

Journal Pre-proof

Effects of Canagliflozin on Cardiovascular, Renal, and Safety Outcomes in Participants With Type 2 Diabetes and Chronic Kidney Disease According to History of Heart Failure: Results From the CRENCE Trial

Ashish Sarraju MD , JingWei Li PhD , Christopher P. Cannon MD , Tara I. Chang MD , Rajiv Agarwal MD , George Bakris MD , David M. Charytan MD , Dick de Zeeuw MD, PhD , Tom Greene PhD , Hidido J.L. Heerspink PharmD, PhD , Adeera Levin MD , Bruce Neal MB ChB, PhD , Carol Pollock MBBS, PhD , David C. Wheeler MD , Yshai Yavin MB ChB , Hong Zhang MD, PhD , Bernard Zinman MD , Vlado Perkovic MBBS, PhD , Meg Jardine MBBS, PhD , Kenneth W. Mahaffey MD

PII: S0002-8703(20)30407-5
DOI: <https://doi.org/10.1016/j.ahj.2020.12.008>
Reference: YMJJ 6290

To appear in: *American Heart Journal*

Received date: August 26, 2020
Accepted date: December 14, 2020

Please cite this article as: Ashish Sarraju MD , JingWei Li PhD , Christopher P. Cannon MD , Tara I. Chang MD , Rajiv Agarwal MD , George Bakris MD , David M. Charytan MD , Dick de Zeeuw MD, PhD , Tom Greene PhD , Hidido J.L. Heerspink PharmD, PhD , Adeera Levin MD , Bruce Neal MB ChB, PhD , Carol Pollock MBBS, PhD , David C. Wheeler MD , Yshai Yavin MB ChB , Hong Zhang MD, PhD , Bernard Zinman MD , Vlado Perkovic MBBS, PhD , Meg Jardine MBBS, PhD , Kenneth W. Mahaffey MD , Effects of Canagliflozin on Cardiovascular, Renal, and Safety Outcomes in Participants With Type 2 Diabetes and Chronic Kidney Disease According to History of Heart Failure: Results From the CRENCE Trial, *American Heart Journal* (2020), doi: <https://doi.org/10.1016/j.ahj.2020.12.008>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Elsevier Inc. All rights reserved.



*Research Letter***Effects of Canagliflozin on Cardiovascular, Renal, and Safety Outcomes in Participants With Type 2 Diabetes and Chronic Kidney Disease According to History of Heart Failure: Results From the CREDENCE Trial**

Ashish Sarraju, MD,¹ JingWei Li, PhD,² Christopher P. Cannon, MD,³ Tara I. Chang, MD,⁴ Rajiv Agarwal, MD,⁵ George Bakris, MD,⁶ David M. Charytan, MD,⁷ Dick de Zeeuw, MD, PhD,⁸ Tom Greene, PhD,⁹ Hiddo J.L. Heerspink, PharmD, PhD,^{2,8} Adeera Levin, MD,¹⁰ Bruce Neal, MB ChB, PhD,^{2,11} Carol Pollock, MBBS, PhD,¹² David C. Wheeler, MD,^{2,13} Yshai Yavin, MB ChB,¹⁴ Hong Zhang, MD, PhD,¹⁵ Bernard Zinman, MD,¹⁶ Vlado Perkovic, MBBS, PhD,^{2,17} Meg Jardine, MBBS, PhD,² Kenneth W. Mahaffey, MD¹

¹Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA; ²The George Institute for Global Health, UNSW Sydney, NSW, Australia; ³Cardiovascular Division, Brigham & Women's Hospital and Baim Institute for Clinical Research, Boston, MA; ⁴Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA; ⁵Indiana University School of Medicine and VA Medical Center, Indianapolis, IN; ⁶Department of Medicine, University of Chicago Medicine, Chicago, IL; ⁷Nephrology Division, NYU School of Medicine and NYU Langone Medical Center, New York, NY, and Baim Institute for Clinical Research, Boston, MA; ⁸Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; ⁹Division of Biostatistics, Department of Population Health Sciences, University of Utah, Salt Lake City, UT; ¹⁰Division of Nephrology, University of British Columbia, Vancouver, BC, Canada; ¹¹Imperial College London, London, UK; ¹²Kolling Institute of Medical Research, Sydney Medical School, University of Sydney, Royal

North Shore Hospital, St Leonards, NSW, Australia; ¹³Department of Renal Medicine, UCL Medical School, London, UK; ¹⁴Janssen Research & Development, LLC, Raritan, NJ; ¹⁵Renal Division of Peking University First Hospital, Beijing, China; ¹⁶Lunenfeld-Tanenbaum Research Institute, Mt Sinai Hospital, University of Toronto, Toronto, ON, Canada; ¹⁷The Royal North Shore Hospital, Sydney, Australia.

