Revista da SOCESP
Sociedade de Cardiologia do Estado de São Paulo

PLATELET ANTIAGGREGATION THERAPY: PRIMARY AND SECONDARY PREVENTION, PECULIARITIES IN ANTICOAGULATION OF THE PATIENT WITH DM

TERAPIA DE ANTIAGREGAÇÃO PLAQUETÁRIA: PREVENÇÃO PRIMÁRIA E SECUNDÁRIA, PECULIARIDADES NA ANTICOAGULAÇÃO DO PACIENTE COM DM

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Received on 04/20/2018,
Accepted on 05/23/2018

ABSTRACT

Diabetes mellitus (DM) is an important and growing health problem, with atherosclerotic disease being an important comorbidity. In addition to the use of drugs, prevention of atherosclerosis involves changes of lifestyle such as exercise, nutrition, weight control, and stopping smoking. The use of aspirin has a well established role in the secondary prevention of cardiovascular disease (CVD) in patients with DM2. However, its use in primary prevention remains controversial, and studies are still in progress. The objective of this study was to carry out a literature review on the main indications for the use of platelet antiaggregation therapy in diabetic patients. In secondary prevention, the use of aspirin is a consensus and dual antiplatelet therapy indicated after acute coronary syndromes. The guidelines do not provide specific information for diabetic patients, or their classic indications for anticoagulation.

Keywords: Diabetes mellitus; Primary prevention; Secondary prevention.

RESUMO

O diabetes mellitus (DM) é um importante e crescente problema de saúde, sendo que a doença aterosclerótica é uma importante comorbidade. Além do uso de fármacos, a prevenção da aterosclerose envolve mudança do estilo de vida como exercícios, nutrição, controle do peso e interrupção do tabagismo. O uso da aspirina possui papel bem estabelecido na prevenção secundária da doença cardiovascular (DCV) em pacientes com DM2, porém, o seu uso na prevenção primária permanece controverso e ainda com estudos em andamento. O objetivo desse estudo consistia em realizar uma revisão na literatura sobre as principais indicações para o uso da terapia de antiagregação plaquetária nos pacientes diabéticos. Já na prevenção secundária, o uso da aspirina é um consenso e a dupla terapia é indicada após síndromes coronárias agudas. As diretrizes não trazem informações específicas aos pacientes diabéticos, assim como, suas indicações clássicas na anticoagulação.

Descritores: *Diabetes mellitus; Prevenção primária; Prevenção secundária.*

PRIMARY PREVENTION OF DIABETES

INTRODUCTION

Even before the use of drugs, emphasis is given to the importance of preventing atherosclerosis in patients with diabetes with lifestyle changes, such as exercise, nutrition, weight control, and smoking cessation.

Although a reduction in cardiovascular mortality has been achieved, the incidence of obesity, metabolic syndrome, and diabetes continues to increase, and estimates from the United States predict that by the year 2050, approximately one in three Americans will have type 2 diabetes (DM2).

Despite the proven benefit of aspirin in the secondary prevention of cardiovascular disease (CVD) in patients with DM2, its use in primary prevention remains controversial. Further, studies examining this association are underway. Several pharmacological, nutritional, risk factor control, and lifestyle change strategies are associated with a sharp reduction in primary prevention of diabetes, as shown in Figure 1.

Three studies evaluated CVD prevention in patients with DM2,[1-3] of which only the Japanese study was identified as a primary prevention study. The Early Treatment Diabetic Retinopathy Study (ETDRS) randomized >3,700 participants with DM1 and DM2 and retinopathy, with approximately one-third

