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FOLLOW-UP OF THE DIABETIC PATIENT WITH CHRONIC CAD: OPTIMIZING DRUG TREATMENT AND MOMENT OF INTERVENTION

ACOMPANHAMENTO DO PACIENTE DIABÉTICO COM DAC CRÔNICA: OTIMIZAÇÃO DO TRATAMENTO MEDICAMENTOSO E MOMENTO DE INTERVENÇÃO

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ABSTRACT

The most common cause of mortality among diabetic patients is cardiovascular disease, one of the main representatives of which is coronary artery disease (CAD). Men aged over 40 years and women over 50 years with type 1 or type 2 DM generally present risk of coronary events of >2% a year. The risk of cardiovascular events or death is higher when there is a clinical diagnosis of chronic CAD following myocardial infarction, cerebrovascular accident (CVA) or transitory ischemic attack, or even in the presence of angina of the chest, dyspnea of ischemic origin (anginal equivalent), intermittent claudication, or aortic disease. The fundamental objectives of treatment of chronic CAD in diabetic patients are no different from those in the non-diabetic population, and include: preventing myocardial infarction and reducing mortality; reducing the symptoms and occurrence of myocardial ischemia, improving quality of life. All diabetic patients with established atherosclerotic cardiovascular disease should receive optimized pharmacological therapy, medications that reduce the incidence of stroke and increase survival, and medications that improve the patients' quality of life. Therefore, it is fundamentally important to begin treatment with medications that reduce morbimortality and to associate, where necessary, medications that control angina and reduce myocardial ischemia. Revascularization intervention in chronic CAD in diabetic patients, whether percutaneous or surgical, should not be considered as an alternative, but rather, as complementary to optimized drug treatment. The best time to perform these interventions is still a motive of various controversies within cardiology, but should be considered when this optimized drug treatment is ineffective. Therefore, the decision on diagnostic and invasive therapeutic intervention will depend, mainly, on the risk to which the patient is exposed, depending on the presence and extent of the myocardial ischemia and the severity of the pain or other symptoms that may indicate an ischemic equivalent (ventricular dysfunction and/or arrhythmia).

Keywords: Diabetes; Coronary disease; Atherosclerosis; Antidiabetics; Antiplatelet agents; Dyslipidemias; Arterial hypertension.

RESUMO

A causa mais comum de mortalidade no paciente diabético é a doença cardiovascular, tendo como um de seus principais representantes a doença arterial coronariana (DAC). Homens acima de 40 anos e mulheres acima de 50 anos com DM tipo um ou tipo dois, geralmente, apresentam risco de eventos coronarianos > 2% ao ano. O risco de eventos cardiovasculares ou óbito será mais elevado quando houver diagnóstico clínico de DAC crônica após infarto do miocárdio, acidente vascular cerebral (AVC) ou ataque isquêmico transitório ou mesmo na presença de angina do peito, dispneia de origem isquêmica (equivalente anginoso), claudicação intermitente ou doença da aorta. Os objetivos fundamentais do tratamento da DAC crônica nos pacientes diabéticos não se diferenciam da população não diabética e incluem: prevenção do infarto do miocárdio e redução da mortalidade; redução dos sintomas e da ocorrência da isquemia miocárdica, proporcionando melhor qualidade de vida. Todos os pacientes diabéticos com doença cardiovascular aterosclerótica estabelecida devem receber terapia farmacológica otimizada, medicamentos que reduzam a incidência de infarto e aumentem a sobrevida e medicamentos que melhorem a qualidade de vida dos pacientes. Dessa forma, é fundamental e de prioridade iniciar o tratamento com medicamentos que reduzam a morbimortalidade e associar, quando necessário, medicamentos que controlem a angina e reduzam a isquemia

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miocárdica. A intervenção de revascularização na DAC crônica em pacientes diabéticos, seja percutânea ou cirúrgica, não deve ser considerada como alternativa, mas sim, como complementar ao tratamento medicamentoso otimizado. O momento dessas intervenções ainda é motivo de diversas controvérsias dentro da cardiologia, mas deve ser considerado quando houver ineficácia desse tratamento medicamentoso otimizado. Portanto, a decisão quanto a intervenção diagnóstica e terapêutica invasiva vai depender, principalmente, do risco a que o paciente é submetido, dependendo da presença e extensão da isquemia miocárdica e da severidade da sintomatologia da dor ou outro sintoma que possa indicar um equivalente isquêmico (disfunção ventricular e/ou arritmia).