Short Title: CREDENCE Outcomes by Prior Heart Failure

Correspondence:

Kenneth W. Mahaffey, MD

Stanford Center for Clinical Research

300 Pasteur Drive

Stanford, CA 94305

Kenneth.Mahaffey@stanford.edu

Phone: 650-723-3096

Fax: 650-725-8381

Clinical Trial Registration: URL: <https://clinicaltrials.gov>. Unique identifier: NCT02065791

Abstract

We aimed to assess the efficacy and safety of canagliflozin in patients with type 2 diabetes and nephropathy according to prior history of heart failure in the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trial. We found that participants with a prior history of heart failure at baseline (15%) were more likely to be older, female, white, have a history of atherosclerotic cardiovascular disease, and use diuretics and beta blockers (all $P < 0.001$), and that, compared with placebo, canagliflozin safely reduced renal and cardiovascular events with consistent effects in patients with and without a prior history of heart failure (all efficacy P interaction > 0.150). These results support the efficacy and safety of canagliflozin in patients with type 2 diabetes and nephropathy regardless of prior history of heart failure.

Keywords: canagliflozin; SGLT2 inhibitor; chronic kidney disease; diabetes; heart failure

Introduction

Sodium glucose co-transporter 2 (SGLT2) inhibitors reduce the risk of cardiovascular (CV) events including hospitalization for heart failure (HHF) in patients with type 2 diabetes mellitus (T2DM) and in patients with heart failure (HF) with reduced ejection fraction (EF) independent of the presence or absence of diabetes.¹⁻⁶ Canagliflozin is an SGLT2 inhibitor that decreases renal and CV events including HHF in patients with T2DM and nephropathy.⁴ In this population that is at elevated risk for adverse outcomes, it remains uncertain whether CV and renal benefits and safety outcomes of canagliflozin are preserved regardless of prior history of HF. We tested whether canagliflozin safely decreases CV and renal events in participants with T2DM and nephropathy with and without a prior history of HF before randomization in the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trial.

Materials and Methods

CREDENCE was a multicenter, double-blind, randomized trial of canagliflozin in participants with T2DM and nephropathy (ClinicalTrials.gov identifier: NCT02065791).⁴ As detailed previously, 4401 participants with hemoglobin A1c between 6.5% to 12.0%, an estimated glomerular filtration rate (eGFR) of 30 to <90 mL per minute per 1.73 m² of body surface area and elevated albuminuria (urinary albumin:creatinine ratio, >300 to 5000 mg/g) were randomized to canagliflozin 100 mg or placebo. Patients were required be on a stable dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks prior to randomization. Patients with New York Heart Association (NYHA) Class IV HF or on

mineralocorticoid receptor antagonist or direct renin inhibitor therapy were excluded. History of HF and NYHA class were recorded by local site investigators at the time of study entry. After identification of increased amputation risk in another canagliflozin trial, a CREDENCE protocol amendment was performed in May 2016, at which time approximately 75% of the study had been enrolled, for which investigators were asked to examine patients' feet and exclude patients with risks for amputation from treatment.^{2,4} The study was approved by the applicable regulatory authorities and ethics committees, and participants provided informed consent.

Categorical variables were summarized as the number of patients with corresponding percentages, and continuous variables were summarized as the mean and standard deviation. Differences in baseline characteristics between participants with a prior history of HF compared with participants without a prior history of HF were evaluated using a χ^2 test for categorical variables, a t test for continuous normally distributed variables, and a Wilcoxon 2-sample test for continuous variables with a skewed distribution (distributions were evaluated using an Anderson–Darling test). In an intention-to-treat approach, prespecified CV, renal, and safety outcomes were analyzed using Cox proportional hazards regression in participants with and without a history of HF and in participants with HF stratified by NYHA class. Homogeneity of treatment effects was tested using *P* values for interaction without adjustment for multiple comparisons and results were interpreted in the context of multiple post hoc analyses performed. Analyses were performed using SAS Enterprise Guide version 7.1, and STATA version 13.1.

