaglifozina e dapaglifozina (o uso de empaglifozina foi residual). O CANVAS aponta na mesma direção do que o EMPA REG e CVD REAL (para a IC e mortalidade global), mas apenas nos doentes em prevenção secundária. O eventual efeito de classe só poderá ser demonstrado com outros estudos próximos, como o VERTIS e o DECLARE. Este último estudo com a dapaglifozina, também poderá confirmar se há benefício numa população mais abrangente do que a do EMPA REG (toda ela em prev. secundária), pois tal como no CVD REAL, a maioria dos doentes no DECLARE estão em prevenção primária.

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Neal B, Perkovic V, Mahaffey KW, for the CANVAS Program Collaborative Group

N Engl J Med 2017; 377:644-6577

BACKGROUND: Canagliflozin is a sodium–glucose cotransporter 2 inhibitor that reduces glycemia as well as blood pressure, body weight, and albuminuria in people with diabetes. We report the effects of treatment with canagliflozin on cardiovascular, renal, and safety outcomes.

METHODS: The CANVAS Program integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

RESULTS: The mean age of the participants was 63.3 years, 35.8% were women, the mean duration of diabetes was 13.5 years, and 65.6% had a history of cardiovascular disease. The rate of the primary outcome was lower with canagliflozin than with placebo (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; 95% confidence interval [CI], 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). Although based on the prespecified hypothesis-testing sequence the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin with respect to the progression of albuminuria (hazard ratio, 0.73; 95% CI, 0.67 to 0.79) and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (hazard ratio, 0.60; 95% CI, 0.47 to 0.77). Adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation (6.3 vs. 3.4 participants per 1000 patient-years; hazard ratio, 1.97; 95% CI, 1.41 to 2.75); amputations were primarily at the level of the toe or metatarsal.

CONCLUSIONS: In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal. (Funded by Janssen Research and Development; CANVAS and CANVAS-R ClinicalTrials.gov numbers, NCT01032629 and NCT01989754, respectively.)

Comentários: alguns dos resultados do CANVAS são consistentes aos que se obtiveram no EMPA REG: redução do objetivo principal (3P MACE) em 14%, hospitalização por IC em 33%, redução de 40% nos outcomes renais. Porém, não se obtiveram diferenças na mortalidade total e na mortalidade CV no CANVAS, ao contrário do EMPA REG, e do ponto de vista de segurança aumentaram as fraturas ósseas em 26%. Houve ainda um substancial incremento de amputações, algo que até à data não tinha sido comprovado para os outos iSGLT2. Sabe-se que os doentes com maior risco de amputação, foram aqueles que tinham doença arterial periférica ou amputação prévia. Apesar de não se saber a causa, a depleção da volémia tem sido apontada como um dos factores potenciais.

Dois terços dos doentes do CANVAS estavam em prevenção secundária e foram estes que tiveram benefício na terapêutica com canaglifozina. Nos doentes em prevenção primária a terapêutica foi neutra em relação ao end point primário. Isto poderá ter que ver com a baixa incidência de eventos cardiovasculares durante o período de tempo do estudo (cerca de três anos) neste sub-grupo de doentes.

Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes

Holman RR, Bethel MA, Mentz RJ, for the EXSCEL Study Group

N Engl J Med 2017; 377:1228-1239

BACKGROUND: The cardiovascular effects of adding once-weekly treatment with exenatide to usual care in patients with type 2 diabetes are unknown.

METHODS: We randomly assigned patients with type 2 diabetes, with or without previous cardiovascular disease, to receive subcutaneous injections of extended-release exenatide at a dose of 2 mg or matching placebo once weekly. The primary composite outcome was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The coprimary hypotheses were that exenatide, administered once weekly, would be noninferior to placebo with respect to safety and superior to placebo with respect to efficacy.

RESULTS In all, 14,752 patients (of whom 10,782 [73.1%] had previous cardiovascular disease) were followed for a median of 3.2 years (interquartile range, 2.2 to 4.4). A primary composite outcome event occurred in 839 of 7356 patients (11.4%; 3.7 events per 100 person-years) in the exenatide group and in 905 of 7396 patients (12.2%; 4.0 events per 100 person-years) in the placebo group (hazard ratio, 0.91; 95% confidence interval [CI], 0.83 to 1.00), with the intention-to-treat analysis indicating that exenatide, administered once weekly, was noninferior to placebo with respect to safety ($P<0.001$ for noninferiority) but was not superior to placebo with respect to efficacy ($P=0.06$ for superiority). The rates of death from cardiovascular causes, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, hospitalization for heart failure, and hospitalization for acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary thyroid carcinoma, and serious adverse events did not differ significantly between the two groups.

CONCLUSIONS: Among patients with type 2 diabetes with or without previous cardiovascular disease, the incidence of major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo. (Funded by Amylin Pharmaceuticals; EXSCEL ClinicalTrials.gov number, NCT01144338

Comentários: o EXSCEL decorreu no ambiente de seguimento habitual do doente, com seguimentos de 6 em 6 meses, estando por isso mais próximo da vida real. O facto de 43% dos doentes terem descontinuado o estudo, deve fazer-nos refletir sobre o benefício desta abordagem e se deveriam ser analisados apenas os doentes que cumpriram efetivamente a terapêutica. Apesar disto, da população ser heterogénea, com um quarto dos doentes em prevenção primária, de 15% dos participantes estarem medicados também com iDDP4, os resultados falharam a superioridade no objetivo primário por pouco (RR 0.91, 95% CI 0.83–1.00, P = 0.06).

O desenho em cadeia hierárquica em que apenas se prosseguia a significância estatística à medida que os diferentes endpoints eram ultrapassados, esbarrou assim no objetivo primário. A redução de morte por todas as causas (HR 0.86, 95% CI, 0.77–0.97), não teve, portanto, significado estatístico e o EXSCEL deve ser assim considerado neutro do ponto de vista de redução de risco vascular.

Effects of acarbose on cardiovascular and diabetes outcomes in patients with coronary heart disease and impaired glucose tolerance (ACE): a randomised, double-blind, placebo-controlled trial

Holman RR, Coleman RL, Chan JC, for the ACE Study Group

Lancet Diabetes Endocrinol 2017; 5: 877–86

Background: the effect of the α-glucosidase inhibitor acarbose on cardiovascular outcomes in patients with coronary heart disease and impaired glucose tolerance is unknown. We aimed to assess whether acarbose could reduce the frequency of cardiovascular events in Chinese patients with established coronary heart disease and impaired glucose tolerance, and whether the incidence of type 2 diabetes could be reduced.

Methods: the Acarbose Cardiovascular Evaluation (ACE) trial was a randomised, double-blind, placebo-controlled, phase 4 trial, with patients recruited from 176 hospital outpatient clinics in China. Chinese patients with coronary heart disease and impaired glucose tolerance were randomly assigned (1:1), in blocks by site, by a centralised computer system to receive oral acarbose (50 mg three times a day) or matched placebo, which was added to standardised cardiovascular secondary prevention therapy. All study staff and patients were masked to treatment group allocation. The primary outcome was a five-point composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospital admission for unstable angina, and hospital admission for heart failure, analysed in the intention-to-treat population (all participants randomly assigned to treatment who provided written informed consent). The secondary outcomes were a three-point composite outcome (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke), death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, development of diabetes, and development of impaired renal function. The safety population comprised all patients who received at least one dose of study medication. This trial is registered with

ClinicalTrials.gov, number NCT00829660, and the International Standard Randomised Controlled Trial Number registry, number ISRCTN91899513.

Findings Between March 20, 2009, and Oct 23, 2015, 6522 patients were randomly assigned and included in the intention-to-treat population, 3272 assigned to acarbose and 3250 to placebo. Patients were followed up for a median of 5·0 years (IQR 3·4–6·0) in both groups. The primary five-point composite outcome occurred in 470 (14%; 3·33 per 100 person-years) of 3272 acarbose group participants and in 479 (15%; 3·41 per 100 person-years) of 3250 placebo group participants (hazard ratio 0·98; 95% CI 0·86–1·11, p=0·73). No significant differences were seen between treatment groups for the secondary three-point composite outcome, death from any cause, cardiovascular death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospital admission for unstable angina, hospital admission for heart failure, or impaired renal function. Diabetes developed less frequently in the acarbose group (436 [13%] of 3272; 3·17 per 100 person-years) compared with the placebo group (513 [16%] of 3250; 3·84 per 100 person-years; rate ratio 0·82, 95% CI 0·71–0·94, p=0·005). Gastrointestinal disorders were the most common adverse event associated with drug discontinuation or dose changes (215 [7%] of 3263 patients in the acarbose group vs 150 [5%] of 3241 in the placebo group [p=0·0007]; safety population). Numbers of non-cardiovascular deaths (71 [2%] of 3272 vs 56 [2%] of 3250, p=0·19) and cancer deaths (ten [<1%] of 3272 vs 12 [<1%] of 3250, p=0·08) did not differ between groups.

Interpretation: in Chinese patients with coronary heart disease and impaired glucose tolerance, acarbose did not reduce the risk of major adverse cardiovascular events, but did reduce the incidence of diabetes.

Comentário: mal-amada por muitos diabetologistas, houve quem vaticinasse o fim da carreira da acarbose quando se soube que não havia redução do risco CV no ACE Study. A realização do estudo apenas na população chinesa e em doentes com "pré diabetes", não responde ao que sucederia em doentes com diabetes estabelecida, ou noutras populações. E a redução de 18% de desenvolvimento de diabetes, abre perspectivas na utilização deste medicamento na prevenção da doença em doentes com intolerância à glicose – fase pré diabetes. Ainda vamos ouvir falar muito de acarbose…

Severe hypoglycaemia among patients with type 2 diabetes requiring emergency hospital admission: The Hypoglycaemia In Portugal Observational Study–Emergency Room (HIPOS–ER)

Conceição J, Dores J, Araújo F, Laires PA, Carr RD, Brodovicz K, Radican L, Nogueira AM

Diabetes Obes Metab. 2018; 20:50–59

Aims: To analyze the prevalence of severe hypoglycaemia in patients with type 2 diabetes (T2DM) treated with antihyperglycaemic agents (AHA) and requiring emergency room (ER) assistance, and to analyze the prevalence according to type of AHA therapy.

Methods: The present study, the Hypoglycaemia In Portugal Observational Study–Emergency Room (HIPOS–ER), was a cross-sectional, observational, multicentre, nationwide study, with specific hypoglycaemia source data collection.

Results: Within the study period, a total of 425 706 admissions were recorded in the ERs of participating hospitals. The prevalence of severe hypoglycaemic episodes in patients with T2DM was 0.074%. In all, 238 patients were included, more than half of whom were on insulin-based therapy (55.0%) and a third of whom (31.5%) were on oral secretagogue-based therapy. In 61.2% of patients primary care was the main diabetes care setting. The median patient age was 77.5 years and the mean duration of diabetes was 19 years. Missing a meal or low carbohydrate meal content was the most frequent cause of hypoglycaemia (55.9%) and the most frequent triggers for seeking emergency assistance were pre-syncope (19.2%) and transient loss of consciousness (17.4%). A total of 44.1% of patients were hospitalized for a median of 5.1 days. Patients in the secretagogue group were admitted to hospital more often than patients in the insulin group (70.7% vs 29.0%; P < .001). Nine patients died.

Conclusions: These findings confirm that severe hypoglycaemia in patients with T2DM requiring ER assistance occurs mainly in those on insulin- and secretagogue-based therapies and is associated with a significant medical burden. Antidiabetic therapy should be individualized to minimize the risk of severe iatrogenic hypoglycaemia, and any intervention to this end should always involve primary care stakeholders.

Comentário: publicado on-line em 2017, o HIPOS-ER foi um passo importante para o estudo da Diabetes em Portugal. O estudo foi pioneiro, por ter como palco um ambiente geralmente hostil para a investigação, tendo decorrido em 7 serviços de urgência de Portugal Continental.

Este estudo transversal, com a duração de um ano, permitiu identificar mais casos de hipoglicemias, do que se o estudo fosse retrospetivo, já que se verificou que em um quarto das notas de alta de doentes que tinham sido internados por hipoglicemia grave, a hipoglicemia não constava como diagnóstico principal à saída. Para isto contribuiu a ocorrência de complicações em 16% dos doentes, tendo o trauma sido a complicação principal. A justificação para estes traumatismos pode dever-se à forma de apresentação da hipoglicemia, com a maioria dos doentes a manifestar-se com pré-síncope (36%), perda transitória do conhecimento (32%) ou coma (10%. O nível médio de glicémia foi 38 mg/dl….

A utilização de fármacos causadores de hipoglicemia (nomeadamente insulina e sulfonilureias) deve ser ponderada num grupo de doentes como o do Hipos ER, em que à fragilidade física (idade média 77 anos, diabetes há 19 anos, doença aterosclerótica prévia em 54%) se associavam condições psicossociais adversas (demência em 23%, escolaridade primária ou menor em 80% dos doentes).

RV Acidente Vascular Cerebral 2016/17

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Introdução

Avanços notáveis no controle do acidente vascular cerebral (AVC) agudo têm sido feitos nos últimos 20 anos. Cinco intervenções com eficácia comprovada e nível de evidência 1 marcaram esta evolução: Unidades de AVC (Langhorne 1993), trombólise (NINDS 1995), aspirina (IST 1997), cirurgia descompressiva (Vahedi 2007) e por último a trombectomia (McLean 2015).

Atualmente o AVC é considerado uma emergência médica com prioridade nos sistemas de triagem, com campanhas para o reconhecimento publico dos sinais de alerta. Os sistemas de saúde reconfiguraram-se para permitir o acesso rápido do doente com AVC a cuidados especializados.

Esta resposta dos sistemas de saúde é um fenómeno que se iniciou em 1995 com o estudo NINDS e a demonstração da eficácia da trombólise no AVC isquémico agudo. Esta evolução terapêutica conduziu à priorização do AVC em sistemas e políticas de saúde facilitando a implementação de Unidades de AVC e de novas intervenções diagnósticas e de terapêuticas antitrombóticas e de reabilitação. O mais recente avanço deu-se em 2015 com a demonstração da eficácia da intervenção endovascular no AVC agudo grave por oclusão proximal de grandes vasos obrigando de novo os sistemas de saúde a uma readaptação e reorganização da rede de cuidados para o AVC.

A seleção de estudos efetuada tenta de alguma forma refletir os avanços verificados em 2016 e 2017 abordando os resultados de vários ensaios com impacto no tratamento e diagnóstico da doença vascular cerebral: os resultados do estudo DANW alargando a janela terapêutica para a trombectomia até às 24 h mediante critérios de perfusão tecidular e de mismatch; Os ensaios CLOSE, RESPECT e Gore REDUCE demonstrando a redução da recorrência de AVC no encerramento percutâneo do FOP no AVC criptogénico; os resultados neutros mas prometedores do CLEAR III na remoção trombolítica da hemorragia intraventricular; o estudo FCET2EC revelando novos dados sobre o efeito da terapia da fala na afasia crónica; e a repercussão positiva da terapia multimodal numa fase tardia do AVC.

São também apresentados resultados de estudos que demonstram a importância da implementação alargada e sistemática de unidades de AIT na redução de recorrência de AVC, refletindo sobre a subutilização de monitorização cardíaca após AVC agudo ou AIT e sobre o seu custo eficácia no diagnóstico de fibrilhação auricular (FA), apresentando a proposta de um novo modelo na etiopatogenia do AVC na FA. Foram também apresentados dados duma análise retrospetiva multicêntrica sobre intervenção endovascular nos AVC da circulação posterior e a importância da trombectomia precoce (<6h) como preditor de prognóstico favorável (mRS≤2) aos 90 dias. São

referidos dois grandes ensaios clínicos randomizados (CREST e ACT1) que comparam o prognóstico a curto e a longo prazo da endarterectomia carotídea versus stenting com resultados sem diferenças significativas na taxa de AVC tardio ipsilateral após os dois procedimentos. Foram também publicadas as guidelines Europeias para a organização de cuidados de intervenção no AVC agudo (EROICAS) e as Guidelines para a reabilitação do adulto com AVC (American Heart Association (AHA) /American Stroke Association (ASA) assim como o Racional científico para os critérios de inclusão ou de exclusão para Alteplase intravenosa no AVC isquémico agudo (AHA/ASA) o que constitui um apoio indispensável na prática clínica.

Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct

Nogueira R.G., Jadhav A.P., Haussen D.C., for the DAWN Trial Investigators

N Engl J Med 2018; 378:11-21. DOI: 10.1056/NEJMoa1706442. Epub 2017 November 11

BACKGROUND The effect of endovascular thrombectomy that is performed more than 6 hours after the onset of ischemic stroke is uncertain. Patients with a clinical deficit that is disproportionately severe relative to the infarct volume may benefit from late thrombectomy.

METHODS We enrolled patients with occlusion of the intracranial internal carotid artery or proximal middle cerebral artery who had last been known to be well 6 to 24 hours earlier and who had a mismatch between the severity of the clinical deficit and the infarct volume, with mismatch criteria defined according to age (<80 years or ≥80 years). Patients were randomly assigned to thrombectomy plus standard care (the thrombectomy group) or to standard care alone (the control group). The coprimary end points were the mean score for disability on the utility-weighted modified Rankin scale (which ranges from 0 [death] to 10 [no symptoms or disability]) and the rate of functional independence (a score of 0, 1, or 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating more severe disability) at 90 days.

RESULTS A total of 206 patients were enrolled; 107 were assigned to the thrombectomy group and 99 to the control group. At 31 months, enrollment in the trial was stopped because of the results of a prespecified interim analysis. The mean score on the utility-weighted modified Rankin scale at 90 days was 5.5 in the thrombectomy group as compared with 3.4 in the control group (adjusted difference [Bayesian analysis], 2.0 points; 95% credible interval, 1.1 to 3.0; posterior probability of superiority, >0.999), and the rate of functional independence at 90 days was 49% in the thrombectomy group as compared with 13% in the control group (adjusted difference, 33 percentage points; 95% credible interval, 24 to 44; posterior probability of superiority, >0.999). The rate of symptomatic intracranial hemorrhage did not differ significantly between the two groups (6% in the thrombectomy group and 3% in the control group, P = 0.50), nor did 90-day mortality (19% and 18%, respectively; P = 1.00).

CONCLUSIONS Among patients with acute stroke who had last been known to be well 6 to 24 hours earlier and who had a mismatch between clinical deficit and infarct, outcomes for disability at 90 days were better with thrombectomy plus standard care than with standard care alone. (Funded by Stryker Neurovascular; DAWN ClinicalTrials.gov number, NCT02142283.)

Comentário: o que o estudo DAWN veio trazer de novo foi a seleção dos doentes para trombectomia para além das 6 h, pela janela tecidular, isto é, pela quantificação do tecido viável, a penumbra isquémica, traduzido em mismatch clinica (NIHSS)/ volume do enfarte. Estes doentes podem ser identificados pela presença de défice neurológico desproporcionadamente grave relativamente à área de enfarte. Outro ponto inovador do estudo foi o ajuste dos critérios de inclusão para a idade, exigindo um core isquémico de menor volume ou seja um maior mismatch para os doentes com mais de 80 anos tendo em conta a sua menor reserva neurológica. De realçar

também os métodos rápidos e precisos usados na medição do core isquémico. O DAWN usou a RMN ou o TAC de perfusão com medições por software automático, para definir a área de enfarte associado a um défice neurológico desproporcionadamente grave. O uso da clínica (NIHSS) como marcador de risco tecidular foi também um ponto inovador. O ensaio foi interrompido aos 31 meses face à probabilidade preditiva de superioridade da trombectomia ultrapassar os 95% para o end point primário.

O estudo DAWN demonstrou que nos doentes com AVC agudo por oclusão proximal de grandes vasos intracranianos, clinicamente bem entre as 6 as 24 h anteriores e com mismatch entre o défice neurológico e o volume do enfarte, a trombectomia associada aos cuidados standard confere melhor prognóstico para a incapacidade e independência funcional aos 90 dias, comparativamente com os cuidados standard isolados.
O NNT (number needed to treat) foi 2 para melhor score para incapacidade aos 90 dias e foi 2,8 para a independência funcional aos 90 dias. No Dawn o valor da independência funcional no grupo submetido a trombectomia, 49%, foi semelhante ao valor reportado na meta-análise dos 5 ensaios publicados em 2015, 46%, em doentes que receberam trombectomia na janela de 6 h. Isto sugere que o uso da janela tecidular na seleção de doentes para trombectomia é pelo menos tão eficaz como o uso da janela temporal.

Este estudo abre perspetivas de utilização da janela de perfusão também para a trombólise (vários ensaios em curso, EXTEND trial) o que poderá permitir uma maior abrangência das técnicas de reperfusão que atualmente dispomos. Os resultados do DAWN não devem ser interpretados como uma liberalização da janela temporal que se mantém crucial como fator de bom prognóstico na seleção dos doentes.Tem grandes implicações no tratamento do AVC agudo porque valida a seleção dos doentes por critérios fisiológicos de existência de tecido cerebral viável para além dos critérios cronológicos de janela temporal permitindo expandir os critérios para trombecto mia e aumentar o numero de doentes que podem beneficiar duma terapêutica muito eficaz e segura

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

Mas J.L., Derumeaux G., Guillon B., for the CLOSE Investigators

N Engl J Med 2017; 377:1011-21. DOI: 10.1056/NEJMoa1705915

BACKGROUND Trials of patent foramen ovale (PFO) closure to prevent recurrent stroke have been inconclusive. We investigated whether patients with cryptogenic stroke and echocardiographic features representing risk of stroke would benefit from PFO closure or anticoagulation, as compared with antiplatelet therapy.

METHODS In a multicenter, randomized, open-label trial, we assigned, in a 1:1:1 ratio, patients 16 to 60 years of age who had had a recent stroke attributed to PFO, with an associated atrial septal aneurysm or large interatrial shunt, to transcatheter PFO closure plus long-term antiplatelet therapy (PFO closure group), antiplatelet therapy

alone (antiplatelet-only group), or oral anticoagulation (anticoagulation group) (randomization group 1). Patients with contraindications to anticoagulants or to PFO closure were randomly assigned to the alternative noncontraindicated treatment or to antiplatelet therapy (randomization groups 2 and 3). The primary outcome was occurrence of stroke. The comparison of PFO closure plus antiplatelet therapy with antiplatelet therapy alone was performed with combined data from randomization groups 1 and 2, and the comparison of oral anticoagulation with antiplatelet therapy alone was performed with combined data from randomization groups 1 and 3.

RESULTS A total of 663 patients underwent randomization and were followed for a mean (±SD) of 5.3±2.0 years. In the analysis of randomization groups 1 and 2, no stroke occurred among the 238 patients in the PFO closure group, whereas stroke occurred in 14 of the 235 patients in the antiplatelet only group (hazard ratio, 0.03; 95% confidence interval, 0 to 0.26; P<0.001). Procedural complications from PFO closure occurred in 14 patients (5.9%). The rate of atrial fibrillation was higher in the PFO closure group than in the antiplatelet-only group (4.6% vs. 0.9%, P = 0.02). The number of serious adverse events did not differ significantly between the treatment groups (P = 0.56). In the analysis of randomization groups 1 and 3, stroke occurred in 3 of 187 patients assigned to oral anticoagulants and in 7 of 174 patients assigned to antiplatelet therapy alone.

CONCLUSIONS Among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke recurrence was lower among those assigned to PFO closure combined with antiplatelet therapy than among those assigned to antiplatelet therapy alone. PFO closure was associated with an increased risk of atrial fibrillation. (Funded by the French Ministry of Health; CLOSE ClinicalTrials.gov number, NCT00562289.)

Comentário: o AVC criptogénico representa uma percentagem importante dos AVC isquémicos (20 a 30%) e o Foramen Ovale Patente (FOP) tem uma prevalência elevada (40%) no AVC criptogénico, superior à encontrada na população em geral (25%). Está demonstrada uma associação entre FOP e o AVC criptogénico particularmente nos indivíduos menores de 55 anos, com shunt direito esquerdo importante e aneurisma do septo auricular. Por este motivo o encerramento do FOP tem sido um assunto muito investigado e debatido.

Em 2017 foram publicados no New England Journal of Medicine três grandes ensaios clínicos randomizados, o CLOSE, estudo aqui selecionado, o RESPECT extended follow up e o Gore REDUCE que demonstram que o encerramento percutâneo do FOP combinado com terapêutica antiagregante leva a uma redução significativa do risco de recorrência de AVC relativamente à terapêutica antiagregante isolada. Estes resultados contrastam com os resultados publicados em 2012 e 2013 de três grandes ensaios (CLOSURE I, PC, RESPECT) que não mostraram superioridade do encerramento do FOP sob a terapêutica antitrombótica na prevenção de AVC recorrente.

Estes ensaios trazem de novo uma maior extensão do período de follow up (RESPECT extended follow up) e uma seleção de doentes com características de risco, como aneurisma do septo interauricular e shunt esquerdo direito importante (CLOSE e REDUCE). Também a correta avaliação de AVC criptogénico assim como uma baixa contribuição de fatores de risco vascular nos doentes estudados (CLOSE) contribuiram para diminuir a probabilidade de outras causas na etiologia do AVC e aumentar a probabilidade do FOP como fator etiologico do

AVC recorrente. Na prática clínica há 2 aspetos importantes na questão do encerramento do FOP um prende-se com o diagnóstico e a caracterização do FOP o outro com a seleção do doente com FOP e AVC criptogénico.

Tendo em conta os resultados destes três grandes ensaios o encerramento do FOP deve ser considerado no doente com menos de 60 anos, AVC criptogénico bem definido e FOP com características de risco.

Thrombolytic removal of intraventricular haemorrhage in treatment of severe stroke: results of the randomised, multicentre, multiregion, placebo-controlled CLEAR III trial.

Hanley DF, Lane K, McBeeN, et al

Lancet. 2017 Feb 11;389(10069):603-611.

BACKGROUND: intraventricular haemorrhage is a subtype of intracerebral haemorrhage, with 50% mortality and serious disability for survivors. We aimed to test whether attempting to remove intraventricular haemorrhage with alteplase versus saline irrigation improved functional outcome.

METHODS: in this randomised, double-blinded, placebo-controlled, multiregional trial (CLEAR III), participants with a routinely placed extraventricular drain, in the intensive care unit with stable, non-traumatic intracerebral haemorrhage volume less than 30 mL, intraventricular haemorrhage obstructing the 3rd or 4th ventricles, and no underlying pathology were adaptively randomly assigned (1:1), via a web-based system to receive up to 12 doses, 8 h apart of 1 mg of alteplase or 0·9% saline via the extraventricular drain. The treating physician, clinical research staff, and participants were masked to treatment assignment. CT scans were obtained every 24 h throughout dosing. The primary efficacy outcome was good functional outcome, defined as a modified Rankin Scale score (mRS) of 3 or less at 180 days per central adjudication by blinded evaluators.

FINDINGS: between Sept 18, 2009, and Jan 13, 2015, 500 patients were randomised: 249 to the alteplase group and 251 to the saline group. 180-day follow-up data were available for analysis from 246 of 249 participants in the alteplase group and 245 of 251 participants in the placebo group. The primary efficacy outcome was similar in each group (good outcome in alteplase group 48% vs saline 45%; risk ratio [RR] 1·06 [95% CI 0·88-1·28; p=0·554]). A difference of 3·5% (RR 1·08 [95% CI 0·90-1·29], p=0·420) was found after adjustment for intraventricular haemorrhage size and thalamic intracerebral haemorrhage. At 180 days, the treatment group had lower case fatality (46 [18%] vs saline 73 [29%], hazard ratio 0·60 [95% CI 0·41-0·86], p=0·006), but a greater proportion with mRS 5 (42 [17%] vs 21 [9%]; RR 1·99 [95% CI 1·22-3·26], p=0·007). Ventriculitis (17 [7%] alteplase vs 31 [12%] saline; RR 0·55 [95% CI 0·31-0·97], p=0·048) and serious adverse events (114 [46%] alteplase vs 151 [60%] saline; RR 0·76 [95% CI 0·64-0·90], p=0·002) were less frequent with alteplase treatment. Symptomatic

bleeding (six [2%] in the alteplase group vs five [2%] in the saline group; RR 1·21 [95% CI 0·37-3·91], p=0·771) was similar.

INTERPRETATION: in patients with intraventricular haemorrhage and a routine extraventricular drain, irrigation with alteplase did not substantially improve functional outcomes at the mRS 3 cutoff compared with irrigation with saline. Protocol-based use of alteplase with extraventricular drain seems safe. Future investigation is needed to determine whether a greater frequency of complete intraventricular haemorrhage removal via alteplase produces gains in functional status

Comentário: A hemorragia cerebral parenquimatosa é uma patologia com elevada morbi-mortalidade e os tratamentos médicos e cirúrgicos actuais não mudam o prognóstico de forma substancial. Quando é complicada por hemorragia intraventricular o prognóstico é ainda pior. Estudos prévios de séries de casos e um ensaio clínico de pequena dimensão sugerem que a mortalidade e, talvez, a incapacidade funcional podem ser mitigadas com a remoção da hemorragia intraventricular usando trombólise intraventricular. Antes deste ensaio não existia evidência de qualidade relativamente à eficácia desta estratégia terapêutica.

Neste ensaio randomizado, duplamente cego e cuidadosamente desenhado, os autores testaram se a administração de bólus intraventriculares de alteplase (através de cateteres de ventriculostomia adequados) podia melhorar o outcome funcional em doentes com hemorragia cerebral com sangue intraventricular através da aceleração da resolução do coágulo intraventricular.

Os 500 pacientes randomizados tinham um hematoma intracerebral de moderada ou pequena dimensão (<30mL), estável em TAC seriados, e hemorragia intraventricular obstruindo o terceiro e quarto ventrículos. Os pacientes tinham menos de 80 anos e eram previamente autónomos.
Os resultados foram neutros: a proporção de pacientes tratados com bólus de alteplase intraventricular que atingiram bons outcomes funcionais aos 6 meses foi semelhante ao grupo controlo que recebeu bólus de solução salina (48% vs 45%; risk ratio 1·06 [95% CI 0·88–1·28]; p=0·554). A mortalidade foi 11% inferior no grupo alteplase, mas à custa de um aumento de 8% na sobrevida de doentes com incapacidade grave. Não foram notadas diferenças em medidas de qualidade de vida auto-reportadas entre os dois grupos. Curiosamente, a mortalidade, re-sangramento sintomático e infecções bacterianas cerebrais foram muitos menos frequentes do que o antecipado e uma maior remoção do coágulo intraventricular foi associada a melhoria dos outcomes funcionais. Infelizmente, apenas 30% dos pacientes submetidos a tratamento com alteplase atingiram o objectivo de redução do coágulo em 80%, o que poderá ser uma das razões que explica a ausência de eficácia na melhoria dos outcomes funcionais.

Como os resultados do ensaio CLEAR III no outcome primário de redução da incapacidade foram neutros, a alteplase intraventricular não pode ser actualmente recomendada para o tratamento de rotina da hemorragia intraventricular na prática clínica. Contudo, a sua administração é segura e os resultados secundários abrem a possibilidade da redução do volume de sangue intraventricular ser uma espécie de biomarcador de tratamento, com melhores resultados a serem observados com maiores reduções do coágulo sanguíneo, particularmente em pacientes com grande volume de sangue intraventricular ad initio. Portanto, a redução agressiva do coágulo

intraventricular, quando conseguida verdadeiramente, poderá melhorar a morbilidade e mortalidade. Novos estudos irão certamente contribuir para o esclarecimento adicional destas questões.

Intensive speech and language therapy in patients with chronic aphasia after stroke: a randomised, open-label, blinded-endpoint, controlled trial in a health-care setting.

Breitenstein C, Grewe T, Flöel A, for the FCET2EC study group.

Lancet. 2017 Apr 15;389(10078):1528-1538

BACKGROUND: treatment guidelines for aphasia recommend intensive speech and language therapy for chronic (≥6 months) aphasia after stroke, but large-scale, class 1 randomised controlled trials on treatment effectiveness are scarce. We aimed to examine whether 3 weeks of intensive speech and language therapy under routine clinical conditions improved verbal communication in daily-life situations in people with chronic aphasia after stroke.

METHODS: in this multicentre, parallel group, superiority, open-label, blinded-endpoint, randomised controlled trial, patients aged 70 years or younger with aphasia after stroke lasting for 6 months or more were recruited from 19 inpatient or outpatient rehabilitation centres in Germany. An external biostatistician used a computer-generated permuted block randomisation method, stratified by treatment centre, to randomly assign participants to either 3 weeks or more of intensive speech and language therapy (≥10 h per week) or 3 weeks deferral of intensive speech and language therapy. The primary endpoint was between-group difference in the change in verbal communication effectiveness in everyday life scenarios (Amsterdam-Nijmegen Everyday Language Test A-scale) from baseline to immediately after 3 weeks of treatment or treatment deferral. All analyses were done using the modified intention-to-treat population (those who received 1 day or more of intensive treatment or treatment deferral). This study is registered with ClinicalTrials.gov, number NCT01540383.

FINDINGS: we randomly assigned 158 patients between April 1, 2012, and May 31, 2014. The modified intention-to-treat population comprised 156 patients (78 per group). Verbal communication was significantly improved from baseline to after intensive speech and language treatment (mean difference 2·61 points [SD 4·94]; 95% CI 1·49 to 3·72), but not from baseline to after treatment deferral (-0·03 points [4·04]; -0·94 to 0·88; between-group difference Cohen's d 0·58; p=0·0004). Eight patients had adverse events during therapy or treatment deferral (one car accident [in the control group], two common cold [one patient per group], three gastrointestinal or cardiac symptoms [all intervention group], two recurrent stroke [one in intervention group before initiation of treatment, and one before group assignment had occurred]); all were unrelated to study participation.

INTERPRETATION: 3 weeks of intensive speech and language therapy significantly enhanced verbal communication in people aged 70 years or younger with chronic aphasia after stroke, providing an effective evidence-based treatment approach in this population. Future studies should examine the minimum treatment intensity required for meaningful treatment effects, and determine whether treatment effects cumulate over repeated intervention periods.

Comentário: durante décadas postulou-se que não era possível melhorar a comunicação verbal em pacientes com afasia crónica (≥6 meses de duração) pós-AVC. Vários ensaios clínicos randomizados prévios tentaram avaliar a eficácia da terapia da fala nesta população, mas os seus resultados foram inconclusivos sobretudo devido a problemas metodológicos. Apesar de diversas meta-análises e revisões sistemáticas publicadas nos últimos anos apontarem para evidência da eficácia da terapia da fala aplicada de forma intensiva (≥5h semanais) na afasia crónica pós-AVC, os seus resultados são frequentemente ignorados e esta população vê repetidamente negado o acesso à terapia da fala.

O ensaio clínico FCET2EC (From Controlled Experimental Trial 2 Everyday Communication) agora publicado é o ensaio randomizado de maior dimensão envolvendo doentes com afasia crónica pós-AVC e avaliando a eficácia da terapia da fala intensiva versus um grupo controlo sem tratamento ou com tratamento de baixa intensidade. O endpoint primário é uma mudança a partir do basal na eficácia da linguagem verbal em cenários de vida real, sendo que se observou uma melhoria em 10% deste outcome no grupo de intervenção intensiva. Os resultados fornecem evidência robusta para a superioridade da terapia da fala individualizada e intensiva (≥10h semanais) durante 3 semanas. Os efeitos permanecem estáveis durante o período de seguimento de 6 meses. Em comparação com outros estudos os critérios de inclusão foram liberais relativamente à etiologia do AVC (isquémico, hemorrágico, hemorragia subaracnoideia) e ao tipo e gravidade de afasia permitindo a generalização destes resultados à população com 70 anos ou menos de idade com afasia crónica pós-AVC. Os resultados deste ensaio podem alterar os recursos de reabilitação alocados a esta população.

Long-Term Improvements After Multimodal Rehabilitation in Late Phase After Stroke: A Randomized Controlled Trial.

Bunketorp-Käll L, Lundgren-Nilsson A, Samuelsson H, et al

Stroke. 2017 Jul;48(7):1916-1924.

BACKGROUND AND PURPOSE: treatments that improve function in late phase after stroke are urgently needed. We assessed whether multimodal interventions based on rhythm-and-music therapy or horse-riding therapy could lead to increased perceived recovery and functional improvement in a mixed population of individuals in late phase after stroke.

METHODS: participants were assigned to rhythm-and-music therapy, horse-riding therapy, or control using concealed randomization, stratified with respect to sex and stroke laterality. Therapy was given twice a week for 12 weeks. The primary outcome was change in participants' perception of stroke recovery as assessed by the Stroke Impact Scale with an intention-to-treat analysis. Secondary objective outcome measures were changes in balance, gait, grip strength, and cognition. Blinded assessments were performed at baseline, postintervention, and at 3- and 6-month follow-up.

RESULTS: one hundred twenty-three participants were assigned to rhythm-and-music therapy (n=41), horse-riding therapy (n=41), or control (n=41). Post-intervention, the perception of stroke recovery (mean change from baseline on a scale ranging from 1 to 100) was higher among rhythm-and-music therapy (5.2 [95% confidence interval, 0.79-9.61]) and horse-riding therapy participants (9.8 [95% confidence interval, 6.00-13.66]), compared with controls (-0.5 [-3.20 to 2.28]); P=0.001 (1-way ANOVA). The improvements were sustained in both intervention groups 6 months later, and corresponding gains were observed for the secondary outcomes.

CONCLUSIONS: multimodal interventions can improve long-term perception of recovery, as well as balance, gait, grip strength, and working memory in a mixed population of individuals in late phase after stroke.

Comentário: este segundo artigo sobre reabilitação numa fase mais tardia pós-AVC surge na sequência do estudo apresentado anteriormente sobre terapia da fala. Agora focando numa série de intervenções multimodais e analizando a percepção de recuperação na fase pós-AVC e outros outcomes secundários como equilíbrio, marcha e cognição, o estudo mostra que é possível melhorar estes outcomes com este tipo de intervenção mesmo quando aplicados numa fase tardia pós-AVC. De notar que, mais uma vez, o trabalho foi levado a cabo envolvendo uma população diversificada de sobreviventes de AVC entre 50 e 75 anos de idade e com um largo espectro de disfunções cognitivas e físicas, o que alarga a sua potencial aplicabilidade clínica. O grau de recuperação percepcionada pelo próprio é uma medida importante porque pode acomodar e reflectir importantes aspectos ligados à forma como os doentes vivienciam a sua incapacidade. Resultados de ensaios clínicos mostrando melhorias sustentáveis na fase crónica pós-AVC são ainda escassos, mas este trabalho fornece indicações importantes sobre a possibilidade de atingir melhorias significativas mesmo com intervenções aplicadas muito

tempo após a fase aguda ou subaguda do AVC. Estudos futuros poderão ajudar a esclarecer aspectos adicionais como o tipo de intervenção, a dose, o timing e a relação custo-efectividade.

One-Year Risk of Stroke after Transient Ischemic Attack or Minor Stroke

Amarenco P, Lavallée PC, Labreuche J, for the TIAregistry.org Investigators

N Engl J Med 2016; 374:1533-42

BACKGROUND Previous studies conducted between 1997 and 2003 estimated that the risk of stroke or an acute coronary syndrome was 12 to 20% during the first 3 months after a transient ischemic attack (TIA) or minor stroke. The TIAregistry.org project was designed to describe the contemporary profile, etiologic factors, and outcomes in patients with a TIA or minor ischemic stroke who receive care in health systems that now offer urgent evaluation by stroke specialists.

METHODS We recruited patients who had had a TIA or minor stroke within the previous 7 days. Sites were selected if they had systems dedicated to urgent evaluation of patients with TIA. We estimated the 1-year risk of stroke and of the composite outcome of stroke, an acute coronary syndrome, or death from cardiovascular causes. We also examined the association of the ABCD2 score for the risk of stroke (range, 0 [lowest risk] to 7 [highest risk]), findings on brain imaging, and cause of TIA or minor stroke with the risk of recurrent stroke over a period of 1 year.

RESULTS From 2009 through 2011, we enrolled 4789 patients at 61 sites in 21 countries. A total of 78.4% of the patients were evaluated by stroke specialists within 24 hours after symptom onset. A total of 33.4% of the patients had an acute brain infarction, 23.2% had at least one extracranial or intracranial stenosis of 50% or more, and 10.4% had atrial fibrillation. The Kaplan–Meier estimate of the 1-year event rate of the composite cardiovascular outcome was 6.2% (95% confidence interval, 5.5 to 7.0). Kaplan–Meier estimates of the stroke rate at days 2, 7, 30, 90, and 365 were 1.5%, 2.1%, 2.8%, 3.7%, and 5.1%, respectively. In multivariable analyses, multiple infarctions on brain imaging, large-artery atherosclerosis, and an ABCD2 score of 6 or 7 were each associated with more than a doubling of the risk of stroke.

CONCLUSIONS We observed a lower risk of cardiovascular events after TIA than previously reported. The ABCD2 score, findings on brain imaging, and status with respect to large-artery atherosclerosis helped stratify the risk of recurrent stroke within 1 year after a TIA or minor stroke. (Funded by Sanofi and Bristol-Myers Squibb.)

Comentário: neste trabalho os autores reportam um baixo risco de AVC após AIT ou AVC minor em doentes observados de forma urgente em Unidades de AIT especializadas. Os dados foram retirados de um grande registo internacional (TIAregistry.org project), não se tratando de um ensaio randomizado não houve grupo comparativo para avaliar se as Unidades especializadas eram superiores às não especializadas. No entanto o risco de AVC após AIT ou AVC minor foi muito inferior ao esperado, corroborando outros estudos recentes (Early Use of Existing Preventive Strategies for Stroke (EXPRESS) study) com reduções superiores a 50%.

