Estimated lifetime-benefit of combined RAAS and SGLT-2 inhibitor therapy in patients with CKD without diabetes

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Abstract

Background and objectives: Despite high rates of complications in patients with CKD without diabetes, the implementation of proven therapies in this group remains low. Expressing the clinical benefit of a therapy in terms of extra years free from the disease or death may facilitate implementation. We estimated lifetime survival free of kidney failure for patients with non-diabetic CKD treated with the combination therapy of ACE inhibitors/ARB and SGLT2 inhibitors relative to patients not treated.

Design, Setting, Participants and Measurements: We used trial-level estimates of the effect of treatment with ACE inhibitors/ARBs (Ramipril/Benazepril) (N=690) and SGLT2 inhibitors (Dapagliflozin) (N=1,398) compared with placebo to derive the effect of combination therapy versus no treatment. Using this effect, we estimated treatment effect of combination therapy to the active treatment group of patients with non-diabetic CKD participating in the DAPA-CKD trial (N=697) and projected event-free and overall survival for those treated and not treated with combination therapy. We also performed our calculations anticipating lower adherence and less pronounced benefits than were observed in the clinical trials. The primary outcome was a composite of doubling of serum creatinine, kidney failure, or death.

Results: The aggregate estimated hazard ratio comparing combination therapy with ACE inhibitor/ARB and SGLT2 inhibitor versus no treatment for the primary endpoint was 0.35 (95%CI:0.30,0.41). For a 50 year-old-patient until the age of 75 years, the estimated survival free from the primary composite endpoint was 17.0 (95%CI:12.4,19.6) years with the combination therapy and 9.6 years (95%CI:8.4,10.7) with no treatment with any of these agents, corresponding to gain in event-free survival of 7.4 (95%CI:6.4,8.7) years. When assuming lower adherence

and less pronounced efficacy of combination therapy, the gain in event free survival ranged from 5.3 years (95%CI: 4.4,6.1) to 5.8 years (95% CI: 4.8,6.8).

Conclusions: Treatment with the combination of ACE inhibitors/ARB and SGLT2 inhibitor in patients with CKD without diabetes is expected to substantially increase kidney failure-free survival.

Introduction:

About half of patients with chronic kidney disease (CKD) do not have diabetes but experience high rates of kidney failure and mortality.[1] These patients are typically treated with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (ACE inhibitors/ARB), particularly when presenting with albuminuria.[2] Recently, the sodium-glucose cotransporter-2 (SGLT2) inhibitor dapagliflozin was shown to reduce the risk of progressive kidney disease by more than 40% and to significantly reduce the risk of hospitalized heart failure and death from cardiovascular and non-cardiovascular causes in patients with CKD and albuminuria, nearly all of whom were already treated with ACE inhibitors/ARB. Despite these observed benefits, the implementation of proven therapies in routine clinical practice remains low. For instance, studies using real-world data suggest that about 50-70% of patients with CKD in whom ACE inhibitors/ARB treatment is recommended are not actively treated, particularly patients with non-diabetic CKD.[4,5] Consequently, understanding barriers to implementation and development of tools that could increase uptake of medication in these patients are highly desired.

In clinical trials, the benefit of treatment is typically expressed in the form of relative risk reduction which may be difficult to communicate to patients, clinicians, and policymakers, and thereby may contribute to delays in implementation of proven therapies in practice. Because patients with CKD are typically treated for a lifetime and different patients start treatment at different ages, expressing the clinical benefit of a therapy in terms of extra years free from the disease or death may facilitate risk communication in clinical management, increase uptake of these therapies in clinical practice, and inform decision-making by policymakers and payers.

Therefore, in this study, we estimated the benefit of pharmacological treatment with the combination of ACE inhibitor/ARB and SGLT2 inhibitor versus no treatment with any of these agents in patients with CKD without diabetes. To this end, we derived aggregate relative risk reduction for the combination therapy from pivotal randomized clinical trials testing individual therapies and used validated actuarial methods[6,7] to project absolute event-free survival gains for kidney failure and mortality.

Materials and Methods

Overall study design

In this study, using overall trial-level estimates from pivotal randomized clinical trials that assessed the efficacy and safety of a ACE inhibitor/ARB and SGLT2 inhibitor in patients with CKD without diabetes, we estimated the cumulative effect of combination therapy with ACE inhibitors/ARB and SGLT2 inhibitors compared to no treatment. To obtain trial-level estimates, we used data from the Ramipril Efficacy In Nephropathy (REIN) trial[8,9], Guangzhou trial from Guangzhou China (NCT00270426)[10], and the DAPA-CKD (NCT03036150)[11] trial. For validation of event-free survival estimates in a non-clinical trial setting, we modelled data from the Chronic Renal Insufficiency Cohort (CRIC). Participants enrolled in each clinical trial and the CRIC observational study provided written consent. The study protocols of the clinical trials included and the CRIC study were approved by the institutional review board at each participating site.