 http://dx.doi.org/10.29381/0103-8559/20182802181-6

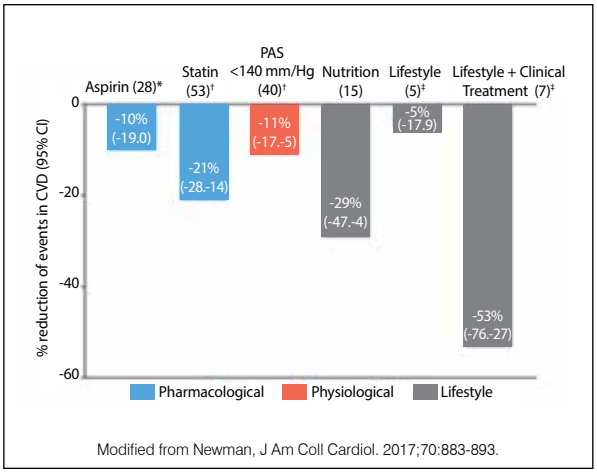

Figure 1. Primary prevention of CVD in patients with DM2.

having CVD. They divided the participants into two groups: aspirin 650 mg daily and placebo groups. The use of aspirin was associated with a significant 17% reduction in fatal or nonfatal myocardial infarction (MI) (hazard ratio [HR]: 0.83, 95% confidence interval [CI]: 0.65–1.03, p = 0.04) and a non-significant increase in stroke. The Prevention of Progression of Arterial Diseases and Diabetes (POPADAD)[2] trial used a factorial design to investigate whether daily aspirin 100 mg with or without antioxidant therapy was more effective than placebo in reducing CVD in 1,276 UK participants aged over 40 years with diabetes and asymptomatic peripheral arterial disease, evaluated using the ankle-brachial index. After a median follow-up of 6.7 years, the primary cardiovascular outcome was 18.2% in patients randomized to the aspirin or placebo group. The Japanese study was an open study on primary prevention evaluating aspirin at a dose of 81–100 mg in 2,539 Japanese subjects with DM2,[3] of which 26% were also taking statins. Despite a broad outcome, which was a composite of angina, multiple forms of peripheral vascular disease, and other outcomes of secondary prevention, the annual event rate was almost 50% lower compared with the ETDRS and POPADAD studies. After 4.4 years, no difference was observed in the composite primary outcome among participants in the aspirin group (68 events, 5.4%) versus the group not receiving aspirin (86 events, 6.7%, HR 0.80, 95% CI: 0.58–1.10). The incidence of fatal coronary and cerebrovascular events, prespecified as secondary outcomes, was significantly reduced in the low-dose aspirin group (p = 0.0037).

Several meta-analyses have been conducted to analyze the effects of aspirin on the primary prevention of CVD in patients with diabetes.[4-6] Although these meta-analyses differ in the inclusion criteria of the trials, the overall results suggest a modest 10% relative reduction in CVD events and a twofold increase in the relative risk of bleeding, predominantly of gastrointestinal (GI) origin, with low doses of aspirin (75–162 mg) per day.

According to the American College of Cardiology and American Heart Association guidelines, a dose of 75–162 mg of aspirin is reasonable for patients with diabetes aged ≥50 years with at least one cardiovascular risk factor (10-year risk >10%) and without increased risk of GI bleeding (class II-A level of evidence B).[7]

The use of aspirin may be reasonable for patients with diabetes aged <50 years with at least one more cardiovascular risk factor and no increased risk of GI bleeding (class II-B level of evidence C). [7]

These criteria include most men and women with diabetes aged over 50 years with at least one major risk factor for CVD. Low doses of aspirin may be reasonable for patients at intermediate risk of CVD (5–10% risk in 10 years).[8]

However, the 2016 European Society of Cardiology guideline on CVD prevention[9] does not recommend the use of antiplatelet therapy in the primary prevention of individuals with diabetes (class III-A).

SECONDARY PREVENTION WITH ANTIAGGREGANTS

Patients with DM and stable and unstable coronary artery disease (CAD) have been reported to have a worse short-term and long-term prognosis of fatal and nonfatal ischemic events and are at higher risk of bleeding after acute coronary syndrome (ACS). This is due to increased activation, reactivity, and platelet aggregation as well as the hypercoagulability state in this group of patients.[10] Therefore, they are at a greater risk of atherothrombosis, and defining the best choice of double antiplatelet therapy (DAPT) is necessary.