Descritores: *Diabetes; Doenças das coronárias; Aterosclerose; Antidiabéticos; Antiagregantes plaquetários; Dislipidemias; Hipertensão arterial.*

INTRODUCTION

The most important manifestation of macrovascular involvement in diabetes mellitus (DM) is coronary artery disease (CAD), which arises from the early and accelerated process of atherosclerosis and leads to increased morbidity and mortality for patients with these conditions.

According to the guidelines of the Brazilian Society of Diabetes (SBD)[1], DM accelerates the onset of cardiovascular diseases (CVD) by approximately 15 years. Thus, men older than 40 years and women older than 50 years with type 1 (T1) or type 2 (T2) DM usually have >2% risk of coronary events per year.[2,3] The risk of cardiovascular events or death is higher when chronic CAD occurs after myocardial infarction, stroke, transient ischemic attack, or even in the presence of angina pectoris, dyspnea of ischemic origin (anginal equivalent), intermittent claudication, or aortic disease. The clinical factors that indicate a high risk of coronary disease in DM, in reference to the SBD guidelines, are presented in Chart 1.

Chart 1. Fatores de risco clínico para DCV em diabéticos.

- Previous clinical manifestation of atherosclerotic disease: coronary, cerebrovascular, or peripheral vascular disease
- Sex: relative risk five-fold higher for women
- Age: >40 years for men and >50 years for women
- Duration of diabetes: for every 10 years of diagnosis, the risk increases by 86%, according to the Framingham study
- Kidney disease (loss of protein in the urine, loss of kidney function)
- Autonomic diabetic neuropathy
- Associated risk factors: systemic arterial hypertension, dyslipidemia, smoking, sedentary lifestyle, early family atherosclerosis, and metabolic syndrome
- Atrial fibrillation is associated with a high risk of embolic stroke

DRUG TREATMENT OF DIABETES IN PATIENTS WITH HEART DISEASE

Sulfonylureas

The safety of the use of sulfonylureas (SU) in patients with CAD has been extensively discussed. This class of hypoglycemic agents acts as an insulin secretagog by blocking ATP-dependent K^+ channels in beta cells.

Similar ATP-dependent K^+ channels in the myocardium are involved in the mechanism of ischemic preconditioning. Therefore, the safety of the use of this class of oral antidiabetic drugs warrants further investigation.

Studies to evaluate the cardiovascular outcomes in patients using SU have identified differences between molecules. A randomized study of patients with coronary heart disease who underwent elective percutaneous coronary intervention (PCI) showed that glimepiride had no deleterious effect on ischemic preconditioning, unlike glibenclamide.[4]

A study on the impact of the preadmission use of sulfonylureas by patients with diabetes and acute myocardial infarction (AMI) on cardiovascular mortality was published by Zeller et al., and showed that the patients using glibenclamide had three-fold higher mortality than those using glimepiride and gliclazide.[5]

Metformin

Metformin is the cornerstone of therapy for T2DM. Traditionally, heart failure (HF) was considered a contraindication for the use of metformin. However, recent evidence has shown otherwise: studies have shown that metformin may even reduce the risk of the incidence of HF and mortality in patients with diabetes while improving survival rates by up to 2 years in those with HF. Furthermore, it appears to exert cardioprotective actions. Although further follow-up data and information on its action in patients with very advanced HF are necessary, the confirmation of the cardiac safety of metformin has profound clinical implications and may encourage its widespread use.[6]

Pioglitazone

Pioglitazone was compared with placebo in 5,238 patients with T2DM and CVD in the PROACTIVE study.[7] The primary endpoint, a composite of peripheral arterial disease, ACS, coronary interventions, all-cause mortality, nonfatal MI, and stroke, was not significantly affected by pioglitazone. However, the secondary endpoint, a composite of nonfatal MI and stroke as the cause of death, was significantly reduced by 16% with pioglitazone during the mean follow-up period of 34.5 months. Hospitalization for congestive heart failure (CHF), in turn, increased by 40% with pioglitazone treatment. The main adverse effects were edema, even without HF, and increased incidence of fractures.

Dipeptidyl peptidase-4 (DPP-4) Inhibitors

In the SAVOR-TIMI 53 study[8], saxagliptin was compared with placebo in 16,492 patients with T2DM and established CVD (78% of cases) and patients with a high risk of heart disease (22% of cases). The study showed neither non-inferiority nor non-superiority of saxagliptin for the primary endpoint, which was a composite of AMI, ischemia, stroke, and cardiovascular death during the median follow-up period of 2.1 years. Hospitalization due to CHF increased by 27%. Alogliptin was investigated in 5,380 patients with T2DM with recent ACS in the EXAMINE study,[9] and was found to be neither non-inferior nor non-superior with respect to the primary endpoint, a composite of cardiovascular death and non-fatal MI or nonfatal stroke, during the median follow-up period of 18 months.