Clinical trials

REIN

Between 1994 and 1995, the REIN trial included 352 patients aged between 18-70 years who were normotensive or hypertensive, had chronic nephropathy and persistent proteinuria (i.e., urinary protein excretion of ≥1 g/day for at least 3 months without evidence of urinary tract infection or overt heart failure) and who had not received ACE inhibitor therapy for at least 2 months. In a stratified randomization procedure based on proteinuria, 177 patients were randomized to ramipril and 175 were randomized to the placebo group and were followed for a median duration of 2.1 years.[8,9]

Guangzhou trial

Between 1999 and 2001, investigators randomized 422 patients with CKD who were 18 to 70 years of age, with serum creatinine concentrations 1.5 to 5.0 mg/dL and urinary protein excretion > 0.3 g/day for three or more months and who had not received ACE inhibitor/ARB for at least six weeks. After an 8-week run-in period, investigators provided 104 patients with serum creatinine concentrations of 1.5 to 3.0 mg/dl 20 mg of benazepril per day, and randomized 224 patients with serum creatinine concentrations of 3.1 to 5.0 mg/dl to 20 mg of benazepril per day or placebo. All patients were treated according to local guidelines. Patients were followed for a median duration of 3.0 years.[10]

DAPA-CKD

Between 2017 and 2020, the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial enrolled 4,304 patients aged 18 years or older with CKD and with or without a diagnosis of diabetes, eGFR between 25 and 75 mL/min/1.73 m2, and urinary albumin: creatinine ratio (UACR) between 200 and 5,000 mg/g. Randomized patients were required to receive an ACE inhibitor or ARB at maximally tolerated dose as part of standard-of-care; 97% of participants were receiving ACE inhibitor or ARB at baseline. Eligible patients were randomly assigned to dapagliflozin 10 mg once daily or a placebo. The median duration of follow-up was 2.4 years. For the present analysis, we incorporated data from patients without diabetes at baseline.[3]

Observational cohort

The CRIC Study is a multi-center, longitudinal, observational cohort study from the United States that enrolled a racially/ethnically diverse sample of persons with CKD (n=3939).[11] Participants were between the ages of 21 and 74 years with a mean

eGFR of 43.4 ml/min/1.73m^2 and median urinary protein excretion of 0.17 g/day in the original cohort. A total of 2,031 (51.6%) CRIC study participants were not diagnosed with diabetes at baseline. For the present analysis, we incorporated data from patients without diabetes and not on ACE inhibitor/ARB with UACR>300 mg/g. The CRIC study protocol was approved by the institutional review board at each participating site.

Clinical outcomes

The primary endpoint for the present analysis was a composite of a sustained doubling of serum creatinine, kidney failure (defined as a sustained eGFR ≤15mL/min/1.73m^2, initiation of dialysis for at least 30 days, or kidney transplantation), or all-cause mortality. The secondary endpoint was a composite of sustained doubling of serum creatinine or kidney failure.

Statistical methods

We estimated the treatment effect with ACE inhibitor, ramipril or benazepril, from t meta-analysis of the individual patient data from the REIN trial and the Guangzhou trial. We estimated the effect of treatment with SGLT2 inhibitor, dapagliflozin, from the DAPA-CKD trial. Assuming independent treatment effects of the ACE inhibitors/ARBs and SGLT2 inhibitors, we determined the combined effect of ACE inhibitors/ARB and SGLT2 inhibitors compared to no treatment using established methods of indirect comparisons (commonly used to assess treatment effects if a placebo were selected in an active-controlled trial).[12,13] We 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).

We calculated event-free survival related to combination therapy with ACE inhibitors/ARB and SGLT2 inhibitors using data derived from DAPA-CKD

participants without diabetes at baseline randomized to dapagliflozin. To estimate event-free survival when not treated with either ACE inhibitor/ARB or SGLT2 inhibitor, we applied the inverse of the effect of combination therapy to the individual patient data of DAPA-CKD participants without diabetes at baseline. By using the inverse of the combination therapy effect, we were able to estimate event-free survival for patients (theoretically) not treated with ACE inhibitors/ARB and SGLT2 inhibitors. Because estimated event-free survival and overall survival depends on the age at the start of the treatment, we calculated and compared projected event-free survival estimates for patients of every age between 50 years and 65 years, until the age of 75 years. To estimate event-free survival starting at different ages, we used validated age-based methods of calculating nonparametric Kaplan-Meier estimates using age (at baseline and at the time of an event or death) as the time component rather than time from randomization.[6] The area under the survival curve reflected projected event-free survival. Age treatment interactions were not observed in any of the included trials and consequently, differences in survival curves reflected projected gain in event-free survival. We applied the inverse of upper and lower bounds of the effect of combination therapy to DAPA-CKD participants randomized to dapagliflozin without diabetes at baseline to estimate uncertainty around these survival gains. Estimates of survival gains were smoothed with a locally weighted scatterplot smoothing procedure (i.e., Lowess smoothing).[14]