A maioria destes doentes foi observado nas 24h após os primeiros sintomas, em 33% observou-se imagem de enfarte em TAC ou em RM cerebral, em 5% diagnosticou-se FA de novo, 67% dos quais tiveram alta hipocoagulados, em 16% constatou-se estenose carotídea, 27% dos quais foram submetidos a revascularização antes da alta. Portanto o rápido diagnóstico foi determinante na implementação efetiva de tratamentos preventivos baseados na evidência. O estudo demonstrou que a implementação alargada e sistemática de Unidades de AIT especializadas pode fazer a diferença no prognóstico.

Os autores encontraram também outros preditores independentes de risco de AVC para além do ABCD2 score tais como a aterosclerose de grandes artérias e a presença de enfartes cerebrais múltiplos em RM, que poderão ser uteis para inclusão futura em modelos de predição de risco.

Underutilization of Ambulatory ECG Monitoring After Stroke and Transient Ischemic Attack. Missed Opportunities for Atrial Fibrillation Detection

Edwards JD, Kapral MK, Fang J for the Investigators of the Registry of the Canadian Stroke Network

Stroke. 2016; 47:1982-1989.

BACKGROUND AND PURPOSE Detection and treatment of atrial fibrillation is a major goal in secondary stroke prevention. Guidelines recommend at least 24 hours of ECG monitoring after stroke. However, it is unclear how often this is done in routine practice.

METHODS: in this longitudinal cohort study using data from the Ontario Stroke Registry, we analyzed consecutive patients presenting to designated stroke centers in Ontario, Canada (2003–2013) with a first acute ischemic stroke or transiente ischemic attack (TIA) in sinus rhythm and without known atrial fibrillation. The primary outcome was the proportion of patients who received at least 24-hour Holter monitoring within 30 days after stroke/TIA. Secondary analyses assessed total duration of ECG monitoring completed within 90 days after stroke/TIA, temporal trends in monitoring use, and use of Holter monitoring relative to echocardiography.

RESULTS: among 17 398 consecutive eligible patients (mean age 68.8±14.3 years), 30.6% had at least 24 hours of Holter monitoring within 30 days after stroke/TIA. Less than 1% of patients received prolonged monitoring beyond 48 hours. The median time to start monitoring was 9 days poststroke (interquartile range 3–25). Stroke/TIA patients were nearly twice as likely to receive an echocardiogram than a Holter monitor within 90 days (odds ratio 1.8, 95% confidence interval 1.67–2.01).

CONCLUSIONS: less than one third of patients in our cohort received guideline-recommended 24-hour Holter monitoring, and <1% received prolonged ambulatory ECG monitoring. These findings highlight a modifiable evidence-practice gap that likely contributes to an overdiagnosis of strokes as cryptogenic, an underdiagnosis of atrial fibrillation, and missed anticoagulant treatment opportunities for secondary stroke prevention.

Comentário: neste estudo coorte longitudinal os autores analisaram 17 398 doentes com AVC isquémico ou AIT sem FA conhecida entre 2003 e 2013 a partir do Ontario Stroke Registry. Constataram após ajuste para os fatores confundidores que a maioria dos doentes não tinham feito Holter de 24h, e menos de <1% realizaram monitorização prolongada. Os autores concluem que esta subutilização da monitorização eletrocardiográfica contribui para o subdiagnóstico de FA com aumento do pool de AVC criptogénicos.

A FA está na etiologia de 15 a 20% dos AVC isquémicos, aumenta 5 vezes o risco de AVC e duplica o risco de recorrência. A mortalidade do AVC relacionado com FA é de 24% no 1º mês e de 50% no primeiro ano. As guidelines recomendam pelo menos 24h de monitorização após o AVC e nas últimas AHA/ASA guidelines de 2014 foi criada uma nova recomendação Classe IIa, nível de evidência C para os doentes com AVC isquémico agudo ou AIT sem causa aparente, no sentido da monitorização prolongada do ritmo (30 dias) nos primeiros 6 meses após o evento para aumentar a identificação da FA oculta.

Esta recomendação vem na sequência de vários estudos realizados que demonstram que cerca de 10% dos AVC isquémicos agudos ou AIT tem diagnóstico de novo de FA durante a admissão hospitalar e que a monitorização continua durante os primeiros 30 dias leva a um aumento adicional de 11 % no seu diagnóstico. Também a interrogação do pacemaker durante o primeiro ano após AVC identifica cerca de 28% de FA oculta. Atualmente existem um conjunto de aparelhos de alta tecnologia que permitem uma monitorização transdérmica ou subcutânea (implantáveis), pacemaker, cardio-desfibriladores cuja leitura melhora muito o diagnóstico de FA oculta. Claramente monitoriza-se menos que o indicado contudo conforme os autores sugerem neste artigo e no artigo que se segue a monitorização é custo efetiva na prevenção do AVC recorrente.

Potential Cost-Effectiveness of Ambulatory Cardiac Rhythm Monitoring After Cryptogenic Stroke

Yong JHE, Thavorn K, Hoch JS, on behalf of the EMBRACE Steering Committee

Stroke. 2016; 47:2380-2385

BACKGROUND AND PURPOSE Prolonged ambulatory ECG monitoring after cryptogenic stroke improves detection of covert atrial fibrillation, but its long-term cost-effectiveness is uncertain.
METHODS We estimated the cost-effectiveness of noninvasive ECG monitoring in patients aged ≥55 years after a recente cryptogenic stroke and negative 24-hour ECG. A Markov model used observed rates of atrial fibrillation detection and anticoagulation from a randomized controlled trial (EMBRACE) and the published literature to predict lifetime costs and effectiveness (ischemic strokes, hemorrhages, life-years, and quality-adjusted life-years [QALYs]) for 30-day ECG (primary analysis) and 7-day or 14-day ECG (secondary analysis), when compared with a repeat 24-hour ECG.

RESULTS Prolonged ECG monitoring (7, 14, or 30 days) was predicted to prevent more ischemic strokes, decrease mortality, and improve QALYs. If anticoagulation reduced stroke risk by 50%, 30-day ECG (at a cost of USD $447) would be highly cost-effective ($2000 per QALY gained) for patients with a 4.5% annual ischemic stroke recurrence risk. Costeffectiveness was sensitive to stroke recurrence risk and anticoagulant effectiveness, which remain uncertain, especially at higher costs of monitoring. Shorter duration (7 or 14 days) monitoring was cost saving and more effective than an additional 24-hour ECG; its cost-effectiveness was less sensitive to changes in ischemic stroke risk and treatment effect.

CONCLUSIONS After a cryptogenic stroke, 30-day ECG monitoring is likely cost-effective for preventing recurrent strokes; 14-day monitoring is an attractive value alternative, especially for lower risk patients. These results strengthen emerging recommendations for prolonged ECG monitoring in secondary stroke prevention. Cost-effectiveness in practice will depend on careful patient selection.

Clinical Implications and Determinants of Left Atrial Mechanical Dysfunction in Patients with Stroke

Kim D, Shim CY, Hong GR, et al

Stroke. 2016; 47:1444-1451

BACKGROUND AND PURPOSE The evaluation of sources of cardioembolism with transesophageal echocardiography (TEE) in patients with stroke is crucial but semi-invasive. We hypothesized that the size and mechanical function of the left atrium (LA) assessed by transthoracic echocardiography (TTE) could provide useful information on high risk of cardioembolism on TEE in patients with stroke. Furthermore, we sought to define the determinants of LA mechanical dysfunction in these
patients.

METHODS A total of 248 patients with acute ischemic stroke (147 men; 64±13 years) who underwent 2-dimensional and speckle tracking TTE followed by TEE were analyzed.

RESULTS LA appendage emptying velocity, prevalence of LA or LA appendage thrombus, prevalence of aortic plaques, and incidence of embolic stroke showed significant differences among the 4 groups classified according to the median values of the LA volume index and global LA longitudinal strain (LALS). Patients at high risk of cardioembolism evidenced by TEE revealed significantly larger LA volume index and lower global LALS than those without. Global LALS (cutoff, 11.5%; area under the curve, 0.947; sensitivity, 100%; specificity, 91%; P<0.001) revealed a significantly better diagnostic power (P=0.04) for LA or LA appendage thrombus than LA volume index (cutoff, 36.2 mL/m2; área under the curve, 0.823; sensitivity, 88%; specificity, 75%; P=0.002). Age, left ventricular systolic function, LA volume index, and pulse wave velocity were independent determinants for global LALS.

CONCLUSIONS LA mechanical dysfunction is closely associated with high risks of cardioembolism. Global LALS assessed by speckle tracking TTE well discriminates the presence of LA or LA appendage thrombus on TEE in patients with acute ischemic stroke.

Atrial Fibrillation and Mechanisms of Stroke. Time for a New Model

Kamel H, Okin PM, Elkind MSV, Iadecola C

Stroke. 2016;47:895-900

Comentário: esta publicação levanta uma questão muito atual sobre a fibrilação auricular (FA) e os mecanismos do AVC, muito bem exposta no artigo de opinião referenciado. Tempo para um novo modelo etiopatogénico da FA?

Apesar da importância da FA pela sua forte associação ao AVC isquémico, não se têm feito grandes avanços na compreensão dos mecanismos dessa relação. Trabalhos recentes sugerem que a patogénese do AVC na FA envolve outros fatores para além da disritmia. Intuitivamente a atividade dos miócitos descoordenados explicam a alteração da contração auricular, a estase e o aumento do risco tromboembólico. Contudo como explicar que um mesmo episódio de FA esteja associado a um maior risco de AVC no idoso comparativamente com o indivíduo jovem. E como explicar os resultados de várias meta-análises de ensaios randomizados demonstrando que o controle de ritmo não diminui o risco de AVC. Colocam-se outras hipóteses tais como a do próprio AVC na patogénese da FA, através do atingimento do sistema nervoso autónomo e da ativação de ruma resposta inflamatória sistémica o que explicaria as FA de novo pós AVC sem dilatação auricular. A FA como um marcador de outras anomalias auriculares (disfunção endotelial, fibrose, alteração da função do miócito, dilatação da aurícula esquerda (AE), disfunção do apêndice auricular) que por si só podem ser causa de AVC e sendo assim podem ser causa de AVC mesmo na ausência de FA, constituindo marcadores de risco de cardio-embolismo auricular. É assim proposto um novo modelo para os mecanismos de AVC na FA colocando a par com a alteração de ritmo o substrato sistémico e a cardiopatia auricular como causa do AVC tromboembólico explicando assim os AVC criptogénicos suspeitos de cardioembolismo sem documentação de FA.

Clinical and Procedural Predictors of Outcomes from the Endovascular Treatment of Posterior Circulation Strokes

Mokin M, Sonig A, Sivakanthan S et al

Stroke. 2016; 47:782-788

BACKGROUND AND PURPOSE Patients with posterior circulation strokes have been excluded from recent randomized endovascular stroke trials. We reviewed the recent multicenter experience with endovascular treatment of posterior circulation strokes to identify the clinical, radiographic, and procedural predictors of successful recanalization and good neurological outcomes.

METHODS We performed a multicenter retrospective analysis of consecutive patients with posterior circulation strokes, who underwent thrombectomy with stent retrievers or primary aspiration thrombectomy (including A Direct Aspiration First Pass Technique [ADAPT] approach). We correlated clinical and radiographic outcomes with demographic, clinical, and technical characteristics.

RESULTS A total of 100 patients were included in the final analysis (mean age, 63.5±14.2 years; mean admission National Institutes of Health Stroke Scale score, 19.2±8.2). Favorable clinical outcome at 3 months (modified Rankin Scale score ≤2) was achieved in 35% of patients. Successful recanalization and shorter time from stroke onset to the start of the procedure were significant predictors of favorable clinical outcome at 90 days. Stent retriever and aspiration
thrombectomy as primary treatment approaches showed comparable procedural and clinical outcomes. None of the baseline advanced imaging modalities (magnetic resonance imaging, computed tomographic perfusion, or computed tomography angiography assessment of collaterals) showed superiority in selecting patients for thrombectomy.

CONCLUSIONS Time to the start of the procedure is an important predictor of clinical success after thrombectomy in patients with posterior circulation strokes. Both stent retriever and aspiration thrombectomy as primary treatment approaches are effective in achieving successful recanalization.

Comentário: cCinco estudos (MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND-IA, REVASCAT) revolucionaram a abordagem e o prognóstico do AVC agudo grave por oclusão proximal de grandes vasos ao demonstrarem a superioridade da intervenção endovascular no seu tratamento. No entanto estes estudos incluíram apenas doentes com AVC da circulação anterior não contemplando os AVC da circulação posterior. Neste grupo específico de doentes os predictores de prognóstico não estão tão bem compreendidos como na circulação anterior. Isto refletiu-se na recente atualização das guidelines da American Heart Association/American Stroke Association para a intervenção endovascular. No que diz respeito aos AVC agudos por oclusão de grandes vasos da circulação posterior a trombectomia pode ser razoável em doentes cuidadosamente selecionados quando iniciada nas primeiras 6 h (classe IIb, nível de evidência C)

Em suma há poucos dados disponíveis para guiar a terapeutica endovascular nos AVC agudos da circulação posterior. Esta análise multicêntrica retrospectiva vem acrescentar informação baseada na evidência sobre a abordagem endovascular num tipo de AVC potencialmente devastador. Os autores analisaram dados referentes a 100 doentes submetidos a trombectomia por oclusões da artéria basilar, da artéria cerebral posterior ou do segmento V4 da artéria vertebral. A análise centrou-se em preditores de prognóstico. Em análise multivariada os predictores de prognóstico favorável aos 90 dias foram a realização da trombectomia nas primeiras 6 horas (P=0.011) e a recanalização dentro de 6 h (P=0.0039) independentemente da trombectomia ter sido efetuada por stent retriever ou por aspiração. 35% dos doentes tiveram prognostico favorável aos 90 dias (escala de Rankin modificada ≤2)

Estes dados importantes indicam que a trombectomia precoce (<6h) para os AVC da circulação posterior melhora o prognóstico clínico.

Long-Term Results of Stenting versus Endarterectomy for Carotid-Artery Stenosis

Brott TG, Howard G, Roubin GS, for the CREST Investigators

N Engl J Med 2016; 374:1021-31

BACKGROUND In the Carotid Revascularization Endarterectomy versus Stenting Trial, we found no significant difference between the stenting group and the endarterectomy group with respect to the primary composite end point of stroke, myocardial infarction, or death during the periprocedural period or any subsequent ipsilateral stroke during 4 years of follow-up. We now extend the results to 10 years.

METHODS Among patients with carotid-artery stenosis who had been randomly assigned to stenting or endarterectomy, we evaluated outcomes every 6 months for up to 10 years at 117 centers. In addition to assessing the primary composite end point, we assessed the primary end point for the long-term extension study, which was ipsilateral stroke after the periprocedural period.

RESULTS Among 2502 patients, there was no significant difference in the rate of the primary composite end point between the stenting group (11.8%; 95% confidence interval [CI], 9.1 to 14.8) and the endarterectomy group (9.9%; 95% CI, 7.9 to 12.2) over 10 years of follow-up (hazard ratio, 1.10; 95% CI, 0.83 to 1.44). With respect to the primary long-term end point, postprocedural ipsilateral stroke over the 10-year follow-up occurred in 6.9% (95% CI, 4.4 to 9.7) of the patients in the stenting group and in 5.6% (95% CI, 3.7 to 7.6) of those in the endarterectomy group; the rates did not differ significantly between the groups (hazard ratio, 0.99; 95% CI, 0.64

to 1.52). No significant between-group differences with respect to either end point were detected when symptomatic patients and asymptomatic patients were analyzed separately.

CONCLUSIONS Over 10 years of follow-up, we did not find a significant difference between patients who underwent stenting and those who underwent endarterectomy with respect to the risk of periprocedural stroke, myocardial infarction, or death and subsequente ipsilateral stroke. The rate of postprocedural ipsilateral stroke also did not differ between groups. (Funded by the National Institutes of Health and Abbott Vascular Solutions; CREST ClinicalTrials.govnumber, NCT00004732.)

Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis

Rosenfield K, Matsumura JS, Chaturvedi S, for the ACT I Investigators

N Engl J Med 2016; 374:1011-20

BACKGROUND Previous clinical trials have suggested that carotid-artery stenting with a device to capture and remove emboli ("embolic protection") is an effective alternative to carotid endarterectomy in patients at average or high risk for surgical complications.

METHODS In this trial, we compared carotid-artery stenting with embolic protection and carotid endarterectomy in patients 79 years of age or younger who had severe carotid stenosis and were asymptomatic (i.e., had not had a stroke, transient ischemic attack, or amaurosis fugax in the 180 days before enrollment) and were not considered to be at high risk for surgical complications. The trial was designed to enroll 1658 patients but was halted early, after 1453 patients underwent randomization, because of slow enrollment. Patients were followed for up to 5 years. The primary composite end point of death, stroke, or myocardial infarction within 30 days after the procedure or ipsilateral stroke within 1 year was tested at a noninferiority margin of 3 percentage points.

RESULTS Stenting was noninferior to endarterectomy with regard to the primary composite end point (event rate, 3.8% and 3.4%, respectively; P = 0.01 for noninferiority). The rate of stroke or death within 30 days was 2.9% in the stenting group and 1.7% in the endarterectomy group (P = 0.33). From 30 days to 5 years after the procedure, the rate of freedom from ipsilateral stroke was 97.8% in the stenting group and 97.3% in the endarterectomy group (P = 0.51), and the overall survival rates were 87.1% and 89.4%, respectively (P = 0.21). The cumulative 5-year rate of stroke-free survival was 93.1% in the stenting group and 94.7% in the endarterectomy group (P = 0.44).

CONCLUSIONS In this trial involving asymptomatic patients with severe carotid stenosis who were not at high risk for surgical complications, stenting was noninferior to endarterectomy with regard to the rate of the primary composite end point at 1 year. In analyses that included up to 5 years of follow-up, there were no significant

differences between the study groups in the rates of non–procedure-related stroke, all stroke, and survival. (Funded by Abbott Vascular; ACT I ClinicalTrials.gov number, NCT00106938.)

Comentário: estes dois grandes ensaios clínicos randomizados (CREST e ACT1) compararam o prognóstico a curto e a longo prazo da endarterectomia carotídea versus stenting carotídeo e trazem-nos dados importantes. Ambos os estudos demonstraram em consonância com estudos multicêntricos anteriores que após o período perioperatório não há diferenças significativas na taxa de AVC tardio ipsilateral após endarterectomia ou stenting. No entanto a generalização dos resultados de ensaios randomizados para a prática clínica e a questão de como melhor tratar o doente assintomático são dois pontos totalmente em aberto.

A seleção dos melhores especialistas na cirurgia e nas técnicas, comprovada pela baixa mortalidade e pelo baixo número de AVC periprocedimento nos ensaios CREST e ACT1, levanta a questão da legitimidade da extrapolação destes resultados para a prática clínica de rotina especialmente nos doentes assintomáticos. Para além disso a eficácia atual da terapêutica médica ótima impõe um esmagamento no limite para o risco da intervenção cirúrgica ou endovascular.

Será importante em futuros ensaios a inclusão de um braço com a melhor terapêutica médica tendo em conta os resultados das últimas décadas sugerindo redução das taxas de AVC com a terapêutica médica ótima independentemente da gravidade da estenose e para valores semelhantes aos conseguidos com endarterectomia ou stenting no CREST e ACT1. O ensaio em curso CREST-2 que inclui um braço com terapêutica médica poderá clarificar estas questões.

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Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke. A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association

Demaerschalk BM, Kleindorfer DO, Adeoye OM, on behalf of the American Heart Association Stroke Council and Council on Epidemiology and Prevention

Stroke. 2016; 47:581-641

PURPOSE To critically review and evaluate the science behind individual eligibility criteria (indication/inclusion and contraindications/exclusion criteria) for intravenous recombinant tissue-type plasminogen activator (alteplase) treatment in acute ischemic stroke. This will allow us to better inform stroke providers of quantitative and qualitative risks associated with alteplase administration under selected commonly and uncommonly encountered clinical circumstances and to identify future research priorities concerning these eligibility criteria, which could potentially expand the safe and judicious use of alteplase and improve outcomes after stroke.

METHODS Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and the American Heart Association's Manuscript Oversight Committee. The writers used systematic literature reviews, references to published clinical and epidemiology studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge and, when appropriate, formulated recommendations using standard American Heart Association criteria. All members of the writing group had the opportunity to comment on and approved the final version of this document. The document underwent extensive American Heart Association internal peer review, Stroke Council Leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the American Heart Association Science Advisory and Coordinating Committee.

RESULTS After a review of the current literature, it was clearly evident that the levels of evidence supporting individual exclusion criteria for intravenous alteplase vary widely. Several exclusionary criteria have already undergone extensive scientific study such as the clear benefit of alteplase treatment in elderly stroke patients, those with severe stroke, those with diabetes mellitus and hyperglycemia, and those with minor early ischemic changes evident on computed tomography. Some exclusions such as recent intracranial surgery are likely based on common sense and sound judgment and are unlikely to ever be subjected to a randomized, clinical trial to evaluate safety. Most other contraindications or warnings range somewhere in between. However, the differential impact of each exclusion criterion varies not only with the evidence base behind it but also with the frequency of the exclusion within the stroke population, the probability of coexistence of multiple exclusion factors in a single patient, and the variation in practice among treating clinicians.

European recommendations on organisation of interventional care in acute stroke (EROICAS)

Fiehler J, Cognard C, Gallitelli M et al

European Stroke Journal 2016, Vol. 1(3) 155–170

Five recently published randomized controlled trials (RCTs) and respective meta-analyses provide strong evidence that endovascular thrombectomy (EVT) combined with best medical treatment (BMT), including intravenous (IV) tissue plasminogen activator (IV thrombolysis, IVT) for eligible patients, improves the outcomes of appropriately selected patients with acute ischemic stroke in the setting of proximal occlusions in the carotid circulation (large vessel occlusion, LVO).

Four out of the five studies were stopped early after a first RCT1 showed the superiority of EVT combined with medical management over medical management alone. Such premature trial termination will on average lead to overestimation of the treatment effect.13 Nonetheless, since all five RCTs showed consistent benefit of EVT over optimal medical management alone, and a dose–effect relation (reperfusion rates vs. clinical outcome), the benefit of EVT is considered established.

After the publication of the "Consensus statement by ESO-Karolinska Stroke Update" as timely response to the new evidence, the purpose of EROICAS is to provide recommendations based on a structured collaborative process conducted by six relevant European professional societies.

Guidelines for Adult Stroke Rehabilitation and Recovery. A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association *Endorsed by the American Academy of Physical Medicine and Rehabilitation and the American Society of Neurorehabilitation*

Winstein CJ, Stein J, Arena R, on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research

Stroke. 2016 Jun;47(6): e98-e169

PURPOSE The aim of this guideline is to provide a synopsis of best clinical practices in the rehabilitative care of adults recovering from stroke.

RESULTS Stroke rehabilitation requires a sustained and coordinated effort from a large team, including the patient and his or her goals, family and friends, other caregivers (eg, personal care attendants), physicians, nurses, physical and occupational therapists, speech-language pathologists, recreation therapists, psychologists, nutritionists, social workers, and others. Communication and coordination among these team members are paramount in maximizing the effectiveness and efficiency of rehabilitation and underlie this entire guideline. Without communication and coordination, isolated efforts to rehabilitate the stroke survivor are unlikely to achieve their full potential.

RV Cardiopatia Isquémica 2016/17

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O maior avanço das últimas décadas da medicina cardiovascular foi a reversão da epidemia da doença das coronárias que teve início após a segunda guerra mundial. Nos últimos 40 anos a mortalidade por enfarte agudo do miocárdio reduziu em mais de 50%. O aumento geral da esperança de vida deve-se em larga medida a esta diminuição da mortalidade cardiovascular. A prevenção da cardiopatia isquémica envolveu em primeiro lugar alterações do estilo de vida com uma dieta e actividade física equilibrada e a evicção do tabaco. Infelizmente o aumento da incidência de obesidade e diabetes tipo 2 nos últimos anos tem contrariado de alguma forma os ganhos dos anos 80 e 90. A prevenção cardiovascular tem-se baseado na melhor compreensão da patogénese, epidemiologia e bom controlo dos factores de risco cardiovascular.

A mortalidade por doença das coronárias tem tido uma diminuição consistente nas últimas décadas em Portugal e pela primeira vez foi registado um valor inferior a 30% das doenças do aparelho circulatório (que inclui o acidente vascular cerebral). A taxa de mortalidade por doenças cerebrovasculares tem sido sempre superior à das doenças isquémicas do coração (incluindo o enfarte agudo do miocárdio), característica muito peculiar do nosso país no contexto europeu por razões que não estão completamente explicadas. Nesta circunstância tem particular relevância, no que diz respeito à cardiopatia isquémica, o bom controlo dos factores de risco cardiovascular, mas também a prevenção secundária e as intervenções terciárias, nomeadamente as Unidades de Intervenção Percutânea no Enfarte Agudo do Miocárdio e a cirurgia de revascularização.

Alguns dos estudos interessantes neste contexto referem-se à avaliação mais fina do risco nos doentes com doença coronária, com novas ferramentas de cálculo de risco, novas modalidades de imagem para a avaliação anatómica e funcional da circulação coronária, ensaios e meta-análises de apoio à decisão da terapêutica e sua intensidade na prevenção secundária e a actualização das recomendações para a utilização e duração da terapêutica antiplaquetária nos doentes a quem foram colocados stents. Ao nível do doente individual o futuro passa pela investigação epidemiológica que ajude a explicar as interacções entre genoma e ambiente de forma a identificar novos alvos para uma estratégia de prevenção primária e secundária mais personalizadas.

Digital Mammography and Screening for Coronary Artery Disease

Margolies L, Salvatore M, Hecht HS, et al

JACC Cardiovasc Imaging. 2016 Apr; 9(4):350-60

Objectives This study sought to determine if breast arterial calcification (BAC) on digital mammography predicts coronary artery calcification (CAC).

Background BAC is frequently noted but the quantitative relationships to CAC and risk factors are unknown.

Methods A total of 292 women with digital mammography and nongated computed tomography was evaluated. BAC was quantitatively evaluated (0 to 12) and CAC was measured on computed tomography using a 0 to 12 score; they were correlated with each other and the Framingham Risk Score (FRS) and the 2013 Cholesterol Guidelines Pooled Cohort Equations (PCE).

Results BAC was noted in 42.5% and was associated with increasing age ($p < 0.0001$), hypertension ($p = 0.0007$), and chronic kidney disease ($p < 0.0001$). The sensitivity, specificity, positive and negative predictive values, and accuracy of BAC >0 for CAC >0 were 63%, 76%, 70%, 69%, and 70%, respectively. All BAC variables were predictive of the CAC score ($p < 0.0001$). The multivariable odds ratio for CAC >0 was 3.2 for BAC 4 to 12, 2.0 for age, and 2.2 for hypertension. The agreements of FRS risk categories with CAC and BAC risk categories were 57% for CAC and 55% for BAC; the agreement was 47% for PCE risk categories for CAC and 54% by BAC. BAC >0 had area under the curve of 0.73 for identification of women with CAC >0, equivalent to both FRS (0.72) and PCE (0.71). BAC >0 increased the area under the curve curves for FRS (0.72 to 0.77; $p = 0.15$) and PCE (0.71 to 0.76; $p = 0.11$) for the identification of high-risk (4 to 12) CAC. With the inclusion of 33 women with established CAD, BAC >0 was significantly additive to both FRS ($p = 0.02$) and PCE ($p = 0.04$) for high-risk CAC.

Conclusions There is a strong quantitative association of BAC with CAC. BAC is superior to standard cardiovascular risk factors. BAC is equivalent to both the FRS and PCE for the identification of high-risk women and is additive when women with established CAD are included

Comentário: a detecção de calcificação arterial mamária evidenciada na mamografia poderá vir a ser uma estratégia de baixo custo para a avaliação do risco coronário. Houve uma elevada correlação entre a calcificação arterial detectada por mamografia e a calcificação coronária quantificada pelo score de cálcio por TAC. Além disso, houve uma comparação favorável com os factores de risco tradicionais. Será uma forma de conseguir mais informação de um exame amplamente utilizado, de forma a avaliar o risco cardiovascular nas mulheres .

Evaluation of computed tomography in patients with atypical angina or chest pain clinically referred for invasive coronary angiography: randomised controlled trial

Dewey M, Rief M, Martus P et al

BMJ 2016; 355: i5441

Objective: to evaluate whether invasive coronary angiography or computed tomography (CT) should be performed in patients clinically referred for coronary angiography with an intermediate probability of coronary artery disease. Design: prospective randomised single centre trial.

Setting: University hospital in Germany. Participants 340 patients with suspected coronary artery disease and a clinical indication for coronary angiography on the basis of atypical angina or chest pain. Interventions: 168 patients were randomised to CT and 172 to coronary angiography. After randomization one patient declined CT and 10 patients declined coronary angiography, leaving 167 patients (88 women) and 162 patients (78 women) for analysis. Allocation could not be blinded, but blinded independent investigators assessed outcomes. Main outcome measure The primary outcome measure was major procedural complications within 48 hours of the last procedure related to CT or angiography.

Results: cardiac CT reduced the need for coronary angiography from 100% to 14% (95% confidence interval 9% to 20%, P<0.001) and was associated with a significantly greater diagnostic yield from coronary angiography: 75% (53% to 90%) v 15% (10% to 22%), P<0.001. Major procedural complications were uncommon (0.3%) and similar across groups. Minor procedural complications were less common in the CT group than in the coronary angiography group: 3.6% (1% to 8%) v 10.5% (6% to 16%), P=0.014. CT shortened the median length of stay in the angiography group from 52.9 hours (interquartile range 49.5-76.4 hours) to 30.0 hours (3.5-77.3 hours, P<0.001). Overall median exposure to radiation was similar between the CT and angiography groups: 5.0 mSv (interquartile range 4.2-8.7 mSv) v 6.4 mSv (3.4-10.7 mSv), P=0.45. After a median follow-up of 3.3 years, major adverse cardiovascular events had occurred in seven of 167 patients in the CT group (4.2%) and six of 162 (3.7%) in the coronary angiography group (adjusted hazard ratio 0.90, 95% confidence interval 0.30 to 2.69, P=0.86). 79% of patients stated that they would prefer CT for subsequent testing. The study was conducted at a University hospital in Germany and thus the performance of CT may be different in routine clinical practice. The prevalence was lower than expected, resulting in an underpowered study for the predefined primary outcome .

Conclusions: CT increased the diagnostic yield and was a safe gatekeeper for coronary angiography with no increase in long term events. The length of stay was shortened by 22.9 hours with CT, and patients preferred non-invasive testing.

Comentário: este estudo sugere que, em doentes com risco intermédio (probabilidade pré-teste de doença coronária de cerca de 35%) a angiografia coronária por TAC consegue que a utilização de coronariografia seja menos necessária, sem excesso de risco de eventos cardiovasculares adversos. É importante salientar que os doentes foram excluídos do estudo se fossem considerados de alto risco (sinais de enfarte do miocárdio ou

múltiplos testes positivos para isquemia). Também foram excluídos participantes com arritmias ou incapacidade de suster a respiração para a realização de TAC ou doentes em diálise.

Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years with Incident Coronary Heart Disease and Death

Carr JJ, Jacobs Jr DR, Terry JG, for the CARDIA Study

***JAMA Cardiol.* 2017;2(4):391-399.**

Importance: Coronary artery calcium (CAC) is associated with coronary heart disease (CHD) and cardiovascular disease (CVD); however, prognostic data on CAC are limited in younger adults.

Objective: To determine if CAC in adults aged 32 to 46 years is associated with incident clinical CHD, CVD, and all-cause mortality during 12.5 years of follow-up.

Design, Setting, and Participants: The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a prospective community-based study that recruited 5115 black and white participants aged 18 to 30 years from March 25, 1985, to June 7, 1986. The cohort has been under surveillance for 30 years, with CAC measured 15 (n = 3043), 20 (n = 3141), and 25 (n = 3189) years after recruitment. The mean follow-up period for incident events was 12.5 years, from the year 15 computed tomographic scan through August 31, 2014.

Main Outcomes and Measures: Incident CHD included fatal or nonfatal myocardial infarction, acute coronary syndrome without myocardial infarction, coronary revascularization, or CHD death. Incident CVD included CHD, stroke, heart failure, and peripheral arterial disease. Death included all causes. The probability of developing CAC by age 32 to 56 years was estimated using clinical risk factors measured 7 years apart between ages 18 and 38 years.

Results: At year 15 of the study among 3043 participants (mean [SD] age, 40.3 [3.6] years; 1383 men and 1660 women), 309 individuals (10.2%) had CAC, with a geometric mean Agatston score of 21.6 (interquartile range, 17.3-26.8). Participants were followed up for 12.5 years, with 57 incident CHD events and 108 incident CVD events observed. After adjusting for demographics, risk factors, and treatments, those with any CAC experienced a 5-fold increase in CHD events (hazard ratio [HR], 5.0; 95% CI, 2.8-8.7) and 3-fold increase in CVD events (HR, 3.0; 95% CI, 1.9-4.7). Within CAC score strata of 1-19, 20-99, and 100 or more, the HRs for CHD were 2.6 (95% CI, 1.0-5.7), 5.8 (95% CI, 2.6-12.1), and 9.8 (95% CI, 4.5-20.5), respectively. A CAC score of 100 or more had an incidence of 22.4 deaths per 100 participants (HR, 3.7; 95% CI, 1.5-10.0); of the 13 deaths in participants with a CAC score of 100 or more, 10 were adjudicated as CHD events. Risk factors for CVD in early adult life identified those above the median risk for developing CAC and, if applied, in a selective CAC screening strategy could reduce the number of people screened for CAC by 50% and the number imaged needed to find 1 person with CAC from 3.5 to 2.2.

Conclusions and Relevance: The presence of CAC among individuals aged between 32 and 46 years was associated with increased risk of fatal and nonfatal CHD during 12.5 years of follow-up. A CAC score of 100 or more was associated with early death. Adults younger than 50 years with any CAC, even with very low scores, identified on a computed tomographic scan are at elevated risk of clinical CHD, CVD, and death. Selective use of screening for CAC might be considered in individuals with risk factors in early adulthood to inform discussions about primary prevention.

Comentário: mais um estudo que realça o papel do score de cálcio na avaliação do risco cardiovascular. Esta ferramenta é importante para definir com acuidade o risco naqueles considerados de risco intermédio.

Development and Validation of a Protein-Based Risk Score for Cardiovascular Outcomes Among Patients With Stable Coronary Heart Disease

Ganz P, Heidecker B, Hveem K, et al

JAMA. 2016 Jun 21;315(23):2532-41.

IMPORTANCE: precise stratification of cardiovascular risk in patients with coronary heart disease (CHD) is needed to inform treatment decisions.

OBJECTIVE: to derive and validate a score to predict risk of cardiovascular outcomes among patients with CHD, using large-scale analysis of circulating proteins.

DESIGN, SETTING, AND PARTICIPANTS: prospective cohort study of participants with stable CHD. For the derivation cohort (Heart and Soul study), outpatients from San Francisco were enrolled from 2000 through 2002 and followed up through November 2011 (≤ 11.1 years). For the validation cohort (HUNT3, a Norwegian population-based study), participants were enrolled from 2006 through 2008 and followed up through April 2012 (5.6 years).

EXPOSURES: Using modified aptamers, 1130 proteins were measured in plasma samples.

MAIN OUTCOMES AND MEASURES: a 9-protein risk score was derived and validated for 4-year probability of myocardial infarction, stroke, heart failure, and all-cause death. Tests, including the C statistic, were used to assess performance of the 9-protein risk score, which was compared with the Framingham secondary event model, refit to the cohorts in this study. Within-person change in the 9-protein risk score was evaluated in the Heart and Soul study from paired samples collected 4.8 years apart.

RESULTS: from the derivation cohort, 938 samples were analyzed, participants' median age at enrollment was 67.0 years, and 82% were men. From the validation cohort, 971 samples were analyzed, participants' median age at enrollment was 70.2 years, and 72% were men. In the derivation cohort, C statistics were 0.66 for refit Framingham, 0.74 for 9-protein, and 0.75 for refit Framingham plus 9-protein models. In the validation cohort, C statistics were 0.64 for refit Framingham, 0.70 for 9-protein, and 0.71 for refit Framingham plus 9-protein models. Adding the 9-protein risk score to the refit Framingham model increased the C statistic by 0.09 (95% CI, 0.06-0.12) in the derivation cohort, and in the validation cohort, the C statistic was increased by 0.05 (95% CI, 0.02-0.09). Compared with the refit Framingham model, the integrated discrimination index for the 9-protein model was 0.12 (95% CI, 0.08-0.16) in the derivation cohort and 0.08 (95% CI, 0.05-0.10) in the validation cohort. In analysis of paired samples among 139 participants with cardiovascular events after the second sample, absolute within-person annualized risk increased more for the 9-protein model (median, 1.86% [95% CI, 1.15%-2.54%]) than for the refit Framingham model (median, 1.00% [95% CI, 0.87%-1.19%]) (P = .002), while among 375 participants without cardiovascular events, both scores changed less and similarly (P = .30).

CONCLUSIONS AND RELEVANCE: among patients with stable CHD, a risk score based on 9 proteins performed better than the refit Framingham secondary event risk score in predicting cardiovascular events, but still provided only modest discriminative accuracy. Further research is needed to assess whether the score is more accurate in a lower-risk population.

Comentário: este estudo mostrou superioridade de previsão de risco com a utilização de um score de risco baseado na proteómica, quando comparado com o score de Framingham em doentes com doença coronária estável. A utilização das duas ferramentas adicionava pouco mais poder de previsão. Como o score baseado nas nove proteínas não está disponível para uso generalizado, teremos de continuar a usar as ferramentas disponíveis. No entanto temos de estar cientes de que o futuro passará pela avaliação do risco utilizando a proteómica e a genómica.

Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial

Mäkikallio T, Holm NR, Lindsay M, Spence MS for the NOBLE study investigators

Lancet 2016;388 (10061):2743-2752.

Background: coronary artery bypass grafting (CABG) is the standard treatment for revascularisation in patients with left main coronary artery disease, but use of percutaneous coronary intervention (PCI) for this indication is increasing. We aimed to compare PCI and CABG for treatment of left main coronary artery disease.

Methods: in this prospective, randomised, open-label, non-inferiority trial, patients with left main coronary artery disease were enrolled in 36 centres in northern Europe and randomised 1:1 to treatment with PCI or CABG. Eligible patients had stable angina pectoris, unstable angina pectoris, or non-ST-elevation myocardial infarction. Exclusion criteria were ST-elevation myocardial infarction within 24 h, being considered too high risk for CABG or PCI, or expected survival of less than 1 year. The primary endpoint was major adverse cardiac or cerebrovascular events (MACCE), a composite of all-cause mortality, non-procedural myocardial infarction, any repeat coronary revascularisation, and stroke. Non-inferiority of PCI to CABG required the lower end of the 95% CI not to exceed a hazard ratio (HR) of 1·35 after up to 5 years of follow-up. The intention-to-treat principle was used in the analysis if not specified otherwise. This trial is registered with ClinicalTrials.gov identifier, number NCT01496651.

Findings: between Dec 9, 2008, and Jan 21, 2015, 1201 patients were randomly assigned, 598 to PCI and 603 to CABG, and 592 in each group entered analysis by intention to treat. Kaplan-Meier 5 year estimates of MACCE were 29% for PCI (121 events) and 19% for CABG (81 events), HR 1·48 (95% CI 1·11–1·96), exceeding the limit for non-inferiority, and CABG was significantly better than PCI (p=0·0066). As-treated estimates were 28% versus 19% (1·55, 1·18–2·04, p=0·0015). Comparing PCI with CABG, 5 year estimates were 12% versus 9% (1·07, 0·67–1·72, p=0·77) for all-cause mortality, 7% versus 2% (2·88, 1·40–5·90, p=0·0040) for non-procedural myocardial infarction, 16% versus 10% (1·50, 1·04–2·17, p=0·032) for any revascularisation, and 5% versus 2% (2·25, 0·93–5·48, p=0·073) for stroke.

Interpretation: the findings of this study suggest that CABG might be better than PCI for treatment of left main stem coronary artery disease.

Comentário: este grande estudo prospectivo aleatorizado demonstrou de uma forma surpreendente uma superioridade aos cinco anos dos resultados da cirurgia coronária em doentes com doença coronária da coronária esquerda principal. Outros estudos, como o EXCEL (N Engl J Med 2016 Oct 31) mostraram não-inferioridade na colocação de stent. Uma das razões para a diferença de resultados poderá ser a de que no ensaio em apreço todos os tipos de complexidade anatómica puderam ser incluídos. A opinião geral, em face destes resultados contraditórios, é que se irá manter a tendência para o aumento do uso da angioplastia percutânea para a revascularização da coronária esquerda. De salientar que as guidelines europeias e americanas recomendam que a maioria destes doentes sejam sujeitos a cirurgia . A utilização da angioplastia percutânea será aceitável nos doentes com doença coronária de complexidade anatómica baixa ou intermédia.

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial.

Al-Lamee R, Thompson D, Dehbi HM, for the ORBITA investigators.

Lancet. 2018; 391(10115):31-40. Epub 2017 Nov 2

Background: Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.

