Evaluating the effects of Canagliflozin ~~Reduces~~ on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Chronic Kidney Disease ~~Regardless of~~according to Baseline HbA1c, Including Those With HbA1c <7%: Results From the CREDENCE Trial

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Data from this study will be made available in the public domain via the Yale University Open Data Access Project (http://yoda.yale.edu/) once the product and relevant indication studied have been approved by regulators in the United States and European Union and the study has been completed for 18 months.

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Traditional management of diabetes mellitus has focused on glycemic control, beginning with lifestyle changes, followed by metformin, and then other classes of antiglycemic agents.[1] Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce cardiovascular (CV) events, including CV death, myocardial infarction (MI) and heart failure, and slow progression of renal dysfunction, including prevention of end-stage kidney disease (ESKD).[2-3] Because initial clinical trials included mostly patients with baseline HbA1c >7%, current guidelines have recommended this class as add-on therapy for patients whose HbA1c is not at goal, typically $\geq$7%.[1] We hypothesized that there would be similar benefits on CV and renal endpoints regardless of baseline HbA1c, including those with HbA1c <7%.

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was a double-blind, randomized trial of canagliflozin 100 mg versus placebo in 4401 patients with type 2 diabetes and chronic kidney disease (CKD).[3] As previously detailed, patients were eligible if they had a hemoglobin A1c level of 6.5 to 12.0%, an estimated glomerular filtration rate (eGFR) of 30 to <90 mL per minute per 1.73 m^2 of body-surface area and albuminuria (urinary albumin-to-creatinine ratio, >300 to 5000 mg/g).[3] Overall, canagliflozin significantly reduced the risk of the primary composite outcome (ESKD, doubling of serum creatinine, or renal or CV death), as well as a renal composite oucome excluding CV death, MACE (major adverse CV events: CV death, nonfatal MI, or nonfatal stroke), a composite of CV death and hospitalization for heart failure (HHF), and the standalone endpoint of HHF. We analyzed CV, renal, and safety outcomes by baseline HbA1c and results are reported without adjustment for multiplicity.

The distribution of patients by baseline HbA1c was <7% (N=650), 7 to <8% (N=1406) and ≥8% (N=2343) with mean values of —6.6%, ——7.4%, and ——9.2%, respectively. Baseline characteristics across the groups ~~differed only modestly~~showed ~~, with~~ a mean age 64.1, 64.0, and 62.1 years; 26.9%, 31.3%, and 37.5% female; 49.5%, 49.3%, and 51.4% with history of atherosclerotic cardiovascular disease (ASCVD); mean duration of diabetes 14.7, 15.8, and 16.1 years; and mean eGFR 53.5, 54.8, and 57.8 mL/min/1.73 m^2, ~~in the HbA1c <7%, 7 to <8%, and ≥8% groups,~~ respectively. The difference in HbA1c at 13 weeks between canagliflozin and placebo was –0.18%, –0.23%, and –0.40% ~~across the 3 groups~~, respectively.

Across categories of baseline HbA1c, treatment with canagliflozin resulted in similar risk reductions of the primary composite outcome, CV death, HHF, and MACE (all *P* interaction non-significant, Figure). Similarly, across baseline HbA1c categories, including in participants with HbA1c <7%, there were no differences in the risk of serious adverse events or other safety events.

We found that canagliflozin reduced the risk of both CV and renal events in patients with type 2 diabetes and CKD ~~irrespective~~ without a significant interaction across the spectrum of ~~of~~ baseline HbA1c values, which includ~~ing in~~ patients with baseline HbA1c between 6.5% and ~~<~~7%, suggesting that treatment of patients with CKD and/or ASCVD is warranted, even if their diabetes is "well controlled." These data support the concept that this class of drugs has clinical benefits regardless of HbA1c. Thus, as recently recommended in the 2019 ESC guidelines,[4] they should be considered for incorporation into regimens for patients based on CV or renal risk rather than HbA1c considerations, and can ~~. They also note that this incorporation for patients with CV and renal risk could~~ be add-on therapy or used as first line treatment.[4]

Further support for this approach comes from a recent trial that found benefit of an SGLT2 inhibitor in patients with heart failure *without* diabetes.[5] The practical implication is that clinicians need to evaluate patients' CV and renal risk and consider using SGLT2 inhibitors for their clinical benefit, and not specifically for glycemic or risk factor control, as we currently also do for ACE inhibitors, statins, and antithrombotic therapy in patients with diabetes and/or CV disease.