In the Clopidogrel in Unstable angina to prevent Recurrent Events study, clopidogrel did not significantly reduce cardiovascular events in individuals with DM.[11]

An important subanalysis performed in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) study stratified patients by DM status. This analysis showed that after treatment with prasugrel, the rate of cardiovascular death (CVD), nonfatal MI, and nonfatal stroke in patients with DM was significantly reduced compared to clopidogrel (Figure 2).[12]

The reduction in the primary outcome in patients with DM was driven primarily by a reduction in the MI rate, such as the results of the overall study population. The MI rate in patients with DM treated with prasugrel was 8.2 vs. 13.2% in patients treated with clopidogrel (P = 0.001).[12] The greater efficacy of prasugrel compared to clopidogrel in the overall study population was achieved at the

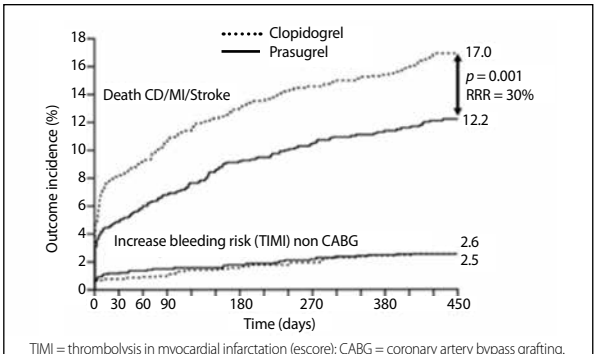

Figure 2. Efficacy and safety of the use of prasugrel and clopidogrel in patients with diabetes at 15-month follow-up (TRITON study - TIMI 38).

expense of an increased rate of bleeding. In this subanalysis of patients with DM, the use of prasugrel did not increase the rate of major bleeding not related to coronary artery bypass surgery compared with the use of clopidogrel: 2.5 vs. 2.6%, respectively; P = 0.81.[13]

In the Platelet Inhibition and Patient Outcomes trial, ticagrelor reduced the primary composite outcome of MCV, MI, or stroke. However, it has similar rates of increased bleeding to clopidogrel. [14]

A subanalysis of this study aimed to investigate the outcome of ticagrelor vs. clopidogrel in patients with DM or inadequate glycemic control. Patients with previous DM (n = 4662), including 1036 insulin-dependent patients, and patients without DM (n = 13951) were analyzed in addition to subgroups selected based on admission hemoglobin A1c levels (HbA1c; n = 15150). In patients with DM, the reduction in the primary composite outcome (HR: 0.88, 95% CI: 0.76–1.03), all-cause mortality (HR: 0.82, 95% CI: 0.66–1.01), and stent thrombosis (HR: 0.65, 95% CI: 0.36–1.17) with no increased bleeding (HR: 0.95, 95% CI: 0.81–1, 12) with the use of ticagrelor was similar to that in the overall cohort, showing no significant interactions with the treatment of diabetes. No difference was observed between patients with or without ongoing insulin treatment. Ticagrelor reduced the primary outcome, all-cause mortality, and stent thrombosis in patients with the above average HbA1c (HR: 0.80, 95% CI: 0.70–0.91, HR: 0.78, 95% CI: 0.65–0.93, and HR: 0.62, 95% CI: 0.39–1.00, respectively) with similar bleeding rates (HR: 0.98, 95% CI: 0.86–1, 12) (14). Thus, it was concluded that, compared to clopidogrel, ticagrelor reduces ischemic events in patients with ACS, regardless of glycemic control, with no increase in major hemorrhagic events.[14]

Therefore, based on the overall analysis of these studies, the European Society of Cardiology does not recommend that decision-making on the choice of P2Y12 inhibitors be based on the presence of diabetes.[15]

No difference in the presence or absence of diabetes was observed for duration of double platelet antiaggregation in the primary outcome of efficacy in the PEGASUS study.[8] The DAPT study found a slight reduction in the relative risk of acute MI in patients with diabetes compared to those without diabetes. However, no statistical significance was found in terms of the ischemic or safety outcomes.[14] Thus, current evidence suggests that DM should not be the only characteristic of the patient evaluated to decide on the type or duration of DAPT.

