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SECONDARY PREVENTION AND CARDIOVASCULAR DISEASE: WHERE ARE WE?

PREVENÇÃO SECUNDÁRIA E DOENÇA CARDIOVASCULAR: ONDE ESTAMOS?

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ABSTRACT

Cardiovascular diseases, particularly those arising from cases of stroke and acute myocardial infarction, have a significant impact on global mortality and hospital admissions around the world. Despite the vast knowledge of the various risk factors involved in the genesis of cardiovascular disease, the number of events remains high and institution of primary and secondary prevention measures is essential and complementary. In recent years, important advances in the field of pharmacological treatment of atherosclerosis and heart failure, particularly those arising from ischemic heart disease, have been published. The main results are highlighted in this article.

Keywords: Secondary Prevention; Atherosclerosis; Heart Failure.

RESUMO

As doenças cardiovasculares, principalmente as decorrentes de casos de acidente vascular cerebral e infarto agudo do miocárdio, têm importante impacto na mortalidade global e nas internações hospitalares em todo o mundo. A despeito do vasto conhecimento dos diversos fatores de risco implicados na gênese da doença cardiovascular, o número de eventos ainda se mantém elevado e a instituição de medidas de prevenção primária e secundária são essenciais e complementares. Nos últimos anos, importantes avanços no campo do tratamento farmacológico de aterosclerose e insuficiência cardíaca, predominantemente em decorrência de cardiopatia isquêmica, foram publicados e seus principais resultados são destacados no presente artigo.

Descritores: *Prevenção Secundária; Aterosclerose; Insuficiência Cardíaca.*

INTRODUCTION

According to the most recent data from the Global Burden of Disease, cardiovascular diseases (CVDs) were the main cause of mortality worldwide in 2017, mainly due to stroke and acute myocardial infarction (AMI). CVDs represent 27% of the causes of death worldwide, with small variations between men and women and in certain regions of the world.[1]

Combating CVDs requires a combination of primary and secondary prevention measures. The INTERHEART study identified nine risk factors for the occurrence of a first AMI event in the global population: dyslipidemia, smoking, diabetes mellitus, systemic arterial hypertension, abdominal obesity, psychosocial factors (stress, anxiety, and depression), fruit and vegetable consumption, physical exercise, and alcoholism. Thus, it is important to focus on non-pharmacological measures such as physical activity, a balanced diet, and smoking cessation in the prevention of CV events as well as available and emerging pharmacological therapies.[2]

Therefore, the occurrence of AMI and development of heart failure (HF) are important causes of hospitalization, morbidity, and mortality worldwide, especially in individuals over 60 years of age.[3] Given the need for the secondary prevention of CV events, many studies have been conducted in recent years. Some recent studies have shown a significant impact of new therapies on CV mortality when added to the current standard treatment of underlying diseases.

The development of therapeutic strategies, involving pharmacological intervention to reduce CV mortality or even non-fatal CV events, represented a great advance in the last decade. It is noteworthy that these advances were only possible thanks to the better knowledge of the pathophysiology of CVD in its various stages. Strategies involving aggressive control of cholesterol, arterial hypertension, and type 2 diabetes mellitus (DM2) were fundamental for improving the treatment of CVDs. Obviously, when discussing secondary prevention, it is important to remember that therapeutic interventions act on the various levels of CVD progression, from atherosclerotic disease progression to heart muscle failure. New therapies involving aggressive cholesterol reduction with PCSK9 inhibitors, inhibitors of factor X activity acting as antithrombotics, and drugs with specific anti-inflammatory properties such as interleukin-1 beta inhibitors provided important advances for reducing CV outcomes.

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Among the main drugs that promote glycemic control and CV protection in individuals with DM2, SGLT-2 inhibitors and GLP-1 analogues are fundamental to improving the outcomes of patients with diabetes having high CV risk. Moreover, knowledge of the effects of natriuretic peptides as a protective factor in HF enabling the development of drugs that inhibit its degradation has brought new attention to preventing the progression of this serious disease.