Methods: ORBITA is a blinded, multicentre randomised trial of PCI versus a placebo procedure for angina relief that was done at five study sites in the UK. We enrolled patients with severe (≥70%) single-vessel stenoses. After enrolment, patients received 6 weeks of medication optimisation. Patients then had pre-randomisation assessments with cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography. Patients were randomised 1:1 to undergo PCI or a placebo procedure by use of an automated online randomisation tool. After 6 weeks of follow-up, the assessments done before randomisation were repeated at the final assessment. The primary endpoint was difference in exercise time increment between groups. All analyses were based on the intention-to-treat principle and the study population contained all participants who underwent randomisation.

Findings: ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase and between Jan 6, 2014, and Aug 11, 2017, 200 patients underwent randomisation, with 105 patients assigned PCI and 95 assigned the placebo procedure. Lesions had mean area stenosis of 84·4% (SD 10·2), fractional flow reserve of 0·69 (0·16), and instantaneous wave-free ratio of 0·76 (0·22). There was no significant difference in the primary endpoint of exercise time increment between groups (PCI minus placebo 16·6 s, 95% CI −8·9 to 42·0, p=0·200). There were no deaths. Serious adverse events included four pressure-wire related complications in the placebo group, which required PCI, and five major bleeding events, including two in the PCI group and three in the placebo group.

Interpretation: In patients with medically treated angina and severe coronary stenosis, PCI did not increase exercise time by more than the effect of a placebo procedure. The efficacy of invasive procedures can be assessed with a placebo control, as is standard for pharmacotherapy.

Comentário: os resultados surpreendentes deste estudo que mostrou que a intervenção coronária tinha a mesma eficácia que um procedimento-placebo em doentes com angina estável e estenose coronária grave devem ser vistos como realçando a importância da terapêutica médica optimizada que deve continuar a primeira linha do tratamento.

Outcomes after Angiography with Sodium Bicarbonate and Acetylcysteine

Weisbord SD, Gallagher M, Jneid H, for the PRESERVE Trial Group.

N Engl J Med. 2017 Nov 12. doi: 10.1056/NEJMoa1710933

BACKGROUND: Intravenous sodium bicarbonate and oral acetylcysteine are widely used to prevent acute kidney injury and associated adverse outcomes after angiography without definitive evidence of their efficacy.

METHODS: Using a 2-by-2 factorial design, we randomly assigned 5177 patients at high risk for renal complications who were scheduled for angiography to receive intravenous 1.26% sodium bicarbonate or intravenous 0.9% sodium chloride and 5 days of oral acetylcysteine or oral placebo; of these patients, 4993 were included in the modified intention-to-treat analysis. The primary end point was a composite of death, the need for dialysis, or a persistent increase of at least 50% from baseline in the serum creatinine level at 90 days. Contrast-associated acute kidney injury was a secondary end point.

RESULTS: The sponsor stopped the trial after a prespecified interim analysis. There was no interaction between sodium bicarbonate and acetylcysteine with respect to the primary end point (P=0.33). The primary end point occurred in 110 of 2511 patients (4.4%) in the sodium bicarbonate group as compared with 116 of 2482 (4.7%) in the sodium chloride group (odds ratio, 0.93; 95% confidence interval [CI], 0.72 to 1.22; P=0.62) and in 114 of 2495 patients (4.6%) in the acetylcysteine group as compared with 112 of 2498 (4.5%) in the placebo group (odds ratio, 1.02; 95% CI, 0.78 to 1.33; P=0.88). There were no significant between-group differences in the rates of contrast-associated acute kidney injury.

CONCLUSIONS: Among patients at high risk for renal complications who were undergoing angiography, there was no benefit of intravenous sodium bicarbonate over intravenous sodium chloride or of oral acetylcysteine over placebo for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of contrast-associated acute kidney injury.

Comentário: este ensaio confirma que o uso de acetilcisteína ou bicarbonato não está associado a maior protecção renal em doentes que vão ser submetidos a coronariografia, e que o uso de soro fisiológico com boa hidratação será suficiente. Vem de encontro a outros resultados que indiciam que o risco de nefrotoxicidade com os novos contrastes utilizados não será tão elevado como se supunha.

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Levine GN, Bates ER, Bittl JA, Brindis RG, et al

J Am Coll Cardiol. 2016; 68(10):1082-115.

Background and Objective: this focused update accounts for 12 new studies on the optimal duration of dual antiplatelet therapy (DAPT) after coronary stenting, particularly later-generation drug-eluting stents (DES). The update affects parts of prior guidelines on percutaneous coronary intervention, coronary artery bypass grafting, stable ischemic heart disease (IHD), ST-segment elevation myocardial infarction (STEMI), non-ST-segment acute coronary syndromes (NSTEACS), and perioperative evaluation for noncardiac surgery. The class (strength) of recommendations is noted below in pertinent places; for levels of evidence, see the complete published update.

Key Points:

1. For most patients with coronary artery disease (CAD), decisions about the duration of DAPT require trade-offs between reduction in ischemic risk and increased bleeding risk. Clinicians should comprehensively assess both the ischemic- and bleeding-risk profiles of each patient, including newly available risk scoring.

2. In patients with stable IHD, DAPT is recommended for 6 to 12 months after DES implantation and ≥1 month after bare-metal stent (BMS) implantation (class I); longer therapy (>12 months) "may be reasonable" (class IIb). In patients with high risk for bleeding or overt bleeding, a shorter DAPT duration (3 months) after DES implantation may be reasonable (class IIb).

3. In ACS (both STEMI and NSTEACS), ≥12 months of DAPT is recommended (class I). Longer therapy may be reasonable (class IIb), particularly if the patient does not have overt bleeding or a high risk for it while on DAPT.

4. Lower-dose aspirin (75–100 mg) should be used in all DAPT regimens.

5. For ACS patients treated with DAPT after stenting, ticagrelor and prasugrel are reasonable $P2Y_{12}$-inhibitor alternatives to clopidogrel (prasugrel only if the patient does not have a history of stroke or high bleeding risk). For medically treated patients, ticagrelor may be preferred to clopidogrel (class IIa).

6. In patients with stable CAD undergoing CABG, it may reasonable to start DAPT soon after surgery and continue it for 12 months to improve vein-graft patency (class IIb).

7. Elective noncardiac surgery should be delayed for 30 days after BMS implantation and, optimally, for 6 months after DES implantation (class I). If the surgery requires discontinuation of the $P2Y_{12}$ inhibitor, aspirin should be continued (class I).

Comentário: as recomendações sobre a duração óptima da antiagregação plaquetária dupla após colocação de stents tem sido variável e inconsistente. Esta actualização tenta uniformizar as várias recomendações e tem em conta os stents de última geração e os vários tipos de doentes. Em geral, as recomendações salientam a segurança de períodos obrigatórios mais curtos de antiagregação dupla e a importância de individualizar os riscos e benefícios tendo em conta os riscos relativos de trombose e hemorragia.

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

Eikelboom JW, Connoly SJ, Bosch J for the COMPASS investigators.

N Engl J Med 2017; 377:1319-133

BACKGROUND: We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS: In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

RESULTS: The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=−4.126), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS: Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events.

Comentário: a aspirina é a base da prevenção secundária da doença cardíaca isquémica. Neste estudo COMPASS com mais de 27000 participantes os investigadores adicionaram o rivaroxabano (2,5 mg bid) à aspirina (100 mg /dia) e compararam com rivaroxabano e aspirina isoladamente. O estudo foi interrompido aos 23 meses pela vantagem verificada com a associação. Quando os eventos hemorrágicos foram incluídos na análise o benefício clínico manteve-se significativo. Este ensaio poderá mudar as recomendações actuais. Seria bem-vinda uma ferramenta de decisão clínica que avaliasse o risco e evento isquémico e o risco hemorrágico destes doentes e que auxiliasse na decisão, assim como um ensaio comparativo entre a associação aspirina com inibidor do factor Xa e a dupla antiagregação plaquetária.

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Cannon CP, Bhatt DL, Oldgren J, for the RE-DUAL PCI Steering Committee and Investigators

N Engl J Med 2017; 377:1513-1524

BACKGROUND: Triple antithrombotic therapy with warfarin plus two antiplatelet agents is the standard of care after percutaneous coronary intervention (PCI) for patients with atrial fibrillation, but this therapy is associated with a high risk of bleeding.

METHODS: In this multicenter trial, we randomly assigned 2725 patients with atrial fibrillation who had undergone PCI to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). Outside the United States, elderly patients (≥80 years of age; ≥70 years of age in Japan) were randomly assigned to the 110-mg dual-therapy group or the triple-therapy group. The primary end point was a major or clinically relevant nonmajor bleeding event during follow-up (mean follow-up, 14 months). The trial also tested for the noninferiority of dual therapy with dabigatran (both doses combined) to triple therapy with warfarin with respect to the incidence of a composite efficacy end point of thromboembolic events (myocardial infarction, stroke, or systemic embolism), death, or unplanned revascularization.

RESULTS: the incidence of the primary end point was 15.4% in the 110-mg dual-therapy group as compared with 26.9% in the triple-therapy group (hazard ratio, 0.52; 95% confidence interval [CI], 0.42 to 0.63; P<0.001 for noninferiority; P<0.001 for superiority) and 20.2% in the 150-mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group, which did not include elderly patients outside the United States (hazard ratio, 0.72; 95% CI, 0.58 to 0.88; P<0.001 for noninferiority). The incidence of the composite efficacy end point was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (hazard

ratio, 1.04; 95% CI, 0.84 to 1.29; P=0.005 for noninferiority). The rate of serious adverse events did not differ significantly among the groups.

CONCLUSIONS: among patients with atrial fibrillation who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with dabigatran and a P2Y12 inhibitor than among those who received triple therapy with warfarin, a P2Y12 inhibitor, and aspirin. Dual therapy was noninferior to triple therapy with respect to the risk of thromboembolic events. (Funded by Boehringer Ingelheim; RE-DUAL PCI ClinicalTrials.gov number, NCT02164864.)

Comentário: até agora os doentes com fibrilhação auricular, a quem era colocado um stent, eram medicados com terapêutica tripla (incluindo aspirina, clopidogrel e um antagonista da vitamina K). Se bem que eficaz na redução de AVC e trombose de stent, essa estratégia contém riscos hemorrágicos bem conhecidos. Este estudo RE-DUAL mostrou menos risco hemorrágico e semelhança nas complicações tromboembólicas, o que aponta para que se opte nesta situação, por uma antigregação dupla ao qual se junta o dabigatrano na presença de fibrilhação auricular não valvular. O estudo PIONEER AF-PCI com rivoraxabano também sugeriu que este outro NOAC poderá ser utilizado como alternativa à varfarina neste contexto.

Risks of Bleeding Recurrence and Cardiovascular Events with Continued Aspirin Use After Lower Gastrointestinal Hemorrhage.

Chan FK, Leung Ki EL, Wong GL, Ching JY, Tse YK, Au KW, Wu JC, Ng SC.

Gastroenterology. 2016 Aug; 151(2):271-7

BACKGROUND & AIMS: it is not clear whether use of low-dose aspirin should be resumed after an episode of lower gastrointestinal (GI) bleeding. We assessed the long-term risks of recurrent lower GI bleeding and serious cardiovascular outcomes after aspirin-associated lower GI bleeding.

METHODS: we performed a retrospective study of patients diagnosed with lower GI bleeding (documented melena or hematochezia and absence of upper GI bleeding) from January 1, 2000 through December 31, 2007 at the Prince of Wales Hospital in Hong Kong. Using the hospital registry, we analyzed data from 295 patients on aspirin and determined their outcomes during a 5-year period. Outcomes included recurrent lower GI bleeding, serious cardiovascular events, and death from other causes, as determined by an independent, blinded adjudication committee. Outcomes were compared between patients assigned to the following groups based on cumulative duration of aspirin use: <20% of the follow-up period (121 nonusers) vs ≥50% of the observation period (174 aspirin users).

RESULTS: within 5 years, lower GI bleeding recurred in 18.9% of aspirin users (95% confidence interval [CI], 13.3%-25.3%) vs 6.9% of nonusers (95% CI, 3.2%-12.5%; P = .007). However, serious cardiovascular events occurred in 22.8% of aspirin users (95% CI, 16.6%-29.6%) vs 36.5% of nonusers (95% CI, 27.4%-45.6%; P = .017), and 8.2% of aspirin users died from other causes (95% CI, 4.6%-13.2%) vs 26.7% of nonusers (95% CI, 18.7%-35.4%; P = .001). Multivariable analysis showed that aspirin use was an independent predictor of rebleeding, but protected against cardiovascular events and death.

CONCLUSIONS: among aspirin users with a history of lower GI bleeding, continuation of aspirin is associated with an increased risk of recurrent lower GI bleeding, but reduced risk of serious cardiovascular events and death.

Comentário: quando temos um doente de elevado risco cardiovascular e que tem uma hemorragia digestiva baixa como devemos proceder? Este mesmo grupo de investigadores mostrou previamente que os doentes de alto risco com hemorragia por úlcera péptica tinham benefício em continuar a aspirina tendo em consideração os respectivos riscos (Ann Intern Med 2010; 152:1). Agora neste estudo retrospectivo chegaram à mesma conclusão para as hemorragias baixas. Uma abordagem cautelosa será sempre a de avaliar o risco/benefício caso a caso, tendo em conta a causa da hemorragia e a sua gravidade.

Low-Dose Aspirin Discontinuation and Risk of Cardiovascular Events. A Swedish Nationwide, Population-Based Cohort Study

Sundström J, Hedberg J, Thuresson M, et al.

Circulation. 2017 Sep 26;136(13):1183-119

Background: There are increasing concerns about risks associated with aspirin discontinuation in the absence of major surgery or bleeding. We investigated whether long-term low-dose aspirin discontinuation and treatment gaps increase the risk of cardiovascular events.

Methods: We performed a cohort study of 601 527 users of low-dose aspirin for primary or secondary prevention in the Swedish prescription register between 2005 and 2009 who were >40 years of age, were free from previous cancer, and had ≥80% adherence during the first observed year of treatment. Cardiovascular events were identified with the Swedish inpatient and cause-of-death registers. The first 3 months after a major bleeding or surgical procedure were excluded from the time at risk.

Results: During a median of 3.0 years of follow-up, 62 690 cardiovascular events occurred. Patients who discontinued aspirin had a higher rate of cardiovascular events than those who continued (multivariable-adjusted hazard ratio, 1.37; 95% confidence interval, 1.34–1.41), corresponding to an additional cardiovascular event observed per year in 1 of every 74 patients who discontinue aspirin. The risk increased shortly after discontinuation and did not appear to diminish over time.

Conclusions: In long-term users, discontinuation of low-dose aspirin in the absence of major surgery or bleeding was associated with a >30% increased risk of cardiovascular events. Adherence to low-dose aspirin treatment in the absence of major surgery or bleeding is likely an important treatment goal.

Comentário: neste estudo observacional, um em cada 74 doentes que interromperam a aspirina sofreram um evento cardiovascular adicional e este risco acrescido notou-se precocemente após a suspensão e não diminuiu com o tempo, reforçando a utilização da aspirina principalmente em prevenção secundária. Esta utilização será para toda a vida nos doentes que toleram o ácido acetilsalicílico.

Association Between Intensity of Statin Therapy and Mortality in Patients with Atherosclerotic Cardiovascular Disease.

Rodriguez, F; Maron DJ , Knowles JW et al

JAMA Cardiol. 2017 Jan 1; 2(1):47-54

Importance: high-intensity statin therapy is recommended for the secondary prevention of atherosclerotic cardiovascular disease (ASCVD). Nevertheless, statin therapy in general, and high-intensity statin therapy in particular, is underused in patients with established ASCVD.

Objective: to determine the association between all-cause mortality and intensity of statin therapy in the Veterans Affairs health care system.

Design, Setting, and Participants: a retrospective cohort analysis was conducted of patients aged 21 to 84 years with ASCVD treated in the Veterans Affairs health care system from April 1, 2013, to April 1, 2014. Patients who were included had 1 or more *International Classification of Diseases, Ninth Revision* codes for ASCVD on 2 or more different dates in the prior 2 years.

Exposures: intensity of statin therapy was defined by the 2013 American College of Cardiology/American Heart Association guidelines, and use was defined as a filled prescription in the prior 6 months. Patients were excluded if they were taking a higher statin dose in the prior 5 years.

Main Outcomes and Measures: the primary outcome was death from all causes adjusted for the propensity to receive high-intensity statins.

Results: the study sample included 509 766 eligible adults with ASCVD at baseline (mean [SD] age, 68.5 [8.8] years; 499 598 men and 10 168 women), including 150 928 (29.6%) receiving high-intensity statin therapy, 232 293 (45.6%) receiving moderate-intensity statin therapy, 33 920 (6.7%) receiving low-intensity statin therapy, and 92 625 (18.2%) receiving no statins. During a mean follow-up of 492 days, there was a graded association between intensity of statin therapy and mortality, with 1-year mortality rates of 4.0% (5103 of 126 139) for those receiving high-intensity statin therapy, 4.8% (9703 of 200 709) for those receiving moderate-intensity statin therapy, 5.7% (1632 of 28 765) for those receiving low-intensity statin therapy, and 6.6% (4868 of 73 728) for those receiving no statin ($P < .001$). After adjusting for the propensity to receive high-intensity statins, the hazard ratio for mortality was 0.91 (95% CI, 0.88-0.93) for those receiving high- vs moderate-intensity statins. The magnitude of benefit of high- vs moderate-intensity statins was similar, for an incident cohort hazard ratio of 0.93 (95% CI, 0.85-1.01). For patients aged 76 to 84 years, the hazard ratio was 0.91 (95% CI, 0.87-0.95). Patients treated with maximal doses of high-intensity statins had lower mortality (hazard ratio, 0.90; 95% CI, 0.87-0.94) compared with those receiving submaximal doses.

Conclusions and Relevance: we found a graded association between intensity of statin therapy and mortality in a national sample of patients with ASCVD. High-intensity statins were associated with a small but significant survival advantage compared with moderate-intensity statins, even among older adults. Maximal doses of high-intensity statins were associated with a further survival benefit.

Comentário: em doentes com doença aterosclerótica, a mortalidade diminuiu à medida que aumentava a dose utilizada de estatina. Esta evidência do mundo real é importante para a escolha da dose de estatinas a usar nesta população de doentes e reforça a utilização de estatinas de elevada intensidade.

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

Ridker, PM, Brendan ME, Thuren, TM, et al.

N Engl J Med 2017; 377:1119-1131

Abstract descrito no capítulo dislipidemias

Comentário: este estudo veio reforçar a prova de conceito do papel da inflamação na aterotrombose, que o seu primeiro autor, Paul Ridker, vem defendendo há décadas. O canakinumab, que inibe a via da imunidade inata da IL-1β, foi moderadamente eficaz na prevenção do enfarte agudo do miocárdio não-fatal. Na minha opinião nunca será uma terapêutica transposta para a clínica dado o aumento de mortalidade por sépsis, além do elevadíssimo custo do tratamento.

Oxygen Therapy in Suspected Acute Myocardial Infarction

Hofmann R , James SK, Jernberg T, et al.

N Engl J Med 2017; 377:1240-1249

BACKGROUND: The clinical effect of routine oxygen therapy in patients with suspected acute myocardial infarction who do not have hypoxemia at baseline is uncertain.

METHODS: In this registry-based randomized clinical trial, we used nationwide Swedish registries for patient enrollment and data collection. Patients with suspected myocardial infarction and an oxygen saturation of 90% or higher were randomly assigned to receive either supplemental oxygen (6 liters per minute for 6 to 12 hours, delivered through an open face mask) or ambient air.

RESULTS: A total of 6629 patients were enrolled. The median duration of oxygen therapy was 11.6 hours, and the median oxygen saturation at the end of the treatment period was 99% among patients assigned to oxygen and 97% among patients assigned to ambient air. Hypoxemia developed in 62 patients (1.9%) in the oxygen group, as compared with 254 patients (7.7%) in the ambient-air group. The median of the highest troponin level during hospitalization was 946.5 ng per liter in the oxygen group and 983.0 ng per liter in the ambient-air group. The primary end point of death from any cause within 1 year after randomization occurred in 5.0% of patients (166 of 3311) assigned to oxygen and in 5.1% of patients (168 of 3318) assigned to ambient air (hazard ratio, 0.97; 95% confidence interval [CI], 0.79 to 1.21; P=0.80). Rehospitalization with myocardial infarction within 1 year occurred in 126 patients (3.8%) assigned to oxygen and in 111 patients (3.3%) assigned to ambient air (hazard ratio, 1.13; 95% CI, 0.88 to 1.46; P=0.33). The results were consistent across all predefined subgroups.

CONCLUSIONS: Routine use of supplemental oxygen in patients with suspected myocardial infarction who did not have hypoxemia was not found to reduce 1-year all-cause mortality.

Comentário: este estudo vem contrariar de forma definitiva a prática clínica habitual de administrar oxigénio em todos os doentes com suspeita de enfarte agudo do miocárdio.

Body-Weight Fluctuations and Outcomes in Coronary Disease

Bangalore S, Fayyad R, Laskey R, et al.

N Engl J Med 2017; 376:1332-1340

BACKGROUND: body-weight fluctuation is a risk factor for death and coronary events in patients without cardiovascular disease. It is not known whether variability in body weight affects outcomes in patients with coronary artery disease.

METHODS: we determined intraindividual fluctuations in body weight from baseline weight and follow-up visits and performed a post hoc analysis of the Treating to New Targets trial, which involved assessment of the efficacy and safety of lowering low-density lipoprotein cholesterol levels with atorvastatin. The primary outcome was any coronary event (a composite of death from coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, revascularization, or angina). Secondary outcomes were any cardiovascular event (a composite of any coronary event, a cerebrovascular event, peripheral vascular disease, or heart failure), death, myo cardial infarction, or stroke.

RESULTS: among 9509 participants, after adjustment for risk factors, baseline lipid levels, mean body weight, and weight change, each increase of 1 SD in body-weight variability (measured according to average successive variability and used as a time-dependent covariate) was associated with an increase in the risk of any coronary event (2091 events; hazard ratio, 1.04; 95% confidence interval [CI], 1.01 to 1.07; P=0.01), any cardiovascular event (2727 events; hazard ratio, 1.04; 95% CI, 1.02 to 1.07; P<0.001), and death (487 events; hazard ratio,1.09; 95% CI, 1.07 to 1.12; P<0.001). Among patients in the quintile with the highest variation in body weight, the risk of a coronary event was 64% higher, the risk of a cardiovascular event 85% higher, death 124% higher, myocardial infarction 117% higher, and stroke 136% higher than it was among those in the quintile with the lowest variation in body weight in adjusted models.

CONCLUSIONS: Among participants with coronary artery disease, fluctuation in body weight was associated with higher mortality and a higher rate of cardiovascular events independent of traditional cardiovascular risk factors.

Comentário: esta análise post hoc chama a atenção para os riscos na flutuação do peso em doentes coronários. A razão para tal ainda não é clara, e pode não haver uma relação de causalidade. Fica a nota de precaução.

RV Insuficiência Cardíaca 2016/17

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Os últimos dois anos (2016/17) serão revistos como anos marcantes no âmbito da Insuficiência Cardíaca (IC). São diversos os factos que contribuem para esta notoriedade. Desde logo foi um período em que foram divulgadas novas recomendações para a abordagem da IC quer pela Sociedade Europeia de Cardiologia quer pelas congéneres Americanas. As novas recomendações encerram em si aspectos relevantes que irão gerar novas perspectivas em diferentes vertentes, desde a categorização de doentes com IC que passa a ser diversa, à recomendação (pela primeira vez) de novos fármacos, quer sejam os antagonistas dos receptores da angiotensina em associação ao inibidor da neprilisina quer seja a ivabradina (no caso das recomendações americanas uma recomendação de novo). Também o uso de dispositivos, nomeadamente de ressincronizarão ventricular é advogado agora nas recomendações em estádios com menos impacto funcional da IC. Embora sem novas recomendações sobre a IC aguda, as novas linhas de orientação sublinham aspectos relevantes da necessidade do início precoce da terapêutica e definem um novo algoritmo terapêutico baseado nas características clínica e hemodinâmicas dos doentes. Este olhar, em alguns aspectos refrescante sugerido nas novas recomendações, irá traduzir-se nos próximos anos no acumular de informação e evidência, que poderá em muito modificar a nossa abordagem dos doentes com IC.

Das imensas publicações na área em 2016/17, saliento algumas que nos dão informação importante na visão da IC, desde logo a informação sobre a sua frequência quer como uma condição clinica já estabelecida, quer como na grande franja de população em risco de IC (estádios A e B). Um novo olhar sobre as comorbilidades na IC iniciou-se em anos recentes e actualmente temos informações que nos ajudam a optar por estratégias clinicas e terapêuticas que se podem ou não associar a melhores resultados (ferropenia, depressão). A perspectiva de uma terapêutica individualizada baseada nas características neuro-humorais em cada momento, tem vindo a ser tentada há diversos anos sem êxito assinalável. Neste período, surgiu pela primeira vez a demonstração de que uma estratégia associando a intensidade de terapêutica diurética de acordo com os níveis de CA125 em doentes agudos, se associa a melhores resultados no médio prazo. Por outro lado, resultados recentes não suportam uma abordagem terapêutica com base nos níveis de peptídeos natriuréticos quer em doentes agudos quer em doentes ambulatórios.

O conhecimento da epidemiologia e práticas na IC aguda, reconhecida como necessidade importante para a adopção de novas estratégias que possam resultar em melhores resultados, foi alvo de diversas publicações das quais seleccionei a que divulga os resultados conhecidos no nosso país e os compara com outras realidades, e na qual é sublinhada a absoluta necessidade de obter mais informação para que possamos delinear melhores estratégias para obtermos mais sucesso nestes doentes ainda com prognóstico muito sombrio.

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC.

Ponikowski P, Voors AA, Anker SD et al

Eur J Heart Fail. 2016; 18(8): 891-975

Comentário: No ano de 20016 emergiram novas recomendações para a abordagem de doentes com IC. É um ponto forte nestas recomendações a necessidade de um diagnóstico positivo de IC (demonstração de disfunção ventricular e/ou alterações estruturais). Surgem novas categorizações dentro do espectro da IC. Os doentes com fracção de ejecção estre os 40 e 49% são agora classificados com doentes com IC e fracção de ejecção intermédia, sendo subjacente a esta ideia a necessidade de conhecer melhor em termos epidemiológicos este grupo, de o individualizar para testar terapêuticas e conhecer a sua história natural. São elencados também critérios precisos para a identificação de doentes com IC e fracção de ejecção preservada (>50%) sendo dado enfase aos peptídeos natriuréticos, às alterações estruturais e da função diastólica. No que concerne à terapêutica farmacológica é sublinhado o papel dos diuréticos, inibidores do enzima de conversão da angiotensina (i-ECAS) e antagonistas mineralocorticoides. Entram ainda nas recomendações pela primeira vez o valsartan associado ao inibidor da neprilisina, como mais valia nos doentes que permanecem sintomáticos apesar do uso de i-ECAS. A ivabradina mantem o seu papel nos doentes sintomáticos em ritmo sinusal com frequência cardíaca acima de 70. No que respeita aos dispositivos, estas recomendações prevêem a sua utilização em todos os doentes sintomáticos (CDI) e terapêutica de resincronização ventricular (CRT) de acordo com critérios específicos em doentes em classe II ou mais elevada.

No que se refere à IC aguda as novas recomendações apesar de não introduzirem novos fármacos para o seu tratamento, sublinham a necessidade de inicio de terapêutica precoce em analogia ao que acontece no síndroma coronário agudo e divulgam um algoritmo terapêutico muito interessante baseado nas características clinicas e hemodinâmicas de cada doente a cada momento (presença/ausência de congestão/hipoperfusão)

Sendo recomendações que irão ser referência nos próximos 4 anos podemos ter a espectativa que vão gerar investigação e conhecimento que serão espelhados nas ulteriores para que melhores abordagens surjam para estes doentes ainda com grande morbilidade e mortalidade.

Heart Failure Stages Among Older Adults in the Community: The Atherosclerosis Risk in Communities Study

Shah AM, Claggett B, Loehr LR, et al

Circulation. 2017; 135(3):224-240

BACKGROUND: Although HF disproportionately affects older adults, little data exist regarding the prevalence of American College of Cardiology/American Heart Association heart failure (HF) stages among older individuals in the community. Additionally, the role of contemporary measures of longitudinal strain (LS) and diastolic dysfunction in defining HF stages is unclear.

METHODS: HF stages were classified in 6,118 participants in the Atherosclerosis Risk in Communities study (age 67 - 91 years) at the fifth study visit as follows: stage A (asymptomatic with HF risk factors but no cardiac structural or functional abnormalities), B (asymptomatic with structural abnormalities, defined as left ventricular hypertrophy, dilation or dysfunction, or significant valvular disease), C1 (clinical HF without prior hospitalization), and C2 (clinical HF with prior hospitalization).

RESULTS: Using the traditional definitions of HF stages, only 5% of examined participants were free of HF risk factors or structural heart disease (Stage 0), 52% were categorized as Stage A, 30% Stage B, 7% Stage C1, and 6% Stage C2. Worse HF stage was associated with a greater risk of incident HF hospitalization or death at a median follow-up of 608 days. LVEF was preserved in 77% and 65% in Stages C1 and C2 respectively. Incorporation of LS and diastolic dysfunction into the Stage B definition reclassified 14% of the sample from Stage A to B and improved the net reclassification index (p=0.028) and integrated discrimination index (p=0.016). Abnormal LV structure, systolic function (based on LVEF and LS), and diastolic function (based on e', E/e', and left atrial volume index) were each independently and additively associated with risk of incident HF hospitalization or death in Stage A and B participants.

CONCLUSIONS: The majority of older adults in the community are at risk for HF (Stages A or B), appreciably more compared to previous reports in younger community-based samples. LVEF is robustly preserved in at least two-thirds of older adults with prevalent HF (Stage C), highlighting the burden of HFpEF in the elderly. LV diastolic function and LS provide incremental prognostic value beyond conventional measures of LV structure and LVEF in identifying persons at risk for HF hospitalization or death.

Comentários: a coorte de idosos demonstra a magnitude da IC na população. Os autores observaram que entre os idosos, apenas 5% não estão em risco de desenvolver IC ou não estão em estádio B ou C da condição. Estes dados são de imensa importância para a definição de políticas de saúde que pretendam reduzir a evolução conhecida entre estádios de IC. Estes resultados ilustram a absoluta necessidade de intervenção precoce para reduzir a taxa de progressão para as formas sintomáticas de IC.

Carbohydrate Antigen-125-Guided Therapy in Acute Heart Failure: CHANCE-HF: A Randomized Study

Núñez J, Llàcer P, Bertomeu-González V, for the CHANCE-HF Investigators.

JACC Heart Fail. 2016; 4(11):833-843

OBJECTIVES: This study sought to evaluate the prognostic effect of carbohydrate antigen-125 (CA125)-guided therapy (CA125 strategy) versus standard of care (SOC) after a hospitalization for acute heart failure (AHF).

BACKGROUND: CA125 has emerged as a surrogate of fluid overload and inflammatory status in AHF. After an episode of AHF admission, elevated values of this marker at baseline as well as its longitudinal profile relate to adverse outcomes, making it a potential tool for treatment guiding.

METHODS: In a prospective multicenter randomized trial, 380 patients discharged for AHF and high CA125 were randomly assigned to the CA125 strategy (n = 187) or SOC (n = 193). The aim in the CA125 strategy was to reduce CA125 to ≤35 U/ml by up or down diuretic dose, enforcing the use of statins, and tightening patient monitoring. The primary endpoint was 1-year composite of death or AHF readmission. Treatment strategies were compared as a time to first event and longitudinally.

RESULTS: Patients allocated to the CA125 strategy were more frequently visited, and treated with ambulatory intravenous loop diuretics and statins. Likewise, doses of oral loop diuretics and aldosterone receptor blockers were more frequently modified. The CA125 strategy resulted in a significant reduction of the primary endpoint, whether evaluated as time to first event (66 events vs. 84 events; p = 0.017) or as recurrent events (85 events vs. 165 events; incidence rate ratio: 0.49; 95% confidence interval: 0.28 to 0.82; p = 0.008). The effect was driven by significantly reducing rehospitalizations but not mortality.

CONCLUSIONS: The CA125 strategy was superior to the SOC in terms of reducing the risk of the composite of 1-year death or AHF readmission. This effect was mainly driven by significantly reducing the rate of rehospitalizations. (Carbohydrate Antigen-125-guided Therapy in Heart Failure [CHANCE-HF]).

Comentários: a ideia de guiar a terapêutica na IC com base em índices de activação neuro-humoral já foi anteriormente ensaiada com resultados divergentes (terapêutica com objectivo de reduzir os níveis de peptídeos natriuréticos). Este estudo realizado em Espanha é o primeiro a demonstrar claramente que uma estratégia com objectivo de reduzir um marcador indirecto de excesso de volume e inflamação após um episodio de IC aguda se associa a melhores resultados a médio prazo.

Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure.

Køber L, Thune JJ, Nielsen JC, Haarbo J, for the DANISH Investigators

N Engl J Med 2016; 375(13):1221-30

Background: the benefit of an implantable cardioverter-defibrillator (ICD) in patients with symptomatic systolic heart failure caused by coronary artery disease has been well documented. However, the evidence for a benefit of prophylactic ICDs in patients with systolic heart failure that is not due to coronary artery disease has been based primarily on subgroup analyses. The management of heart failure has improved since the landmark ICD trials, and many patients now receive cardiac resynchronization therapy (CRT).

Methods: in a randomized, controlled trial, 556 patients with symptomatic systolic heart failure (left ventricular ejection fraction, ≤35%) not caused by coronary artery disease were assigned to receive an ICD, and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. The secondary outcomes were sudden cardiac death and cardiovascular death.

Results: after a median follow-up period of 67.6 months, the primary outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (hazard ratio, 0.87; 95% confidence interval [CI], 0.68 to 1.12; P=0.28). Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (hazard ratio, 0.50; 95% CI, 0.31 to 0.82; P=0.005). Device infection occurred in 27 patients (4.9%) in the ICD group and in 20 patients (3.6%) in the control group (P=0.29).

Conclusions: in this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. (DANISH ClinicalTrials)

Comentários: este ensaio clínico é como uma pedra no charco no âmbito do uso de cardiodesfibriladores implantados (CDI) para prevenção primária na IC. As recomendações actuais fazem indicação para o implante de CDI em todos os doentes sintomáticos (com expectativa de sobrevida superior a 1 ano) independentemente da etiologia da IC. De facto, estas indicações em doentes não isquémicos nunca tinham sido especificamente avaliadas prospectivamente, mas incluídas nas recomendações baseado em resultados de subgrupos. Este estudo vem fazer repensar o potencial valor dos CDI em doentes não isquémicos onde de acordo com estes resultados não é sugerido valor terapêutico para seu uso. A questão levantada pode ter um carácter mais vasto, levando a questionar quer algumas recomendações e principalmente o que as alicerça quando baseada em resultados secundários ou de subgrupos.

Usefulness of Iron Deficiency Correction in Management of Patients With Heart Failure

Wienbergen H, Pfister O, Hochadel M, for the RAID-HF (Registry Analysis of Iron Deficiency–Heart Failure) REGISTRY Study Group.

Am J Cardiol. 2016 Dec 15;118(12):1875-1880

Iron deficiency (ID) has been identified as an important co-morbidity in patients with heart failure (HF). Intravenous iron therapy reduced symptoms and rehospitalizations of iron-deficient patients with HF in randomized trials.

The present multicenter study investigated the "real-world" management of iron status in patients with HF. Consecutive patients with HF and ejection fraction ≤40% were recruited and analyzed from December 2010 to October 2015 by 11 centers in Germany and Switzerland.

Of 1,484 patients with HF, iron status was determined in only 923 patients (62.2%), despite participation of the centers in a registry focusing on ID and despite guideline recommendation to determine iron status. In patients with determined iron status, a prevalence of 54.7% (505 patients) for ID was observed. Iron therapy was performed in only 8.5% of the iron-deficient patients with HF; 2.6% were treated with intravenous iron therapy.

The patients with iron therapy were characterized by a high rate of symptomatic HF and anemia.

In conclusion, despite strong evidence of beneficial effects of iron therapy on symptoms and rehospitalizations, diagnostic and therapeutic efforts on ID in HF are low in the actual clinical practice, and the awareness to diagnose and treat ID in HF should be strongly enforced.

Comentários: a abordagem das comorbilidades é hoje um foco importante na abordagem da IC. O deficit de ferro e anemia são vastamente reconhecidos como factores associados a piores resultados e a sua correcção está associada a melhoria sintomática e de morbilidade. Este estudo demonstra que apesar desse conhecimento, a práctica clínica está ainda muito distanciada dos objectivos terapêuticos nestes doentes. Para além do interesse neste aspecto específico da deficiência de ferro, este estudo ilustra os "gaps" entre a evidência científica e o mundo real, que é hoje reconhecida como uma deficiência major impedindo muitos doentes de usufruir das melhores terapêuticas em cada momento.

Effect of Escitalopram on All-Cause Mortality and Hospitalization in Patients with Heart Failure and Depression: The MOOD-HF Randomized Clinical Trial.

Angermann CE, Gelbrich G, Störk S, for the MOOD-HF Study Investigators and Committee Members.

JAMA. 2016; 315(24):2683-93

Importance: depression is frequent in patients with heart failure and is associated with adverse clinical outcomes. Long-term efficacy and safety of selective serotonin reuptake inhibitors in these patients are unknown.

Objective: to determine whether 24 months of treatment with escitalopram improves mortality, morbidity, and mood in patients with chronic systolic heart failure and depression.

Design, Setting, and participants: The Effects of Selective Serotonin Re-Uptake Inhibition on Morbidity, Mortality, and Mood in Depressed Heart Failure Patients (MOOD-HF) study was a double-blind, placebo-controlled randomized clinical trial conducted at 16 tertiary medical centers in Germany. Between March 2009 and February 2014, patients at outpatient clinics with New York Heart Association class II-IV heart failure and reduced left ventricular ejection fraction (<45%) were screened for depression using the 9-item Patient Health Questionnaire. Patients with suspected depression were then invited to undergo a Structured Clinical Interview based on the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) to establish the diagnosis.

Interventions: patients were randomized 1:1 to receive escitalopram (10-20 mg) or matching placebo in addition to optimal heart failure therapy. Study duration was 24 months.

Main Outcomes and Measures: The composite primary outcome was time to all-cause death or hospitalization. Prespecified secondary outcomes included safety and depression severity at 12 weeks of treatment (including the titration period), which were determined using the 10-item Montgomery-Åsberg Depression Rating Scale (total possible score, 0 to 60; higher scores indicate more severe depression).

Results: a total of 372 patients (mean age, 62 years; 24% female) were randomized and had taken at least 1 dose of study medication when the data and safety monitoring committee recommended the trial be stopped early. During a median participation time of 18.4 months (n = 185) for the escitalopram group and 18.7 months (n = 187) for the placebo group, the primary outcome of death or hospitalization occurred in 116 (63%) patients and 119 (64%) patients, respectively (hazard ratio, 0.99 [95% CI, 0.76 to 1.27]; P = .92). The mean Montgomery-Åsberg Depression Rating Scale sum score changed from 20.2 at baseline to 11.2 at 12 weeks in the escitalopram group and from 21.4 to 12.5 in the placebo group (between-group difference, -0.9 [95% CI,-2.6 to 0.7]; P = .26). Safety parameters were comparable between groups.

Conclusions and Relevance: In patients with chronic heart failure with reduced ejection fraction and depression, 18 months of treatment with escitalopram compared with placebo did not significantly reduce all-cause mortality or hospitalization, and there was no significant improvement in depression. These findings do not support the use of escitalopram in patients with chronic systolic heart failure and depression.

Comentários: este estudo pretendeu avaliar o uso de um inibidor da recaptação da serotonina em doentes com IC e fracção de ejecção diminuída. A depressão é uma comorbilidade com impacto reconhecido na IC. Os resultados

não mostraram benefícios em termos de redução nos índices de depressão ou de outros com esta terapêutica. Com a análise limitada ao fármaco específico avaliado, estes resultados não sugerem, contudo, o benefício no uso de antidepressivos em doentes com IC. É necessário explorar outras estratégias para abordar esta comorbilidade.

Prevalence and prognostic impact of frailty and its components in non-dependent elderly patients with heart failure

Vidán MT, Blaya-Novakova V, Sánchez E, Ortiz J, Serra-Rexach JA, Bueno H.

Eur J Heart Fail. 2016; 18(7):869-75

AIMS: The aim of this study was to evaluate the prevalence, clinical features, and the independent impact of frailty-a geriatric syndrome characterized by the decline of physiological systems-and its components, on prognosis after heart failure (HF) hospitalization.

METHODS AND RESULTS: FRAIL-HF is a prospective cohort study including 450 non-dependent patients ≥70 years old hospitalized for HF. Frailty was screened according to the biological phenotype criteria (low physical activity, weight loss, slow walking speed, weak grip strength, and exhaustion). The independent influence of frailty on mortality, functional decline, and readmission risks was calculated adjusted for HF characteristics and co-morbidities. Mean age was 80 ± 6 years; 76% fulfilled frailty criteria. Frail patients were older, more often female, but showed no differences in chronic co-morbidities, LVEF, and NT-proBNP levels. Slow walking speed was the most discriminative component between frail (89.2%) and non-frail patients (26%). Overall, 1-year survival was 89% in the non-frail group and 75% in frail subjects (P = 0.003). After adjusting for age, gender, chronic and acute co-morbidities, NYHA, and NT-proBNP, frail patients showed higher risks for 30-day functional decline [odds ratio (OR) 2.20, 95% confidence interval (CI) 1.19-4.08], 1-year all-cause mortality [hazard ratio (HR) 2.13, 95% CI 1.07-4.23], and 1-year readmission (OR 1.96, 95% CI 1.14-3.34). The association of individual components with 1-year adjusted mortality risk was HR 2.14, 95% CI 1.05-4.39 for low physical activity and HR 1.77, 95% CI 0.95-3.29 for slow walking speed.