Sitagliptin was evaluated in 14,671 patients with T2DM and CVD in the TECOS study[10] during the mean follow-up period of 3 years. It also showed non-inferiority for death from CVD, nonfatal AMI, non-fatal stroke, and hospitalization for CHF.

The effect of linagliptin on cardiovascular events is currently under examination in two studies, CAROLINA[11] and CARMELINA[12], with no results published so far; however, the authors do not intend to conduct a controlled, randomized trial on the effect of the DDP-4 inhibitor vildagliptin on cardiovascular outcomes.

Glucagon-like peptide (GLP)-1 analogs

In the LEADER study[13], the once-daily subcutaneous administration of the glucagon-like peptide-1 (GLP-1) receptor against liraglutide was compared with placebo in 9340 patients with T2DM and established CVD in 81% of patients and patients ≥60 years of age, for whom liraglutide was associated with microalbuminuria. The primary endpoint, a composite of nonfatal MI, non-fatal stroke, and cardiovascular death, significantly decreased by approximately 13% during the follow-up period of 3.8 years. The incidence of HF did not significantly decrease. Cardiovascular death and all-cause mortality were reduced by 22% and 15%, respectively. Although there was no significant increase in adverse effects, there was a significantly high rate of drug discontinuation owing to gastrointestinal symptoms and acute biliary disease.

Semaglutide, another once-weekly subcutaneous GLP-1 analog, reduced cardiovascular death, non-fatal MI, or non-fatal stroke by 26% in the SUSTAIN-6 study[14], in which 3297 patients with T2DM and history of CVD (59%) or at high risk for CVD (41%) were followed up for 3.8 years. The main benefit was the relative reduction of 35% in the occurrence of non-fatal stroke. Although there was a lower incidence of serious adverse events, a lower rate of new cases, and no worsening of nephropathy with semaglutide, more patients discontinued treatment owing to gastrointestinal disorders. Although the rate of retinopathy was significantly higher with semaglutide, worsening of retinopathy was associated with intensive glycemic control and a rapid reduction in A1C.

In the recently published EXSCEL study[15], once-weekly exenatide (prolonged action) was compared with placebo in 14,752 patients with T2DM, of which 73% were patients with established CVD. There was a non-significant trend with respect to a reduction in the primary endpoint, which was a composite of nonfatal MI, nonfatal stroke, and cardiovascular death (P = 0.6), and a 14% reduction in all-cause mortality.

In the ELIXA study[16], no benefits of lixisenatide were observed in patients with T2DM and ACS. Furthermore, more patients in the lixisenatide arm discontinued treatment owing to gastrointestinal disturbances during the mean follow-up period of 2.1 years.

Gliflozins or sodium-glucose co-transporter (SGLT)-2 inhibitors

In the EMPA-REG OUTCOME study[17], the effects of empagliflozin (10 mg or 25 mg daily) were compared with those of placebo in 7,020 patients with T2DM and established CVD, of which 76% were patients with CAD.

The relevant exclusion criteria were patients with ACS within 2 months and glomerular filtration rate (GFR) <30 mL/min. The primary endpoint, a composite of nonfatal MI (excluding silent), non-fatal stroke, and cardiovascular death, was significantly reduced by 14% during the mean follow-up period of 3.1 years. Cardiovascular death and all-cause mortality were reduced by 38% and 32%, respectively.

Simultaneously, hospitalization for HF decreased by 35%, but nonfatal stroke was slightly higher in the group using empagliflozin. It is important to emphasize that the benefits of the use of empagliflozin were manifested in patients with established CVD and that the use of renin-angiotensin-aldosterone system inhibitors, statins, and aspirin was associated with this medication. Empagliflozin therapy was associated with genital infections.

The CANVAS study[18] analyzed the effects of canagliflozin in 10,142 patients with T2DM, of which 65% had a history of CVD, over the mean follow-up period of 2.4 years. There was a 14% reduction in the primary endpoint, which was a composite of nonfatal MI, nonfatal stroke, and cardiovascular death, and a 33% reduction in hospitalization for HF. Canagliflozin was associated with an increased risk of toe amputation and fractures with low trauma, and genital infection in men. Retrospective data from real-world studies led to the hypothesis that other SGLT2 inhibitors could also affect hospitalization for HF and death from CVD. However, the results from ongoing randomized controlled trials with the SGLT2 inhibitors dapagliflozin (DECLARE-TIMI58, NCT01730534) and ertugliflozin (Vertis CV, NCT01986881) are required to confirm the beneficial cardiovascular effects of these gliflozins.

