Circulation

ORIGINAL RESEARCH ARTICLE

Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria

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BACKGROUND: Sodium glucose cotransporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), and the nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone all individually reduce cardiovascular, kidney, and mortality outcomes in patients with type 2 diabetes and albuminuria. However, the lifetime benefits of combination therapy with these medicines are not known.

METHODS: We used data from 2 SGLT2i trials (CANVAS [Canagliflozin Cardiovascular Assessment] and CREDENCE [Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation]), 2 ns-MRA trials (FIDELIO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease] and FIGARO-DKD [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease]), and 8 GLP-1 RA trials to estimate the relative effects of combination therapy versus conventional care (renin-angiotensin system blockade and traditional risk factor control) on cardiovascular, kidney, and mortality outcomes. Using actuarial methods, we then estimated absolute risk reductions with combination SGLT2i, GLP-1 RA, and ns-MRA in patients with type 2 diabetes and at least moderately increased albuminuria (urinary albumin:creatinine ratio ≥30 mg/g) by applying estimated combination treatment effects to participants receiving conventional care in CANVAS and CREDENCE.

RESULTS: Compared with conventional care, the combination of SGLT2i, GLP-1 RA, and ns-MRA was associated with a hazard ratio of 0.65 (95% CI, 0.55–0.76) for major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death). The corresponding estimated absolute risk reduction over 3 years was 4.4% (95% CI, 3.0–5.7), with a number needed to treat of 23 (95% CI, 18–33). For a 50-year-old patient commencing combination therapy, estimated major adverse cardiovascular event–free survival was 21.1 years compared with 17.9 years for conventional care (3.2 years gained [95% CI, 2.1–4.3]). There were also projected gains in survival free from hospitalized heart failure (3.2 years [95% CI, 2.4–4.0]), chronic kidney disease progression (5.5 years [95% CI, 4.0–6.7]), cardiovascular death (2.2 years [95% CI, 1.2–3.0]), and all-cause death (2.4 years [95% CI, 1.4–3.4]). Attenuated but clinically relevant gains in event-free survival were observed in analyses assuming 50% additive effects of combination therapy, including for major adverse cardiovascular

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events (2.4 years [95% CI, 1.1–3.5]), chronic kidney disease progression (4.5 years [95% CI, 2.8–5.9]), and all-cause death (1.8 years [95% CI, 0.7–2.8]).

CONCLUSIONS: In patients with type 2 diabetes and at least moderately increased albuminuria, combination treatment of SGLT2i, GLP-1 RA, and ns-MRA has the potential to afford relevant gains in cardiovascular and kidney event-free and overall survival.

Key Words: diabetes mellitus, type 2 ■ heart failure ■ mortality ■ renal insufficiency, chronic ■ treatment outcome

ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- In this actuarial analysis using data from large-scale randomized outcome trials, combination treatment with SGLT2 inhibitors, GLP-1 receptor agonists and non-steroidal MRA in people with type 2 diabetes and at least moderately increased albuminuria was projected to afford substantial gains in cardiovascular, kidney and overall survival.
- Lifetime gains in event-free and overall survival were observed across the range of ages studied.

What Are the Clinical Implications?

- Implementation of the "4 pillars" of therapy for diabetes and chronic kidney disease – RAS blockade, SGLT2 inhibitors, GLP-1 receptor agonists and non-steroidal MRA – has the potential to offer major benefits to many individuals.
- Patients with type 2 diabetes at high cardiorenal risk should be prioritized for combination treatment with these "4 pillars" of guideline-directed medical therapy.

Nonstandard Abbreviations and Acronyms

AMPLITUDE-O	Effect of Efpeglenatide on Cardiovascular Outcomes
CANVAS	Canagliflozin Cardiovascular Assessment
CKD	chronic kidney disease
CREDENCE	Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation
eGFR	estimated glomerular filtration rate
ELIXA	Evaluation of Lixisenatide in Acute Coronary Syndrome
EXSCEL	Exenatide Study of Cardiovascular Event Lowering
FIDELIO-DKD	Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease
FIGARO-DKD	Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease
GLP-1 RA	glucagon-like peptide-1 receptor agonists
Harmony	Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus
LEADER	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results
MACE	major adverse cardiovascular events
ns-MRA	nonsteroidal mineralocorticoid receptor antagonist
PIONEER-6	A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes
REWIND	Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes
SGLT2i	sodium glucose cotransporter 2 inhibitor
SUSTAIN-6	Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes
UACR	urine albumin:creatinine ratio

Major guidelines recommend multiple medicines, proven in randomized trials, to reduce cardiovascular events and chronic kidney disease (CKD) progression in patients with type 2 diabetes.[1,2] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce cardiovascular events, progression of CKD, and mortality in patients with type 2 diabetes.[3,4] The nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) finerenone more recently has been shown to reduce cardiovascular events and CKD progression in patients with type 2 diabetes and albuminuria.[5]

Although SGLT2i and ns-MRA have more pronounced effects on heart failure and kidney outcomes, GLP-1 RA may yield greater reductions in atherosclerotic events, such as myocardial infarction and stroke.[3,6] The different types of events prevented with these classes of medicines and their contrasting mechanisms of action, targeting hemodynamic, metabolic, and inflammatory or fibrotic pathways of injury, have led to considerable interest in the potential benefits of combination therapy to address the multiple, interrelated pathophysiological mechanisms of type 2 diabetes and further reduce cardiorenal risk.[7]

Large clinical outcome trials establishing the benefits of these medicines followed patients for a median of 1.5 to 4 years.[3,4] Yet, in clinical practice, patients are typically treated over much longer time frames. Estimating the benefits of treatment beyond the traditional time frame of a randomized trial may provide clinically relevant information that can inform shared decision-making by patients and clinicians and policy decisions regarding access to these medicines.

We therefore used data from large-scale randomized outcome trials of SGLT2i, GLP-1 RA, and ns-MRA to estimate relative and absolute effects, as well as lifetime gains in cardiorenal event-free and overall survival with a combination treatment of these medicines compared with conventional care in patients with type 2 diabetes and albuminuria.

METHODS

This age-based (actuarial) survival analysis used pooled individual participant data from 2 SGLT2i outcome trials (CANVAS [Canagliflozin Cardiovascular Assessment] and CREDENCE [Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation]; n=14 543),[8,9] a trial-level meta-analysis of all 8 completed outcome trials of GLP-1 RA (n=60 080),[3] and pooled individual participant data from 2 ns-MRA trials (FIDELIO-DKD [Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease] and FIGARO-DKD [Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease]; n=13 026). All compared the medicines of interest against placebo on a background of conventional care, defined as renin angiotensin system blockade and traditional risk factor control.[10,11] Ethics committees approved these trials at each site, and all participants provided written informed consent.

