Received: 11 June 2023 | Revised: 7 July 2023 | Accepted: 19 July 2023

DOI: 10.1111/dom.15232

ORIGINAL ARTICLE

WILEY

Estimated lifetime benefit of novel pharmacological therapies in patients with type 2 diabetes and chronic kidney disease: A joint analysis of randomized controlled clinical trials

Hiddo J. L. Heerspink PhD[1,2] | Priya Vart PhD[1] | Niels Jongs PhD[1] | Brendon L. Neuen MD[2] | George Bakris MD[3] | Brian Claggett PhD[4] | Muthiah Vaduganathan MD[4] | Finnian McCausland MD[4] | Kieran F. Docherty MBChB[5] | Pardeep S. Jhund PhD[5] | Scott D. Solomon MD[4] | Vlado Perkovic PhD[2,6] | John J. V. McMurray MD[5]

[1]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

[2]The George Institute for Global Health, Sydney, Australia

[3]American Heart Association Comprehensive Hypertension Center, University of Chicago Medicine and Biological Sciences, Chicago, Illinois, USA

[4]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[5]BHF Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

[6]University of New South Wales, Sydney, Australia

Correspondence
Hiddo J.L. Heerspink, Department Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Hanzeplein 1, 9700 RB Groningen, Netherlands.
Email: h.j.lambers.heerspink@umcg.nl

Funding information
Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Grant/Award Number: 917.15.306

Abstract

Aim: To estimate the lifetime benefit of a combination treatment of sodium-glucose co-transporter 2 (SGLT2) inhibitors and mineralocorticoid-receptor antagonists (MRA) in patients with type 2 diabetes and chronic kidney disease (CKD).

Materials and Methods: The cumulative effect of combination treatment was derived from trial-level estimates of the effect of an SGLT2 inhibitor (canagliflozin) and MRA (finerenone) from the CREDENCE (N = 4401) and FIDELIO (N = 5734) trials, respectively. The cumulative effect was applied to the control group of patients with type 2 diabetes in the DAPA-CKD trial (N = 1451) to estimate long-term gains in event-free and overall survival. The analysis was repeated in an observational study. The primary outcome was a composite endpoint of doubling of serum creatinine, end-stage kidney disease or death because of kidney failure.

Results: The hazard ratio of combination treatment for the primary outcome was 0.50 [95% confidence interval (CI): 0.44, 0.57]. At age 50 years, the estimated event-free survival from the primary outcome was 16.7 years (95% CI: 18.1, 21.0) with combination treatment versus 10.0 years (95% CI: 6.8, 12.3) with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers resulting in an incremental gain of 6.7 years (95% CI: 5.5, 7.9). In an observational study, the estimated gain in event-free survival regarding primary outcome was 6.3 years (95% CI: 5.2, 7.3). In a conservative scenario, assuming low adherence (70% of the observed adherence) and less pronounced efficacy (70% of the observed efficacy with 2% yearly decline) of combination therapy, gain in event-free survival regarding primary outcome was 2.5 years (95% CI: 2.0, 2.9).

Conclusions: Combined disease-modifying treatment with an SGLT2 inhibitor and MRA in patients with type 2 diabetes and CKD may substantially increase the number of years free from kidney failure and mortality.

KEYWORDS
chronic kidney disease, mineralocorticoid receptor antagonist, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

The recommended treatment for patients with type 2 diabetes and chronic kidney disease (CKD) consists of lifestyle modification, optimization of glycaemic control, and treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).[1] Despite showing that ARBs reduce the risk of heart and kidney failure in patients with type 2 diabetes and CKD,[2,3] the residual risk of kidney failure and cardiovascular complications remains substantial for many patients. In the past 3 years, two new pharmacological treatment classes have been shown to improve further the outcomes in patients with type 2 diabetes and CKD. The first of these was sodium-glucose cotransporter 2 (SGLT2) inhibitors[4,5] followed by the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone.[6] The benefits on cardiovascular and kidney outcomes with these new drug classes were proven on top of maximal tolerated doses of ACE inhibitors or ARBs in the respective clinical trials. Moreover, in a recent clinical trial, the combination of an SGLT2 inhibitor and MRA resulted in a complete additive effect on albuminuria and blood pressure compared with either therapy alone suggesting the combination may reduce the risk of kidney failure more than either therapy alone.[7] Importantly, in this trial, no safety concerns were observed. On the contrary, the potassium level and incidence of hyperkalaemia was lower with combination treatment compared with MRA treatment.[7]

Despite these advances, the implementation of these proven therapies in routine clinical practice is slow. Observational studies and registries around the world have frequently shown that the use of ACE inhibitors and ARBs remains low, and the uptake of SGLT2 inhibitors in patients with type 2 diabetes in the high-risk group, such as those with heart failure or CKD, is modest.[8,9] In addition, under-prescription of these agents in patients from minority ethnic groups, low socioeconomic status groups, or both, may lead to further exacerbation of the well-described disparities in kidney and cardiovascular outcomes.

Clinical trials that showed the benefit of these new therapies followed patients for approximately 2.5 years, while in clinical practice, patients typically are treated over a lifetime. Translation of the observed relative risk reduction in clinical trials to an estimated lifetime benefit may be easier to understand for patients and may enhance patient-clinician dialogue, increase uptake of these therapies in clinical practice and inform decision making by policymakers and payers.[10]

We therefore estimated the cumulative benefit of two new drug classes, SGLT2 inhibitors and MRA versus conventional therapy in patients with type 2 diabetes and CKD by making indirect comparisons of two randomized controlled clinical trials using a previously validated methods from cardiology trials.[11,12] We applied this method to estimate the relative risk reduction with combined treatment and, subsequently, to estimate the lifetime benefit assuming constant treatment effects over time. We repeated these analyses using data from an observational cohort study and for several conservative scenarios anticipating a lower treatment adherence and efficacy in the real world.

2 | MATERIALS AND METHODS

The efficacy and safety of canagliflozin and finerenone were compared with placebo and added to standard care was tested in patients with type 2 diabetes and CKD in the CREDENCE and FIDELIO trials respectively. The data underlying the findings described in this article may be obtained upon publication in accordance with Janssen's and Bayer's data sharing policy.

