SUPPLEMENTARY DATA

Supplementary Table 1. Association between severe hypoglycaemic events (SHEs) and subsequent major adverse cardiovascular event (MACE) or death outcomes in cardiovascular outcome trials

	Total population or subgroup in trial	MACE/death outcomes	Adj. HR (95% CI)
VADT	All	Cardiovascular mortality	4·04 (1·45-11·28)†
ACCORD	Intensive arm	Annualized mortality	1·41 (1·03-1·93)
	Standard arm	Annualized mortality	2·30 (1·46-3·65)
ADVANCE	All	3-point MACE	2·88 (2·01-4·12)
		Cardiovascular death	2·68 (1·72-4·19)
		All-cause death	2·69 (1·97-3·67)
ORIGIN	All	3-point MACE	1·58 (1·24–2·02)
		Cardiovascular death	1·71 (1·27–2·30)
		All-cause death	1·74 (1·39–2·19)
SAVOR-TIMI 53	All	CV death	1·81 (1·06-2·87)
		Heart failure hospitalisation	2·42 (1·27-4·60)
EXAMINE	All	3-point MACE	1·80 (1·04-2·89)

The time sequence for an SHE after a non-fatal MACE has not been evaluated at all.
ACCORD=Action to Control Cardiovascular Risk in Diabetes; ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; EXAMINE=Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; ORIGIN=Outcome Reduction with an Initial Glargine Intervention; SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53; VADT=Veterans Affairs Diabetes Trial.
*Cardiovascular death, non-fatal myocardial infarction/stroke. †Unadjusted.

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Supplementary Table 2. Baseline characteristics for participants with SHEs who had or did not have a CV event (intention-to-treat population)

	Without a CV Event (N=235)	With a CV Event (N=68)
Age at Randomisation (years)[1]		
Mean (SD)	66.9 (8.3)	67.9 (7.7)
<65 years	90 / 231 (39.0%)	19 / 67 (28.4%)
>=65 years	141 / 231 (61.0%)	48 / 67 (71.6%)
<70 years	138 / 231 (59.7%)	38 / 67 (56.7%)
>=70 years	93 / 231 (40.3%)	29 / 67 (43.3%)
Sex		
Male	150 / 235 (63.8%)	43 / 68 (63.2%)
Female	85 / 235 (36.2%)	25 / 68 (36.8%)
Race		
White	136 / 235 (57.9%)	40 / 68 (58.8%)
Black	13 / 235 (5.5%)	8 / 68 (11.8%)
Asian	59 / 235 (25.1%)	15 / 68 (22.1%)
Other	27 / 235 (11.5%)	5 / 68 (7.4%)
Duration[2] of type 2 diabetes (years)		
Median (Q1, Q3)	14.0 (7.0, 22.0)	13.5 (8.0, 22.5)
Diabetes duration 15 years or more	113 / 235 (48.1%)	33 / 68 (48.5%)
Diabetes therapy at baseline (alone or in combination)		
Sulfonylurea	110 / 235 (46.8%)	30 / 68 (44.1%)
Metformin	177 / 235 (75.3%)	49 / 68 (72.1%)
Thiazolidinedione (includes Pioglitazone)	7 / 235 (3.0%)	1 / 68 (1.5%)
Insulin	97 / 235 (41.3%)	32 / 68 (47.1%)
Not on Sulfonylurea or Insulin	33 / 235 (14.0%)	7 / 68 (10.3%)
Pre-existing vascular disease	234 / 235 (99.6%)	68 / 68 (100.0%)
Prior MI	85 / 235 (36.2%)	33 / 68 (48.5%)
Prior congestive heart failure	37 / 235 (15.7%)	17 / 68 (25.0%)
Current smoking	22 / 235 (9.4%)	3 / 68 (4.4%)
Qualifying HbA1c (mmol/mol)		
Median (Q1, Q3)	56.3 (51.9, 60.7)	55.2 (51.5, 60.1)
Qualifying HbA1c (%)		
Median (Q1, Q3)	7.3 (6.9, 7.7)	7.2 (6.9, 7.7)
Qualifying HbA1c categories		
<7%	66 / 235 (28.1%)	21 / 68 (30.9%)
7 - <7.5%	79 / 235 (33.6%)	18 / 68 (26.5%)
>=7.5%	90 / 235 (38.3%)	29 / 68 (42.6%)
eGFR (mL/min/1.73m^2)		
Median (Q1, Q3)	66.0 (54.0, 85.5)	60.0 (47.0, 71.0)
Renal function[3]		
eGFR <60 mL/min/1.73m^2	78 / 232 (33.6%)	33 / 68 (48.5%)
eGFR >=60 mL/min/1.73m^2	154 / 232 (66.4%)	35 / 68 (51.5%)
UACR categories		
<30 g/mol Creatinine	60 / 104 (57.7%)	13 / 26 (50.0%)
30 - <300 g/mol Creatinine	38 / 104 (36.5%)	8 / 26 (30.8%)
>=300 g/mol Creatinine	6 / 104 (5.8%)	5 / 26 (19.2%)
Systolic blood pressure (mmHg)		
Mean (SD)	135.8 (19.1)	140.0 (18.2)
Diastolic blood pressure (mmHg)		
Median (Q1, Q3)	75.2 (11.4)	74.9 (11.5)
Body mass index categories		
<25 kg/m^2	48 / 233 (20.6%)	7 / 68 (10.3%)
25 - <30 kg/m^2	88 / 233 (37.8%)	33 / 68 (48.5%)
30 - <35 kg/m^2	61 / 233 (26.2%)	15 / 68 (22.1%)
>=35 kg/m^2	36 / 233 (15.5%)	13 / 68 (19.1%)
Weight (kg)		
Mean (SD)	81.1 (19.1)	84.7 (20.7)
Medications taken at time of randomisation		
Statins	196 / 235 (83.4%)	61 / 68 (89.7%)
ACE inhibitors or angiotensin receptor blockers	185 / 235 (78.7%)	56 / 68 (82.4%)
Diuretics	103 / 235 (43.8%)	41 / 68 (60.3%)

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	Without a CV Event (N=235)	With a CV Event (N=68)
Calcium channel blockers	84 / 235 (35.7%)	25 / 68 (36.8%)
Beta blockers	144 / 235 (61.3%)	50 / 68 (73.5%)
Aspirin	192 / 235 (81.7%)	53 / 68 (77.9%)
Other platelet antagonists	54 / 235 (23.0%)	23 / 68 (33.8%)

1: Age is missing among patients enrolled in Lithuania because the entire birth date including year was not available.
2: Duration = (year of randomisation - year of diagnosis) + 1.
3: MDRD formula was used to calculate the eGFR. Site reported values are presented in the table.