Letter to the Editor: "AHA Scientific Statement on Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease"

We read with interest the article by Rangaswami et al describing the implementation of newer antidiabetic agents for the treatment of patients with diabetes and chronic kidney disease (**1**). The article provides an important overview of the evidence for clinicians; however, we wish to clarify two errors in the reporting of data from the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

The CANVAS Program was an integrated analysis of two similarly designed trials, CANVAS and CANVAS-Renal (CANVAS-R), which were designed to evaluate the effects of the sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin versus placebo on cardiovascular outcomes (**2**). These trials had different durations of follow-up and different ratios of randomization between the active treatment and placebo; therefore, simply reporting the proportion of patients with a particular event will not give a reliable representation of the treatment effect. For this reason, all CANVAS Program publications refrain from reporting outcomes data as percentages and instead provide data as rates per 1000 patient-years.

We noticed, however, that Figure 1 in the Scientific Statement reports the proportion of events for each of the outcomes shown across studies, including the CANVAS Program (**1**). Thus, the figure suggests that the rate of cardiovascular death was higher with canagliflozin versus placebo, which is inconsistent with the published findings from the CANVAS Program (**2**). Event rates per 1000 patient-years, not percentages, should be reported for CANVAS Program data in all panels of Figure 1.

In addition, the CANVAS Program enrolled patients with eGFR ≥30 mL/min/1.73 m^2 and had no albuminuria restrictions (**2**); however, it is not listed in all appropriate categories of Table 2. The CANVAS Program should be added to the eGFR 30-44 mL/min/1.73 m^2 and 45-59 mL/min/1.73 m^2 rows for all albuminuria categories in Table 2.

We thank you for your consideration of these corrections.

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References

1. Rangaswami J, et al. Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease: A Scientific Statement From the American Heart Association. *Circulation.* 2020;142(17):e265-e286.
2. Neal B, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017;377(7):644-657.

Response to letter regarding "**Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease: A Scientific Statement From the American Heart Association"**

Janani Rangaswami, MD; on behalf of the Writing Group

The Writing Group of the AHA Scientific Statement titled "Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease" would like to thank Drs. Neal and Matthews for their letter requesting clarification on the representation of proportion of events in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program in Figure 1, and the eGFR and albuminuria criteria for CANVAS listed in Table 2[1]. As outlined by the authors, the CANVAS program was an integrated analysis of 2 similarly designed trials but had different durations of follow-up and ratios of randomization between the treatment arm and placebo[2]. Figure 1 in the Scientific Statement reports the proportion of events for key outcomes across the studies reviewed by the Writing Group within the stated timeline. In order to keep the format uniform, the figure used event rates across all studies including data reported in a prior version of the supplementary data files from the CANVAS trial publication.

We have now modified Figure 1 by separating the CANVAS program into its two component studies, CANVAS and CANVAS-R, utilizing raw data obtained from an earlier published version of the CANVAS appendix under Supplementary Table S6. In the revised Figure 1, the rates for cardiovascular death are lower in the canagliflozin group versus placebo in both sub-studies, which is consistent with the original findings from the trial. We have also added CANVAS to the eGFR cutoffs of 30-44mL/min/1.73m^2 and 45-59mL/min/1.73m^2 across all albuminuria categories in Table 2. Given the nuances with representing data from the integrated CANVAS program along with the other cardiovascular outcomes trials with the sodium glucose

co-transporter inhibitors, we believe that this modification aligns with the data reported from the CANVAS program and offers appropriate context to the reader when interpreting cardiorenal outcomes with canagliflozin.

References:

1. Rangaswami J, Bhalla V, de Boer IH, Staruschenko A, Sharp JA, Singh RR, Lo KB, Tuttle K, Vaduganathan M, Ventura H and McCullough PA. Cardiorenal Protection With the Newer Antidiabetic Agents in Patients With Diabetes and Chronic Kidney Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2020;142:e265-e286.
2. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M and Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England Journal of medicine*. 2017;377:644-657.

The corrections noted above have been made to the current online version of the article, which is available at https://www.ahajournals.org/doi/10.1161/CIR.0000000000000920