All supporting information regarding treatment effects is available in this article; individual participant data from CANVAS and CREDENCE, which were used to model survival, are available in the public domain through the Yale University Open Data Access Project (http://yoda.yale.edu/).

CANVAS and CREDENCE

CANVAS and CREDENCE were randomized, double-blind, placebo-controlled, event-driven trials evaluating the effects of the SGLT2i canagliflozin on cardiovascular, kidney, and safety outcomes in 14 543 participants with type 2 diabetes at high cardiovascular risk (CANVAS) or with albuminuric CKD (CREDENCE). CANVAS (comprising CANVAS and CANVAS-R [A Study of the Effects of Canagliflozin (JNJ-28431754) on Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus]) enrolled 10 142 participants with type 2 diabetes and established cardiovascular disease or multiple cardiovascular risk factors, whereas CREDENCE enrolled 4401 participants with type 2 diabetes and albuminuric CKD, defined as an estimated glomerular filtration rate (eGFR) of 30 to 90 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and a urine albumin:creatinine ratio (UACR) of 300 to 5000 mg/g. Conventional care was guided by best practices instituted by local guidelines, with use of the maximum tolerated or labeled dose of renin-angiotensin system blockade mandated for entry into the CREDENCE trial.

GLP-1 RA Outcome Trials

A trial-level meta-analysis of 8 randomized, double-blind, placebo-controlled cardiovascular outcome trials (ELIXA [Evaluation of Lixisenatide in Acute Coronary Syndrome], LEADER [Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results], SUSTAIN-6 [Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes], EXSCEL [Exenatide Study of Cardiovascular Event Lowering], Harmony Outcomes [Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies, on Major Cardiovascular Events in Subjects With Type 2 Diabetes Mellitus], REWIND [Dulaglutide and Cardiovascular Outcomes in Type 2 Diabetes], PIONEER-6 [A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes], and AMPLITUDE-O [Effect of Efpeglenatide on Cardiovascular Outcomes]) involving 60 080 participants summarized the effects of GLP-1 RA on type 2 diabetes.[3] Information about participant characteristics and standard care for these trials has been published. ELIXA enrolled patients with acute coronary syndrome; all other trials included patients with stable cardiovascular disease or multiple risk factors. We used overall effect estimates that included ELIXA to be as conservative as possible in our estimates for combination therapy, as the benefits of GLP-1 RA on the studied outcomes, in general, were larger after excluding ELIXA.[3]

FIDELIO-DKD and FIGARO-DKD

FIDELIO-DKD and FIGARO-DKD were 2 randomized, double-blind, placebo-controlled trials that evaluated the effects of the ns-MRA finerenone on CKD progression and cardiovascular events, respectively, in 13 026 patients with type 2 diabetes and albuminuric CKD. FIDELIO enrolled 5674 patients with eGFR of 25 to 75 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and UACR of >300 mg/g. FIGARO recruited 7352 patients with eGFR of 25 to 90 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and UACR of 30 to 300 mg/g or eGFR of >60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and UACR of 300 to 5000 mg/g. All participants in both trials were required to receive the maximum tolerated or labeled dose of renin-angiotensin system blockade.

Outcomes

The primary outcome for this analysis was major adverse cardiovascular events (MACE), defined as nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Other

outcomes included hospitalization for heart failure; CKD progression (defined as doubling of serum creatinine, kidney failure, or death resulting from kidney failure); cardiovascular death; and all-cause mortality. In all trials, outcomes were centrally adjudicated by expert blinded end point committees.

Statistical Analysis

As placebo-treated participants in CANVAS and CREDENCE were used as the "base" population to model survival and the absolute effects of combination therapy, for consistency, we based the relative effects of SGLT2i on cardiorenal outcomes on effect estimates for canagliflozin from the same pooled individual participant trial data. We also did this because the effect of SGLT2i on the primary MACE outcome was not available or pooled in a published meta-analysis for all completed SGLT2 inhibitor outcome trials. As a sensitivity analysis, we used SGLT2i treatment effects obtained from available published meta-analyses.[4,6] Treatment effects for GLP-1 RA were obtained from a trial-level meta-analysis of all 8 completed randomized outcome trials of GLP-1 RA.[3] Treatment effects for ns-MRA were obtained from pooled individual participant pooled data from FIDELIO-DKD and FIGARO-DKD (FIDELITY)[5] and by requesting unpublished data from the investigators for the MACE outcome.

We estimated the relative effects of combination cardiometabolic therapy with SGLT2i, GLP-1 RA, and ns-MRA versus conventional care using established methods for making indirect comparisons that have been applied to both heart failure and CKD trials, assuming independent and additive treatment effects for all medicines.[12–14] These methods have been commonly used in active-controlled trials to estimate the assumed effect of an intervention against a putative placebo. The main combination treatment effect is estimated from the multiplicative product of the treatment effects from each derivative trial (ie, treatment effects additive on the log[hazard ratio] scale). The 95% CIs were estimated as the square root of the sum of squared standard errors of the logarithmic hazard ratios (HRs) from each of the component trials. We also estimated the effects of combination therapy, assuming 50% additivity of GLP-1 RA and ns-MRA when added to SGLT2i. In additional sensitivity analyses, we estimated the lifetime benefits of combination therapy assuming an annual 2% decrease in efficacy over time.

Absolute risk reductions and numbers needed to treat at 1 and 3 years were estimated based on relative treatment effects applied to unadjusted event rates in participants with type 2 diabetes and UACR of ≥30 mg/g receiving conventional care in CANVAS and CREDENCE (ie, the pooled placebo arm). We simulated event-free and overall survival by applying treatment effects of combination therapy to participants with type 2 diabetes and UACR of ≥30 mg/g receiving conventional care (ie, those randomly assigned to placebo) in CANVAS and CREDENCE using validated age-based methods to calculate nonparametric Kaplan-Meier estimates of event-free and overall survival.[12] Details of this method have been previously published.[12,15,16] In brief, age (at baseline and at the time of the event and death) was used as the time component, rather than time from randomization. Because event-free and overall survival depends on patient age at the start of treatment, we calculated projected survival estimates for every age between 50 and 65 years. We first estimated long-term survival of participants with type 2 diabetes and at least moderately increased albuminuria (UACR ≥30 mg/g) in CANVAS and CREDENCE who were receiving conventional care and then simulated projected survival of these patients if treated with combination therapy, with uncertainty around survival gains based on the inverse of the upper and lower CIs of the relative effect of combination therapy. We restricted our analysis to patients with at least moderately increased albuminuria because FIDELIO and FIGARO did not recruit participants with UACR of <30 mg/g. All analyses were done using Stata 17 (StataCorp 2021 Stata Statistical Software: Release 17; StataCorp LLC, College Station, TX).

