Supplementary materials

Real-world comparisons between glucagon-like peptide-1 receptor agonists and other glucose lowering agents in type 2 diabetes: Retrospective analyses of cardiovascular and economic outcomes in England

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Supplementary methods

Study Design and Datasets

Linkage between Clinical Practice Research Datalink (CPRD) Aurum and Hospital Episode Statistics (HES) data records is conducted by National Health Service (NHS) Digital, a trusted third party; data are linked on a patient level using an 8-stage algorithm. The identifiers (date of birth, gender, NHS number, postcode of residence) required for linkage are sent directly from the originating general practice to NHS Digital. CPRD holds only a local patient identifier which is meaningful only at the patients' registered general practice. This identifier is pseudonymised a second time before being made available to researchers and analysts with access to the database. Access to the dataset is initiated through the submission of an application by the research organisation to the CPRD Research Data Governance (RDG) body. Data analysis was carried out in accordance with the Standard Operating Procedures (SOPs) of CorEvitas, Specialty EMR Data (formerly Health iQ).

Costing methods

Secondary care costs included all-cause and cardiovascular (CV)-related inpatient admissions and outpatient appointments. Admissions were classified as CV-related if the admission was associated with a primary International Classification of Diseases 10th Revision (ICD-10) diagnosis code for ischaemic heart disease, cerebrovascular disease, or peripheral vascular disease. CV-related appointments were defined as those that involved cardiology and vascular surgery specialties. All healthcare visits were stratified by the staff type and capped at one staff type consultation per day.

Tariff reimbursement payments for the HES are based on health resource groups (HRGs). HRGs are analogous to disease-related groups (DRGs) in Germany and the United States. HRGs were applied to each type of resource use listed above. Costs associated with each HRG are published by NHS Digital annually. The contemporary national tariff for each financial year (published by NHS England) was applied to the resource use occurring in that year. Where a resource use event (e.g., an inpatient admission) straddled a financial year, it was costed according to the financial year in which the patient was admitted. Once costs in each financial year were obtained, the findings were inflated using NHS Cost Inflation Index (NHSCII) to the most recent currency year available for the NHSCII in the Unit Cost of Health and Social Care, published annually by the Personal Social Service Research Unit (PSSRU). This method of cost inflation is recommended by NICE.

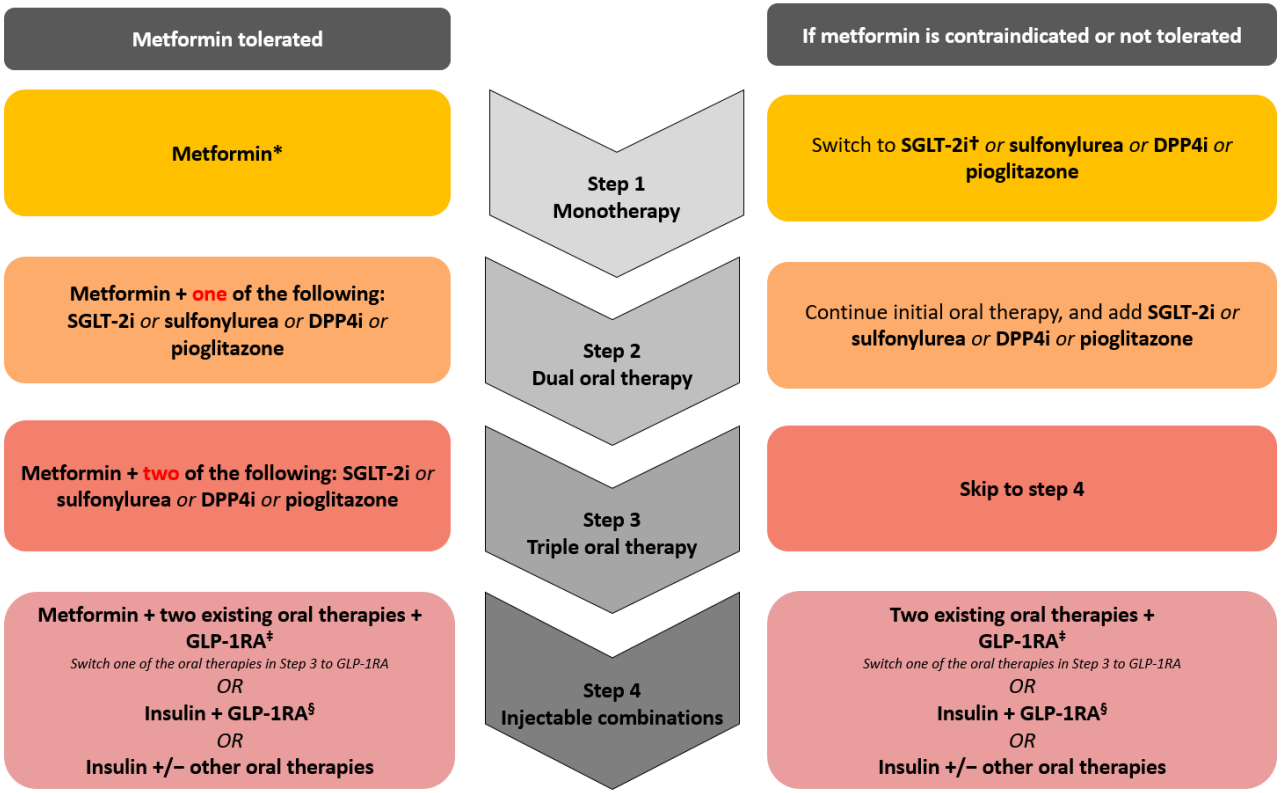
Where healthcare events were observed but did not have an HRG with a corresponding cost (invalid HRG), simple imputation was used to ensure that all observed data were costed. Simple imputation was performed as follows:

Inpatient stays: Inpatient admission costs vary with patients' diagnoses (ICD-10 codes) and procedures (Office of Population Censuses and Surveys version 4 [OPCS-4] codes) as well as the treating specialty. If any relevant information is missing, admissions do not 'group' into a HRG with a corresponding cost (invalid HRG). To estimate the cost, the median cost amongst all inpatient admissions with a 'valid' or costing HRG were calculated and then applied to all admissions with invalid HRGs.

Outpatient appointments: Outpatient costs were determined by treating speciality and whether the consultation was led by a senior clinician "consultant led" or not. Where outpatient appointments are observed with an invalid HRG, the cost will be imputed. To estimate the cost, the median cost amongst

all OP appointments with a ‘valid’ or costing HRG were calculated and then applied to all appointments with invalid HRGs.

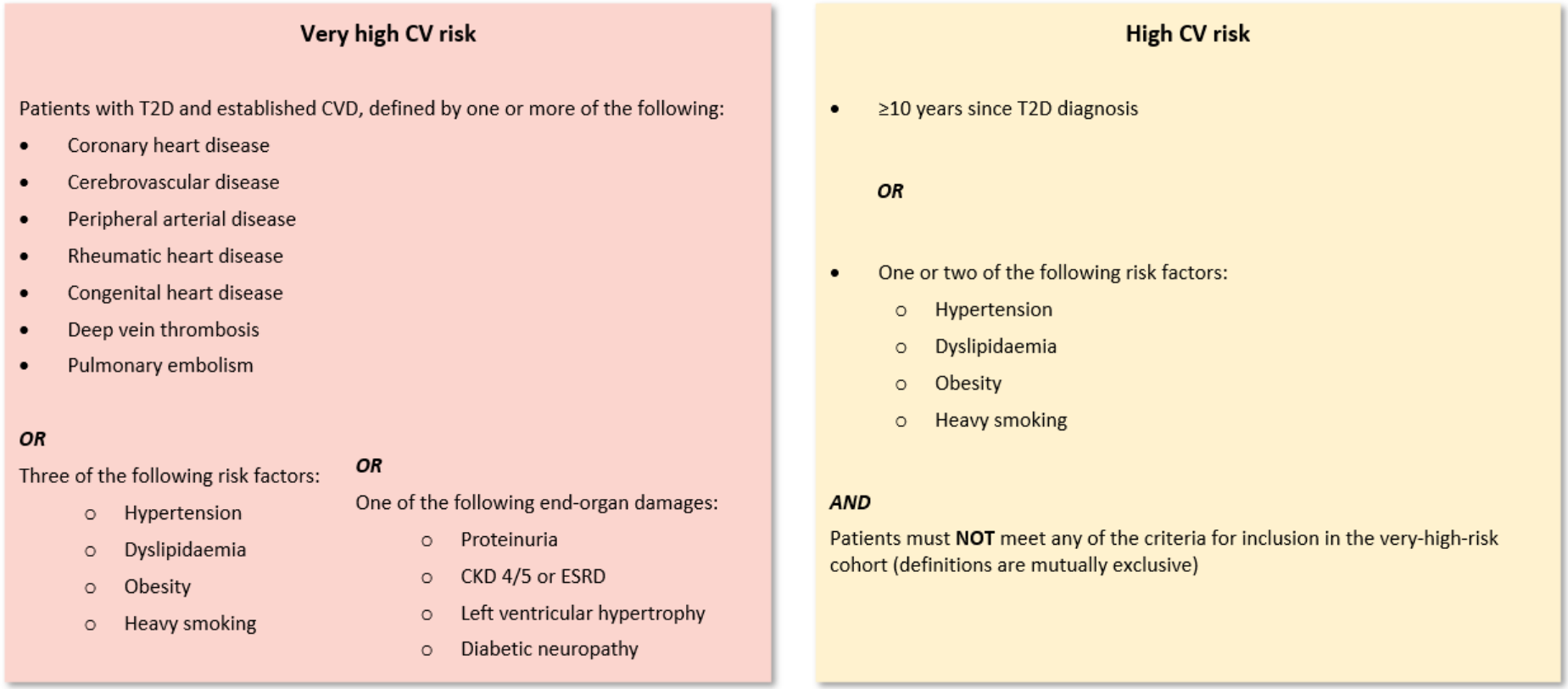
Figure S1. Lines of therapy for T2D in England, according to the 2022 NICE guidelines (1, 2)



