Reply

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REPLY: Mediators of the Effects of Canagliflozin on Heart Failure

Central Role of the Cardiorenal Axis

Mediation analysis of the CANVAS (CANagliflozin cardioVascular Assessment Study) Program was performed in an attempt to identify the mechanism(s) by which the sodium glucose co-transporter (SGLT)-2 inhibitor (SGLT2i) canagliflozin benefits the cardiovascular system, in particular, by reducing the risk for hospitalization for heart failure (1). The results of this analysis showed that the benefit of canagliflozin could be mediated substantively by changes in albuminuria and hematocrit. In a letter to the editor, Dr. Bryan and colleagues supported the idea that changes in these 2 factors may indicate an effect of the drug on the cardiorenal axis through improved vascular function and organ oxygenation. Both albuminuria and hematocrit have indeed been associated with risk for renal and cardiovascular disease.

Albuminuria appears to represent much more than simply a failing filter in the glomerulus and likely reflects a general leakage of albumin in all capillary beds leading to low-grade inflammation and vascular dysfunction. The reason for this leakage may be impairment of the endothelial glycocalyx, a gel-like layer covering the vascular endothelium (2).

Changes in hematocrit may be attributable to decreased tissue oxygenation leading to organ failure. Earlier, post hoc analyses of the RENAAL (Reduction of Endpoints in Non-insulin-dependent diabetes mellitus [NIDDM] with the Angiotensin II Antagonist Losartan) study showed that low hemoglobin is a driving force for the high residual risk in patients with type 2 diabetes and nephropathy (3).

The question remains, how does canagliflozin decrease albuminuria and increase hematocrit? As Bryan and colleagues correctly state, better courses of action than our conventional clinical chemistry biomarkers could make an important contribution. The CANVAS Program stored plasma and urine samples, and multiple analyses are ongoing to search for new mechanistic biomarker profiles by using high-throughput assays measuring proteomics, metabolomics, and genomics; for example, the Biomarker Enterprise to Attack Diabetic Kidney Disease (BEAt-DKD) project. In conjunction with data from the more recently completed CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (4), we hope to greatly improve our understanding of how SGLT2i protect against renal and cardiovascular outcomes. This work may also discover novel molecular pathways in the pathophysiology of diabetes and identify new targets for more effective therapies. These efforts are needed to address the residual risk in the population even after successful trials with SGLT2i.

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Please note: Dr. Heerspink is a consultant for AbbVie, Astellas, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, and Mitsubishi Tanabe; and has received grant support from AbbVie, AstraZeneca, Boehringer Ingelheim, and Janssen. Dr. Li is a full-time employee of the George Institute for Global Health. Dr. Neal is a member of advisory boards of and a consultant for Janssen and Mitsubishi Tanabe. Dr. de Zeeuw has served on advisory boards and/or as a speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, Mitsu bishi Tanabe; has served on Steering Committees and/or as a speaker for AbbVie and Janssen; and has served on Data Safety and Monitoring Committees for Bayer.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Heart Failure* author instructions page.

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