CONCLUSION: Frailty is highly prevalent even among non-dependent elderly HF patients, and is an independent predictor of early disability, long-term mortality, and readmission. Individual frailty components may be useful for risk prediction.

Comentários: estudo que ilustra a multidisciplinaridade necessária na abordagem de doentes com IC. A avaliação da fragilidade mostra-se como muito relevante. Trabalho em linha com estratégias a desenvolver baseadas no doente ("patient-centered")

Antiplatelet versus anticoagulation treatment for patients with heart failure in sinus rhythm

Shantsila E, Lip GY

Cochrane Database Syst Rev. 2016 Sep 15;9:CD003333.

BACKGROUND: Morbidity in patients with chronic heart failure is high, and this predisposes them to thrombotic complications, including stroke and thromboembolism, which in turn contribute to high mortality. Oral anticoagulants (e.g. warfarin) and antiplatelet agents (e.g. aspirin) are the principle oral antithrombotic agents. Many heart failure patients with sinus rhythm take aspirin because coronary artery disease is the leading cause of heart failure. Oral anticoagulants have become a standard in the management of heart failure with atrial fibrillation. However, a question remains regarding the appropriateness of oral anticoagulants in heart failure with sinus rhythm. This update of a review previously published in 2012 aims to address this question.

OBJECTIVES: To assess the effects of oral anticoagulant therapy versus antiplatelet agents for all-cause mortality, non-fatal cardiovascular events and risk of major bleeding in adults with heart failure (either with reduced or preserved ejection fraction) who are in sinus rhythm.

SEARCH METHODS: We updated the searches in September 2015 on CENTRAL (The Cochrane Library), MEDLINE and Embase. We searched reference lists of papers and abstracts from cardiology meetings and contacted study authors for further information. We did not apply any language restrictions. Additionally, we searched two clinical trials registers: ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal apps.who.int/trialsearch/) (searched in July 2016).

SELECTION CRITERIA: We included randomised controlled trials comparing antiplatelet therapy versus oral anticoagulation in adults with chronic heart failure in sinus rhythm. Treatment had to last at least one month. We compared orally administered antiplatelet agents (aspirin, ticlopidine, clopidogrel, prasugrel, ticagrelor, dipyridamole) versus anticoagulant agents (coumarins, warfarin, non-vitamin K oral anticoagulants).

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion and assessed the risks and benefits of antithrombotic versus antiplatelet therapy using relative measures of effects, such as risk ratios (RR), accompanied with 95% confidence intervals (CI). The data extracted included data relating to the study design, patient characteristics, study eligibility, quality, and outcomes. We used GRADE criteria to assess the quality of the evidence.

MAIN RESULTS: This update identified one additional study for inclusion, adding data for 2305 participants. This addition more than doubled the overall number of patients eligible for the review. In total, we included four randomised controlled trials (RCTs) with a total of 4187 eligible participants. All studies compared warfarin with aspirin. One RCT additionally compared warfarin with clopidogrel. All included RCTs studied patients with heart failure with reduced ejection fraction. Analysis of all outcomes for warfarin versus aspirin was based on 3663 patients from four RCTs. All-cause mortality was similar for warfarin and aspirin (RR 1.00, 95% CI 0.89 to 1.13; 4 studies; 3663 participants; moderate quality evidence). Oral anticoagulation was associated with a reduction in non-fatal cardiovascular events, which included non-fatal stroke, myocardial infarction, pulmonary embolism, peripheral arterial embolism (RR 0.79, 95% CI 0.63 to 1.00; 4 studies; 3663 participants; moderate quality evidence). The rate of major bleeding events was twice as high in the warfarin groups (RR 2.00, 95% CI 1.44 to 2.78; 4 studies; 3663 participants; moderate quality evidence). We generally considered the risk of bias of the

included studies to be low. Analysis of warfarin versus clopidogrel was based on a single RCT (N = 1064). All-cause mortality was similar for warfarin and clopidogrel (RR 0.93, 95% CI 0.72 to 1.21; 1 study; 1064 participants; low quality evidence). There were similar rates of non-fatal cardiovascular events (RR 0.85, 95% CI 0.50 to 1.45; 1 study; 1064 participants; low quality evidence). The rate of major bleeding events was 2.5 times higher in the warfarin group (RR 2.47, 95% CI 1.24 to 4.91; 1 study; 1064 participants; low quality evidence). Risk of bias for this study can be summarised as low.

AUTHORS' CONCLUSIONS: There is evidence from RCTs to suggest that neither oral anticoagulation with warfarin or platelet inhibition with aspirin is better for mortality in systolic heart failure with sinus rhythm (high quality of the evidence for all-cause mortality and moderate quality of the evidence for non-fatal cardiovascular events and major bleeding events). Treatment with warfarin was associated with a 20% reduction in non-fatal cardiovascular events but a twofold higher risk of major bleeding complications (high quality of the evidence). We saw a similar pattern of results for the warfarin versus clopidogrel comparison (low quality of the evidence). At present, there are no data on the role of oral anticoagulation versus antiplatelet agents in heart failure with preserved ejection fraction with sinus rhythm. Also, there were no data from RCTs on the utility of non-vitamin K antagonist oral anticoagulants compared to antiplatelet agents in heart failure with sinus rhythm.

Comentários: meta-análise muito interessante que confirma o maior risco associado ao uso de hipocoagulantes "clássicos" em doentes com disfunção sistólica em ritmo sinusal com benefício modesto em termos de morbimortalidade. A questão do uso de hipocoagulantes orais "clássicos" em doentes com IC em ritmo sinusal fica encerrada com esta meta-análise.

Heart Failure with Recovered Ejection Fraction in a Cohort of Elderly Patients with Chronic Heart Failure.

Trullàs JC, Manzano L, Formiga F, from the investigators from the RICA Registry.

Cardiology. 2016; 135(3):196-201

OBJECTIVE: The aim of this study was to determine whether patients with heart failure (HF) who recover left ventricular ejection fraction (LVEF), termed here as 'Rec-HF', have a distinct clinical profile and prognosis compared with patients with HF and reduced LVEF (HF-REF) or HF and preserved LVEF (HF-PEF).

METHODS: We evaluated and classified patients from the Spanish Heart Failure Registry into three categories based on enrollment/follow-up echocardiograms: HF-PEF (LVEF ≥50%), HF-REF (LVEF persistently <50%) and Rec-HF (LVEF on enrollment <50% but normalized during follow-up).

RESULTS: A total of 1,202 patients were included, 1,094 with HF-PEF, 81 with HF-REF and 27 with Rec-HF. The three groups included patients of advanced age (mean age 75 years) with comorbidities. Rec-HF patients were younger, with a better functional status, lower prevalence of diabetes mellitus, dementia and cerebrovascular disease, and higher prevalence of COPD. The etiology of HF was more frequently ischemic and alcoholic and less frequently hypertensive. After a median follow-up of 367 days, the unadjusted hazard ratios for death in the Rec-HF versus HF-PEF and HF-REF groups were 0.11 (95% CI 0.02-080; p = 0.029) and 0.31 (95% CI 0.04-2.5; p = 0.274). Results were statistically nonsignificant in multivariate-adjusted models.

CONCLUSION: Rec-HF is also present in elderly patients with HF but it is necessary to further investigate the natural history and optimal pharmacologic management of this 'new HF syndrome'.

Comentários: esta avaliação de um registo em curso na Península Ibérica em Serviços de Medicina Interna é um alerta para um grupo específico de doentes com prognóstico diferente dos outros fenótipos de IC. As sociedades cientificas americanas já tinham chamado a atenção, para estes doentes que poderão ter uma abordagem terapêutica diversa.

A closer look at acute heart failure: Putting Portuguese and European data into perspective

Fonseca C, Araújo I, Marques F, Brás D, Bettencourt P

Rev Port Cardiol. 2016; 35(5):291-304

Introduction and Objectives: acute heart failure (AHF) is a heterogeneous clinical syndrome requiring urgent therapy. The prognosis is poor after the index hospitalization, with a high risk for rehospitalization and early death. The costs of managing AHF are thus increasing rapidly. A literature review was performed to gather and compare data on prevalence and treatment and to identify gaps in AHF management, based on European and Portuguese studies.

Methods: a literature search from 1995 to 2014 was conducted in selected databases (BIOSIS Previews, EMBASE and Ovid MEDLINE).

Results and Discussion: seven portuguese and nine European studies were analyzed. The mean age of AHF patients was ≥65 years and 30-50% were women. Coronary artery disease (42.3% vs. 61.9%) and hypertension (53.3% vs. 76.7%) were identified as primary etiologies in Europe and in Portugal. Similar proportions of heart failure with preserved ejection fraction were found in the Portuguese (19.9-44.7%) and European (32.8-39.1%) studies. Overall, all-cause mortality rates were comparable (six months: 9.3-25.5% vs. 13.5-27.4%; one year: 15.9-31% vs. 17.4-46.5%), as was in-hospital mortality (5.5-14% vs. 3.8-12%) in Portuguese and European studies, respectively. Length of stay was comparable. The studies were performed in very different hospital settings and data on treatment were scarce.

Conclusions: gaps were identified in treatment and clinical pathways of patients with AHF. Based on the results of this review, collection and investigation of data on the disease and treatment solutions, training in disease management, and improved organization of healthcare should be the subject of further investment.

Comentários: estudo realizado em Portugal que avalia sete coortes (seis das quais em Serviços de Medicina Interna) e que chama a atenção para as lacunas ainda muito importantes entre as melhores estratégias e a sua utilização no mundo real. Estas observações deverão ser a génese de mudanças conducentes a que os doentes tenham acesso às melhores abordagens.

Proteomic diversity of high-density lipoprotein explains its association with clinical outcome in patients with heart failure.

Emmens JE, Jones DJL, Cao TH, et al

Eur J Heart Fail. 2017 Dec 18. doi: 10.1002/ejhf.1101

Aims: previously, low high-density lipoprotein (HDL) cholesterol was found to be one of the strongest predictors of mortality and/or heart failure (HF) hospitalisation in patients with HF. We therefore performed in-depth investigation of the multifunctional HDL proteome to reveal underlying pathophysiological mechanisms explaining the association between HDL and clinical outcome.

Methods and Results: we selected a cohort of 90 HF patients with 1:1 cardiovascular death/survivor ratio from BIOSTAT-CHF. A novel optimised protocol for selective enrichment of lipoproteins was used to prepare plasma. Enriched lipoprotein content of samples was analysed using high resolution nanoscale liquid chromatography-mass spectrometry-based proteomics, utilising a label free approach. Within the HDL proteome, 49 proteins significantly differed between deaths and survivors. An optimised model of 12 proteins predicted death with 76% accuracy (Nagelkerke R2 =0.37, P < 0.001). The strongest contributors to this model were filamin-A (related to crosslinking of actin filaments) [odds ratio (OR) 0.31, 95% confidence interval (CI) 0.15-0.61, P = 0.001] and pulmonary surfactant-associated protein B (related to alveolar capillary membrane function) (OR 2.50, 95% CI 1.57-3.98, P < 0.001). The model predicted mortality with an area under the curve of 0.82 (95% CI 0.77-0.87, P < 0.001). Internal cross validation resulted in 73.3 ± 7.2% accuracy.

Conclusion: this study shows marked differences in composition of the HDL proteome between HF survivors and deaths. The strongest differences were seen in proteins reflecting crosslinking of actin filaments and alveolar capillary membrane function, posing potential pathophysiological mechanisms underlying the association between HDL and clinical outcome in HF.

Comentários: este é um dos primeiros estudos a explorar o potencial da proteómica em descobrir novos mecanismos fisiopatológicos com relevância clínica do trajecto de doentes com Insuficiência Cardíaca. Este é uma área à qual devemos estar atentos, pois muito conhecimento é esperado com a exploração da proteómica e é espectável que tenha impacto clínico num futuro próximo.

NT-proBNP-Guided Therapy in Acute Decompensated Heart Failure: The PRIMA II Randomized Controlled Trial.

Stienen S, Salah K, Moons AH, Bakx AL, van Pol , Kortz M, Ferreira JP, Marques I et al

Circulation. 2017 Dec 14. pii: CIRCULATIONAHA.117.029882

Background -The concept of natriuretic peptide guidance has been extensively studied in chronic heart failure (HF) patients, with only limited success. The effect of NT-proBNP-guided therapy in acute decompensated HF (ADHF) patients using a relative NT-proBNP target has not been investigated. The aim of this study was to assess whether NT-proBNP-guided therapy of ADHF patients using a relative NT-proBNP target would lead to improved outcome compared with conventional therapy.

Methods -We conducted a prospective randomized, controlled trial to study the impact of in-hospital guidance for ADHF treatment by a predefined NT-proBNP target (>30% reduction from admission to discharge) versus conventional treatment. ADHF patients with NT-proBNP levels of > 1700 ng/L were eligible. After achieving clinical stability, 405 patients were randomized to either NT-proBNP-guided or conventional treatment (1:1). The primary endpoint was dual, i.e. a composite of all-cause mortality and HF readmissions in 180 days, and the number of days alive out of the hospital in 180 days. Secondary endpoints were all-cause mortality within 180 days, HF readmissions within 180 days, and a composite of all-cause mortality and HF readmissions within 90 days.

Results -Significantly more patients in the NT-proBNP-guided therapy group were discharged with an NT-proBNP reduction of >30% (80% versus 64%, P=0.001). Nonetheless, NT-proBNP-guided therapy did not significantly improve the combined event rate for all-cause mortality and HF readmissions (HR for NT-proBNP-guided therapy, 0.96; 95% CI, 0.72 to 1.37; P=0.99), or the median number of days alive outside of the hospital (178 vs. 179 days for NT-proBNP vs. conventional patients, P=0.39). Guided therapy also did not significantly improve any of the secondary endpoints.

Conclusions -The PRIMA II demonstrates that that guidance of HF therapy to reach an NT-proBNP reduction of >30% after clinical stabilization did not improve 6-months outcome. Clinical Trial Registration -URL: http://www.trialregister.nl Unique Identifier: NTR3279.

Comentários: na senda dos ensaios que procuram demonstrar o interesse da titulação da terapêutica de doentes com Insuficiência Cardíaca com base em biomarcadores, foi muito recentemente divulgado este estudo. Tem a participação de um centro Português e que nos traz informação muito relevante. Não demonstrando vantagens em titular a terapêutica para uma desativação neuro-humoral, este estudo levanta também questões muito interessantes como por exemplo o significado de não conseguir a desactivação neuro-humoral como indicador de prognóstico muito desfavorável.

Exercise testing in heart failure: a contemporary discussion in an era of novel diagnostic techniques and biomarkers.

Moneghetti KJ, Christle JW, Myers J, Haddad F

Curr Opin Cardiol. 2017 Dec 8. doi: 10.1097

Purpose of veview: the purpose of this review is to highlight recent advances in the field of exercise testing for patients with heart failure.

Recent Findings: the importance of assessment of cardiorespiratory fitness (CRF) and exercise testing in heart failure is highlighted in the consensus recommendation of the American Heart Association. Contemporary studies have validated the independent and incremental strength of CRF metrics in patients with heart failure and coronary artery disease. The use of respiratory gas analysis and imaging or hemodynamics during physical exercise is feasible and results in high prognostic utility across the continuum of heart failure. Understanding how CRF metrics complement existing and novel biomarkers and risk scores is an emerging subject of scientific inquiry.

Summary: In the current era of personalized medicine, integrating CRF, imaging and circulating biomarkers will allow us to further develop individualized strategies for improving outcome in patients with heart failure.

Comentários: revisão muito interessante sobre as métricas avaliadas nos teste cardiorrespiratórios em doentes com Insuficiência Cardíaca e de como estas são complementares de outros índices com interesse prognóstico. Uma revisão que para além do interesse específico expõe os aspetos sistémicos da Insuficiência Cardíaca.

Adherence to Mediterranean Diet and All-Cause Mortality After an Episode of Acute Heart Failure: Results of the MEDIT-AHF Study.

JACC Heart Fail. 2017 Nov 27. pii: S2213-1779(17)30683-2.

Miró Ò, Estruch R, Martín-Sánchez FJ, for the ICA-SEMES Research Group

Objectives: The authors sought to evaluate clinical outcomes of patients after an episode of acute heart failure (AHF) according to their adherence to the Mediterranean diet (MedDiet).

Background: It has been proved that MedDiet is a useful tool in primary prevention of cardiovascular diseases. However, it is unknown whether adherence to MedDiet is associated with better outcomes in patients who have already experienced an episode of AHF.

Methods: We designed a prospective study that included consecutive patients diagnosed with AHF in 7 Spanish emergency departments (EDs). Patients were included if they or their relatives were able to answer a 14-point score of adherence to the MedDiet, which classified patients as adherents (≥9 points) or nonadherents (≤8 points). The primary endpoint was all-cause mortality at the end of follow-up, and secondary endpoints were 1-year ED revisit without hospitalization, rehospitalization, death, and a combined endpoint of all these variables for patients discharged after the index episode. Unadjusted and adjusted hazard ratios (HRs) were calculated.

Results: We included 991 patients (mean age of 80 ± 10 years, 57.8% women); 523 (52.9%) of whom were adherent to the MedDiet. After a mean follow-up period of 2.1 ± 1.3 years, no differences were observed in survival between adherent and nonadherent patients (HR of adherents [HRadh] = 0.86; 95% confidence interval [CI]: 0.73 to 1.02). The 1-year cumulative ED revisit for the whole cohort was 24.5% (HRadh = 1.10; 95% CI: 0.84 to 1.42), hospitalization 43.7% (HRadh = 0.74; 95% CI: 0.61 to 0.90), death 22.7% (HRadh = 1.05; 95% CI: 0.8 to 1.38), and combined endpoint 66.8% (HRadh = 0.89; 95% CI: 0.76 to 1.04). Adjustment by age, hypertension, peripheral arterial disease, previous episodes of AHF, treatment with statins, air-room pulsioxymetry, and need for ventilation support in the ED rendered similar results, with no statistically significant differences in mortality (HRadh = 0.94; 95% CI: 0.80 to 1.13) and persistence of lower 1-year hospitalization for adherents (HRadh = 0.76; 95% CI: 0.62 to 0.93).

Conclusions: Adherence to the MedDiet did not influence long-term mortality after an episode of AHF, but it was associated with decreased rates of rehospitalization during the next year.

Comentários: os aspectos nutricionais têm vindo a adquirir relevo na abordagem de doentes com Insuficiência Cardíaca em diversas vertentes. Por exemplo, a estratégia de consumo muito limitado de sal nesta população, apesar de adoptada pela comunidade médica, tem ainda pouca evidência. Este estudo demonstra que a médio prazo, apesar de não ter benefícios em termos de mortalidade, a dieta Mediterrânica associa-se a menor morbilidade. Estes resultados suportam a sua "prescrição" a doentes com Insuficiência Cardíaca.

Meta-Analysis of Soluble Suppression of Tumorigenicity-2 and Prognosis in Acute Heart Failure.

Aimo A, Vergaro G, Ripoli A, et al

JACC Heart Fail. 2017; 5(4):287-296

Objectives: the aim of this study was to perform a meta-analysis of currently available data regarding the prognostic significance of soluble suppression of tumorigenecity-2 (sST2) concentration in acute heart failure (AHF).

Background: Concentration of sST2 may have prognostic value in AHF. A comprehensive assessment of all available studies regarding sST2 in AHF is lacking.

Methods: Three databases (MEDLINE, Cochrane Library, and Scopus) were searched. Inclusion criteria were follow-up studies, papers published in English, enrollment of patients with AHF, and availability of median hazard ratios for all-cause death and other outcome measures, when available.

Results: Ten studies were included, with a global population of 4,835 patients and a median follow-up duration of 13.5 months. The following global hazard ratios calculated for log2(sST2) were admission sST2 and all-cause death, 2.46 (95% confidence interval [CI]: 1.80 to 3.37; p < 0.001); discharge sST2 and all-cause death, 2.06 (95% CI: 1.37 to 3.11; p < 0.001); admission sST2 and cardiovascular death, 2.29 (95% CI: 1.41 to 3.73; p < 0.001); discharge sST2 and cardiovascular death, 2.20 (95% CI: 1.48 to 3.25; p < 0.001); admission sST2 and heart failure (HF) hospitalization, 1.21 (95% CI: 0.96 to 1.52; p = 0.060); discharge sST2 and HF hospitalization, 1.54 (95% CI: 1.03 to 2.32; p = 0.007); admission sST2 and all-cause death or HF hospitalization, 1.74 (95% CI: 1.24 to 2.45; p < 0.001); and discharge sST2 and all-cause death or HF hospitalization, 1.63 (95% CI: 1.14 to 2.33; p < 0.001).

Conclusions: Plasma sST2 has prognostic value with respect to all-cause and cardiovascular death as well as the composite outcome of all-cause death or HF hospitalization, with both admission and discharge values having prognostic efficacy. Discharge sST2, but not admission sST2, is predictive of HF rehospitalization during follow-up.

Comentários: Esta meta analise traz um novo biomarcador para a "ribalta". Os autores descrevem o valor do ST2 como biomarcador associado ao prognóstico em doentes com Insuficiência Cardíaca Aguda. De notar que esta associação ao prognóstico é independente dos níveis de peptídeos natriuréticos. A estratificação prognostica em doentes com Insuficiência Cardíaca será sempre baseada em múltiplos índices, refletindo a sua natureza sistémica e fisiopatológica. O ST2 parece ser um dos biomarcadores com interesse relevante na estratificação destes doentes. O seu valor como possível modelador da abordagem terapêutica não está ainda estudado.

Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association.

Circulation. 2017; 135(22):e1054-e1091

Chow SL, Maisel AS, Anand I, et al

Background and Purpose: Natriuretic peptides have led the way as a diagnostic and prognostic tool for the diagnosis and management of heart failure (HF). More recent evidence suggests that natriuretic peptides along with the next generation of biomarkers may provide added value to medical management, which could potentially lower risk of mortality and readmissions. The purpose of this scientific statement is to summarize the existing literature and to provide guidance for the utility of currently available biomarkers.

Methods: The writing group used systematic literature reviews, published translational and clinical studies, clinical practice guidelines, and expert opinion/statements to summarize existing evidence and to identify areas of inadequacy requiring future research. The panel reviewed the most relevant adult medical literature excluding routine laboratory tests using MEDLINE, EMBASE, and Web of Science through December 2016. The document is organized and classified according to the American Heart Association to provide specific suggestions, considerations, or contemporary clinical practice recommendations.

Results: a number of biomarkers associated with HF are well recognized, and measuring their concentrations in circulation can be a convenient and noninvasive approach to provide important information about disease severity and helps in the detection, diagnosis, prognosis, and management of HF. These include natriuretic peptides, soluble suppressor of tumorgenicity 2, highly sensitive troponin, galectin-3, midregional proadrenomedullin, cystatin-C, interleukin-6, procalcitonin, and others. There is a need to further evaluate existing and novel markers for guiding therapy and to summarize their data in a standardized format to improve communication among researchers and practitioners.

Conclusions: HF is a complex syndrome involving diverse pathways and pathological processes that can manifest in circulation as biomarkers. A number of such biomarkers are now clinically available, and monitoring their concentrations in blood not only can provide the clinician information about the diagnosis and severity of HF but also can improve prognostication and treatment strategies.

Comentários: as primeiras recomendações na era da utilização dos biomarcadores na prática clínica começam a emergir. As recomendações da American Heart Association reconhecem o seu interesse no diagnóstico, estratificação e abordagem terapêutica em doentes com Insuficiência Cardíaca. É um trabalho muito equilibrado e permite uma visão global da evidência já disponível e das perspectivas futuras neste tema que se irá tornar angular nos próximos anos.

Effect of Natriuretic Peptide-Guided Therapy on Hospitalization or Cardiovascular Mortality in High-Risk Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial

Felker GM, Anstrom KJ, Adams KF et al

JAMA. 2017 Aug 22;318(8):713-720

Importance: the natriuretic peptides are biochemical markers of heart failure (HF) severity and predictors of adverse outcomes. Smaller studies have evaluated adjusting HF therapy based on natriuretic peptide levels ("guided therapy") with inconsistent results.

Objective: to determine whether an amino-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided treatment strategy improves clinical outcomes vs usual care in high-risk patients with HF and reduced ejection fraction (HFrEF).

Design, Settings, and Participants: The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study was a randomized multicenter clinical trial conducted between January 16, 2013, and September 20, 2016, at 45 clinical sites in the United States and Canada. This study planned to randomize 1100 patients with HFrEF (ejection fraction ≤40%), elevated natriuretic peptide levels within the prior 30 days, and a history of a prior HF event (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care.

Interventions: Patients were randomized to either an NT-proBNP-guided strategy or usual care. Patients randomized to the guided strategy (n = 446) had HF therapy titrated with the goal of achieving a target NT-proBNP of less than 1000 pg/mL. Patients randomized to usual care (n = 448) had HF care in accordance with published guidelines, with emphasis on titration of proven neurohormonal therapies for HF. Serial measurement of NT-proBNP testing was discouraged in the usual care group.

Main Outcomes and Measures: The primary end point was the composite of time-to-first HF hospitalization or cardiovascular mortality. Prespecified secondary end points included all-cause mortality, total hospitalizations for HF, days alive and not hospitalized for cardiovascular reasons, the individual components on the primary end point, and adverse events.

Results: The data and safety monitoring board recommended stopping the study for futility when 894 (median age, 63 years; 286 [32%] women) of the planned 1100 patients had been enrolled with follow-up for a median of 15 months. The primary end point occurred in 164 patients (37%) in the biomarker-guided group and 164 patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% CI, 0.79-1.22; P = .88). Cardiovascular mortality was 12% (n = 53) in the biomarker-guided group and 13% (n = 57) in the usual care group (HR, 0.94; 95% CI; 0.65-1.37; P = .75). None of the secondary end points nor the decreases in the NT-proBNP levels achieved differed significantly between groups.

Conclusions and Relevance: In high-risk patients with HFrEF, a strategy of NT-proBNP-guided therapy was not more effective than a usual care strategy in improving outcomes.

Comentário: O estudo Guide-IT não demonstrou interesse na otimização terapêutica baseada em níveis de NT-proBNP. Se por um lado os resultados foram dececionantes para este tipo de abordag em eles também levantaram questões interessantes e relevantes abrindo novas perspectivas de investigação. Estudos prévios sugerem benefício desta abordagem, especialmente em doentes sem comorbilidades. No ensaio Guide-IT os doentes selecionados tiveram taxas de utilização de fármacos modificadores do prognóstico muito elevadas, facto que pode ter "amortecido" o beneficio espectável mas estes resultados sugerem que o cumprimento das recomendações para o tratamento de doentes com Insuficiência Cardíaca poderã o ser o suficiente par obter bons resultados. Se existem sub-grupos de doentes que terão beneficio com esta abordagem e uma questão que devera ser investigada adicionalmente.

RV Fibrilação auricular 2016/17

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Uma trabuzana varre a Europa.

Em 2010, na Europa, mais de 8 milhões de pessoas foram afetados por um acidente vascular cerebral (1,3 milhões com AVC recentemente diagnosticado nesse mesmo ano). A fibrilação auricular (FA) afeta atualmente aproximadamente 10 milhões de europeus. O envelhecimento iterado da população determina que o número de europeus com FA deverá aumentar para 25-30 milhões no ano de 2050. As dimensões e atributos do trombo na FA faz com que o AVC seja mais grave e com maior risco de morte intra-hospitalar, maior o grau de incapacidade bem como a permanência hospitalar, menor probabilidade de retorno do doente ao seu lar e com risco aumentado de AVC recorrente.

A carga financeira imposta aos países europeus pelo AVC é enorme. Em 2010, o custo estimado do AVC na Europa foi de € 64 bilhões. Assumindo que 15% dos AVC foram causados pela FA e que esses AVC são geralmente mais graves, os custos anuais atribuídos estarão próximos dos 10 mil milhões de euros. Aproximadamente dois terços (66%) destes custos foram custos diretos de saúde; 26% foram custos diretos não médicos e cerca de 8% foram custos indiretos (e.g. perda de produtividade ou reforma antecipada).

Em Portugal, a FA também é a arritmia mais frequente (Bonhorst D, et al. Rev Port Cardiol. 2010; 29 (3): 331-50). Mais presente nas idades mais avançadas (a partir dos 50 anos, a incidência de FA duplica em cada década de vida), a FA afeta cerca de 2,5% da população portuguesa, com valores mais importantes depois dos 70 anos (cerca de 6-10%). Além do mais, um terço dos doentes portugueses com FA desconhece a sua existência. O risco anual de AVC isquémico na FA é de 3 a 5% e é influenciado (e majorado) pela presença de outros problemas concomitantes (e.g. idade, hipertensão arterial, diabetes ou insuficiência cardíaca). A FA é também um importante preditor independente de mortalidade e de perda de qualidade de vida, além de aumentar também o risco de declínio cognitivo e demência.

Em 2010, em Portugal, 4 070 mortes foram atribuídas à FA (3,8% da mortalidade total). A carga de doença atribuível à FA foi estimada em 23 084 DALY (anos de vida perdidos ajustados pela incapacidade, a soma dos anos perdidos devido à mortalidade precoce e o número de anos vividos com incapacidade, ajustados para a gravidade da doença): 10 521 resultantes das mortes prematuras (1,7% do total de DALY devido a morte em 2010 em Portugal) e 12 563 por invalidez. Os custos totais estimados diretos atribuíveis à FA (preços de 2013) foram 115 milhões de euros: 34 milhões de euros com cuidados hospitalares e 81 milhões nos cuidados ambulatórios. Os custos indiretos resultantes da perda de produção por incapacidade foram estimados em 25 milhões de euros. A FA tem, pois, entre nós, um impacto social importante e foi responsável em 2013 por um custo total de € 140 milhões, cerca de 0,08% do produto interno bruto (Gouveia M, et al. Rev Port Cardiol. 2015; 34 (1): 1-11).

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC).

Kirchhof P, Benussi S, Kotecha D, et al

Eur Heart J. 2016; 37(38): 2893-962.

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Furthermore, the number of patients with AF is predicted to rise steeply in the coming years. To meet the growing demand for effective care of patients with AF, new information is continually generated and published, and the last few years have seen substantial progress. Therefore, it seems timely to publish this 2nd edition of the ESC guidelines on AF. Reflecting the multidisciplinary input into the management of patients with AF, the Task Force includes cardiologists with varying subspecialty expertise, cardiac surgeons, stroke neurologists, and specialist nurses amongst its members. (…). Further to adhering to the standards for generating recommendations that are common to all ESC guidelines (see preamble), this Task Force discussed each draft recommendation during web-based conference calls dedicated to specific chapters, followed by consensus modifications and an online vote on each recommendation. Only recommendations that were supported by at least 75% of the Task Force members were included in the guidelines. We hope that these guidelines will help to deliver good care to all patients with AF based on the current state-of-the-art evidence in 2016.

Comentário: *inevitável. Como omitir a publicação das novas recomendações europeias na abordagem da fibrilação auricular (FA)?! Irrecusável.*

A estratégia terapêutica da FA evoluiu substancialmente na última década. Assim o impôs as novas opções terapêuticas disponíveis (em particular os anticoagulantes orais diretos) e a estruturação e definição de planos de intervenção inovadores. Temos agora ao nosso dispor as novas diretrizes da prática clínica na FA, suportadas – desejavelmente – pela melhor evidência científica, complementadas pelos melhores dados epidemiológicos e pelos pareceres de reconhecidos especialistas. Idealmente, estas recomendações foram desenvolvidas na procura da melhoria de resultados clínicos e da qualidade dos cuidados prestados à população com FA, cada vez mais idosa e com as mais diversas comorbilidades, que amplificam a complexidade e a especificidade da nossa atuação. No centro da nossa atuação continua a estar o doente. Reconhecer a tomada de decisão centrada no doente é estar atento ao encadeamento biopsicossocial do doente e da doença, que contextualiza a decisão clínica, o suporte científico da mesma, a informação clínica, a aderência ao tratamento e os objetivos que são pretendidos e desejavelmente alcançados.

Centrar no e com o doente a decisão partilhada é agregar à prática médica as suas perspetivas, crenças, expectativas e objetivos na vida, na saúde e na doença. É também comunicar e reconhecer os benefícios e danos potenciais, os custos e os inconvenientes que uma opção – qualquer que ela seja! – tem para o doente e, em última análise, para a melhor diligência da evidência disponível. Permitam-me a ousadia de salientar alguns dos muitos pontos importantes: a pronto reconhecimento do doente em FA, a afirmação do risco de acidente vascular cerebral e a redução do mesmo, as opções terapêuticas disponíveis – maximizando benefício e minimizando os riscos da

anticoagulação oral, o posicionamento real – e não ilusório – da antiagregação plaquetária e a perspetivação correta do controlo e do ritmo cardíaco.

Por isso, talvez valha também a pena de concatenar as diretrizes europeias com as canadianas –muito didáticas –, também publicadas em 2016 (Macle L, et al. Can J Cardiol. 2016; 32(10): 1170-85), e também, necessariamente, com o consenso europeu para os cuidados primários (Hobbs FR, et al. Eur J Prev Cardiol. 2016; 23(5): 460-73). A Medicina Geral e Familiar é, com a Medicina Interna e a Cardiologia (e, depois, a Neurologia), uma das pilastras essenciais no tratamento destes doentes.

Entretanto, gostaria de chamar a atenção para um óbvio tão mitigado… Não somos ainda capazes de –com base nos processos subjacentes ao risco de AVC –personalizar estratégias de prevenção definidoras e estruturantes nos doentes de alto risco. No entanto, os dados do INTERSTROKE, publicados este ano (O'Donnell MJ, et al. Lancet. 2016; 388(10046): 761-75) indicam que, a nível populacional, as causas primárias do AVC não têm nada de ininteligível. Coletivamente, 10 fatores aclaram 91% do risco populacional atribuído de AVC. As doenças cardíacas como a FA contribuem para 9% do risco. As restantes são – por ordem decrescente – a hipertensão arterial (48%), o sedentarismo e a inatividade física (36%), a dislipidemia (27%), a dieta não saudável (23%), o aumento do perímetro abdominal – e, por inferência, a obesidade – (19%), os fatores psicossociais (e.g. depressão) (17%), o tabagismo ativo (12%), o consumo excessivo de álcool (6%) e a diabetes mellitus (4%) (no conjunto, o risco excede os 100% porque vários fatores de risco podem coexistir num mesmo doente).

A propósito, gostaria de evocar um artigo recente que recorda o caminho já trilhado, mas também as dificuldades, os escolhos e as contrariedades que persistem ainda nas mais recentes recomendações (Barnett AS, et al. JAMA Cardiol. 2017; 2(3): 319-23). A apreciação das sucessivas diretrizes clínicas- de 2001 a 2014 – na FA (suportadas pelo American College of Cardiology, American Heart Association e Heart Rhythm Society) asseguram que, no total, o número de recomendações aumentou de 96 em 2001 para 113 em 2014.No entanto, talvez um pouco surpreendentemente, as classes de recomendação e os níveis de evidência pouco alteraram: só 43,4% das recomendações são de classe I (os benefícios superam largamente os riscos), proporção análoga às de classe IIa/IIb (os benefícios superam ou são iguais aos riscos); o nível A da evidência é, consistentemente, muito pouco frequente (só 8,8%), apesar do incremento muito discreto das recomendações de nível B (em 2001, eram 30,5% e alcançaram 39,8, em 2014). O corrente – sem sequer criticável, mas não deixa de ser importante constatar – é as recomendações derivarem do consenso mais generalizado de peritos (51,3% das recomendações. Atentemos: em2014, das recomendações da classe I, 59,2% tinham suporte de nível C. Urge dedicarmos mais atenção aos estudos – provavelmente da iniciativa de investigador! – que precisariam de ser efectivados para que a tão desejada evidência fosse mais acareada. A Medicina – por maioria de razão a Medicina cardiovascular – é uma arte e uma ciência. A abordagem da FA – por natureza complexa, multidisciplinar e multifatorial –, ainda que suportada em recomendações, não deixa de ser uma arte. Partilhar decisões com o doente (e, por vezes, com o seu cuidador) é também, obrigatoriamente, admitir a qualidade diversa da evidência que trespassa as directrizes clínicas. Isto também é parte da arte, do talento e destreza do ato médico.

Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis.

Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA.

***BMJ.* 2016; 354: i4482. doi: 10.1136/bmj.i4482.**

Objective: To quantify the association between atrial fibrillation and cardiovascular disease, renal disease, and death.

Design: Systematic review and meta-analysis. Data sources: Medline and Embase.

Eligibility criteria: Cohort studies examining the association between atrial fibrillation and cardiovascular disease, renal disease, and death. Two reviewers independently extracted study characteristics and the relative risk of outcomes associated with atrial fibrillation: specifically, all-cause mortality, cardiovascular mortality, major cardiovascular events, any stroke, ischaemic stroke, haemorrhagic stroke, ischaemic heart disease, sudden cardiac death, congestive heart failure, chronic kidney disease, and peripheral arterial disease. Estimates were pooled with inverse variance weighted random effects meta-analysis.

Results: 104 eligible cohort studies involving 9 686 513 participants (587 867 with atrial fibrillation) were identified. Atrial fibrillation was associated with an increased risk of all cause mortality (relative risk 1.46, 95% confidence interval 1.39 to 1.54), cardiovascular mortality (2.03, 1.79 to 2.30), major cardiovascular events (1.96, 1.53 to 2.51), stroke (2.42, 2.17 to 2.71), ischaemic stroke (2.33, 1.84 to 2.94), ischaemic heart disease (1.61, 1.38 to 1.87), sudden cardiac death (1.88, 1.36 to 2.60), heart failure (4.99, 3.04 to 8.22), chronic kidney disease (1.64, 1.41 to 1.91), and peripheral arterial disease (1.31, 1.19 to 1.45) but not haemorrhagic stroke (2.00, 0.67 to 5.96). Among the outcomes examined, the highest absolute risk increase was for heart failure. Associations between atrial fibrillation and included outcomes were broadly consistent across subgroups and in sensitivity analyses.

Conclusions: Atrial fibrillation is associated with an increased risk of death and an increased risk of cardiovascular and renal disease. Interventions aimed at reducing outcomes beyond stroke are warranted in patients with atrial fibrillation.

*Comentário: **é** comum afirmarmos – sem termos, em consciência, das suas mais largas implicações – que a fibrilação auricular (FA), a arritmia mais comum dos idosos, está arrolada a maior morbilidade e mortalidade cardiovascular (CV) e a um elevado potencial de embolização (o risco de acidente vascular cerebral (AVC) aumenta de 4-5 vezes nos doentes com FA). O AVC cardioembólico tem um pior prognóstico, com maior risco secundário de hemorragia, maior deterioração das funções cognitivas e maior taxa de mortalidade a médio prazo.*

Esta meta-análise de 104 coortes (9,7 milhões de doentes, 590 000 com FA) certifica que a FA está também associada a excesso de risco de morbilidade e mortalidade CV. Após um acompanhamento médio de 3 a 6 anos, a FA esteve associada a um risco significativamente mais alto de doença arterial periférica (DAP), doença cardíaca isquémica e renal crônica, morte súbita cardíaca, eventos adversos major e morte CV, AVC e insuficiência cardíaca (com riscos relativos entre 1,3 para DAP e 5,0 para IC). Os resultados foram consistentes em todos subgrupos de doentes (independentes da idade ou dos antecedentes de cardiopatia isquémica ou AVC) e transversais às características inerentes de cada coorte (e.g. população e origem do estudo e tempo de acompanhamento).

Especificamente, de acordo com este estudo – que reputo de fundamental – a FA esteve associada aos sequentes aumentos no risco absoluto:

- *Insuficiência cardíaca congestiva: 11,1 eventos por 1 000 doentes-ano*
- *Doença renal crónica: 6,6 / 1 000*
- *Mortalidade por todas as causas: 3,8 / 1000 e mortalidade cardiovascular: 2,6 / 1000*
- *AVC total: 3,6 / 1000 e isquémico: 2,9 / 1000*
- *Cardiopatia isquémica: 1,4 / 1000 e morte cardíaca súbita, 0,6 / 1000*

Neste complexo redundante fisiopatológico em que a FA aumenta o risco de patologias que, por sua vez, amplificam o risco da FA e das suas potenciais complicações major, temos, no entanto, de anotar que uma associação não afirma ou estabelece causalidade. Os autores, aliás, muito corretamente, referem que a FA pode estar a operar como um marcador de predisposição para os efeitos adversos renais e CV aqui sublinhados. Reconhecê-lo é intender como a carga total da doença atribuível à FA, em Portugal, é de 23 084 DALY e o custo global da doença estimado é de € 140,7 milhões (≈ 0, 08% do produto interno bruto) (Gouveia M, et al. Rev Port Cardiol. 2015; 34(1): 1-11). Esta perspetiva, mais real e mais alargada, é um imperativo suplementar para estruturar e definir estratégias de intervenção que confrontem a prevenção do AVC, mas também para as outras entidades e realidades clínicas que estão com a FA associadas.