In addition to the use of thienopyridine and P2Y12 receptor blockers, acetylsalicylic acid (ASA) is widely recommended in the literature in cases of secondary and tertiary prevention, both for individuals with or without diabetes. The Second International Study of Infarct Survival evaluated the use of ASA and streptokinase and the association of both drugs. The use of ASA alone reduced all-cause mortality by 23%, while the use of ASA associated with streptokinase reduced all-cause mortality by 42%. There was a decrease in mortality of 25 ± 7%, when it was used in the first 0–4 hours of symptom onset, 21 ± 7% in 5–12 hours, and 21 ± 12% in 13–24 hours. Subsequent meta-analyses supported the key role of ASA in reducing mortality and cardiovascular events in both short and long term.

The CURRENT-OASIS-78 study evaluated the use of a maintenance dose of ASA in patients with ACS (29% of whom had ST-segment elevation MI undergoing primary percutaneous coronary intervention) in one of its arms. This study did not show difference between the usual maintenance dose (75–100 mg per day) and the high dose (300–325 mg per day) in the prevention of CVD, MI, or stroke in 30 days (P = 0.61, with IC 0.86–1.09). Moreover, no difference was observed in the incidence of major bleeding (P = 0.90, with CI 0.84–1.17).[16]

Another important study using ASA was the Antiplatelet Trialists' Collaboration. This meta-analysis was performed on men and women who had MI, stroke, transient ischemic attack, or history of CVD (vascular surgery, angioplasty, angina, etc.). The reduction in vascular events was 25% in men and women, and a sharp decrease was observed in risk in individuals with diabetes compared to individuals without diabetes. In this study, the dose of ASA used ranged from 75 to 325 mg/day, and the efficacy was equal to that of high doses.

The Bezafibrate Infarction Prevention study, in turn, compared the effects of treatment with ASA in 2368 patients with DM2 with CAD and 8,586 individuals without diabetes. About 52% of those with diabetes and 56% of individuals without diabetes used ASA. After a 5-year follow-up, it was observed that the benefits of treatment with ASA in the treated individuals were greater than those in the untreated individuals. The percentages mortality among patients with and without diabetes treated with ASA were, respectively, 10.9% versus 15.9%. The percentages of all-cause mortality were 18.4% and 26.2%, respectively. The authors concluded that the significant reduction in death among cardiac patients and DM2 with CAD is related to the use of ASA.[17]

ANTICOAGULATION IN PATIENTS WITH DIABETES

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with a fivefold increase in stroke risk. DM2 is an independent risk factor for the occurrence of stroke and AF. In patients with AF, DM2 alone is a factor that accounts for a 2–3.5% increase in the annual stroke rate. Among patients with AF, diabetes is associated with a greater number of symptoms, poorer quality of life, and increased risk of death and hospitalizations not directly related to thromboembolic or hemorrhagic events. Conversely, the subgroup with diabetes was not directly addressed in studies with direct oral anticoagulants (DOACs). Therefore, overlap in the pathophysiology of AF and DM2 needs to be fully elucidated.

In the venous system, a subanalysis of the RECORD[18] study revealed hyperglycemia in patients undergoing hip surgery as a risk factor for thromboembolism.

