Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Men or women ≥30 years of age at time of diabetes diagnosis; for American Indians, age is >20 years at time of diagnosis
2. Duration of diagnosed diabetes <10 years determined as accurately as possible based on available records at screening
3. HbA1c criteria (at final run-in visit, ~2 weeks prior to randomization): 6.8-8.5%
4. Taking a daily dose of >1000 mg metformin for a minimum of 8 weeks at final run-in
5. Willingness to administer daily subcutaneous injections, take a second glucose-lowering drug after randomization, potentially initiate insulin and intensify insulin therapy if study metabolic goals are not met, and perform self-monitoring of blood glucose
6. Fluent in either English or Spanish
7. A negative pregnancy test for all females of childbearing potential (i.e. pre-menopausal, and not surgically sterile)
8. Provision of signed and dated informed consent prior to any study procedures

Exclusion Criteria

1. Suspected type 1 diabetes (lean with polyuria, polydipsia, and weight loss with little response to metformin) or "secondary" diabetes due to specific causes (e.g. previously diagnosed monogenic syndromes, pancreatic surgery, pancreatitis)
2. Current or previous (within past 6 months) treatment with any diabetes drug/glucose-lowering medication other than metformin (limited use of no longer than seven days is allowed, for example during hospitalization)
3. More than 10 years of treatment with metformin at time of screening
4. History of intolerance or allergy or other contraindications to any of the proposed study medications
5. Resides in the same household with another GRADE study participant
6. Current need for any specific glucose-lowering medications solely for other conditions, for example for polycystic ovary syndrome
7. Symptomatic hyperglycemia requiring immediate therapy during screening or run-in, in the judgment of the physician
8. A life-threatening event within 30 days prior to screening or currently planned major surgery
9. Any major cardiovascular event in previous year, including history of myocardial infarction, stroke, or vascular procedure such as coronary artery or peripheral bypass grafting, stent placements (peripheral or coronary) or angioplasty.
10. Plans for pregnancy during the course of the study for women of child-bearing potential
11. History of or planning bariatric surgery, including banding procedures or surgical gastric and/or intestinal bypass (if banding removed, may be considered eligible after 1 year).
12. History of congestive heart failure (NYHA 3 or greater)
13. History of pancreatitis
14. Any new diagnosis of cancer in the previous 5 years (other than non-melanoma skin cancer), or treatment for any cancer in the previous 5 years (other than non-melanoma skin cancer). Exceptions may be made, at the discretion of the local Principal Investigator and after review by the subcommittee overseeing protocol implementation, for cancers, such as some thyroid cancers, that have a benign clinical course and are not expected to interfere with conduct of the study.
15. Personal or family history of MEN-2 or family history of medullary thyroid cancer
16. Estimated GFR (eGFR) <30 ml/min/1.73 m2 or end stage renal disease requiring renal replacement therapy
17. History of severe liver disease or acute hepatitis or ALT >3 times upper limit of normal
18. Current alcoholism or excessive alcohol intake
19. Previous organ transplant
20. Treatment with oral or systemic glucocorticoids (other than short-term treatment, for example for poison ivy) or disease likely to require periodic or regular glucocorticoid therapy (inhaled steroids and/or physiological replacement treatment are allowed, e.g. for Addison's disease)
21. Treatment with atypical antipsychotics known to be associated with a high risk of metabolic dysfunction

22. History of hemolytic anemia, chronic transfusion requirement, or other condition rendering HbA1c results unreliable as indicator of chronic glucose levels, or hematocrit <35 for males and <33 for females
23. Clinically or medically unstable with expected survival <1 year
24. Unwillingness to permit sites to contact the PCP to communicate information about the study and the participant's data
25. At the time of final run-in, no identified PCP to provide non-study care. (Note: in cases where a study MD serves as the participant's PCP, another study provider must assume GRADE management decisions for the participant during the study.)
26. Participation in another interventional clinical trial
27. Previous randomization in the GRADE study
28. In the opinion of the principal investigator (PI), any other factor, including language barrier, likely to limit compliance with the protocol