Uma palavra adicional para lembrar um artigo de 2016 que chama a atenção para uma maior vulnerabilidade de género na morbimortalidade CV relacionada com a FA (Emdin CA, et al. BMJ. 2016 Jan 19;532:h7013. doi: 10.1136/bmj.h7013). Esta outra meta-análise que incluiu 30 estudos de coorte, num total de quase 4,4 milhões de indivíduos, avaliou a associações específica do género entre a FA e a morbilidade e mortalidade CV. Aparentemente, as mulheres com FA tinham um risco maior que os homens para a mortalidade total, AVC, mortalidade e eventos CV e insuficiência cardíaca (em termos absolutos, a FA, nas mulheres, esteve relacionado com 1,8 óbitos adicionais por 1000 doentes-ano, 3,1 AVC adicionais, 4,3 mortes CV, 0,6 eventos cardíacos e 6,1 casos de insuficiência cardíaca). Parece, assim, justificado a importância que é dada ao género feminino no CHA_2DS_2-VASc e também a questionar se haverá – entretanto – diferenças relacionadas com o género na hemostasia e nos mecanismos fisiopatológicos de trombose que justifiquem estratégias antitrombóticas específicas, com eficácia variegada, que tornem mais efetiva o tratamento da FA e prevenção das complicações nas mulheres.

A propósito (perturbador!), na mulher, a FA recentemente diagnosticada está associada ao aumento do risco de cancro (e vice-versa) (Conen D, et al. JAMA Cardiol. 2016; 1(4): 389-96). Uma análise recente de 35 000 mulheres saudáveis do Women's Health Study, acompanhadas durante 19 anos, notou que 4% desenvolveram FA e 15% cancro. As mulheres com FA de novo tiveram taxas significativamente maiores de cancro incidente (1,4 vs. 0,8 por 100 pessoas-anos) – efeito que perdurou para além de um ano após o diagnóstico de FA – da mesma forma que as mulheres com o diagnóstico de novo de cancro exibiram também taxas mais elevadas de FA de novo (0,38 vs. 0,24 eventos por 100 pessoas-ano); no entanto, no caso, a diferença só foi significativa nos primeiros 3 meses. De base, muito provavelmente, multifatorial e mecanismos ainda não elucidados, mas partilhando, possivelmente, fatores de risco que são comuns, podemos admitir que o maior risco de hemorragia com a anticoagulação oral em doentes com cancro (em particular com localização gastrointestinal) pode coadjuvar a sua deteção e o maior diagnóstico, mas – de momento – longe de constituir uma escora à implementação do rastreio do cancro nos doentes com FA. Malhas que a medicina tece… mas que torna relevante e estruturante o senso clínico…

"Do tempo ao coração minado pelo cancro/Dos rins ao infinito incubado na cólera" apontava David Mourão-Ferreira no poema "Do tempo ao coração". E eis que, em 2017, um registo norueguês, com cerca de 1,3

milhão de adultos entre 52 e 82 anos, dos quais 7% estavam medicados com varfarina, o uso com este antivitamínico K (AVK) esteve acomunado a uma menor incidência de cancro entre os adultos > 50 anos (Haaland GS, et al. JAMA Intern Med. 2017; 177(12): 1774-80). Concretizando, após um período médio de acompanhamento de 6 anos, a taxa de novos casos de cancro foi maior nos doentes não medicados com varfarina (10,6% vs. 9,4%; razão da taxa de incidência [IRR] 0.84; IC95%, 0.82-0.86)). O uso da varfarina esteve associado a taxas de incidência menores de cancro da próstata (IRR 0,6; 0,65-0,72), pulmão (0,80; 0,75-0,86) e mama (0,90; 0,82-1,00). Uma análise de subgrupo, realizada de modo a excluir os doentes que possam ter sido anticoagulados na sequência de doença tromboembólica associada a malignidade oculta, sublinhou que as maiores reduções de risco foram observadas nos doentes com FA/flutter auricular.

Porquê? Novos motivos e mecanismos são aventados e o bloqueio de algum traço de malignidade agressiva das células carcinomatosas pode – potencialmente – condicionar o desenvolvimento e progressão neoplásica (a inibição da via do GAS6-AXL, recetor AXL da tirosina quinase, presente nas células imunológicas e cancerosas, pela varfarina pode ser o possível "target-off" dos AVK): Nota: estudos recentes indiciam que este recetor e a respetiva via de sinalização podem ter um papel central na proliferação e sobrevivência de tumor, no fenótipo da célula estaminal e na metástase e resistência à terapia anticancerosa (Rankin EB, Giaccia AJ. Cancers (Basel). 2016; 8(11). pii: E103). Entretanto, reconheçamos que os estudos populacionais não inferir qualquer relação de causalidade e que os doentes medicados com varfarina a longo prazo podem ser distintos, em aspectos importantes (e.g. susceptibilidade e modificação dietética, restrição alcoólica e de outros fármacos passíveis de interacções e modificação dos estilos de vida) dos não medicados.

Uma revisão da Cochrane (Kahale LA, et al. Cochrane Database Syst Rev. 2017 Dec 29;12:CD006466. doi: 10.1002/14651858.CD006466.pub6.) sugere que não há um aparente benefício na mortalidade a um ano dos doentes com cancro e sem indicação terapêutica ou profiláctica para e da anticoagulação oral (mesmo nos doentes com AVK…), mas, pelo contrário, aventa um maior risco de hemorragia.

Um outro registro – desta vez sueco –, com mais de 440 mil adultos com FA e sem antecedentes de demência, assevera que os doentes sujeitos a anticoagulação oral tiveram uma redução de 29% no risco de desenvolvimento de demência (durante o acompanhamento – de 2006 a 2014 –, cerca de 6% da coorte desenvolveram demência, 1,73 diagnósticos por 100 pacientes-ano), sem diferença aparente entre os doentes com varfarina ou com anticoagulantes orais diretos (Friberg L, Rosenqvist M. Eur Heart J. 2017 Oct 24. doi: 10.1093/eurheartj/ehx579). Uma vez que o tempo do diagnóstico de FA para o início do tratamento se comportou como um fator de risco independente para a demência, o início precoce do tratamento é surge como um imperativo na preservação da função cognitiva.

Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes.

Swiryn S, Orlov MV, Benditt DG, for the RATE Registry Investigators.

Circulation. 2016; 134(16): 1130-40.

Background: The RATE Registry (Registry of Atrial Tachycardia and Atrial Fibrillation Episodes) is a prospective, outcomes-oriented registry designed to document the prevalence of atrial tachycardia and/or fibrillation (AT/AF) of any duration in patients with pacemakers and implantable cardioverter defibrillators (ICDs) and evaluate associations between rigorously adjudicated AT/AF and predefined clinical events, including stroke. The appropriate clinical response to brief episodes of AT/AF remains unclear.

Methods: Rigorously adjudicated electrogram (EGM) data were correlated with adjudicated clinical events with logistic regression and Cox models. Long episodes of AT/AF were defined as episodes in which the onset and/or offset of AT/AF was not present within a single EGM recording. Short episodes of AT/AF were defined as episodes in which both the onset and offset of AT/AF were present within a single EGM recording.

Results: We enrolled 5379 patients with pacemakers (N=3141) or ICDs (N=2238) at 225 US sites (median follow-up 22.9 months). There were 359 deaths. There were 478 hospitalizations among 342 patients for clinical events. We adjudicated 37 531 EGMs; 50% of patients had at least one episode of AT/AF. Patients with clinical events were more likely than those without to have long AT/AF (31.9% vs. 22.1% for pacemaker patients and 28.7% vs. 20.2% for ICD patients; P<0.05 for both groups). Only short episodes of AT/AF were documented in 9% of pacemaker patients and 16% of ICD patients. Patients with clinical events were no more likely than those without to have short AT/AF (5.1% vs. 7.9% for pacemaker patients and 11.5% vs. 10.4% for ICD patients; P=0.21 and 0.66, respectively).

Conclusions: In the RATE Registry, rigorously adjudicated short episodes of AT/AF, as defined, were not associated with increased risk of clinical events compared with patients without documented AT/AF.

Subclinical Atrial Fibrillation in Older Patients.

Healey JS, Alings M, Ha A, Leong-Sit P, for the ASSERT-II Investigators.

Circulation. 2017; 136(14): 1276-83.

Background: Long-term continuous electrocardiographic monitoring shows a substantial prevalence of asymptomatic, subclinical atrial fibrillation (SCAF) in patients with pacemakers and patients with cryptogenic stroke. Whether SCAF is also common in other patients without these conditions is un known.

Methods: We implanted subcutaneous electrocardiographic monitors (St. Jude CONFIRM-AF) in patients ≥65 years of age attending cardiovascular or neurology outpatient clinics if they had no history of atrial fibrillation but had any of the following: CHA2DS2-VASc score of ≥2, sleep apnea, or body mass index >30 kg/m2. Eligibility also required either left atrial enlargement (≥4.4 cm or volume ≥58 mL) or increased (≥290 pg/mL) serum NT-proBNP (N-terminal pro-B-type natriuretic peptide). Patients were monitored for SCAF lasting ≥5 minutes.

Results: Two hundred fifty-six patients were followed up for 16.3±3.8 months. Baseline age was 74±6 years; mean CHA_2DS_2-VASc score was 4.1±1.4; left atrial diameter averaged 4.7±0.8 cm; and 48% had a prior stroke, transient ischemic attack, or systemic embolism. SCAF ≥5 minutes was detected in 90 patients (detection rate, 34.4%/y; 95% confidence interval [CI], 27.7-42.3). Baseline predictors of SCAF were increased age (hazard ratio [HR] per decade, 1.55; 95% CI, 1.11-2.15), left atrial dimension (HR per centimeter diameter, 1.43; 95% CI, 1.09-1.86), and blood pressure (HR per 10 mm Hg, 0.87; 95% CI, 0.78-0.98), but not prior stroke. The rate of occurrence of SCAF in those with a history of stroke, systemic embolism, or transient ischemic attack was 39.4%/y versus 30.3%/y without (P=0.32). The cumulative SCAF detection rate was higher (51.9%/y) in those with left atrial volume above the median value of 73.5 mL.

Conclusions: SCAF is frequently detected by continuous electrocardiographic monitoring in older patients without a history of atrial fibrillation who are attending outpatient cardiology and neurology clinics. Its clinical significance is unclear.

Clinical trial registration: www.clinicaltrials.gov. Unique identifier: NCT01694394.

*Comentário: **s**ituemos o problema. Habitualmente, a fibrilação auricular (FA) é classificada com base na duração dos episódios. Por outro lado, na FA ocorrem mudanças estruturais e funcionais auriculares – em doentes com hipertensão, doença coronária e várias cardiomiopatias – que promovem a propagação e manutenção de atividade elétrica anormal. Além disso, outras comorbilidades tais como a diabetes, a doença pulmonar, o hipotireoidismo e a apneia obstrutiva do sono (AOS), assim como a obesidade, são reconhecidos fatores para o desenvolvimento da FA. A cirurgia cardiotorácica, incluindo cirurgia de revascularização miocárdica, é também um fator de risco substancial para o desenvolvimento da FA no pós-operatório.*

Pode-se, assim, falar da FA detetada ou diagnosticada pela primeira vez (independente da duração e da presença ou não de sintomas); da FA paroxística, recorrente (mais de 2 episódios) com duração < 24 a 48 horas, que terminam espontaneamente (mas podem também durar até 7 dias) – depois, a taxa de conclusão espontânea é baixa e a anticoagulação é justificada –; da FA persistente, com duração > 7 dias e que exige a cardioversão elétrica ou intervenção farmacológica; da FA persistente de longa duração > 1 ano; e da FA permanente. Além disso, fala-se de FA solitária (ou idiopática) quando ocorre em doentes < 60 anos sem doença cardiovascular estrutural ou ecocardiográfica (que poderia ser paroxística, persistente ou permanente), de FA silenciosa,

assintomática (achada em rotina ou após complicação clínica) e de FA autonómica (vagal ou adrenérgica), em que o sistema nervoso autónomo desempenha um papel central na sua génese.

A FA aumenta o risco de eventos tromboembólicos sistémicos (SEE) (nomeadamente de acidente vascular cerebral). A frequência e duração dos episódios de FA que aumentam o risco de SEE são atualmente ponto de estudo (e de altercação frequente). Permanece insondado se o incremento do risco depende de um qualquer limiar de densidade de FA (parecendo incontestável que o risco está bem presente com uma FA > 5 minutos). Aparentemente, neste de registo agora publicado, com mais de 5 300 doentes, pequenos surtos, limitados no tempo (< 10 a 20 segundos) de FA não estiveram associadas com SEE. Com um período médio de acompanhamento de 23 meses, os doentes com eventos clínicos (morte, ida à urgência ou hospitalização por insuficiência cardíaca, arritmia auricular ou ventricular, AVC/AIT e síncope); aparentaram uma maior probabilidade de taquidisritmia de maior duração ao contrário dos doentes com episódios de curta duração. Por isso, nestes indivíduos, os riscos da anticoagulação pode superar os seus benefícios. No entanto, recordemos, que o risco de AVC não depende só dos fatores arrolados ao ritmo, mas também do substrato do tecido auricular e de fatores de risco vascular sistémicos (Fabritz L, et al. Nat Rev Cardiol. 2016; 13(4): 230-7).

Anote-se, entretanto, que trabalhos recentes sugerem que, nos doentes com AVC de causa indeterminada (AVC criptogénico), a monitorização continuada pós-evento leva a detecção de FA intermitente em 5 a 20%. A monitorização prolongada (durante 10 dias) por Holter de 400 doentes com > 60 anos após a ocorrência de um AVC isquémico, aos 3 e aos 6 meses, verificou que foi detetada FA em 14% dos doentes (Wachter R, et al. Find-AF(randomised) Investigators and Coordinators. Lancet Neurol. 2017; 16(4): 282-90) e iniciaram anticoagulação oral.

No estudo ASSERT II (Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor), com 256 doentes com ≥ 65 anos, sem antecedentes de FA, mas com risco elevado de FA subclínica (CHA_2DS_2-VASc ≥ 2, apneia do sono ou índice de massa corporal > 30 kg/m^2, além da dilatação da aurícula esquerda e de níveis plasmáticos do fragmento N-terminal do peptídeo natriurético tipo B [NT-ProBNP]]) e quase 50% com AVC/SEE prévio, com monitores eletrocardiográficos subcutâneos implantados, acompanhados por um período médio de 16 meses, um terço teve um episódio de FA, pelo menos, com ≥ 5 minutos (taxa de deteção anual de 34%). Os preditores da FA subclínica abarcaram a idade mais avançada, a maior dilatação auricular e a pressão arterial sistólica mais baixa. Temos, no entanto, de ter em conta que estes resultados, pelos critérios de inclusão detalhados e pelo elevado número de doentes com antecedentes de AVC/SEE, podem não ser generalizáveis. Por outro lado, pela falta de poder estatístico e porque só 4 dos doentes tiveram AVC isquémico (curiosamente, nenhum com FA subclínica), não é possível discernir se e quando devemos anticoagular.

Por outro lado, inesperadamente, a U.S. Preventive Services Task Force (USPSTF), no final de 2017, não endossou o rastreio electrocardiográfico na detecção de FA (ou na prevenção cardiovascular). Difícil de entender! A USPSTF declara que não há evidências suficientes recomendar a realização (ou estar contra) na triagem de FA em idosos assintomáticos (mas não subestima a triagem oportunista ou cuidados habituais de primeira observação – e subsequentes – a prestar em adultos mais velhos) (www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement/ atrial-fibrillation-screening-with-electrocardiography). *Difícil de julgar já que um número substancial de doentes (em especial os internados com AVC), para além da imaginável presença de FA, tem muitas outras condições cardíacas relevantes (e.g. isquemia do miocárdio ou outras disritmias ventriculares). Admitamos: a apreciação de um ECG pré-internamento pode ser muito útil! Numa avaliação recente de 259 doentes com AVC (idade média de 76 anos e 90% com AVC isquémico) 28% já tinham FA prévia, conhecida, e 17% dos doentes aparentaram FA de novo. Além disso, em muitos casos foi possível reconhecer outras alterações eletrocardiográficas relevantes (Bobinger T, et al.*

Neurology. 2017; 88(20): 1894-8). Uma certeza: um ECG pré-hospitalar pode reter informações diagnósticas marcantes que podem, em última análise, não estar disponíveis nos traçados obtidos no acesso do doente ao hospital (e.g. urgência) (Boothroyd LJ, et al. Prehosp Emerg Care. 2013; 17(2): 187-92). Um bom exemplo: os idosos com AVC, que, frequentemente, ostentam anomalias cardíacas coexistentes. A identificação destas alterações – pré-existentes – pode ajudar a fundamentar uma abordagem diagnóstica e terapêutica diversa. Temos, pois, um longo caminho a percorrer ainda antes de fundamentarmos – com base em evidências – um plano terapêutico personalizado na prevenção do SEE associado com a FA.

Tentemos um pequeno passo supletivo. "Caminhante, não há caminho/se faz caminho ao andar" (António Machado). Por exemplo, ao contrário da definição operacional apontada, n uma série de doentes com FA isolada, foi possível definir várias anomalias imperceptíveis na aurícula e no ventrículo esquerdo. Assim, num estudo de 2016 (Wijesurendra RS, et al. Circulation. 2016; 134(15): 1068-81), a par de causas genéticas e de taquicardias auriculares focais, alterações subtis na função auricular ou ventricular esquerda parecem contribuir para a FA e serem até mais patentes nos doentes em que a FA persiste apesar do ilusório sucesso da ablação. Será um possível motivo de estudo e reflexão na nossa abordagem fundamentada da FA isolada!

Esta ponderação é, ainda, mais pertinente quando o seguimento de 10 anos de mais de 700 doentes com FA paroxística, num dos registos canadianos (Canadian Registry of Atrial Fibrillation – CARAF), confirma que 36% destes doentes "progridem" para FA persistente (e 30% morrem de qualquer causa nos primeiros 10 anos depois de terem, pela primeira vez, o diagnóstico de FA) (Padfield GJ, et al. Heart Rhythm. 2017; 14(6): 801-7). Ainda mais, os doentes com FA paroxística são substancialmente menos atreitos a serem tratados com anticoagulantes orais do que doentes com FA persistente ou permanente (Isaew A, et al. Heart. 2017; 103(19): 1502-7). Retomando os dados do CARAF… Anotem-se os fatores pronunciados como prognóstico na progressão da FA paroxística para persistente: a idade, a presença de dilatação da aurícula esquerda, de regurgitação mitral ou de estenose aórtica e a coexistência de hipertrofia ventricular esquerda (no entanto, depois de ponderar o risco concorrente de morte por todas as causas, a hipertrofia ventricular esquerda e a estenose aórtica deixaram de ser significativas!).

Mas, não esqueçamos o fundamental: os doentes com episódios de FA com duração > 24 horas têm um risco de SEE especialmente elevado!... (Witt CT, et al. Heart Rhythm. 2015; 12(12): 2368-75). Ao fim de 2,4 anos, a taxa anual de FA clínica foi significativamente maior nos doentes com episódios de FA de maior duração, tendo-se verificado em 40% destes doentes um evento trombótico, mesmo após o ajustamento para o CHA_2DS_2-VASc respetivo. De facto, o diagnóstico precoce de FA é extremamente importante. Por exemplo, a avaliação da ecocardiografia transesofágica em doentes com AVC pretensamente embólico parece ter um lugar importante na avaliação destes doentes (Katsanos AH, et al. Neurology. 2016; 87(10): 988-95). Situando: entre as etiologias mais comuns do AVC isquémico estão a aterosclerose dos grandes vasos, a doença oclusiva dos pequenos vasos e, naturalmente, as situações cardioembólicas (de que a FA é um paradigma). No entanto, em cerca de 20-30% dos AVC em que se admite um possível substrato embólico não se consegue – apesar de uma aturada avaliação clínica e imagiológica – descortinar uma fonte específica de embolismo. Nestes casos vale a pena ressaltar o papel central da TEE (na deteção, por exemplo, de trombose auricular esquerda, de foramen oval permeável, coexistindo com uma trombose venosa profunda ou de fibroelastoma cardíaco). Numa meta-análise, com 3 562 doentes com AVC isquémico, a taxa de iniciação de anticoagulação oral, em função dos resultados do TEE, foi de 8,7%. No entanto, tendo em conta que a média de idades deste coorte era de 44 anos (e um NIH Stroke Scale mediano de 5), julgamos que numa população mais idosa (> 60 anos), com AVC embólico de etiologia desconhecida será mandatório – talvez preferível! – pautar a necessidade de monitorização prolongada de eventos, na procura de uma FA, acautelando o uso mais seletivo de uma eventual TEE. Uma revisão sistemática recente (Sposato LA, et al. Lancet Neurol. 2015; 14(4): 377-87), com 28 290 estudos, 50 dos quais com 11 658 doentes, mostrou que em 23,7% dos

doentes foi possível fazer o diagnóstico de FA pós-AVC, com a combinação sequencial dos métodos de monitorização cardíaca. Deste modo, a relação global de doentes com AVC/AIT conhecidos com FA parece ser superior ao previamente antecipado.

Uma palavra de ponderação para evocar que não há benefício clínico comprovado para iniciar ou manter anticoagulação oral a longo prazo nos doentes com FA secundária (Quon MJ, et al. JACC Clin Electrophysiol 2017; doi: 10.1016/j.jacep.2017.08.003). Nos doentes com FA transitória durante a hospitalização por síndrome coronária aguda, sépsis ou doença pulmonar aguda, a prescrição de um anticoagulante oral – na alta hospitalar – não aparentou qualquer benefício clínico (redução do risco de AVC) aos 3 anos (e pode modular negativamente o risco hemorrágico) e a recorrência de FA só ocorreu em cerca de metade dos mais de 2 300 doentes (idade média ≈ 78 anos) incluídos neste registo. No entanto, há que ter em conta a discordância deste estudo com a informação derivada do Framingham Heart Study (Lubitz SA, et al. Circulation. 2015; 131(19): 1648-55). Neste coorte a recorrência de FA foi muito mais comum… ocorreu aliás, em 544 dos 846 com FA secundária (com taxas de recorrência aos 5, 10 e 15 anos de 42%, 56% e 62%, respetivamente). O risco de AVC e de mortalidade total nos doentes com precipitantes conhecidos de FA (e.g. cirurgia, infeção, enfarte agudo do miocárdio, tireotoxicose, libação alcoólica aguda, pericardite aguda, embolismo pulmonar ou outra pneumopatia aguda) foi similar ao dos doentes com FA "idiopática". Assim, parece judicioso que, na ausência de dados mais robustos, a decisão terapêutica assente na judiciosa avaliação particularizada, individual… Entretanto, esperemos que estudos futuros sejam capazes de aclarar se a maior cuidado no rastreio de recorrência da FA ou a adesão às normas gerais de abordagem clínica desta arritmia nos doentes com fatores precipitantes reversíveis reconhecidos reduzem (ou não) a morbimortalidade cardiovascular e total.

Stability of International Normalized Ratios in patients taking long-term warfarin therapy (Letter].

Pokorney SD, Simon DN, Thomas L, Gersh BJ, Hylek EM, Piccini JP, Peterson ED.

JAMA. 2016; 316(6): 661-3.

Warfarin substantially decreases stroke risk among patients with atrial fibrillation yet has a narrow therapeutic window (international normalized ratio [INR] values of 2.0-3.0) and is associated with multiple drug and food interactions. Non–vitamin K oral anticoagulants do not require drug monitoring and have similar or improved safety and efficacy relative to warfarin but are more costly. Whether patients previously stable on warfarin should be switched to non–vitamin K oral anticoagulants remains controversial but may be informed by determining whether patients receiving warfarin who have stable INR values remain stable over time.

Comentário: os anti vitamínicos K (AVK) foram, até há algum tempo, a pedra de toque na prevenção do acidente vascular cerebral (AVC) na fibrilação auricular (FA). O efeito anticoagulante dos AVK é medido pelo índice normalizado internacional (INR). A faixa recomendada do INR para a prevenção de AVC nos doentes com FA não valvular é de 2,0 a 3,0. A diminuição do INR de 2,0 para 1,7 está arrolada à duplicação do risco de AVC isquémico e a mudança para 1,4 duplica de novo o risco. Um INR > 4 está associado a um risco aumentado de hemorragia subdural. A proporção de tempo mantida com um INR de 2-3, - corretamente definida como tempo em intervalo terapêutico (TTR) – foi validada como um preditor prognóstico da efetividade terapêutica da anticoagulação. A análise posterior do ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) mostrou que é necessário um TTR de, pelo menos, 58-65% para afirmar o benefício da varfarina na prevenção do AVC na FA.

Como os AVK tem um intervalo terapêutico estreito e há grande variabilidade nas dosagens requeridas, é largamente reconhecido o risco de insuficiência e sobredosagem terapêutica. O reconhecimento de que os polimorfismos nos genes CYP2C9 e VKORC1 – conjuntamente com a área de superfície corporal e com a idade – serem responsáveis por ≈ 50% da variabilidade da dose diária de AVK fez antever a possibilidade do seu ajuste ser controlado, pelo menos em parte, pelo genótipo respetivo. Embora alguns resultados preliminares tenham sido promitentes, a genotipagem na prescrição de AVK não está recomendada, dada a falta de dados suficientes de ensaios controlados aleatorizados, janela de utilidade relativamente breve e custo-benefício incerto.

Entretanto, esta carta ao JAMA confirma que a estabilidade do INR permanece um problema não resolvido: só um terço dos doentes que tinham tido INR estáveis durante 6 meses (80% dos INR entre 2,0-3,0), permaneceram controlados a mais longo prazo. Um quarto dos doentes foi considerado estável durante os primeiros 6 meses (com base na mediana de oito determinações do INR). Destes, só 34% mantiveram essa condição no ano subsequente (mediana de 13 medições de INR). Além disso, mesmo nos doentes que mantiveram, durante 6 meses, INR sempre na faixa terapêutica, só 37% mantiveram a estabilidade terapêutica no ano seguinte. Assim, apesar de podermos cogitar que a estabilidade inicial – durante vários meses – na anticoagulação faria prever a maior estabilidade a longo prazo, estes resultados "do mundo real" mostra como esta consideração é fútil e potencialmente deletéria.

Em Portugal, uma meta-análise recente revela que a prevalência da terapêutica anticoagulante oral nos doentes portugueses com FA é de 40% (IC 95%: 32-48%), mais elevada na comunidade (45%; IC 95%: 37-52 %) do que nos estudos hospitalares (36%; IC95%: 24-48%), embora esta diferença não tenha sido significativa (p =0,20) (Caldeira D, et al. Rev Port Cardiol. 2014; 33(9): 555-60). A menor prevalência da anticoagulação no hospital pode resultar

da idade mais avançada dos doentes e da maior presença de comorbilidades poderão adulterar a perceção do risco de hemorragia e limitar a sua utilização.

O aparecimento dos NOAC (anticoagulantes orais diretos e específicos) tornou fundamental identificar os doentes que podem continuar a fazer um AVK, garantindo um TTR adequado. Recordamos, entretanto, que o aperfeiçoamento da pontuação SAMe-TT_2R_2 pode ter um papel importante na melhor definição da estratégia terapêutica anticoagulante oral (Ruiz-Ortiz M, et al. Thromb Haemost. 2015; 114(4): 695-701): os doentes com SAMe-TT_2R_2 de O-1 podem permanecer com AVK, mas nos doentes mais suscetíveis a pior controlo do INR, com uma pontuação SAMe-$TT_2R_2 \geq 2$ um NOAC representa uma melhor opção terapêutica. Assim, ainda que não de uma forma definitiva – que só tempo e a experiência clínica afirmarão – os melhores postulante para os NOAC são os doentes com contraindicação ou submetidos a tratamentos concomitantes passíveis de interações medicamentosas (DDI) "melindrosas" com os AVK; que não conseguem atingir um INR em intervalo terapêutico (TTR) de, pelo menos, 65%; com previsíveis dificuldades na monitorização do INR (ou com hábitos etanólicos acentuados); com risco muito elevado de AVC podem, assim, beneficiar da anticoagulação conseguida pelos NOAC; assim como os doentes com maior HAS-BLED e, consequentemente, com maior risco de hemorragia.

Comparative efficacy of clinical events prevention of five anticoagulants in patients with atrial fibrillation (a network meta-analysis)

Guo L, Li S, Wang P, Zhong X, Hong Y

Am J Cardiol. 2017; 119(4): 585-93.

Atrial fibrillation (AF) ranks the most prevailing type of cardiac rhythm disorder and AF patients are associated with a significantly increased risk of stroke compared to others. This study is designed to assess the relative efficacy of several clinical events prevention anticoagulants in patients with AF. Conventional pairwise meta-analysis was performed with fixed-effect model initially, then network meta-analysis was performed with random-effects model within results illustrated by cumulative odds ratios (ORs) and corresponding 95% credible interval (CrI). The rank probabilities of each treatment outcomes were summarized by the surface under the cumulative ranking curve (SUCRA). We conducted a systematic review and collected key clinical data from 37 studies with respect to 5 anticoagulant treatments for AF. Patients treated with rivaroxaban and apixaban are associated with a reduced risk of stroke compared to those treated with warfarin (OR 0.72, 95% CrI 0.53 to 0.88; OR 0.68, 95% CrI 0.48 to 0.91). Rivaroxaban (SUCRA [0.712) appears to be the most preferable one with respect to vascular events, and both apixaban (SUCRA [0.720) and rivaroxaban (SUCRA [0.678) are preferable to others with respect to stroke. Dabigatran outperforms others with respect to the outcome of mortality (SUCRA [0.695), hemorrhage events (SUCRA [0.747), and myocardial infarction (SUCRA [0.620). In conclusion, dabigatran has a noticeable and comprehensive advantage compared to others with respect to preventing several complications including hemorrhage events, myocardial infarction, and mortality. In addition, apixaban may be the best choice of preventing stroke, and rivaroxaban is more preferable to others with respect to preventing vascular events.

Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study.

Larsen TB, Skjøth F, Nielsen PB, Kjældgaard JN, Lip GY.

BMJ. 2016; 353: i3189. doi: 10.1136/bmj.i3189.

Objective: To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.

Design: Observational nationwide cohort study.

Setting: Three Danish nationwide databases, August 2011 to October 2015.

Participants: 61 678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran 150 mg (n=12 701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).

Main outcomes measures: Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.

Results: When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% v 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).

Conclusion: All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis.

López-López JA, Sterne JAC, Thom HHZ, et al

BMJ. 2017 ; 359:j5058. doi: 10.1136/bmj.j5058.

Objective: To compare the efficacy, safety, and cost effectiveness of direct acting oral anticoagulants (DOACs) for patients with atrial fibrillation.

Design: Systematic review, network meta-analysis, and cost effectiveness analysis.

Data sources: Medline, PreMedline, Embase, and The Cochrane Library.

Eligibility criteria for selecting studies: Published randomised trials evaluating the use of a DOAC, vitamin K antagonist, or antiplatelet drug for prevention of stroke in patients with atrial fibrillation. Results 23 randomised trials involving 94 656 patients were analysed: 13 compared a DOAC with warfarin dosed to achieve a target INR of 2.0-3.0. Apixaban 5 mg twice daily (odds ratio 0.79, 95% confidence interval 0.66 to 0.94), dabigatran 150 mg twice daily (0.65, 0.52 to 0.81), edoxaban 60 mg once daily (0.86, 0.74 to 1.01), and rivaroxaban 20 mg once daily (0.88, 0.74 to 1.03) reduced the risk of stroke or systemic embolism compared with warfarin. The risk of stroke or systemic embolism was higher with edoxaban 60 mg once daily (1.33, 1.02 to 1.75) and rivaroxaban 20 mg once daily (1.35, 1.03 to 1.78) than with dabigatran 150 mg twice daily. The risk of all-cause mortality was lower with all DOACs than with warfarin. Apixaban 5 mg twice daily (0.71, 0.61 to 0.81), dabigatran 110 mg twice daily (0.80, 0.69 to 0.93), edoxaban 30 mg once daily (0.46, 0.40 to 0.54), and edoxaban 60 mg once daily (0.78, 0.69 to 0.90) reduced the risk of major bleeding compared with warfarin. The risk of major bleeding was higher with dabigatran 150 mg twice daily than apixaban 5 mg twice daily (1.33, 1.09 to 1.62), rivaroxaban 20 mg twice daily than apixaban 5 mg twice daily (1.45, 1.19 to 1.78), and rivaroxaban 20 mg twice daily than edoxaban 60 mg once daily (1.31, 1.07 to 1.59). The risk of intracranial bleeding was substantially lower for most DOACs compared with warfarin, whereas the risk of gastrointestinal bleeding was higher with some DOACs than warfarin. Apixaban 5 mg twice daily was ranked the highest for most outcomes, and was cost effective compared with warfarin.

Conclusions: The network meta-analysis informs the choice of DOACs for prevention of stroke in patients with atrial fibrillation. Several DOACs are of net benefit compared with warfarin. A trial directly comparing DOACs would overcome the need for indirect comparisons to be made through network meta-analysis.

Systematic review registration: PROSPERO CRD 42013005324.

*Comentário: **e**stes são apenas 3 dos muitos estudos (meta-análises e da "vida real") que, ao longo destes anos mais recentes, vão sendo publicados acerca dos anticoagulantes orais diretos (NOAC) versus varfarina (antivitamínicos K, AVK). Todos – mesmo quando importantes – devem ser olhados com redobrada atenção e merecedores da nossa atenção e pragmatismo.*

Muitas desvantagens dos AVK – já aqui sublinhadas – propiciaram o desenvolvimento dos NOAC. Com uma atividade anticoagulante previsível, atuando num único elemento-chave da coagulação (daí a preferência pela designação de "anticoagulantes orais diretos ou específicos"), uma semivida curta e interações medicamentosas mínimas e conjeturáveis (porque sustentadas na sua farmacocinética), os NOAC são uma alternativa favorável à

varfarina. Globalmente, os ensaios capitais que compararam os NOAC com a varfarina, na FA não valvular, demonstraram – de forma indelével – a sua eficácia na redução do risco de AVC e tromboembolismo sistémico e perfil de segurança superior aos AVK na redução do risco de hemorragia e mortalidade. Uma meta-análise já clássica (Ruff CT, et al. Lancet. 2014; 383(9921): 955-62), com os 4 principais estudos clínicos e 72 000 doentes com FA (idade média: 72 anos; acompanhamento médio: 2 a 4 anos), afirmou que, em comparação com a varfarina, os NOAC estiveram acomunados a menos 19% AVC e embolismo sistémico (à custa de 51% menos AVC hemorrágicos) e com idêntica eficácia na prevenção do AVC isquémico e do enfarte do miocárdio. Por outro lado, os NOAC foram associados a uma redução de 52% na hemorragia intracraniana (HIC) e de 10% na mortalidade por todas as causas (mas com um aumento do risco hemorragia gastrointestinal). Curiosamente, uma análise agregada dos dados de segurança de todos os ensaios clínicos de fase III (na FA e no tromboembolismo venoso) com NOAC não confirmou este maior risco hemorragia gastrointestinal (Caldeira D, et al. Aliment Pharmacol Ther. 2015; 42: 1239-49).

Nesta análise de efetividade "da vida real" – aqui publicitada –, durante o 1º ano de tratamento com a dose padrão de NOAC ou varfarina, o risco de AVC ou embolia sistémica foi significativamente menor com rivaroxabano – mas sem diferença significativa entre tratamentos no risco de AVC isquémico isolado –, enquanto que o risco combinado de morte por qualquer causa, qualquer hemorragia ou hemorragia major foi significativamente menor com apixabano e dabigatrano e o risco de HCI foi significativamente menor com dabigatrano e o rivaroxabano. Num primeiro olhar sobre estes dados vale a pena comentar que em nenhum dos parâmetros analisados os AVK foram superiores aos NOAC. Individualmente, cada um dos NOAC aparecem arrolados a vantagens e desvantagens relativas, mas que podem derivar em potenciais efeitos de confusão derivados da natureza observacional do estudo. Ainda está por determinar – não estando certo se alguma vez será possível ou até desejável! – qual o "melhor" NOAC para todos os doentes com FA…

A este propósito gostaria de ressaltar que os "dados da vida real" revestem-se de especial importância e complementam, de forma indispensável, a melhor medicina baseada na evidência. A evidência é necessária – ninguém duvida –, mas é, frequentemente, insuficiente numa tomada de decisão centrada no doente. Centrar no doente a decisão partilhada é uma imposição da prática médica. É comunicar e reconhecer os benefícios e danos potenciais, os custos e os inconvenientes que uma opção tem para o doente e, em última análise, para a melhor aplicabilidade da evidência disponível. Os dados "da vida real" ambicionam retrucar à universalidade clínica da utilização de um novo medicamento e robustecer a confiança do clínico e do doente. Mas para isso o cuidado metodológico é fundamental (tanto nos registos como nas meta-análises) e deve ser o mais completo possível sobre todas as perspetivas, preceituando a atenção sobre o potencial viés de canalização dos doentes no novo medicamento, o rápido deslocamento de doentes com diferentes níveis de risco basal na fase inicial de comercialização ou, por exemplo, o défice de dados – e o pequeno número de doentes – com redução da precisão de efeito em análise e limites em subgrupos do estudo.

As meta-análises já realizadas (e outras a realizar) não podem desconhecer a diversidade dos grupos comparadores – com risco basal diferente –, o que, necessariamente, atenua a validade da comparação indireta e obriga ao ajuste preciso das características dos doentes incluídos, e a perda a vantagem da aleatorização, assumindo um pretenso efeito de classe, que deve ser complementado por dados epidemiológicos futuros. Estas meta-análises têm que apreciar a heterogeneidade dos diversos estudos e a composição desigual do comparador e reconhecer que o pressuposto frequente de que o efeito do tratamento mantém-se constante em populações com diferentes riscos absolutos pode e é comumente injustificável (a composição de fatores de risco afeta o risco basal e a interpretação dos resultados…). Por outro lado, os estudos da "vida real" têm de ponderar a sua validade interna e externa (que pode variar consideravelmente), a probidade e qualidade da base de dados em análise, o

tempo de análise para evento e o período de exposição e, finalmente, no conjunto, a correta compreensão dos seus pontos fortes e limitações.

Entrementes, vários registos nacionais e internacionais foram encetados para computar a prática clínica, coletar dados sobre o tratamento com os anticoagulantes orais diretos e concatenar a prática clínica com as recomendações emanadas sobre a abordagem da FA. Como é fácil de constatar – e, provavelmente, previsível! – o desenho e a metodologia destes registos variam substancialmente e têm evoluído ao longo da última década (Mazurek M, et al. Am J Med. 2017; 130(2): 135-45). Os critérios de inclusão nos registos são também muito diversos. No GLORIA-AF e no GARFIELD-AF, apenas são incluídos doentes com FA de novo o que não ocorre noutros registos (e.g. PREFER-AF). Em alguns casos (PREFER-AF, ORBIT-AF), para além da FA não valvular, também é facilitado a inclusão de doentes com arritmia valvular. O grau de risco de SEE/AVC é também díspar. Para obviar ao possível efeito aliciado pela anticoagulação anterior, o GLORIA-AF excluiu doentes com uso prévio de AVK, o que não ocorreu nos restantes registos. Avaliar – e comparar – os seus dados e resultados é também conhecer estas voltas e as suas nuances.

Nesta discussão o mais importante – isto, sim, realmente fundamental! – 1 em cada 3 doentes com FA e risco elevado de tromboembolismo continua a não receber anticoagulação oral (Hsu JC, et al. J Am Coll Cardiol. 2016; 67(25) :2913-23): 38% dos doentes continuavam a fazer ácido acetilsalicílico isoladamente. O editorial acompanhante enfatizava: "a aspirina não é um anticoagulante, a aspirina é ineficaz para a prevenção de tromboembolismo relacionados com a FA não valvular". Ponto. Além disso, um grande número de doentes com FA interrompe o tratamento com AVK no período de um ano, especialmente quando submetidos a cardioversão elétrica ou ablação por radiofrequência (Barnes GD, et al. JAMA Cardiol. 2017; 2(3): 341-3). Para lá da cardioversão elétrica (e ablação por radiofrequência) – que deveriam manter a anticoagulação oral durante 4 a 8 semanas (ou indefinidamente se o risco de AVC for significativo!) –, foram preditores da descontinuação do tratamento um valor menor no CHA_2DS_2-VASc ou um tempo no intervalo terapêutico inferior no primeiro ano.

Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry.

Steinberg BA, Shrader P, Thomas L, for the ORBIT-AF Investigators and Patients.

J Am Coll Cardiol. 2016; 68(24): 2597-604.

Background: Although non-vitamin K antagonist oral anticoagulants (NOACs) do not require frequent laboratory monitoring, each compound requires dose adjustments on the basis of certain clinical criteria.

Objectives: This study assessed the frequency of off-label NOAC doses among AF patients and the associations between off-label dose therapy and clinical outcomes in community practice.

Methods: We evaluated 5,738 patients treated with a NOAC at 242 ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II) sites. NOAC doses were classified as either underdosed or overdosed, consistent with Food and Drug Administration labeling. Longitudinal outcomes (median follow-up: 0.99 years) included stroke or systemic embolism, myocardial infarction, major bleeding (International Society of Thrombosis and Haemostasis criteria), cause-specific hospitalization, and all-cause mortality.

