Supplementary Appendix

Supplement to: The GRADE Study Research Group. Glycemia reduction in type 2 diabetes — microvascular and cardiovascular outcomes. N Engl J Med 2022;387:1075-88. DOI: 10.1056/NEJMoa2200436

This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix

Glycemia Reduction Approaches in Type 2 Diabetes: A Comparative Effectiveness (GRADE) Study Microvascular and Cardiovascular Outcomes

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All authors affirm that authorship is merited based on the ICMJE authorship criteria. David M. Nathan, John M. Lachin, John B. Buse, Steven E. Kahn, Heidi Krause-Steinrauf, Mary E. Larkin, Rodica Pop-Busui, and Deborah J. Wexler contributed to the conception and design of the research. David M. Nathan, John M. Lachin, John B. Buse, Andrea Cherrington, Stephen P. Fortmann, Jennifer B. Green, Steven E. Kahn, M. Sue Kirkman, Heidi Krause-Steinrauf, Mary E. Larkin, Lawrence S. Phillips, Rodica Pop-Busui, Michael Steffes, Margaret Tiktin, Deborah J. Wexler, and Naji Younes contributed to the acquisition of data. John M. Lachin, Heidi-Krause-Steinrauf, Ionut Bebu, Mark Tripputi, and Naji Younes contributed to the statistical analysis of data. David M. Nathan, John M. Lachin, John B. Buse, Henry B. Burch, Steven E. Kahn, Stephen P. Fortmann, Jennifer B. Green, M. Sue Kirkman, Heidi Krause-Steinrauf, Mary E. Larkin, Lawrence S. Phillips, Rodica Pop-Busui, Michael Steffes, Deborah J. Wexler, Margaret Tiktin, Mark Tripputi, and Naji Younes contributed to the interpretation of data and results. David M. Nathan, John M. Lachin, and John B. Buse contributed to the acquisition of funding. David M. Nathan, John M. Lachin, John B. Buse, Stephen P. Fortmann, Jennifer B. Green, M. Sue Kirkman, Heidi Krause-Steinrauf, Mary E. Larkin, Michael Steffes, Margaret Tiktin, and Deborah J. Wexler contributed to the supervision and management of the research. David M. Nathan, John M. Lachin, Ionut Bebu, Henry B. Burch, John B. Buse, Andrea L. Cherrington, Stephen P. Fortmann, Jennifer B. Green, Steven E. Kahn, M. Sue Kirkman, Heidi Krause-Steinrauf, Mary E. Larkin, Lawrence S. Phillips, Rodica Pop-Busui, Michael Steffes, Margaret Tiktin, Mark Tripputi, Deborah J. Wexler, and Naji Younes contributed to the drafting and the critical revision of the manuscript. John M. Lachin and David M. Nathan are the guarantors of this work and as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. David M. Nathan, M.D. and John M. Lachin, Sc.D. wrote the first draft of the manuscript and decided to publish the paper.

Section S3. Laboratory Methods. GRADE Central Biochemical Laboratory Assays and Quality Control.

Quality control was overseen by a committee composed of GRADE investigators who evaluated precision through inter-day coefficients of variation for each assay in the GRADE Central Biochemical Laboratory (CBL). Trueness was assessed by comparison of CBL results with the assigned values for reference materials, mostly procured from the National Institute of Standards and Technology (NIST).

Accuracy for all lipid measurements was also monitored quarterly through participation of the CBL in the CDC Lipid Standardization Program. Total Cholesterol (TC) was measured using a cholesterol oxidase method; HDL-Cholesterol (HDL-C) was measured using a direct method; and triglycerides were assayed using a glycerol-blanked enzymatic method. If the concentration of triglycerides was <400 mg/dL, LDL-C was calculated using the Friedewald equation as LDL-C = TC – HDL-C – triglycerides/5.0.

Creatinine was measured in serum and urine by an enzymatic method monitored quarterly in the CBL using NIST standard materials. Urine albumin was measured using an immunoturbidimetric method standardized against a reference preparation and also monitored quarterly in the CBL.

Section S4. Summary of Other Measurement Methods Relevant to Microvascular and Cardiovascular Outcomes.

All assessments done at baseline. Following randomization, participants were seen at all sites

Quarterly with measurement of:

Hemoglobin A1c, blood pressure and weight using standardized methods. Assessment of adverse events, medical history and study drug adherence, concomitant non-study medications were recorded along with any history of GI distress, shortness of breath or hypoglycemia, using standardized forms.

IN ADDITION

Every 6 months:

Renal function was evaluated with serum creatinine (eGFR) and urine albumin:creatinine ratio (urine samples delayed in menstruating women).

Annually:

Fasting visits included lipids (after at least an 8 hour fast), peripheral neuropathy (ankle reflexes, light touch with 10-gram monofilament, vibration perception with 128 MHz tuning fork) and foot exam.

Bi-annually:

Waist:hip circumference, and electrocardiogram.

Other:

Height at year 4 and cognitive assessments at years 4 and 6.

Section S5. Categorization of Subgroups Based on Baseline Variables.

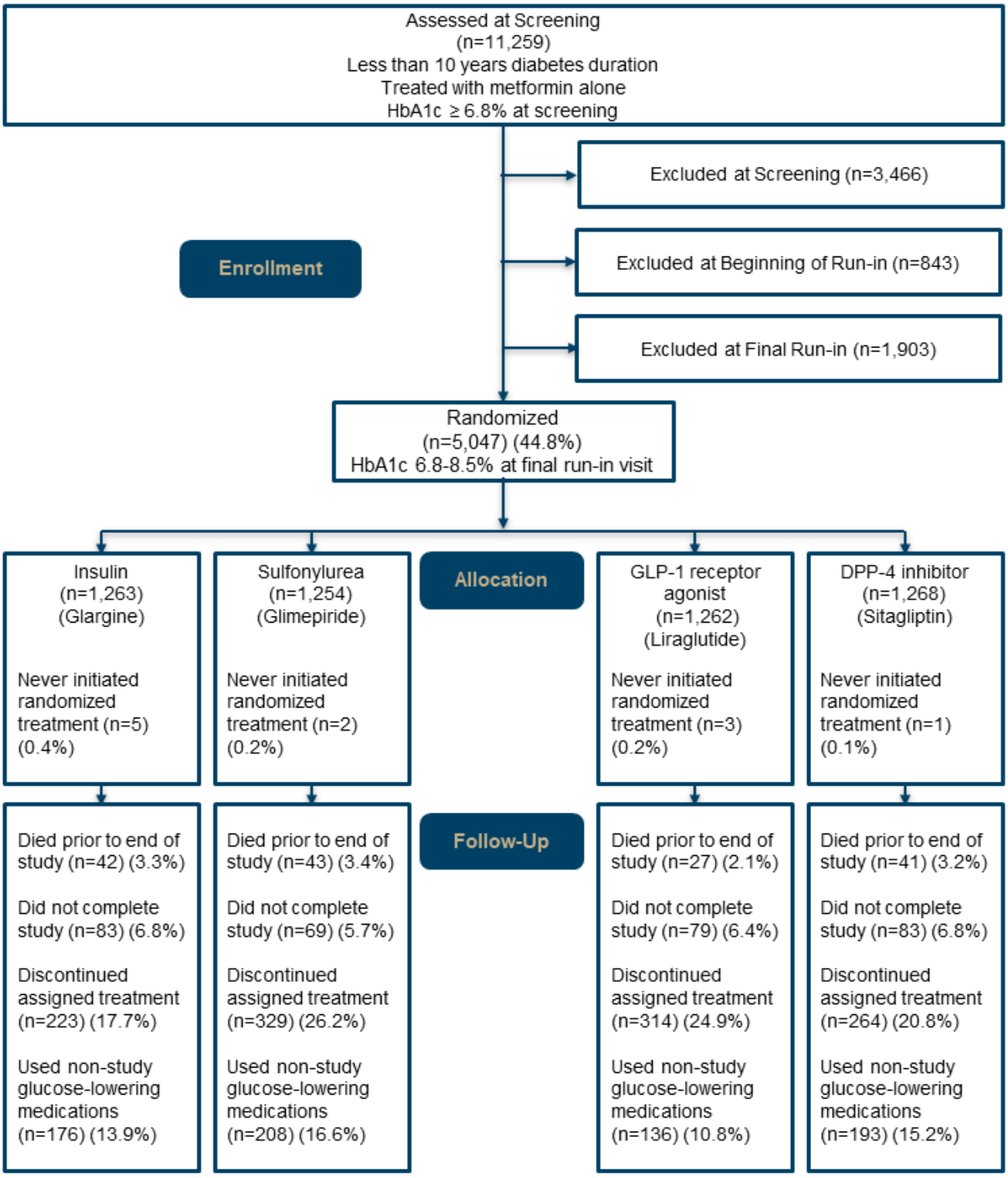
Demographic (based on self-report)

- Age (tertiles): <45, 45-59, ≥60 years
- Sex: Men, Women
- Race: White, Black, Other
- Ethnicity: Hispanic, Non-hispanic
- Sex: Men, Women
- Diabetes duration (tertiles}: 0-2.5, >2.5-5.4, >5.4-11

Clinical

- BMI (tertiles): 18.2-30.7, 30.8-36.2, ≥36.3 kg/m^2
- HbA1c (tertiles): 6.8-7.2, 7.3-7.7, 7.8-8.5 %

Figure S1. Consolidated Standards of Reporting Trials (CONSORT) Diagram.



HbA1c (mmol/mol) = (HbA1c% * 10.93) – 23.5
Completed Study refers to a subject who completed their last expected visit (i.e., close-out visit).

Figure S2. Per-protocol Cumulative Incidence of Microvascular Outcomes.

Per-protocol cumulative incidence of confirmed moderately increased albuminuria, severely increased albuminuria, impaired eGFR <60 ml/min/1.73 m^2 and diabetic peripheral neuropathy (DPN) over 6.5 years of follow-up among those free of each condition at baseline. Participants who developed incident end-stage kidney disease (dialysis, transplantation or kidney disease mortality) during the study were included in each albuminuria outcome. The numbers plotted below the x-axis of each panel are the number or participants at risk for the outcome at each follow-up timepoint. Hazard ratio and other comparisons among groups are presented in Table S3.