*In people with chronic HF or established ASCVD, dual therapy with an SGLT-2i is recommended once tolerability of metformin is confirmed. In people at high risk of CVD, consider adding an SGLT-2i; †In people with chronic HF or established ASCVD, select an SGLT-2i if metformin is contraindicated or not tolerated. In people at high risk of CVD, consider an SGLT-2i if metformin is contraindicated or not tolerated; ‡Only in people with a BMI of ≥35 with an additional obesity-related complication, or those with a lower BMI who would benefit from weight loss for significant obesity-related complications or individuals for whom insulin-based therapy would have significant occupational implications; §With specialist care advice and ongoing support.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; HF, heart failure; NICE, National Institute of Health and Care Excellence; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes.

Figure S2. Definitions of patients at high or very high CV risk based on the 2019 European Society of Cardiology Guidelines (3)



CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; ESRD, end-stage renal disease; T2D, type 2 diabetes.

Table S1. Covariates considered for adjustment in the Cox proportional hazards regression models for time-to-first MACE[a] and all-cause death

Variable	Definition
age[b]	Age of individual in years at date of index prescription, included in the model as a continuous variable
gender[b]	Gender of individual at date of index prescription (male or female)
prior_mace[b]	Occurrence of a non-fatal myocardial infarction or non-fatal stroke event one year prior to the date of index prescription (yes or no)
time_from_diab[b]	Time in years since diabetes diagnosis at the date of index prescription
prior_dpp4[b]	Prescription of a DPP4 inhibitor prior to the date of index prescription (yes or no)
ethnicity	Ethnicity of individual at date of index prescription (White, Black, Mixed or other, South Asian)
region	Region of England the individual was living in at the date of index prescription (East of England, East Midlands, London, North East, North West, South East Coast, South West, West Midlands, Yorkshire and Humber)
smoking	Smoking status of individual at the date of index prescription (current smoker, ex-smoker, non-smoker)
alcohol intake	Alcohol consumption of individual at date of index prescription (heavy, non-heavy)
IMD	Index of Multiple Deprivation quintile at date of index prescription, based on the Index of Multiple Deprivation 2019 (1, 2, 3, 4, 5)
BMI[b]	Body mass index category at time of index prescription (<18.5 kg/m^2, 18–24.9 kg/m^2, 25.0–29.9 kg/m^2, 30.0–39.9 kg/m^2, ≥40 kg/m^2)
HbA1c	HbA1c level at time of index prescription (<6.5%, 6.5–7.4%, 7.5–7.9%, ≥8.0%)
rheumatoid_arthritis_sle	Rheumatoid arthritis or SLE diagnosis prior to the date of index prescription (yes or no)
end_stage_renal_failure	End-stage renal failure diagnosis prior to the date of index prescription (yes or no)
cancer	Any cancer diagnosis prior to the date the date of index prescription (yes or no)
copd	COPD diagnosis prior to the date the date of index prescription (yes or no)
stroke	Occurrence of a non-fatal stroke event prior to the date the date of index prescription (yes or no)
ckd3_4	Stage 3 or 4 CKD diagnosis prior to the date the date of index prescription (yes or no)
peripheral_vascular_disease	Peripheral vascular disease diagnosis prior to the date the date of index prescription (yes or no)
depression	Ongoing depression at date of index prescription (yes or no)
hypertension	Hypertension diagnosis prior to the date the date of index prescription (yes or no)
chronic_liver_disease	Chronic liver disease diagnosis prior to the date the date of index prescription (yes or no)
atrial_fibrillation	Atrial fibrillation diagnosis prior to the date the date of index prescription (yes or no)
ischaemic_heart_disease	Ischaemic heart disease diagnosis prior to the date the date of index prescription (yes or no)
metformin	Metformin prescribed within 90 days of index drug prescription (yes or no)
sulfonylurea	Sulfonylurea prescribed within 90 days of index drug prescription (yes or no)
sglt2[b]	Any SGLT2 inhibitor prescribed within 90 days of index drug prescription (yes or no)
pioglitazone	Pioglitazone prescribed within 90 days of index drug prescription (yes or no)
meglitinide	Meglitinide prescribed within 90 days of index drug prescription (yes or no)
ace	Any ACE inhibitor prescribed within 90 days of index drug prescription (yes or no)
statins	Any statin prescribed within 90 days of index drug prescription (yes or no)

