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Are gliflozins the new statins for diabetes?

Dario Giugliano [a,*], Maria Ida Maiorino [b], Miriam Longo [a], Katherine Esposito [b]

[a] Division of Endocrinology and Metabolic Disease, Department of Advanced Medical and Surgical Sciences, Università L. Vanvitelli, Naples, Italy

[b] Diabetes Unit, Department of Advanced Medical and Surgical Sciences, Università L. Vanvitelli, Naples, Italy

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Since the first demonstration by the 4S (Scandinavian Simvastatin Survival Study) trial that treatment of dyslipidemia significantly decreased by 55% the risk of major cardiovascular events (MACE) in patients with type 2 diabetes (T2D) [1], statins have been consecrated as vital drugs for cardiovascular (CV) prevention. Twenty-five year later the original publication of the 4S trial, the American Diabetes Association (ADA) claims that for patients of all ages with diabetes and atherosclerotic cardiovascular disease (ASCVD) or 10-year ASCVD risk >20%, high-intensity statin therapy should be added to lifestyle therapy [2].

The story of gliflozins is more recent and started in 2015 with the publication of the EMPA-REG trial [3], belonging to the so called CVOTs (cardiovascular outcome trials) family, born as a consequence of the FDA guidance for industry to exclude inacceptable CV damage by new anthyperglycemic drugs. So, the astonishing 32% reduction of total mortality and 14% decrease in MACE after 48 months of treatment with empagliflozin in more than 7000 T2D patients at high CV risk hit hard. Four year later the publication of the EMPA-REG trial, the ADA claims [4] that among patients with T2D who have established ASCVD, sodium–glucose cotransporter 2 inhibitors (also known as gliflozins) with demonstrated cardiovascular disease benefit are recommended as part of the antihyperglycemic regimen. Gliflozins ran quickly as they had the A bullet (maximal scientific evidence) from ADA faster than statins.

Table 1 put together the evidence so far accumulated about the CV effects of statins and gliflozins in T2D. The CV statin data are extracted from the landmark meta-analysis [5] including data from over 18,000 patients with diabetes from 14 randomized trials of statin therapy (mean follow-up 4.3 years): in all diabetic participants, statin therapy reduced the 5-year incidence of MACE by about a fifth per each mmol/L (39 mg/dl) reduction in LDL cholesterol, associated with a 10% proportional reduction in all-cause mortality and 12% reduction in vascular mortality. The gliflozin data are extracted from three identified trials with 34,322 patients [3,6,7]: gliflozins reduced MACE by 11%, with even greater benefit in patients with ASCVD, associated with 19% reduction of CV death and a nonsignificant 17% reduction of total death.

Except for stroke, that was reduced by statins only, there are many similarities between the CV effects of statins and gliflozins, especially with regard to the reduction of ASCVD risk (MACE and CV death); moreover, heart failure (HF) and some kidney outcomes are also positively influenced by treatment with both drugs. In up to 17 trials with 132,538 participants, statins modestly (10%) reduced the risk of non-fatal HF hospitalization [8]. The three trials with gliflozins

* Corresponding author at: University Hospital, Università L. Vanvitelli, Piazza L. Miraglia 2, 80138 Naples, Italy.
E-mail address: dario.giugliano@unicampania.it (D. Giugliano).
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Table 1 – Cardiovascular outcomes in meta-analyses of statin and gliflozin trials.

Outcome	Statins RR (95% CI)	Heterogeneity	Gliflozins RR (95% CI)	Heterogeneity
MACE	0.79 (0.72–0.86)*	Very low	0.89 (0.83–0.96)*	Very low
with prior ASCVD	0.80 (0.74–0.88)*	Very low	0.86 (0.79–0.95)†	Very low
Non fatal MI	0.78 (0.69–0.87)*	Very low	0.88 (0.70–0.97)$	Very low
All cause death	0.90 (0.87–0.93)*	High	0.83 (0.70–0.99)$	Very low
CV death	0.88 (0.75–1.03)	High	0.81 (0.63–1.05)	Low
Stroke	0.79 (0.67–0.93)*	Low	1.02 (0.61–0.79)	Low
Hospitalization for HF	0.90 (0.84–0.97)	Very low	0.69 (0.61–0.79)*	Very low

MACE, major cardiovascular events; ASCVD, atherosclerotic cardiovascular disease; RR, relative risk; MI, myocardial infarction; HF, heart failure.

Low or very low heterogeneity indicate small or very small variations between studies.

* P =/< 0.001.

† P = 0.002.

$ P = 0.01.

(empagliflozin, canagliflozin, dapagliflozin) [3,6,7] all revealed a robust and significant reduction in the risk of hospitalization for HF, ranging from 27% to 35%, and independent of presence of HF at baseline [9]. For example, the benefit of HF risk reduction ranged from 49% to 29%, respectively, in patients with or without HF at baseline in the CANVAS trial [9]. Moreover, canagliflozin reduced the overall risk of HF events with no clear difference in effects between those with preserved or reduced ejection fraction [10], while dapagliflozin reduced the risk of hospitalization for HF and CV death to a greater extent in patients with reduced ejection fraction [11]. As far as kidney outcomes are concerned, a meta-analysis [12] of 57 eligible studies with 143,888 participants showed that the rate of decline in estimated glomerular filtration rate (eGFR) was lower (0.41 mL/min/1.73 m^2 per year) in statin recipients as compared with controls, without an apparent beneficial effect for kidney failure events. On the other hand, gliflozins [13] reduced the risk of progression of renal disease by 45%, and caused an even lower rate of decline in estimated glomerular filtration rate (1.35 mL/min/1.73 m^2 per year) in diabetic patients.