eMethods 2. Supplementary Methods

Analysis of Secondary Outcomes

The secondary outcomes are the change in eGFR from baseline to year 1 and from baseline to end of study, mean eGFR over the entire study, time to progression to eGFR<60 mL/min/1.73m^2 among those with baseline eGFR above that threshold, time to 40% decline in eGFR to an eGFR<60 mL/min/1.73m^2, time to doubling of UACR to a level of ≥30 mg/g creatinine, and time to KDIGO category increase from baseline. For each of the seven secondary outcomes, a test for treatment heterogeneity was performed within the appropriate model as described below. The p-values from these seven tests were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate procedure. For any outcome for which the adjusted p-value is significant at the 0.05 level, we performed the six pairwise tests comparing each treatment to every other treatment using contrasts from the model and adjusting the six p-values for multiple comparisons using the Holm procedure. The followings models were used for the secondary outcomes:

eGFR change between baseline and year 1: used a linear regression model with the year 1 eGFR as the response and treatment and baseline eGFR as covariates. The model included all participants with a year 1 visit.

Mean eGFR over the entire study: used a GEE model with treatment group as the only covariate and an AR1 initial correlation structure.

Time to event outcomes: each of the remaining five secondary outcomes was tested using a logrank test. The analysis for time to progression to eGFR <60 ml/min/1.73m 2 is restricted to participants whose baseline eGFR was ≥ 60 ml/min/1.73m^2. The remaining analyses included all participants with at least one visit after the baseline visit.

Subgroup Analyses of the Co-primary Outcomes

For each of the two primary outcomes for each of the nine subgroups we conducted a test of treatment heterogeneity across all levels of the subgroup variable for a total of 18 tests. The tests of heterogeneity were conducted as follows:

For the first primary outcome (eGFR slope from Year 1), the test was conducted using the same GEE model as described in the statistical analysis section, adding a term for subgroup as well as interactions for subgroup by each of the terms in the original model. A likelihood ratio test of the three-way interaction of treatment group by time by subgroup tests for heterogeneity of slopes in this model.

For the second primary outcome (time to kidney disease progression), terms for subgroup and a treatment-by-subgroup interaction are added to the model described in the statistical analysis section. A test of the interaction tests for treatment heterogeneity across subgroups.

The nine p-values for each outcome are adjusted for false discovery using the Benjamini-Hochberg method (each outcome is adjusted separately). If the adjusted p-value for a given outcome and subgroup were significant at the 0.05 level, we prespecified that we would perform the six pairwise comparisons of treatments group within each stratum of the subgroup variable. Each set of six pairwise comparison would be separately adjusted for multiple comparisons using the Holm method.

Sensitivity Analyses

Per-protocol sensitivity analyses were censored at the last visit prior to deviation from the assigned treatment regimen. Deviations from protocol included discontinuation of metformin, discontinuation of the randomly assigned second medication, or addition of any glucose-lowering medication other than the randomly assigned medication and protocolized treatment (i.e., the addition of glargine and aspart insulin if HbA1c rose above 7.5%, confirmed). Thus, per-protocol analyses included participants who met the following criteria: 1) at least one follow-up visit; 2) reported taking at least 1 dose of metformin and of their randomized study medication.

Addition of SGLT2 inhibitor or off-protocol use of GLP-1 receptor agonist. The second set of sensitivity analyses explored the effect of the addition of SGLT2 inhibitor to any treatment group or GLP-1 receptor agonist use in the

sitagliptin, glimepiride, or glargine treatment groups on the primary outcomes. These analyses modeled change in effect at the time of addition of the new medication using time-varying covariates.

Statistical Analysis Plan

The final statistical analysis plan (SAP) for this this manuscript was version 0.14, February 18, 2022. Analyses followed the SAP with the following deviations. Mediation analyses were proposed in Sub Aim 1 but were not pursued given the robust null findings among treatment groups. The composite Wei-Lachin standardized test of trend proposed for the secondary outcomes was suspended due to technical issues with combining analyses from GEE models and proportional hazards models.

