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CRITICAL ANALYSIS OF THE STUDIES THAT HAVE CHANGED CLINICAL PRACTICE: DIABETES MELLITUS AND CARDIOVASCULAR DISEASES

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: DIABETES MELLITUS E DOENÇAS CARDIOVASCULARES

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ABSTRACT

The importance of therapy for patients with diabetes mellitus (DM) in reducing cardiovascular events is well-known and, therefore, there is interest in confirming the cardiovascular safety of the different antihyperglycemic therapies available on the market. The objective of this review is to discuss three large recently-published studies, LEADER, CANVAS and DECLARE – TIME 58, which evaluated the effect of the medications in question on morbidity and cardiovascular mortality as compared to a placebo.

Keywords: Diabetes Mellitus, Type 2; Liraglutide; Canagliflozin.

RESUMO

Já é bem conhecida a importância da terapêutica para os pacientes com diabetes mellitus (DM) no que diz respeito à redução dos eventos cardiovasculares e, por isso, existe interesse em comprovar a segurança cardiovascular das diferentes terapias anti-hiperglicêmicas disponíveis no mercado. O objetivo desta revisão consiste em discutir três grandes estudos publicados recentemente, LEADER, CANVAS e DECLARE – TIME 58, que avaliaram o efeito sobre morbidade e mortalidade cardiovascular das medicações em questão em comparação com placebo.

Descritores: *Diabetes Mellitus Tipo 2; Liraglutide; Canagliflozina.*

INTRODUCTION

Diabetes mellitus (DM) is a heterogeneous disease related to several micro and macrovascular complications and represents one of the main causes of mortality today and its incidence is on the rise.[1] Hyperglycemia is closely associated with the onset of vascular diseases, and therefore the importance of risk stratification, follow-up and specific treatment. The main causes of cardiovascular death in this population are coronary artery disease, stroke, and peripheral arterial disease.[2] In 2008, the US Food and Drug Administration (FDA) mandated cardiovascular safety assessments for new antidiabetic treatments. In this context, new therapies have been developed in two drug classes - type 1 glucagon-like peptide receptor agonists (GLP-1) and sodium glucose 2 co-carrier inhibitors (SGLT2) - which have not only shown safety but in some studies superiority in reduction of cardiovascular events. In this review we will discuss three studies that have changed recent clinical practice, LEADER; CANVAS and DECLARE - TIMI, published in the New England Journal of Medicine respectively in June 2016, August 2017 and January 2019.

TRIALS IN DIABETES AND CARDIOVASCULAR DISEASE

LEADER (Liraglutide and Cardiovascular Outcome in Type 2 Diabetes)

Multicenter, double-blind, randomized, placebo-controlled study that included a total of 9340 patients and approximately 3.8-year follow-up. Published in 2016, it was an important participant from our country and evaluated the cardiovascular outcomes of liraglutide (GLP1 analogue) in patients with high cardiovascular risk DM2. Patients were older than 50 years and at least one coexisting cardiovascular disease or older than 60 years or older and at least one cardiovascular risk factor (microalbuminuria or proteinuria, systemic arterial hypertension, left ventricular hypertrophy, systolic or diastolic dysfunction of the left ventricle and / or ankle-arm index less than 0.90). The primary outcome was randomization time until the first occurrence of cardiovascular event (death from cardiovascular causes, nonfatal acute myocardial infarction or nonfatal stroke) and as secondary outcomes,

the randomization time until the first occurrence of: death from cardiovascular causes nonfatal AMI, nonfatal stroke, coronary revascularization or hospitalization for unstable angina or heart failure; death from any cause, microvascular complications (nephropathy, neoplasms and pancreatitis).[3]

The hypothesis of non-inferiority of liraglutide over placebo was confirmed, as well as a significant 13% reduction in the risk of primary composite endpoint with a 22% reduction in cardiovascular death and a 15% reduction in all-cause death in the liraglutide group (CI 95%, 0.74-0.97; p = 0.02) and a significant reduction in the occurrence of microvascular events by 16% (95% CI 0.73-0.97; p = 0.02). However, the rates of nonfatal myocardial infarction, nonfatal CVA, and hospitalization for HF were lower but not significant in the liraglutide group compared to the placebo group. Regarding adverse events leading to discontinuation of medication, gastrointestinal events (nausea, diarrhea, vomiting, constipation, abdominal pain and dyspepsia) stand out. There was no significance in the incidence of pancreatitis between the groups.