RESULTS

The estimated HRs for treatment with SGLT2i, GLP-1RA, and ns-MRA, alone and in combination, for cardiovascular, kidney, and mortality outcomes are displayed in Figures 1 and 2. Compared with conventional care, the addition of combination SGLT2i, GLP-1 RA, and ns-MRA was associated with an HR of 0.65 (95% CI, 0.55–0.76) for the primary outcome of MACE (Figure 1). The estimated relative treatment effects of combination therapy on other outcomes were: HR 0.45 (95% CI, 0.34–0.58) for hospitalization for heart failure; HR 0.42 (95% CI, 0.31–0.56) for CKD progression; HR 0.64 (95% CI, 0.51–0.80) for cardiovascular death; and HR 0.67 (95% CI, 0.55–0.80) for all-cause mortality. Estimated relative treatment effects for combination therapy using SGLT2i effect estimates from published meta-analyses were essentially unchanged (Table S1). Relative treatment effects of combination therapy assuming 50% additivity were modestly attenuated: MACE (HR, 0.73 [95% CI, 0.62–0.87]), heart failure hospitalization (HR, 0.53 [95% CI, 0.41–0.70]), CKD progression (HR, 0.51 [95% CI, 0.38–0.68]), cardiovascular death (HR, 0.73 [95% CI, 0.58–0.92]), and all-cause mortality (HR, 0.75 [95% CI, 0.63–0.90]).

We estimated absolute risk reductions and survival gains for SGLT2i, GLP-1 RA, and ns-MRA in 3482 participants with type 2 diabetes and UACR of ≥30 mg/g who received conventional care in CANVAS and CREDENCE. Baseline characteristics for these populations are provided in Table S2. Over a median follow-up of 2.5 years (interquartile range, 2.0–3.2), 439 of 3482 (12.6%) participants experienced the primary outcome; 202 (5.8%) were hospitalized for heart failure; 252 (7.2%) experienced CKD progression; 232 (6.7%) died from cardiovascular disease; and 330 (9.5%) died of any cause.

The estimated absolute risk reduction over 3 years for the primary outcome with combination SGLT2i, GLP-1 RA, and ns-MRA was 4.4% (95% CI, 3.0–5.7), with the corresponding number needed to treat of 23 (95% CI, 18–33; Table S3). Absolute risk reductions over 3 years were 3.4% for heart failure hospitalization, 4.4% for CKD progression, 2.4% for cardiovascular death, and 3.1% for all-cause mortality, with corresponding numbers needed to treat summarized in Table S3.

Among patients 50 years of age, estimated event-free survival for the primary outcome was 21.1 years with combination SGLT2i, GLP-1 RA, and ns-MRA, and 17.9

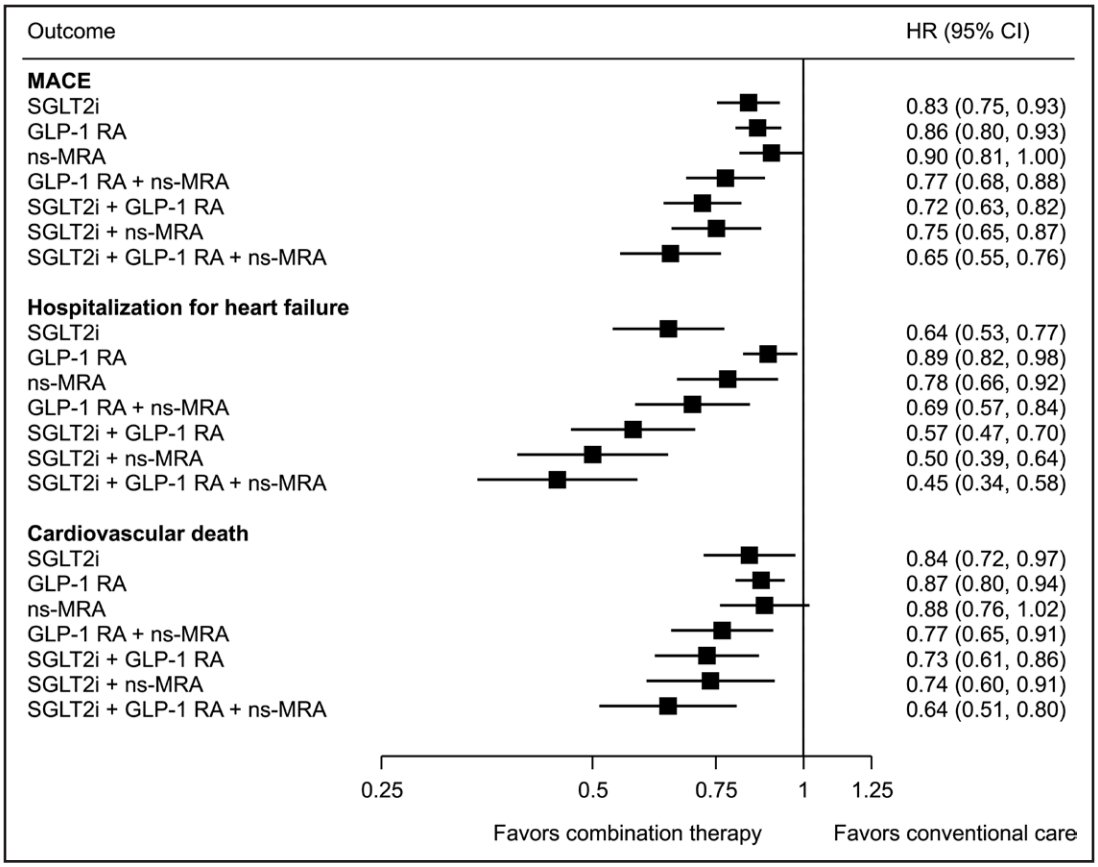

Figure 1. Estimated treatment effects on cardiovascular outcomes with SGLT2i, GLP-1 RA, and ns-MRA, alone and in combination, when added to renin-angiotensin system blockade in patients with type 2 diabetes.