eTable 1. Characteristics of included and excluded participants

	Included	Excluded	p-value
	4,949 (98.1%)	98 (1.9%)	
Demographics			
Age at baseline visit (years)	57.2+/-10.0	55.9+/-9.6	0.186
Age group (years)			0.493
<45 years	604 (12.2%)	15 (15.3%)	
45-59 years	2,278 (46.0%)	47 (48.0%)	
60+ years	2,067 (41.8%)	36 (36.7%)	
Female sex	1,796 (36.3%)	41 (41.8%)	0.306
Race			0.239
Am Ind/Alaska Native	135 (2.7%)	2 (2.0%)	
Asian/Hawaiian/Pacific Isl	207 (4.2%)	3 (3.1%)	
Black or African-American	974 (19.7%)	26 (26.5%)	
White	3,258 (65.8%)	56 (57.1%)	
Other/unknown	375 (7.6%)	11 (11.2%)	
Ethnicity			0.006
Non-Hispanic	4,012 (81.7%)	65 (69.9%)	
Hispanic	901 (18.3%)	28 (30.1%)	
Education completed			0.001
<High school	349 (7.1%)	15 (15.3%)	
College degree or above	2,153 (43.5%)	27 (27.6%)	
HS graduate	1,015 (20.5%)	24 (24.5%)	
Some college	1,431 (28.9%)	32 (32.7%)	
Blood pressure (BP)			
Systolic (mmHg)	128.3+/-14.7	128.7+/-16.3	0.824
Diastolic (mmHg)	77.3+/-9.8	77.6+/-11.7	0.825
Treated with ACEI/ARB	2,882 (58.2%)	51 (52.0%)	0.260
History of hypertension	3,279 (66.3%)	60 (61.2%)	0.350
Baseline ASCVD (MI plus stroke)	322(6.5%)	6(6.1%)	1.000
Diabetes			
BMI (kg/m^2)	34.3+/-6.8	34.1+/-7.0	0.795
Duration of diabetes (years)	4.2+/-2.7	3.5+/-2.5	0.005
HbA1c (%)	7.5+/-0.5	7.5+/-0.5	0.364
HbA1c (mmol/mol)	58.3+/-5.3	58.8+/-5.1	0.364
Renal			
eGFR (mL/min/1.73m^2)	94.8+/-16.8	96.2+/-17.4	0.443
eGFR < 60	124 (2.5%)	1 (1.0%)	0.543
Urine ACR median/IQR (mg/g)	6.4 [3.0, 16.9]	7.4 [3.3, 13.2]	0.765
Moderately elevated albuminuria	706 (14.3%)	10 (10.2%)	0.317
Severely elevated albuminuria	84 (1.7%)	0 (0.0%)	0.366

eTable 2. Clinical characteristics related to kidney outcomes at years 1 and 4.

eTable 2a. Clinical characteristics at 1 year

	All	Glargine	Glimepiride	Liraglutide	Sitagliptin	p-value
N	4,813	1,193	1,202	1,203	1,215	
Blood pressure (BP)						
Systolic ($mmHg$)	127.8±15.2	128.7±15.4	128.7±14.7	126.2±15.3	127.8±15.4	<0.001
Diastolic ($mmHg$)	75.9±9.8	76.0±9.8	75.9±9.5	75.9±9.8	75.6±9.9	0.838
Treated with ACEI/ARB	2,916 (60.6%)	736 (61.7%)	741 (61.6%)	720 (59.9%)	719 (59.2%)	0.482
Hypertension	4,506 (93.6%)	1,133 (95.0%)	1,136 (94.5%)	1,116 (92.8%)	1,121 (92.3%)	0.015
Treatment of hypertension	3,609 (75.0%)	911 (76.4%)	903 (75.1%)	903 (75.1%)	892 (73.4%)	0.421
Diabetes						
BMI (kg/m^2)	34.0±6.7	34.5±6.8	34.6±6.9	33.1±6.4	33.7±6.6	<0.001
Duration of diabetes (years)	4.3±2.7	4.2±2.7	4.4±2.8	4.2±2.7	4.2±2.7	0.462
HbA1c (%)	6.8±0.9	6.8±0.8	6.8±0.8	6.7±0.9	7.0±0.9	<0.001
Kidney parameters						
eGFR ($mL/min/1.73m^2$)	93.7±17.5	93.5±17.1	93.9±17.4	93.4±18.0	93.8±17.4	0.873
eGFR < 60	183 (3.8%)	41 (3.4%)	40 (3.3%)	54 (4.5%)	48 (4.0%)	0.424
Urine ACR median/IQR (mg/g)	5.9 [2.9, 16.0]	6.0 [2.9, 15.8]	5.9 [2.9, 17.3]	6.1 [3.0, 15.9]	5.6 [2.9, 15.5]	0.561
Moderately elevated albuminuria	648 (13.5%)	156 (13.1%)	175 (14.6%)	161 (13.4%)	156 (12.9%)	0.625
Severely elevated albuminuria	73 (1.5%)	17 (1.4%)	21 (1.7%)	17 (1.4%)	18 (1.5%)	0.901