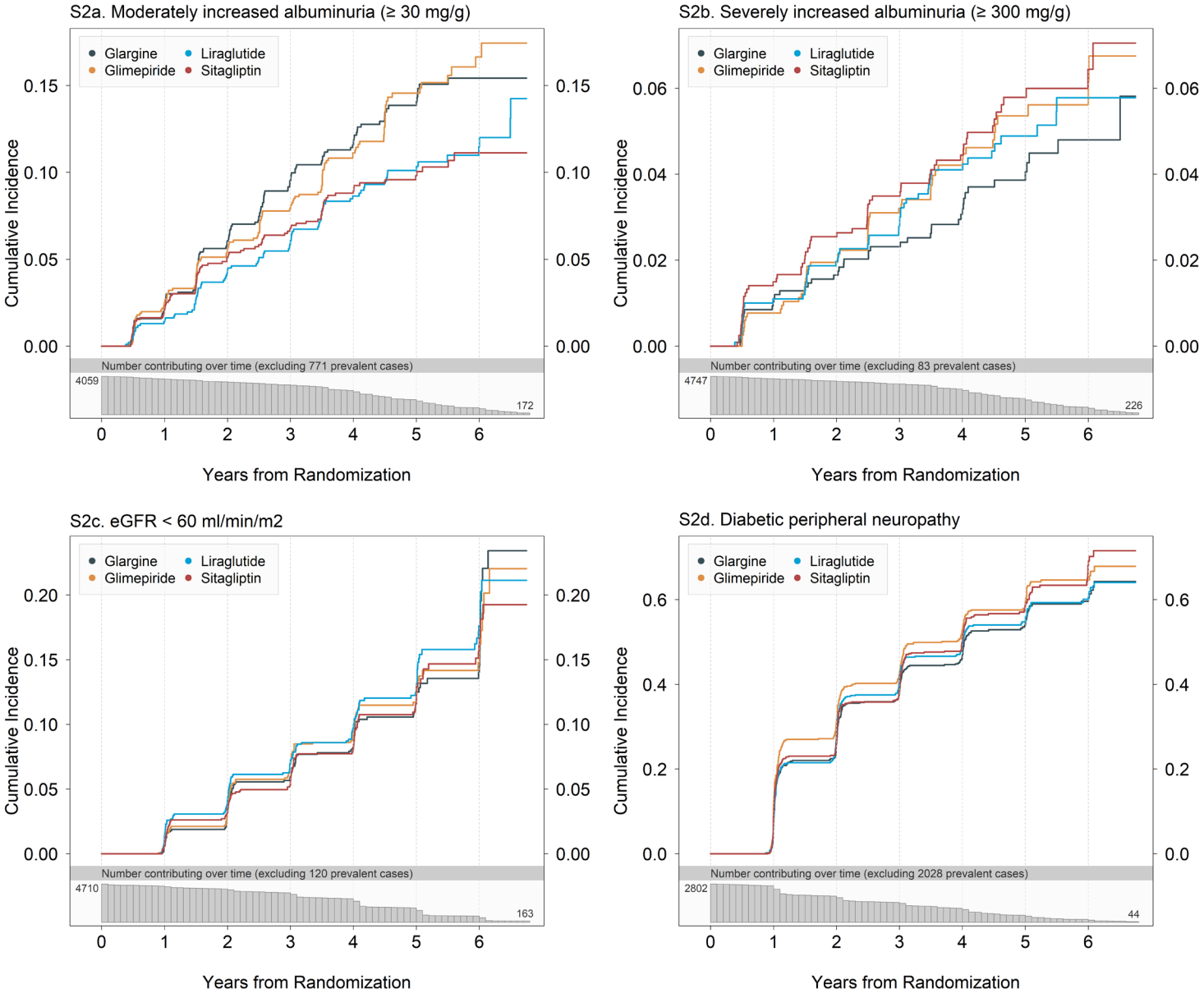


Figure S3. Per-protocol Cumulative Incidence of Heart Failure, any Cardiovascular Disease (CVD) Events, Major Adverse Cardiovascular Events (MACE), CV Death and All-cause Mortality.

Per-protocol cumulative incidence of heart failure, any CVD events, MACE, CV death and all-cause mortality over 6.5 years of follow-up. The numbers plotted below the x-axis of each panel are the number or participants at risk for the outcome at each follow-up timepoint. Hazard ratio and other comparisons among groups are presented in Table S4.

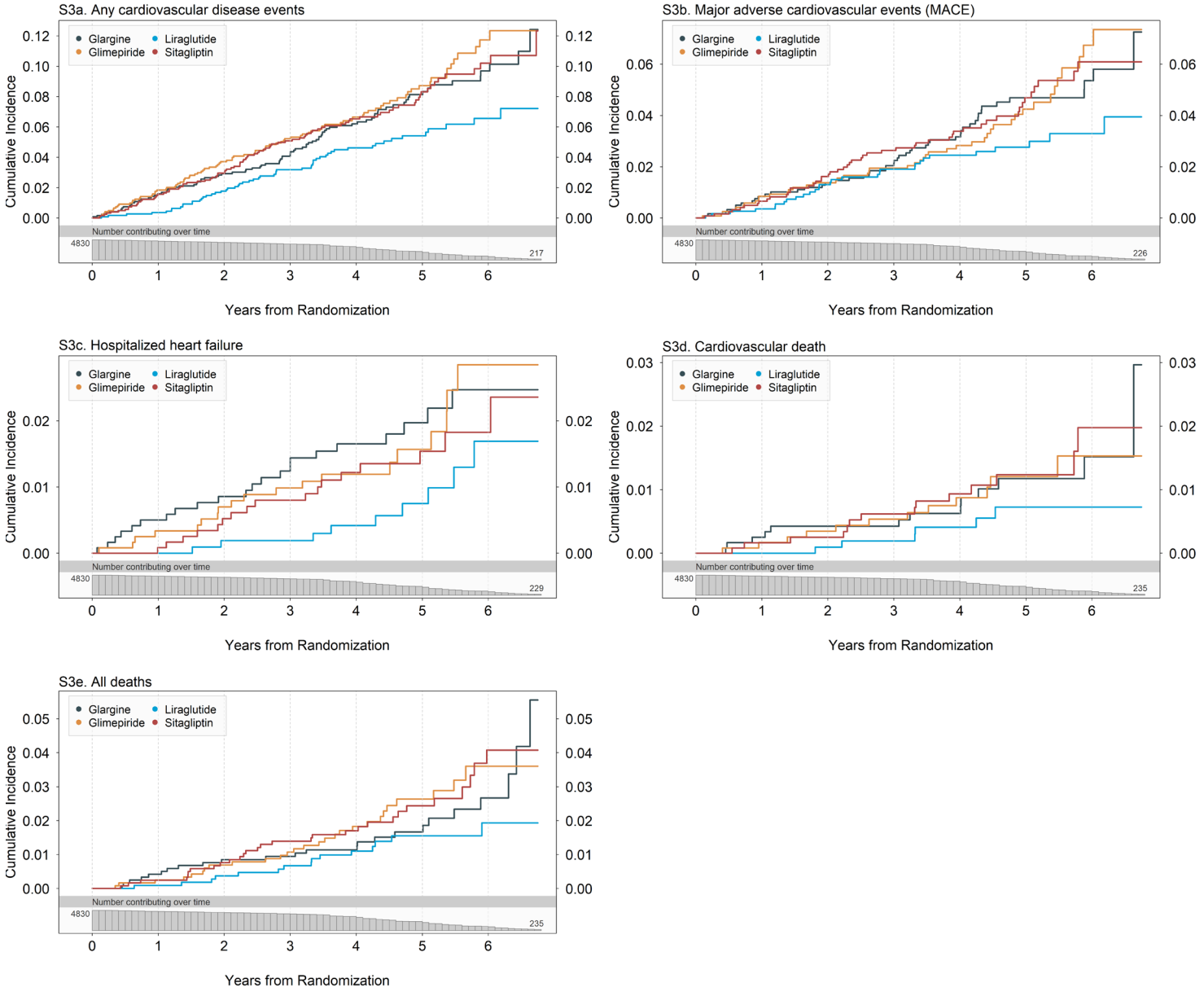


Table S1. Selected Baseline Characteristics of the Study Cohort.[1]

Characteristic	Total	Glargine*	Glimepiride	Liraglutide	Sitagliptin
N participants	5,047	1,263	1,254	1,262	1,268
Clinical Risk Factors					
BMI (kg/m²)	34.3 ± 6.8	34.4 ± 6.8	34.3 ± 6.9	34.3 ± 6.7	34.1 ± 6.8
Weight (kg)	100.0 ± 22.3	100.7 ± 22.3	99.7 ± 22.5	100.2 ± 22.9	99.3 ± 21.7
Diabetes duration (years)	4.2 ± 2.7	4.2±2.7	4.3±2.8	4.2±2.7	4.2±2.7
HbA1c (%)†	7.5±0.5	7.5±0.5	7.5±0.5	7.5±0.5	7.5±0.5
HbA1c <7%	725(14.4%)	184(14.6%)	184(14.7%)	180(14.3%)	177(14.0%)
Lipids					
LDL (mg/dL) †	90.5±31.7	91.6±32.2	89.4±31.2	91.5±31.8	89.6±31.5
HDL (mg/dL) †	43.4±10.6	43.4±10.5	43.6±10.1	43.4±11.2	43.3±10.5
Triglycerides (mg/dL) †	154.0±121.6	151.7±114.9	153.7±124.8	157.0±131.5	153.5±114.4
Dyslipidemia[2]	4,852(96.1%)	1,211(95.9%)	1,213(96.7%)	1,208(95.7%)	1,220(96.2%)
Lipid lowering medication use					
Lipid Lowering Use (any)	3,321(65.8%)	825(65.3%)	857(68.3%)	795(63.0%)	844(66.6%)
Statin Use	3,210(63.6%)	803(63.6%)	824(65.7%)	765(60.6%)	818(64.5%)
Hypertension					
SBP ≥140 mm/Hg	1,082(21.4%)	274(21.7%)	264(21.1%)	279(22.1%)	265(20.9%)
SBP (mm/Hg)	128.3±14.7	128.6±14.8	128.2±14.3	128.3±15.0	128.3±14.9
DBP (mm/Hg)	77.3±9.9	77.5±10.0	77.0±9.6	77.4±10.0	77.3±9.8
Hypertension[3]	3,879(76.9%)	973(77.0%)	963(76.8%)	980(77.7%)	963(75.9%)
Blood pressure medication use					
BP meds (any)	3,496(69.3%)	882(69.8%)	865(69.0%)	890(70.5%)	859(67.7%)
ACEi/ARB	2,933(58.1%)	724(57.3%)	742(59.2%)	738(58.5%)	729(57.5%)
BP meds (other than ACEi/ARB)	118(2.3%)	30(2.4%)	24(1.9%)	29(2.3%)	35(2.8%)
Baseline renal function					
UACR (mg/g) †	31.5±139.3	27.2±87.9	36.9±187.8	32.9±150.0	28.9±111.0
Moderately increased albuminuria (UACR ≥30 mg/g)	800(15.9%)	191(15.1%)	201(16.0%)	213(16.9%)	195(15.4%)
Severely increased albuminuria (UACR ≥300 mg/g)	84(1.7%)	17(1.3%)	27(2.2%)	22(1.7%)	18(1.4%)

(continued)

eGFR (mL/min/1.73m^2) †	94.9±16.8	94.6±16.7	95.2±16.9	94.2±17.3	95.4±16.3
eGFR <60 mL/min/1.73m^2	125(2.5%)	35(2.8%)	28(2.2%)	34(2.7%)	28(2.2%)
Baseline prevalence of DPN, stroke/MI					
DPN	2,115(41.9%)	507(40.1%)	517(41.2%)	549(43.5%)	542(42.7%)
Stroke/MI[4]	324(6.4%)	80(6.3%)	76(6.1%)	77(6.1%)	91(7.2%)

Abbreviations: BMI- body mass index (kg/m^2), LDL-low density lipoprotein, HDL- high density lipoprotein, SBP- systolic blood pressure, DBP-diastolic blood pressure, ACEi- angiotensin converting enzyme inhibitor, ARB- angiotensin receptor blocker, UACR-urine albumin:creatinine ratio, DPN-diabetic peripheral neuropathy, MI- myocardial infarction.