GLP-1 RA indicates glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death); ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; and SGLT2i, sodium glucose cotransporter-2 inhibitor.

years with conventional care (difference, 3.2 years [95% CI, 2.1–4.3]; Figure 2). Gains in event-free survival for heart failure hospitalization were 3.2 years (95% CI, 2.4–4.0), 5.5 years (95% CI, 4.0–6.7) for CKD progression, 2.2 years (95% CI, 1.2–3.0) for cardiovascular death, and 2.4 years (95% CI, 1.4–3.4) for all-cause mortality (Figures 3 through 6). Gains in event-free and overall survival were consistent in analyses using SGLT2i treatment effect estimates from published meta-analyses (Table S4).[4,6] In analyses assuming 50% additive effects (Figures S1 and S2), estimated gains in event-free and overall survival were modestly attenuated: MACE (2.4 years [95% CI, 1.1–3.5]), heart failure hospitalization (2.7 years [95% CI, 1.7–3.5]), CKD progression (4.5 years [95% CI, 2.8–5.9]), cardiovascular death (1.6 years [95% CI, 0.5–2.5]), and all-cause mortality (1.8 years [95% CI, 0.7–2.8]). These estimates were similar in additional sensitivity analyses assuming an annual 2% decrease in efficacy over time (Figures S3 and S4).

Absolute gains in event-free and overall survival were evident across all ages studied, with the greatest absolute benefit in younger patients. For the primary outcome, gains in event-free survival with combination SGLT2i, GLP-1 RA, and ns-MRA at 55, 60, and 65 years of age were 2.7 (95% CI, 1.8–3.6), 2.1 (95% CI, 1.4–2.7), and 1.3 (95% CI, 0.9–1.8), respectively (Figure 3). Gains in event-free and overall survival were still observed across different ages assuming 50% additive effects and an annual 2% decrease in efficacy over time (Figures S1 through S4).

DISCUSSION

In this cross-trial analysis, combination treatment with SGLT2i, GLP-1 RA, and ns-MRA was projected to result in relevant gains in cardiovascular and kidney event-free survival, as well as overall survival in patients with type 2 diabetes and at least moderately increased albuminuria. Despite modest attenuation of effects, relevant gains in event-free and overall survival were still observed in analyses assuming 50% additive effects and if efficacy waned over time. These findings highlight major opportunities to delay or potentially avert cardiovascular events and premature death with combined use of SGLT2i, GLP-1RA, and ns-MRA for patients with type 2 diabetes at high cardiorenal risk.

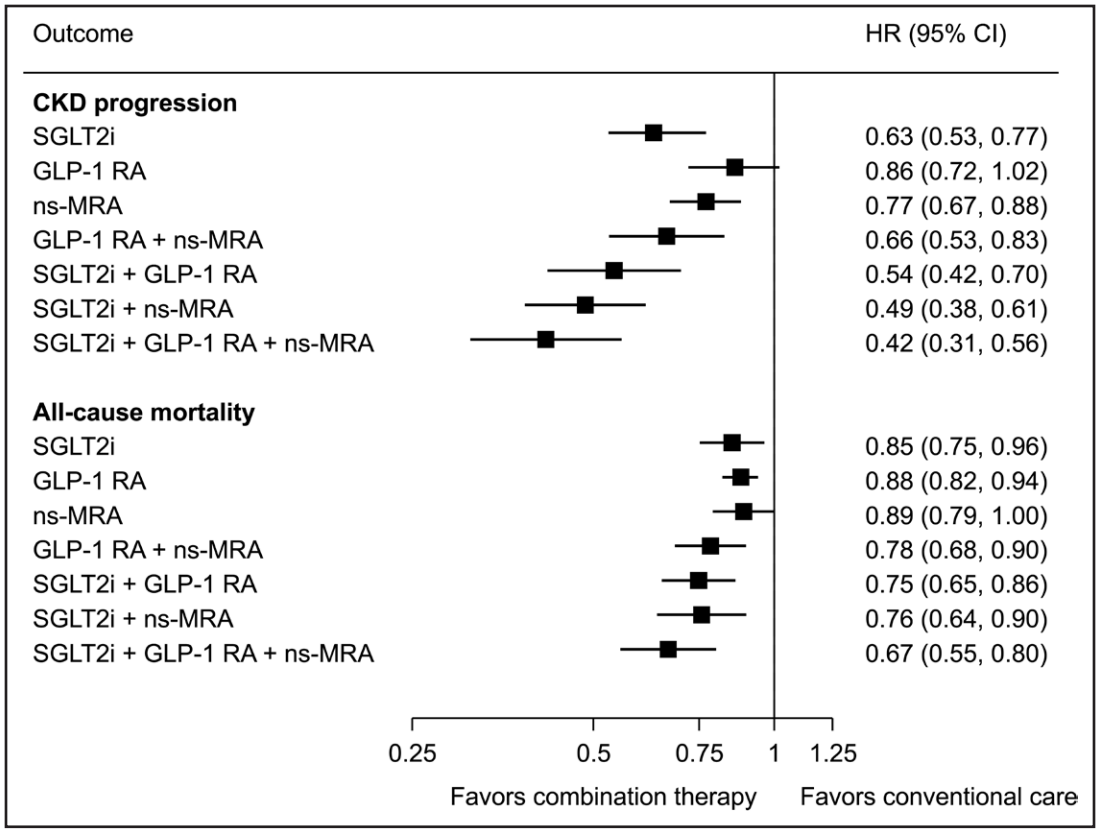

Figure 2. Estimated treatment effects on CKD progression and all-cause mortality with SGLT2i, GLP-1 RA, and ns-MRA, alone and in combination, when added to renin-angiotensin system blockade in patients with type 2 diabetes.
CKD progression defined as doubling of serum creatinine, kidney failure, or death resulting from kidney failure, apart from with GLP-1 RAs, for which it was defined as sustained reduction in kidney function, kidney failure, or death resulting from kidney failure. CKD indicates chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; ns-MRA, nonsteroidal mineralocorticoid receptor antagonist; and SGLT2i, sodium glucose cotransporter-2 inhibitor.