Results: Overall, 541 NOAC-treated patients (9.4%) were underdosed, 197 were overdosed (3.4%), and 5,000 were dosed according to U.S. labeling (87%). Compared with patients receiving the recommended dose, those who were receiving off-label doses were older (median: 79 and 80 years of age vs. 70 years of age, respectively; $p < 0.0001$), more likely female (48% and 67% vs. 40%, respectively; $p < 0.0001$), less likely to be treated by an electrophysiologist (18% and 19% vs. 27%, respectively; $p < 0.0001$), and had higher CHA2DS2-VASc scores (96% and 97% ≥2 vs. 86%, respectively; $p < 0.0001$) and higher ORBIT bleeding scores (25% and 31% >4 vs. 11%, respectively; $p < 0.0001$). After dose adjustment, NOAC overdosing was associated with increased all-cause mortality compared with recommended doses (adjusted hazard ratio: 1.91; 95% confidence interval [CI]: 1.02 to 3.60; $p = 0.04$). Underdosing was associated with increased cardiovascular hospitalization (adjusted hazard ratio: 1.26; 95% CI: 1.07 to 1.50; $p = 0.007$).

Conclusions: A significant minority (almost 1 in 8) of U.S. patients in the community received NOAC doses inconsistent with labeling. NOAC over- and underdosing are associated with increased risk for adverse events. (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II [ORBIT-AF II]; NCT01701817).

Comentário: "Primum non nocere" (termo atribuída a Hipócrates – 460AC-377AC – que escreveu: "o médico deve… ter dois objetivos, fazer o bem e evitar fazer o mal"). Este antagonismo no arbítrio médico é tão comum na anticoagulação oral (o AVC é um processo da "natureza", a hemorragia é algo que fomentámos!…). Fica, entretanto, uma reflexão de Paolo Mantegazza, antropólogo e fisiologista italiano do século XIX: " é muito maior o mal que pode fazer um médico ignorante, do que o bem que pode fazer um médico sabedor".

Voltemos, pois, à vida real" (Steinberg BA, et al.; ORBIT-AF Investigators and Patients. J Am Coll Cardiol. 2016; 68(24): 2597-604). No final de 2016 tomámos consciência (ignorávamos realmente?) que cerca de 13% dos 5 738 doentes com FA não valvular medicados com NOAC não estão a fazer a dose adequada. Globalmente, 5 000 doentes (87%) mantinham doses consistentes e adequadas, 541 (9,4%) estavam com doses inferiores às indicadas e 197 (3,4%) com doses maiores que as indicadas. O não cumprimento da dose indicada esteve arrolado a idades

mais avançadas, ao género feminino, a um CHA_2DS_2-VASc ≥ 2 e a uma pontuação hemorrágica maior. A sobredosagem, aparentemente, condicionou maior mortalidade total, ao contrário da subdosagem que propiciou mais hospitalizações cardiovasculares.

Surpreendente: 721 (6%) doentes foram excluídos por não terem qualquer avaliação da função renal, durante um ano de acompanhamento. Um estudo observacional recente alvitra que o risco tromboembólico e hemorrágico em 17 349 doentes com FA (idade média, 73 anos; 53% mulheres) aumenta com o agravamento da função renal (Bonde AN, et al. Stroke. 2016; 47(11): 2707-13). A incidência cumulativa de AVC/SEE e hemorragia major aumentou com a diminuição iterada da taxa de filtração glomerular (TGF). Assim, a disfunção renal dilata os benefícios e os riscos de anticoagulação (no caso com AVK…) na FA que devem ser estudados, clarificados e fundamentados.

Voltemos à posologia não cumprida dos NOAC na FA na disfunção renal (Yao X, et al. J Am Coll Cardiol. 2017; 69(23): 2779-90). O declínio da função renal é frequente nos pacientes com FA anticoagulados. Os NOAC, particularmente o dabigatrano e o rivaroxabano, parecem estar acomunados a um risco menor de efeitos adversos renais do que a varfarina (o dabigatrano com menor risco de declínio da TFG ≥ 30%; o rivaroxabano com uma diminuição do risco de declínio da TFG ≥ 30%, duplicação da creatinina e lesão renal aguda) (Yao X, et al. J Am Coll Cardiol. 2017; 70(21) :2621-32). No coorte agora em análise – 15 000 doentes com FA, que, entre 2010 e 2015, iniciaram apixabano, dabigatrano ou rivaroxabano (acompanhamento médio de 3,6 meses) – em quase 1 500 doentes com indicação para redução da dose (por disfunção renal coexistente), 43% receberam a dose padrão (relacionada com maior risco de hemorragia major, apesar de não ter – neste curto acompanhamento – discrepâncias na taxa de AVC); nos 13 000 doentes sem indicação para redução de dose, 13% estiveram submedicados (a subdosagem de apixabano – ao contrário do que pareceu ocorrer com o dabitrano e o rivaroxabano – esteve ligada a um maior risco de AVC, sem variação do risco de hemorragia major). Uma análise multivariada provou que a idade mais avançada foi o fator mais relevante na subdosagem inapropriada em doentes sem disfunção renal significativa.

De fato, a par da disfunção renal, a idade avançada é um dos fatores mais prevalentes e condicionadores da opção por uma dose reduzida de NOAC (com ou sem fundamentação e com alguns "proveitos" e muitos "prejuízos). Num coorte dinamarquês com 56 000 doentes com FA, ponderado por propensão, foi avaliada a eficácia e a segurança de doses reduzidas de NOAC (dabigatrano 110 mg bid, apixabano 2,5 mg bid e rivaroxabano 15 mg od) quando comparados com a varfarina (Nielsen PB, et al. BMJ. 2017 Feb 10; 356:j510. doi: 10.1136/bmj.j510). Ao fim de 1 ano, o risco de AVC isquémico e embolia sistémica foi comparável, mas – anote-se! – o risco de morte foi significativamente maior com o rivaroxabano (razão de risco [HR], 1,48) e apixabano (HR, 1,52) do que entre os usuários de varfarina (o dabigatrano, em dose "reduzida" aparentou um risco de hemorragia e de AVC hemorrágico). A análise restrita a doentes com indicação expressa para redução da dosagem (idade ≥80 anos e/ou disfunção renal), sublinha que o rivaroxabano esteve associado a um risco significativamente menor de AVC isquémico/SEE (HR, 0,63) – mas com um maior risco de morte, comum ao rivaroxabano (HR, 1,48) e ao apixabano (1,23) – e que o apixabano aparentou um menor risco hemorrágico (HR, 0,78) e o dabigatrano menor risco de AVC hemorrágico (HR, 0,46). Este e os outros citados são um desafio à nossa prática clínica. O ajuste da dose na FA (assim como em outras entidades clínicas…) deve ser fundamentado (Heidbuchel H, et al. Europace. 2015; 17(10): 1467-507):

- *Para o dabigatrano, a dose diária recomendada de 220 mg tomados como uma cápsula de 110 mg duas vezes por dia recomenda-se:*
  - *Doentes com idade ≥ 80 anos;*

- *Doentes que tomam concomitantemente verapamilo*
- *Nos casos derivados da avaliação individual do risco tromboembólico e hemorrágico: doentes com idade 75 e os 80 anos; com compromisso renal moderado; com gastrite, esofagite ou refluxo gastroesofágico; ou outros doentes com risco aumentado de hemorragia.*

- *Para o apixabano, a redução da dose para 2,5 mg tomada por via oral, duas vezes por dia é recomendada nos doentes com FA não valvular e com, pelo menos, duas das seguintes características:*
  - *Idade ≥ 80 anos;*
  - *Peso corporal ≤ 60 kg;*
  - *Creatinina sérica ≥ 1,5 mg/dl (133 micromol/l).*
- *Para o edoxabano, a dose recomendada é de 30 mg de edoxabano uma vez por dia em doentes com um ou mais dos fatores clínicos seguintes:*
  - *Compromisso renal moderado ou grave (depuração da creatinina [ClCr] 15 - 50 ml/min)*
  - *Baixo peso corporal ≤ 60 kg*
  - *Uso concomitante dos seguintes inibidores da glicoproteína-P (gp-P): ciclosporina, dronedarona, eritromicina ou cetoconazol.*
- *Para o rivaroxano, nos doentes com compromisso renal moderado (taxa de depuração da creatinina de 30 - 49 ml/min) ou grave (taxa de depuração da creatinina de 15 - 29 ml/min) a dose recomendada é de 15 mg uma vez por dia.*

Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study.

Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GY, Larsen TB.

BMJ. 2017 Feb 10; 356:j510. doi: 10.1136/bmj.j510.

Objective: To examine clinical effectiveness and safety of apixaban 2.5 mg, dabigatran 110 mg, and rivaroxaban 15 mg compared with warfarin among patients with atrial fibrillation who had not previously taken an oral anticoagulant.

Design: Propensity weighted (inverse probability of treatment weighted) nationwide cohort study. Setting Individual linked data from three nationwide registries in Denmark.

Participants: Patients with non-valvular atrial fibrillation filling a first prescription for an oral anticoagulant from August 2011 to February 2016. Patients who filled a prescription for a standard dose non-vitamin K antagonist oral anticoagulant (novel oral anticoagulants, NOACs) were excluded. To control for baseline differences in the population, a propensity score for receipt of either of the four treatment alternatives was calculated to apply an inverse probability treatment weight. Intervention Initiated anticoagulant treatment (dabigatran 110 mg, rivaroxaban 15 mg, apixaban 2.5 mg, and warfarin).

Main outcome measures: Patients were followed in the registries from onset of treatment for the primary effectiveness outcome of ischaemic stroke/systemic embolism and for the principal safety outcome of any bleeding events.

Results Among 55 644 patients with atrial fibrillation who met inclusion criteria, the cohort was distributed according to treatment: apixaban n=4400; dabigatran n=8875; rivaroxaban n=3476; warfarin n=38 893. The overall mean age was 73.9 (SD 12.7), ranging from a mean of 71.0 (warfarin) to 83.9 (apixaban). During one year of follow-up, apixaban was associated with higher (weighted) event rate of ischaemic stroke/systemic embolism (4.8%), while dabigatran, rivaroxaban, and warfarin had event rates of 3.3%, 3.5%, and 3.7%, respectively. In the comparison between a non-vitamin K antagonist oral anticoagulant and warfarin in the inverse probability of treatment weighted analyses and investigation of the effectiveness outcome, the hazard ratios were 1.19 (95% confidence interval 0.95 to 1.49) for apixaban, 0.89 (0.77 to 1.03) for dabigatran, and 0.89 (0.69 to 1.16) for rivaroxaban. For the principal safety outcome versus warfarin, the hazard ratios were 0.96 (0.73 to 1.27) for apixaban, 0.80 (0.70 to 0.92) for dabigatran, and 1.06 (0.87 to 1.29) for rivaroxaban.

Conclusion: In this propensity weighted nationwide study of reduced dose non-vitamin K antagonist oral anticoagulant regimens, apixaban 2.5 mg twice a day was associated with a trend towards higher rates of ischaemic stroke/systemic embolism compared with warfarin, while rivaroxaban 15 mg once a day and dabigatran 110 mg twice a day showed a trend towards lower thromboembolic rates. The results were not significantly different. Rates of bleeding (the principal safety outcome) were significantly lower for dabigatran, but not significantly different for apixaban and rivaroxaban compared with warfarin.

Early start of DOAC after ischemic stroke: Risk of intracranial hemorrhage and recurrent events.

Seiffge DJ, Traenka C, Polymeris A, et al

Neurology. 2016; 87(18): 1856-62.

Objective: In patients with recent acute ischemic stroke (AIS) and atrial fibrillation, we assessed the starting time of direct, non-vitamin K antagonist oral anticoagulants (DOACs) for secondary prevention, the rate of intracranial hemorrhage (ICH), and recurrent ischemic events during follow-up.

Methods: We included consecutive patients with nonvalvular atrial fibrillation admitted to our hospital for AIS or TIA (index event) who received secondary prophylaxis with DOAC or vitamin K antagonists (VKAs). Follow-up was at least 3 months. In the primary analysis, we compared rates of ICH and recurrent ischemic events (AIS or TIA) between patients with early (≤7 days since event; DOAC early) and those with late (>7 days, DOAC late) start of DOAC.

Results: Two hundred four patients were included (median age 79 years, 89% AIS) and total follow-up time was 78.25 patient-years. One hundred fifty-five patients received DOAC with a median delay of 5 days after the index event (interquartile range 3-11) and 49 received VKA. DOAC was started early in 100 patients (65%). We observed

one ICH (1.3%/y) and 6 recurrent AIS (7.7%/y). The ICH occurred in a patient taking VKA. No significant difference in the rate of recurrent AIS between DOAC early (5.1%/y) and DOAC late (9.3%/y, p = 0.53) was observed.

Conclusions: Even if DOACs are often started early after an index event, the risk of ICH appears to be low. Among all patients receiving anticoagulation, the rate of recurrent events was 6 times higher than the rate of ICH.

Long-term antithrombotic treatment in intracranial hemorrhage survivors with atrial fibrillation.

Korompoki E, Filippidis FT, Nielsen PB, et al

Neurology. 2017; 89(7): 687-96.

Objective: To perform a systematic review and meta-analysis of studies reporting recurrent intracranial hemorrhage (ICH) and ischemic stroke (IS) in ICH survivors with atrial fibrillation (AF) during long-term follow-up.

Methods: A comprehensive literature search including MEDLINE, EMBASE, Cochrane library, clinical trials registry was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. We considered studies capturing outcome events (ICH recurrence and IS) for ≥3 months and treatment exposure to vitamin K antagonists (VKAs), antiplatelet agents (APAs), or no antithrombotic medication (no-ATM). Corresponding authors provided aggregate data for IS and ICH recurrence rate between 6 weeks after the event and 1 year of follow-up for each treatment exposure. Meta-analyses of pooled rate ratios (RRs) were conducted with the inverse variance method.

Results: Seventeen articles met inclusion criteria. Seven observational studies enrolling 2,452 patients were included in the meta-analysis. Pooled RR estimates for IS were lower for VKAs compared to APAs (RR = 0.45, 95% confidence interval [CI] 0.27-0.74, p = 0.002) and no-ATM (RR = 0.47, 95% CI 0.29-0.77, p = 0.002). Pooled RR estimates for ICH recurrence were not significantly increased across treatment groups (VKA vs. APA: RR = 1.34, 95% CI 0.79-2.30, p = 0.28; VKA vs. no-ATM: RR = 0.93, 95% CI 0.45-1.90, p = 0.84).

Conclusions: In observational studies, anticoagulation with VKA is associated with a lower rate of IS than APA or no-ATM without increasing ICH recurrence significantly. A randomized controlled trial is needed to determine the net clinical benefit of anticoagulation in ICH survivors with AF.

Comentário: em 2015, as recomendações eram claras (Heidbuchel H, et al. Europace. 2015; 17(10): 1467-507). A continuação ou a descontinuação de um anticoagulante oral direto (NOAC) após um AVC isquémico depende do tamanho do enfarte e da gravidade do AVC. No entanto, reconheciam que os dados clínicos sobre o momento da reinstituição da anticoagulação após um AVC/AIT são ainda muito parcelares. Por isso, as recomendações aceitaram a chamada regra "1-3-6-12 dias": nos doentes com FA e AIT, a anticoagulação oral (ACO) pode ser iniciada no dia 1 (ou pode ser continuada se já estavam anticoagulados); nos doentes com AVC ligeiro (NIHSS < 8),

a ACO pode ser iniciada 3 dias depois (após a exclusão de hemorragia intracraniana); nos doentes com AVC moderado (NIHSS 8-16), a ACO pode ser iniciada 5-7 dias depois; e, finalmente, no AVC grave (NIHSS > 16) 12-14 dias depois (tendo o cuidado de descartar uma eventual transformação hemorrágica do AVC isquémico inicial).

Nos estudos clínicos com NOAC foram excluídos os doentes com antecedentes prévios, nas 2 semanas anteriores, de AVC isquémico. Anote-se que o período de tempo que decorre logo após um AVC embólico é, indubitavelmente, o momento de maior risco de transformação hemorrágica. Neste estudo, do total de 155 doentes medicados com um NOAC, 100 receberam este tratamento precocemente (≤7 dias após o evento) e 55 só mais tarde (>7 dias); o NIHSS mediano foi de 3 no grupo precoce e 7 no outro grupo. Após 3 a 6 meses, houve 6 eventos isquémicos recorrentes e 1 hemorragia cerebral (num doente medicado com um AVK). Não houve diferença significativa na taxa de AVC recorrente nos doentes com início precoce (5,1% ao ano) ou tardio do tratamento com NOAC (9,3% ao ano, P = 0,53). No entanto, reconheçamos que a gravidade do AVC era muito ligeira e que são os doentes com AVC mais graves (ou com mau controlo da pressão arterial) que estão mais sujeitos a transformação hemorrágica. A resposta final vai continuar dependente de estudos em realização como o RE-SPECT ESUS (clinicaltrials.gov NCT02239120). Até lá parece-me aceitável manter a regra "empírica" dos "1-3-6-12 dias"…

Uma nota para evocar a importância que tem a presença (e a carga) de microhemorragias cerebrais (CMB) – e de leucoaraiose… – no risco de hemorragia intracerebral (HIC) associada a anticoagulação oral na FA (Charidimou A, et al.; International META-MICROBLEEDS Initiative. Neurology. 2017; 89(23): 2317-26). Esta recente revisão sistemática e meta-análise, em 9 coortes hospitalares e 1 552 doentes – 30% com, pelo menos, um foco de CMB (e 7% cinco ou mais CMB) – comprovou que esta presença esteve arrolada a uma probabilidade quase 3 vezes maior HIC, com um aparente efeito de dose (já que a maior prevalência de CMB ampliava o risco de HIC. Há, no entanto, que anotar que, globalmente, os episódios de HIC – ainda que graves! – são relativamente raros, que os protocolos de deteção e valorização das CMB não estão harmonizados e que não inclui as populações que não tinham uma ressonância cerebral (MRI) basal (e que, em última análise, podem diferir significativamente dos doentes avaliados), assim como não englobou doentes não anticoagulados (por razões clínicas ou, quiçá, imagiológicas…)

E a incerteza terapêutica que rodeia o reinício da ACO nos doentes com antecedentes de HIC? Por analogia com os AVK, admitimos que a administração de NOAC pode ser reiniciada 4-8 semanas, se o risco cardioembólico for elevado e o risco estimado de nova HIC for baixo. Pelo contrário, no doente com um risco cardioembólico baixo e um risco elevado de hemorragia, a ACO deve ser reconsiderada. Recentemente (Chao TF, et al. Circulation. 2016; 133(16): 1540-7), com base em 12 917 doentes com história de HIC e FA de novo, acompanhados durante mais de 3 anos, a varfarina esteve associada a um menor risco de AVC isquémico, mas um maior risco de HIC. Uma análise com base no CHA_2DS_2-VASc sugere que a relação de benefício-risco nestes doentes só é auspiciosa com uma pontuação ≥6. Curiosamente, a presença de diabetes e de doença vascular foram fatores preditores de HIC recorrente e os antiagregantes plaquetários não reduziram o risco de AVC isquémico, mas aumentaram o risco de HIC.

Este foi também um tópico recorrente em 2017. Uma meta-análise de três coortes observacionais (RETRACE, ERICH e MGH), com dados diretos de 1 012 doentes com FA não valvular, sobreviventes de HIC atribuída à varfarina (INR > 1,5), sugere que o reinício da anticoagulação oral esteva associada a menor mortalidade, a menor incidência de AVC (incitado pela redução dos AVC isquémicos) e a um prognóstico funcional mais favorável (classificação de Rankin de 0-3), independentemente da localização lobar ou não. Surpreendentemente – mas notifique-se que numa análise secundária de só 190 doentes com HIC lobar, confirmada por MRI! – a menor mortalidade e a melhor funcionalidade neurológica permaneceu, mesmo quando existia angiopatia amiloide cerebral (Biffi A, et al. Ann Neurol. 2017; 82(5): 755-65). No mesmo sentido, numa revisão sistemática com 6 estudos e 2 452 doentes e um

tempo médio para a retomada da anticoagulação oral de 7 a 9 semanas, a razão da taxa de AVC isquémico foi significativamente menor com o AVK (taxa anual de 3,2%) do que com o antiagregante plaquetário (9,5%) (ou sem tratamento; 6,1%), sem qualquer aumento significativo da HIC. Face a estes dados, parece auspicioso reconhecer que a retoma da anticoagulação oral pode ser a opção para a maioria dos doentes com FA e antecedentes de HIC. Os NOAC, com um menor risco (e menos grave) de HIC, são – por tudo isso – uma opção promitente neste grupo de doentes (Wilson D et al. Neurology. 2016; 86(4):360-6).

Entretanto uma chamada de atenção para 2 artigos centrais com NOAC na área cardiovascular. N os doentes com FA submetidos a cardioversão eletiva, a ACO está indicada 3 semanas antes e 4 semanas após o procedimento. Se um ecocardiograma transesofágico (TEE) exclui um trombo na aurícula esquerda, a cardioversão pode ser efetuada em segurança sem ACO pré-procedimento (o que não exclui a necessidade da anticoagulação pós-procedimento). O edoxabano foi tão seguro e eficaz como o esquema padrão (de enoxaparina-varfarina), se a ACO foi administrada durante 3 semanas antes da cardioversão ou mais imediata quando foi guiada por TEE (Goette A, et al. Lancet. 2016; 388(10055): 1995-2003). A incidência do objetivo primário (AVC, embolia sistémica, infarto do miocárdio ou mortalidade cardiovascular) foi similar com edoxabano (<1%) e enoxaparina-varfarina (1%), assim como a incidência de hemorragia não major (1% em ambos os grupos). Neste contexto continuam em aberto algumas questões (discutidas no editorial acompanhante): a atuação fundamentada nos doentes com instabilidade hemodinâmica submetidos a cardioversão urgente, na FA com duração < 48 horas e nos doentes com trombo auricular esquerdo…

Entretanto, os doentes anticoagulados com FA submetidos a angioplastia primária com stents necessitam de dupla antiagregação. O estudo PIONEER-AF (Gibson CM, et al. N Engl J Med. 2016; 375(25): 2423-34) pretendeu aquilatar a melhor forma de prevenir a hemorragia nestes doentes e aleatorizou 2 124 doentes com FA não valvular para uma de 3 estratégias diversas após a colocação do stent: rivaroxabano, 15 mg dia + um inibidor de $P2Y_{12}$ durante 12 meses; rivaroxabano, 2,5 mg duas vezes ao dia + dose baixa de aspirina + inibidor de $P2Y_{12}$ durante 1, 6 ou 12 meses; e dose ajustada de varfarina + aspirina em dose baixa + inibidor de $P2Y_{12}$ durante 1, 6 ou 12 meses. A hemorragia clinicamente significativa foi significativamente menos frequente com 15 mg (16,8%) ou 2,5 mg (18%) de rivaroxabano do que com varfarina + DAPT (26,7%). A incidência do parâmetro de eficácia composto (mortalidade cardiovascular, infarto do miocárdio ou AVC ao fim de 1 ano) foi semelhante nos 3 grupos. Afirmemos: o curto período de acompanhamento, o tamanho relativamente pequeno da amostra e a ausência da dose padrão do rivaroxabano (20 mg/dia) na FA limitam o seu impacto. É um primeiro passo, outros têm de ser dados. Há, no entanto, que afirmar que PIONEER-AF é muito sossegador no que se refere à trombose do stent, que, geralmente, ocorre no 1º ano após a colocação do stent, e à hospitalização recorrente e mortalidade por todas as causas (Gibson CM, et al. Circulation. 2017; 135(4): 323-33).

RV Tromboembolismo Venoso 2016/17

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O Tromboembolismo Venoso (TEV) é relativamente comum, reduz a sobrevida e leva a custos substanciais em cuidados de saúde. Trata-se de uma doença complexa e multifatorial, que envolve interações entre a predisposição para trombose (adquirida ou herdada) e fatores de risco (como a idade, a obesidade, o internamento hospitalar, o cancro, o trauma, imobilidade, gravidez e puerpério, contracepção oral, etc).

Apesar de identificados os fatores de risco e os preditores de recorrência, e de se encontrar disponível profilaxia primária e secundária eficaz, a incidência de TEV parece manter-se relativamente constante ou mesmo com ligeira tendência crescente.

O ano de 2016 fica assinalado como o ano de afirmação deste grupo de patologias como um problema de saúde pública a nível mundial.

Foi também ano de publicação, na revista Chest, do suplemento "Antithrombotic Therapy for VTE Disease, Guideline and Expert Panel Report", a 10ª edição das orientações do American College of Chest Physicians nesta área. As novidades mais relevantes introduzidas neste documento foram (1) a sugestão da utilização dos anticoagulantes diretos (dabigatrano, rivaroxabano, apixabano ou edoxabano) em primeira linha terapêutica do TEV em doentes sem cancro ativo (nível de evidência 2B), (2) a possibilidade de utilizar aspirina nos doentes com TEV não-provocado que manifestem vontade (aos 3 meses de terapêutica) de suspenderem a anticoagulação e (3) a recomendação de tratamento em ambulatório ou internamento muito curto para os doentes com Embolia Pulmonar de baixo risco.

Em 2017 parece cada vez mais clara a distinção entre eventos TEV provocados e não-provocados, tendo contribuído para este facto a publicação do The Scientific and Standardization Committee (SSC) da International Society on Thrombosis and Haemostasis. Esta separação de nomenclatura ajuda na decisão a tomar no que respeita à duração da terapêutica, que agora se encontra mais dependente da existência ou ausência de fatores de risco chamados major. Todavia, ainda não se dissiparam as dúvidas acerca do tempo ideal de terapêutica anticoagulante nos doentes com TEV.
Relativamente aos doentes oncológicos (com doença ativa) as heparinas de baixo peso molecular continuam a ser a estratégia terapêutica recomendada. Contudo, com a recente publicação (já em 2017) de ensaios clínicos de fase 3 que envolvem a comparação de eficácia e segurança dos anticoagulantes diretos vs HBMP, abre-se todo um potencial de utilização destes fármacos e milhares de doentes poderão beneficiar desta estratégia, no que respeita ao conforto e segurança no tratamento destas patologias.

No âmbito (sempre controverso) das trombofilias, caminha-se no sentido de realizar estudos identificadores de estados pró-trombóticos hereditários somente a doentes em que exista forte suspeita (pela anamnese da história pessoal e familiar de risco) e que manifestem vontade de suspender a terapêutica anticoagulante (principalmente em contexto de um evento TEV não provocado).

Constata-se progressivamente que a utilização de filtros na veia cava inferior (sempre de forma temporária) fica reservada para as situações de contra-indicação absoluta à anticoagulação.
Mantém-se a controvérsia relativamente ao benefício da utilização das meias de compressão elástica na profilaxia primária em doentes em situação de risco. A indicação para a sua utilização, durante pelo menos 2 anos, (na prevenção do síndroma pós-trombótico em doentes com Trombose Venosa Profunda prévia) foi abolida das guidelines do ACCP (nível de evidencia 2B).

2018 será o ano de confirmação dos dados de eficácia e segurança dos anticoagulantes diretos (provenientes dos múltiplos registos que nos fornecem dados da vida real) nos vários subgrupos de doentes (Oncológicos, com Doença Renal Crónica, Trombofilias, etc).

Inflammation and thrombosis – testing the hypothesis with anti-inflammatory drug trials

Caterina R, D'UgoE, Libby P

Thromb Haemost 2016; 116: 1012–1021

The hypothesis of atherosclerosis as an inflammatory process has been a leitmotiv in cardiology for the past 20 years, and has now led to the launch of clinical trials aimed at testing whether drugs that primarily target inflammation can reduce cardiovascular events. Inflammation indeed drives all phases of atherosclerosis, from inception, through progression, and ultimately acute thrombotic complications (plaque rupture and probably plaque erosion). Since plaque rupture and erosion cause most acute coronary syndromes, appropriately tuned anti-inflammatory treatments should limit myocardial infarction and cardiovascular death. Beyond interrupting inflammation related plaque disruption, such treatments might, however, also ameliorate the propensity to thrombosis once the trigger (plaque rupture or erosion) has occurred. Several lines of evidence support this view: experimental data document the role of inflammation in platelet activation, tissue factor mediated coagulation, hyperfibrinogenaemia, impaired activity of natural anticoagulants (including those expressed by endothelial cells), and reduced fibrinolytic activity. Supporting evidence also derives from the involvement of inflammation in venous thrombosis, a process that commonly occurs in the absence of traditional risk factors for atherosclerosis but is associated with several inflammatory diseases including obesity. Ongoing trials, in addition to evaluating effects on primary outcomes, will afford the opportunity to probe the possibility that anti-inflammatory interventions that yield salutary changes in biomarkers of the thrombotic/fibrinolytic balance also translate into reduction of clinical events.

Comentário: a Trombose constitui per si um elemento crítico no processo aterosclerótico, sendo frequentemente o agente final que precipita as manifestações clínicas. A ruptura ou a erosão da placa expõe as camadas subendoteliais altamente trombogénicas e inicia o processo de adesão e agregação plaquetária e posteriormente a formação de fibrina, precipitando o aparecimento de coágulos.

A Inflamação pode, de forma indireta, causar trombose promovendo a aterosclerose e as suas complicações. Pode também promover diretamente a Trombose, aumentando o risco trombótico, fruto do incremento da trombogenicidade sanguínea ou de uma fibrinólise ineficaz. O apoio a esta hipótese deriva de evidências do papel da inflamação no TEV, um processo que pode ocorrer (na ausência dos fatores de risco tradicionais de aterosclerose), num leito vascular geralmente poupado por esta doença.

A prova deste conceito pode agora emergir de análises secundárias provenientes dos ensaios clínicos em curso com agentes anti-inflamatórios.

Esta revisão analisa as ligações entre a inflamação e trombose, ajudando a preparar o cenário para a interpretação dos resultados de ensaios clínicos com agentes anti-inflamatórios em doentes em risco de desenvolverem eventos ateroscleróticos.

Venous thromboembolism risk and prophylaxis in the Portuguese hospital care setting: The ARTE study

Ferreira D, Sousa JA, Felicíssimo P, França A

Rev Port Cardiol. 2017; 36(11):823---830

Introduction: venous thromboembolism (VTE) is a relatively common complication during hospital stay and determination of VTE risk is critical to choosing the best prophylactic strategy for each patient.

Objectives: in the present study we studied the risk profile for VTE in hospitalized patients in a group of hospitals in Portugal.

Methods: based on an open cohort of 4248 patients hospitalized in surgical, internal medicine, orthopedic or oncology departments, we determined thromboembolic risk at admission by applying a new score, modified from the Caprini and Khorana scores. Thrombotic, embolic and bleeding events and death were assessed during hospital stay and at three and six months after discharge.

Results: the median duration of hospital stay was five days and thromboembolic prophylaxis was implemented in 67.2% (n=2747) of the patients. A low molecular weight heparin was used as prophylaxis in the majority of cases (88.3%). Most patients were classified as high (68%) or intermediate risk (27%). The overall incidence of thromboembolic events was 1.5%. Major bleeding events were recorded in 3.89% of patients and all-cause mortality was 3.4%.

Conclusions: In this study, we propose a modified VTE risk score that effectively risk-stratifies a mixed inpatient population during hospital stay. The use of this score may result in improvement of thromboprophylaxis practices in hospitals.

Comentário: partindo dos registos internacionais que demonstram a insuficiente taxa de medidas profiláticas de TEV em doentes hospitalizados, os autores reuniram informação sólida e relevante (4090 doentes) sobre perfis de risco de VTE nos quatro grandes grupos de doentes em risco (médicos, cirúrgicos, oncológicos e ortopédicos) nos hospitais portugueses.
A referir a elevada taxa de doentes em moderado e alto risco de TEV (95%) e a utilização de profilaxia de 67,2% em internamento.
Constatam a dificuldade existente na estratificação do risco, fruto da heterogeneidade de fatores de risco, de doentes, de patologias e de circunstâncias. Propõem assim um novo score que engloba os conhecidos Caprini e Khorana e que foi projetado para aplicação em todos os tipos de doente hospitalizados.
A ausência (ou a utilização inadequada) de medidas profiláticas após a alta corrobora os dados de estudos prévios, chamando a atenção para a necessidade da extensão da profilaxia em ambulatório.

Pulmonary Embolism in Portugal: Epidemiology and In-Hospital Mortality

Gouveia M, Pinheiro L, Costa J, Borges M

Acta Med Port 2016 Jul-Aug;29(7-8):432-440

Introduction: In Portugal, the epidemiology of acute pulmonary embolism is poorly understood. In this study, we sought to characterize the pulmonary embolism from the hospital data and evaluate its in-hospital mortality and respective prognostic factors.

Material and Methods: The study used diagnostic related groups data from National Health System hospitals from 2003 to 2013 and National Statistics Institute population data to establish the evolution of admissions with the diagnosis of pulmonary embolism, their in hospital mortality rates and the population incidence rates. Diagnosis-related group microdata were used in a logit regression modeling in-hospital mortality as a function of individual characteristics and context variables.

Results: Between 2003 and 2013 there were 35,200 episodes of hospitalization in patients with 18 or more years in which one of the diagnoses was pulmonary embolism (primary diagnosis in 67% of cases). The estimated incidence rate in 2013 was 35/100,000 population (≥ 18 years). Between 2003 and 2013, the annual number of episodes kept increasing, but the in-hospital mortality rate decreased (from 31.8% to 17% for all cases and from 25% to 11.2% when pulmonary embolism was the main diagnosis). The probability of death decreases when there is a computerized tomography scan registry or when patients are females and increases with age and the presence of co-morbidities.

Discussion: In the last decade there was an increased incidence of pulmonary embolism likely related to an increased number of dependents and bedridden. However, there was a in-hospital mortality reduction of such size that the actual mortality in the general population was reduced. One possible explanation is that there has been an increase in episodes of pulmonary embolism with incrementally lower levels of severity, due to the greater capacity of diagnosis of less severe cases. Another possible explanation is greater effectiveness of hospital care. According to the logistic regression analysis, improvements in hospital care effectiveness in recent years are primarily responsible for the mortality reduction.

Conclusion: About 79% of the reduction of in-hospital mortality of pulmonary embolism between 2003 and 2013 can be attributed to greater effectiveness of hospital care and the rest to the favorable change in patient characteristics associated with risk of death.

Comentário: Excelente caracterização da epidemiologia e da evolução da mortalidade por Embolia Pulmonar em Portugal, durante uma década. Prova que apesar da (habitual) dificuldade de obtenção de dados no nosso país, é possível traçar o perfil desta patologia e retirar alguma informação acerca das co-morbilidades acompanhantes e contribuintes para a sua taxa de mortalidade.

Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope

Prandoni P, Lensing AWA, Prins MH, for the PESIT Investigators

N Engl J Med 2016; 375:1524-1531

Background: The prevalence of pulmonary embolism among patients hospitalized for syncope is not well documented, and current guidelines pay little attention to a diagnostic workup for pulmonary embolism in these patients.

Methods: We performed a systematic workup for pulmonary embolism in patients admitted to 11 hospitals in Italy for a first episode of syncope, regardless of whether there were alternative explanations for the syncope. The diagnosis of pulmonary embolism was ruled out in patients who had a low pretest clinical probability, which was defined according to the Wells score, in combination with a negative d-dimer assay. In all other patients, computed tomographic pulmonary angiography or ventilation–perfusion lung scanning was performed.

Results: A total of 560 patients (mean age, 76 years) were included in the study. A diagnosis of pulmonary embolism was ruled out in 330 of the 560 patients (58.9%) on the basis of the combination of a low pretest clinical probability of pulmonary embolism and negative d-dimer assay. Among the remaining 230 patients, pulmonary embolism was identified in 97 (42.2%). In the entire cohort, the prevalence of pulmonary embolism was 17.3% (95% confidence interval, 14.2 to 20.5). Evidence of an embolus in a main pulmonary or lobar artery or evidence of perfusion defects larger than 25% of the total area of both lungs was found in 61 patients. Pulmonary embolism was identified in 45 of the 355 patients (12.7%) who had an alternative explanation for syncope and in 52 of the 205 patients (25.4%) who did not.

Conclusions: Pulmonary embolism was identified in nearly one of every six patients hospitalized for a first episode of syncope.

Comentário: em doentes internados, o diagnóstico de embolia pulmonar foi realizado em cerca de 17% dos doentes que tiveram um primeiro episódio sincopal (aproximadamente 1/6). A taxa de diagnóstico foi mais elevada no subgrupo que não tinha uma explicação alternativa para a síncope. Este artigo lembra-nos a necessidade de aplicação dos scores de probabilidade pré-teste na correta avaliação diagnóstica do TEV.

Posteriormente a esta publicação, Oqab et al. (Am J Emerg Med. 2017 Sep 14) contestaram estes números com a realização de uma pesquisa sistematizada. Com a informação de nove estudos encontrados (6608 doentes com síncope) foi possível estimar a prevalência de Embolia Pulmonar em doentes com síncope no serviço de urgência em 0.8% (95% CI 0.5-1.3%, I 2=0%) e no internamento em 1.0% (95% CI 0.5-1.9%, I 2=0), contrastando com os valores de Prandoni et al. (3.8% e 17.3% respetivamente).

Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH

Kearon C, Ageno W, Cannegieter SC, for the Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease

J Thromb Haemost 2016; 14: 1480–3

Whether an episode of venous thromboembolism (VTE) was unprovoked or provoked by an environmental (or acquired) risk factor and, if it was provoked, whether the provoking factor was transient or persistent, has important prognostic and treatment implications. If thrombosis was provoked by a major transient risk factor, such as recent surgery, there is a very low risk of recurrence after stopping therapy. At the other extreme, if thrombosis was provoked by a persistent and progressive risk factor, such as metastatic cancer, there is a high risk of recurrence after stopping therapy. Patients with neither an important transient nor persistent provoking risk factor for thrombosis, who are often referred to as having 'unprovoked' VTE, have an intermediate risk of recurrence after stopping therapy. Because of the implications for risk of recurrence and how long patients should be treated, it is often important to be able to categorize episodes of VTE as being provoked or unprovoked. This SSC statement discusses issues that are relevant to this categorization and proposes criteria that can be used in clinical practice and for clinical research to categorize episodes of VTE as provoked by a transient risk factor, provoked by a persistent risk factor or unprovoked. Our goal is to standardize what is meant by these terms, identify the strengths and limitations of this terminology, and improve the consistency with which patients are categorized into one of these three groups. Greater consistency in the use of this categorization is expected to benefit clinical practice and investigation.

Comentário: o subcomité para o controlo na anticoagulação do ISTH redigiu esta orientação que define bem as diferenças entre TEV provocado e não-provocado.
As implicações prognósticas e terapêuticas decorrentes desta separação são óbvias, esclarecedoras e extremamente úteis na ajuda de decisão na prática clínica. O objetivo deste documento é também visar a homogeneidade das definições de TEV, simplificando os termos e permitindo melhor com unicação interpares.

Antithrombotic Therapy for VTE Disease - CHEST Guideline and Expert Panel Report

Kearon C, Akl EA, Ornelas J, et al

Chest. 2016; 149(2):315-352

BACKGROUND: We update recommendations on 12 topics that were in the 9th edition of these guidelines, and address 3 new topics.

METHODS: We generate strong (Grade 1) and weak (Grade 2) recommendations based on high- (Grade A), moderate- (Grade B), and low- (Grade C) quality evidence.

RESULTS: For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy, and suggest VKA therapy over low-molecular-weight heparin (LMWH; Grade 2C). For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C). We have not changed recommendations for who should stop anticoagulation at 3 months or receive extended therapy. For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (Grade 1B). For DVT, we suggest not using compression stockings routinely to prevent PTS (Grade 2B). For subsegmental pulmonary embolism and no proximal DVT, we suggest clinical surveillance over anticoagulation with a low risk of recurrent VTE (Grade 2C), and anticoagulation over clinical surveillance with a high risk (Grade 2C). We suggest thrombolytic therapy for pulmonary embolism with hypotension (Grade 2B), and systemic therapy over catheter-directed thrombolysis (Grade 2C). For recurrent VTE on a non-LMWH anticoagulant, we suggest LMWH (Grade 2C); for recurrent VTE on LMWH, we suggest increasing the LMWH dose (Grade 2C).

CONCLUSIONS: Of 54 recommendations included in the 30 statements, 20 were strong and none was based on high-quality evidence, highlighting the need for further research.

Comentário: entre 2012 e 2016, assistiu-se à publicação de vários ensaios envolvendo os anticoagulantes diretos (Apixabano, Dabigatrano, Edoxabano e Rivaroxabano) no tratamento do TEV. Durante este período, foram também realizados alguns estudos focando tópicos como a terapêutica trombolítica sistémica (na Embolia Pulmonar) e local guiada por catéter (na Trombose Venosa Profunda), a importância dos métodos de compressão mecânicos e a utilização de heparinas de baixo peso molecular na extensão da profilaxia em doentes oncológicos. Daí a necessidade de actualização destas guidelines, consideradas pela comunidade médica internacional como umas da mais representativas e relevantes nesta área.

Treatment of Venous Thromboembolism with New Anticoagulant Agents

Becattini C, Agnelli G

J Am Coll Cardiol. 2016; 67(16):1941-55.

Venous thromboembolism (VTE) is a common disease associated with high risk for recurrences, death, and late sequelae, accounting for substantial health care costs. Anticoagulant agents are the mainstay of treatment for deep vein thrombosis and pulmonary embolism. The recent availability of oral anticoagulant agents that can be administered in fixed doses, without laboratory monitoring and dose adjustment, is a landmark change in the treatment of VTE. In Phase III trials, rivaroxaban, apixaban, edoxaban (antifactor Xa agents), and dabigatran (an antithrombin agent) were noninferior and probably safer than conventional anticoagulation therapy (low-molecular-weight heparin followed by vitamin K antagonists). These favorable results were confirmed in specific patient subgroups, such as the elderly and fragile. However, some patients, such as those with cancer or with intermediate- to high-risk pulmonary embolism, were underrepresented in the Phase III trials. Further clinical research is required before new oral anticoagulant agents can be considered standard of care for the full spectrum of patients with VTE.

