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SGLT-2 Inhibitors: Discrepancy Between MACE Reduction and Incident MI & Stroke

--Manuscript Draft--

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Question	**Response**
SPECIAL REQUESTS In place of a cover letter, enter specific comments or requests to the editors here	March 30, 2023 To Paul M. Stewart, MD, FRCP, FMedSci Editor-in-chief Elect, Journal of Clinical Endocrinology & Metabolism Sangeeta Kashyap, MD, Associate Editor, Journal of Clinical Endocrinology & Metabolism Dear Dr. Stewart and Dr. Kashyap, I have enclosed my manuscript “SGLT-2 Inhibitors: Discrepancy Between MACE Reduction and Incident MI & Stroke” for consideration for publication as a commentary. I feel that this manuscript in its current form would be of interest to the readership of Journal of Clinical Endocrinology & Metabolism (JCEM), as when paired with the accompanying meta-analsyis that is in press, it highlights the discrepancy between ischemic events (MI and Stroke) and MACE reduction with SGLT-2i. Importantly, it highlights that the ischemic events associated with 3-P MACE were not statistically significant, andI further suggest that the inherent MACE reduction with SGLT-2i may be due to heart failure risk reduction. I certify that I will take public responsibility for the contents, have contributed significantly to the drafting, and have approved the final version. I attest that all applicable subject protection guidelines and regulations were followed in the conduct of this research. The work has not been published and is not under consideration elsewhere. Thank you for your consideration of this manuscript and we look forward to your response. If you require further information, please do not hesitate to contact me. Sincerely, David T. Broome, MD
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Since 2008, the FDA has mandated inclusion of 3-point major adverse cardiovascular events (MACE) as primary composite endpoints (cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke) to establish cardiovascular safety in novel therapeutic trials investigating antihyperglycemic agents[1]. This shift in focus eventually led to the joint consensus report from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) 2022 suggesting that sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are a preferred agent in patients with Type 2 Diabetes who are high risk for atherosclerotic cardiovascular disease (ASCVD)[2]. Further, in people with heart failure, CKD, established CVD, or multiple risk factors for CVD, the decision to use SGLT-2i (or GLP-1 RA) with proven benefit has been determined to be independent of the background use of metformin and independent of baseline HbA1c[2,3]. With the recent recommendations for use of SGLT-2i, there have been studies that investigate the mechanisms by which SGLT-2i reduce MACE. More specifically, in examining four major clinical trials investigating SGLT-2i in MACE, a recent meta-analysis has suggested that the effect of SGLT-2i reduce the risk of MACE independent of their ability to reduce incident MI and stroke[4]. In this commentary, we will discuss this recent met-analysis and its clinical impact on the use of SGLT-2i as an antihyperglycemic agent for the reduction of MACE.

Mukhopadhyay et al performed a meta-analysis utilizing pooled data from four eligible trials (EMPA-REG[5], VERTIS CV[6], CANVAS[7], and the DECLARE TIMI 58[8]), which resulted in 42,568 subjects. The 3-P MACE factors analyzed in this meta-analysis were 4,176 subjects for Total MACE, 2,157 for MI, and 1,288 for stroke. In their results, it was reported that SGLT-2i did not reduce either MI or stroke individually, or in totality [Mantel Haenszel (MH) risk ratio: fatal and nonfatal MI 0.93 (95% CI 0.85, 1.01), stroke 1.00 (95% CI 0.98, 1.11), total ASCVD events 0.95 (95% CI 0.89, 1.02), nonfatal ASCVD (combined nonfatal MI and nonfatal stroke) 0.94 (95% CI 0.88, 1.02)]. Based on these results, the authors concluded that SGLT-2i seem to reduce MACE without any discernible significant reduction in incident MI or stroke (both fatal and non-fatal), and therefore, the authors concluded that the mechanism for SGLT-2i efficacy may be unrelated to anti-atherogenic effects. Mukhopadhyay et al highlighted that heart failure was later included as part of the 5-P MACE primary outcome parameters (nonfatal MI, nonfatal stroke, CV death, coronary revascularization, or unstable angina requiring hospitalization) for antihyperglycemic clinical trials, in which SGLT-2i were found to be effective in heart failure related outcomes.

The meta-analysis reported by Mukhupadhyay et al[4] is compelling in the sense that it is important that researchers and clinicians meet results with an appropriate amount of skepticism and determine the primary driver of the composite endpoint (such as 3-P and 5-P MACE, respectively). SGLT-2i were able to reduce the composite 3-P MACE, but they were not able to reduce individual endpoints of incident MI and stroke. Importantly, the trials that later examined SGLT-2i and the ability to reduce 5-P MACE were able to identify what potentially may be the cause for reduced MACE with SGLT-2i: reduced risk for heart failure exacerbation and/or heart failure progression.

Most recently, SGLT-2i have been demonstrated to reduce the risk for cardiovascular mortality, progression of heart failure, and reduce the risk for heart failure exacerbation. Therefore, it seems like a plausible explanation that the primary driver for SGLT-2i reducing MACE, may be due to optimization of heart failure and volume status. The explanation is intuitive given that SGLT-2 inhibitors reduce renal tubular glucose reabsorption, which then leads to volume reduction via osmotic diuresis and natriuresis. The highlighted findings by Mukhopadhyay P et al[4] represent an opportunity for the FDA to reconsider the stratification of cardiovascular mortality analyses in clinical trials, as suggested by the authors, and in future mandates consider separating cardiovascular mortality events associated with ischemic events from those associated with heart failure.

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