2.1 | Overall study design

In this study, using overall trial-level estimates from pivotal placebo-controlled randomized clinical trials that assessed the efficacy and safety of an SGLT2 inhibitor and MRA, the cumulative effect of combined pharmacological treatment compared with conventional therapy with an ACE inhibitor or ARB was estimated. We selected all pivotal phase 3 clinical trials enrolling patients with type 2 diabetes and CKD that showed a significant risk reduction in the primary kidney outcome with the new and currently approved pharmacological intervention. The CREDENCE (clinicaltrials.gov NCT02065791),[4] FIDELIO-DKD (NCT02540993)[6] and DAPA-CKD (NCT03036150)[5] trials met these criteria and were included. Data from an observational cohort study, i.e. the Chronic Renal Insufficiency Cohort (CRIC) Study, was utilized to assess the robustness of our results in non-clinical settings.[13] Participants enrolled in each trial and the CRIC Study provided written consent. Details of included clinical trials and observational study are presented in Appendix S1. The study protocol of each clinical trial and the CRIC Study was approved by the institutional review board at each participating site and participants provided written informed consent.

2.2 | Clinical outcomes

The primary endpoint was a composite of a sustained doubling of serum creatinine, end-stage kidney disease [ESKD defined as a

sustained estimated glomerular filtration rate (eGFR) ≤15 mL/min/1.73 m^2, initiation of dialysis for at least 30 days, or kidney transplantation], or death because of kidney failure. The secondary outcome was ESKD. Heart failure hospitalization and all-cause mortality were examined as additional endpoints. These outcomes were adjudicated by independent event adjudication committees in all trials using pre-defined rigorous endpoint definitions. For the actuarial analysis, event-free survival was estimated for the primary composite renal endpoint, ESKD, heart failure hospitalization and all-cause mortality.

2.3 | Statistical methods

We obtained from each trial the individual treatment effects and estimated the 95% confidence interval (CI) for the combined effect from the square root of the sum of squared standard errors of the individual logarithmic hazard ratios (HRs).[14,15] Given that no heterogeneity was noted in the effect of the SGLT2 inhibitor or MRA across any of the key subgroups, including age, we used reported estimates of treatment effect for the overall population in a clinical trial to derive their combined effect. Using these estimates and previously validated methods,[11–16] we estimated the average duration of event-free survival from non-parametric Kaplan-Meier estimates while using age (at baseline and at the time of an event or death) as the time component rather than time from randomization. In this approach, the area under the survival curve reflects event-free and overall survival for an average patient of a given age and allows estimation of the long-term treatment effect.[11,12,16] We used data of patients with type 2 diabetes in the placebo group of the DAPA-CKD trial to obtain event-free survival with and without combination treatment. To obtain event-free survival with the combination treatment, we applied the combined treatment effect to the non-parametric Kaplan-Meier estimates of the conventional treatment and recalculated area under the curve.

Because most patients in our study were between the ages of 50 and 70 years, we calculated and compared event-free survival and overall survival between conventional and combination treatment for every age between 50 and 70 years with a starting age of 50 years. Survival benefits were estimated until the age of 80 years. To plot the survival gain, estimated survival gains were smoothened in a locally weighted smoothing procedure as described previously.[17]

We calculated the effect of comprehensive pharmacological treatment versus conventional treatment on the primary composite kidney outcome in subgroup of patients defined by baseline age (<65/≥65 years), sex (male/female), eGFR (<45/≥45 mL/min/1.73 m^2), UACR (≤1000/>1000 mg/g) and glycated haemoglobin (≤7.5%/>7.5%) using the subgroup-specific treatment effect from each trial. For this individual patient, data from each clinical trial were obtained and subsequently event-free survival and survival gain in each subgroup was estimated. Among patients <65 years, survival gain was estimated between 35 and 64 years and among patients ≥65 years, survival gain was estimated between 65 and 95 years.

We performed several additional analyses to assess the robustness of our findings. First, we investigated event-free survival gain regarding the primary outcome in the CRIC Study. Secondly, we performed analyses to assess the impact of possible non-additive effects of the individual treatments, the impact of non-adherence beyond the duration of the clinical trial, and the influence of a possible non-constancy of treatment effect over time. Details of these analyses are described in Appendix S2. Finally, we applied the combined treatment effect to the placebo group of the CREDENCE trial rather than to the patients with diabetes in the placebo group of the DAPA-CKD trial.

All analyses were done using Stata 17 (StataCorp. 2021; Stata Statistical Software: Release 17; StataCorp LLC). $p < .05$ was considered statistically significant.

TABLE 1 Baseline patient characteristics and background medical therapy

Characteristics	CREDENCE (N = 4401)	FIDELIO (N = 5674)
Treatment	Canagliflozin vs. placebo	Finerenone vs. placebo
Enrolment period	2014-2017	2015-2018
Age, years	63.0 ± 9.2	65.6 ± 9.1
Female sex, n (%)	494 (33.9)	1691 (29.8)
Race, n (%)		
White	2931 (66.6)	3592 (63.3)
Black	224 (5.1)	264 (4.7)
Asian	877 (19.9)	1440 (25.4)
Other	369 (8.4)	378 (6.7)
Systolic blood pressure, mmHg	140.0 (15.6)	138.0 (14.4)
Diastolic blood pressure, mmHg	78.3 (9.4)	76 (10)
HbA1c, %	8.3 (1.3)	7.7 (1.3)
eGFR, mL/min/1.73 m^2	56.2 ± 18.2	44.3 ± 12.6
Urinary albumin/creatinine ratio, mg/g	927 (463–1833)	852 (446–1634)
Baseline medications		
ACE inhibitors, n (%)	1922 (43.7)	1942 (34.2)
ARB, n (%)	2480 (56.4)	3725 (65.7)
Diuretics, n (%)	2057 (46.7)	3214 (56.6)
Insulin, n (%)	2884 (65.5)	3637 (64.1)
Statin, n (%)	3036 (69.0)	4215 (74.3)

Note: Data are reported as mean (SD) except for urinary albumin/creatinine ratio, which is reported as median (25th-75th percentile). Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

3 | RESULTS

The patient characteristics of the CREDENCE (N = 4401), and FIDELIO-DKD (N = 5674) trials are shown in Table 1. The mean age was 63.0 and 65.6 years, mean eGFR was 56.2 and 44.3 mL/