Results

A total of 652 (15%) participants had a history of HF. Participants with prior history of HF were older (65 years vs 63 years), were more likely to be white (88% vs 63%) and female (39% vs 33%), had a shorter mean duration of diabetes (15 years vs 16 years), had a similar eGFR (57 mL/min/1.73 m² vs 56 mL/min/1.73 m²), and had a higher prevalence of established atherosclerotic CV disease (81% vs 45%) compared to those without prior history of HF (**Table I**). More participants with prior history of HF were on beta-blockers (60.6% vs 36.7%) and loop diuretics (40.5% vs 18.4%). Among participants with a history of HF, 204 (31%) had NYHA Class I HF, 359 (55%) had NYHA Class II HF, 70 (11%) had NYHA Class III HF, and 19 (3%) had missing NYHA class information at baseline.

Overall, compared with placebo, canagliflozin significantly reduced the risk of the primary composite outcome, composite of CV death and HHF, and HHF alone in CREDENCE.⁴ Participants with a prior history of HF had higher CV event rates during the study compared to those without (**Figure 1**). Canagliflozin consistently reduced events, including the primary composite endpoint, CV death or HHF, HHF alone, and renal outcomes compared with placebo in participants with and without a history of HF (all *P* interaction >0.150). In participants with HF stratified by NYHA class, canagliflozin reduced the risk of the primary composite endpoint compared with placebo with no evidence of heterogeneity of treatment effect by NYHA class subgroup (*P* interaction 0.227). In those without a prior history of HF, the Number Needed to Treat (NNT) was 20 for the primary composite outcome, 28 for CV death or HHF, and 45 for HHF alone.

Canagliflozin use led to significantly decreased risk of all adverse events (AEs) compared with placebo though with some evidence of treatment effect heterogeneity by prior history of HF (P interaction 0.024; **Figure 2**). Canagliflozin resulted in significantly lower risk of serious AEs and renal-related AEs compared with placebo with consistent effects in patients with or without prior HF (P interaction >0.50). Across additional safety outcomes including amputation, fracture, osmotic diuresis, and volume depletion, there were no significant differences between patients randomized to canagliflozin or placebo, with consistent effects in patients with or without prior HF (P interaction >0.06).

Sources of Funding

This study was supported by Janssen Research & Development, LLC.

Discussion

Overall, canagliflozin safely reduced renal and CV events in participants with T2DM and nephropathy with consistent effects in patients with or without a prior history of HF. In patients without a prior history of HF, canagliflozin use was associated with robust effect sizes for the reduction of CV death and HHF and HHF alone. There is accumulating evidence regarding SGLT2 inhibitor efficacy specifically in patients with HF, including in patients with HF with reduced EF in the published Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial and the recently completed Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-REDUCED) trial, which met its primary endpoint, as well as the recent SOLOIST-WHF trial in patients with T2DM and HF with reduced and preserved EF.⁵⁻⁷ Several trials are ongoing in patients with HF with preserved

EF.⁸ Our present findings support the initiation of canagliflozin in patients with T2DM and nephropathy for CV and renal outcome benefit regardless of a prior history of HF. Our findings align with 2019 European Society of Cardiology guidelines that recommend SGLT2 inhibitor initiation in patients with T2DM and proteinuria given elevated CV risk.⁹

In the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program Analysis, the benefit of canagliflozin on CV death or HHF compared with placebo was potentially greater in those with a prior history of HF compared to those without.¹⁰ This finding was not matched in the present CREDENCE analysis. It is unclear whether this is due to differences in population characteristics or HF classification or findings due to chance.

Strengths of this study include rigorous trial conduct and outcome adjudication by independent committees blinded to trial arm assignment. Findings may be limited by low numbers of events among participants with prior history of HF and considered hypothesis-generating. Classification of history of HF was not verified by study investigators, and EF information, echocardiography data, or baseline HF biomarker data were not collected. There may therefore be misclassification of patients regarding the presence or absence of a prior history of HF, and the study is unable to differentiate between prior HF with reduced versus preserved EF.