CANVAS (Canagliglozin and Cardiovascular and Renal Events in Type 2 Diabetes)

In 2017 this study was published which compared the use of canagliflozin (SGLT2 inhibitor) in 10,142 patients with DM2 and established cardiovascular disease (66%) or at risk of cardiovascular disease, with an average follow-up of 2.4 years. It is a randomized, multicenter, double-blind, placebo-controlled trial which primary endpoint was cardiovascular death, nonfatal myocardial infarction and nonfatal CVA. Canagliflozin was associated with a 14% reduction in the primary endpoint rate compared with the placebo group (26.9 vs 31.5 per 1000 participant-years; RR = 0.86; 95% CI 0.75-0.97) without significant change in all-cause mortality. A possible benefit has been shown regarding albuminuria progression (RR 0.73; 95% CI 0.67-0.79) and also in the composite outcome of reduced glomerular filtration rate, need for renal replacement therapy or death from renal causes (RR 0.60; 95% CI 0.47-0.77), and hospitalizations for heart failure (RR 0.67; 95% CI 0.52-0.87). On the other hand, as it is a medication that inhibits glucose reabsorption, there is an increase in glycosuria and consequent higher incidence of genital infections as already observed with empagliflozin. In addition, there was a significant increase in amputations, mostly at metatarsal height (6.3 vs. 3.4 cases per 1000 patient-years; RR 1.97), but [4] OBSERVE -4D study presented in the ADA 2018, did not confirm increased risk.

DECLARE- TIMI 58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes)

In 2018, this publication evaluated the efficacy and cardiovascular safety of dapagliflozin. Randomized, double-blind, placebo-controlled, multicenter clinical study of 17,160 patients with T2DM followed for 5 years with a history of established cardiovascular disease or multiple risk factors. The non-inferiority safety composite primary endpoint for cardiovascular death, nonfatal acute myocardial infarction, and nonfatal CVA was achieved, as well as a significant reduction in the co-primary composite endpoint for hospitalization for heart failure or cardiovascular death. As for secondary endpoints, no impairment of renal function (4.3% x 5.5% in the placebo group) was observed in patients using SGLT2.inhibitors.[5]

Here it is worth highlighting the importance of the benefit of medication administration in DM patients in primary prevention since only 40% of the study patients had previous cardiovascular events. And unlike CANVAS study, there was no increased risk of amputation with dapagliflozin but there was a higher number of ketoacidosis and urinary tract infections.

DISCUSSION

For patients with DM requiring pharmacological treatment, the use of metformin as a drug of choice is further recommended as it acts to significantly reduce microvascular complications and intrinsic combined diabetes outcomes and is a widely known drug in clinical practice at a reduced cost, and because it is safe when combined with other drugs.[6] Next, the choice should involve medications that not only act on the glycemic target but also reduce cardiovascular risks, including GLP1 analogs and SGLT2.[7,8] inhibitors. (Table 1) GLP-1 analogs are the most potent class for reducing HbA1c in addition to weight loss and have now been included in several guidelines as the drug of choice for patients with DM and high cardiovascular risk.[9] On the other hand, liraglutide is an injectable medication and there is no evidence to prove its benefit in combination with DDP4 inhibitors.

In contrast, SGLT2 inhibitors, well discussed in the EMPA-REG, CANVAS, and DECLARE studies have shown benefit in

Table 1.