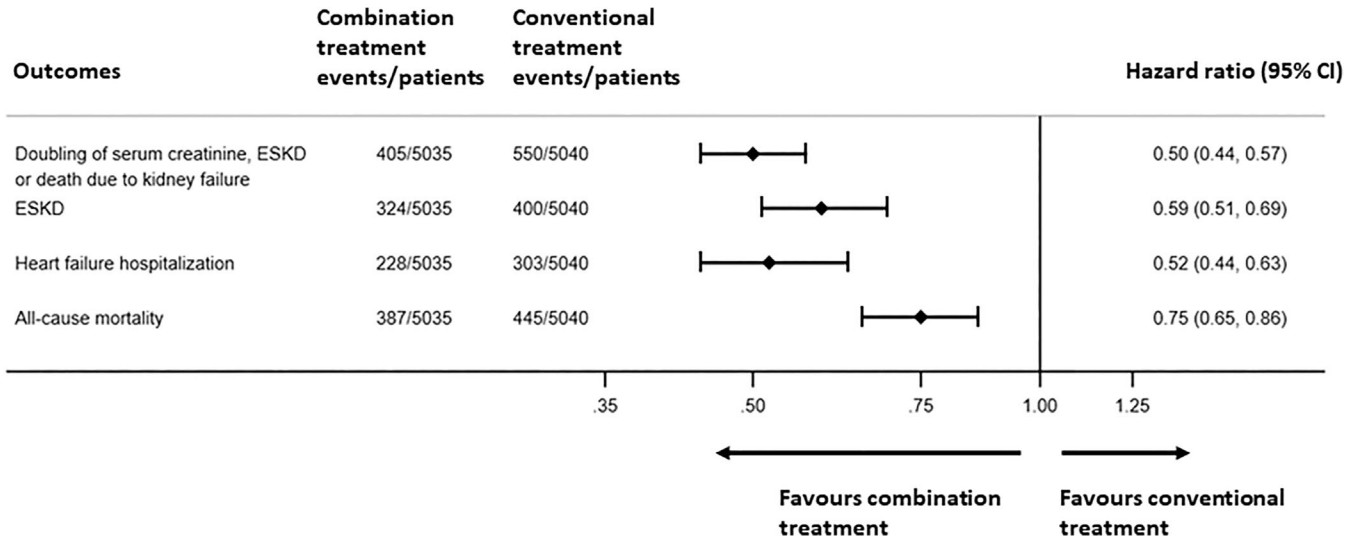

FIGURE 1 Estimated relative treatment effects of combination disease-modifying pharmacological treatment on key endpoints. ESKD, end-stage kidney disease.

min/1.73 m^2, and median UACR was 927 mg/g and 801 mg/g in CREDENCE and FIDELIO-DKD, respectively. An ACE inhibitor or ARB was prescribed for all participants.

The HR for the derived treatment effect of a combination of an SGLT2 inhibitor (canagliflozin) and MRA (finerenone) as an adjunct to conventional treatment (ACE inhibitor or ARB) versus conventional treatment alone on the primary composite kidney endpoint was 0.50 (95% CI 0.44, 0.57; Figure 1). The HRs for the effect of combined pharmacological treatment versus conventional treatment on ESKD, hospitalization for heart failure and all-cause mortality were 0.59 (95% CI 0.51, 0.69), 0.52 (95% CI 0.44, 0.63) and 0.75 (95% CI 0.65, 0.86), respectively (Figure 1). The HRs of monotherapy with canagliflozin and finerenone for each outcome are presented in Figure S1.

We estimated the survival in 1451 patients with type 2 diabetes and CKD in the placebo group of the DAPA-CKD trial. Their mean age at baseline was 64.7 years (SD 9.5); 980 (67.5%) were men, 790 participants (54.4%) were white and 451 (31.1%) Asian. The mean ± SD eGFR was 43.6 ± 12.6 mL/min/1.73 m^2 and the median UACR was 1004 mg/g (interquartile interval: 492-2018). An ACE inhibitor or ARB was prescribed in nearly all participants [N = 1412 (97.3%; Table S1)]. In this cohort, 173 patients (11.9%) experienced the primary composite kidney outcome during a median follow-up of 2.1 years [event rate 6.0 events per 100 patient-years (95% CI 5.2, 7.0)]. During follow-up, 109 (7.5%) patients progressed to ESKD [3.7 per 100 patient-years (95% CI 3.1, 4.5)], 64 patients were hospitalized for heart failure [2.1 per 100 patient-years (95% CI 1.6, 2.6)] and 113 (7.8%) died [3.5 per 100 patient-years (95% CI 2.9, 4.2)].

The aggregate treatment effect of comprehensive pharmacological treatment was estimated to result in an absolute risk reduction of 7.7-10.1% over 3 years, with a corresponding number needed to treat of 10-13 to prevent one primary kidney outcome. Absolute risk reductions in ESKD, heart failure hospitalization and all-cause mortality with combined disease-modifying treatment were estimated to be 3.7%-6.0%, 1.0%-2.8% and 1.6%-4.1% over 3 years, respectively.

For patients starting treatment at age 50 years, the estimated survival free from the primary composite kidney outcome was 16.7 years (95% CI 15.5, 17.9) with combined and 10.0 years (95% CI 6.8, 12.3) with conventional treatment corresponding to a gain of 6.7 years (95% CI 5.5, 7.9; Figure 2). The SGLT2 inhibitor contributed 4.1 years (2.1, 6.2) to the survival gain while MRA was 2.7 years (1.0, 4.2). The combined pharmacological treatment was estimated to lead to an incremental gain of 4.8 (95% CI 3.5, 6.0) years in ESKD-free survival [19.3 years (95% CI 17.9, 20.4) vs. 14.4 years (95% CI 10.5, 17.1); Figure 3] and 3.1 (95% CI 2.3, 3.7) years incremental gain in survival free from heart failure hospitalization (event-free survival with combined pharmacological therapy 26.0 years (95% CI 25.2, 26.6) and 22.9 years (95% CI 19.1, 24.6) with the ACE inhibitor or ARB treatment; Figure S2). The estimated overall survival was 22.1 years (95% CI 21.2, 23.0) with the combined treatment and 20.1 years (95% CI 15.9, 21.3) with conventional treatment [difference 2.0 years (95% CI 1.1, 2.9); Figure S3]. At age 50 years, the combined pharmacological treatment was also estimated to lead to an incremental gain of 5.2 (95% CI 4.2, 6.3) years from the composite endpoint of doubling serum creatinine, ESKD or all-cause mortality and 3.8 (95% CI 3.0, 4.8) years from the composite cardiovascular endpoint (Figures S4 and S5, respectively).