The complex pathophysiology underpinning the development and progression of cardiovascular and kidney disease in people with type 2 diabetes calls for a multifaceted approach to improve clinical outcomes. The concept of combination therapy with SGLT2i, GLP-1 RA, and ns-MRA, in addition to treatment with renin-angiotensin system blockade in patients with albuminuria, is therefore attractive, as these medicines target metabolic dysregulation, hemodynamic perturbations, and inflammation through differing and complementary mechanisms of action. For example, SGLT2i reduces intraglomerular pressure (among other actions), ns-MRA reduces inflammation and fibrosis, whereas GLP-1 RA addresses the underlying metabolic abnormalities that are pathognomonic of type 2 diabetes.[7] Such a "pillared" approach is reminiscent of our contemporary guideline-supported management strategy for heart failure with reduced ejection fraction.[17,18]

There are several lines of evidence supporting a multimedicine approach to patients with type 2 diabetes at high cardiorenal risk. First, short-term randomized trials demonstrate that combined use of SGLT2i and GLP-1 RA improves intermediate markers of cardiorenal risk better than either therapy alone.[19–23] In a preclinical randomized trial using an animal model of CKD, combination renin-angiotensin system blockade, SGLT2i, and ns-MRA resulted in a substantial improvement in survival compared with single- or 2-medicine regimens.[24] These results are supported by a randomized trial on patients with CKD that demonstrated that SGLT2i and the steroidal MRA eplerenone reduced albuminuria to a greater extent than either alone.[25]

Second, subgroup analyses from large, randomized outcome trials suggest that the effects of each medicine are not modified by background care, indicating additive effects. The AMPLITUDE-O trial included the largest proportion of patients receiving SGLT2i at baseline (15.2%) of any GLP-1 RA outcome trial, with stratified randomization by baseline or anticipated use of SGLT2i.[26] In this trial, reductions in cardiovascular events with efpeglenatide were consistent regardless of SGLT2i use. In the DECLARE-TIMI 58 trial (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis in Myocardial Infarction 58), effects of dapagliflozin were similarly consistent regardless of GLP-1 RA use.[27] In the pooled FIDELITY analysis, the effects of finerenone on cardiorenal outcomes were consistent regardless of SGLT2i and GLP-1 RA use,[28] although only a small proportion of patients

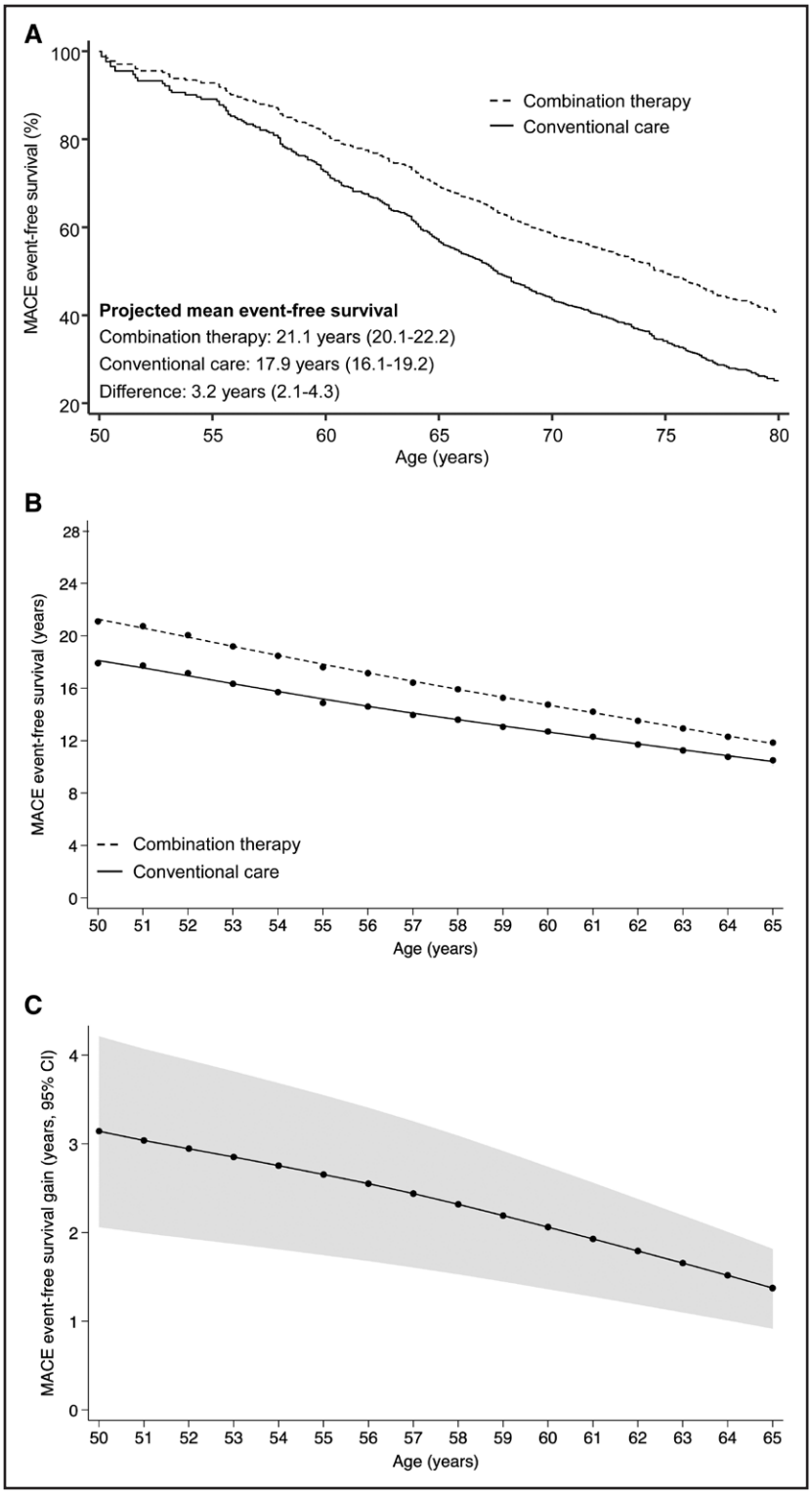

Figure 3. Treatment benefits of combination sodium glucose cotransporter-2 inhibitor, glucagon-like peptide-1 receptor agonist, and nonsteroidal mineralocorticoid receptor antagonist on survival free from MACE when added to renin-angiotensin system blockade in patients with type 2 diabetes and urine albumin:creatinine ratio ≥30 mg/g. **A**, Event-free survival among people 50 years of age at baseline. **B**, Mean event-free survival with combination therapy vs conventional care for every age between 50 and 65 years. **C**, Gains in event-free survival by for every age between 50 and 65 years. MACE indicates major adverse cardiovascular events.

were receiving SGLT2i or GLP-1 RA in these trials. Third, there may be safety advantages of using SGLT2i and ns-MRA in combination because of the reduction in risk of hyperkalemia observed with SGLT2i.[29] Finally, routinely collected observational data from the United Kingdom support the randomized evidence, with combination SGLT2i and GLP-1 RA use associated with the lowest risk of MACE in a primary prevention population compared with either agent alone.[30] Thus, currently available data support the concept of additive cardiorenal protection with combined use of each medicine class.