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J. Baldassare and R. Edwards are full-time employees of Janssen Research & Development, LLC.

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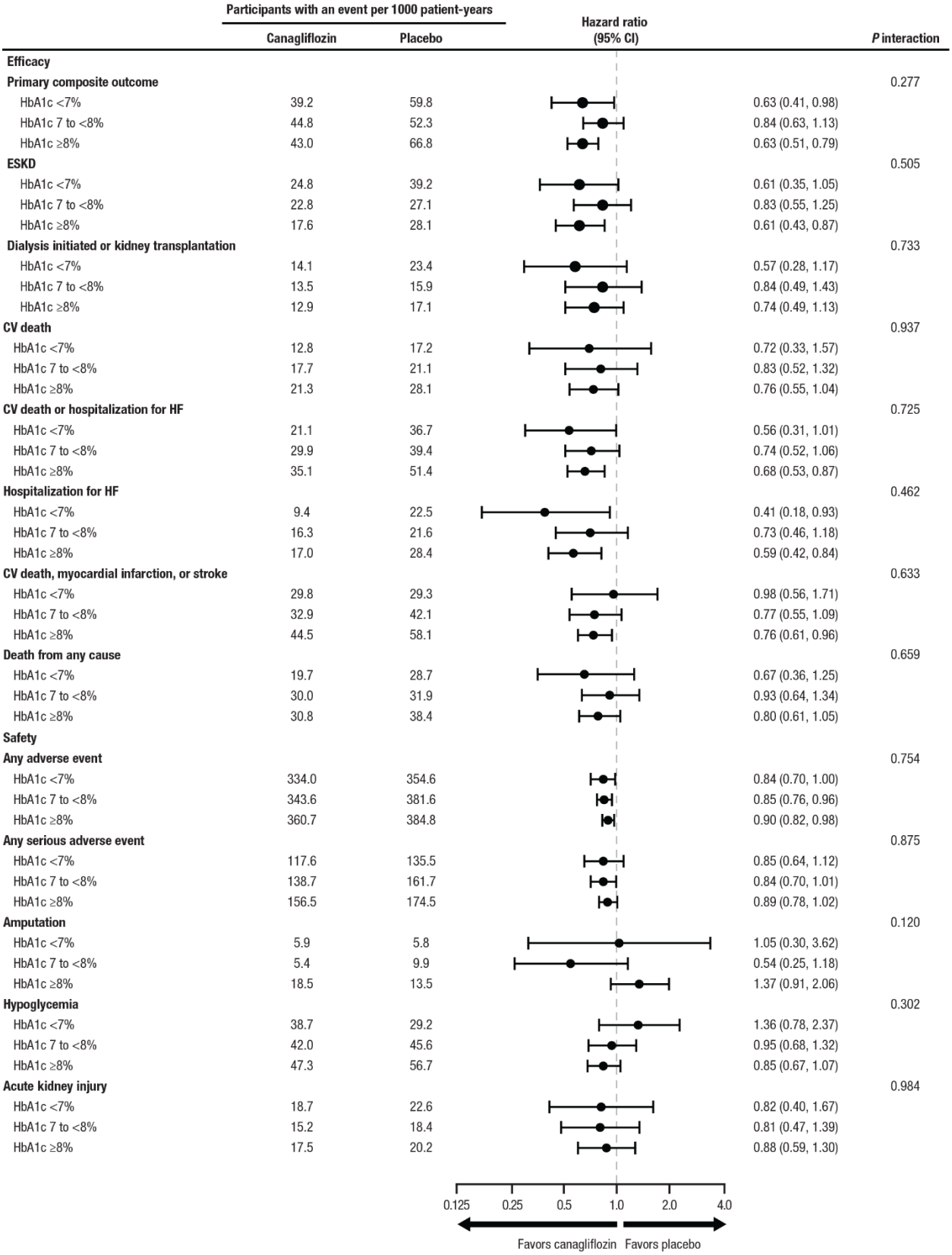
Figure. Efficacy and safety outcomes by baseline HbA1c.



CI, confidence interval; CV, cardiovascular; ESKD, end-stage kidney disease; HF, heart failure.