As expected, there was greater gain among younger patients compared with older patients because of their anticipated longer life expectancy (Figure 2). With combined pharmacological treatment, a 60-year old patient was estimated to gain 3.2 additional years (95% CI 2.7, 3.7; Figure 2B) and a 70-year old was estimated to gain 1.1 additional years (95% CI 0.9, 1.2) free of the composite primary kidney outcome (Table S2). These numbers for ESKD are presented in Table S3.

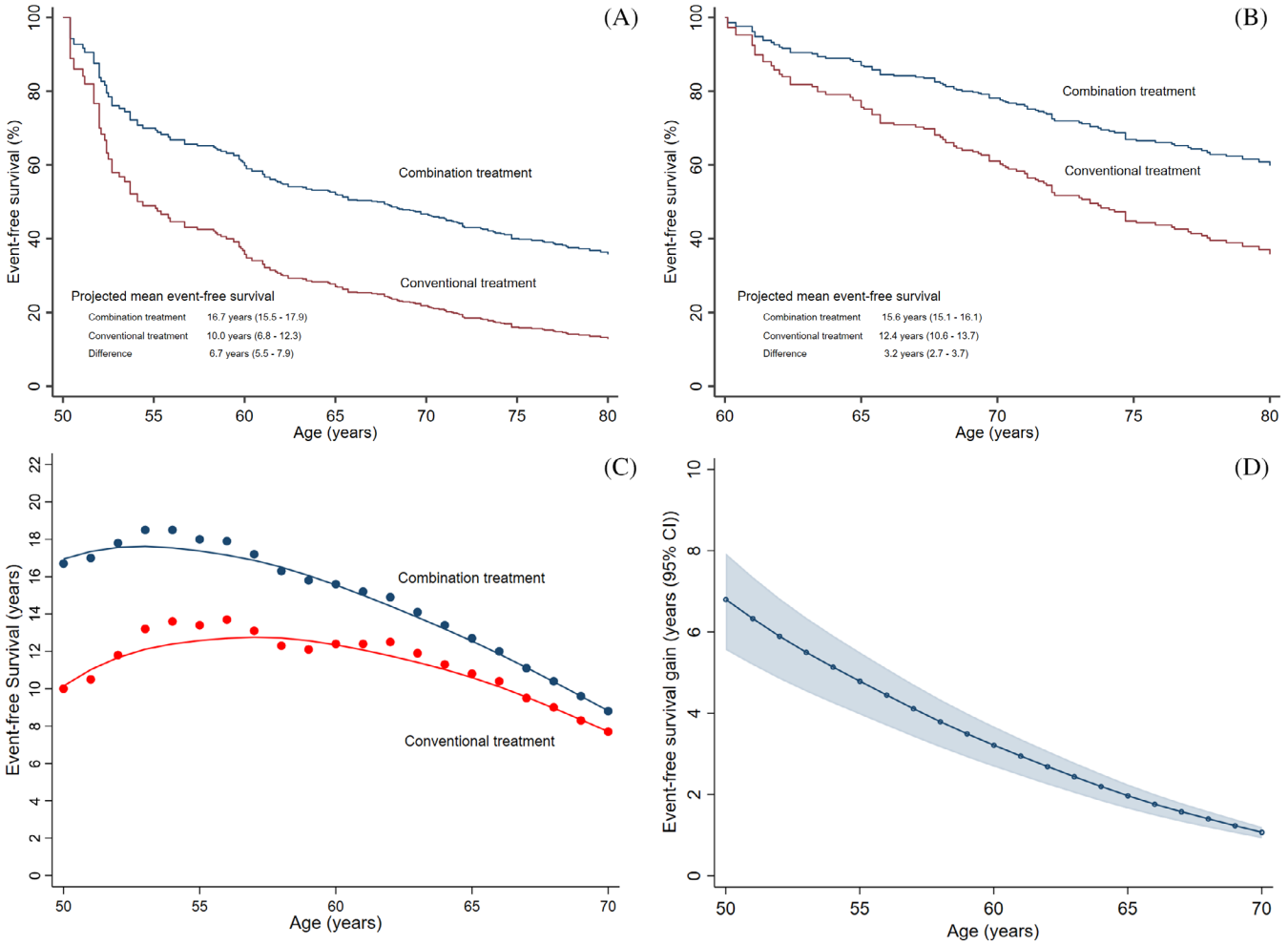

FIGURE 2 A,B, Event-free survival, and C,D, treatment benefits with combined pharmacological treatment (sodium-glucose co-transporter 2 inhibitor, mineralocorticoid-receptor antagonists) on top of conventional treatment (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) versus conventional treatment for the composite kidney outcome consisting of doubling of serum creatinine, end-stage kidney disease, or death because of kidney failure. A, Kaplan-Meier estimated curves for patients starting at age 50 years. B, Kaplan-Meier estimated curves for patients starting at age 60 years.

The HRs for combined treatment effect were consistent across investigated subgroups is presented in Figure S6. At age 50 years, additional years of estimated event-free survival of the composite primary kidney endpoint were similar in those with eGFR <45 and ≥45 mL/min/1.73 m^2 but there was a greater gain in those with UACR >1000 mg/g versus ≤1000 mg/g [6.0 years (95% CI: 4.6, 7.4) vs. 3.8 years (95% CI: 1.5, 5.5); Figure S7]. The incremental gains in ESKD-free survival with combined pharmacological treatment across combined levels of UACR (≤1000, >1000 to ≤1500, >1500 mg/g) and age (50, 60 and 70 years) were greater at younger ages and a higher level of UACR (Figure S8). This pattern was less clear across various levels of eGFR (<30, 30-44, ≥45 mL/min/1.73 m^2) and starting age (Figure S8).

In the CRIC Study, 449 patients (33.2%) experienced the primary composite kidney outcome [event rate 5.8 events per 100 patient-years (95% CI 5.3, −6.4)] during follow-up. Applying the benefit of combined versus conventional treatment showed that the incremental gain in life years free from the primary composite kidney outcome was 6.3 years (95% CI 5.2, 7.3) (Figure 4).