In conclusion, canagliflozin safely reduced renal and CV events in patients with T2DM and nephropathy with consistent effects in patients with or without a prior history of HF. These

results support the initiation of canagliflozin for CV and renal benefit in patients with T2DM and nephropathy regardless of a prior history of HF.

Acknowledgments

We thank all participants, investigators, and trial teams for their participation in the trial.

CREDENCE was sponsored by Janssen Research & Development, LLC, and was conducted collaboratively by the sponsor, an academic-led Steering Committee, and an Academic Research Organization, George Clinical. Analyses were performed by George Clinical and independently confirmed by the sponsor. Technical editorial assistance was provided by Dana Tabor, PhD, of MedErgy, and was funded by Janssen Scientific Affairs, LLC.

Data Access and Analysis

Ashish Sarraju had full access to the data in the study and takes responsibility for its integrity and the data analysis.

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.

CRedit Author Statement

Ashish Sarraju: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Visualization

JingWei Li: Methodology, Formal analysis, Writing – Review & Editing

Christopher P. Cannon: Investigation, Writing – Review & Editing

Tara I. Chang: Investigation, Writing – Review & Editing

Rajiv Agarwal: Investigation, Writing – Review & Editing

George Bakris: Investigation, Writing – Review & Editing

David M. Charytan: Investigation, Writing – Review & Editing

Dick de Zeeuw: Investigation, Writing – Review & Editing

Tom Greene: Investigation, Writing – Review & Editing

Hiddo J.L. Heerspink: Investigation, Writing – Review & Editing

Adeera Levin: Investigation, Writing – Review & Editing

Bruce Neal: Investigation, Writing – Review & Editing

Carol Pollock: Investigation, Writing – Review & Editing

David C. Wheeler: Investigation, Writing – Review & Editing

Yshai Yavin: Investigation, Writing – Review & Editing

Hong Zhang: Investigation, Writing – Review & Editing

Bernard Zinman: Investigation, Writing – Review & Editing

Vlado Perkovic: Investigation, Writing – Review & Editing

Meg Jardine: Conceptualization, Methodology, Investigation, Writing – Review & Editing,
Supervision

Kenneth W. Mahaffey: Conceptualization, Methodology, Investigation, Writing – Review & Editing, Supervision

Declaration of Interest

Ashish Sarraju has nothing to disclose.

JingWei Li has nothing to disclose.

Christopher P. Cannon has received research grants from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Merck, Janssen, and Pfizer; and has received consulting fees from Aegerion, Alnylam, Amarin, Amgen, Applied Therapeutic, Ascendia, Boehringer Ingelheim, Bristol-Myers Squibb, Corvidia, HLS Therapeutics, Innovent, Janssen, Kowa, Merck, Pfizer, and Sanofi.

Tara I. Chang has received funding paid by Janssen Pharmaceuticals to Stanford University for serving as a national leader for CREDENCE; has served as a consultant for Bayer, Janssen Pharmaceuticals, Novo Nordisk, Fresenius Medical Care, Tricida, Gilead and AstraZeneca; and has received grant support from Satellite Healthcare.

Rajiv Agarwal has received research funding from GlaxoSmithKline; has received personal fees from Akebia, Bayer, Johnson & Johnson, Boehringer Ingelheim, Takeda, Daiichi Sankyo, Amgen, AstraZeneca, Sanofi, Celgene, Reata, Relypsa, GlaxoSmithKline, Gilead, ER Squibb and Sons, Fresenius, Ironwood Pharmaceuticals, Otsuka, Opko, and Eli Lilly; and has served as

associate editor of the *American Journal of Nephrology* and *Nephrology Dialysis Transplantation* and as an author on UpToDate.

George Bakris has received research funding paid to the University of Chicago for serving as principal investigator on national clinical trials for Bayer, Janssen, AbbVie, Novo Nordisk, Takeda, and CVRX; has served as a consultant for Merck, Relypsa, Boehringer Ingelheim, Takeda, NxStage Medical, Sanofi, Daiichi Sankyo, AbbVie, Pfizer, Eli Lilly, Novo Nordisk, and AstraZeneca; has served on a steering committee for Vascular Dynamics; has served as editor of the *American Journal of Nephrology* and *Nephrology*, as editor-in-chief of UpToDate, and as Nephrology and Hypertension section editor of UpToDate; and as associate editor of *Diabetes Care*, *Hypertension Research*, and *Nephrology Dialysis Transplantation*.