Thus, this article presents the main studies with encouraging results related to therapies for the secondary prevention of CV events, especially atherosclerosis, DM2, and HF.

SACUBITRIL/VALSARTAN FOR REDUCING MORTALITY IN HF

PARADIGM-HF Study

The PARADIGM-HF study, published in 2014, was conducted in 1043 centers in 47 countries and randomized 8399 patients with NYHA II-IV HF with reduced ejection fraction (values less than 35% or 40%) to treatment with sacubitril/valsartan or enalapril 10 mg 12/12 h. With a mean follow-up of 27 months, the study was interrupted early due to positive results favorable to the group using sacubitril/valsartan. The primary outcome, CV mortality or hospitalization for HF, showed a 20% reduction in the sacubitril/valsartan group, with a number needed to treat of 21. The secondary outcomes analyzed in isolation, including CV mortality, hospitalization for HF, and all-cause mortality, showed a reduction of 20%, 21%, and 16% respectively. The main adverse effect observed was symptomatic hypotension, but without leading to permanent discontinuation of the drug. No differences were observed in the occurrence of angioedema. It is noteworthy that patients with decompensated acute HF were excluded from the study. [4]

PIONEER-HF Study

Published in February 2019, the PIONEER-HF study aimed to analyze the impact of sacubitril/valsartan therapy in patients with decompensated acute HF. The use of sacubitril/valsartan was compared to that of enalapril in 881 patients older than 18 years with a left ventricular ejection fraction less than 40% and initial diagnosis of acute HF in 129 centers in the United States. The sacubitril/valsartan group showed a greater reduction in NT-proBNP levels after 4 and 8 weeks of hospitalization than the enalapril group (-47% and -25%). There were no differences in all-cause mortality, need for ventricular pacing therapy, or need for heart transplantation.[5]

PCSK-9 INHIBITORS FOR REDUCING EVENTS IN SECONDARY CVD PREVENTION

FOURIER Study

The FOURIER (*Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk*) study, published in 2018, analyzed the impact of the PCSK9 inhibitor, evolucumab, in patients with established atherosclerotic disease who received standard therapy with moderate- to high-intensity statins compared to placebo. A total of 24081 patients were selected among 1242 centers in 49 countries with a mean follow-up of 26 months. The inclusion criteria were age 40–85 years and clinical evidence of atherosclerotic disease (AMI, non-hemorrhagic stroke, symptomatic peripheral arterial disease [PAD]). Patients with severe ventricular dysfunction, hemorrhagic stroke, uncontrolled hypertension, thyroid changes, liver dysfunction, active infection, or neoplasia were excluded from the study. There was a 15% reduction in the primary outcome of CV death, AMI, stroke, hospitalization for unstable angina, or coronary revascularization (relative risk [RR], 0.85; 95% confidence interval [CI], 0.79–0.92; $p < 0.001$). Despite a 27% reduction in AMI rates (RR, 0.73; 95% CI, 0.65–0.82; $p < 0.001$) and 21% reduction in stroke (RR, 0.79; 95% CI, 0.66–0.95; $p = 0.01$), no reduction in CV or all-cause mortality was noted. Furthermore, low-density lipoprotein (LDL) levels decreased by 59%, with mean values from 92 to 30 mg/dL in the evolucumab group. That study reported no potential negative effects of the intense reduction in LDL levels, such as recent-onset diabetes or neurocognitive effects.[6]

ODISSEY Study

The ODISSEY study, published in February 2019, aimed to determine the safety and efficacy of alirocumab versus placebo in patients with recent acute coronary syndrome (ACS) who were already receiving high or maximum tolerated doses of statins. A total of 18924 patients older than 40 years with ACS in the last 1–12 months before randomization with a mean follow-up of 2.8 years were randomized. The dose of alirocumab was titrated to between 75 mg and 150 mg with subcutaneous administration and nightly frequency aiming at an LDL cholesterol value of 25–50 mg/dL. The primary outcome, major cardiac events (death of coronary disease, incidence of AMI, ischemic stroke, unstable angina), showed a 15% reduction in in the alirocumab group (RR, 0.85; 95% CI, 0.78–0.93; $p < 0.001$), mainly with reduction of AMI, stroke, and unstable angina. With regard to the secondary outcomes, a reduction in all-cause mortality (3.5% and 4.1%, $p = 0.026$) and coronary artery bypass grafting rates (7.7% and 8.8%, $p = 0.009$) was observed. Patients with a baseline LDL greater than 100 mg/dL benefited more from the analyzed therapy.[7]