The *European Medicines Agency* (EMA) warns of the increased risk of volume depletion in elderly patients; therefore, SGLT2 inhibitors should be discontinued for patients who undergo major surgeries or have serious illnesses, because of the increased risk of normoglycemic diabetic ketoacidosis.

Insulin

Severe hypoglycemia is a major risk for subsequent cardiovascular events, but the causal relationship is still uncertain. People who have severe hypoglycemia could also have cardiovascular events, as they are fragile and have many comorbidities. NPH insulin significantly increased the risk of hypoglycemia in patients with the same HbA1c level, compared with insulin glargine.

The analysis of data collected during the ORIGIN trial[19] with insulin glargine showed that severe hypoglycemia and severe nocturnal hypoglycemia predicted cardiovascular events and mortality in people at a high risk of cardiovascular events and early T2DM. Insulin glargine had a neutral effect on cardiovascular events and was safe for use in patients with chronic CAD.

In the DEVOTE study[20], insulin degludec was compared with insulin glargine. A total of 85.2% of the enrolled patients had established CVD, chronic kidney disease, or both conditions. The mean age was 65 years, the mean duration of diabetes was 16.4 years, and the mean HbA1c level was 8.4%. The main outcome was the first occurrence of a cardiovascular event (CVD death, non-fatal MI, or non-fatal stroke) with the same safety for insulin degludec in elderly and high-risk patients. The mean HbA1c level decreased to 7.5% in both groups after 2 years, but the mean fasting glucose level was significantly lower in the degludec group than in the glargine group. Severe hypoglycemia occurred in 187 (4.9%) patients in the degludec group and in 252 (6.6%) patients in the glargine group.

The optimal drug therapy during the follow-up of patients with diabetes and chronic CAD includes the use of metformin in all patients with a TFGe ≥30 mL/min, except those with hepatic, pulmonary, and lactic acidosis. The dose should be adjusted based on GFR. When an SU is required, preference should be given to gliclazide or glimepiride; glibenclamide should be avoided because of its potential effect on ischemic preconditioning.

As pioglitazone increases the risk of HF, functional examination with echocardiography should be performed before the use of this drug in patients with chronic CAD. Most DPP-4 inhibitors are neutral with respect to cardiovascular safety, except for saxagliptin, which increased the incidence of hospitalization for HF in this patient population.

Whenever possible, SGLT2 inhibitors should be part of the treatment of diabetes that functions as secondary prevention of CVD, except in cases in which the patient has previous amputations or is susceptible to peripheral arterial insufficiency, owing to the risk of toe amputation, as observed in the CANVAS study with canagliflozin. Care should also be taken when SGLT2 inhibitors are administered with other diuretics to avoid hypotension and volume depletion. GLP1 analogs are promising drugs for the treatment of patients with established CVD. However, a reduction in the rate of hospitalization for HF in patients treated with this class of drugs has not been demonstrated. However, a reduction in cardiovascular death has been demonstrated in patients treated with liraglutide and semaglutide. As patients with T2DM and symptoms of insulinopenia, such as weight loss, polyuria, and polydipsia, have longer disease durations, they need to use insulin. For these patients, the preferential therapy is the use of slow insulin analogs that promote a lower incidence of hypoglycemia.

Optimal drug therapy

The primary goals in the treatment of patients with diabetes and chronic CAD are not different from the non-diabetic population and include: the prevention of myocardial infarction and the reduction of mortality; a reduction in the symptoms and the occurrence of myocardial ischemia; and the achievement of a better quality of life.

All patients with diabetes and established atherosclerotic CVD should receive optimal drug therapy, drugs that reduce the incidence of infarction and increase survival, and drugs that improve quality of life. Thus, it is fundamental to start treatment with drugs that reduce morbidity and mortality and to add, when necessary, drugs that control angina and reduce myocardial ischemia.[21]

ANTIPLATELET AGENTS

Acetylsalicylic acid (ASA)

The antithrombotic effects of ASA arise from the irreversible inhibition of cyclooxygenase-1, with the consequent blockade of the synthesis of thromboxane A2.

The meta-analysis by the "*Antithrombotic Trialists' Collaboration*"[22], which assessed more than 350,000 individuals randomized into 280 studies comparing aspirin vs. aspirin, placebo, or other antiplatelet agents, observed that approximately 3,000 patients had stable angina, and that aspirin reduced the risk of cardiovascular events (death, MI, and stroke), on average, by 33%.