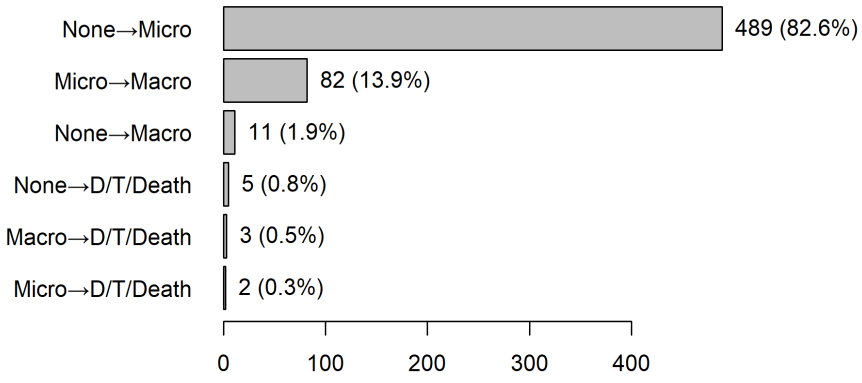
Continuous variables are summarized as mean +/- standard deviation or as the median (interquartile range). Categorical variables are summarized as counts and column percentages.
The p-values are based on t-test for continuous variables and chi-squared tests for binary and categorical variables.

eTable 2b. Clinical characteristics at 4 years

	All	Glargine	Glimepiride	Liraglutide	Sitagliptin	p-value
N	3,895	963	966	983	983	
Blood pressure (BP)						
Systolic ($mmHg$)	128.4±16.2	129.5±16.6	128.6±16.0	127.3±16.3	128.3±15.7	0.047
Diastolic ($mmHg$)	75.9±9.7	76.5±9.8	75.3±9.7	76.0±9.7	75.7±9.7	0.055
Treated with ACEI/ARB	2,510 (64.4%)	644 (66.9%)	644 (66.7%)	593 (60.3%)	629 (64.0%)	0.008
Hypertension	3,595 (92.3%)	900 (93.5%)	903 (93.5%)	887 (90.2%)	905 (92.1%)	0.021
Treatment of hypertension	3,201 (82.2%)	807 (83.8%)	806 (83.4%)	786 (80.0%)	802 (81.6%)	0.097
Diabetes						
BMI (kg/m^2)	33.8±6.8	34.3±6.9	34.2±6.9	33.1±6.6	33.5±6.9	<0.001
Duration of diabetes (years)	4.3±2.7	4.3±2.7	4.3±2.8	4.3±2.7	4.2±2.7	0.467
HbA1c (%)	7.2±1.2	7.1±1.1	7.3±1.1	7.1±1.1	7.2±1.2	0.010
Kidney parameters						
eGFR ($mL/min/1.73m^2$)	87.4±19.5	87.3±19.5	87.9±19.4	87.0±19.7	87.4±19.4	0.756
eGFR < 60	373 (9.6%)	91 (9.4%)	91 (9.4%)	99 (10.1%)	92 (9.4%)	0.945
Urine ACR median/IQR (mg/g)	7.9 [4.0, 21.3]	7.9 [3.9, 21.7]	8.4 [4.2, 22.9]	7.6 [3.9, 20.5]	7.3 [3.9, 19.4]	0.115
Moderately elevated albuminuria	614 (16.0%)	149 (15.7%)	178 (18.7%)	152 (15.6%)	135 (14.0%)	0.040
Severely elevated albuminuria	104 (2.7%)	23 (2.4%)	27 (2.8%)	24 (2.5%)	30 (3.1%)	0.762