In a sensitivity analysis, combination treatment still showed a substantial gain over conventional treatment (Appendix S1 and Figure S9). For example, assuming that adding MRAs to SGLT2 inhibitors results in a 70% additive treatment effect, that 70% of patients who were compliant during the clinical trial remain treatment compliant during long-term treatment, and that the efficacy of combined pharmacological treatment decreases by 2% per year, at age 50 years, for patients starting treatment at age 50 years, the estimated gain in survival free (95% CI 2.0, 2.9) (Appendix S2; Figure panel D).

4 | DISCUSSION

The pharmacological management of patients with type 2 diabetes and CKD includes the use of an ACE inhibitor or an ARB in addition to

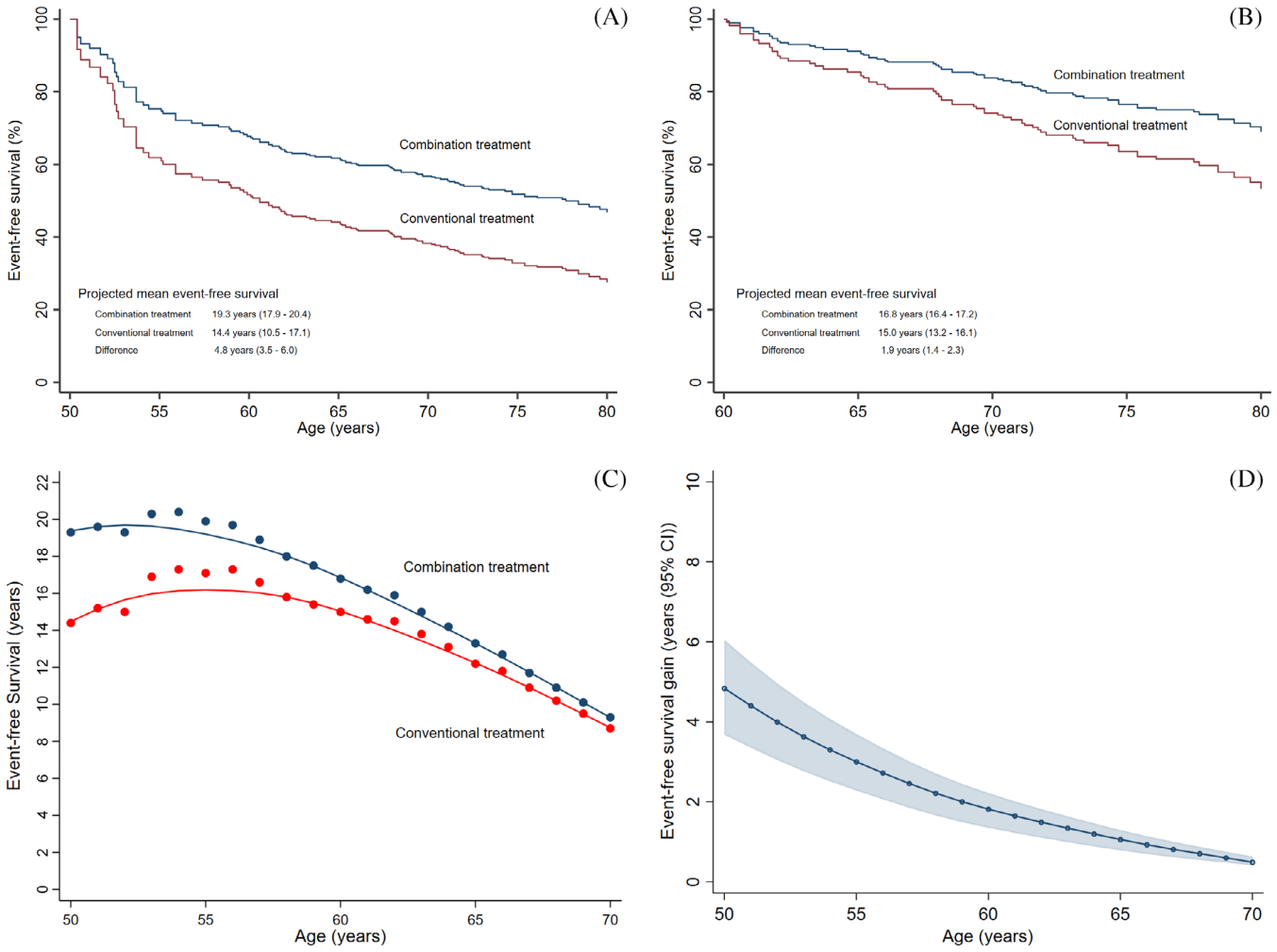

FIGURE 3 A,B Event-free survival, and C,D, treatment benefits with combined pharmacological treatment (sodium-glucose co-transporter 2 inhibitor, mineralocorticoid-receptor antagonists) on top of conventional treatment (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) for end-stage kidney disease. A, Kaplan-Meier estimated curves for patients starting at age 50 years. B, Kaplan-Meier estimated curves for patients starting at age 60 years.

blood pressure and glucose control but is often insufficient to halt the progression of kidney disease. In recent clinical trials, SGLT2 inhibitors and MRA have yielded clear nephroprotective benefits, with each class having been individually showed to slow decline in kidney function and reduce the risk of kidney failure when used as an adjunct to an ACE inhibitor or ARB.[5,6] Our analyses showed that when compared with conventional treatment using only an ACE inhibitor or ARB, the use of combination pharmacological disease-modifying agents substantially reduced the risk of major kidney outcomes and heart failure hospitalizations by 50%. Assuming independent, additive and constant treatment effects, combined therapy was estimated gain in survival free from kidney outcomes with combined therapy was approximately 7 years. A comparable gain in event-free survival for kidney outcomes was observed in data from an observational study. In conservative scenarios, assuming lower treatment adherence and efficacy compared with that observed in clinical trials, a lower but meaningful gain in survival free from kidney outcomes was observed such that event-free survival gain ranged between 1.2 and 5 years for the efficacy of 50-90% of the observed efficacy with a yearly decline in efficacy of 1%-5%. These data highlight the potential of a combined approach with disease-modifying agents to improve substantially the prognosis of patients with type 2 diabetes and CKD.