At a dose of 325 mg on alternate days, aspirin was found to reduce the incidence of MI in an asymptomatic population with no known disease in the "*Physicians' Health Study*".[23] In the SAPAT ("*Swedish Angina Pectoris Aspirin Trial*") study[24], the addition of aspirin to sotalol at a dose of 75 mg/day in patients with CAD reduced the incidence of primary MI and sudden death events by 34%, and the incidence of secondary events by 32%. Thus, aspirin is still the most efficient antiplatelet agent and should always be prescribed, except for the rare cases of contraindications (allergy or intolerance, active bleeding, hemophilia, active peptic ulcer disease) or a high likelihood of gastrointestinal or genitourinary bleeding. Aspirin is recommended for all patients.

The *American Diabetes Association* (ADA) recommends the use of aspirin at a dose of 75 to 162 mg/day for all patients with diabetes and a history of AMI, vascular revascularization, ischemic cerebrovascular disease, peripheral arterial disease, claudication, or angina.

Thienopyridine derivatives

Clopidogrel is an antagonist of platelet activation mediated by adenosine diphosphate (ADP), an important pathway for platelet aggregation. They also reduce the level of circulating fibrinogen and partially block the glycoprotein IIb/IIIa receptor, preventing its binding to fibrinogen and the von Willebrand factor.

Studies comparing the antiplatelet effects of this drug with that of aspirin only included patients with AMI, stroke, and/or peripheral arterial disease and did not evaluate patients with chronic coronary disease.[25]

Treatment of dyslipidemia:

Several clinical and epidemiological studies support the hypothesis that individuals with T2DM have increased cardiovascular risk. The lipid phenotype often found in this population consists of hypertriglyceridemia and low HDL-c. The mean concentration of LDL-c is generally not quantitatively different, but is distinguishable by the high atherogenicity observed owing to the presence of small and dense particles. A meta-analysis conducted in 2008 by the CTT[26], which included 14 randomized

clinical trials involving 18,686 participants with T2DM, demonstrated a relative risk reduction proportional to the level of LDL-c reduction: for each 1 mmol/L LDL-c reduction, statins reduced overall mortality by 9% in people with diabetes and 13% in the non-diabetic population, with equal benefit for both populations. There was a 21% reduction in major cardiovascular events in both populations. In patients with diabetes, there was a reduction in the MI, coronary revascularization and. Therefore, it was concluded that the effects of statins in patients with diabetes were similar to those observed in patients without diabetes. Furthermore, the effects were not dependent on previous cardiovascular events or the baseline characteristics of the patients.

Statins

The reduction of LDL-C by HMG-CoA reductase inhibitors (statins) remains the most validated therapy by clinical trials for decreasing the incidence of cardiovascular events.

In a meta-analysis of 26 clinical studies comprising 170,000 patients, it was found that for every 40 mg/dL reduction of LDL-c caused by statins, there was a 10% reduction in all-cause mortality, which reflected the great extent of the reduction in the number of deaths by DAC (-20%).[27]

Studies have also shown a reduction in acute coronary events, the need for myocardial revascularization, and the incidence of stroke. Based on this evidence, the use of statins is recommended as the first choice for primary and secondary prevention therapies.

Statins are recommended for patients with diabetes, who are a high-risk group and experience unequivocal benefit arising from drug therapy with statins. A recent update to the Brazilian Guidelines on Dyslipidemia and Prevention of SBC showed that patients with diabetes and chronic CAD are at a high-risk and should have a primary goal of LDL <50 mg/dL and a secondary goal of non-HDL <80 mg/dL. Therefore, they should be treated with potent statins, such as atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg/day alone or in combination with ezetimibe 10 mg/day.[28]

Ezetimibe

Ezetimibe inhibits the absorption of cholesterol at the brush border of the small intestine through selective action on the NPC1-L1 receptors and inhibition of the intestinal transport of cholesterol. The inhibition of cholesterol absorption (largely of biliary cholesterol) leads to a decrease in hepatic cholesterol levels and stimulation of LDLR synthesis, with a consequent reduction in plasma LDL-c levels of between 10% and 25%. The IMPROVE-IT study showed a significant reduction in cardiovascular events after acute coronary syndrome for the use of statin and ezetimibe[29] compared with simvastatin monotherapy. The pre-defined subgroup of participants with T2DM experienced additional benefit for the primary outcomes (cardiovascular death, myocardial infarction, and documented unstable angina requiring rehospitalization, coronary revascularization ≥30 days, or stroke).

Fibrates

Clinical studies have shown inconsistent results with regard the benefit of fibrate monotherapy for the reduction of cardiovascular events. In a meta-analysis of 18 studies and 45,058 participants, fibrate therapy reduced the relative risk of cardiovascular events by 10% and coronary events by 13%, with no benefit in mortality. Retrospective analyses of these studies indicated a greater benefit when patients with elevated plasma TG (>204 mg/dL) and low HDL-c (<34 mg/dL) were selected. However, this information requires confirmation in prospective studies.