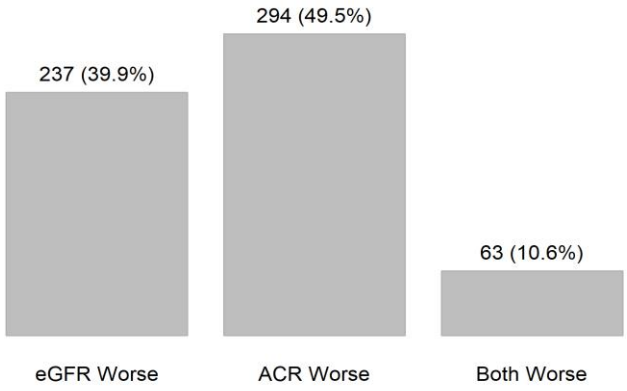
Continuous variables are summarized as mean +/- standard deviation or as the median (interquartile range). Categorical variables are summarized as counts and column percentages. The p-values are based on t-test for continuous variables and chi-squared tests for binary and categorical variables.

eFigure 1. Distribution of composite kidney outcome components
Events among the 592 participants with confirmed kidney disease progressions. The label D/T/Death refers to dialysis, transplant or death.



eFigure 2. Distribution of KDIGO category progression

Among the 594 participants with a confirmed KDIGO category worsening, distribution of those with eGFR stage progression, albuminuria (ACR) stage progression, or progression in both eGFR and albuminuria stage



eTable 3. Heterogeneity across subgroups

The models used for the tests of treatment heterogeneity across the levels of pre-specified subgroup variable are based on a GEE models are described in the method section. The false-discovery adjusted p-values are in the table below:

	Adjusted P Values	
Outcome	eGFR slope from year 1	Kidney disease progression
Age	0.99	0.71
Sex	0.81	0.71
Race	0.42	0.71
Ethnicity	0.99	0.71
HbA1c	0.97	0.71
BMI	0.69	0.71
Duration of diabetes	0.97	0.71
hypertension	0.69	0.71
eGFR<60	0.98	0.71

eResults. Supplementary Results of per-protocol and off-protocol use of SGLT2 inhibitor and GLP-1 receptor agonist analyses

As previously reported, adherence to assigned treatment regimen differed across treatment groups. Rates of permanent discontinuation of assigned study medication were 14% in the glargine group, 23% in the glimepiride group, 23% in the liraglutide group, and 19% in the sitagliptin group (NEJM 2022; 387;1063-74). Per-protocol analyses conducted among participants (n=4,800) who followed the protocol throughout the study (either continued on their originally assigned medication combination or added insulin per protocol when HbA1c increased above 7.5%) showed lower event rates overall with no significant differences across treatment arms in the majority of outcomes, including eGFR slope (eTable 4). Per-protocol analyses showed a numerically lower but non-significant hazard ratios for kidney disease progression in the liraglutide (HR 0.85 [95% CI 0.66, 1.09]) and sitagliptin (HR 0.77 [95% CI 0.60, 0.99]) relative to glargine groups with no significant difference across treatment groups (p-value for treatment group differences: 0.073), eTable 5.

Over the course of the study, 4.9% of participants started an SGLT2 inhibitor, with some differences by treatment arms: 4.8% in glargine, 5.8% in glimepiride, 2.9% in liraglutide, 6.2% in the sitagliptin arm. Similarly, there was differential use of non-study GLP-1 receptor agonist, with 7.0% in glargine, 7.7% in glimepiride, 2.9% in liraglutide (e.g, switch to a different GLP-1 RA), and 6.3% in the sitagliptin arms (eTable 5 for rates of these medication classes). In analyses modeling the change in effect at the time of addition of SGLT2 inhibitor or off-protocol GLP-1 receptor agonist (without censoring as was done in per protocol analyses), there were no differences across treatment groups in composite kidney disease progression or eGFR slope from year 1 (eTable 7).