[1] Statistics are mean ± SD for continuous and N (%) for categorical characteristics

[2]At least one of the following: Taking lipid-lowering medication; history or diagnosis of dyslipidemia or hyperlipidemia; or study-measured LDL ≥100 mg/dL, Triglycerides 150 mg/dL or HDL <40 mg/dL for men, <50 mg/dL for women

[3]At least one of the following: Taking hypertensive medication at screening or baseline visit; history or diagnosis of hypertension at screening or baseline visit; or study-measured Systolic BP ≥140 mmHg, or Diastolic BP ≥90 mmHg at baseline visit

[4]Occurred >1 year before randomization.

*Glargine- insulin glargine 100 U/mL

†SI unit conversion factors

Measure	**Standard Units**	**SI units**	**Conversion factor (Standard to SI units)**
eGFR	mL/min/1.73m^2	mL/sec/1.73m^2	Standard x 0.01670 = SI
UACR	mg/g	mg/mmol	Standard x 0.11300 = SI
Cholesterol	mg/dL	mmol/L	Standard x 0.02586 = SI
Triglyceride	mg/dL	mmol/L	Standard x 0.01130 = SI
HDL / LDL	mg/dL	mmol/L	Standard x 0.02586 = SI
HbA1c	%	mmol/mol	Standard x 10.93 – 23.5 = SI

Table S2. Comparison with Type 2 Diabetes in US (NHANES 2018).

Background information on the race, ethnicity, age, sex, and other relevant phenotypic characteristics of the broader population affected by Type 2 diabetes and with similar major eligibility characteristics as for the GRADE cohort (age ≥ 30 years, duration < 10 years, HbA1c 6.8-8.5%, and treated with metformin only) from the National Health and Nutrition Examination Study (NHANES), compared with the GRADE cohort.

	GRADE	**NHANES**
Primary study aim	Glycemic durability of second diabetes medication after metformin	Subsample of NHANES participants meeting similar criteria (below)
Study Characteristics		
Key eligibility criteria	• Age ≥30 years • T2DM <10 years • HbA1c 6.8-8.5% (51-69 mmol/mol) taking metformin monotherapy	• Age ≥30 years • T2DM <10 years • HbA1c 6.8-8.5% (51-69 mmol/mol) taking metformin monotherapy
Randomized intervention	Medications representing four classes: Sulfonylurea (glimepiride), DPP-4 inhibitor (sitagliptin), GLP-1 analog (liraglutide), or insulin (glargine)	n/a
Primary outcome	Time to primary failure, defined as A1c ≥7% (53 mmol/mol), confirmed	n/a
Years of Study Conduct	2013-2021	2011-2014
Baseline Characteristics of Randomized Cohort		
Demographic		
N	5,047	120 (representing population n= 2,000,987)
Age ± SD (years)	57.2 ± 10.0	57.9 ± 12.0
Sex (% male)	63.6	55.9
Race/Ethnicity (%)		
Caucasian	65.8	62.1†
African Ancestry	19.8	15.1†
Hispanic	18.6	12.1
Asian	3.6	8.5†
American Indian	2.8 (AI/AN)	-
Pacific Islander	0.6	-
Clinical		
Duration of diabetes (years), mean ± SD	4.2 ± 2.7	4.2 ± 2.5
Weight ± SD (kg)	99.9 ± 22.3	95.8 ± 27.2
BMI ± SD (kg/m^2)	34.3 ± 6.8	33.2 ± 8.2

(continued)

Systolic BP (mmHg)	128.3 ± 14.7	132.2 ± 18.2
Diastolic BP (mmHg)	77.3 ± 9.8	74.1 ± 11.4
Current Smoking (%)	13.8	14.2
History of CVD (%)	6.6	7.2
Education, years (%)		
<13	7.2	
13-16	49.6	
≥ 17	43.2	
< High school	7.2	16.8
High school graduate	20.6	24.9
Some college	29.0	30.8
≥ College degree	43.2	27.5

Biochemical		
Glycemia		
Fasting Plasma Glucose		
mg/dL	151.5 ± 30.8	161.7 ± 35.0
mmol/L	8.41 ± 1.71	9.0 ± 1.9
HbA1c		
%	7.5 ± 0.5	7.4 ± 0.6
mmol/mol	58 ± 5.5	57 ± 6.6
Fasting Insulin		
pmol/L	129.4 ± 95.4	122.2 ± 96.4
mU/L	21.6 ± 15.9	20.4 ± 16.1
Lipids		
Total Cholesterol		
mg/dL	163.8 ± 37.8	183.2 ± 58.5
mmol/L	4.24 ± 0.98	4,74 ± 1.51
LDL cholesterol		
mg/dL	90.5 ± 31.7	n/a
mmol/L	2.3 ± 0.8	
HDL cholesterol		
mg/dL	43.4 ± 10.6	43.3 ± 10.9
mmol/L	1.1 ± 0.3	1.12 ± 0.2
Triglycerides		
mg/dL	154.0 ± 121.6	246.5 ± 518.7
mmol/L	1.74 ± 1.37	2.8 ± 5.9

Table abbreviations: GRADE: Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study; T2DM: type 2 diabetes; FPG: fasting plasma glucose; CVD: cardiovascular disease; LVH: left ventricular hypertrophy; MI: myocardial infarction; CHF: congestive heart failure.
† Non-Hispanic

Table (modified) from: Wexler DJ, Krause-Steinrauf H, Crandall JP, Florez HJ, Hox SH, Kuhn A, Sood A, Underkofler C, Aroda VR, GRADE Research Group. Baseline Characteristics of Randomized Participants in the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE). Diabetes Care, 2019;11(43):2098-2107.

Table S3. Per-protocol Analyses of Microvascular Outcomes.

Same as Table 1 of the main text but in the per-protocol population consisting of participants who had at least one quarterly visit taking study medication. Only visits at which per-protocol participants were adherent to the protocol were included in the analysis (i.e. visits where participants had not stopped study medication and had not initiated non-study glucose lowering medication(s)).

	Glargine (N=1263)	Glimepiride (N=1254)	Liraglutide (N=1262)	Sitagliptin (N=1268)	Total (N=5047)
Moderately increased albuminuria[1]					
Number of cases (%)	134 (13.1%)	134 (13.1%)	109 (11.4%)	111 (10.6%)	488 (12.0%)
Number at risk[5]	1028	1022	954	1049	4053
Crude Rate (CI)	3.14 (2.63,3.71)	3.27 (2.74,3.87)	2.71 (2.23,3.27)	2.53 (2.08,3.05)	2.91 (2.66,3.18)
Pairwise HR (CI[†])					
Glargine		1.00 (0.78,1.28)	1.37 (1.04,1.80)	1.40 (1.07,1.84)	
Glimepiride			1.37 (1.04,1.80)	1.41 (1.07,1.84)	
Liraglutide				1.02 (0.77,1.37)	
One vs. others combined HR (CI[†])	1.24 (1.01,1.53)	1.25 (1.01,1.54)	0.82 (0.65,1.03)	0.79 (0.63,1.00)	
Severely increased albuminuria[2]					
Number of cases (%)	56 (4.7%)	64 (5.4%)	60 (5.3%)	66 (5.4%)	246 (5.2%)
Number at risk[5]	1198	1190	1129	1220	4737
Crude Rate (CI)	1.07 (0.81,1.39)	1.28 (0.99,1.64)	1.23 (0.94,1.59)	1.26 (0.98,1.61)	1.21 (1.06,1.37)
Pairwise HR (CI[†])					
Glargine		0.80 (0.54,1.18)	0.86 (0.57,1.28)	0.75 (0.51,1.10)	
Glimepiride			1.07 (0.73,1.57)	0.94 (0.65,1.36)	
Liraglutide				0.88 (0.60,1.28)	
One vs. others combined HR (CI[†])	0.80 (0.58,1.11)	1.08 (0.80,1.47)	0.99 (0.72,1.35)	1.17 (0.87,1.58)	
eGFR[3] **<60 ml/min/m**^{2}					
Number of cases (%)	143 (12.5%)	150 (12.9%)	159 (14.5%)	142 (11.9%)	594 (12.9%)
Number at risk[5]	1149	1174	1098	1190	4611
Crude Rate (CI)	3.07 (2.59,3.62)	3.30 (2.79,3.87)	3.65 (3.10,4.26)	2.98 (2.51,3.51)	3.24 (2.99,3.51)
Pairwise HR (CI[†])					
Glargine		0.98 (0.77,1.26)	0.89 (0.70,1.14)	1.03 (0.80,1.32)	
Glimepiride			0.91 (0.71,1.16)	1.05 (0.82,1.35)	
Liraglutide				1.15 (0.90,1.47)	
One vs. others combined HR (CI[†])	0.97 (0.79,1.18)	0.99 (0.81,1.21)	1.12 (0.92,1.37)	0.93 (0.76,1.14)	

(continued)

Diabetic peripheral neuropathy[4]					
Number of cases (%)	362 (49.9%)	379 (53.2%)	322 (49.4%)	368 (52.1%)	1431 (51.2%)
Number at risk[5]	726	712	652	707	2797
Crude Rate (CI)	16.1 (14.5,17.8)	18.6 (16.8,20.6)	16.47 (14.7,18.4)	17.6 (15.9,19.5)	17.2 (16.3,18.1)
Pairwise HR (CI[†])					
Glargine	0.86 (0.74,0.99)	0.96 (0.83,1.12)	0.90 (0.78,1.04)	0.86 (0.74,0.99)	
Glimepiride		1.12 (0.97,1.31)	1.05 (0.91,1.22)		
Liraglutide			0.94 (0.81,1.09)		
One vs. others combined HR (CI[†])	0.91 (0.80,1.02)	1.11 (0.99,1.26)	0.95 (0.84,1.08)	1.04 (0.92,1.17)	

[1]Moderately increased albuminuria -urine albumin creatinine ratio ≥30 mg/gm, confirmed.