The effects of fenofibrate on microvascular disease in patients with T2DM were examined in two large studies in isolation and in combination with simvastatin. The treatment reduced the incidence and progression of retinopathy, decreased micro and macroalbuminuria, and delayed the loss of renal function. Furthermore, it reduced amputations, mainly distal type.[30]

PCSK9 inhibitors

It is known that the functionality and number of LDLRs expressed on the surface of hepatocytes is a determinant factor of plasma LDL levels. PCSK9 is an enzyme that plays an important role in lipid metabolism through the modulation of LDLR density.[31] The inhibition of PCSK9 prevents the binding of LDLR to PCSK9 and the subsequent lysosomal degradation of LDLR, which increases the receptor density at the hepatocyte surface and the clearance of circulating LDL particles. Alirocumab and evolocumab, two fully human PCSK9 inhibitors, were approved in Brazil for commercialization in 2016. Both are administered by subcutaneous injection: alirocumab every 2 weeks at 75 mg or 150 mg, and evolocumab every 2 weeks at 140 mg or 420 mg once per month.

This drug class significantly reduced LDL-c concentrations compared with placebo (mean reduction of 60%). The FOURIER ("*Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk trial*")[32] study evaluated more than 27,500 very high-risk patients (AMI, stroke, or peripheral arterial disease; symptomatic PAD) receiving lipid-lowering treatment with a high or moderate intensity, with statins and/or ezetimibe. They were randomized to receive evolocumab (on a regimen of 140 mg every 15 days, or 420 mg once monthly), or placebo (every 15 days, or once monthly) with the primary goal of assessing cardiovascular mortality, AMI, stroke, unstable angina requiring hospitalization, or coronary revascularization, and the secondary goal of assessing cardiovascular death, AMI, or stroke. Patients were followed for 2.2 years (median); a 59% reduction in LDL-c was observed compared with placebo, starting from an LDL-c baseline of 92 mg/dL and reaching 30 mg/dL after 48 months ($p < 0.001$). Evolocumab reduced the primary endpoint by 15% compared with placebo (1,344 [9.8%] patients vs. 1,563 [11.3%] patients; Hazard Ratio (HR): 0.85; 95% confidence interval (CI): 0.79–0.92; $p < 0.001$) and the key secondary endpoint was 20% (816 [5.9%] vs. 1.013 [7.4%], HR: 0.80, 95% CI: 0.73–0.88, $p < 0.001$). The results were consistent across subgroups, including those in the lower quartiles of baseline LDL-c levels (median, 74 mg/dL). There was no difference between groups in the occurrence of adverse events (including new cases of diabetes and neurocognitive events), except for injection site reactions, which were more frequent with evolocumab (2.1% vs. 1.6%).

The outcomes of evaluation of patients with PAD by the Fourier study were recently published. Patients with PAD represented 13.2% of the study population; 43.4% of these

had diabetes, which demonstrated that the evolocumab group had a reduction in peripheral vascular events (RR 27%, RA 4.1%, and NNT of 25).[33]

The ODYSSEY Outcomes study ("*Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab*") will evaluate cardiovascular outcomes in more than 18,000 patients with acute coronary syndrome with the use of alirocumab. The results of this study will be published soon.[33]

The use of PCSK9 inhibitors (evolocumab and alirocumab) in the treatment of dyslipidemia is only recommended for patients with high cardiovascular risk, receiving treatment with statins at the highest tolerated dose, associated or not associated with ezetimibe, and that did not achieve the recommended LDL-c or non-HDL-c targets.

RENIN-ANGIOTENSIN SYSTEM BLOCKADE

The benefits of ACE inhibitors in the treatment of CAD were demonstrated in clinical trials that included asymptomatic patients with reduced EF and individuals with ventricular dysfunction after AMI.[34]

In individuals at higher risk, the benefits of reduced deaths and events were observed, especially in the presence of DM.[35] Improvements in the hemodynamic profile, subendocardial perfusion, and stabilization of atherosclerotic plaques justified their routine use in all patients with CAD, regardless of prior myocardial infarction, DM, or ventricular dysfunction. The randomized, double-blind, EUROPA study[36] showed that perindopril ACEI reduced the combined primary endpoint (cardiovascular death, myocardial infarction, or cardiac arrest), as well as the secondary endpoint (stroke and worsening of renal function) in patients with CAD and in the absence of cardiac insufficiency, ventricular dysfunction, independently of the presence of other factors, such as peripheral vascular disease. More than 60% of these patients used beta-blockers, 50% used statins, and 92% used antiplatelet agents. The major endpoint of the study was reduced from 10% in the placebo group to 8% in the perindopril group and required the treatment of 50 patients for 4 years to avoid one of these events. Thus, the benefits of ACEI were confirmed, even in the population of patients with CAD considered to be at lower risk. The benefits of the ACEI class are many; thus, they should be considered routinely in the presence of ventricular dysfunction, and/or HF, and/or DM.