Updated major guidelines already recommend a multimedicine strategy, tailored to individuals' residual cardiorenal risk. The Kidney Disease Improving

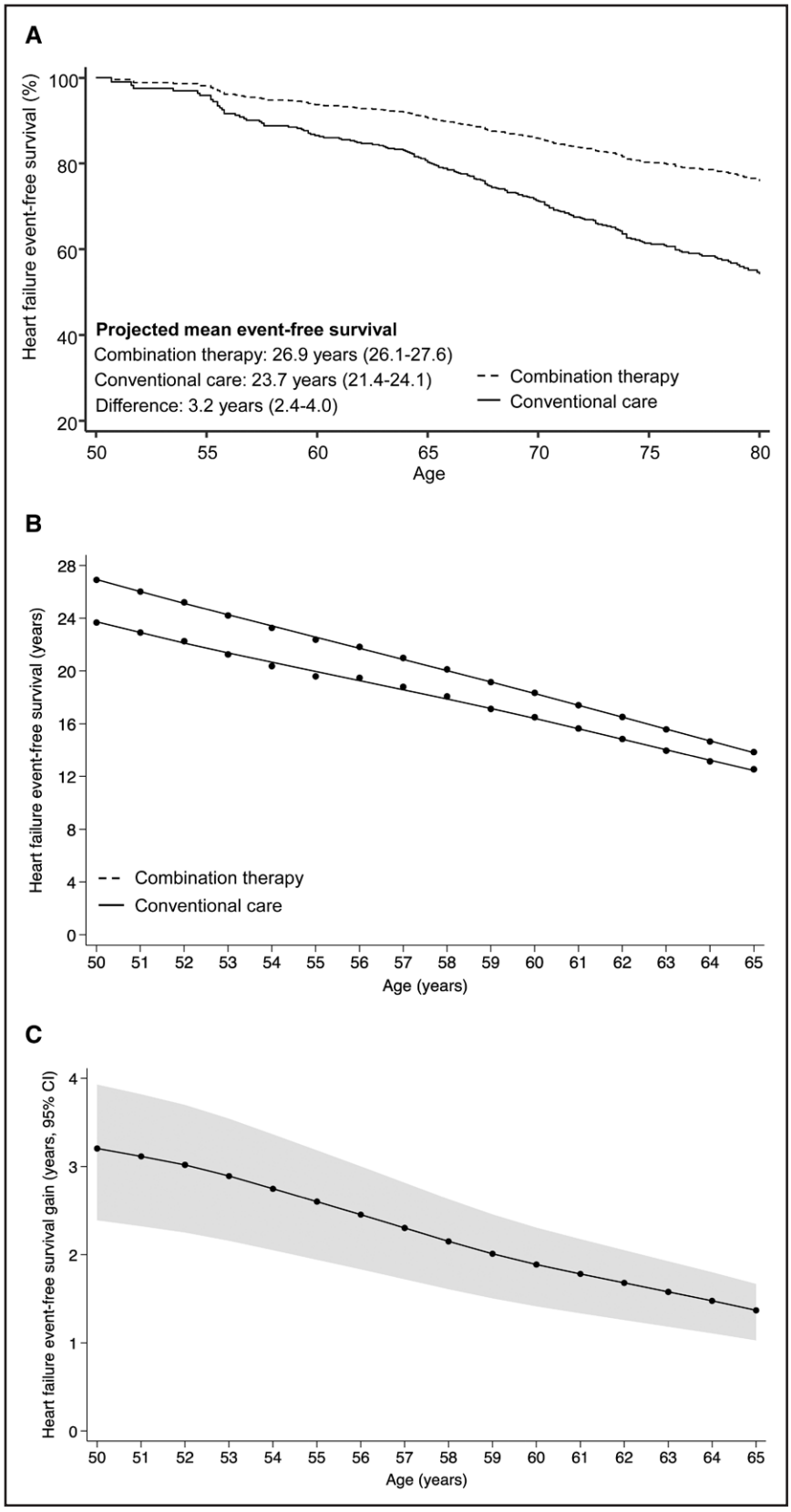

Figure 4. Treatment benefits of combination sodium glucose cotransporter-2 inhibitor, glucagon-like peptide-1 receptor agonist, and nonsteroidal mineralocorticoid receptor on survival free from hospitalization for heart failure when added to renin-angiotensin system blockade in patients with type 2 diabetes and urine albumin:creatinine ratio ≥30 mg/g.

A, Event-free survival among people 50 years of age at baseline. **B**, Mean event-free survival with combination therapy vs conventional care for every age between 50 and 65 years. **C**, Gains in event-free survival by for every age between 50 and 65 years. MACE indicates major adverse cardiovascular events.

Global Outcomes Guidelines recommend a stepwise approach to managing type 2 diabetes and CKD, with renin-angiotensin system blockade and SGLT2i as first-line therapy, and GLP-1 RA and ns-MRA recommended next for additional cardiorenal protection.[1] Likewise, joint guidelines from the American Diabetes