[2]Severely increased albuminuria -urine albumin creatinine ratio ≥300 mg/gm

[3]eGFR- estimated glomerular filtration rate. Participants with incident end-stage kidney disease (dialysis, transplant or renal death) that developed during the study were included in both categorical albuminuria outcomes.

[4]Assessed using the Michigan Neuropathy Screening Instrument

[5]Excludes prevalent cases at baseline

[†]Confidence intervals are unadjusted for multiple comparisons

Glargine = insulin glargine 100 U/mL

60 ml/min/m2 = 1.002 ml/sec/m2 (eGFR threshold for defining impaired renal function)

Table S4. Per-protocol Analyses of Cardiovascular Outcomes.

Same as Table 3 of the main text but in the per-protocol population consisting of participants who had at least one quarterly visit taking study medication. Only visits at which per-protocol participants were adherent to the protocol were included in the analysis (i.e. visits where participants had not stopped study medication and had not initiated non-study glucose lowering medication(s)).

	Glargine (N=1263)	Glimepiride (N=1254)	Liraglutide (N=1262)	Sitagliptin (N=1268)	Total (N=5047)
Any CVD[1]					
Number of cases (%)	105 (8.6%)	114 (9.4%)	75 (6.5%)	118 (9.5%)	412 (8.6%)
Number at risk[4]	1215	1217	1150	1238	4820
Crude Rate (CI)	1.99 (1.63,2.41)	2.26 (1.87,2.72)	1.51 (1.18,1.89)	2.23 (1.85,2.67)	2.00 (1.81,2.21)
Pairwise HR (CI†)					
Glargine		0.90 (0.67,1.20)	1.50 (1.07,2.10)	0.97 (0.72,1.30)	
Glimepiride			1.67 (1.20,2.32)	1.08 (0.81,1.44)	
Liraglutide				0.65 (0.46,0.90)	
One vs. others combined HR (CI†)	1.09 (0.86,1.40)	1.26 (0.99,1.60)	0.64 (0.48,0.85)	1.14 (0.90,1.45)	
MACE[2]					
Number of cases (%)	60 (4.9%)	58 (4.8%)	43 (3.7%)	67 (5.4%)	228 (4.7%)
Number at risk[4]	1215	1217	1150	1238	4820
Crude Rate (CI)	1.12 (0.85,1.44)	1.13 (0.86,1.46)	0.86 (0.62,1.15)	1.25 (0.97,1.59)	1.09 (0.95,1.24)
Pairwise HR (CI†)					
Glargine		1.01 (0.67,1.51)	1.53 (0.97,2.41)	0.98 (0.66,1.45)	
Glimepiride			1.52 (0.96,2.41)	0.97 (0.65,1.44)	
Liraglutide				0.64 (0.41,1.00)	
One vs. others combined HR (CI†)	1.15 (0.82,1.60)	1.13 (0.81,1.59)	0.65 (0.44,0.96)	1.18 (0.85,1.65)	
Heart Failure[3]					
Number of cases (%)	23 (1.9%)	30 (2.5%)	14 (1.2%)	30 (2.4%)	97 (2.0%)
Number at risk[4]	1215	1217	1150	1238	4820
Crude Rate (CI)	0.43 (0.27,0.64)	0.58 (0.39,0.83)	0.28 (0.15,0.46)	0.55 (0.37,0.79)	0.46 (0.37,0.56)
Pairwise HR (CI†)					
Glargine		1.10 (0.60,2.04)	2.30 (1.06,5.00)	1.30 (0.69,2.44)	
Glimepiride			2.09 (0.95,4.59)	1.17 (0.61,2.26)	
Liraglutide				0.56 (0.25,1.26)	
One vs. others combined HR (CI†)	1.49 (0.88,2.51)	1.30 (0.76,2.24)	0.49 (0.24,0.99)	1.05 (0.60,1.85)	

(continued)

Cardiovascular death					
Number of cases (%)	19 (1.6%)	16 (1.3%)	8 (0.7%)	21 (1.7%)	64 (1.3%)
Number at risk[4]	1215	1217	1150	1238	4820
Crude Rate (CI)	0.35 (0.21,0.55)	0.31 (0.18,0.50)	0.16 (0.07,0.31)	0.39 (0.24,0.59)	0.30 (0.23,0.39)
Pairwise HR (CI[†])					
Glargine		1.02 (0.47,2.23)	2.02 (0.77,5.30)	0.92 (0.43,1.96)	
Glimepiride			1.98 (0.74,5.27)	0.90 (0.42,1.95)	
Liraglutide				0.46 (0.18,1.19)	
One vs. others combined HR (CI[†])	1.24 (0.64,2.38)	1.21 (0.62,2.37)	0.49 (0.21,1.15)	1.38 (0.73,2.63)	
All Deaths					
Number of cases (%)	39 (3.2%)	42 (3.5%)	23 (2.0%)	40 (3.2%)	144 (3.0%)
Number at risk[4]	1215	1217	1150	1238	4820
Crude Rate (CI)	0.70 (0.50,0.96)	0.79 (0.57,1.07)	0.45 (0.28,0.67)	0.72 (0.52,0.98)	0.67 (0.56,0.79)
Pairwise HR (CI[†])					
Glargine		0.86 (0.50,1.48)	1.55 (0.82,2.94)	0.85 (0.50,1.45)	
Glimepiride			1.80 (0.96,3.39)	0.99 (0.59,1.67)	
Liraglutide				0.55 (0.29,1.03)	
One vs. others combined HR (CI[†])	1.04 (0.66,1.65)	1.27 (0.81,2.00)	0.58 (0.34,1.01)	1.29 (0.83,2.00)	

[1]Any CVD (cardiovascular disease)- first of any MACE, unstable angina requiring hospitalization or revascularization, heart failure requiring hospitalization, or any revascularization event.

[2]MACE- major adverse cardiovascular events including CVD death, non-fatal myocardial infarction or non-fatal stroke.

[3]Hospitalized heart failure.

[4]Excludes prevalent cases at baseline

[†]Confidence intervals are unadjusted for multiple comparisons

Glargine = insulin glargine 100 U/mL

Table S5. Subgroup Analyses of Outcomes

Table S5.A: Sub-group analyses of microvascular outcomes stratified according to seven pre-specified baseline factors. Since the analysis did not correct for multiple subgroup factors, per the Journal statistical guidelines, only a descriptive presentation is provided that includes the number of outcome cases (*Ne*) and the crude rate (hazard) per 100 patient years of follow-up with uncorrected 95% confidence limits.

		Moderately increased albuminuria (>= 30 mg/g)			**Severely increased albuminuria (>= 300 mg/g)**			**eGFR < 60 ml/min/m2**		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Sex										
Male	Glargine	676	92	2.99 (2.41, 3.67)	796	45	1.17 (0.86, 1.57)	752	97	2.98 (2.42, 3.64)
	Glimepiride	640	99	3.40 (2.76, 4.14)	762	47	1.28 (0.94, 1.70)	751	93	2.84 (2.29, 3.48)
	Liraglutide	667	83	2.71 (2.16, 3.36)	799	53	1.40 (1.05, 1.83)	780	112	3.34 (2.75, 4.02)
	Sitagliptin	662	76	2.49 (1.97, 3.12)	780	46	1.24 (0.91, 1.65)	757	95	2.93 (2.37, 3.58)
Female	Glargine	390	44	2.37 (1.73, 3.19)	444	14	0.63 (0.34, 1.05)	422	47	2.45 (1.80, 3.25)
	Glimepiride	406	36	1.86 (1.30, 2.57)	458	17	0.75 (0.44, 1.20)	447	58	2.94 (2.23, 3.80)
	Liraglutide	373	38	2.06 (1.46, 2.83)	430	17	0.77 (0.45, 1.24)	404	58	3.10 (2.36, 4.01)
	Sitagliptin	408	39	1.99 (1.41, 2.72)	466	20	0.86 (0.53, 1.33)	451	50	2.42 (1.80, 3.20)
Race										
White	Glargine	714	91	2.77 (2.23, 3.40)	825	41	1.03 (0.74, 1.39)	782	104	3.02 (2.47, 3.66)
	Glimepiride	673	89	2.89 (2.32, 3.56)	789	40	1.05 (0.75, 1.43)	772	114	3.48 (2.87, 4.18)
	Liraglutide	678	73	2.29 (1.80, 2.88)	797	42	1.09 (0.78, 1.47)	762	121	3.65 (3.03, 4.36)
	Sitagliptin	712	78	2.36 (1.87, 2.95)	841	43	1.07 (0.77, 1.44)	815	104	2.97 (2.42, 3.60)
Black	Glargine	214	23	2.28 (1.45, 3.43)	246	11	0.90 (0.45, 1.61)	232	22	2.18 (1.36, 3.30)
	Glimepiride	229	31	2.88 (1.95, 4.08)	262	13	1.00 (0.53, 1.71)	257	27	2.30 (1.51, 3.34)
	Liraglutide	209	20	1.97 (1.20, 3.04)	244	17	1.40 (0.82, 2.25)	239	19	1.75 (1.05, 2.73)
	Sitagliptin	197	22	2.37 (1.48, 3.59)	221	12	1.11 (0.57, 1.94)	211	24	2.53 (1.62, 3.77)
All Others	Glargine	138	22	3.47 (2.17, 5.25)	169	7	0.83 (0.33, 1.72)	160	18	2.48 (1.47, 3.92)
	Glimepiride	144	15	2.15 (1.20, 3.54)	169	11	1.32 (0.66, 2.37)	169	10	1.27 (0.61, 2.33)
	Liraglutide	153	28	3.98 (2.64, 5.75)	188	11	1.20 (0.60, 2.15)	183	30	3.66 (2.47, 5.23)
	Sitagliptin	161	15	1.92 (1.08, 3.17)	184	11	1.20 (0.60, 2.14)	182	17	1.99 (1.16, 3.19)