We performed several additional analyses. First, we estimated gain in event-free survival for the primary and secondary composite endpoints in a non-clinical trial setting using data from patients without diabetes at baseline enrolled in the CRIC study. Since a substantial number of patients in the CRIC study were not treated with ACE inhibitors/ARB, and SGLT2 inhibitors were not used in persons without

diabetes, we were able to compare and validate the projected event free survival derived from the DAPA-CKD trial when not treated with either ACE inhibitors/ARB or SGLT2 inhibitors. In CRIC study analysis, patients were not censored for change in ACEi/ARB use during follow-up since this data was not verified against objective assessment (e.g. pharmacy claim) and the reported ACEi/ARB use was suggested to be stable over time.[15] Second, we estimated gain in event-free survival when comparing treatment with SGLT2 inhibitors to the treatment with ACE inhibitors/ARB inhibitors. For this purpose, we used data from the treatment and placebo arms of the DAPA-CKD trial. Third, we estimated benefits of combination therapy when assuming scenarios regarding additivity of effects of individual treatment (assuming effect additivity of SGLT2i between 120% and 50% of the reported treatment efficacy), adherence to combined medication (assuming medication adherence between 50% and 100% of the observed adherence in included clinical trials), change in treatment efficacy over the years after the start of treatment (assuming a yearly change in the efficacy of the combination therapy between 3% yearly increase to 10% yearly decline compared to the previous year) and combination of these mentioned scenarios. Finally, in a sensitivity analysis, we repeated our analyses when directly applying the combination therapy effect to the placebo group of the REIN trial and Guangzhou trial. Because the REIN trial and the Guangzhou trial did not include patients older than 70 years, we estimated event-free survival between 50 and 70 years.

We conducted all analyses using Stata 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Two-sided P-values <0.05 were considered statistically significant.

Results:

Baseline characteristics of patients in the REIN trial (N=322), the Guangzhou trial, (N=328), and the DAPA-CKD trial (N=4,304) are shown in **Table 1**. Mean age ranged from 45 to 62 years, mean eGFR from 20 to 43 ml/min/1.73m^2, and median UACR from 949 to 1,499 mg/g.

The estimated HR for the combination of ACE inhibitor/ARB and SGLT2 inhibitor versus no treatment with any of these agents for the primary composite endpoint of doubling of serum creatinine, kidney failure, or all-cause death was 0.35 (95%CI: 0.30, 0.41; **Figure 1**) and for doubling of serum creatinine or kidney failure was 0.33 (95%CI: 0.27, 0.41; **Figure 1**).

A total of 697 patients without diabetes were randomized to the active treatment arm in the DAPA-CKD trial. The mean age of these participants at baseline was 57 ± 15 years; a total of 215 (31%) were women, 373 (54%) were white and 268 (38%) were Asian. Mean eGFR was 42 ± 11 ml/min/1.73m^2 and median UACR was 870 mg/g (25%, 75% range 472 – 1,533) (**Table S1**). During a median follow-up of 2.1 years, a total of 52 (7.5%) patients experienced the primary composite endpoint (as defined here, not from the clinical trial itself) and 40 (5.7%) experienced the secondary composite endpoint (again, as defined here) (event rate 3.9 events per 100 patient-years [95% CI 3.0, 5.1] and 3.0 events per 100 patient-years [95% CI 2.2, 4.1], respectively).

The estimated difference in absolute risk when treated with the combination of ACE inhibitor/ARB and SGLT2 inhibitor and when not treated with either of these agents was 16.8-28.8% over 3 years for the primary composite endpoint and 14.5-22.3% over 3 years for the secondary composite endpoint. The corresponding

number needed to treat was 4 to 6 to prevent one primary composite endpoint and 5 to 7 to prevent one secondary composite endpoint.

Between the age of 50 years and 75 years, the estimated survival free from the primary composite endpoint was 17.0 years (95%CI: 12.4, 19.6) with the combination therapy and 9.6 years (95%CI: 8.4, 10.7) with no treatment (difference 7.4 years (95%CI: 6.4, 8.7; **Figure 2**). The corresponding gain in event-free survival for the secondary composite endpoint was 8.0 years (95%CI 6.3, 9.6) (**Figure 3**).