Comentário: Um dos bons artigos (a que estes autores nos habituaram) que detalha a evidência dos anticoagulantes diretos (ainda chamados NOACs ou novos anticoagulantes orais) no tratamento do TEV quer na fase aguda quer na extensão da profilaxia. Aborda também de forma sucinta, os dados existentes para algumas das chamadas subpopulações como os idosos frágeis e doentes oncológicos.
Um resumo claro e objetivo dos principais ensaios clínicos de fase III no TEV.

Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis

Vedantham S, Goldhaber SZ, Julian JA, for the ATTRACT Trial Investigators

N Engl J Med 2017; 377:2240-52.

BACKGROUND: the post-thrombotic syndrome frequently develops in patients with proximal deep-vein thrombosis despite treatment with anticoagulant therapy. Pharmacomechanical catheter directed thrombolysis (hereafter "pharmacomechanical thrombolysis") rapidly removes thrombus and is hypothesized to reduce the risk of the post-thrombotic syndrome.

METHODS: we randomly assigned 692 patients with acute proximal deep-vein thrombosis to receive either anticoagulation alone (control group) or anticoagulation plus pharmacomechanical thrombolysis (catheter-mediated or device-mediated intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting). The primary outcome was development of the post-thrombotic syndrome between 6 and 24 months of follow-up.

RESULTS: between 6 and 24 months, there was no significant between-group difference in the percentage of patients with the post-thrombotic syndrome (47% in the pharmacomechanical- thrombolysis group and 48% in the control group; risk ratio, 0.96; 95% confidence interval [CI], 0.82 to 1.11; P = 0.56). Pharmacomechanical thrombolysis led to more major bleeding events within 10 days (1.7% vs. 0.3% of patients, P = 0.049), but no significant difference in recurrent venous thromboembolism was seen over the 24-month follow-up period (12% in the pharmacomechanical-thrombolysis group and 8% in the control group, P = 0.09). Moderate-to-severe post-thrombotic syndrome occurred in 18% of patients in the pharmacomechanical-thrombolysis group versus 24% of those in the control group (risk ratio, 0.73; 95% CI, 0.54 to 0.98; P = 0.04). Severity scores for the post-thrombotic syndrome were lower in the pharmacomechanical thrombolysis group than in the control group at 6, 12, 18, and 24 months of follow-up (P<0.01 for the comparison of the Villalta scores at each time point), but the improvement in quality of life from baseline to 24 months did not differ significantly between the treatment groups.

CONCLUSIONS: among patients with acute proximal deep-vein thrombosis, the addition of pharmacomechanical catheter-directed thrombolysis to anticoagulation did not result in a lower risk of the post-thrombotic syndrome but did result in a higher risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute and others; ATTRACT ClinicalTrials.gov number, NCT00790335.)

Comentários: O estudo CAVENT que envolveu 250 doentes mostrou redução do Síndroma Pós-trombótico em doentes com TVP íleo-femoral extensa, mas não conseguiu demonstrar melhoria da qualidade de vida dos doentes dos que fizeram trombólise guiada por catéter. Por esta razão os autores das guidelines do ACCP não alteraram a sua recomendação (favorável à terapêutica convencional nestas situações). Os resultados deste novo ensaio vêm corroborar a ideia de que esta modalidade terapêutica tem que ficar reservada para um grupo muito restrito de doentes selecionados, que possam beneficiar de revascularização urgente para prevenir complicações imediatas e não com o intuito de prevenção do Síndroma pós-Trombótico a longo prazo.

Early, real-world experience with direct oral anticoagulants in the treatment of intermediate-high risk acute pulmonary embolism

Santos SM, Cunha S, Baptista R et al

Rev Port Cardiol. 2017;36(11):801---806

Introduction; intermediate-high risk pulmonary embolism (IHR-PE) has a poor prognosis, but is under-represented in trials of direct oral anticoagulants (DOACs) in venous thromboembolic disease (VTE). We aimed to assess whether the administration of DOACs was equivalent to the conventional (CONV) treatment of low-molecular weight heparin bridged with warfarin for treating IHR-PE.

Methods: We conducted a retrospective cohort study including 59 consecutive patients admitted with IHR-PE and followed for up to three months after discharge. Two groups were created based on the anticoagulant strategy: CONV (n=35) and DOAC (n=24). The efficacy endpoints were death, recurrent PE, estimated pulmonary artery systolic pressure (PASP), right ventricular systolic function (RVSF) at discharge, and length of stay; the safety endpoint was major bleeding.

Results: the two groups were similar regarding demographics, PE etiology and markers of clinical severity. There were four in-hospital deaths in the CONV group and none in the DOAC group. No recurrent PE or major bleeding event was recorded in either group. At discharge, neither PASP nor RVSF was different between the groups. Patients in the DOAC group were discharged 1.7 days earlier on average than patients in the CONV group (4.7±2.4 vs. 3.0±1.5 days, p=0.002).

Conclusions: the adoption of a DOAC treatment strategy in this real-world cohort of IHR-PE patients was associated with similar efficacy and safety to the CONV approach. The fact that monitoring of anticoagulation effect was unnecessary probably led to the significant reduction in length of stay.

Comentário: continua a existir em alguns clínicos a convicção que, em situações de trombose mais extensa que condiciona alterações obstrutivas graves (TVP proximal oclusiva, ou Embolia Pulmonar de Alto Risco), deve ser utilizada na fase aguda a heparina não-fraccionada em detrimento de outros anticoagulantes. É prática comum a utilização posterior de antagonistas da vitamina K nestas situações. A utilização de anticoagulantes diretos em doentes com EP de alto risco ou risco intermédio levanta algumas dúvidas, essencialmente por não existirem dados nestes subgrupos de doentes. Os autores demonstram (apesar de uma amostra reduzida) que a utilização destes fármacos nestas circunstâncias é eficaz e segura.

Long-term risk of venous thrombosis after stopping anticoagulants for a first unprovoked event: A multi-national cohort

Rodger MA, Scarvelis D, Kahn SR et al

Thromb Res. 2016 Jul; 143:152-8.

Background: Choosing short-term (3-6 months) or indefinite anticoagulation after a first unprovoked venous thromboembolic event (VTE) is a common and difficult clinical decision. The long-term absolute risk of recurrent VTE after a first unprovoked VTE, in all patients and sub-groups, is not well established, hindering decision making.

Methods: we conducted a multi-center multi-national prospective cohort study in first unprovoked VTE patients to establish the long-term risk of recurrent VTE after short-term anticoagulation in first unprovoked VTE patients (and sub-groups). We followed patients for symptomatic suspected VTE off of OAT. Suspected recurrent VTE was investigated with reference to baseline imaging and then independently and blindly adjudicated.

Findings: We recruited 663 participants between October 2001 and March 2006 with the last follow-up in April 2014. During a mean 5.0 years of follow-up, 165/663 suspected VTE (in 408 patients) were adjudicated as recurrent VTE resulting in an annualized risk of recurrent VTE of 5.0% (95% CI: 4.2-5.8%) with a cumulative risk of 29.6% at 8 years. Men had a 7.6% (95% CI: 6.3-9.2%) annual risk of recurrent VTE. High risk women (2 or more HERDOO2 points; see text) had an annual risk of recurrent VTE of 5.9% (95% CI: 4.2-8.1%). Low risk women (1 or 0 HERDOO2 points) had 1.1% (95% CI: 0.6-2.0%) annual risk of recurrent VTE with a cumulative risk of 8.7% at 8 years.

Interpretation: Men and high-risk women with unprovoked VTE should be considered for long-term anticoagulant therapy given a high risk of recurrent VTE after long-term follow-up. Women with a low HERDOO2 score may be able to safely discontinue anticoagulants.

Comentário: excelente artigo que aborda o difícil tema do risco de recorrência após um episódio de TEV não provocado. Continua a ser o "calcanhar de Aquiles" de quem trata este grupo de patologias.
Continua a ser um grande desafio identificar e estratificar o risco de recorrência dos doentes que tiveram um evento TEV e que não necessitam de terapêutica anticoagulante indefinida. A persistência da positividade do dímero D e a observação de trombo residual no Doppler venoso estão associados a aumento de risco de recorrência de TEV.
Os autores salientam a necessidade de utilização de scores preditores de risco de recorrência como o HERDOO2 score na ajuda à decisão de suspensão da terapêutica anticoagulante.

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

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N Engl J Med 2017; 376:1211-1222

BACKGROUND: although many patients with venous thromboembolism require extended treatment, it is uncertain whether it is better to use full- or lower-intensity anticoagulation therapy or aspirin.

METHODS: in this randomized, double-blind, phase 3 study, we assigned 3396 patients with venous thromboembolism to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All the study patients had completed 6 to 12 months of anticoagulation therapy and were in equipoise regarding the need for continued anticoagulation. Study drugs were administered for up to 12 months. The primary efficacy outcome was symptomatic recurrent fatal or nonfatal venous thromboembolism, and the principal safety outcome was major bleeding.

RESULTS: a total of 3365 patients were included in the intention-to-treat analyses (median treatment duration, 351 days). The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving aspirin (hazard ratio for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; hazard ratio for 10 mg of rivaroxabano vs. aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the aspirin group; the rates of clinically relevant nonmajor bleeding were 2.7%, 2.0%, and 1.8%, respectively. The incidence of adverse events was similar in all three groups.

CONCLUSIONS: among patients with venous thromboembolism in equipoise for continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates. (Funded by Bayer Pharmaceuticals; EINSTEIN CHOICE ClinicalTrials.gov number, NCT02064439.)

Comentário: já em 2013, Agnelli et al (N Engl J Med 2013; 368:699-708) demonstraram com o ensaio Amplify Extension que após 6 a 12 meses de anticoagulação, os doentes que prolongavam a terapêutica com apixabano na dose de 2,5 mg ou 5 mg duas vezes ao dia tinham menos recorrências, sem aumento de eventos hemorrágicos major, comparativamente ao placebo. Weitz et al reportam neste ensaio os dados de 3365 doentes com TEV que após 6 a 12 meses de terapêutica anticoagulante inicial e nos quais havia dúvidas acerca da continuidade terapêutica, foram aleatorizados para receber rivaroxabano uma vez por dia em doses de 20 mg ou 10 mg vs aspirina. Os resultados fornecem evidência para suportar esquemas de terapêutica anticoagulante com doses baixas, ou por outras palavras, realizar a verdadeira profilaxia secundária, permitindo prevenir mais eventos e com maior segurança clínica.

Incidence of venous thrombosis in a large cohort of 66329 cancer patients: results of a record linkage study

Blom JW, Vanderschoot JPM, Oostindie MJ et al

J Thromb Haemost. 2006 Mar;4(3):529-35

Background: The incidence of venous thrombosis (VT) for cancer patients is increased compared with patients without cancer, but estimations of the incidence for different types of cancer have rarely been made because of the low incidence of various types of cancer. Large registries offer an opportunity to study the risk of VT in large cohorts of cancer patients, which is essential in decisions on prophylactic anti-coagulant treatment.

Methods: This cohort study estimates the incidence of VT in cancer patients by using record linkage of a Cancer Registry and an Anticoagulation Clinic database in the Netherlands. Cumulative incidences in patients with different types of malignancies were estimated. We calculated relative risks (RRs) in relation to the presence of distant metastases and treatment.

Results: Tumors of the bone, ovary, brain, and pancreas are associated with the highest incidence of VT (37.7, 32.6, 32.1, and 22.7/1000/0.5 year). Patients with distant metastases had a 1.9-fold increased risk [RR: 1.9; 95% confidence interval (CI): 1.6–2.3]. Chemotherapy leads to a 2.2-fold increased risk (RR: 2.2; 95% CI:1.8–2.7) and hormonal therapy leads to a 1.6-fold increased risk (RR: 1.6; 95% CI: 1.3–2.1) compared with patients not using these treatment modalities. Patients with radiotherapy or surgery did not have an increased risk.

Conclusions: We compared the overall incidences of VT in the first half year in our study to the risk of major bleeding as described in the literature. For patients with distant metastases, for several types of cancer, prophylactic anti-thrombotic treatment could be beneficial.

Occult cancer screening in patients with venous thromboembolism: guidance from the SSC of the ISTH

Delluc A, Antic D, Lecumberri R, Ay C, Meyer G, Carrier M

J Thromb Haemost 2017; 15: 2076–9.

“Venous thromboembolism (VTE) can be the first manifestation of cancer. Although four prospective studies have suggested that limited occult cancer screening might be adequate after a first unprovoked VTE [1–4], there is no evidence that it should be applied to all VTE patients (provoked events, unusual site VTE, etc.). Furthermore, other uncertainties, such as which tests should be performed or whether occult cancer screening sho uld be performed after a recurrent VTE event, still remain. Our objective is to provide guidance on the different management options for clinicians facing these frequent challenges”.

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Raskob GE, van Es N, Verhamme P, for the Hokusai VTE Cancer Investigators

N Engl J Med 2017 December 12, 2017DOI: 10.1056/NEJMoa1711948

BACKGROUND: low-molecular-weight heparin is the standard treatment for cancer-associated venous thromboembolism. The role of treatment with direct oral anticoagulant agents is unclear.

METHODS: in this open-label, noninferiority trial, we randomly assigned patients with cancer who had acute symptomatic or incidental venous thromboembolism to receive either low-molecular-weight heparin for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily (edoxaban group) or subcutaneous dalteparin at a dose of 200 IU per kilogram of body weight once daily for 1 month followed by dalteparin at a dose of 150 IU per kilogram once daily (dalteparin group). Treatment was given for at least 6 months and up to 12 months. The primary outcome was a composite of re- current venous thromboembolism or major bleeding during the 12 months after randomization, regardless of treatment duration.

RESULTS: of the 1050 patients who underwent randomization, 1046 were included in the modified intention-to-treat analysis. A primary-outcome event occurred in 67 of the 522 patients (12.8%) in the edoxaban group as compared with 71 of the 524 patients (13.5%) in the dalteparin group (hazard ratio, 0.97; 95% confidence interval [CI], 0.70 to 1.36; P = 0.006 for noninferiority; P=0.87 for superiority). Recurrent venous thromboembolism occurred in 41 patients (7.9%) in the edoxaban group and in 59 patients (11.3%) in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2). Major bleeding occurred in 36 patients (6.9%) in the edoxaban group and in 21 patients (4.0%) in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6).

CONCLUSIONS: oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower, but the rate of major bleeding was higher with edoxaban than with dalteparin. (Funded by Daiichi Sankyo; Hokusai VTE Cancer ClinicalTrials.gov number, NCT02073682.)

Comentário: Primeiro ensaio que compara diretamente a eficácia e segurança de um dos anticoagulantes diretos (desenhado para atingir a não inferioridade) com uma heparina de baixo peso molecular, considerado o "state of the art" na terapêutica do TEV em doentes oncológicos. Apesar de resultados de eficácia animadores, algum cuidado será necessário na seleção dos doentes no que respeita aos endpoints de segurança. Com a publicação prevista para 2018 dos resultados do estudo SELECT D que comparou o rivaroxabano com a dalteparina nos primeiros 6 meses e posteriormente (nos doentes com evidência de trombose residual) com o placebo, mais se ficará a saber acerca do comportamento deste grupo de fármacos nos doentes oncológicos.

Thrombophilia Testing and Venous Thrombosis

Connors JM

N Engl J Med 2017; 377:1177-87

"Ordering thrombophilia tests is easy; determining whom to test and how to use the results is not. Although inherited and acquired thrombophilias are acknowledged to increase the risk of venous thromboembolism (VTE), the majority of patients with VTE should not be tested for thrombophilia.

Data showing the clinical usefulness and benefits of testing are limited or nonexistent, as are data supporting the benefit of primary or secondary VTE prophylaxis based on thrombophilia status alone. Testing for inherited thrombophilia is controversial, with some arguing that these tests should never be performed. No validated testing guidelines have been published. The American College of Chest Physicians does not give guidance on thrombophilia testing in its ninth edition of clinical practice guidelines for antithrombotic therapy or its 2016 VTE update, whereas the American Society of Hematology's 2013 Choosing Wisely campaign recommends not testing for thrombophilia in adults with VTE who have major transient risk factors.
According to the most comprehensive guide, Clinical Guidelines for Testing for Heritable Thrombophilia, published by the British Committee for Standards in Haematology, "It is not possible to give a validated recommendation as to how such patients (and families) should be selected" for testing. Although similar guidelines advise limiting testing to a narrow range of specific clinical situations and patients, the recommendations are not uniform. These recommendations have been developed in response to indiscriminate testing practices and misconceptions regarding the role of thrombophilia status in the management of VTE…".

Comentário: o acontecimento de um evento TEV resulta frequentemente da adição de factores circunstanciais num doente com um "terreno" genético predisponente. Apesar de apresentarem um risco aumentado de TEV, os doentes com trombofilias hereditárias parecem não ter um risco maior de recorrência que aqueles sem alterações genéticas. A seleção de doentes para realização de testes genéticos de estados protrombóticos deve ser rigorosa e obedecer a alguns critérios.
Esta publicação fornece pistas e orientações para uma correta abordagem dos exames a requisitar quando o clínico suspeita de uma trombofilia hereditária.

Guidance for the evaluation and treatment of hereditary and acquired thrombophilia

Stevens SM., Woller SC., Bauer KA et al

J Thromb Thrombolysis (2016) 41:154–164

Thrombophilias are hereditary and/or acquired conditions that predispose patients to thrombosis. Testing for thrombophilia is commonly performed in patients with venous thrombosis and their relatives; however such testing usually does not provide information that impacts management and may result in harm. This manuscript, initiated by the Anticoagulation Forum, provides clinical guidance for thrombophilia testing in five clinical situations: following 1) provoked venous thromboembolism, 2) unprovoked venous thromboembolism; 3) in relatives of patients with thrombosis, 4) in female relatives of patients with thrombosis considering estrogen use; and 5) in female relatives of patients with thrombosis who are considering pregnancy. Additionally, guidance is provided regarding the timing of thrombophilia testing. The role of thrombophilia testing in arterial thrombosis and for evaluation of recurrent pregnancy loss is not addressed. Statements are based on existing guidelines and consensus expert opinion where guidelines are lacking. We recommend that thrombophilia testing not be performed in most situations. When performed, it should be used in a highly selective manner, and only in circumstances where the information obtained will influence a decision important to the patient, and outweigh the potential risks of testing. Testing should not be performed during acute thrombosis or during the initial (3-month) period of anticoagulation.

Comentário: Não existem, até à data, ensaios prospetivos e aleatorizados que tenham testado a utilidade ou benefício da utilização de testes laboratoriais para despiste de trombofilias hereditárias (os autores exceptuam as situações de trombose arterial em contexto de perda fetal recorrente). A evidência nesta área provém de alguns estudos epidemiológicos.
Este documento revê a evidência publicada e pretende fornecer aos clínicos algumas orientações no que respeita à importância dos testes de trombofilias na decisão da duração da terapêutica anticoagulante após um evento TEV e também em prevenção primária do TEV em familiares de doentes com estas patologias/estados pro-trombóticos.

A multicenter prospective study of risk factors and treatment of unusual site thrombosis

Ma K, Wells P, Guzman C et al

Thromb Res. 2016 Aug; 144:100-5.

Unusual site deep vein thrombosis (USDVT) is an uncommon form of venous thromboembolism (VTE) with heterogeneity in pathophysiology and clinical features. While the need for anticoagulation treatment is generally accepted, there is little data on optimal USDVT treatment. The TRUST study aimed to characterize the epidemiology, treatment and outcomes of USDVT. From 2008 to 2012, 152 patients were prospectively enrolled at 4 Canadian centers. After baseline, patients were followed at 6, 12 and 24 months. There were 97 (64%) cases of splanchnic, 33 (22%) cerebral, 14 (9%), jugular, 6 (4%) ovarian and 2 (1%) renal vein thrombosis. Mean age was 52.9 years and 113 (74%) cases were symptomatic. Of 72 (47%) patients tested as part of clinical care, 22 (31%) were diagnosed with new thrombophilia. Of 138 patients evaluated in follow-up, 66 (48%) completed at least 6 months of anticoagulation.

Estrogen exposure or inflammatory conditions preceding USDVT were commonly associated with treatment discontinuation before 6 months, while previous VTE was associated with continuing anticoagulation beyond 6 months. During follow-up, there were 22 (16%) deaths (20 from cancer), 4 (3%) cases of recurrent VTE and no fatal bleeding events. Despite half of USDVT patients receiving b6 months of anticoagulation, the rate of VTE recurrence was low and anticoagulant treatment appears safe. Thrombophilia testing was common and thrombophilia prevalence was high. Further research is needed to determine the optimal investigation and management of USDVT.

Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting

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N Engl J Med 2017; 376:515-25

BACKGROUND: The use of thromboprophylaxis to prevent clinically apparent venous thromboembolism after knee arthroscopy or casting of the lower leg is disputed. We compared the incidence of symptomatic venous thromboembolism after these procedures between patients who received anticoagulant therapy and those who received no anticoagulant therapy.

METHODS: We conducted two parallel, pragmatic, multicenter, randomized, controlled, open-label trials with blinded outcome evaluation: the POT-KAST trial, which included patients undergoing knee arthroscopy, and the POT-CAST trial, which included patients treated with casting of the lower leg. Patients were assigned to receive either a prophylactic dose of low-molecular-weight heparin (for the 8 days after arthroscopy in the POT-KAST trial or during the full period of immobilization due to casting in the POT-CAST trial) or no anticoagulant therapy. The primary outcomes were the cumulative incidences of symptomatic venous thromboembolism and major bleeding within 3 months after the procedure.

RESULTS In the POT-KAST trial, 1543 patients underwent randomization, of whom 1451 were included in the intention-to-treat population. Venous thromboembolism occurred in 5 of the 731 patients (0.7%) in the treatment group and in 3 of the 720 patients (0.4%) in the control group (relative risk, 1.6; 95% confidence interval [CI], 0.4 to 6.8; absolute difference in risk, 0.3 percentage points; 95% CI, −0.6 to 1.2). Major bleeding occurred in 1 patient (0.1%) in the treatment group and in 1 (0.1%) in the control group (absolute difference in risk, 0 percentage points; 95% CI, −0.6 to 0.7). In the POT-CAST trial, 1519 patients underwent randomization, of whom 1435 were included in the intention-to-treat population. Venous thromboembolism occurred in 10 of the 719 patients (1.4%) in the treatment group and in 13 of the 716 patients (1.8%) in the control group (relative risk, 0.8; 95% CI, 0.3 to 1.7; absolute difference in risk, −0.4 percentage points; 95% CI, −1.8 to 1.0). No major bleeding events occurred. In both trials, the most common adverse event was infection.

CONCLUSIONS: The results of our trials showed that prophylaxis with low-molecular-weight heparin for the 8 days after knee arthroscopy or during the full period of immobilization due to casting, was not effective for the prevention of symptomatic venous thromboembolism.

Comentário: dois ensaios que fornecem evidência contra a necessidade de realização de tromboprofilaxia farmacológica em doentes com talas gessadas dos membros inferiores ou após artroscopia do joelho. Contudo, os autores salientam que a profilaxia deve ser considerada nos doentes de maior risco, principalmente naqueles com outros fatores de risco de TEV não relacionados com a fratura ou a artroscopia.

Management of distal deep vein thrombosis

Robert-Ebadi H, Righini M

Thromb Res. 2017 Jan; 149:48-55

Isolated distal deep vein thrombosis (DVT), also known as calf DVT, represents up to 50% of all lower limb DVT in ultrasound series and is therefore a frequent medical condition. Unlike proximal DVT and pulmonary embolism (PE), which have been extensively studied and for which management is well standardized, much less is known on the optimal management of isolated calf DVT.

Recent data arising from registries and non-randomized studies suggest that most distal DVTs do not extend to the proximal veins and have an uneventful follow-up when left untreated. This data had some impact on the international recommendations which recently stated that ultrasound surveillance instead of systematic therapeutic anticoagulation might be an option for selected low-risk patients. However, robust data arising from randomized studies are scarce. Indeed, only five randomized trials assessing the need for anticoagulation for calf DVT have been published.

Many of these trials had an open-label design and were affected by methodological limitations. The only randomized placebo-controlled trial included low-risk patients (outpatients without cancer or previous venous thromboembolic events (VTE)) and was hampered by a limited statistical power.

Nevertheless, data from this trial tend to confirm that the use of therapeutic anticoagulation in low-risk patients with symptomatic calf DVT is not superior to placebo in reducing VTE, but is associated with a significantly higher risk of bleeding. Further randomized studies are needed to define the best therapy for high-risk patients (inpatients, patients with active cancer or previous VTE), and the optimal dose and duration of treatment.

Comentário: Há muito tempo que se debate a necessidade de tratar os doentes com TVP distal, sendo que a evidência não é clara, nem no que respeita ao benefício da anticoagulação nem sequer no tempo de terapêutica. Aparentemente, doentes de baixo risco, sem cancro activo ou TEV prévio, podem ser seguidos sem necessidade de anticoagulação. Em todos os outros doentes com TVP distal, não está bem estabelecida a melhor estratégia a seguir, sendo necessários mais estudos direcionados.

One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial

Mol GC, van de Ree MA, Klok F A, et al

BMJ 2016;353:i2691

Objective: To study whether stopping elastic compression stockings (ECS) after 12 months is non-inferior to continuing them for 24 months after proximal deep venous thrombosis.

Design: Multicentre single blind non-inferiority randomised controlled trial. Setting: Outpatient clinics in eight teaching hospitals in the Netherlands, including one university medical centre. Participants: Patients compliant with compression therapy for 12 months after symptomatic, ultrasound proven proximal deep venous thrombosis of the leg. Interventions: Continuation or cessation of ECS 12 months after deep venous thrombosis.

Main outcome measures: The primary outcome was the incidence of post-thrombotic syndrome 24 months after diagnosis of deep venous thrombosis, as assessed by the standardised Villalta scale in an intention to treat analysis. The predefined non-inferiority margin was 10%. The main secondary outcome was quality of life (VEINES-QOL/Sym).

Results: 518 patients compliant with ECS and free of post-thrombotic syndrome were randomised one year after diagnosis of deep venous thrombosis to stop or continue ECS therapy for another year. In the stop-ECS group, 51 of 256 patients developed post-thrombotic syndrome, with an incidence of 19.9% (95% confidence interval 16% to 24%). In the continue-ECS group, 34 of 262 patients developed post-thrombotic syndrome (incidence 13.0%, 9.9% to 17%), of whom 85% used ECS six or seven days a week during the study period, for an absolute difference of 6.9% (95% confidence interval upper limit 12.3%). Because the upper limit of the 95% confidence interval exceeds the predefined margin of 10%, non-inferiority was not reached. The number needed to treat to prevent one case of post-thrombotic syndrome by continuing ECS was 14 (95% confidence interval lower limit 8). Quality of life did not differ between the two groups.

Conclusion: Stopping ECS after one year in compliant patients with proximal deep venous thrombosis seemed not to be non-inferior to continuing ECS therapy for two years in this non-inferiority trial.

Comentário: A utilização de meias de compressão elástica em doentes com episódio recente de TVP no intuito de prevenção do Síndroma Pós-Trombótico deixou de ser recomendada nas últimas Guidelines do ACCP. Contudo, para os doentes sintomáticos, justifica-se um período de "experiência" uma vez que a bibliografia existente não é conclusiva.
Neste estudo, aparentemente e apesar não se ter obtido não inferioridade, a utilização de meias de compressão elástica durante mais de um ano parece reduzir a probabilidade de desenvolvimento de Síndroma Pós-Trombótico. De qualquer forma, este é um tema ainda muito controverso e sem evidência robusta, que permita recomendações claras.

As guidelines do ACCP de 2012 emitiram uma recomendação fraca (2B) a favor da utilização de meias de compressão graduadas com comprimento até ao joelho, de 30-40 mmHg durante 2 anos após TVP dos membros inferiores.

Com base no SOX Study (Lancet. 2014 Mar 8;383(9920):880-8) que avaliou as meias de compressão e que não mostrou nenhum benefício na redução da incidência da síndrome pós-trombótica, as guidelines de 2016 mudaram essa posição e sugerem (2B) a não utilização rotineira das meias de compressão após a TVP.
No entanto, é razoável usar meias de compressão em doentes para alivio sintomático e redução de edema.

Guidance for the prevention and treatment of the post-thrombotic syndrome

Kahn SR, Galanaud JP, Vedantham S, Ginsberg JS

J Thromb Thrombolysis (2016) 41:144–153

The post-thrombotic syndrome (PTS) is a frequent, potentially disabling complication of deep vein thrombosis (DVT) that reduces quality of life and is costly. Clinical manifestations include symptoms and signs such as leg pain and heaviness, edema, redness, telangiectasia, new varicose veins, hyperpigmentation, skin thickening and in severe cases, leg ulcers. The best way to prevent PTS is to prevent DVT with pharmacologic or mechanical thromboprophylaxis used in high risk patients and settings.

In patients whose DVT is treated with a vitamin K antagonist, subtherapeutic INRs should be avoided. We do not suggest routine use of elastic compression stockings (ECS) after DVT to prevent PTS, but in patients with acute DVT related leg swelling that is bothersome, a trial of ECS is reasonable. We suggest that selecting patients for catheter directed thrombolytic techniques be done on a case-by-case basis, with a focus on patients with extensive thrombosis, recent symptoms onset, and low bleeding risk, who are seen at experienced hospital centers. For patients with established PTS, we suggest prescribing 20–30 mm Hg knee-length ECS to be worn daily. If ineffective, a stronger pressure stocking can be tried. We suggest that intermittent compression devices or pneumatic compression sleeve units be tried in patients with moderate-to-severe PTS whose symptoms are inadequately controlled with ECS alone. We suggest that a supervised exercise training program for 6 months or more is reasonable for PTS patients who can tolerate it. We suggest that management of postthrombotic ulcers should involve a multidisciplinary approach. We briefly discuss upper extremity PTS and PTS in children.

Rivaroxaban vs Fondaparinux in the Treatment of Superficial Vein Thrombosis - the Surprise Trial

Beyer-Westendorf J, Schellong S, Gerlach H, et al

Blood 2016 128:85

Background: the current standard of therapy in superficial vein thrombosis (SVT) comprises subcutaneous injections of the indirect factor Xa inhibitor fondaparinux for up to 45 days, which was highly effective compared to placebo in the CALISTO trial. However, fondaparinux is expensive, requires daily injections and cost-effectiveness in SVT therapy has been questioned. Rivaroxaban is a direct oral factor Xa inhibitor, which has been shown to be effective in the prevention and treatment of venous thromboembolism (VTE). We hypothesized that SVT patients at high risk for VTE complications may be treated as efficacious and safe with rivaroxaban as with fondaparinux.

Methods: the SURPRISE trial, a randomized, open-label blinded outcome event adjudication trial, compared rivaroxaban 10 mg once daily with fondaparinux 2.5 mg once daily in patients with SVT at high risk of VTE complications (defined as supragenual SVT + age > 65 years, male sex, previous VTE, cancer, autoimmune disease or SVT of non-varicose veins). Treatment duration for both treatments was 45+5 days with an observational period until day 90+10. The primary efficacy outcome was a composite endpoint of deep vein thrombosis, pulmonary embolism, SVT progression towards the saphenofemoral junction, SVT recurrence or all cause death in the per-protocol analysis at day 45. A predefined sensitivity analysis was performed in all randomized patients (full analysis set). The primary safety outcome was the rate of ISTH major bleeding during treatment. Further outcome measures included the composite efficacy outcome up to day 90, each component of the primary efficacy outcome, rates of surgical treatment of SVT and rates of major VTE (composite of symptomatic PE or symptomatic proximal DVT or VTE-related death) at days 45 and 90. The trial was designed to test for non-inferiority of rivaroxaban compared to fondaparinux with respect to the primary efficacy outcome and to the rates of ISTH major bleeding.

Results: a total of 472 patients were randomized (mean age 60.3 years; 60.4% female) and treated with rivaroxaban (n=236) or fondaparinux (n=236). Mean treatment duration was 44.0 days for rivaroxaban and 44.8 days for fondaparinux. Until day 45+5, the primary efficacy outcome (n=435 in per-protocol analysis set) occurred in 3.3% (95%-CI 0.90; 5.73) of patients treated with rivaroxaban and 1.8% (95%-CI 0.05; 3.52) of patients receiving fondaparinux (absolute difference between rivaroxaban and fondaparinux was 1.53%; one-sided upper CI limit 4.03%; p-value for non-inferiority 0.025). Until day 90+10, the respective rates were 7.1% for rivaroxaban and 6.7% for fondaparinux (absolute difference 0.41; one-sided upper CI limit 4.41%; p-value for non-inferiority 0.047). Non-inferiority of rivaroxaban vs. fondaparinux was preserved in the full analysis set. No major bleeding occurred, and rates of non-major, clinically relevant bleeding were 2.5 vs. 0.4% for day 45+5 and 2.5 vs. 0.9% for day 90+10 in safety set for rivaroxaban and fondaparinux, respectively.

Conclusions: in high-risk SVT patients, rivaroxaban was non-inferior to fondaparinux in preventing thromboembolic complications with comparable safety. VTE events were predominantly SVT recurrence. Few cases of DVT and PE occurred, which indicates that a 45 days course of rivaroxaban 10 mg or fondaparinux 2.5 mg is sufficient to prevent serious complications in this specific subset of SVT patients. As to whether oral rivaroxaban offers a better quality of life compared to 45 days of injections, this has to be investigated in future studies. We

found higher SVT complications rates in both treatment arms compared to the fondaparinux arm in the CALISTO trial. Therefore, patients at higher VTE risk can be identified by use of a simple risk factor assessment, which may help to improve cost-effectiveness of SVT therapy. However, the concept of SVT risk stratification needs to be further investigated, since patients without additional risk factors may not need anticoagulant therapy at all.

Outcomes After Vena Cava Filter Use in Noncancer Patients with Acute Venous Thromboembolism A Population-Based Study

White RH, Brunson A, Romano PS, Li Z, Wun T

Circulation. 2016; 133:2018-2029.

Background: Evidence that vena cava filters (VCFs) are beneficial is limited. Methods and Results: we retrospectively analyzed all noncancer patients admitted to nonfederal California hospitals for acute venous thromboembolism from 2005 to 2010. Analysis was stratified by the presence/absence of a contraindication to anticoagulation (active bleeding, major surgery). Outcomes were death within 30 or 90 days of admission and the 1-year incidence of recurrent venous thromboembolism manifested as pulmonary embolism or deep vein thrombosis. Propensity score methods were used to account for observed systematic differences in baseline characteristics between patients treated and those not treated with a VCF. Among 80 697 patients with no contraindication to anticoagulation, VCF use (n=7762, 9.6%) did not significantly reduce the 30-day risk of death (hazard ratio [HR], 1.12; 95% confidence interval [CI], 0.98–1.28). Among 3017 patients with active bleeding, VCF use (n=1095, 36.3%) reduced the 30-day risk of death by 32% (HR, 0.68; 95% CI, 0.52–0.88) and the 90-day risk by 27% (HR, 0.73; 95% CI, 0.59–0.90). VCF use (n=489, 33.8%) did not reduce mortality among 1445 patients who underwent major surgery (HR, 1.1; 95% CI, 0.71–1.77). In all subgroups, filter use did not reduce the risk of subsequent pulmonary embolism. However, the risk of subsequent deep vein thrombosis increased by 50% among VCF patients with no contraindication (HR, 1.53; 95% CI, 1.34–1.74) and by 135% among VCF patients with active bleeding (HR, 2.35; 95% CI, 1.56–3.52).

Conclusions: VCF use significantly reduced the short-term risk of death only among patients with acute venous thromboembolism who had a contraindication to anticoagulation because of active bleeding. These results support the findings of a randomized clinical trial and current guidelines that recommend VCF use only in patients who cannot receive anticoagulation treatment.

Comentário: nesta publicação de autores com vasta experiência nesta área, o uso do filtro na veia cava inferior não reduziu o risco de morte em doentes com TEV que não tinham hemorragia concomitante, mas reduziu a taxa de mortalidade em 32% aos 30 dias e em 27% aos 90 dias em doentes com TEV com hemorragia activa. O risco de TVP subsequente aumentou em 50% nos doentes com TEV sem hemorragia e mais do que duplicou em pacientes com TEV com hemorragia activa. Em nenhum subgrupo, o uso do filtro reduziu o risco de Embolia Pulmonar recorrente.

Venous thromboembolism: Past, present and future

Schulman S; Ageno W; Konstantinides SV

Thromb Haemost 2017; 117: 1219–1229

Venous thromboembolism (VTE), the third most frequent acute cardiovascular syndrome, is associated with a considerable disease burden which continues to grow along with the longer life expectancy of the population worldwide. In the past century, parenteral heparin prophylaxis was established for hospitalised patients at elevated risk of VTE. More recently, non-vitamin K antagonist oral anticoagulants (NOACs) with a direct inhibiting effect on factor Xa or thrombin, underwent extensive testing in clinical trials and have been approved for patients undergoing hip or knee replacement. Clinical investigation is ongoing in further areas of thromboprophylaxis, including medical prophylaxis in patients and high-risk situations in the outpatient setting. The diagnostic approach to suspected VTE is now based on advanced imaging techniques and robust diagnostic algorithms which ensure high sensitivity and specificity. Nevertheless, the role of clinical, or pre-test, probability assessment remains crucial to avoid overdiagnosis and treatment errors. Advances in reperfusion strategies, along progressive establishment of the NOACs as the new standard of anticoagulation treatment, have simplified the management of VTE, improving outcomes and particularly safety. While new molecular targets for anticoagulation are being investigated in the quest to further reduce bleeding risk, adjusting the initial regimen to the patient's risk and finding the optimal duration of anticoagulation after an index VTE event will be some of the top priorities in the years to come. Importantly, and in parallel to new drugs and technical advances in imaging, incentives such as hospital accreditation and funding based on evidence-based practice need to be implemented to increase guideline adherence.

Comentário: as estratégias diagnósticas, preventivas e terapêuticas do TEV têm evoluído bastante nas últimas décadas. Apesar do crescente conhecimento dos mecanismos fisiopatológicos e dos factores de risco deste grupo de patologias, existem ainda inúmeras dúvidas no que respeita à sua melhor abordagem clínica e epidemiológica. Ainda não são claros os preditores de recorrência em doentes que sofreram um evento TEV não-provocado. Também não é claro qual o melhor score de predição de recorrência. Será que os existentes (Viena, DASH, HER-DOO-2) são suficientes ou podem ser melhorados?

A terapêutica indefinida em full-dose será a melhor opção para os doentes com TEV não-provocado? Ou as opções de utilização de aspirina, estatina ou baixas doses de anticoagulantes diretos serão as opções de futuro? Que doentes com TVP proximal extensa beneficiam de terapêutica trombolítica, em que doses e com ou sem adjuvante mecânico? Será que a implantação de stents venoso reduzem o aparecimento de Síndroma pós-trombótico a longo prazo?
A estratégia terapêutica utilizada na TVP e EP pode ser reproduzida com sucesso em doentes com Trombose do território esplâncnico ou cerebral?

RV MIX 2016/17

Francisco Araújo, Pedro von Hafe

As doenças crónicas, em particular as doenças sistémicas têm sido, de uma forma ou outra, implicadas no risco cardiovascular. Não quisemos por isso deixar de tocar três entidades clinicas com relevância nesta área: a DPOC, as doenças reumáticas e a depressão. Algumas têm contribuído na procura de mecanismos fisiopatológicos comuns como a inflamação, que possam ser alvo de intervenção terapêutica. Nem sempre é fácil encontrar nexos de causalidade, face à prevalência tão comum de alguns destas entidades clinicas e a ciência como sempre progride com avanços e recuos, quando os resultados dos estudos não correspondem à hipótese formulada.

Pareceu-nos importante salientar o efeito que uma medicação ou terapêutica para uma determinada doença pode causar a nível cardiovascular, já que a segurança para os nossos doentes deve estar em primeiro lugar. Isto é particularmente relevante na área da cardio-oncologia, que graças à maior sobrevida dos doentes tratados com esquemas de radio ou quimioterapia, desenvolvem síndromes clínicos que condicionam risco de morte ou de morbilidade significativos.

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Khera A.V., Emdin C.A., Drake I, et al

N Engl J Med. 2016; 375(24): 2349-2358

BACKGROUND Both genetic and lifestyle factors contribute to individual-level risk of coronary artery disease. The extent to which increased genetic risk can be offset by a healthy lifestyle is unknown.

METHODS Using a polygenic score of DNA sequence polymorphisms, we quantified genetic risk for coronary artery disease in three prospective cohorts — 7814 participants in the Atherosclerosis Risk in Communities (ARIC) study, 21,222 in the Women's Genome Health Study (WGHS), and 22,389 in the Malmö Diet and Cancer Study (MDCS) — and in 4260 participants in the cross-sectional BioImage Study for whom genotype and covariate data were available. We also determined adherence to a healthy lifestyle among the participants using a scoring system consisting of four factors: no current smoking, no obesity, regular physical activity, and a healthy diet.