(continued)

		Moderately increased albuminuria (>= 30 mg/g)			Severely increased albuminuria (>= 300 mg/g)			eGFR < 60 ml/min/m2		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Ethnicity										
Hispanic	Glargine	177	20	2.50 (1.52, 3.85)	213	13	1.28 (0.68, 2.18)	203	12	1.31 (0.68, 2.28)
	Glimepiride	196	17	1.84 (1.07, 2.94)	225	10	0.92 (0.44, 1.69)	226	14	1.41 (0.77, 2.36)
	Liraglutide	183	24	2.77 (1.78, 4.12)	225	18	1.67 (0.99, 2.63)	219	22	2.28 (1.43, 3.45)
	Sitagliptin	200	24	2.61 (1.67, 3.88)	235	12	1.06 (0.55, 1.84)	232	17	1.65 (0.96, 2.65)
Non-Hisp	Glargine	878	116	2.84 (2.35, 3.41)	1016	46	0.92 (0.67, 1.23)	963	131	3.10 (2.59, 3.68)
	Glimepiride	839	116	2.99 (2.47, 3.58)	981	52	1.08 (0.81, 1.42)	959	135	3.22 (2.70, 3.81)
	Liraglutide	852	97	2.41 (1.96, 2.94)	999	52	1.06 (0.80, 1.40)	961	147	3.47 (2.93, 4.08)
	Sitagliptin	861	89	2.20 (1.77, 2.71)	1001	53	1.09 (0.82, 1.43)	968	126	2.97 (2.47, 3.54)
Age (years)										
<45	Glargine	125	12	2.05 (1.06, 3.58)	149	5	0.69 (0.22, 1.62)	141	2	0.30 (0.04, 1.10)
	Glimepiride	140	15	2.31 (1.29, 3.80)	157	8	1.05 (0.45, 2.06)	159	1	0.14 (0.00, 0.78)
	Liraglutide	128	17	2.71 (1.58, 4.34)	149	5	0.66 (0.22, 1.55)	150	6	0.86 (0.32, 1.87)
	Sitagliptin	127	16	2.67 (1.52, 4.33)	148	8	1.11 (0.48, 2.18)	145	3	0.44 (0.09, 1.27)
45-59	Glargine	512	58	2.43 (1.84, 3.14)	596	25	0.85 (0.55, 1.26)	573	43	1.65 (1.20, 2.22)
	Glimepiride	468	43	1.93 (1.40, 2.60)	538	21	0.80 (0.49, 1.22)	541	42	1.71 (1.23, 2.31)
	Liraglutide	471	48	2.12 (1.56, 2.81)	554	27	0.99 (0.65, 1.43)	538	53	2.16 (1.62, 2.83)
	Sitagliptin	521	36	1.42 (0.99, 1.97)	597	24	0.81 (0.52, 1.21)	582	32	1.19 (0.82, 1.69)
60+	Glargine	429	66	3.38 (2.61, 4.30)	495	29	1.20 (0.81, 1.73)	460	99	5.17 (4.20, 6.29)
	Glimepiride	438	77	3.90 (3.08, 4.88)	525	35	1.38 (0.96, 1.92)	498	108	5.21 (4.28, 6.29)
	Liraglutide	441	56	2.77 (2.10, 3.60)	526	38	1.52 (1.08, 2.09)	496	111	5.36 (4.41, 6.45)
	Sitagliptin	422	63	3.36 (2.59, 4.30)	501	34	1.44 (1.00, 2.02)	481	110	5.68 (4.67, 6.85)

(continued)

		Moderately increased albuminuria (>= 30 mg/g)			Severely increased albuminuria (>= 300 mg/g)			eGFR < 60 ml/min/m2		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
BMI (kg/m^2)										
18.2-30.7	Glargine	354	44	2.65 (1.93, 3.56)	403	18	0.90 (0.53, 1.43)	378	55	3.36 (2.53, 4.37)
	Glimepiride	357	44	2.65 (1.93, 3.56)	417	24	1.18 (0.76, 1.75)	409	44	2.44 (1.77, 3.28)
	Liraglutide	344	51	3.22 (2.40, 4.24)	391	23	1.21 (0.77, 1.82)	372	51	3.09 (2.30, 4.06)
	Sitagliptin	399	40	2.17 (1.55, 2.96)	440	12	0.56 (0.29, 0.99)	426	54	2.94 (2.21, 3.83)
30.7-36.3	Glargine	362	43	2.55 (1.85, 3.44)	418	14	0.68 (0.37, 1.15)	396	50	2.86 (2.12, 3.77)
	Glimepiride	349	44	2.67 (1.94, 3.59)	394	18	0.92 (0.55, 1.46)	386	53	3.13 (2.34, 4.09)
	Liraglutide	369	35	1.98 (1.38, 2.76)	433	20	0.93 (0.57, 1.44)	418	56	2.99 (2.26, 3.88)
	Sitagliptin	338	30	1.87 (1.26, 2.67)	398	24	1.24 (0.79, 1.84)	385	45	2.66 (1.94, 3.56)
36.3-74.3	Glargine	350	49	3.09 (2.29, 4.09)	417	26	1.29 (0.84, 1.89)	399	38	2.13 (1.51, 2.93)
	Glimepiride	337	47	3.07 (2.25, 4.08)	406	22	1.14 (0.71, 1.72)	400	54	3.11 (2.34, 4.06)
	Liraglutide	326	35	2.25 (1.57, 3.13)	403	26	1.34 (0.88, 1.97)	393	63	3.72 (2.86, 4.76)
	Sitagliptin	331	45	2.89 (2.11, 3.87)	406	30	1.53 (1.03, 2.18)	395	46	2.61 (1.91, 3.48)
HbA1c (%)										
6.8-7.2	Glargine	395	41	2.20 (1.58, 2.98)	467	17	0.74 (0.43, 1.18)	435	59	3.05 (2.32, 3.93)
	Glimepiride	410	41	2.08 (1.49, 2.82)	484	32	1.35 (0.92, 1.91)	474	67	3.21 (2.49, 4.08)
	Liraglutide	418	43	2.18 (1.58, 2.94)	487	30	1.28 (0.86, 1.82)	464	67	3.32 (2.57, 4.22)
	Sitagliptin	403	44	2.33 (1.69, 3.13)	459	19	0.85 (0.51, 1.33)	444	58	2.98 (2.26, 3.85)
7.2-7.7	Glargine	331	40	2.61 (1.86, 3.55)	385	26	1.38 (0.90, 2.03)	367	50	3.11 (2.31, 4.11)
	Glimepiride	334	47	3.09 (2.27, 4.11)	388	18	0.95 (0.57, 1.51)	380	48	2.89 (2.13, 3.84)
	Liraglutide	312	43	2.89 (2.09, 3.89)	364	19	1.05 (0.63, 1.64)	352	53	3.38 (2.53, 4.42)
	Sitagliptin	349	34	2.04 (1.41, 2.85)	406	19	0.95 (0.57, 1.49)	390	36	2.07 (1.45, 2.86)
7.7-8.5	Glargine	340	55	3.60 (2.71, 4.68)	388	16	0.85 (0.49, 1.39)	372	35	2.14 (1.49, 2.98)
	Glimepiride	302	47	3.47 (2.55, 4.61)	348	14	0.83 (0.45, 1.40)	344	36	2.40 (1.68, 3.32)
	Liraglutide	310	35	2.42 (1.68, 3.36)	378	21	1.15 (0.71, 1.76)	368	50	3.06 (2.27, 4.04)
	Sitagliptin	318	37	2.54 (1.79, 3.51)	381	28	1.55 (1.03, 2.24)	374	51	3.16 (2.35, 4.15)

(continued)

		Moderately increased albuminuria (>= 30 mg/g)			Severely increased albuminuria (>= 300 mg/g)			eGFR < 60 ml/min/m2		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Diabetes Duration (yrs)										
0-2.5	Glargine	352	42	2.64 (1.90, 3.56)	406	13	0.66 (0.35, 1.14)	378	32	1.92 (1.32, 2.72)
	Glimepiride	353	40	2.45 (1.75, 3.34)	403	14	0.71 (0.39, 1.20)	397	45	2.57 (1.88, 3.44)
	Liraglutide	353	45	2.77 (2.02, 3.70)	423	21	1.04 (0.64, 1.59)	413	65	3.70 (2.86, 4.72)
	Sitagliptin	365	46	2.72 (1.99, 3.63)	417	18	0.89 (0.53, 1.41)	409	34	1.87 (1.30, 2.62)
2.5-5.4	Glargine	384	46	2.49 (1.82, 3.32)	450	27	1.18 (0.78, 1.72)	431	52	2.66 (1.99, 3.49)
	Glimepiride	320	46	3.00 (2.19, 4.00)	382	20	1.04 (0.63, 1.60)	376	48	2.83 (2.09, 3.75)
	Liraglutide	329	30	1.86 (1.25, 2.65)	384	19	0.99 (0.59, 1.54)	369	37	2.19 (1.54, 3.02)
	Sitagliptin	361	34	1.97 (1.37, 2.76)	423	21	1.00 (0.62, 1.53)	410	54	2.94 (2.21, 3.84)
5.4-11.2	Glargine	330	48	3.23 (2.38, 4.29)	384	19	1.04 (0.63, 1.62)	365	60	3.85 (2.94, 4.96)
	Glimepiride	373	49	2.91 (2.15, 3.84)	435	30	1.46 (0.98, 2.08)	425	58	3.22 (2.45, 4.17)
	Liraglutide	358	46	2.76 (2.02, 3.68)	422	30	1.47 (0.99, 2.10)	402	68	3.83 (2.97, 4.85)
	Sitagliptin	343	35	2.20 (1.53, 3.06)	405	27	1.41 (0.93, 2.05)	388	57	3.46 (2.62, 4.48)

(continued)