The use of warfarin associated with lipid-lowering drugs was retrospectively analyzed in a cohort that included 465,918 patients with diabetes who received glipizide or glimepiride between 2006 and 2011; 71,895 (15.4%) were also prescribed with warfarin. The main outcome was a visit to the emergency

department or hospital admission with a primary diagnosis of hypoglycemia in patients taking warfarin and glipizide/ glimepiride compared to patients taking glipizide/glimepiride alone. Multivariate logistic regression was used to adjust for individual characteristics. Secondary outcomes were a composite of fall-related fracture and altered mental status/ consciousness. Patients taking glipizide/glimepiride had fewer hospital admissions or emergency room visits due to hypoglycemia than those who also used warfarin compared to warfarin-free quarters. The risk of hypoglycemia associated with concomitant use was greater among people who used warfarin for the first time as well as those aged between 65 and 74 years. Concomitant use of warfarin and glipizide/ glimepiride was also associated with hospital admission or emergency room visits for fall-related fractures (3919/416 479 v 20 759/3 938 939, adjusted odds ratio of 1.47, 1.41–1.54) and altered mental status/consciousness (2490/416 479 v 14 414/3 938 939, adjusted odds ratio 1.22, 1.16–1.29). The study supports the hypothesis of a positive association between the use of warfarin and glipizide/ glimepiride and visits to the hospital/emergency admission department for hypoglycemia and related diagnoses, particularly in patients who started warfarin recently. Such findings suggest a significant interaction between these drugs.

Samos[19] et al. published a pilot study evaluating the impact of diabetes on the effect of DOACs. This prospective study involved 65 patients with non-valvular AF (20 treated with dabigatran, 110 mg/twice daily; 28 treated with rivaroxaban, 15 mg/day; 17 treated with apixaban, 5 mg/ twice daily). Of these, 25 patients had DM2 (8 treated with dabigatran, 11 treated with rivaroxaban, and 6 treated with apixaban). The activity of anticoagulants was tested using the Hemoclot® thrombin inhibitor assay in patients treated with dabigatran and the anti-factor Xa chromogenic assay in patients treated with rivaroxaban and apixaban before and 2 hours after drug administration. No difference was observed in DOAC activity (dabigatran $p = 0.76$, rivaroxaban $p = 0.19$, apixaban $p = 0.24$) in patients with DM2. Coleman et al.[20] evaluated 5517 patients on rivaroxaban (20% received the reduced dose) and 5515 patients on warfarin with non-valvular AF and diabetes (97% with DM2). Rivaroxaban was as effective and safe as warfarin in this group of patients.

Brambatti et al.[21] evaluated patients with and without diabetes with AF and the relative efficacy of each dose of dabigatran (150 mg twice and 110 mg twice) versus warfarin. Of the 18,113 patients included in the RE-LY study, 4221 patients (23.3%) had DM. Patients with DM were younger (70.9 vs. 71.7 years), more likely to have hypertension (86.6% vs. 76.5%), CAD (37.4% vs. 24.9%), and peripheral vascular disease (5.6% vs 3.2%) (all $p < 0.01$). Time in the therapeutic range for patients treated with warfarin was 65% for patients with diabetes versus 68% for patients without diabetes ($p < 0.001$). Regardless of the treatment employed, stroke or systemic embolism was more common among patients with DM (1.9% per year vs. 1.3% per year, $p < 0.001$). DM was also associated with an increased risk of death (5.1% per year vs. 3.5% per year, $p < 0.001$) and major bleeding (4.2% per year vs. 3.0% per year, $p < 0.001$). The absolute reduction in stroke or systemic embolism with dabigatran compared to warfarin was greater among patients with DM than in those without DM (dabigatran 110 mg: 0.59% per year vs. 0.05% per year; dabigatran of 150 mg: 0.89% per year vs. % per year). The authors concluded that compared to patients without DM, patients with DM and AF had greater absolute risk reduction in embolic events when treated with dabigatran.