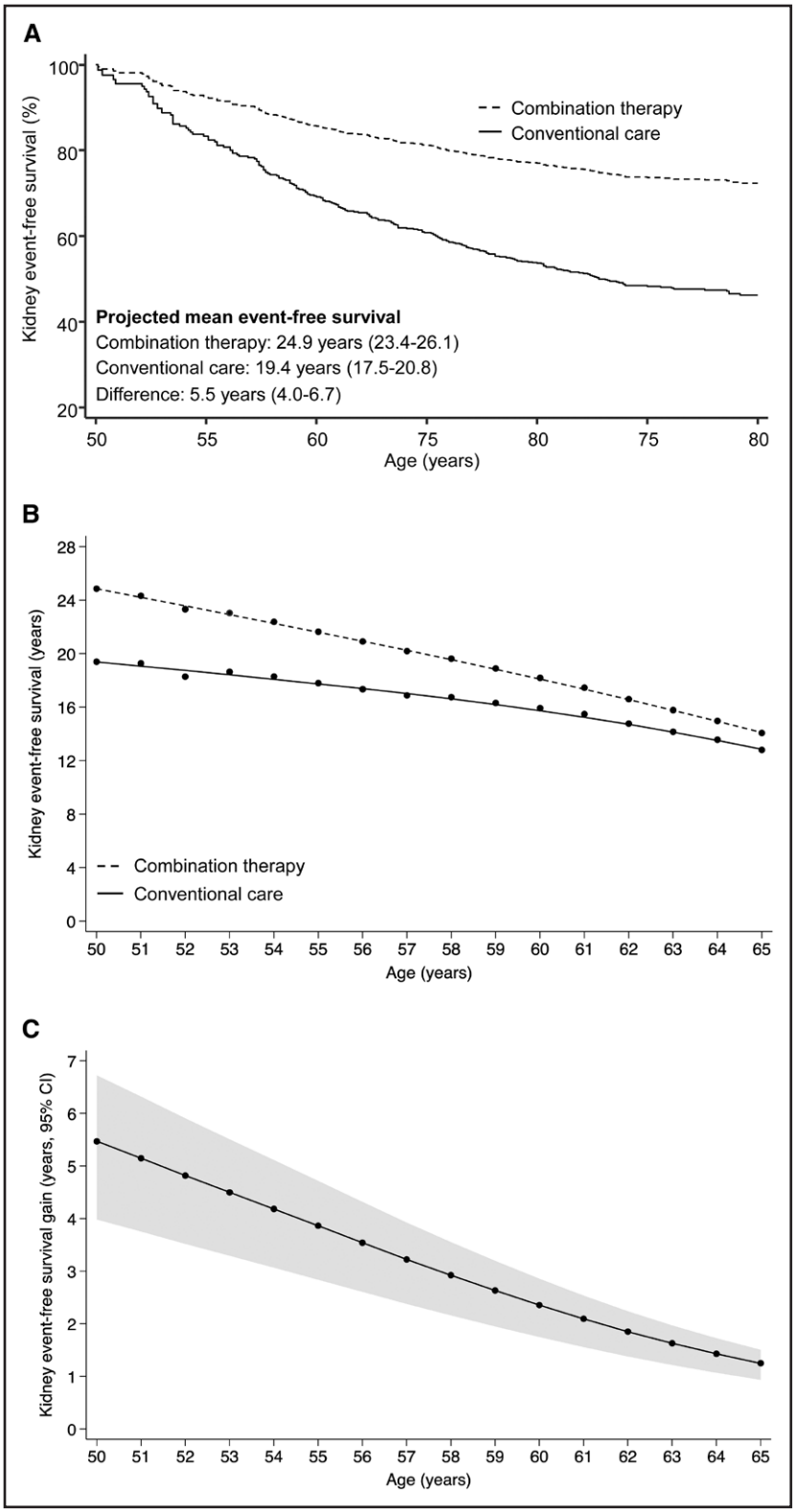

Figure 5. Treatment benefits of combination sodium glucose cotransporter-2 inhibitor, glucagon-like peptide-1 receptor agonist, and nonsteroidal mineralocorticoid receptor on survival free from chronic kidney disease progression when added to renin-angiotensin system blockade in patients with type 2 diabetes and albuminuria (urine albumin:creatinine ratio ≥30 mg/g). **A**, Event-free survival among people 50 years of age at baseline. **B**, Mean event-free survival with combination therapy vs conventional care for every age between 50 and 65 years. **C**, Gains in event-free survival by for every age between 50 and 65 years. Chronic kidney disease progression is defined as doubling of serum creatinine, kidney failure, or death resulting from kidney failure.

Association and the European Association for the Study of Diabetes recommend that a GLP-1RA is added preferentially as second-line therapy for a patient receiving an SGLT2i and vice versa.[2] The United Kingdom National Institute for Clinical Excellence recommends adding finerenone to an SGLT2i for patients with type 2 diabetes and CKD who have residual albuminuria.[31] By quantifying gains in survival with these medicines, our findings may help inform shared decision-making by patients and clinicians, and may increase the uptake of these guideline-supported medicines, which, to date, has been suboptimal in patients with diabetes and

