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Commentary

Antiatherosclerotic Effects of Sodium-Glucose Cotransporter 2 Inhibitors: An Underrecognized Piece of the Big Puzzle?

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Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcome trial; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) have radically changed the management of type 2 diabetes, and, in addition to effectively lowering blood glucose, they have been shown to attenuate cardiorenal risk. It is quite interesting that, unlike many other drugs, the scientific community first realized the ability of gliflozins to improve cardiorenal outcomes and subsequently sought to unravel the relevant mechanisms. The full spectrum of pathways that mediate the off-target effects of the class remains obscure. However, these are believed to be largely related to natriuresis, improved heart pump energetics, downregulation of systemic inflammation and sympathetic activity, and amelioration of endothelial dysfunction. Oxidative stress has recently emerged as a key mechanism involved in the development and progression of atherosclerosis and other diabetic complications. SGLT2is are believed to exert antioxidant properties through multiple mechanisms that result in a decrease in free radical production or an improvement in cellular antioxidant capacity (1).

The traditional distinction with respect to the cardiorenal benefits of the new glucose-lowering agents suggests that SGLT2is primarily improve heart failure (HF) and chronic kidney disease (CKD) outcomes. The other game-changing class, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), mostly affects endpoints related to atherosclerotic disease. This perspective is supported not only by abundant data derived from the cardiovascular outcome trials (CVOTs) of the 2 categories, but also from a number of "reasonable extrapolations." First, the clinical benefits of SGLT2is become evident within the first few weeks of administration, in contrast to GLP-1 RAs, which require several months to reduce the risk of cardiovascular (CV) events compared with placebo. Such a rapid improvement in clinical status implies that the involved mechanisms are independent of the development of atherosclerosis, which is known to progress slowly, and the same is applicable for its regression. Second, post hoc analyses of CVOTs indicate that the cardiorenal effects of GLP-1 RAs are significantly mediated by an improvement in classical atherosclerosis risk factors, including glycemia and lipid profile (2), and are most evident at the secondary prevention level, when atherosclerosis has already been established. This is not the case with SGLT2is whose benefits have been shown to be mainly dependent on changes in markers of plasma volume (3) and apply to a wide range of patients, regardless of the history of CV disease. Regarding the effects of the class on lipid profile, a recent meta-analysis suggested that the use of SGLT2is is associated with an increase in total and low-density lipoprotein cholesterol levels (4), which might be a concern in patients at high CV risk, as is the case for the vast majority of people with diabetes. In contrast, a positive effect on triglyceride and high-density lipoprotein cholesterol concentrations was documented.

On the other hand, a recent study by Chen et al (5) demonstrated the ability of dapagliflozin to stabilize atherosclerotic plaques in a mouse model of diabetic atherosclerosis resembling plaque instability/rupture as seen in patients. Specifically, animals treated with SGLT2is manifested increased fibrosis, augmented collagen accumulation, and significant upregulation of the expression of vasculoprotective factors. Empagliflozin has been shown to mitigate endothelial dysfunction and atherogenesis in diabetic ApoE$^{-/-}$ mice, with downregulation of vasoconstrictive eicosanoids and inflammation in the vasculature and perivascular adipose tissue proposed as potential mechanisms

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(6). Pennig et al have demonstrated that empagliflozin-treated mice manifest decreased proliferation of plaque resident macrophages and leukocyte adhesion to the vascular wall compared with control animals (7). Collectively, these novel data seem to provide evidence for genuine antiatherosclerotic effects of SGLT2is and challenge the notion that their benefits are solely restricted to HF and CKD.

Another interesting question is whether all SGLT2is possess the same magnitude of antiatherogenic potential. It is definitely hard to answer, considering the scarcity of relevant data. From a strictly mechanistic perspective, however, it could be said that dual SGLT1 and 2 inhibitors (like sotagliflozin) might have an advantage. One plausible explanation for this phenomenon is that intestinal inhibition of SGLT1 may result in a higher concentration of endogenous GLP-1, thus leading to potentially enhanced cardioprotective properties of SGLT1/2is compared with pure SGLT2is (8).

In conclusion, SGLT2is continue to surprise us, constantly opening new doors to an era of heart and kidney protection within and beyond the spectrum of diabetes. Their rather underestimated antiatherogenic properties represent 1 more challenge for future research in the field of cardiometabolic medicine. Data from mechanistic studies are required along with targeted randomized trials and real-world evidence to reveal the full potential of the class to improve atherosclerotic outcomes.

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Author Contributions

T.K. reviewed the literature and drafted the first version of the manuscript. P.V., G.M. and K.K. reviewed the literature and edited the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

T.K. has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Pharmaserve Lilly, and Novo Nordisk, for advisory boards from Novo Nordisk, and has participated in sponsored studies by Eli-Lilly and Novo Nordisk. P.V. has received honoraria for lectures/advisory boards from Sanofi, Grunenthal, and Lilly. G.M. has received honoraria for lectures from AstraZeneca and Novo Nordisk. K.K. has received honoraria for lectures/advisory boards and research support from Astra Zeneca, Boehringer Ingelheim, Pharmaserve Lilly, Sanofi-Aventis, ELPEN, MSD, and Novo Nordisk.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Yaribeygi H, Atkin SL, Butler AE, Sahebkar A. Sodium-glucose cotransporter inhibitors and oxidative stress: an update. *J Cell Physiol*. 2019;234(4):3231-3237.
2. Buse JB, Bain SC, Mann JFE, *et al*. LEADER trial investigators. cardiovascular risk reduction with liraglutide: an exploratory mediation analysis of the LEADER Trial. *Diabetes Care*. 2020;43(7):1546-1552.
3. Inzucchi SE, Zinman B, Fitchett D, *et al*. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care*. 2018;41(2):356-363.
4. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, Simental-Mendía LE. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: a systematic review and meta-analysis of 48 randomized controlled trials. *Pharmacol Res*. 2020;160:105068.
5. Chen YC, Jandeleit-Dahm K, Peter K. Sodium-glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin stabilizes diabetes-induced atherosclerotic plaque instability. *J Am Heart Assoc*. 2022;11(1):e022761.
6. Ganbaatar B, Fukuda D, Shinohara M, *et al*. Empagliflozin ameliorates endothelial dysfunction and suppresses atherogenesis in diabetic apolipoprotein E-deficient mice. *Eur J Pharmacol*. 2020;875:173040.
7. Pennig J, Scherrer P, Gissler MC, *et al*. Glucose lowering by SGLT2-inhibitor empagliflozin accelerates atherosclerosis regression in hyperglycemic STZ-diabetic mice. *Sci Rep*. 2019;9(1):17937.
8. Koufakis T, Mustafa OG, Tsimihodimos V, Ajjan RA, Kotsa K. Insights into the results of sotagliflozin cardiovascular outcome trials: is dual inhibition the cherry on the cake of cardiorenal protection? *Drugs*. 2021;81(12):1365-1371.