		Diabetic peripheral neuropathy (DPN)		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)
Sex				
Male	Glargine	470	253	16.17 (14.23, 18.28)
	Glimepiride	432	268	19.60 (17.32, 22.09)
	Liraglutide	433	255	18.57 (16.36, 21.00)
	Sitagliptin	431	246	17.75 (15.60, 20.11)
Female	Glargine	281	140	14.60 (12.28, 17.23)
	Glimepiride	296	159	16.29 (13.86, 19.03)
	Liraglutide	271	127	12.63 (10.53, 15.03)
	Sitagliptin	292	159	15.68 (13.33, 18.31)
Race				
White	Glargine	499	274	16.47 (14.58, 18.54)
	Glimepiride	474	287	19.03 (16.89, 21.36)
	Liraglutide	450	255	17.26 (15.21, 19.52)
	Sitagliptin	464	255	16.43 (14.48, 18.58)
Black	Glargine	154	72	13.79 (10.79, 17.37)
	Glimepiride	153	84	16.76 (13.37, 20.76)
	Liraglutide	145	64	12.17 (9.37, 15.54)
	Sitagliptin	145	86	18.21 (14.57, 22.49)
All Others	Glargine	98	47	13.89 (10.21, 18.47)
	Glimepiride	101	56	16.76 (12.66, 21.77)
	Liraglutide	109	63	16.78 (12.90, 21.47)
	Sitagliptin	114	64	17.00 (13.09, 21.71)

(continued)

		Diabetic peripheral neuropathy (DPN)		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)
Ethnicity				
Hispanic	Glargine	146	67	13.07 (10.13, 16.60)
	Glimepiride	151	85	16.99 (13.57, 21.01)
	Liraglutide	140	67	13.19 (10.22, 16.75)
	Sitagliptin	165	75	13.10 (10.30, 16.42)
Non-Hisp	Glargine	599	322	16.14 (14.43, 18.00)
	Glimepiride	570	339	18.68 (16.74, 20.77)
	Liraglutide	561	314	16.91 (15.09, 18.89)
	Sitagliptin	551	328	18.22 (16.31, 20.31)
Age (years)				
<45	Glargine	113	45	10.84 (7.91, 14.50)
	Glimepiride	114	54	13.54 (10.17, 17.67)
	Liraglutide	107	44	10.33 (7.51, 13.87)
	Sitagliptin	107	44	11.10 (8.07, 14.90)
45-59	Glargine	380	182	13.61 (11.70, 15.73)
	Glimepiride	356	184	15.23 (13.11, 17.60)
	Liraglutide	349	173	14.25 (12.21, 16.54)
	Sitagliptin	369	197	15.71 (13.60, 18.07)
60+	Glargine	258	166	21.53 (18.38, 25.06)
	Glimepiride	258	189	25.66 (22.13, 29.59)
	Liraglutide	248	165	22.33 (19.05, 26.01)
	Sitagliptin	247	164	21.86 (18.64, 25.47)

(continued)

		Diabetic peripheral neuropathy (DPN)		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)
BMI (kg/m^2)				
18.2-30.7	Glargine	275	131	13.32 (11.14, 15.81)
	Glimepiride	262	141	15.37 (12.94, 18.13)
	Liraglutide	245	129	14.88 (12.43, 17.68)
	Sitagliptin	278	144	15.21 (12.83, 17.91)
30.7-36.3	Glargine	233	126	16.39 (13.65, 19.51)
	Glimepiride	242	134	16.40 (13.74, 19.43)
	Liraglutide	245	132	16.36 (13.69, 19.40)
	Sitagliptin	232	132	17.62 (14.74, 20.90)
36.3-74.3	Glargine	242	136	17.64 (14.80, 20.86)
	Glimepiride	222	151	25.06 (21.22, 29.39)
	Liraglutide	212	119	16.97 (14.06, 20.31)
	Sitagliptin	211	127	18.07 (15.07, 21.50)
HbA1c (%)				
6.8-7.2	Glargine	285	161	17.28 (14.72, 20.17)
	Glimepiride	289	162	16.92 (14.42, 19.74)
	Liraglutide	282	136	13.75 (11.53, 16.26)
	Sitagliptin	282	162	17.41 (14.83, 20.30)
7.2-7.7	Glargine	238	122	15.20 (12.62, 18.15)
	Glimepiride	237	141	18.57 (15.63, 21.90)
	Liraglutide	211	122	17.20 (14.28, 20.54)
	Sitagliptin	231	126	16.10 (13.41, 19.17)
7.7-8.5	Glargine	228	110	13.93 (11.44, 16.78)
	Glimepiride	202	124	19.79 (16.46, 23.59)
	Liraglutide	211	124	18.23 (15.17, 21.74)
	Sitagliptin	210	117	17.02 (14.08, 20.40)

(continued)

		Diabetic peripheral neuropathy (DPN)		
Subgroups	Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)
Diabetes Duration (yrs)				
0-2.5	Glargine	249	113	13.56 (11.18, 16.31)
	Glimepiride	253	143	17.06 (14.38, 20.10)
	Liraglutide	256	122	13.59 (11.29, 16.23)
	Sitagliptin	258	137	15.97 (13.40, 18.87)
2.5-5.4	Glargine	281	164	17.71 (15.10, 20.63)
	Glimepiride	221	130	17.91 (14.97, 21.27)
	Liraglutide	227	135	18.07 (15.15, 21.39)
	Sitagliptin	229	132	17.66 (14.77, 20.94)
5.4-11.2	Glargine	221	116	15.17 (12.54, 18.20)
	Glimepiride	254	154	19.75 (16.76, 23.13)
	Liraglutide	221	125	17.03 (14.17, 20.29)
	Sitagliptin	235	136	17.21 (14.44, 20.36)

[1]Number at risk; [2]Number of events

Note that all subgroup factors were assessed at baseline.

Table S5.B: Sub-group analyses of major cardiovascular outcomes stratified according to seven pre-specified baseline factors and a post-hoc analysis of those who reported a history of MI or Stroke at least one year prior. Since the analysis did not correct for multiple subgroup factors, per the Journal statistical guidelines, only a descriptive presentation is provided that includes the number of outcome cases (*Ne*) and the crude rate (hazard) per 100 patient years of follow-up with uncorrected 95% confidence limits.

			Any cardiovascular disease events			**Major adverse cardiovascular events (MACE)**			**Hospitalized heart failure**		
Subgroups		Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Sex											
Male		Glargine	808	88	2.31 (1.85, 2.85)	808	52	1.33 (0.99, 1.75)	808	18	0.46 (0.27, 0.72)
		Glimepiride	777	84	2.29 (1.82, 2.83)	777	38	1.00 (0.71, 1.37)	777	21	0.55 (0.34, 0.84)
		Liraglutide	818	68	1.75 (1.36, 2.22)	818	40	1.01 (0.72, 1.38)	818	9	0.22 (0.10, 0.43)
		Sitagliptin	795	97	2.61 (2.12, 3.19)	795	55	1.44 (1.08, 1.87)	795	21	0.54 (0.33, 0.83)
Female		Glargine	449	25	1.12 (0.72, 1.65)	449	13	0.58 (0.31, 0.98)	449	8	0.35 (0.15, 0.70)
		Glimepiride	470	31	1.34 (0.91, 1.90)	470	21	0.90 (0.56, 1.37)	470	9	0.38 (0.18, 0.73)
		Liraglutide	433	15	0.68 (0.38, 1.12)	433	8	0.36 (0.15, 0.71)	433	5	0.22 (0.07, 0.52)
		Sitagliptin	469	24	1.03 (0.66, 1.53)	469	14	0.59 (0.32, 0.99)	469	9	0.38 (0.17, 0.72)
Race											
White		Glargine	833	74	1.87 (1.47, 2.34)	833	43	1.06 (0.77, 1.43)	833	13	0.32 (0.17, 0.54)
		Glimepiride	804	83	2.19 (1.74, 2.71)	804	38	0.97 (0.69, 1.33)	804	19	0.48 (0.29, 0.75)
		Liraglutide	808	58	1.48 (1.12, 1.91)	808	31	0.78 (0.53, 1.11)	808	8	0.20 (0.09, 0.39)
		Sitagliptin	850	88	2.21 (1.77, 2.72)	850	46	1.12 (0.82, 1.50)	850	19	0.46 (0.27, 0.71)
Black		Glargine	251	24	1.96 (1.26, 2.92)	251	14	1.13 (0.62, 1.89)	251	10	0.81 (0.39, 1.49)
		Glimepiride	270	24	1.82 (1.17, 2.71)	270	17	1.26 (0.74, 2.02)	270	11	0.82 (0.41, 1.46)
		Liraglutide	250	16	1.29 (0.73, 2.09)	250	10	0.79 (0.38, 1.46)	250	4	0.32 (0.09, 0.81)
		Sitagliptin	225	24	2.18 (1.39, 3.24)	225	17	1.52 (0.88, 2.43)	225	7	0.62 (0.25, 1.28)
All Others		Glargine	173	15	1.76 (0.98, 2.90)	173	8	0.92 (0.40, 1.82)	173	3	0.34 (0.07, 1.00)
		Glimepiride	173	8	0.92 (0.40, 1.80)	173	4	0.45 (0.12, 1.15)	173	0	0.00 (0.00, 0.42)
		Liraglutide	193	9	0.96 (0.44, 1.82)	193	7	0.74 (0.30, 1.53)	193	2	0.21 (0.03, 0.75)
		Sitagliptin	189	9	0.94 (0.43, 1.79)	189	6	0.62 (0.23, 1.35)	189	4	0.41 (0.11, 1.06)

(continued)