We estimated absolute event-free survival gains for every year of age between 50 to 65 years until the age of 75 years (**Figures 2 and Figure 3**). Regarding primary endpoint, gain in event free survival for the age of 55 years, 60 years, and 65 years were 5.6 years (95% CI: 4.8, 6.6), 3.6 years (95% CI: 3.0, 4.2), and 2,8 (2.3, 3.3) respectively. When investigated for a 70 years old until the age of 75 years, the gain in event free survival regarding primary end point was was 0.7 years (95% CI: 0.6, 0.9). For secondary endpoint, these numbers for the age of 55 years, 60 years, 65 years and 70 years were 5.9 years (95% CI: 4.6, 7.2), 3.2 years (95% CI: 2.5, 4.0), 2,4 years (95% CI: 1.8, 3.0) and 0.6 years (95% CI: 0.5, 0.8), respectively. As expected, the gain among younger patients was more pronounced, owing to higher rates of non-kidney disease-related deaths in older patients.

In the first additional analysis, the aggregate treatment effect was applied to the CRIC study participants with CKD without diabetes not using ACE inhibitor/ARB or SGLT2 inhibitor treatment (N=242, mean age 55 ± 13 years, mean eGFR 38 ± 14 mL/min/1.73m2, and median UACR 730 [25%, 75% range 377-1,710]). During a median follow-up of 7.7 (IQR 5.6-8.7) years, 135 primary composite (incidence rate 10.9 [9.2-12.9] per 100 patient-years) and 107 secondary composite endpoints (incidence rate 8.6 [7.1-10.4] per 100 patient-years) were observed. In CRIC, for the

primary composite endpoint, the projected event-free survival for a participant aged 50 years treated with combination ACE inhibitor/ARB and SGLT2 inhibitor treatment was 16.3 years (95% CI: 15.2, 17.3) and 8.6 years (95% CI: 6.0, 11.0) when untreated, corresponding to an event-free survival gain of 7.7 years (95% CI: 6.7, 8.7; Figure 4). The corresponding gain in event-free survival for the secondary composite endpoint was 7.9 years (95% CI: 6.6, 9.0; **Figure 4**).

When comparing combination therapy versus treatment with ACE inhibitor/ARB only, the gain in event-free survival for a 50-years old with combination therapy was 2.5 years (95% CI: 1.3, 3.7; **Figure S1**) for the primary composite endpoint and 2.5 years (95% CI: 0.4, 4.9; **Figure S1**) for the secondary composite endpoint. Finally, when assuming the possibility of: 1) the effects of ACE inhibitor/ARB and SGLT2 inhibitors being not fully additive, 2) low adherence to the combination therapy, or 3) decline in the efficacy of the combination therapy over time, the gain in event-free survival was attenuate though remained clinically meaningful (**Figure S2**). Estimates in event-free survival were 6.8 years (95% CI: 5.7, 8.0), 5.3 years (95% CI: 4.4, 6.1) and 5.8 years (95% CI: 4.8, 6.8) when assuming a sub-additive (70%) effect, sub-optimal adherence (70%) and a decline in efficacy of combination therapy by 2% per year, respectively (**Figure S2**). If all of the above conditions were met, the estimated gain in event-free was 3.7 years (95%CI: 3.0, 4.3; **Figure S3**). Finally, when directly applying the combination therapy effect to the placebo group of the REIN trial and the Guangzhou trial, the estimated gain in event-free survival for both of the kidney endpoints assessed was similar to that obtained from our main analyses (**Figure S4**).

Discussion:

In this study, results from clinical trials and observational data show that a patient of age 50 years with CKD without diabetes, when treated with a combination of ACE inhibitor/ARB and SGLT2 inhibitors, may experience about 7 additional years free of kidney failure and death compared to a person not treated with these agents. In a conservative approach assuming that the effect of combination therapy is not completely additive, and waning treatment adherence and treatment efficacy over time, there was a considerable gain in event-free survival. These results highlight the potential and the opportunity to lower the burden of CKD complications by delaying or even preventing kidney failure and premature death if currently available treatments can be appropriately utilized.

About 40-60% of patients with CKD do not have diabetes.[11,16,17] These patients often have other comorbidities and remain at a high risk of kidney failure and death. These patients are typically treated with ACE inhibitor/ARB when presented with albuminuria.[18] Recently, the SGLT2 inhibitor dapagliflozin has been shown to improve prognosis in patients with CKD without diabetes on top of the treatment with a maximum tolerated dose of ACE inhibitor/ARB.[3] Recent guidelines already recommend SGLT2 inhibitors and ACE inhibitor/ARB as first line treatment in patients with CKD without diabetes.[19] Unfortunately, despite clinical recommendations, the uptake of medications remains low, [4,17,20] in part due to limited awareness of treatment benefits, suboptimal risk communication between patients and physicians, and costs associated with medication.[21] The present study provides estimates of treatment benefit expressed in extra years free from the disease or death that is easy to understand for patients, clinicians, and policymakers. This may facilitate risk communication in clinical management, increase uptake of these

therapies in clinical practice, and inform decision-making by policymakers and payers.