The two disease-modifying therapy classes are believed to confer nephroprotection via different mechanistic pathways.[18,19] Analyses from pivotal trials, including the FIDELIO-DKD and DAPA-CKD trials, suggest that the benefits of the investigated drug classes are independent and possibly complementary. In the FIDELIO-DKD trial, the benefit of finerenone in slowing progressive kidney function loss was consistent regardless of SGLT2 inhibitor use at baseline.[20] Conversely, dapagliflozin was similarly safe and efficacious in reducing major kidney and heart failure outcomes in patients with CKD or heart failure who were, or were not, prescribed MRAs.[21–23] Moreover, in a prospective clinical trial initiation of combined treatment with SGLT2 inhibitors and MRA on top of ACE inhibitor or ARB treatment resulted in a full additive albuminuria-lowering effect, supporting potential incremental benefits of this combination on clinically meaningful outcomes.[7]

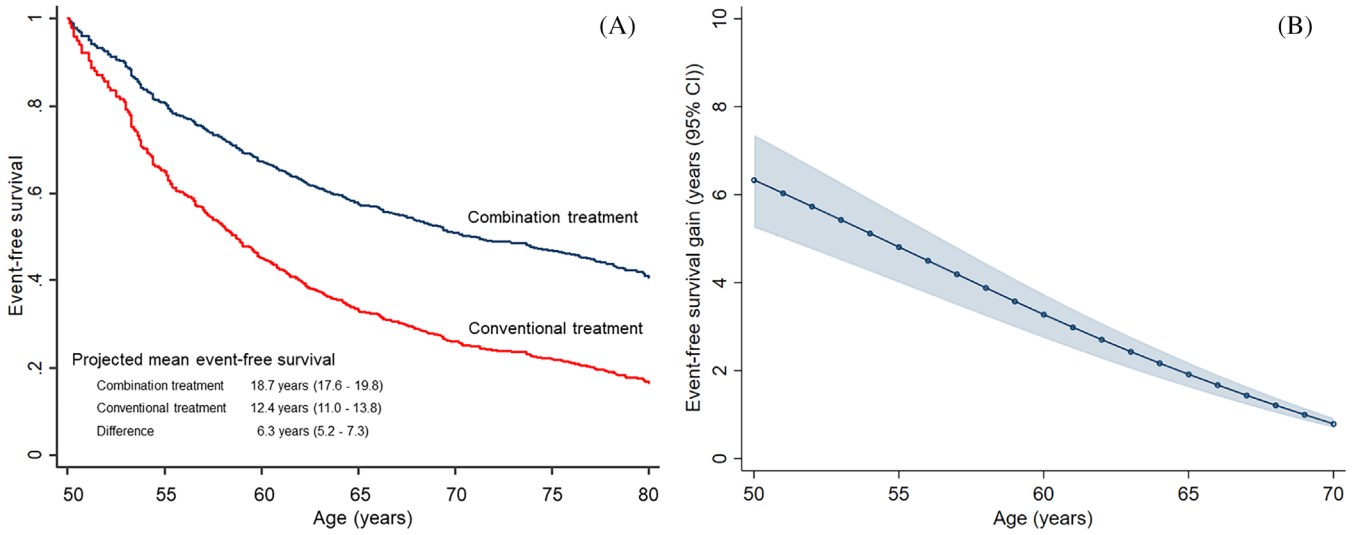

FIGURE 4 A, Event-free survival with combined pharmacological treatment (sodium-glucose co-transporter 2 inhibitor, mineralocorticoid-receptor antagonists) on top of conventional treatment (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) for the primary composite kidney outcome in the Chronic Renal Insufficiency Cohort (CRIC) study for a patient starting at age 50 years. B, Event-free survival gain for all ages between 50 and 70 years.

Clinical practice guidelines for patients with diabetic kidney disease are rapidly evolving and currently recommend the use SGLT2 inhibitors for patients whose eGFR is >20 mL/min/1.73 m^2.[1] Based on the FIDELIO-DKD trial, the non-steroidal MRA finerenone has also been approved for clinical use and is added to the guideline-recommended treatment. Although a short-term clinical trial reported the benefit on surrogate outcomes with combined SGLT2 and MRA therapy and two other clinical trials ongoing,[7,24,25] clinical trials investigating long-term clinical effects of combined use of an SGLT2 inhibitor and MRA are unlikely to be conducted. Consequently, we used existing validated methods, originally developed from cardiology trials, to derive a treatment effect and projected substantial gain in event-free survival resulting from combination therapy with an SGLT2 inhibitor and MRA. We previously used the same method to show the long-term benefit of combined renin-angiotensin system inhibition and SGLT2 inhibition in patients without type 2 diabetes and CKD and extend these findings in this study to newer therapies in patients with type 2 diabetes and CKD.[26] Recent practice guidelines for patients with heart failure recommend clustered or near-simultaneous initiation of recommended medical therapies guided by structured ambulatory programmes or in hospital settings.[27] Such an approach of clustered initiation of guideline-recommended, disease-modifying, therapies may be a viable strategy to reduce adverse outcomes in high-risk patients with type 2 diabetes and CKD as well.

We reported on estimated survival gains with combination therapy, but there may also be safety advantages. Agents that inhibit the renin-angiotensin-aldosterone system cause hyperkalaemia, in particular in patients with type 2 diabetes and CKD. Indeed, although the non-steroidal MRA, finerenone, slowed the progression of CKD and prevented cardiovascular events, like steroidal MRAs, finerenone also increased the risk of hyperkalaemia.[6] SGLT2 inhibitors reduce the risk of hyperkalaemia as shown in the CREDENCE trial, making the combination of SGLT2 inhibitors and MRAs an attractive treatment option from a safety perspective as well.[28,29] However, additional safety data from clinical trials and real-world clinical practice registries are required to understand safety and tolerability of individual and combined treatment strategies with these agents.

Anticipated gains in event-free survival were observed across key subgroups. Generally, patients at the highest risk of complications, those with higher glycated haemoglobin or more severe albuminuria, were projected to gain the most event-free survival years. In addition, event-free survival of younger patients who are expected to have a longer projected survival and treatment duration derived more benefit compared with older patients whose life expectancy is shorter. These data highlight the importance of early identification and appropriate treatment of high-risk patients with diabetic kidney disease. In this respect, recent studies indicate there are substantial opportunities to improve early recognition of diabetic kidney disease and use of proven disease-modifying therapies including SGLT2 inhibitors. The optimum communication of trial results to patients may help overcome barriers to treatment uptake. Specifically, translating relative risk reductions to benefit for an individual patient has been shown difficult to conceptualize for patients. Because the progression of diabetic kidney disease takes many years and trials are conducted over a follow-up shorter than life expectancy of patients, projections of lifetime application beyond the duration of a trial may help in communicating potential lifetime benefits and implementation of new therapies.