eTable 4. eGFR slope, per-protocol analyses

	1-year	Chronic		Total
	Mean (CI), mL/min/1.73m^2	Mean (CI), mL/min/1.73m^2 per year	Difference in rate of change (95% CI), mL/min/1.73m^2 per year	
Overall	-1.15 (-1.42, -0.88)	-1.99 (-2.08, -1.89)	-	-1.85 (-1.94, -1.76)
By treatment assignment				
Glargine	-0.92 (-1.45, -0.38)	-1.99 (-2.18, -1.81)	0 (reference group)	-1.84 (-2.01, -1.67)
Glimepiride	-1.31 (-1.84, -0.77)	-1.91 (-2.10, -1.72)	-0.08 (-0.35, 0.18)	-1.81 (-1.99, -1.63)
Liraglutide	-0.94 (-1.50, -0.38)	-2.09 (-2.29, -1.89)	0.09 (-0.18, 0.37)	-1.83 (-2.01, -1.65)
Sitagliptin	-1.41 (-1.95, -0.88)	-1.97 (-2.15, -1.78)	-0.03 (-0.29, 0.24)	-1.91 (-2.07, -1.74)

1-year denotes change from baseline to 1 year. Chronic denotes change from 1 year to last observation. Total denotes change from baseline to trial end. Per-protocol analyses were censored at the last visit prior to deviation from the assigned treatment regimen, including discontinuation of metformin, the randomly assigned medication, or addition of any glucose-lowering medication other than the randomly assigned medication and protocolized treatment. P value for heterogeneity=0.657.

eTable 5. Kidney outcomes, per-protocol analyses

Treatment assignment	N (%)	Cumulative incidence at year 4 (%)	Unadjusted IR per 100 person-year	HR (95% CI)
Kidney disease progression*				
All treatment groups	498 (10.3%)	9.98 (8.97, 10.99)	2.51 (2.29, 2.73)	-
Glargine	138 (11.3%)	10.99 (8.87, 13.10)	2.74 (2.29, 3.20)	1 (reference group)
Glimepiride	139 (11.4%)	10.90 (8.78, 13.02)	2.86 (2.38, 3.33)	1.03 (0.82, 1.31)
Liraglutide	112 (9.7%)	9.01 (7.06, 10.96)	2.33 (1.90, 2.76)	0.85 (0.66, 1.09)
Sitagliptin	109 (8.8%)	8.99 (7.11, 10.87)	2.12 (1.72, 2.52)	0.77 (0.60, 0.99)
Incident eGFR <60 mL/min/1.73m^2				
All treatment groups	249 (5.2%)	4.93 (4.22, 5.65)	1.35 (1.18, 1.52)	-
Glargine	57 (4.7%)	4.64 (3.25, 6.02)	1.21 (0.90, 1.53)	1 (reference group)
Glimepiride	64 (5.3%)	5.40 (3.91, 6.90)	1.40 (1.05, 1.74)	1.16 (0.81, 1.65)
Liraglutide	69 (6.0%)	5.65 (4.07, 7.23)	1.57 (1.20, 1.95)	1.30 (0.91, 1.84)
Sitagliptin	59 (4.8%)	4.10 (2.84, 5.36)	1.23 (0.92, 1.54)	1.01 (0.70, 1.46)
40% decline eGFR to <60 mL/min/1.73m^2				
All treatment groups	45 (0.9%)	0.77 (0.49, 1.05)	0.23 (0.16, 0.30)	-
Glargine	10 (0.8%)	0.75 (0.19, 1.31)	0.20 (0.08, 0.33)	1 (reference group)
Glimepiride	11 (0.9%)	0.75 (0.18, 1.32)	0.23 (0.09, 0.36)	1.30 (0.54, 3.14)
Liraglutide	11 (1.0%)	0.66 (0.13, 1.20)	0.24 (0.10, 0.38)	1.31 (0.55, 3.16)
Sitagliptin	13 (1.0%)	0.90 (0.31, 1.50)	0.26 (0.12, 0.40)	1.44 (0.62, 3.37)
UACR doubling to >30 mg/g				
All treatment groups	500 (10.4%)	10.13 (9.09, 11.17)	2.63 (2.40, 2.87)	-
Glargine	134 (11.0%)	10.85 (8.69, 13.02)	2.78 (2.31, 3.25)	1 (reference group)
Glimepiride	140 (11.5%)	11.06 (8.88, 13.24)	3.00 (2.50, 3.50)	1.08 (0.85, 1.37)
Liraglutide	113 (9.8%)	9.29 (7.27, 11.30)	2.45 (2.00, 2.91)	0.88 (0.69, 1.13)
Sitagliptin	113 (9.1%)	9.28 (7.34, 11.22)	2.31 (1.89, 2.74)	0.83 (0.65, 1.07)
KDIGO stage progression				
All treatment groups	570 (11.8%)	10.23 (9.23, 11.24)	2.87 (2.63, 3.10)	-
Glargine	155 (12.7%)	11.67 (9.49, 13.84)	3.14 (2.65, 3.64)	1 (reference group)
Glimepiride	158 (13.0%)	11.27 (9.15, 13.40)	3.16 (2.66, 3.65)	1.00 (0.80, 1.25)
Liraglutide	124 (10.7%)	8.91 (7.02, 10.79)	2.58 (2.12, 3.03)	0.82 (0.65, 1.04)
Sitagliptin	133 (10.7%)	9.07 (7.19, 10.94)	2.59 (2.15, 3.03)	0.82 (0.65, 1.03)