ACE inhibitors/ARB and SGLT2 inhibitors are believed to exhibit kidney protective effects via similar and distinct pathways.[22] ACE inhibitors/ARB mainly inhibit the conversion and binding of angiotensin II to its receptor, and thereby inhibit the intra-renal RAAS and reduce glomerular hyperfiltration.[23,24] Although it has been suggested that SGLT2 inhibitors inhibit the intra-renal RAAS, clinical studies have shown that they reduce glomerular hyperfiltration through activation of tubule-glomerular feedback secondary to inhibition of the reabsorption of glucose and sodium in proximal tubules of the kidneys.[25] Thereby, from a mechanistic perspective, these SGLT inhibitors may exhibit an independent and additive effect when combined with ACE inhibitors/ARB. Importantly, in our study, the aggregate treatment effect was estimated assuming complete additivity of individual treatment effects and, in line, the observed event-free survival among patients on ACE inhibitors/ARB and SGLT2 inhibitors (i.e., among patients in the active treatment arm of the DAPA-CKD trial) was essentially similar to the estimated event-free survival obtained by applying the aggregate treatment effect to those not on either of the agents.

Strengths of this study include the use of individual patient data from key clinical trials that allowed harmonization of endpoints and therefore a robust estimation of the combination therapy effect. Additionally, the availability of data from the observational cohort allowed validation of results in a ‘real-life’ setting. There are also several limitations. First, for the combination therapy, there was no direct information available on the effect additivity, constancy, and adherence over a lifetime. Regarding effect additivity, besides the known mechanism of action of ACE

inhibitors/ARB and SGLT2 inhibitors, the possibility of other unknown overlapping pathways cannot be completely ruled out. Similarly, it is unclear whether combination therapy will continue to exhibit the same effect throughout life. Although treatment with ACE inhibitors/ARB and SGLT2 inhibitors have been shown to exhibit consistent benefit over a long time,[26,] persistence in use of RAAS inhibition in clinical practice can be variable and in some settings quite poor, often due to concerns regarding the use of RAAS inhibitors in advanced CKD and episodes of hyperkalemia or acute kidney injury.[27] Thereby, benefit experienced by patients may be lower than estimated. However, it should be noted that in a detailed assessment of various possibilities of effect additivity, constancy, and treatment adherence results showed considerable clinical benefit with the combination therapy. Second, the study investigated the benefits of combination therapy regarding kidney outcomes, and mortality and did not investigate associated costs. SGLT2 inhibitors were recently added to the World Health Organization's Essential Medicines List and are becoming available in generic form in many global markets, which is expected to improve their affordability and accessibility. This study also did not investigate the adverse effects of combination therapy. However, combination therapy is reported to have a similar safety profile as ACE inhibitors/ARB alone, which has been widely studied and are demonstrated to be safe. In this study the effect of SGLT2 inhibitors was based on dapagliflozin alone. Results of other SGLT2 inhibitors (e.g. Empagliflozin) are expected in near future and at present it is unclear whether efficacy of other SGLT2 inhibitors is comparable to dapagliflozin and whether this effect is similar among patients with and without diabetes. Finally, individuals examined in this study were assumed to be representative of patients with CKD without diabetes in routine clinical practice.

In conclusion, combination disease-modifying treatment with ACE inhibitors/ARB and SGLT2 inhibitors in patients with CKD without diabetes but with proteinuria may substantially increase the number of years free from kidney failure and mortality. Treatment benefit with the combination therapy remains considerable even in presence of lower effect additivity, treatment adherence, and decline in treatment efficacy over time.

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Conflicts of Interest

PV, NJ and GR report no conflicts of interest

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DW has an ongoing consultancy contract with AstraZeneca and has received honoraria from Amgen, Astellas, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Mundipharma, Merck Sharp and Dohme, Tricida, Vifor and Zidus,

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FFH: is a member of the DAPA-CKD study executive committee and is a study investigator. She has received personal fees from AbbVie.