David M. Charytan has received fees paid by Janssen Pharmaceuticals to the Baim Institute for work on the CREDENCE trial steering committee and as scientific lead; he received salary support from the Baim Institute for this work through October 2018. After that time, he received consulting fees from Baim. He has consulted for Amgen, AstraZeneca, Medtronic/Covidien, Zoll, Fresenius, Daiichi Sankyo, Douglas and London, Eli Lilly, Merck, Gilead, GlaxoSmithKline, and Novo Nordisk; has served on data safety and monitoring boards for AstraZeneca and Allena Pharmaceuticals; and has served on a CEC for Merck and PLC Medical.

Dick de Zeeuw has served on advisory boards and/or as speaker for Bayer, Boehringer Ingelheim, Fresenius, Mundipharma, and Mitsubishi 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.

Tom Greene has served as a consultant for Janssen, Durect, and AstraZeneca; and has received grant support from CSL and Boehringer Ingelheim.

Hiddo J.L. Heerspink has served as 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.

Adeera Levin serves as a scientific advisor to Boehringer Ingelheim, AstraZeneca, Reata, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); is chair of the data safety and monitoring board for NIDDK and Kidney Precision Medicine; is an advisor for the University of Washington Kidney Research Institute Scientific Advisory Committee; and is funded by the Canadian Institute of Health Research and Kidney Foundation of Canada. She is on the steering committee for CREDENCE; and has received fees for time as CREDENCE national coordinator from Janssen, directed to her academic team.

Bruce Neal is supported by an Australian National Health and Medical Research Council Principal Research Fellowship; holds a research grant for this study from Janssen; and has held research grants for other large-scale cardiovascular outcome trials from Roche, Servier, and Merck Schering-Plough. His institution has received consultancy, honoraria, or travel support for

contributions he has made to advisory boards and/or the continuing medical education programs of Abbott, Janssen, Novartis, Pfizer, Roche, and Servier.

Carol Pollock has received honoraria for serving on advisory boards and as a speaker for Merck Sharpe & Dohme, AstraZeneca, and Boehringer Ingelheim/Eli Lilly.

David C. Wheeler has received consultancy fees from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck Sharpe and Dohme, Mitsubishi, Mundipharma, Napp, Ono Pharma, Reata, Tricidia, and Vifor Fresenius.

Yshai Yavin is a full-time employee of Janssen Research & Development, LLC.

Hong Zhang has received consulting fees from Janssen.

Bernard Zinman has served as a consultant and received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi; and has received grant support from Boehringer Ingelheim, Novo Nordisk, and AstraZeneca.

Vlado Perkovic has received fees for advisory boards, steering committee roles, or scientific presentations from AbbVie, Astellas, Astra Zeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Dimerix, Durect, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Pfizer, PharmaLink, Relypsa, Retrophin, Sanofi, Servier, Vifor, and Tricida.

Meg Jardine is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research projects that have received unrestricted funding from Baxter, Amgen, Eli Lilly, and Merck Sharpe & Dohme; serves on a steering committee sponsored by CSL; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim, and Vifor; and has spoken at scientific meetings sponsored by Janssen, with any consultancy, honoraria, or travel support paid to her institution.

Kenneth W. Mahaffey has received research support from Afferent, Amgen, Apple, Inc, AstraZeneca, Cardiva Medical, Inc, Daiichi Sankyo, Ferring, Google (Verily), Johnson & Johnson, Luitpold, Medtronic, Merck, National Institutes of Health (NIH), Novartis, Sanofi, St. Jude, and Tenax; and has served as a consultant (speaker fees for continuing medical education events only) for Abbott, Ablynx, AstraZeneca, Baim Institute, Boehringer Ingelheim, Bristol-Myers Squibb, Elsevier, GlaxoSmithKline, Johnson & Johnson, MedErgy, Medscape, Mitsubishi, MyoKardia, NIH, Novartis, Novo Nordisk, Portola, Radiometer, Regeneron, Springer Publishing, and the University of California, San Francisco.

References

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657.