Per-protocol analyses were censored at the last visit prior to deviation from the assigned treatment regimen, including discontinuation of metformin, the randomly assigned medication, or addition of any glucose-lowering medication other than the randomly assigned medication and protocolized treatment.

eTable 6. Participants with SGLT2 inhibitor (SGLT-2i) and non-protocol GLP-1 receptor agonist (GLP-1 RA) use (drop-in)

Sensitivity analyses were performed to evaluate whether SLGT2 inhibitor or non-protocol GLP-1 receptor agonist started by usual care clinicians altered eGFR slope or hazard ratio for kidney disease progression by treatment arm. Non-protocol medication use rate (drop-in) was low overall but differed by treatment arm. The majority of drop-in occurred after 2018. There were no differences in eGFR slope or kidney disease progression by SGLT2i or eGFR drop-in.

	All	Glargine	Glimepiride	Liraglutide	Sitagliptin	p-value
On SGLT-2i	248 (4.9%)	60 (4.8%)	73 (5.8%)	36 (2.9%)	79 (6.2%)	<0.001
On GLP-1 RA	300 (5.9%)	88 (7.0%)	96 (7.7%)	36 (2.9%)	80 (6.3%)	<0.001
On either GLP-1 RA or SGLT-2i	489 (9.7%)	132 (10.5%)	151 (12.0%)	69 (5.5%)	137 (10.8%)	<0.001
On both GLP-1 RA and SGLT-2i	59 (1.2%)	16 (1.3%)	18 (1.4%)	3 (0.2%)	22 (1.7%)	0.003

eTable 7. Effect of SGLT2 inhibitors or off-protocol GLP-1 receptor agonists

P-value for the time-dependent effect of SGLT2 inhibitors and GLP-1 agonists on the eGFR slope from year 1 and kidney disease progression

	SGLT2 inhibitors		Off-protocol GLP-1 agonists	
	eGFR slope from year 1	**Kidney disease progression**	**eGFR slope from year 1**	**Kidney disease progression**
Glargine	0.20	0.05*	0.24	0.80
Glimepiride	0.20	0.42	0.15	0.70
Liraglutide	0.80	0.22		
Sitagliptin	0.19	0.06*	0.35	0.56

P-values within a column are adjusted for false discovery using the Benjamini-Hochberg method.

* P values are derived from a proportional hazards model for kidney disease progression with terms for treatment, a time-dependent covariate for SGLT2 use and an interaction term, adjusted for false discovery. In the model, the interaction term is not significant but the main effect for SGLT2 is positive and significant if no adjustment for false discovery is made, suggesting increased risk of kidney disease progression after introduction of SGLT2 inhibitor in all groups: HR 1.8 (glargine), 1.3 (glimepiride), 1.8 (liraglutide) and 2.1 (sitagliptin). Given that SGLT2s were added selectively in patients with cardiac or kidney indications very late in the study, it is likely that these HRs are related to confounding by indication.