Author contribution

HJLH and PV were involved in the design of the study. PV was involved in writing of the manuscript. HJLH, DW, GR, FFH, MV, FMC were involved in data collection. PV performed the data analyses. HJLH, PV, NJ, FMC, MV were involved in 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 had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. HJLH attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Supplementary Material

Contents:

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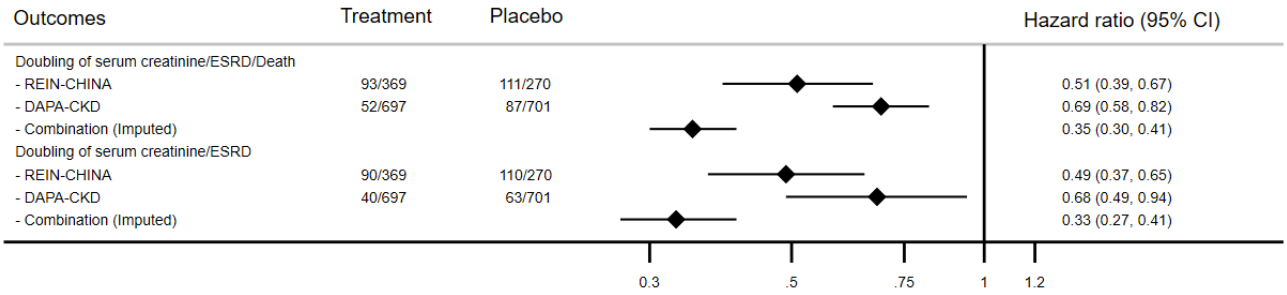
Table 1: Baseline patient characteristics and background medical therapy

Characteristics	REIN (N=322)	Guangzhou, CHINA (N=328)	DAPA-CKD (N=4,304)
Treatment	Ramipril vs. Placebo	Benazepril vs. Placebo	Dapagliflozin vs. Placebo
Enrolment period	1994-1995	1999-2001	2017-2020
Age, years	49 ± 14	45 ± 15	62 ± 12
Female sex, N (%)	73 (23)	162 (49)	1,425 (33)
Race, N (%)			
White	320 (99)	-	2290 (53)
Black	2 (0.6)	-	191 (4)
Asian	-	376 (100)	1467 (34)
Other	-	-	356 (8.3)
Systolic blood pressure, mmHg	144±18	152±25	137±17
eGFR, mL/min/1.73m^2	39±18	20±9	43±12
Urinary Albumin: creatinine ratio, mg/g	1499 (774, 2506)*	1484 (835, 2133)*	949 (477, 1885)
Weight, kg	72.2±12.0	60.4±11.8	81.7±20.6
Baseline medications, N (%)			
Diuretics	-	181 (55)	1882 (44)
Beta-blockers	-	163 (50)	1680 (39)

Abbreviations: REIN= Ramipril Efficacy In Nephropathy; DAPA-CKD= Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease

*estimated

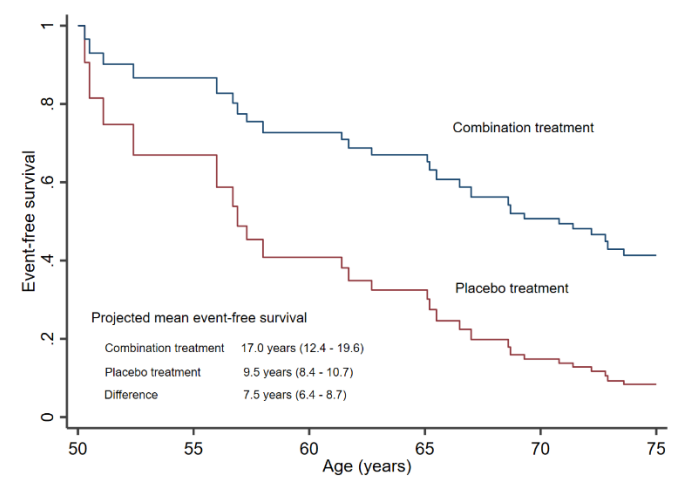
Figure 1: Estimated relative treatment effects of combination treatment with RAAS and SGLT2 inhibitors on key outcomes



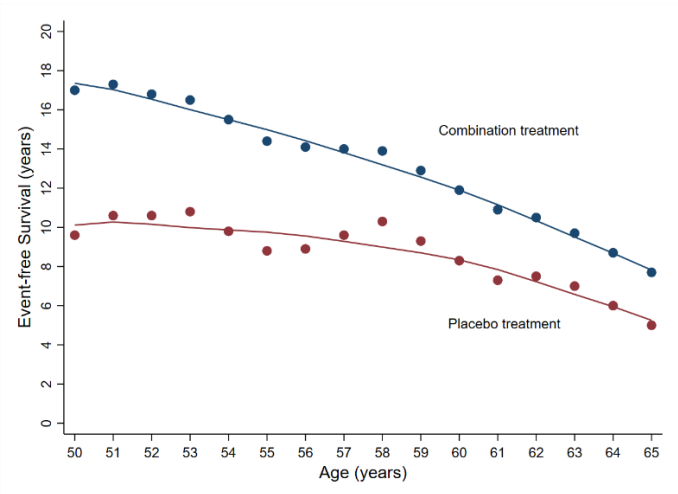
Abbreviations: RAAS=Renin-angiotensin-aldosterone system; SGLT2=sodium-glucose co-transporter-2; REIN= Ramipril Efficacy In Nephropathy; DAPA-CKD= Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease

Figure 2: Event-free survival (Panel A and Panel B) and treatment benefits (Panel C and Panel D) with combination treatment vs placebo treatment for Doubling of serum creatinine/end-stage kidney disease/death

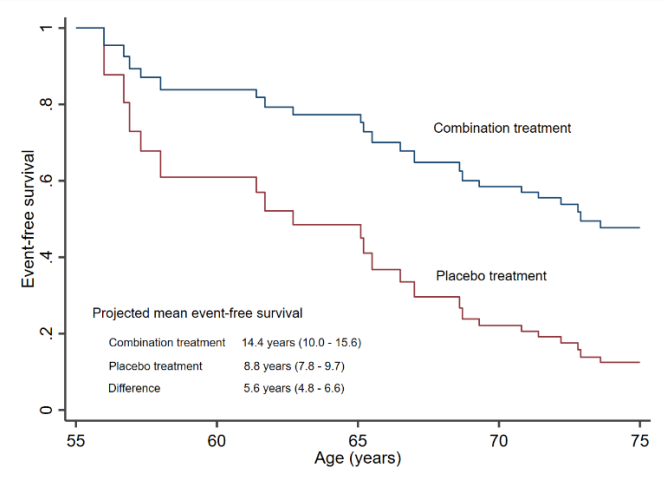
A) Kaplan-Meier estimated curves for patients starting at age 50 year



C) Treatment benefits on event-free survival



B) Kaplan-Meier estimated curves for patients starting at age 55 year



D) Difference in event-free survival between two treatments

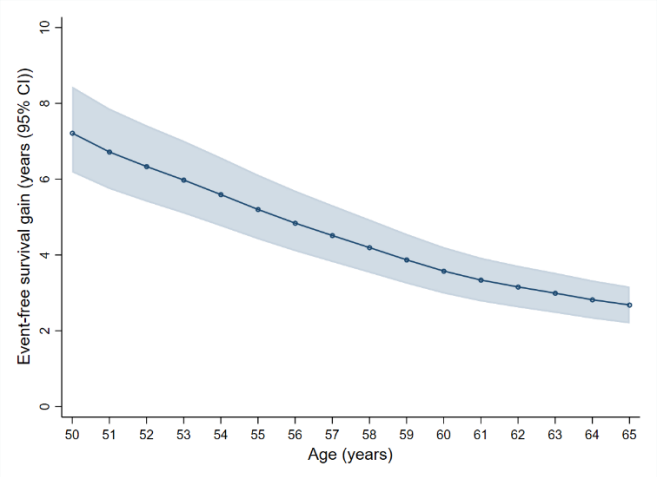
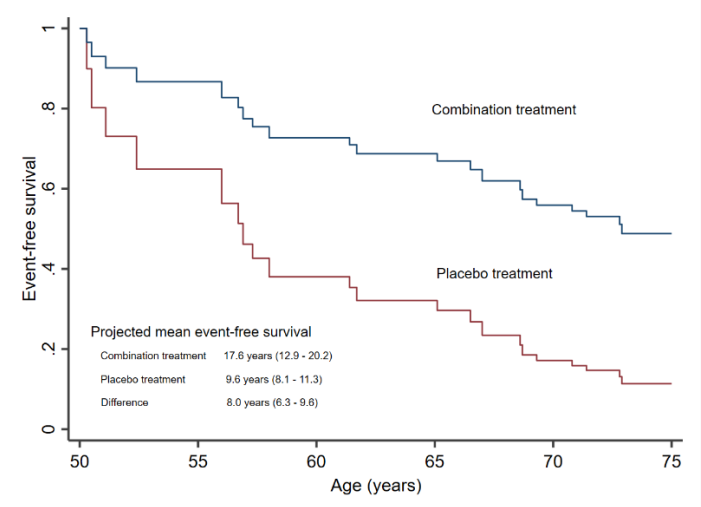
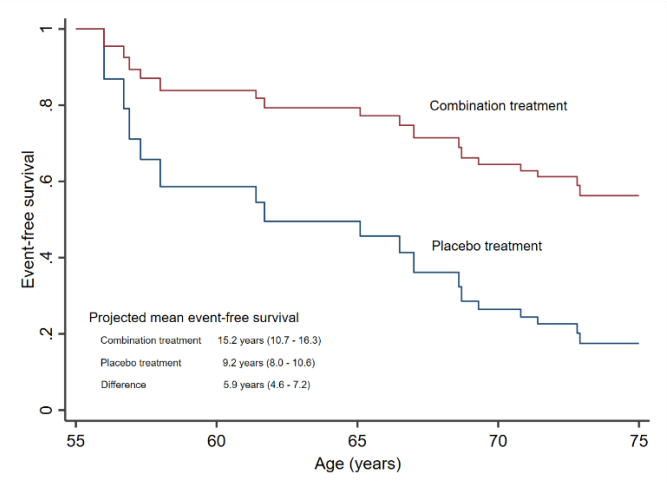