This study has limitations. First, individual therapy was assumed to have incremental clinical benefits. Besides the known mechanism of action of SGLT2 inhibitors and MRAs, there may be other unknown pathways through which that therapy acts and these pathways of action may be overlapping between therapies. In addition, the

CREDENCE and DAPA-CKD trials were discontinued early, which may increase the risk of overestimating effect sizes.[30] Therefore, the estimated incremental survival gain achieved with combined pharmacological treatment may be overestimated. Secondly, treatment was assumed to have a constant effect over the lifetime. Because of the lack of data on long-term efficacy, it is unclear whether therapies will continue to exert clinical benefit throughout life. Moreover, adherence to therapies may change over longer periods, which may also influence longer-term efficacy. To account for these assumptions, various sensitivity analyses were performed, which showed that clinically relevant gains in kidney and overall survival could be obtained also when the three disease-modifying drugs were assumed to be non-additive or waned over time, for example, because of increased non-adherence.-Thirdly, the study investigated the benefits of combined treatment regarding kidney outcomes, cardiovascular outcomes and mortality, and did not investigate associated adverse events and costs. Finally, because of the possibility of competing risk from death, there may be an overestimation of event-free survival. However, the significant reduction in overall mortality achieved with combined pharmacological therapy provides a survival advantage and thus increases the likelihood of experiencing kidney and cardiovascular outcomes.

Combined disease-modifying pharmacological treatment with SGLT2 inhibitors, MRAs and endothelin receptor antagonists, compared with conventional treatment, may substantially improve long-term health outcomes, including kidney failure and heart failure hospitalization, and prolong overall survival in patients with type 2 diabetes and CKD. In case of lower than observed treatment adherence and efficacy in included clinical trials, the gain in event-free survival from the combination treatment may still be meaningful.

AUTHOR CONTRIBUTIONS

HJLH was involved in the design of the study and interpretation of the data. HJLH and PV wrote the first draft of the manuscript and PV was involved in data interpretation. HJLH, JJVM, FM, VP, BN, GB were involved in data collection, and analysis/interpretation of the data. PV and NJ performed the data analyses. BC, MV, KD, FM, and PJ were involved in the analysis of the data and interpretation of results. All authors reviewed the manuscript drafts for important intellectual content, provided approval of the final version for submission and take responsibility for the accuracy and integrity of the data including ensuring that any questions are appropriately investigated and resolved. HJLH is the guarantor and corresponding author, and as such accepts full responsibility for the overall content of the work and conduct of the study, had access to the data, and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

ACKNOWLEDGEMENTS

We would like to thank participants of the CREDENCE, FIDELIO-DKD, DAPACKD and CRIC studies for their contribution.

FUNDING INFORMATION

HJL Heerspink is supported by a VIDI grant from the Netherlands Organization for Scientific Research (917.15.306) and by a grant from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement No 115974. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA. J.J.V.M. is supported by a British Heart Foundation Centre of Research Excellence Grant (RE/18/6/34217).

The funders of the clinical trials had no role in the study design, data analysis, data interpretation or writing of the report. The first author had full access to all the data in the study and is responsible for the decision to submit the manuscript for publication.

CONFLICT OF INTEREST STATEMENT

JN and PV report no conflicts of interest. HJLH has received funding/honoraria and consulting fees for Steering Committee membership and/or advisory board participation from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Pharma, Dimerix, Gliead, GoldFinsch, Janssen, Fresenius, Merck, MundiPharma, Mitsubishi Tanabe, NovoNordisk and Travere Pharmaceuticals. BL Neuen has received fees for advisory boards, scientific presentations, trial steering committee roles and travel support from AstraZeneca, Bayer and Janssen with all honoraria paid to his institution. BC reports personal fees from Amgen, Boehringer-Ingelheim, Cardurion, Corvia, Myokardia and Novartis. GB reports personal fees from Merck, Bayer, KBP Biosciences, Ionis, Alnylam, Astra Zeneca, Quantum Genomics, Horizon, Novo Nordisk DiaMedica Therapuetics, other from Bayer, Vascular Dynamics, Novo Nordisk, Janssen. SDS reports grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, US2.AI, personal fees from Abbott, Action, Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, GSK, Lilly, Merck, Myokardia, Novartis, Roche, Theracos, Quantum Genomics, Cardurion, Janssen, Cardiac Dimensions, Tenaya, Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent, Sarepta. MV has received research grant support or served on advisory boards for American Regent, Amgen, AstraZeneca, Bayer AG, Baxter Healthcare, Boehringer Ingelheim, Cytokinetics, Lexicon Pharmaceuticals, Relypsa, and Roche Diagnostics, speaker engagements with Novartis and Roche Diagnostics, and participates on clinical endpoint committees for studies sponsored by Galmed and Novartis. FMC reports research grants from National Institute of Health (NDDK), Fifth Eye, Advanced Instruments and Satellite Healthcare. KFD has received honoraria for lectures from AstraZeneca, and his employer, the University of Glasgow, has been remunerated by AstraZeneca for his time spent working on the DAPA-HF trial. PSJ reports consultancy fees from Novartis, AstraZeneca, Boehringer Ingelheim, NovoNordisk, Research Grants from Novartis and Analog Devices Inc and lecture fees from Novartis and Astrazeneca. Dr. Perkovic reports fees from Janssen and AbbVie during the conduct of the study; honoraria from Bayer, GSK, Bristol-Myers Squibb Company, Eli Lilly, Pfizer, Servier, AstraZeneca, NovoNordisk, Pharmalink, Relypsa, Baxter Sanofi, Gliead, Novartis, Durect, Astellas, Merck, Tricida, Dimerix, Mundipharma, Metavant, UptoDate, Mitsubishi Tanabe, Novo Nordisk

outside the submitted work and received grants from GSK, Pfizer, National Health and Medical Research Council outside the submitted work. JJVM has received payments to his employer, Glasgow University, for his work on clinical trials, consulting and other activities from AstraZeneca, Cytokinetics, KBP Biosciences, Amgen, Bayer, Theracos, Ionis Pharmaceuticals, Dalcor Pharmaceuticals, Novartis, GlaxoSmithKline, Bristol Myers Squibb, Boehringer Ingelheim, Cardurion and Alnylam, and has received personal lecture fees from Abbott, Alkem Metabolics, Eris Life Sciences, Hickma, Lupin, Sun Pharmaceuticals, Medscape/Heart.org, ProAdWise Communications, Radcliffe Cardiology, Servier and the Corpus.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15232.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained upon reasonable request and in accordance with the governing structure of the respective clinical trials and observational study.