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers are alternatives for patients who do not tolerate ACEIs. A recent meta-analysis consisting of 24 randomized studies with 61,961 patients with stable CAD without HF demonstrated a 26% reduction in RR and 16% in RR mortality, in addition to a lower incidence of stroke, AMI, HF, and angina.[37]

BETA-ADRENERGIC BLOCKERS

Beta-adrenergic blockers, whether isolated or in combination with other antianginal agents, are the first-choice drugs for the treatment of stable angina, in addition to offering benefits in terms of mortality and reduction in myocardial infarction after acute coronary events. The risk of cardiovascular death and reinfarction, even today, with current infarct therapy, is reduced by approximately 13%. The COMMIT study[38] showed that beta-adrenergic blockers were the only antianginal drugs that are proven to prevent reinfarction and improve survival in patients post-AMI. They are effective for the reduction in the intensity and frequency of anginal episodes and increasing tolerance to stress. However, there is no firm evidence of decreased mortality in patients with chronic CAD with no recent AMI or HF.[39]

Randomized clinical trials to evaluate the effects of beta-adrenergic blockers in the treatment of CAD in the presence of symptoms or ischemia showed a reduction in the number of angina attacks, the degree of ischemia, and increased tolerance to physical effort. In the ASIST (*Atenolol Silent Ischemic Study*)[40], the incidence of ischemic episodes recorded by a continuous 48 h Holter ECG monitoring after 4 weeks of atenolol treatment was significantly lower than in the placebo group. In the atenolol group, there was a significant reduction in ischemic episodes, a lower incidence of complex ventricular arrhythmias, fewer hospitalizations, lower incidence of myocardial infarction, and a reduced need for CABG in patients with chronic coronary disease.

TIBBS (*Total Ischemia Burden Bisoprolol Study*)[41] compared the effects of bisoprolol with those of nifedipine in patients with asymptomatic and/or symptomatic myocardial ischemia. The total number of ischemic episodes, symptomatic or asymptomatic, recorded over a 48 h Holter ECG, was significantly lower in patients receiving bisoprolol.

Davies et al.[42] compared the effects of atenolol with those of amlodipine for the reduction of symptomatic and asymptomatic myocardial ischemia. The effects of both drugs on the symptomatic ischemic episodes reported by Holter were satisfactory and similar; however, atenolol was more effective for the reduction of heart rate. During ET, amlodipine was more effective, significantly delaying the time for the appearance of the same ischemic changes. Combination therapies conferred additional benefits.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are usually used in combination with or to replace beta blockers in the case of contraindications or adverse events. Their action on coronary and peripheral vasodilation, and on the reduction in contractility of some contribute to the improvement of the angina symptomatology.

Long-acting diltiazem, verapamil, or second-generation dihydropyridine derivatives (amlodipine and felodipine) are the most recommended drugs.

The combination of beta-blockers and calcium antagonists has been shown to be more effective in the duration of exercise tolerance, and they are better tolerated than monotherapy.[43]

Dihydropyridine derivatives (nifedipine, amlodipine, and others), benzothiazepines (diltiazem), and phenylalkylamines (verapamil) are the three major subgroups of calcium channel blockers that specifically block L-type calcium channels. The pharmacological effects differentiate these three subgroups in terms of vasodilatory capacity, reduced capacity of myocardial contractility, and reduced capacity of impulse conduction velocity in the atrioventricular node.

Verapamil reduces atrioventricular conduction, has a negative inotropic effect, and relaxes vascular smooth muscle, which increases coronary flow and reduces afterload.

Dihydropyridines relax vascular smooth muscle, do not change the speed of atrioventricular conduction, and increase heart frequency by reflex mechanisms.

Diltiazem has similar effects to verapamil, except for myocardial depression, which was less severe in the benzodiazepine subgroup. Unlike beta-adrenergic blockers, calcium channel blockers did not reduce mortality when used after myocardial infarction, although they were shown to be fairly effective for the reduction of myocardial ischemia, angina pectoris and silent ischemia[44], and vasospastic angina.[45] The use of diltiazem or verapamil, associated with beta-blockers, should be avoided owing to the higher risk of severe bradycardia compared with the other options available. They are also contraindicated in the presence of ventricular dysfunction.