There are also differences between statins and gliflozins. The first relates to a general CVOTs shortcoming: most participants had advanced atherosclerotic risk or established ASCVD, which limits generalizability of the data to a broader diabetic population. On the contrary, the proportional reduction in MACE per each mmol/L reduction in LDL cholesterol by statin is similar irrespective of a previous history of vascular disease, sex, age, treated hypertension, body-mass index, systolic or diastolic blood pressure, smoking history, and estimated glomerular filtration rate. Another cause of divergence relates to the mediators of drug effects. Statins exert their benefits on CV risk via the reduction of LDL cholesterol, hence the leitmotif "lowest is better or even best". On the other hand, it is still a matter of discussion whether gliflozins act through the reduction of hemoglobin A1c (amelioration of glycemic control), and, if yes, to what extent. For example, it seems that the striking reduction of HF risk exerted by gliflozins is completely dissociated from its effect to reduce A1c levels; on the other hand, the antihyperglycemic action of gliflozins may play some role in the mediation of their benefit on MACE risk [9]. There seems to be a plausible biological explanation for these divergent effects of gliflozins, as their main and perhaps sole antihyperglycemic effect, i.e. glycosuria, induces diuresis and natriuresis and hence lower extracellular volume and arterial blood pressure. This in turn may be responsible for the rapid and consistent amelioration of HF risk.

The beneficial effects of gliflozins on cardiorenal risk occurred in T2D patients at the top of their optimal CV therapy, which included statins in a percentage of about 75% of the enrolled patients; in particular, the use of statins in participants allocated to newer antihyperglycemic drugs was 77.4% in EMPA-REG trial [3], 74.7% in CANVAS trial [6], and 74.9% in DECLARE trial [7]. Patients with T2D are at high risk of CV death and adverse CV outcomes. By using evidence-based therapies, including antithrombotics, angiotensin converting enzyme inhibitors, statins, and beta-blockers, and now antihyperglycemic drugs with proven CV benefits, physicians can improve both glucose control and, importantly, the CV outcome for patients with T2D at high risk for or with established ASCVD [14]. This fits with the Berlin Declaration [15] which recommends that by 2025 all countries should have a nationally agreed minimum drugs list for the management of T2D, including treatments for hyperglycemia, hypertension and high lipid levels as a minimum.

In conclusions, the similarities between statins and gliflozins on the cardiovascular and perhaps cardiorenal risk of the T2D patient seem clinically more important than their differences; however, before gliflozins can be labeled as the new statins, many tasks should be addressed and resolved, including, although not limited to generalizability of their effects to a broader diabetic population, longer follow up for the identification of longer-term safety issues, the cost, and durability of the antihyperglycemic effect. So, the combination of gliflozins, statins and optimal glycemic control may have additive benefits on vascular complications in patients with T2D.

Conflict of interest disclosure

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REFERENCES

[1] Pedersen K1, Kjekshus TR, Faergeman J, Olsson AG O, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diab Care 1997;20(4):614–20.
[2] Standards of Medical Care in Diabetes—2019. 10. Cardiovascular disease and risk management. Diab Care 2019;42(Suppl. 1):S103–23.
[3] Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.
[4] Standards of Medical Care in Diabetes—2019. 9. Pharmacologic approaches to glycemic treatment. Diab Care 2019;42(Suppl. 1):S90–S102.
[5] Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371(9608):117–25.
[6] Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644–57.
[7] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347–57.
[8] Preiss D, Campbell RT, Murray HM, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. Euro Heart J 2015;36(24):1536–46.
[9] Giugliano D, Meier JJ, Esposito K. Heart failure and type 2 diabetes: from cardiovascular outcome trials, with hope. Diab Obesity Metab 2019. https://doi.org/10.1111/dom.13629.
[10] Figtree GA, Rådholm K, Barrett TD, et al. Effects of canagliflozin on heart failure outcomes associated with preserved and reduced ejection fraction in type 2 diabetes: results from the CANVAS program. Circulation 2019. https://doi.org/10.1161/CIRCULATIONAHA.119.040057.
[11] Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019. https://doi.org/10.1161/CIRCULATIONAHA.119.040130.
[12] Su X, Zhang L, Lv J, et al. Effect of statins on kidney disease outcomes: a systematic review and meta-analysis. Am J Kidney Dis 2016;67(6):881–92.
[13] Toyama T, Neuen BL, Min Jun M, et al. Effect of SGLT2 inhibitors on cardiovascular, renal and safety outcomes in patients with type 2 diabetes mellitus and chronic kidney disease: a systematic review and meta-analysis. Diab Obesity Metab 2019. https://doi.org/10.1111/dom.13648. March.
[14] Cosentino F, Ceriello A, Baeres FMM, et al. Addressing cardiovascular risk in type 2 diabetes mellitus: a report from the European Society of Cardiology Cardiovascular Roundtable. Eur Heart J 2018. https://doi.org/10.1093/eurheartj/ehy677. Nov 16.
[15] Ceriello A, Gavin 3rd JR, Boulton AJM, et al. Berlin Declaration Steering Group. The Berlin Declaration: a call to action to improve early actions related to type 2 diabetes. How can specialist care help? Diab Res Clin Pract 2018;139(5):392–9.