RIVAROXABAN FOR SECONDARY PREVENTION OF CVD

COMPASS Study

The COMPASS (*Cardiovascular Outcomes for People Using Anticoagulation Strategies*) study, published in 2017, compared the effects of three treatments: (1) rivaroxaban 2.5 mg 12/12 h associated with acetylsalicylic acid (ASA), (2) rivaroxaban 5 mg 12/12 h and (3) ASA alone in patients with established coronary artery disease (CAD) or PAD. A total of 27,395 patients in 33 countries with a mean follow-up of 23 months were randomized. The primary outcome of CV death, AMI, and non-fatal stroke, showed a reduction of 1.3% in absolute risk and 24% in RR, with a greater reduction in the group with rivaroxaban and ASA than in the ASA alone group. A greater reduction in severe CV events or lower limb amputations was observed in the subgroup of patients with PAD, in which the association of rivaroxaban and ASA caused an annual reduction of 1.54% of limb amputation in symptomatic patients. Combined therapy was associated with an absolute increase of 1.2% in the risk of major bleeding compared to ASA at the expense of gastrointestinal bleeding, with similar levels of intracranial bleeding.[8]

CANAKINUMAB FOR INTERLEUKIN-1 BLOCKING AND IMPROVING CV OUTCOMES

CANTOS study

Given the hypothesis that interleukin-mediated inflammation promotes the development of atherosclerotic plaque and progression to AMI as shown by the higher levels of inflammatory markers in patients with a history of CV events, the CANTOS (*Canakinumab Antiinflammatory Thrombosis Outcome Study*) was performed and published in 2017. Patients over 18 years of age with a history of previous AMI and an ultrasensitive C-reactive protein (uCRP) level ≥ 2 mg/dL were randomized into four groups, including three with different doses of canakinumab (50 mg, 150 mg, 300 mg), a monoclonal anti-interleukin-1 human beta antibody, and placebo. Thus, 10,061 patients in 1132 centers in 40 countries with a mean follow-up of 3.7 years were included. Canakinumab 150 mg was associated with an absolute reduction of 0.6% in the primary outcome (death due to CV, AMI, or stroke), mainly due to a greater reduction in the incidence of AMI. No differences were observed in CV or all-cause mortality. The uCRP levels decreased by 19.1%, 33.8%, and 37.7% with doses of 50 mg, 150 mg, and 300 mg, respectively. Patients in the canakinumab group had an absolute increase of 0.13% in fatal infection rates. The findings of the CANTOS study support the hypothesis that inflammation plays a role in atherosclerosis, but considering the absence of a mortality benefit and the increase in infection rates, further studies on the benefits of the proposed therapy on hard outcomes are needed to provide more accurate conclusions. [9]

LIRAGLUTIDE AND SECONDARY PREVENTION IN DM2

LEADER Study

The LEADER study (*Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcomes Results*), published in 2018, randomized 9,340 patients with DM2 and a high CV risk to liraglutide or placebo. At a mean follow-up of 3.8 years, liraglutide was associated with a significant reduction (13%) in the primary outcome, CV mortality, AMI, and non-fatal stroke ($p < 0.001$), as well as a 15% reduction in all-cause mortality ($p = 0.02$). The rate of hospitalization for HF decreased by 13%, the incidence of microvascular events (retinopathy or nephropathy) decreased by 16%, and the mean decrease in HbA1c in the group that used liraglutide was 0.4%. The main adverse events in the liraglutide group were increased acute cholecystitis (3.1% and 1.9%, $p < 0.001$). Thus, with empagliflozin and metformin, liraglutides comprise the group of hypoglycemic agents with proven CV benefit.[10]