3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.
4. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med.* 2019;380(24):2295-2306.
5. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008.
6. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med.* 2020;doi: 10.1056/NEJMoa2030183.
7. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med.* 2020;383(15):1413-1424.
8. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc.* 2019;8(20):e013389.
9. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J.* 2019.
10. Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program. *Circulation.* 2018;138(5):458-468.

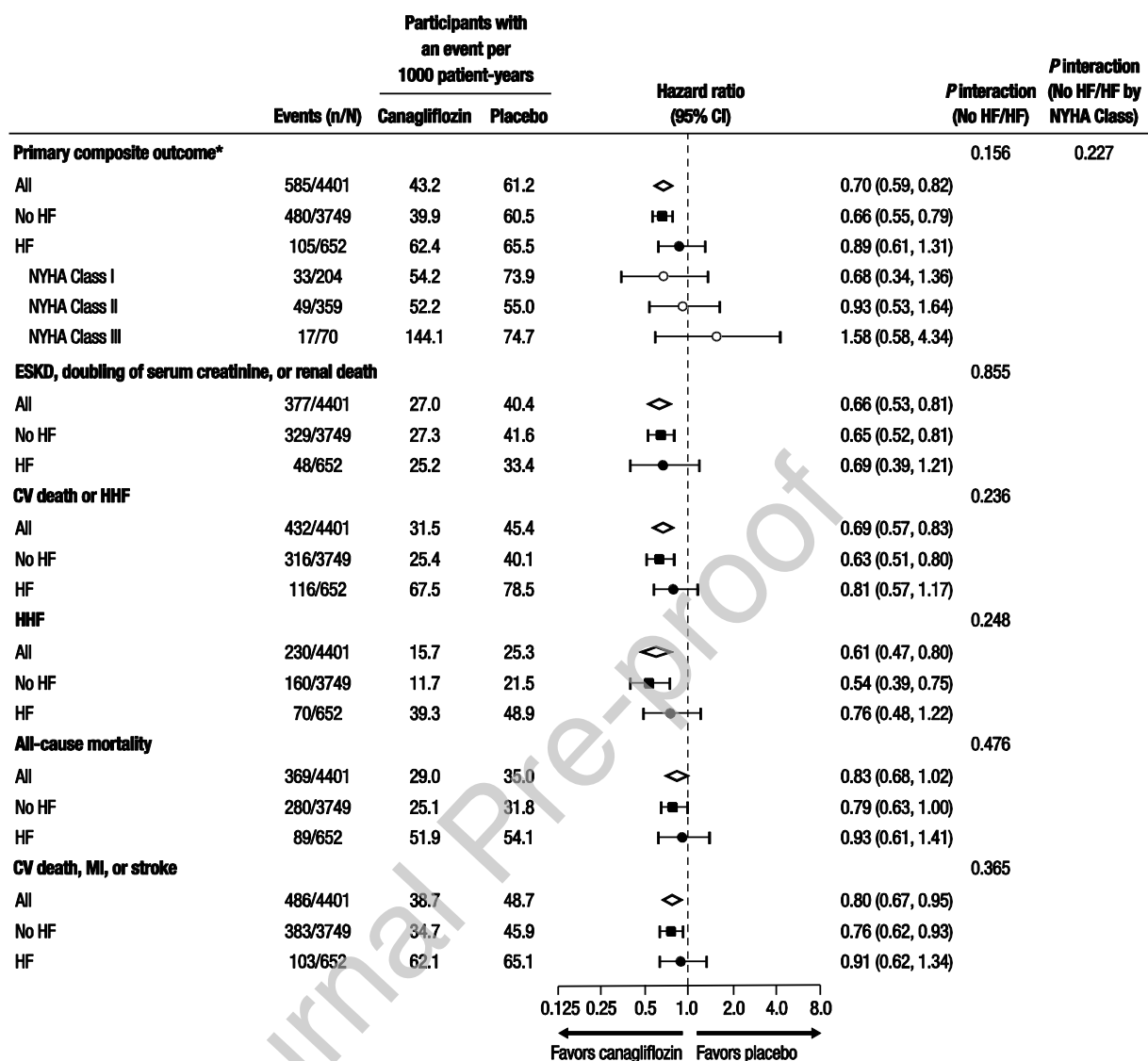


Figure 1. Efficacy outcomes by prior history of HF.