Figure 3: Event-free survival (Panel A and Panel B) and treatment benefits (Panel C and Panel D) with combination treatment vs placebo treatment for Doubling of serum creatinine/end-stage kidney disease

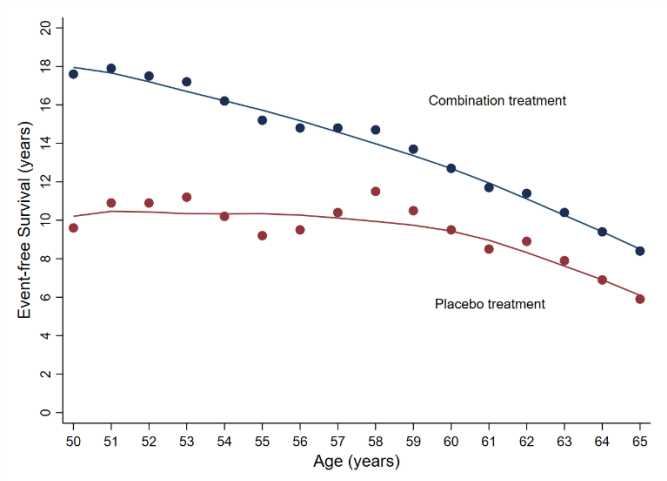
A) Kaplan-Meier estimated curves for patients starting at age 50 year



B) Kaplan-Meier estimated curves for patients starting at age 55 year



C) Treatment benefits on event-free survival



D) Difference in event-free survival between two treatments

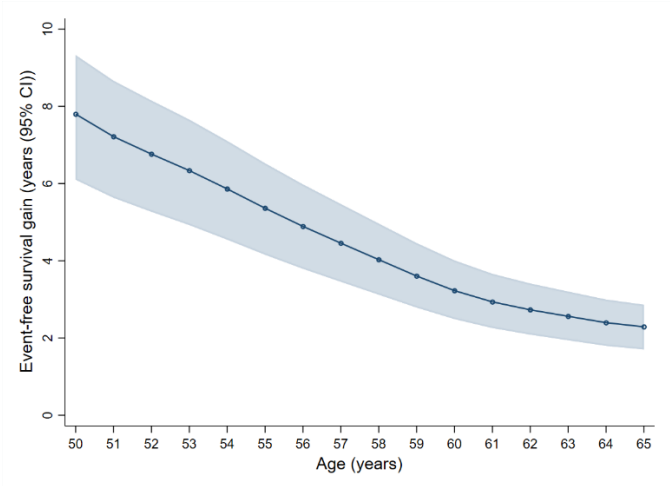
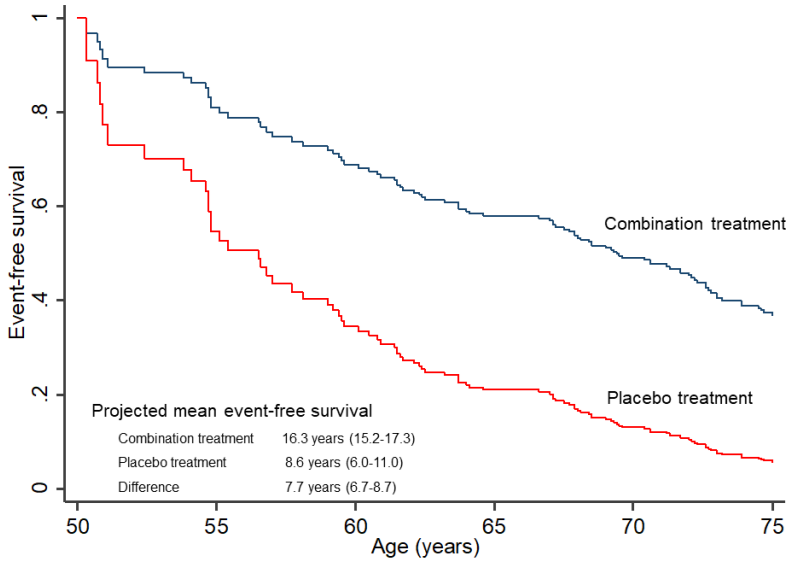


Figure 4: In Chronic Renal Insufficiency Cohort (CRIC), event-free survival with combination treatment vs placebo treatment for doubling of serum creatinine/end-stage kidney disease/death (Panel A) and doubling of serum creatinine/end stage kidney disease (Panel B).

A)



B)