ORCID

Hiddo J. L. Heerspink https://orcid.org/0000-0002-3126-3730
Priya Vart https://orcid.org/0009-0006-3963-2605
Brendon L. Neuen https://orcid.org/0000-0001-9276-8380
Muthiah Vaduganathan https://orcid.org/0000-0003-0885-1953
Pardeep S. Jhund https://orcid.org/0000-0003-4306-5317
John J. V. McMurray https://orcid.org/0000-0002-6317-3975

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO. Clinical practice guideline for diabetes Management in Chronic Kidney Disease. *Kidney Int*. 2020;2020(98):S1-S115.
2. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
3. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-860.
4. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295-2306.
5. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436-1446.
6. Bakris GL, Agarwal R, Anker SD, et al. Effect of Finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med*. 2020;383:2219-2229.
7. Provenzano M, Puchades MJ, Garofalo C, et al. Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: a randomized crossover clinical trial. *J Am Soc Nephrol*. 2022;19:ASN.2022020207:1569-1580.
8. Tuttle KR, Alicic RZ, Duru OK, et al. Clinical characteristics of and risk factors for chronic kidney disease among adults and children: an analysis of the CURE-CKD registry. *JAMA Netw Open*. 2019;2:e1918169.
9. Eberly LA, Yang L, Eneanya ND, et al. Association of Race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US. *JAMA Netw Open*. 2021;4:e216139.
10. Martin SS, Sperling LS, Blaha MJ, et al. Clinician-patient risk discussion for atherosclerotic cardiovascular disease prevention: importance to implementation of the 2013 ACC/AHA guidelines. *J Am Coll Cardiol*. 2015;65:1361-1368.
11. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121-128.
12. Claggett B, Packer M, McMurray JJ, et al. Estimating the long-term treatment benefits of sacubitril-valsartan. *N Engl J Med*. 2015;373:2289-2290.
13. Feldman HI, Appel LJ, Chertow GM, et al. Chronic renal insufficiency cohort (CRIC) study investigators. The chronic renal insufficiency cohort (CRIC) study: design and methods. *J Am Soc Nephrol*. 2003;14:S148-S153.
14. Durrleman S, Chaikin P. The use of putative placebo in active control trials: two applications in a regulatory setting. *Stat Med*. 2003;22:941-952.
15. Fisher LD, Gent M, Buller HR. Active-control trials: how would a new agent compare with placebo? A method illustrated with clopidogrel, aspirin, and placebo. *Am Heart J*. 2001;141:26-32.
16. Ferreira JP, Docherty KF, Stienen S, et al. Estimating the lifetime benefits of treatments for heart failure. *JACC Heart Fail*. 2020;8:984-995.
17. Cleveland W. Robust locally weighted regression and smoothing scatterplots. *J Am Stat Assoc*. 1979;74:7-836.
18. Sen T, Heerspink HJL. A kidney perspective on the mechanism of action of sodium glucose co-transporter 2 inhibitors. *Cell Metab*. 2021;33:732-739.
19. Grune J, Beyhoff N, Smeir E, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for Finerenone's antifibrotic activity. *Hypertension*. 2018;71:599-608.
20. Rossing P, Filippatos G, Agarwal R, et al. Finerenone in predominantly advanced CKD and type 2 diabetes with or without sodium-glucose Cotransporter-2 inhibitor therapy. *Kidney Int Rep*. 2021;7:36-45.
21. Shen L, Kristensen SL, Bengtsson O, et al. Dapagliflozin in HFrEF patients treated with mineralocorticoid receptor antagonists: an analysis of DAPA-HF. *JACC Heart Fail*. 2021;9:254-264.
22. Ferreira JP, Zannad F, Pocock SJ, et al. Interplay of mineralocorticoid receptor antagonists and empagliflozin in heart failure: EMPEROR-reduced. *J Am Coll Cardiol*. 2021;77:1397-1407.
23. Provenzano M, Jongs N, Vart P, et al. The kidney protective effects of the sodium–glucose cotransporter-2 inhibitor, dapagliflozin, are present in patients with chronic kidney disease treated with mineralocorticoid receptor antagonists. *Kidney Int Rep*. 2021;7:436-443.
24. Agarwal R, Anker SD, Filippatos G, et al. Effects of canagliflozin versus finerenone on cardiorenal outcomes: exploratory post hoc analyses from FIDELIO-DKD compared to reported CREDENCE results. *Nephrol Dial Transplant*. 2022;37:1261-1269.
25. Efficacy, Safety and Tolerability of AZD9977 and Dapagliflozin in Participants With Heart Failure and Chronic Kidney Disease – Full Text View – ClinicalTrials.gov. Accessed on July 18, 2022.
26. Vart P, Vaduganathan M, Jongs N, et al. Estimated lifetime benefit of combined RAAS and SGLT2 inhibitor therapy in patients with Albuminuric CKD without diabetes. *Clin J Am Soc Nephrol*. 2022;17(12):1754-1762.
27. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.
28. Neuen BL, Oshima M, Perkovic V, et al. Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: the CREDENCE trial. *Eur Heart J*. 2021;42:4891-4901.
29. Neuen BL, Oshima M, Agarwal R, et al. Sodium-glucose cotransporter 2 inhibitors and risk of hyperkalemia in people with type 2 diabetes: a meta-analysis of individual participant data from randomized, controlled trials. *Circulation*. 2022;145:1460-1470.

30. Guyatt GH, Briel M, Glasziou P, Bassler D, Montori VM. Problems of stopping trials early. *BMJ*. 2012;344:e3863.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Heerspink HJL, Vart P, Jongs N, et al. Estimated lifetime benefit of novel pharmacological therapies in patients with type 2 diabetes and chronic kidney disease: A joint analysis of randomized controlled clinical trials. *Diabetes Obes Metab*. 2023;25(11):3327-3336. doi:10.1111/dom.15232