LONG-ACTING NITRATES

Although long-acting nitrates are used widely, the deterioration of endothelial dysfunction has been described as a potential complication of their chronic use; this occurs via the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system, as well as an increase in endothelin production, superoxide production, and phosphodiesterase activity. With regard to protection against cardiovascular events, the ISIS-4[46] and GISSI-3 studies[47] showed that nitrates did not modify morbidity and mortality rates at 4 to 6 weeks after myocardial infarction. An extensive review on the effects of the IV nitroglycerin, mononitrate, and isosorbide dinitrate nitrates[48] called into question the use of long-acting nitrates over time to treat patients with chronic CAD.[49] These studies show that the tolerance that is quickly achieved with sustained use is related to such changes.

Trimetazidine is a substance with metabolic and anti-ischemic effects without any effect on cardiovascular hemodynamics. Its benefits have been attributed to the preservation of intracellular levels of adenosine triphosphate (ATP) and phosphocreatine, with the same residual oxygen level; reduced acidosis, calcium overload, and accumulation of free radicals induced by ischemia; and preservation of the cell membranes. The administration of this agent did not alter heart rate and blood pressure during rest or physical exertion.[50]

Several studies have shown that the association of long-acting nitrates with beta-adrenergic blockers or calcium channel antagonists has reduced angina and exercise-induced ischemia. A recent, retrospective, observational study showed that the use of trimetazidine, combined with optimal therapy in patients with HF, promoted a reduction in the risk of cardiovascular mortality and overall mortality.[51] A reduction in hospitalizations due to cardiovascular causes in patients with LV dysfunction treated with trimetazidine was shown in a recent meta-analysis.[52]

Ivabradine is a specific inhibitor of the If current at the sinus node. As a result, it acts exclusively on heart rate without affecting blood pressure, myocardial contractility, intracardiac conduction, and ventricular repolarization; its effects occur during exertion and at rest. In non-inferiority studies, the antianginal efficacy was similar to those of atenolol and amlodipine.[53]

The BEAUTIFUL study[54] showed that ivabradine reduced the occurrence of infarction, as well as the need for revascularization, in a subgroup of patients: those with CAD associated with ventricular dysfunction and a resting heart rate of ≥70 bpm. Ivabradine may be used as an alternative for patients who do not tolerate beta-blockers and for patients with diabetes, as it does not interfere with glucose metabolism, and could be associated with beta-blockers.

Ranolazine is a piperazine derivative; similar to trimetazidine, it protects the patient against ischemia by an increase in glucose metabolism in comparison with fatty acids. However, its strongest effect appears to be the inhibition of the late sodium current. This current is activated in ischemia, which leads to intracellular calcium overload in the ischemic tissue and, consequently, an increase in ventricular wall stiffness, and a reduction in capillary compliance, and compression. Thus, the inhibition of this current by ranolazine during an ischemic insult improves myocardial function. Its antianginal efficacy has been demonstrated when used as a monotherapy and in combination with other anti-ischemic drugs. There is an increase in exercise tolerance, a reduction in the number of ischemic episodes, and a reduction in nitrate consumption. The metabolism of this drug occurs in the liver (cytochrome CYP3A4). Thus, caution is recommended owing to potential drug interactions (including simvastatin, digoxin, diltiazem, and verapamil). Increased QT interval may also occur. Similar to trimetazidine, ranolazine does not reduce major cardiovascular complications.[55]

THE MOMENT OF INTERVENTION

Revascularization intervention (percutaneous or surgical) in patients with diabetes and chronic CAD, either percutaneous or surgical, should not be considered as an alternative, but as a complementary action to optimal drug therapy. The timing of these interventions is still a controversial topic among cardiologists, but a consensus is that it should be considered when the optimal drug therapy is ineffective. This ineffectiveness may be due to inadequate drug therapy (a lack of adherence or non-optimal therapeutic regimen) or a failure in the treatment, which may occur owing to the progression of the atherosclerotic disease or by non-adherence to the recommendations of lifestyle changes.

Two large controlled studies in patients with mild to moderate stable angina (COURAGE[56] and BARI-2D[57]) reported that patients selected and randomized for percutaneous intervention did not show significant differences in death rates or myocardial infarction compared with those who received the optimal drug therapy.

Therefore, the invasive therapeutic strategy chosen depends on the severity of the symptomatology and the ischemic area, on patients' tolerance to antianginal drugs, age, presence of comorbidities, quality of life, and life prospects.

The decision for invasive diagnostic and therapeutic intervention depends mainly on the risk to the patient, which is assessed by the occurrence and extent of myocardial ischemia and the severity of the symptomatology of pain or another ischemic equivalent symptom (ventricular dysfunction and/or arrhythmia).

CONFLITOS DE INTERESSE

Os autores declaram não possuir conflitos de interesse na realização deste trabalho.

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