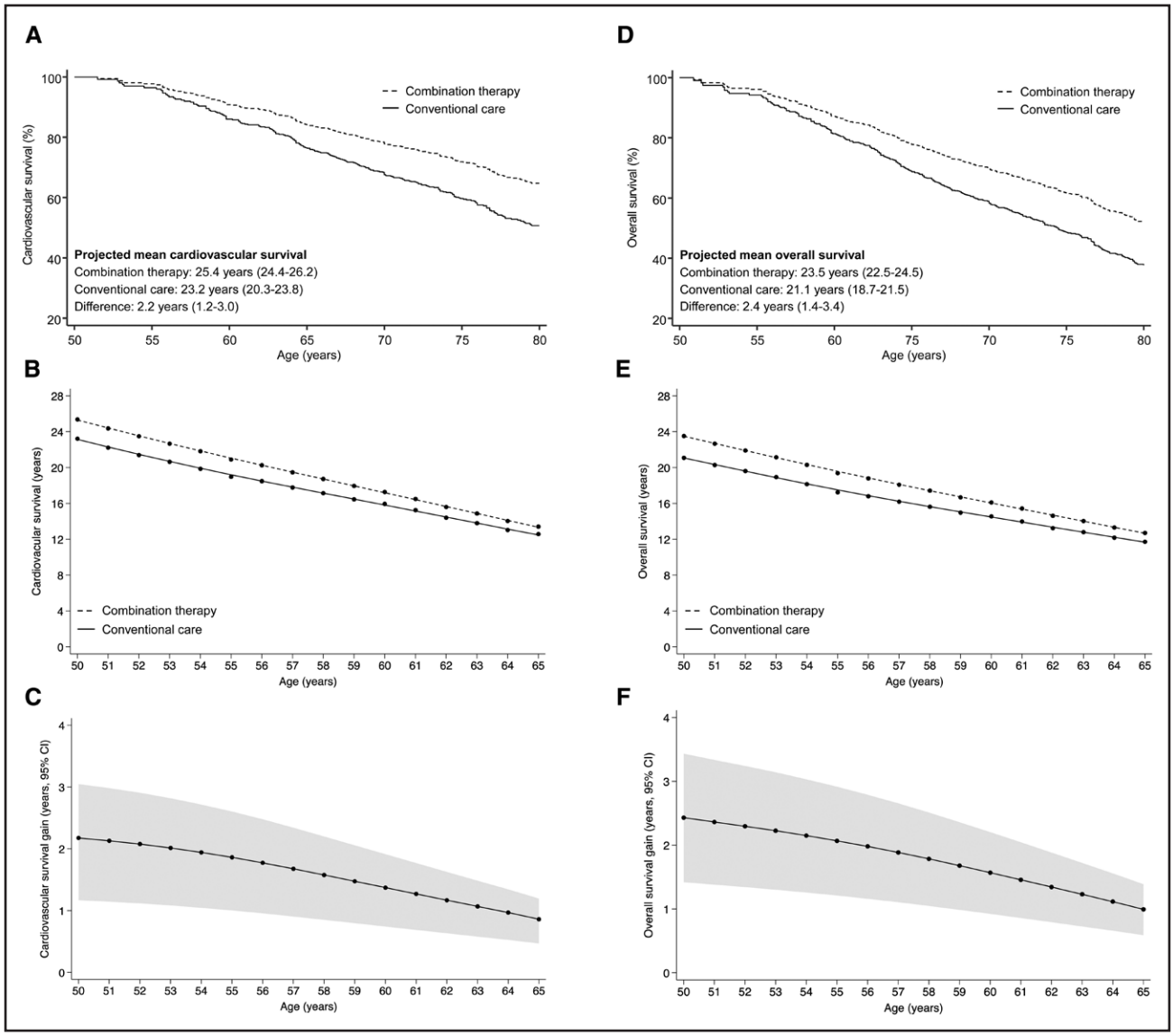

Figure 6. Treatment benefits of combination sodium glucose cotransporter-2 inhibitor, glucagon-like peptide-1 receptor agonist, and nonsteroidal mineralocorticoid receptor on cardiovascular and overall mortality when added to renin-angiotensin system blockade in patients with type 2 diabetes and albuminuria (urine albumin:creatinine ratio ≥30 mg/g).
A and **D**, Cardiovascular and overall survival among people 50 years of age at baseline. **B** and **E**, Mean cardiovascular and overall survival with combination therapy vs conventional care for every age between 50 and 65 years. **C** and **F**, Gains in cardiovascular and overall survival by for every age between 50 and 65 years.

established cardiovascular disease or CKD in routine practice.[32,33]

Although the benefits of combination therapy are very likely to offer major benefits to many individuals, a substantial proportion of patients with type 2 diabetes and albuminuria are still yet to receive even one of these medicines,[32] highlighting the multilevel challenges to global implementation of multidrug regimens. Cost is a major and often-cited barrier to wider adoption of these evidence-based medicines. However, implementation gaps have been observed even for lower-cost therapies for cardiovascular and kidney disease,[34] and some of these therapies are now available (or soon to be available) in generic formulations. At the societal level, costs of therapeutic care must be balanced against the potential downstream economic effect of reducing multiple adverse health outcomes, especially the provision of dialysis for kidney failure, which is among the costliest treatments provided in most health care systems around the world.[35,36] Thus, broad-based economic evaluations of the cost-effectiveness of these medicines, alone and in combination, will also help inform health care policymakers and payers. From a practical perspective, how to best initiate and minimize side effects to maintain persistent use of these medicines is a critically important area for

research, as is a better understanding of the resources required to do so.

With the growing burden of cardio-renal-metabolic comorbidities, additional randomized evidence would be welcome. The CONFIDENCE trial (Combination Effect of Finerenone and Empagliflozin) will evaluate the effect of finerenone and empagliflozin compared with either alone on a primary outcome of change in albuminuria in 807 patients with type 2 diabetes and CKD.[37] The PRECIDENTD pragmatic randomized trial (Prevention of Cardiovascular and Diabetic Kidney Disease in Type 2 Diabetes) is underway and will prospectively assess the effects of combination SGLT2i and GLP-1 RA versus either therapy alone on clinical outcomes for 9000 patients with type 2 diabetes with established cardiovascular disease or with multiple cardiovascular risk factors.[38] In addition, the FLOW trial (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) is evaluating the effect of semaglutide on a primary outcome of sustained 50% decline in eGFR, kidney failure, or death resulting from cardiovascular disease or kidney failure in 3534 patients with type 2 diabetes and albuminuric CKD (15.5% of whom were receiving SGLT2i at baseline).[39] The trial has been stopped on the basis of recommendations from the data monitoring committee after prespecified efficacy criteria were met at an interim analysis, confirming the renoprotective effects of GLP-1 RA for patients with type 2 diabetes; results are expected this year.[40]

This analysis relies on several assumptions that are important to recognize when interpreting our findings. Our lifetime projections assume that treatment effects and adherence remain consistent over time, although this may not be the case in routine practice. However, it is noteworthy that our modeling does incorporate nonadherence and treatment discontinuation as observed during the trials (in keeping with an intention-to-treat approach). In addition, attenuated but clinically relevant benefits were still observed in models assuming waning treatment effects over time. It is possible that SGLT2i, GLP-1 RA, and ns-MRA may have some overlap in their mechanisms of benefit, and thus combination treatment effects may be subadditive; nevertheless, important gains in event-free survival were still observed assuming only 50% additivity. Other important factors such as discontinuation because of cost, polypharmacy, or side effects are likely to affect the applicability of these results at a population level. We assume a class effect for each of the 3 classes of medicines, but this may not be the case, especially for GLP-1 RA. Nevertheless, use of trial-level data of all completed GLP-1 RA trials offers the most conservative estimate of the benefits of this class of medicine, and sensitivity analyses using published SGLT2i meta-analyses yielded effectively identical results. Estimates for the effect of GLP-1RA on CKD progression were based on a trial-level meta-analysis in which the CKD progression end point definition, specifically eGFR decline threshold, varied across trials. In addition, absolute survival gains were modeled on patients in CANVAS and CREDENCE and may not be generalizable to routine care settings. It is notable that previous estimated survival projections using these same actuarial methods applied to clinical trials closely aligned with survival observed during long-term post-trial follow-up.[15,41] Nevertheless, while awaiting randomized evidence of combination therapy, our findings provide support for the notion that meaningful gains in cardiorenal event-free and overall survival can be anticipated using these classes of medicines simultaneously.

In summary, for patients with type 2 diabetes and at least moderately increased albuminuria, treatment with combination SGLT2i, GLP-1 RA, and ns-MRA has the potential to afford relevant gains in cardiovascular and kidney event-free and overall survival.

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Supplemental Material

Tables S1–S4

Figures S1–S4

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