			Any cardiovascular disease events			Major adverse cardiovascular events (MACE)			Hospitalized heart failure		
Subgroups		Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Ethnicity											
Hispanic		Glargine	218	12	1.14 (0.59, 1.99)	218	6	0.56 (0.21, 1.22)	218	1	0.09 (0.00, 0.52)
		Glimepiride	231	12	1.06 (0.55, 1.85)	231	7	0.61 (0.25, 1.26)	231	2	0.17 (0.02, 0.63)
		Liraglutide	229	8	0.70 (0.30, 1.39)	229	5	0.44 (0.14, 1.02)	229	3	0.26 (0.05, 0.76)
		Sitagliptin	238	11	0.94 (0.47, 1.69)	238	7	0.60 (0.24, 1.23)	238	5	0.42 (0.14, 0.99)
Non-Hisp		Glargine	1028	99	2.00 (1.63, 2.44)	1028	58	1.15 (0.87, 1.49)	1028	25	0.49 (0.32, 0.72)
		Glimepiride	1002	103	2.15 (1.76, 2.61)	1002	52	1.05 (0.79, 1.38)	1002	28	0.56 (0.37, 0.81)
		Liraglutide	1017	75	1.52 (1.19, 1.90)	1017	43	0.86 (0.62, 1.16)	1017	11	0.22 (0.11, 0.39)
		Sitagliptin	1016	109	2.26 (1.85, 2.72)	1016	61	1.23 (0.94, 1.58)	1016	25	0.50 (0.32, 0.73)
Age (years)											
<45		Glargine	150	6	0.82 (0.30, 1.79)	150	5	0.68 (0.22, 1.60)	150	0	0.00 (0.00, 0.50)
		Glimepiride	162	4	0.51 (0.14, 1.31)	162	1	0.13 (0.00, 0.70)	162	1	0.13 (0.00, 0.70)
		Liraglutide	153	2	0.25 (0.03, 0.92)	153	1	0.13 (0.00, 0.71)	153	1	0.13 (0.00, 0.71)
		Sitagliptin	151	4	0.53 (0.14, 1.35)	151	4	0.53 (0.14, 1.35)	151	0	0.00 (0.00, 0.48)
45-59		Glargine	604	38	1.28 (0.91, 1.76)	604	25	0.83 (0.54, 1.23)	604	5	0.17 (0.05, 0.39)
		Glimepiride	553	40	1.49 (1.06, 2.02)	553	24	0.87 (0.56, 1.30)	553	12	0.44 (0.23, 0.76)
		Liraglutide	559	38	1.38 (0.98, 1.90)	559	22	0.79 (0.50, 1.20)	559	7	0.25 (0.10, 0.51)
		Sitagliptin	602	37	1.24 (0.88, 1.71)	602	21	0.70 (0.43, 1.07)	602	8	0.26 (0.11, 0.52)
60+		Glargine	503	69	2.94 (2.29, 3.72)	503	35	1.44 (1.00, 2.00)	503	21	0.86 (0.53, 1.31)
		Glimepiride	532	71	2.83 (2.21, 3.57)	532	34	1.30 (0.90, 1.82)	532	17	0.64 (0.37, 1.03)
		Liraglutide	539	43	1.68 (1.21, 2.26)	539	25	0.96 (0.62, 1.42)	539	6	0.23 (0.08, 0.49)
		Sitagliptin	511	80	3.46 (2.74, 4.31)	511	44	1.82 (1.32, 2.44)	511	22	0.89 (0.56, 1.35)

(continued)

			Any cardiovascular disease events			Major adverse cardiovascular events (MACE)			Hospitalized heart failure		
Subgroups		Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
BMI (kg/m^2)											
18.2-30.7		Glargine	408	37	1.87 (1.32, 2.58)	408	23	1.14 (0.72, 1.71)	408	6	0.29 (0.11, 0.64)
		Glimepiride	423	36	1.78 (1.24, 2.46)	423	16	0.77 (0.44, 1.25)	423	4	0.19 (0.05, 0.48)
		Liraglutide	394	19	0.98 (0.59, 1.53)	394	9	0.46 (0.21, 0.87)	394	1	0.05 (0.00, 0.28)
		Sitagliptin	444	42	2.01 (1.45, 2.72)	444	28	1.31 (0.87, 1.90)	444	8	0.37 (0.16, 0.73)
30.7-36.3		Glargine	421	31	1.51 (1.03, 2.15)	421	14	0.67 (0.37, 1.13)	421	8	0.39 (0.17, 0.76)
		Glimepiride	401	41	2.11 (1.52, 2.87)	401	21	1.05 (0.65, 1.61)	401	13	0.65 (0.35, 1.11)
		Liraglutide	443	35	1.62 (1.13, 2.25)	443	21	0.96 (0.59, 1.47)	443	6	0.27 (0.10, 0.59)
		Sitagliptin	406	38	1.96 (1.39, 2.69)	406	23	1.16 (0.73, 1.74)	406	9	0.45 (0.20, 0.85)
36.3-74.3		Glargine	426	45	2.24 (1.63, 3.00)	426	28	1.36 (0.90, 1.97)	426	12	0.57 (0.30, 1.00)
		Glimepiride	420	37	1.85 (1.30, 2.55)	420	22	1.07 (0.67, 1.63)	420	13	0.63 (0.34, 1.08)
		Liraglutide	412	29	1.46 (0.98, 2.09)	412	18	0.89 (0.53, 1.41)	412	7	0.34 (0.14, 0.71)
		Sitagliptin	412	41	2.04 (1.47, 2.77)	412	18	0.87 (0.52, 1.38)	412	13	0.63 (0.33, 1.07)
HbA1c (%)											
6.8-7.2		Glargine	474	47	2.06 (1.51, 2.74)	474	28	1.20 (0.80, 1.74)	474	13	0.55 (0.29, 0.95)
		Glimepiride	494	41	1.69 (1.22, 2.30)	494	23	0.93 (0.59, 1.39)	494	8	0.32 (0.14, 0.63)
		Liraglutide	496	28	1.16 (0.77, 1.68)	496	18	0.74 (0.44, 1.17)	496	5	0.20 (0.07, 0.48)
		Sitagliptin	465	32	1.42 (0.97, 2.01)	465	16	0.70 (0.40, 1.13)	465	8	0.35 (0.15, 0.68)
7.2-7.7		Glargine	389	38	2.03 (1.43, 2.78)	389	21	1.09 (0.68, 1.67)	389	9	0.47 (0.21, 0.88)
		Glimepiride	399	43	2.28 (1.65, 3.07)	399	21	1.08 (0.67, 1.65)	399	12	0.61 (0.32, 1.07)
		Liraglutide	370	28	1.53 (1.01, 2.21)	370	12	0.64 (0.33, 1.12)	370	6	0.32 (0.12, 0.70)
		Sitagliptin	411	42	2.12 (1.53, 2.87)	411	25	1.24 (0.80, 1.82)	411	10	0.49 (0.23, 0.89)
7.7-8.5		Glargine	394	28	1.49 (0.99, 2.15)	394	16	0.83 (0.48, 1.36)	394	4	0.21 (0.06, 0.53)
		Glimepiride	354	31	1.85 (1.26, 2.62)	354	15	0.87 (0.49, 1.43)	354	10	0.58 (0.28, 1.06)
		Liraglutide	385	27	1.45 (0.96, 2.12)	385	18	0.96 (0.57, 1.52)	385	3	0.16 (0.03, 0.46)
		Sitagliptin	388	47	2.59 (1.90, 3.45)	388	28	1.50 (1.00, 2.17)	388	12	0.63 (0.33, 1.11)

(continued)

			Any cardiovascular disease events			Major adverse cardiovascular events (MACE)			Hospitalized heart failure		
Subgroups		Treatment	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Diabetes Duration (yrs)											
0-2.5		Glargine	411	41	2.14 (1.53, 2.90)	411	25	1.28 (0.83, 1.88)	411	6	0.30 (0.11, 0.65)
		Glimepiride	415	42	2.14 (1.55, 2.90)	415	20	0.99 (0.60, 1.53)	415	12	0.59 (0.31, 1.03)
		Liraglutide	431	33	1.62 (1.11, 2.27)	431	21	1.01 (0.63, 1.55)	431	8	0.38 (0.16, 0.75)
		Sitagliptin	424	38	1.87 (1.32, 2.57)	424	16	0.77 (0.44, 1.25)	424	14	0.67 (0.37, 1.12)
2.5-5.4		Glargine	458	42	1.85 (1.33, 2.50)	458	25	1.08 (0.70, 1.6)	458	11	0.47 (0.23, 0.84)
		Glimepiride	390	43	2.23 (1.61, 3.01)	390	26	1.32 (0.86, 1.93)	390	13	0.65 (0.35, 1.12)
		Liraglutide	389	25	1.28 (0.83, 1.90)	389	16	0.81 (0.46, 1.32)	389	3	0.15 (0.03, 0.44)
		Sitagliptin	427	42	2.01 (1.45, 2.72)	427	28	1.32 (0.88, 1.90)	427	7	0.33 (0.13, 0.67)
5.4-11.2		Glargine	388	30	1.62 (1.09, 2.31)	388	15	0.79 (0.44, 1.31)	388	9	0.48 (0.22, 0.91)
		Glimepiride	442	30	1.43 (0.96, 2.04)	442	13	0.60 (0.32, 1.03)	442	5	0.23 (0.08, 0.54)
		Liraglutide	431	25	1.18 (0.77, 1.75)	431	11	0.51 (0.26, 0.92)	431	3	0.14 (0.03, 0.41)
		Sitagliptin	412	41	2.13 (1.53, 2.89)	412	25	1.27 (0.82, 1.87)	412	9	0.45 (0.21, 0.85)
Stroke/MI History[3]											
No		Glargine	1177	95	1.66 (1.35, 2.03)	1177	55	0.95 (0.71, 1.23)	1177	22	0.38 (0.24, 0.57)
		Glimepiride	1172	92	1.62 (1.31, 1.99)	1172	48	0.83 (0.61, 1.10)	1172	22	0.38 (0.24, 0.57)
		Liraglutide	1174	71	1.24 (0.96, 1.56)	1174	44	0.76 (0.55, 1.02)	1174	14	0.24 (0.13, 0.40)
		Sitagliptin	1173	90	1.58 (1.27, 1.95)	1173	50	0.86 (0.64, 1.14)	1173	22	0.38 (0.24, 0.57)
Yes		Glargine	80	18	5.37 (3.18, 8.48)	80	10	2.81 (1.35, 5.17)	80	4	1.09 (0.30, 2.80)
		Glimepiride	75	23	7.63 (4.84, 11.45)	75	11	3.23 (1.61, 5.78)	75	8	2.26 (0.97, 4.45)
		Liraglutide	77	12	3.43 (1.77, 5.99)	77	4	1.08 (0.29, 2.77)	77	0	0.00 (0.00, 0.98)
		Sitagliptin	91	31	8.56 (5.82, 12.15)	91	19	4.82 (2.90, 7.53)	91	8	1.90 (0.82, 3.74)

[1]Number at risk; [2]Number of events

[3]Post-hoc analysis of those who had a history of stroke or MI ≥ 1 year before randomization. Stroke within 1 year of randomization was a study exclusion criteria. Note that all subgroup factors were assessed at baseline.

Table S5.C: Sub-group analyses of mortality outcomes stratified according to seven pre-specified baseline factors and a post-hoc analysis of those who reported a history of MI or Stroke at least one year prior. Since the analysis did not correct for multiple subgroup factors, per the Journal statistical guidelines, only a descriptive presentation is provided that includes the number of outcome cases (*Ne*) and the crude rate (hazard) per 100 patient years of follow-up with uncorrected 95% confidence limits.