Drug	Class	Outcome	Important Adverse Events
Liraglutide (LEADER Study)	GLP-1 Agonists	- 13% MACE reduction - Reduction of high mortality for cardiovascular causes - Weight and low blood sugar reduction - Secondary prevention	Nausea and diarrhea vomiting, constipation, abdominal pain and dyspepsia
Canagliflozin (CANVAS Study)	SGLT2 Inhibitors	- 14% reduction in CV events - Decreased progression of albuminuria - Decreased need for hemodialysis and death from renal causes - Majority as a secondary prevention	Increased amputations
Dapagliflozin (DECLARE TIME 58 Study)	SGLT2 Inhibitors	- Reduction in hospitalizations for HF - Acts as a primary cardiovascular prevention drug - Did not reduce MACE	Mild increase in diabetic ketoacidosis, urinary tract infections, Fournier gangrene and necrotizing fasciitis

heart failure. Importantly, DECLARE design included patients with lower cardiovascular risk than other studies in the same class, making SGLT2 inhibitors as a potential drug of choice for primary prevention. Among them, canagliflozin was associated with a reduction in cardiovascular events, but it was also associated with an increase in amputation rates, while dapagliflozin was not related to a decrease in mortality, but significantly reduced hospitalizations for heart failure. We have, therefore, as a question, the fact that trial DECLARE did not reduce MACE compared to other medications of the same class. One hypothesis would be the fact that the patients in this study had less cardiovascular risk. Further research is still needed. However, the beneficial effect of SGLT2 inhibitors on decreasing hospitalizations for HF was clear.

CONCLUSION

New perspectives on antidiabetics are available for the patient with DM2. Currently, medications with cardiovascular safety are recommended and that fit the profile of the coronary disease patient. Among the medications studied, SGLT2 inhibitors and GLP1 analogs demonstrated not only cardiovascular safety but also reduced cardiovascular outcomes and death. If metformin associated to lifestyle-related changes is not sufficient to achieve adequate glycemic levels, the introduction of such medications should be considered. Note SGLT2 inhibitors that have not only shown reduced mortality (EMPA-REG study) but also reduced hospitalizations for heart failure (CANVAS and DECLARE). Such studies not only changed DM treatment paradigms but also improved survival of this population.

CONFLICTS OF INTEREST

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

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REFERENCES

1. **Balakumar P, Maung-U K, Jagadeesh G. Prevalence and Prevention of cardiovascular disease and diabetes mellitus. Pharmacol Res. 2016;113:600-9.**
2. Smith JW, Marcus FI, Serokman R. Prognosis of patients with diabetes *mellitus* after acute myocardial infarction. Am J Cardiol. 1984;54(7):718-21.
3. **Marso SP, Daniels GH, Brown- Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311-22.**
4. **Neal B, Perkovich V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017;377(7):644-57**
5. **Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, et al. American Association Of Clinical Endocrinologists and American College of Endocrinologu Position Statement on The Association of SGLT-2 Inhibitors and diabetic Ketoacidoses. Endocrine Practice. 2016;22:753-62.**
6. Ito H, Ishida H, Takeuchi Y, Antoku S, Abe M, Mifune M, et al. Long – term effect of metformin on blood glucose control in non-obese patients with type 2 diabetes mellitus. Nutr Metab (Lond). 2010;7:83.
7. Klonoff DC, Buse JB, Nielsen LL, Guan X, Bowlus CL, Holcombe JH, et al. Exenatide effets on diabetes, obesity, cardiovascular risk factors and hepatic biomarkers in patients with type 2 diabetes treated at least 3 years. Curr Med Res Opin 2008;24:275-86.
8. Wajcberg E, Amarah A. Liraglutide in the management of type 2 diabtetes. Drug Des Devel Ter. 2010;4: 279-90.
9. **Saraiva FK, Sposito AC. Cardiovascular effects of glucagon- -like peptide 1 (GLP-1) receptor agonists. Cardiovasc Diabetol. 2014;13:142.**