HF, heart failure; CI, confidence interval; NYHA, New York Heart Association; ESKD, end-stage kidney disease; CV, cardiovascular; HHF, hospitalization for heart failure; MI, myocardial infarction.

*ESKD, doubling of serum creatinine, or renal or CV death.

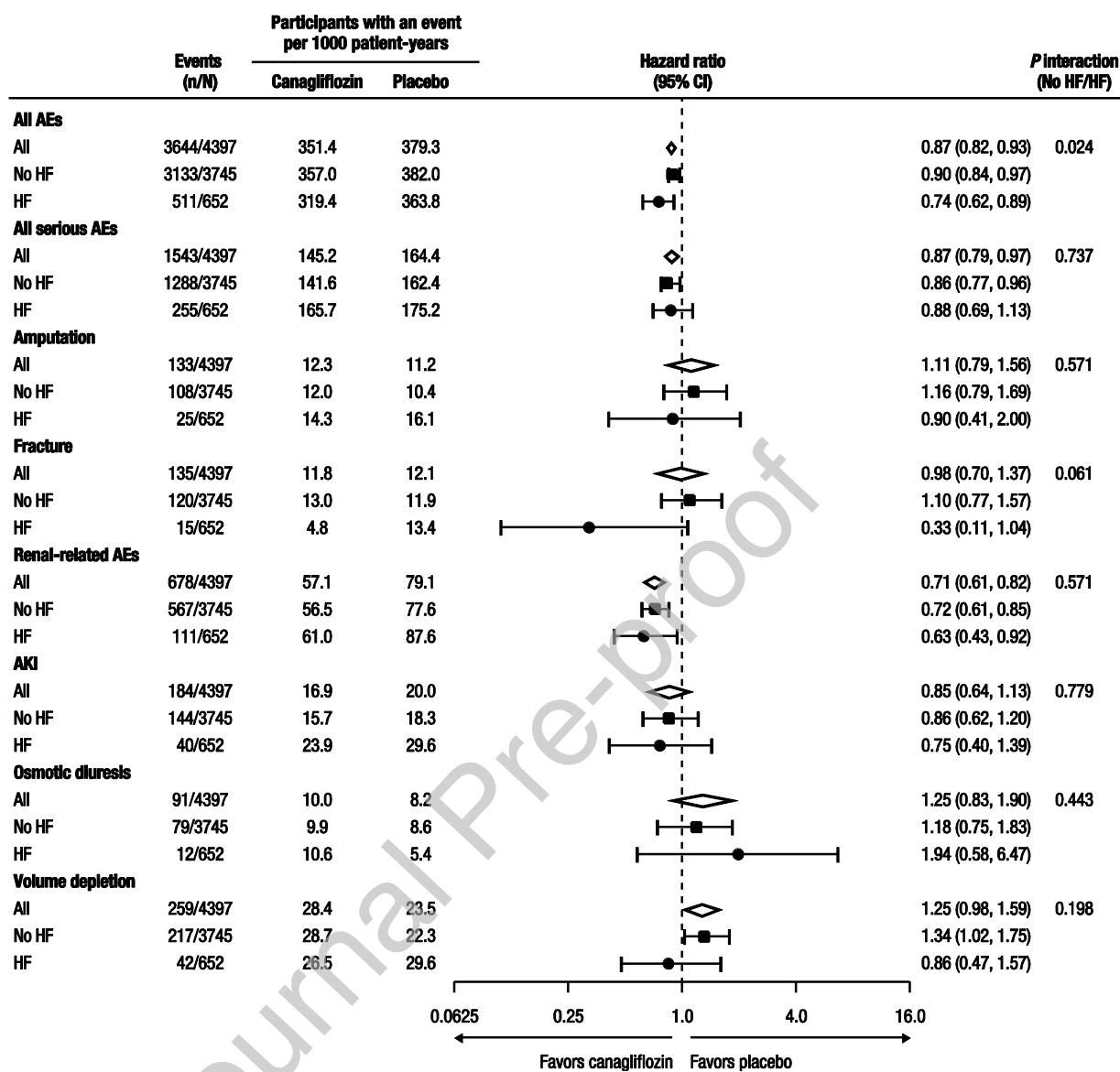


Figure 2. Safety outcomes by prior history of HF.

HF, heart failure; CI, confidence interval; AE, adverse event; AKI, acute kidney injury.