			Cardiovascular death			**All deaths**		
Subgroups		Treatment	N[1]	Ne[2]	Rate (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Sex								
Male		Glargine	808	19	0.48 (0.29, 0.74)	811	37	0.90 (0.63, 1.24)
		Glimepiride	777	10	0.26 (0.12, 0.47)	778	33	0.83 (0.57, 1.17)
		Liraglutide	818	9	0.22 (0.10, 0.42)	823	24	0.58 (0.37, 0.86)
		Sitagliptin	795	18	0.46 (0.27, 0.73)	798	33	0.82 (0.56, 1.15)
Female		Glargine	449	2	0.09 (0.01, 0.32)	452	5	0.21 (0.07, 0.49)
		Glimepiride	470	6	0.25 (0.09, 0.55)	476	10	0.41 (0.20, 0.75)
		Liraglutide	433	0	0.00 (0.00, 0.16)	439	3	0.13 (0.03, 0.37)
		Sitagliptin	469	3	0.13 (0.03, 0.37)	469	8	0.32 (0.14, 0.64)
Race								
White		Glargine	833	13	0.31 (0.17, 0.54)	837	26	0.61 (0.40, 0.89)
		Glimepiride	804	11	0.28 (0.14, 0.49)	808	33	0.80 (0.55, 1.13)
		Liraglutide	808	6	0.15 (0.05, 0.32)	815	19	0.46 (0.27, 0.71)
		Sitagliptin	850	13	0.31 (0.16, 0.53)	853	29	0.67 (0.45, 0.96)
Black		Glargine	251	6	0.47 (0.17, 1.03)	253	11	0.84 (0.42, 1.50)
		Glimepiride	270	4	0.29 (0.08, 0.74)	271	9	0.63 (0.29, 1.20)
		Liraglutide	250	2	0.16 (0.02, 0.56)	251	6	0.46 (0.17, 0.99)
		Sitagliptin	225	5	0.44 (0.14, 1.02)	225	7	0.59 (0.24, 1.21)
All Others		Glargine	173	2	0.23 (0.03, 0.82)	173	5	0.55 (0.18, 1.28)
		Glimepiride	173	1	0.11 (0.00, 0.63)	175	1	0.11 (0.00, 0.61)
		Liraglutide	193	1	0.10 (0.00, 0.58)	196	2	0.20 (0.02, 0.71)
		Sitagliptin	189	3	0.31 (0.06, 0.90)	189	5	0.51 (0.17, 1.19)

(continued)

			Cardiovascular death			All deaths		
Subgroups		Treatment	N[1]	Ne[2]	Rate (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Ethnicity								
Hispanic		Glargine	218	2	0.19 (0.02, 0.67)	220	4	0.35 (0.10, 0.90)
		Glimepiride	231	1	0.09 (0.00, 0.48)	234	4	0.33 (0.09, 0.84)
		Liraglutide	229	1	0.09 (0.00, 0.48)	234	2	0.16 (0.02, 0.59)
		Sitagliptin	238	3	0.25 (0.05, 0.74)	240	4	0.32 (0.09, 0.82)
Non-Hisp		Glargine	1028	18	0.35 (0.21, 0.55)	1032	37	0.70 (0.49, 0.96)
		Glimepiride	1002	15	0.30 (0.17, 0.49)	1006	39	0.76 (0.54, 1.04)
		Liraglutide	1017	8	0.16 (0.07, 0.31)	1022	25	0.48 (0.31, 0.70)
		Sitagliptin	1016	18	0.35 (0.21, 0.56)	1017	37	0.71 (0.50, 0.98)
Age (years)								
<45		Glargine	150	1	0.14 (0.00, 0.75)	152	3	0.38 (0.08, 1.10)
		Glimepiride	162	0	0.00 (0.00, 0.46)	165	0	0.00 (0.00, 0.43)
		Liraglutide	153	0	0.00 (0.00, 0.47)	154	0	0.00 (0.00, 0.45)
		Sitagliptin	151	1	0.13 (0.00, 0.73)	151	1	0.13 (0.00, 0.70)
45-59		Glargine	604	8	0.26 (0.11, 0.52)	606	12	0.38 (0.20, 0.67)
		Glimepiride	553	6	0.22 (0.08, 0.47)	555	13	0.46 (0.24, 0.78)
		Liraglutide	559	3	0.11 (0.02, 0.31)	562	6	0.20 (0.07, 0.44)
		Sitagliptin	602	7	0.23 (0.09, 0.47)	605	13	0.41 (0.22, 0.70)
60+		Glargine	503	12	0.48 (0.25, 0.84)	505	27	1.05 (0.69, 1.53)
		Glimepiride	532	10	0.37 (0.18, 0.69)	534	30	1.11 (0.75, 1.58)
		Liraglutide	539	6	0.23 (0.08, 0.49)	546	21	0.77 (0.47, 1.17)
		Sitagliptin	511	13	0.52 (0.28, 0.89)	511	27	1.06 (0.70, 1.55)

(continued)

			Cardiovascular death			All deaths		
Subgroups		Treatment	N[1]	Ne[2]	Rate (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
BMI (kg/m^2)								
18.2-30.7		Glargine	408	6	0.29 (0.11, 0.63)	409	14	0.66 (0.36, 1.11)
		Glimepiride	423	4	0.19 (0.05, 0.48)	425	12	0.56 (0.29, 0.97)
		Liraglutide	394	4	0.20 (0.06, 0.52)	400	11	0.53 (0.27, 0.95)
		Sitagliptin	444	9	0.41 (0.19, 0.78)	446	17	0.75 (0.44, 1.20)
30.7-36.3		Glargine	421	5	0.24 (0.08, 0.56)	424	12	0.55 (0.28, 0.96)
		Glimepiride	401	4	0.20 (0.05, 0.50)	403	14	0.67 (0.37, 1.12)
		Liraglutide	443	2	0.09 (0.01, 0.32)	446	9	0.39 (0.18, 0.74)
		Sitagliptin	406	8	0.39 (0.17, 0.78)	406	12	0.58 (0.30, 1.01)
36.3-74.3		Glargine	426	10	0.47 (0.23, 0.87)	428	15	0.68 (0.38, 1.12)
		Glimepiride	420	8	0.38 (0.17, 0.76)	423	17	0.79 (0.46, 1.26)
		Liraglutide	412	3	0.15 (0.03, 0.43)	414	7	0.33 (0.13, 0.67)
		Sitagliptin	412	4	0.19 (0.05, 0.49)	413	12	0.56 (0.29, 0.97)
HbA1c (%)								
6.8-7.2		Glargine	474	8	0.34 (0.15, 0.66)	476	16	0.65 (0.37, 1.05)
		Glimepiride	494	8	0.32 (0.14, 0.63)	498	21	0.82 (0.51, 1.25)
		Liraglutide	496	5	0.20 (0.07, 0.47)	498	12	0.47 (0.24, 0.82)
		Sitagliptin	465	4	0.17 (0.05, 0.44)	466	14	0.58 (0.32, 0.98)
7.2-7.7		Glargine	389	9	0.46 (0.21, 0.87)	391	14	0.69 (0.38, 1.16)
		Glimepiride	399	5	0.25 (0.08, 0.59)	400	14	0.69 (0.38, 1.16)
		Liraglutide	370	3	0.16 (0.03, 0.46)	374	10	0.51 (0.25, 0.94)
		Sitagliptin	411	7	0.34 (0.14, 0.69)	412	13	0.61 (0.32, 1.04)
7.7-8.5		Glargine	394	4	0.21 (0.06, 0.53)	396	12	0.59 (0.31, 1.04)
		Glimepiride	354	3	0.17 (0.04, 0.50)	356	8	0.44 (0.19, 0.86)
		Liraglutide	385	1	0.05 (0.00, 0.29)	390	5	0.25 (0.08, 0.58)
		Sitagliptin	388	10	0.52 (0.25, 0.96)	389	14	0.71 (0.39, 1.20)

(continued)

			Cardiovascular death			All deaths		
Subgroups		Treatment	N[1]	Ne[2]	Rate (95% CI)	N[1]	Ne[2]	Rate/100yrs (95% CI)
Diabetes Duration (yrs)								
0-2.5		Glargine	411	9	0.45 (0.20, 0.85)	413	15	0.72 (0.40, 1.18)
		Glimepiride	415	7	0.34 (0.14, 0.70)	418	16	0.75 (0.43, 1.21)
		Liraglutide	431	3	0.14 (0.03, 0.42)	434	9	0.41 (0.19, 0.78)
		Sitagliptin	424	7	0.33 (0.13, 0.68)	425	15	0.69 (0.38, 1.13)
2.5-5.4		Glargine	458	7	0.30 (0.12, 0.61)	460	13	0.53 (0.28, 0.91)
		Glimepiride	390	5	0.25 (0.08, 0.58)	390	15	0.73 (0.41, 1.21)
		Liraglutide	389	3	0.15 (0.03, 0.44)	395	7	0.34 (0.13, 0.69)
		Sitagliptin	427	8	0.37 (0.16, 0.73)	428	10	0.45 (0.21, 0.82)
5.4-11.2		Glargine	388	5	0.26 (0.09, 0.61)	390	14	0.71 (0.39, 1.19)
		Glimepiride	442	4	0.18 (0.05, 0.47)	446	12	0.54 (0.28, 0.94)
		Liraglutide	431	3	0.14 (0.03, 0.41)	433	11	0.50 (0.25, 0.89)
		Sitagliptin	412	6	0.30 (0.11, 0.64)	413	16	0.77 (0.44, 1.26)
Stroke/MI History[3]								
No		Glargine	1177	18	0.31 (0.18, 0.48)	1183	36	0.59 (0.41, 0.81)
		Glimepiride	1172	14	0.24 (0.13, 0.40)	1178	35	0.58 (0.40, 0.81)
		Liraglutide	1174	8	0.14 (0.06, 0.27)	1185	25	0.41 (0.26, 0.60)
		Sitagliptin	1173	15	0.26 (0.14, 0.42)	1176	32	0.53 (0.36, 0.75)
Yes		Glargine	80	3	0.79 (0.16, 2.32)	80	6	1.55 (0.57, 3.38)
		Glimepiride	75	2	0.54 (0.07, 1.97)	76	8	2.07 (0.89, 4.08)
		Liraglutide	77	1	0.27 (0.01, 1.48)	77	2	0.53 (0.06, 1.90)
		Sitagliptin	91	6	1.36 (0.50, 2.95)	91	9	1.97 (0.90, 3.73)

[1]Number at risk; [2]Number of events

[3]Post-hoc analysis of those who had a history of stroke or MI ≥ 1 year before randomization. Stroke within 1 year of randomization was a study exclusion criteria. Note that all subgroup factors were assessed at baseline.