RESULTS The relative risk of incident coronary events was 91% higher among participants at high genetic risk (top quintile of polygenic scores) than among those at low genetic risk (bottom quintile of polygenic scores) (hazard ratio, 1.91; 95% confidence interval [CI], 1.75 to 2.09). A favourable lifestyle (defined as at least three of the four healthy lifestyle factors) was associated with a substantially lower risk of coronary events than an unfavourable lifestyle (defined as no or only one healthy lifestyle factor), regardless of the genetic risk category. Among participants at high genetic risk, a favourable lifestyle was associated with a 46% lower relative risk of coronary events than an unfavourable lifestyle (hazard ratio, 0.54; 95% CI, 0.47 to 0.63). This finding corresponded to a reduction in the standardized 10-year incidence of coronary events from 10.7% for an unfavourable lifestyle to 5.1% for a favourable lifestyle in ARIC, from 4.6% to 2.0% in WGHS, and from 8.2% to 5.3% in MDCS. In the BioImage Study, a favourable lifestyle was associated with significantly less coronary-artery calcification within each genetic risk category.

CONCLUSIONS Across four studies involving 55,685 participants, genetic and lifestyle factors were independently associated with susceptibility to coronary artery disease. Among participants at high genetic risk, a favourable lifestyle was associated with a nearly 50% lower relative risk of coronary artery disease than was an unfavourable lifestyle.

Comentários (FA): ou seja, podemos nascer ricos (do ponto de vista de saúde) e estragar este património com o que estilo de vida que adaptarmos. Mas também podemos ter uns genes "pobrezinhos" que nos condicionam à partida o dobro do risco CV e conseguir ultrapassar este estigma através de uma vida mais saudável, reduzindo até 50% esse risco "caminhando direito por linhas tortas".

Variation in *PCSK9* and *HMGCR* and Risk of Cardiovascular Disease and Diabetes

Ference BA, Robinson JG, Brook RD, et al

N Engl J Med 2016; 375:2144-2153

BACKGROUND Pharmacologic inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9) are being evaluated in clinical trials for the treatment of cardiovascular disease. The effect of lowering low-density lipoprotein (LDL) cholesterol levels by inhibiting PCSK9 on the risk of cardiovascular events or diabetes is unknown.

METHODS We used genetic scores consisting of independently inherited variants in the genes encoding PCSK9 and 3-hydroxy-3-methylglutaryl–coenzyme A reductase (HMGCR; the target of statins) as instruments to randomly assign 112,772 participants from 14 studies, with 14,120 cardiovascular events and 10,635 cases of diabetes, to groups according to the number of LDL cholesterol–lowering alleles that they had inherited. We compared the effects of lower LDL cholesterol levels that were mediated by variants in *PCSK9, HMGCR,* or both on the risk of cardiovascular events and the risk of diabetes.

RESULTS Variants in *PCSK9* and *HMGCR* were associated with nearly identical protective effects on the risk of cardiovascular events per decrease of 10 mg per deciliter (0.26 mmol per liter) in the LDL cholesterol level: odds ratio for cardiovascular events, 0.81 (95% confidence interval [CI], 0.74 to 0.89) for *PCSK9* and 0.81 (95% CI, 0.72 to 0.90) for *HMGCR*. Variants in these two genes were also associated with very similar effects on the risk of diabetes: odds ratio for each 10 mg per deciliter decrease in LDL cholesterol, 1.11 (95% CI, 1.04 to 1.19) for *PCSK9* and 1.13 (95% CI, 1.06 to 1.20) for *HMGCR*. The increased risk of diabetes was limited to persons with impaired fasting glucose levels for both scores and was lower in magnitude than the protective effect against cardiovascular events. When present together, *PCSK9* and *HMGCR* variants had additive effects on the risk of both cardiovascular events and diabetes.

CONCLUSIONS In this study, variants in *PCSK9* had approximately the same effect as variants in *HMGCR* on the risk of cardiovascular events and diabetes per unit decrease in the LDL cholesterol level. The effects of these variants were independent and additive.

Comentários (PvH); As mutações que afectam a PCSK9 tiveram o mesmo efeito que as mutações que influenciam a função da reductase da HMGCoA (onde actuam as estatinas) no risco cardiovascular e diabetes. Observou-se que estes efeitos são independentes e que quando combinados tinham um efeito aditivo. Estes resultados podem ser extrapolados de um ponto de vista conceptual para os benefícios de tratamento precoce de longo prazo de redução do colesterol através das estatinas e inibidores da PCSK9.

Association between prediabetes and risk of cardiovascular disease and all-cause mortality: systematic review and meta-analysis

Huang Y, Cai X, Mai W, Li M, Hu Y

BMJ. 2016; 355: i5953

OBJECTIVES: to evaluate associations between different definitions of prediabetes and the risk of cardiovascular disease and all-cause mortality. DESIGN Meta-analysis of prospective cohort studies. DATA SOURCES Electronic databases (PubMed, Embase, and Google Scholar). SELECTION CRITERIA Prospective cohort studies from general populations were included for meta-analysis if they reported adjusted relative risks with 95% confidence intervals for associations between the risk of composite cardiovascular disease, coronary heart disease, stroke, all-cause mortality, and prediabetes.

METHODS: two authors independently reviewed and selected eligible studies, based on predetermined selection criteria. Prediabetes was defined as impaired fasting glucose according to the criteria of the American Diabetes Association (IFG-ADA; fasting glucose 5.6-6.9 mmol/L), the WHO expert group (IFG-WHO; fasting glucose 6.1-6.9 mmol/L), impaired glucose tolerance (2 hour plasma glucose concentration 7.8-11.0 mmol/L during an oral glucose tolerance test), or raised haemoglobin A_{1c} (HbA_{1c}) of 39-47 mmol/mol (5.7-6.4%) according to ADA criteria or 42-47 mmol/mol (6.0-6.4%) according to the National Institute for Health and Care Excellence (NICE) guideline. The relative risks of all-cause mortality and cardiovascular events were calculated and reported with 95% confidence intervals.

RESULTS: 53 prospective cohort studies with 1 611 339 individuals were included for analysis. The median follow-up duration was 9.5 years. Compared with normoglycemia, prediabetes (impaired glucose tolerance or impaired fasting glucose according to IFG-ADA or IFG-WHO criteria) was associated with an increased risk of composite cardiovascular disease (relative risk 1.13, 1.26, and 1.30 for IFG-ADA, IFG-WHO, and impaired glucose tolerance, respectively), coronary heart disease (1.10, 1.18, and 1.20, respectively), stroke (1.06, 1.17, and 1.20, respectively), and all-cause mortality (1.13, 1.13 and 1.32, respectively). Increases in HBA_{1c} to 39-47 mmol/mol or 42-47 mmol/mol were both associated with an increased risk of composite cardiovascular disease (1.21 and 1.25, respectively) and coronary heart disease (1.15 and 1.28, respectively), but not with an increased risk of stroke and all-cause mortality.

CONCLUSIONS: prediabetes, defined as impaired glucose tolerance, impaired fasting glucose, or raised HbA_{1c}, was associated with an increased risk of cardiovascular disease. The health risk might be increased in people with a fasting glucose concentration as low as 5.6 mmol/L or HbA_{1c} of 39 mmol/mol.

Comentários (PvH): esta análise reforça o conceito de que há um aumento dos eventos cardiovasculares associados a valores mais baixos de glicemias em jejum do que aqueles que definem a diabetes, lembrando que a doença é um contínuo e que as causas subjacentes como a resistência à insulina estão presentes antes do seu diagnóstico, com o risco cardiovascular associado.

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

McEvoy RD, Antic NA, Heeley E, et al for the SAVE Investigators

N Engl J Med 2016; 375:919-931

BACKGROUND Obstructive sleep apnea is associated with an increased risk of cardiovascular events; whether treatment with continuous positive airway pressure (CPAP) prevents major cardiovascular events is uncertain.

METHODS After a 1-week run-in period during which the participants used sham CPAP, we randomly assigned 2717 eligible adults between 45 and 75 years of age who had moderate-to-severe obstructive sleep apnea and coronary or cerebrovascular disease to receive CPAP treatment plus usual care (CPAP group) or usual care alone (usual-care group). The primary composite end point was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. Secondary end points included other cardiovascular outcomes, health-related quality of life, snoring symptoms, daytime sleepiness, and mood.

RESULTS Most of the participants were men who had moderate-to-severe obstructive sleep apnea and minimal sleepiness. In the CPAP group, the mean duration of adherence to CPAP therapy was 3.3 hours per night, and the mean apnea–hypopnea index (the number of apnea or hypopnea events per hour of recording) decreased from 29.0 events per hour at baseline to 3.7 events per hour during follow-up. After a mean follow-up of 3.7 years, a primary end-point event had occurred in 229 participants in the CPAP group (17.0%) and in 207 participants in the usual-care group (15.4%) (hazard ratio with CPAP, 1.10; 95% confidence interval, 0.91 to 1.32; P=0.34). No significant effect on any individual or other composite cardiovascular end point was observed. CPAP significantly reduced snoring and daytime sleepiness and improved health-related quality of life and mood.

CONCLUSIONS Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease.

Comentários (PvH): o CPAP é o tratamento habitual para a apneia obstrutiva do sono, que se sabe ser um factor de risco de doença cardiovascular. Neste estudo não houve qualquer indicação de que a utilização do CPAP reduzisse esse risco. No entanto é importante salientar que houve uma melhoria da sintomatologia.

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial.

Vestbo J, Anderson JA, Brook RD, for the SUMMIT Investigators

Lancet 2016; 387(10030):1817-26

BACKGROUND: Chronic obstructive pulmonary disease (COPD) often coexists with cardiovascular disease. Treatments for airflow limitation might improve survival and both respiratory and cardiovascular outcomes. The aim of this study was to assess whether inhaled treatment with a combined treatment of the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol could improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk.

METHODS: In this double-blind randomised controlled trial (SUMMIT) done in 1368 centres in 43 countries, eligible patients were aged 40-80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV1) between 50% and 70% of the predicted value, a ratio of post-bronchodilator FEV1 to forced vital capacity (FVC) of 0,70 or less, a smoking history of at least 10 pack-years, and a score of 2 or greater on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Enrolled patients were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive once daily inhaled placebo, fluticasone furoate (100 μg), vilanterol (25 μg), or the combination of fluticasone furoate (100 μg) and vilanterol (25 μg). The primary outcome was all-cause mortality, and secondary outcomes were on-treatment rate of decline in forced expiratory volume in 1 s (FEV1) and a composite of cardiovascular events. Safety analyses were performed on the safety population (all patients who took at least one dose of study drug) and efficacy analyses were performed on the intention-to-treat population (safety population minus sites excluded with Good Clinical Practice violations). This study is registered with ClinicalTrials.gov, number NCT01313676.

FINDINGS: Between Jan 24, 2011, and March 12, 2014, 23 835 patients were screened, of whom 16 590 were randomised. 16 485 patients were included in the intention-to-treat efficacy population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group. Compared with placebo, all-cause mortality was unaffected by combination therapy (hazard ratio [HR] 0·88 [95% CI 0·74-1·04]; 12% relative reduction; p=0·137) or the components (fluticasone furoate, HR 0·91 [0·77-1·08]; p=0·284; vilanterol, 0·96 [0·81-1·14]; p=0·655), and therefore secondary outcomes should be interpreted with caution. Rate of decline in FEV1 was reduced by combination therapy (38 mL per year [SE 2·4] vs 46 mL per year [2·5] for placebo, difference 8 mL per year [95% CI 1-15]) with similar findings for fluticasone furoate (difference 8 mL per year [95% CI 1-14]), but not vilanterol (difference -2 mL per year [95% CI -8 to 5]). Combination therapy had no effect on composite cardiovascular events (HR 0·93 [95% CI 0·75-1·14]) with similar findings for fluticasone furoate (0·90 [0·72-1·11]) and vilanterol (0·99 [0·80-1·22]). All treatments reduced the rate of moderate and severe exacerbation. No reported excess risks of pneumonia (5% in the placebo group, 6% in the combination group, 5% in the fluticasone furoate group, and 4% in the vilanterol group) or adverse cardiac events (17% in the placebo group, 18% in the combination group, and 17% in the fluticasone furoate group, and 17% in the vilanterol group) were noted in the treatment groups.

INTERPRETATION: In patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes, reduced exacerbations, and was well tolerated. Fluticasone furoate, alone or in combination with vilanterol, seemed to reduce FEV1 decline.

Comentários (FA): os doentes com DPOC morrem mais de doença cardiovascular do que da própria doença de base. Vários mecanismos têm sido implicados neste acréscimo de RV na DPOC, incluindo a inatividade física, a inflamação sistémica persistente de baixo grau, a disfunção endotelial, a activação neurohumoral, as arritmias, a variabilidade tensional acrescida. Neste estudo, a terapêutica combinada de um b-agonista de longa acção e de um corticoide, não atingiu o objetivo principal (a redução de 12% de mortalidade total vs placebo). Mas ficou demonstrada a segurança desta associação terapêutica numa população com DPOC moderada e com RV acrescido. Existiu uma redução do declínio da FEV1 e dos episódios de descompensação da DPOC, o que poderá mudar o curso da doença.

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Nissen SE, Yeomans ND, Solomon DH for the PRECISION Trial Investigators

N Engl J Med 2016; 375(26): 2519-2529

BACKGROUND The cardiovascular safety of celecoxib, as compared with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), remains uncertain.

METHODS Patients who required NSAIDs for osteoarthritis or rheumatoid arthritis and were at increased cardiovascular risk were randomly assigned to receive celecoxib, ibuprofen, or naproxen. The goal of the trial was to assess the noninferiority of celecoxib with regard to the primary composite outcome of cardiovascular death (including hemorrhagic death), nonfatal myocardial infarction, or nonfatal stroke. Noninferiority required a hazard ratio of 1.12 or lower, as well as an upper 97.5% confidence limit of 1.33 or lower in the intention-to-treat population and of 1.40 or lower in the ontreatment population. Gastrointestinal and renal outcomes were also adjudicated.

RESULTS A total of 24,081 patients were randomly assigned to the celecoxib group (mean [±SD] daily dose, 209±37 mg), the naproxen group (852±103 mg), or the ibuprofen group (2045±246 mg) for a mean treatment duration of 20.3±16.0 months and a mean follow up period of 34.1±13.4 months. During the trial, 68.8% of the patients stopped taking the study drug, and 27.4% of the patients discontinued follow-up. In the intention-to-treat analyses, a primary outcome event occurred in 188 patients in the celecoxib group (2.3%), 201 patients in the naproxen group (2.5%), and 218 patients in the ibuprofen group (2.7%) (hazard ratio for celecoxib vs. naproxen,

0.93; 95% confidence interval [CI], 0.76 to 1.13; hazard ratio for celecoxib vs. ibuprofen, 0.85; 95% CI, 0.70 to 1.04; P<0.001 for noninferiority in both comparisons). In the on-treatment analysis, a primary outcome event occurred in 134 patients in the celecoxib group (1.7%), 144 patients in the naproxen group (1.8%), and 155 patients in the ibuprofen group (1.9%) (hazard ratio for celecoxib vs. naproxen, 0.90; 95% CI, 0.71 to 1.15; hazard ratio for celecoxib vs. ibuprofen, 0.81; 95% CI, 0.65 to 1.02; P<0.001 for noninferiority in both comparisons). The risk of gastrointestinal events was significantly lower with celecoxib than with naproxen (P=0.01) or ibuprofen (P=0.002); the risk of renal events was significantly lower with celecoxib than with ibuprofen (P=0.004) but was not significantly lower with celecoxib than with naproxen (P=0.19).

CONCLUSIONS At moderate doses, celecoxib was found to be non-inferior to ibuprofen or naproxen with regard to cardiovascular safety.

Comentários (FA): um estudo que demonstra a segurança cardiovascular do celecoxibe em comparação com dois dos AINE mais prescritos, incluindo aquele que até à data tinha melhores resultados neste campo, o naproxeno. Como esperado, é sobretudo na segurança gastrointestinal que há diferença do celecoxibe comparativamente aos dois AINE, com redução de 49% de eventos GI major vs naproxeno e de 57% vs ibuprofeno, mesmo quando todos os doentes foram medicados com esomeprazol. A fraca adesão à medicação durante o estudo reflete a dificuldade de realizar estudos deste género a longo prazo em patologias como a osteoartrose ou a artrite reumatoide, mas na vida real essa é também a realidade. A dose utilizada de celecoxibe foi limitada aos 200 mg dia, podendo esta dose ser insuficiente para um adequado controlo da dor. Os resultados não devem ser extrapolados para doses mais elevadas do fármaco.

Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis

Ljung L , Rantapää-Dahlqvist S, Jacobsson LTH, Askling J , for the ARTIS Study Group

Ann Rheum Dis 2016;75: 2087-2094

Objectives: whether the increased risk of comorbidities, such as cardiovascular disease, in rheumatoid arthritis (RA) can be reverted by particular antirheumatic therapies, or response to these, is unclear but of critical clinical importance. We wanted to investigate whether response to tumour necrosis factor inhibitors (TNFi) translates into a reduced risk for acute coronary syndrome (ACS).

Methods: a cohort of patients with RA initiating a first TNFi 2001–2012 was identified in the Swedish Biologics Register. The association between European League Against Rheumatism (EULAR) response after 3–8 months of treatment (assessed using the first, the best and the measurement closest to 5 months, respectively), and the risk of incident ACS during the subsequent year was analyzed in Cox regression models. Adjustments included cardiovascular risk factors, joint surgery, RA duration, education and work disability.

Results: during 6592 person-years among TNFi initiators (n=6864, mean age 55 years, 77% women), 47 ACS occurred. The adjusted HRs (95% CI), which were similar to the crude HRs, of the 1-year risk of ACS among EULAR good responders compared with non-responders were 0.5 (0.2 to 1.4), 0.4 (0.2 to 0.9) and 0.5 (0.2 to 1.2), for the first, the best and the evaluation closest to 5 months, respectively. EULAR moderate responders had equal risk to that of EULAR non-responders, who, compared with the general population referents (n=34 229), had a more than twice the risk of ACS. For good responders, there was no statistically significant difference in risk versus the general population.

Conclusions: optimized RA disease control has the potential to revert otherwise increased risks for ACS in RA

Comentário (PvH): estes resultados mostram que a terapêutica anti- FNT-alfa não previne por si só os eventos coronários agudos nos doentes com artrite reumatoide, mas indica que será o controlo da própria doença que leva à redução dos eventos, salientando a importância da inflamação crónica como factor de risco coronário.

Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis

Lazzerini PE, Capecchi PL, Laghi-Pasini F

European Heart Journal 2017; 38: 1717–1727

Rheumatoid arthritis (RA) is a chronic immuno-mediated disease primarily affecting the joints, characterized by persistent high-grade systemic inflammation. Cardiovascular morbidity and mortality are significantly increased in RA, with >50% of premature deaths attributable to cardiovascular disease. In particular, RA patients were twice as likely to experience sudden cardiac death compared with non-RA subjects, pointing to an increased propensity to develop malignant ventricular arrhythmias. Indeed, ventricular repolarization (QT interval) abnormalities and cardiovascular autonomic nervous system dysfunction, representing two well-recognized risk factors for life-threatening ventricular arrhythmias in the general population, are commonly observed in RA. Moreover, large population-based studies seem to indicate that also the prevalence of atrial fibrillation is significantly higher in RA subjects than in the general population, thus suggesting that these patients are characterized by an abnormal diffuse myocardial electrical instability. Although the underlying mechanisms accounting for the pro-arrhythmogenic substrate in RA are probably intricate, the leading role seems to be played by chronic systemic inflammatory activation, able to promote arrhythmias both indirectly, by accelerating the development of ischaemic heart disease and congestive heart failure, and directly, by affecting cardiac electrophysiology.

In this integrated mechanistic view, lowering the inflammatory burden through an increasingly tight control of disease activity may represent the most effective intervention to reduce arrhythmic risk in these patients. Intriguingly, these considerations could be more generally applicable to all the diseases characterized by chronic

systemic inflammation, and could help elucidate the link between low-grade chronic inflammation and arrhythmic risk in the general population.

Comentário (FA): num ano em que se voltou a falar tanto do risco residual inflamatório em doentes com doença aterosclerótica, e de como estudos como o CANTOS abrem novas perspetivas para a redução de eventos cardiovasculares, é interessante esta ligação entre inflamação e risco arritmogénico. Claro que será importante perceber se o risco de arritmia e morte súbita estão relacionados com a inflamação, ou com as alterações estruturais induzidas por esta (como a fibrose) ou com eventos coronários prévios.

Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study

Laughlin-Tommaso SK, Zaraq K, Weaver AL, et al.

Menopause. 2017 Dec 28. [Epub ahead of print]

Objective: The aim of the study was to determine the long-term risk of cardiovascular disease and metabolic conditions in women undergoing hysterectomy with bilateral ovarian conservation compared with age-matched referent women.

Methods: Using the Rochester Epidemiology Project records-linkage system, we identified 2,094 women who underwent hysterectomy with ovarian conservation for benign indications between 1980 and 2002 in Olmsted County, Minnesota. Each woman was age-matched (±1 y) to a referent woman residing in the same county who had not undergone prior hysterectomy or any oophorectomy. These two cohorts were followed historically to identify de novo cardiovascular or metabolic diagnoses. We estimated hazard ratios (HRs) and 95% CIs using Cox proportional hazards models adjusted for 20 preexisting chronic conditions and other potential confounders. We also calculated absolute risk increases and reductions from Kaplan–Meier estimates.

Results: Over a median follow-up of 21.9 years, women who underwent hysterectomy experienced increased risks of de novo hyperlipidemia (HR 1.14; 95% CI, 1.05-1.25), hypertension (HR 1.13; 95% CI, 1.03-1.25), obesity (HR 1.18; 95% CI, 1.04-1.35), cardiac arrhythmias (HR 1.17; 95% CI, 1.05-1.32), and coronary artery disease (HR 1.33; 95% CI, 1.12-1.58). Women who underwent hysterectomy at age ≤35 years had a 4.6-fold increased risk of congestive heart failure and a 2.5-fold increased risk of coronary artery disease.

Conclusions: Even with ovarian conservation, hysterectomy is associated with an increased long-term risk of cardiovascular and metabolic conditions, especially in women who undergo hysterectomy at age ≤35 years. If these associations are causal, alternatives to hysterectomy should be considered to treat benign gynecologic conditions.

Comentário (PvH): as mulheres que foram submetidas a histerectomia mesmo sem anexectomia têm um acréscimo de risco cardiovascular e alterações metabólicas, incluindo hipertensão arterial, obesidade, dislipidemia, doença coronária e insuficiência cardíaca, principalmente se a intervenção é feita antes dos 40 anos. Devem ser encorajadas alternativas não-cirúrgicas para situações como fibromiomas, endometriose e prolapso uterino, que são as grandes razões para a realização de histerectomia.

Migraine and risk of cardiovascular disease in women: prospective cohort study

Kurth K, Winter AC, Eliassen AH et al

BMJ 2016;353:i2610

Abstract: Objective To evaluate the association between migraine and incident cardiovascular disease and cardiovascular mortality in women.

Design Prospective cohort study among Nurses' Health Study II participants, with follow-up from 1989 and through June 2011.

Participants 115 541 women aged 25-42 years at baseline and free of angina and cardiovascular disease. Cumulative follow-up rates were more than 90%.

Main outcome measures The primary outcome of the study was major cardiovascular disease, a combined endpoint of myocardial infarction, stroke, or fatal cardiovascular disease. Secondary outcome measures included individual endpoints of myocardial infarction, stroke, angina/coronary revascularization procedures, and cardiovascular mortality.

Results 17 531 (15.2%) women reported a physician's diagnosis of migraine. Over 20 years of follow-up, 1329 major cardiovascular disease events occurred and 223 women died from cardiovascular disease. After adjustment for potential confounding factors, migraine was associated with an increased risk for major cardiovascular disease (hazard ratio 1.50, 95% confidence interval 1.33 to 1.69), myocardial infarction (1.39, 1.18 to 1.64), stroke (1.62, 1.37 to 1.92), and angina/coronary revascularization procedures (1.73, 1.29 to 2.32), compared with women without migraine. Furthermore, migraine was associated with a significantly increased risk for cardiovascular disease mortality (hazard ratio 1.37, 1.02 to 1.83). Associations were similar across subgroups of women, including by age (<50/≥50), smoking status (current/past/never), hypertension (yes/no), postmenopausal hormone therapy (current/not current), and oral contraceptive use (current/not current).

Conclusions Results of this large, prospective cohort study in women with more than 20 years of follow-up indicate a consistent link between migraine and cardiovascular disease events, including cardiovascular mortality. Women with migraine should be evaluated for their vascular risk. Future targeted research is warranted to identify preventive strategies to reduce the risk of future cardiovascular disease among patients with migraine.

Comentários (FA): a enxaqueca (pelo menos aquela com aura) tem sido relacionada ao risco aumentado de AVC. A razão para esta associação não é clara, tendo sido implicadas causas como a disfunção endotelial, a inflamação, aspetos genéticos comuns, o aumento da prevalência de fatores de risco CV … Também não é claro se a utilização de fármacos utilizados na enxaqueca (AINEs, vasoconstritores), poderão ter influenciado o resultado. Este estudo demonstra que não só o AVC, mas que os eventos cardiovasculares como um todo são afetados com um aumento do risco de eventos CV em 50%. A enxaqueca surge assim como um marcador de risco doença cardiovascular, e neste estudo isso foi independente da idade, da utilização de terapêutica de substituição ou da pílula, da presença de hipertensão ou do hábito de fumar. Não há dados sobre se a prevenção da enxaqueca poderá reduzir o risco de eventos no futuro. E já agora, este estudo restringe-se ao género feminino…

Antidepressant use and risk of cardiovascular outcomes in people aged 20 to 64: cohort study using primary care database

Coupland C, Hill T, Morriss R, Moore M, Arthur A, Hippisley-Cox J

BMJ. 2016 Mar 22;352:i1350. doi: 10.1136/bmj.i1350

Abstract Objective To assess associations between different antidepressant treatments and rates of three cardiovascular outcomes (myocardial infarction, stroke or transient ischaemic attack, and arrhythmia) in people with depression.

Design Cohort study: Setting UK general practices contributing to the QResearch primary care database. Participants 238 963 patients aged 20 to 64 years with a first diagnosis of depression between 1 January 2000 and 31 July 2011. Exposures Antidepressant class (tricyclic and related antidepressants, selective serotonin reuptake inhibitors, other antidepressants), dose, duration of use, and commonly prescribed individual antidepressant drugs. Main outcome measures First diagnoses of myocardial infarction, stroke or transient ischaemic attack, and arrhythmia during five years' follow-up. Cox proportional hazards models were used to estimate hazard ratios, adjusting for potential confounding variables.

Results During five years of follow-up, 772 patients had a myocardial infarction, 1106 had a stroke or transient ischaemic attack, and 1452 were diagnosed as having arrhythmia. No significant associations were found between antidepressant class and myocardial infarction over five years' follow-up. In the first year of follow-up, patients treated with selective serotonin reuptake inhibitors had a significantly reduced risk of myocardial infarction (adjusted hazard ratio 0.58, 95% confidence interval 0.42 to 0.79) compared with no use of antidepressants; among individual drugs, fluoxetine was associated with a significantly reduced risk (0.44, 0.27 to 0.72) and lofepramine with a significantly increased risk (3.07, 1.50 to 6.26). No significant associations were found between antidepressant class or individual drugs and risk of stroke or transient ischaemic attack. Antidepressant class was not significantly associated with arrhythmia over five years' follow-up, although the risk was significantly increased during the first 28 days of treatment with tricyclic and related antidepressants (adjusted hazard ratio 1.99, 1.27 to 3.13). Fluoxetine was associated with a significantly reduced risk of arrhythmia (0.74, 0.59 to 0.92) over five years, but citalopram was not significantly associated with risk of arrhythmia even at high doses (1.11, 0.72 to 1.71 for doses ≥40 mg/day).

Conclusions This study found no evidence that selective serotonin reuptake inhibitors are associated with an increased risk of arrhythmia or stroke/transient ischaemic attack in people diagnosed as having depression between the ages of 20 to 64 or that citalopram is associated with a significantly increased risk of arrhythmia. It found some indication of a reduced risk of myocardial infarction with selective serotonin reuptake inhibitors, particularly fluoxetine, and of an increased risk with lofepramine.

Comentários (FA): a depressão deve constar da lista de factores de risco cardiovascular, tal como a diabetes e a hipertensão. Nos doentes com cardiopatia isquémica a depressão é frequente e aumenta o risco de morte. É importante não desvalorizar a doença e tratá-la. Há duvidas sobre a segurança dos fármacos utilizados na sua terapêutica e este estudo demonstra a segurança cardiovascular de alguns dos medicamentos mais usados entre nós.

Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study

Li L, Geraghty OC, Mehta Z, on behalf of the Oxford Vascular Study

Lancet. 2017; 390(10093):490-499

Lifelong antiplatelet treatment is recommended after ischaemic vascular events, on the basis of trials done mainly in patients younger than 75 years. Upper gastrointestinal bleeding is a serious complication, but had low case fatality in trials of aspirin and is not generally thought to cause long-term disability. Consequently, although co-prescription of proton-pump inhibitors (PPIs) reduces upper gastrointestinal bleeds by 70–90%, uptake is low, and guidelines are conflicting. We aimed to assess the risk, time course, and outcomes of bleeding on antiplatelet treatment for secondary prevention in patients of all ages.

Methods: We did a prospective population-based cohort study in patients with a first transient ischaemic attack, ischaemic stroke, or myocardial infarction treated with antiplatelet drugs (mainly aspirin based, without routine PPI use) after the event in the Oxford Vascular Study from 2002 to 2012, with follow-up until 2013. We determined type, severity, outcome (disability or death), and time course of bleeding requiring medical attention by face-to-face follow-up for 10 years. We estimated age-specific numbers needed to treat (NNT) to prevent upper gastrointestinal bleeding with routine PPI co-prescription on the basis of Kaplan–Meier risk estimates and relative risk reduction estimates from previous trials. Findings: 3166 patients (1582 [50%] aged ≥75 years) had 405 first bleeding events (n=218 gastrointestinal, n=45 intracranial, and n=142 other) during 13 509 patient-years of follow-up. Of the 314 patients (78%) with bleeds admitted to hospital, 117 (37%) were missed by administrative coding. Risk of non-major bleeding was unrelated to age, but major bleeding increased steeply with age (≥75 years hazard ratio [HR] 3·10, 95% CI 2·27–4·24; p<0·0001), particularly for fatal bleeds (5·53, 2·65–11·54; p<0·0001), and was sustained during long-term follow-up. The same was true of major upper gastrointestinal bleeds (≥75 years HR 4·13, 2·60–6·57; p<0·0001), particularly if disabling or fatal (10·26, 4·37–24·13; p<0·0001). At age 75 years or older, major upper gastrointestinal bleeds were mostly disabling or fatal (45 [62%] of 73 patients vs 101 [47%] of 213 patients with recurrent ischaemic stroke), and outnumbered disabling or fatal intracerebral haemorrhage (n=45 vs n=18), with an absolute risk of 9·15 (95% CI 6·67–12·24) per 1000 patient-years. The estimated NNT for routine PPI use to prevent one disabling or fatal upper gastrointestinal bleed over 5 years fell from 338 for individuals younger than 65 years, to 25 for individuals aged 85 years or older.

Interpretation: In patients receiving aspirin-based antiplatelet treatment without routine PPI use, the long-term risk of major bleeding is higher and more sustained in older patients in practice than in the younger patients in previous trials, with a substantial risk of disabling or fatal upper gastrointestinal bleeding. Given that half of the major bleeds in patients aged 75 years or older were upper gastrointestinal, the estimated NNT for routine PPI use to prevent such bleeds is low, and co-prescription should be encouraged.

Comentários (FA): com um NNT de apenas 25 doentes (com mais de 85 anos) para prevenir uma hemorragia major, a associação de um inibidor da bomba de protões (IBP) a doentes sob antigregação, dá que pensar. O risco de hemorragia fatal aumenta significativamente com o avançar da idade e neste caso a diferença entre a estratégia de usar ou não um IBP, foi significativa. Em doentes mais jovens, persistem dúvidas sobre a vantagem desta associação, já que o risco hemorrágico é menor. Por outro lado, permanece a interrogação, sobre a eventual perda de eficácia do antiagregante quando se associa um IBP, nomeadamente para alguns fármacos, como o clopidogrel.

Ticagrelor versus Clopidogrel in Symptomatic Peripheral Artery Disease

Hiatt WR, Fowkes FGR, Heizer G, et al for the EUCLID Trial Investigators

N Engl J Med 2017; 376:32-40

BACKGROUND Peripheral artery disease is considered to be a manifestation of systemic atherosclerosis with associated adverse cardiovascular and limb events. Data from previous trials have suggested that patients receiving clopidogrel monotherapy had a lower risk of cardiovascular events than those receiving aspirin. We wanted to compare clopidogrel with ticagrelor, a potent antiplatelet agent, in patients with peripheral artery disease

METHODS In this double-blind, event-driven trial, we randomly assigned 13,885 patients with symptomatic peripheral artery disease to receive monotherapy with ticagrelor (90 mg twice daily) or clopidogrel (75 mg once daily). Patients were eligible if they had an ankle–brachial index (ABI) of 0.80 or less or had undergone previous revascularization of the lower limbs. The primary efficacy end point was a composite of adjudicated cardiovascular death, myocardial infarction, or ischemic stroke. The primary safety end point was major bleeding. The median follow-up was 30 months.

RESULTS The median age of the patients was 66 years, and 72% were men; 43% were enrolled on the basis of the ABI and 57% on the basis of previous revascularization. The mean baseline ABI in all patients was 0.71, 76.6% of the patients had claudication, and 4.6% had critical limb ischemia. The primary efficacy end point occurred in 751 of 6930 patients (10.8%) receiving ticagrelor and in 740 of 6955 (10.6%) receiving clopidogrel (hazard ratio, 1.02; 95% confidence interval [CI], 0.92 to 1.13; P=0.65). In each group, acute limb ischemia occurred in 1.7% of the patients (hazard ratio, 1.03; 95% CI, 0.79 to 1.33; P=0.85) and major bleeding in 1.6% (hazard ratio, 1.10; 95% CI, 0.84 to 1.43; P=0.49).

CONCLUSIONS In patients with symptomatic peripheral artery disease, ticagrelor was not shown to be superior to clopidogrel for the reduction of cardiovascular events. Major bleeding occurred at similar rates among the patients in the two trial groups. (Funded by AstraZeneca; EUCLID ClinicalTrials.gov number, NCT01732822.

Comentários (FA): desde o estudo CAPRIE que o clopidogrel é muitas vezes o antiagregante preferido quando falamos de doença arterial periférica, se bem que o benefício versus aspirina parece limitar-se aos doentes fumadores. Os resultados do EUCLID não deverão alterar esta estratégia. Por outro lado, a dupla antiagregação de aspirina com clopidogrel ou vorapaxar não tem sido consensual. A utilização de aspirina e anticoagulante em baixas doses (como no COMPASS) é outra estratégia a considerar no futuro próximo, nos doentes com mais alto risco.

Population screening and intervention for vascular disease in Danish men (VIVA): a randomised controlled trial

Lancet. 2017; 390(10109):2256-2265

Lindholt JS, Søgaard R

Background: Abdominal aortic aneurysm is the only cardiovascular disease targeted by population screening. In this study, we test the effect of screening and subsequent intervention for abdominal aortic aneurysm, peripheral arterial disease, and hypertension combined.

Methods: In this randomised controlled trial, we randomly allocated (1:1) all men aged 65–74 years living in the Central Denmark Region to screening for abdominal aortic aneurysm, peripheral arterial disease, and hypertension, or to no screening. We based allocation on computer-generated random numbers from 1 to 100 in blocks of 1067 to 4392, stratified by 19 municipalities. Only the non-screening group and the investigator assessing outcomes were masked. We invited participants who were found to have abdominal aortic aneurysm or peripheral arterial disease back for confirmation and eventual initiation of relevant pharmacological therapy. We further offered participants with abdominal aortic aneurysm annual control or surgical repair. We referred participants with suspected hypertension to their general practitioner. The primary outcome was all-cause mortality, assessed 5 years after randomisation, analysed in all randomly allocated participants except for those who had incorrect person identification numbers. This trial is registered at ClinicalTrials.gov, number NCT00662480.

Findings: between Oct 8, 2008, and Jan 11, 2011, we randomly allocated 50 156 participants, with 25 078 (50%) each in the screening and non-screening groups. Four (<1%) participants in the screening group were lost to follow-up. After a median follow-up of 4·4 years (IQR 3·9–4·8), 2566 (10·2%) of 25 074 participants in the screening group and 2715 (10·8%) of 25 078 in the non-screening group had died. This finding resulted in a significant hazard ratio of 0·93 (95% CI 0·88–0·98; p=0·01), an absolute risk reduction of 0·006 (0·001–0·011), and a number needed to invite of 169 (89–1811). Incidences of diabetes (3995 per 100 000 person-years in the screening group vs 4129 per 100 000 person-years in the non-screening group), intracerebral haemorrhage (146 vs 140), renal failure (612 vs 649), cancer (3578 vs 3719), or 30-day mortality after cardiovascular surgery (44·57 vs 39·33) did not differ between groups.

Interpretation: the observed reduction of mortality risk from abdominal aortic aneurysm, peripheral arterial disease, and hypertension has never been seen before in the population screening literature and can be linked primarily to initiation of pharmacological therapy. Health policy makers should consider implementing combined screening whether no screening or isolated abdominal aortic aneurysm screening is currently offered.

Comentários (FA): interessantíssimo. Se a redução em 7% na mortalidade relativa, pode não vos parecer suficiente, um NNT de 169, é melhor ao que se obtém na maioria dos rastreios na área do cancro. Esta estratégia permitiu diagnosticar 3,3 % de doentes com aneurismas da aorta abdominal (AAA), 10,9% com doença arterial periférica e 10,5 de hipertensos não conhecidos, com introdução ou optimização da terapêutica (médica, cirúrgica, cessação tabágica), sem aparentes complicações dessas intervenções. Apenas homens foram incluídos, pelo que os resultados não devem ser extrapolados para a população em geral, já que a incidência de AAA nas mulheres é reconhecidamente mais baixa.

Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease

Jaiswal S, Natarajan P, Silver AJ, et al.

N Engl J Med 2017; 377:111-121

BACKGROUND: Clonal hematopoiesis of indeterminate potential (CHIP), which is defined as the presence of an expanded somatic blood-cell clone in persons without other hematologic abnormalities, is common among older persons and is associated with an increased risk of hematologic cancer. We previously found preliminary evidence for an association between CHIP and atherosclerotic cardiovascular disease, but the nature of this association was unclear.

METHODS: We used whole-exome sequencing to detect the presence of CHIP in peripheral-blood cells and associated such presence with coronary heart disease using samples from four case–control studies that together enrolled 4726 participants with coronary heart disease and 3529 controls. To assess causality, we perturbed the function of Tet2, the second most commonly mutated gene linked to clonal hematopoiesis, in the hematopoietic cells of atherosclerosis-prone mice.

RESULTS: In nested case–control analyses from two prospective cohorts, carriers of CHIP had a risk of coronary heart disease that was 1.9 times as great as in noncarriers (95% confidence interval [CI], 1.4 to 2.7). In two retrospective case–control cohorts for the evaluation of early-onset myocardial infarction, participants with CHIP had a risk of myocardial infarction that was 4.0 times as great as in noncarriers (95% CI, 2.4 to 6.7). Mutations in DNMT3A, TET2, ASXL1, and JAK2 were each individually associated with coronary heart disease. CHIP carriers with these mutations also had increased coronary-artery calcification, a marker of coronary atherosclerosis burden. Hypercholesterolemia-prone mice that were engrafted with bone marrow obtained from homozygous or heterozygous Tet2 knockout mice had larger atherosclerotic lesions in the aortic root and aorta than did mice that had received control bone marrow. Analyses of macrophages from Tet2 knockout mice showed elevated expression of several chemokine and cytokine genes that contribute to atherosclerosis.

CONCLUSIONS: The presence of CHIP in peripheral-blood cells was associated with nearly a doubling in the risk of coronary heart disease in humans and with accelerated atherosclerosis in mice.

Comentário (PvH): os factores de risco tradicionais não explicam todo o risco de eventos cardiovasculares. Inúmeros factores de risco de desenvolvimento de aterosclerose estão a ser investigados. Os resultados destas análises, que associam a hematopoiese clonal de significado indeterminado com o risco de enfarte do miocárdio e o desenvolvimento de aterosclerose, são importantes para um melhor conhecimento do processo aterosclerótico e do risco cardiovascular.

2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology

Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al

Eur Heart J (2016) 37 (36): 2768-2801

…Advances in treatment have led to improved survival of patients with cancer, but have also increased morbidity and mortality due to treatment side effects. Cardiovascular diseases (CVDs) are one of the most frequent of these side effects, and there is a growing concern that they may lead to premature morbidity and death among cancer survivors. This may be the result of cardiotoxicity, which involves direct effects of the cancer treatment on heart function and structure, or may be due to accelerated development of CVD, especially in the presence of traditional cardiovascular risk factors…

Comentários (FA): um dos temas da moda, em que apenas uma abordagem multidisciplinar pode reconhecer esta condição clínica e permitir que se tome conhecimento sobre uma complicação, (tantas vezes subdiagnosticada), do cancro e das suas terapêuticas. A sobrevivência ao cancro não depende apenas da cura desta doença, mas também da prevenção, reconhecimento e tratamento das complicações da sua terapêutica