Ezekowitz et al.[22] compared the clinical outcomes in patients with AF, with and without diabetes, anticoagulated with apixaban. The main efficacy parameters were adverse events and mortality; safety outcome was clinically relevant and non-serious severe hemorrhage. A total of 4547/18201 (24.9%) patients who had diabetes were younger (69 *versus* 70 years) and had higher incidence of CAD (39 vs. 31%), mean CHADS score (2.9 vs. 1.9), and HAS-BLED scores (1.9 vs. 1.7), higher (all $P < 0.0001$) than patients without diabetes. Patients with diabetes on apixaban had lower rates of adverse events (HR 0.75, 95% CI 0.53–1.05), all-cause mortality (HR 0.83, 95% CI 0.67–1.02), cardiovascular mortality (HR 0.89, 95% CI 0.66–1.20), intracranial hemorrhage (HR 0.49, 95% CI 0.25–0.95), and a similar rate of MI (HR 1.02, 95% CI 0.62–1.67) compared to warfarin. For major bleeding, a quantitative interaction ($P = 0.003$) was observed with a greater reduction in major bleeding in patients without diabetes, even after multivariate adjustment. The authors concluded that apixaban has similar benefits in reducing stroke and decreasing mortality, and causes less intracranial bleeding compared with warfarin in both patients with and without diabetes.

To demonstrate the benefits of using rivaroxaban in a similar scenario, Bansilau et al.[23] evaluated the safety and efficacy of using rivaroxaban compared to warfarin in patients with non-valvular AF and DM in a prespecified secondary analysis of the ROCKET AF study. Of the 5,695 patients with DM, 40% were younger, more obese, and had persistent AF. The relative efficacy of rivaroxaban and warfarin for prevention of stroke and systemic embolism ($P = 0.53$) was similar. The safety of rivaroxaban vs. warfarin in terms of major bleeding ($P = 0.43$), significant or clinically insignificant bleeding ($P = 0.17$), and intracerebral hemorrhage ($P = 0.67$) was also similar. However, adjusted exploratory analyses showed stroke rates 1.3, 1.5, and 1.9 times higher at the end of two years and vascular mortality and myocardial infarction in patients with DM. The relative efficacy and safety of rivaroxaban vs. warfarin were similar in patients with and without DM, supporting the use of rivaroxaban as an alternative to warfarin in patients with diabetes with AF.

Recently, the Compass study,[24] in which 38% of the patients had diabetes, significantly contributed to the treatment of chronic CAD, demonstrating benefits in the use of aspirin in habitual doses associated with a low dose of rivaroxaban, reducing major events and cardiovascular mortality. This concept may represent a paradigm shift in the clinical management of these patients since until then the prolonged and exclusive use of antiplatelet agents was the recommended procedure.

Although the guidelines still have unspecific recommendations for patients with diabetes with AF, experts recommend the use of CHADs and CHADsVasc scores in the risk stratification for embolic events, in which the presence of diabetes

is given the same weight as hypertension, heart failure, and age >75 years (Chart 1).

The use of anticoagulants in patients with diabetes with or without obstructive atherosclerotic disease is likely to increase, since the population is aging, and the consequent increasing incidence of atrial fibrillation will eventually challenge cardiologists to deal with patients with greater complexity and severity. For both embolic and bleeding events, elderly patients with many associated comorbidities, such as growing diabetes, will be routine in the daily clinical practice. The need for periodic reevaluations, biochemical controls, and high complexity examinations will raise costs and will certainly be one of the key challenges for cardiology in the future.

Chart 1. CHADs score for risk stratification for embolic events.

Risk factor	Score
Age >75 years	1
SAH	1
Heart failure	1
Diabetes	1
Previous TIA or stroke	2

CONCLUSION

The use of antiaggregants and anticoagulants in patients with diabetes has been increasingly recommended for several cases. In addition to being recommended for secondary prevention, which is an application already established in the literature, its use for primary prevention has also been a subject of research. Conversely, there is a risk of bleeding with the use of these drugs, as many patients are elderly and have several associated comorbidities. Thus, the literature serves as a reference for guiding patients' treatment and indication, considering that each case must be individualized for better clinical practice. There is consensus on the use of aspirin for secondary prevention, and double therapy is recommended after ACSs. The guidelines do not provide information specific to patients with diabetes, such as the classic indications for anticoagulation.

CONFLICTS OF INTEREST

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

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