GLIFLOZINS AND SECONDARY PREVENTION IN DM2

EMPA-REG Study

The EMPA-REG OUTCOME study, published in 2015, conducted in in 590 centers in 42 countries, compared the effects of empagliflozin 10 or 25 mg with placebo in 7020 patients over 18 years of age with DM2, a body mass index below 45 kg/m^2, and a history of CVD (defined by previous MI, multivessel CAD, or single-vessel CAD with a positive stress test or previous hospitalization for unstable angina, previous stroke, or occlusive PAD). The primary outcome, CV mortality, AMI, or non-fatal stroke, was decreased by 14% in the empagliflozin group with mean follow-up time of 3.1 years. All-cause mortality was decreased by 32%, CV mortality by 38%, and hospitalization for HF by 35%. The empagliflozin group experienced an increased number of genital infections, especially among women.[11]

CANVAS Study

The CANVAS study, published in 2017, conducted in in 667 centers in 30 countries, aimed to analyze the impact of canagliflozin (daily doses of 100 and 300 mg) in 10,142 patients with DM2 (defined by HbA1c ≥ 7.0%) and history of CVD or high risk for its development. At a mean follow-up of 3.9 years, canagliflozin was associated with a 14.6% reduction in the primary outcome comprising CV death, AMI, and non-fatal stroke and a 33% reduction in hospitalization for HF despite only a slight reduction in HbA1c levels (0.58%). However, as observed in other SGLT2 inhibitors, there was an increase in the incidence of genital infections; canagliflozin in particular was associated with a significant increase in the risk of lower limb amputations, especially of the hallux and metatarsals.[12]

DECLARE Study

The DECLARE study, published in October 2018 and updated in January 2019, aimed to evaluate the CV safety of dapagliflozin in patients with established DM2 and CVD or with multiple risk factors. To this end, 17,160 patients (8582 in the dapagliflozin 10 mg/day group, 8578 in the placebo group) were followed up for a mean 4.2 years. The inclusion criteria in the study were: age ≥ 40 years, diagnosis of DM2, glycosylated hemoglobin ≥ 6.5% but ≤ 12%, glomerular filtration rate greater than 60 mL/min, and established CVD or presence of multiple risk factors (men aged ≥ 55 years or women aged ≥ 60 years with arterial hypertension, dyslipidemia, or smoking status). In the analysis of the primary safety outcome (comprised of major adverse CV events - namely CV death, AMI, or ischemic stroke), dapagliflozin met the pre-specified criterion of non-inferiority (upper limit of 95% CI, <1.3; $p < 0.001$ for non-inferiority). In two primary efficacy analyses, no difference was found in reduction of MACE versus placebo (8.8% in the dapagliflozin group, 9.4% in the placebo group; hazard ratio [HR], 0.93; 95% CI, 0.84–1.03; $p = 0.17$). However, a lower rate of CV death or hospitalization for HF was observed (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73–0.95; $p = 0.005$), this result being related to a lower rate of hospitalization for HF (HR, 0.73; 95% CI, 0.61–0.88) since there was no intergroup difference in CV death (HR, 0.98; 95% CI, 0.82–1.17). Regarding the secondary efficacy outcomes, a renal event occurred in 4.3% of patients in the dapagliflozin group versus 5.6% of the patients in the placebo group (HR, 0.76; 95% CI, 0.67–0.87), and there was no significant intergroup difference in all-cause mortality. However, diabetic ketoacidosis was more common in the dapagliflozin group than in the placebo group

(0.3% vs. 0.1%, p = 0.02), and the rate of genital infections leading to treatment discontinuation or that were considered serious adverse events was higher in the dapagliflozin group (0.9% vs. 0.1%, p < 0.001).[13]

CONCLUSION

Therefore, as can be seen in the studies above, important advances in the control of established CVD have emerged in recent years that have resulted in the reduction of isolated or combined relevant outcomes. The choice of new drugs for clinical use must meet strict criteria and be approved by regulatory authorities before being administered.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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