Variable	Definition
antip	Any antiplatelet therapy prescribed within 90 days of index drug prescription (yes or no)
beta	Any beta-blocker prescribed within 90 days of index drug prescription (yes or no)
arb	Any ARB prescribed within 90 days of index drug prescription (yes or no)
drug_count	Number of different drug types prescribed within 90 days of index drug prescription
admi_count	Number of prior hospital admissions in the year before index prescription
consultation_count	Number of prior primary care appointments in the year before index prescription

[a]Composite MACE (non-fatal MI, non-fatal stroke, or CV-related death) and its individual components; [b]Select covariates were forced into the Cox proportional hazards regression model. All other covariates were considered for adjustment by the LASSO automatic feature selection tool.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; HbA1c, haemoglobin A1C; LASSO, least absolute shrinkage selection operator; MACE, major adverse cardiovascular event; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter-2; SLE, systemic lupus erythematosus.

Table S2. Covariates considered for adjustment in the generalised linear models for HCRU-related outcomes and costs

Variable	Definition
age[a]	Age of individual in years at date of index prescription, included in the model as a continuous variable
gender[a]	Gender of individual at date of index prescription (male or female)
follow_up_months[a]	Follow-up duration from index prescription, months
time_from_diab[a]	Time in years since diabetes diagnosis at the date of index prescription
prior_dpp4[a]	Prescription of a DPP4 inhibitor prior to the date of index prescription (yes or no)
ethnicity	Ethnicity of individual at date of index prescription (White, Black, Mixed or other, South Asian)
region	Region of England the individual was living in at the date of index prescription (East of England, East Midlands, London, North East, North West, South East Coast, South West, West Midlands, Yorkshire and Humber)
smoking	Smoking status of individual at the date of index prescription (current smoker, ex-smoker, non-smoker)
alcohol intake	Alcohol consumption of individual at date of index prescription (heavy, non-heavy)
IMD	Index of Multiple Deprivation quintile at date of index prescription, based on the Index of Multiple Deprivation 2019 (1, 2, 3, 4, 5)
BMI[a]	Body mass index category at time of index prescription (<18.5 kg/m^2, 18–24.9 kg/m^2, 25.0–29.9 kg/m^2, 30.0–39.9 kg/m^2, ≥40 kg/m^2)
HbA1c	HbA1c level at time of index prescription (<6.5%, 6.5–7.4%, 7.5–7.9%, ≥8.0%)
rheumatoid_arthritis_sle	Rheumatoid arthritis or SLE diagnosis prior to the date of index prescription (yes or no)
end_stage_renal_failure	End-stage renal failure diagnosis prior to the date of index prescription (yes or no)
cancer	Any cancer diagnosis prior to the date the date of index prescription (yes or no)
copd	COPD diagnosis prior to the date the date of index prescription (yes or no)
stroke	Occurrence of a non-fatal stroke event prior to the date the date of index prescription (yes or no)
ckd3_4	Stage 3 or 4 CKD diagnosis prior to the date the date of index prescription (yes or no)
peripheral_vascular_disease	Peripheral vascular disease diagnosis prior to the date the date of index prescription (yes or no)
depression	Ongoing depression at date of index prescription (yes or no)
hypertension	Hypertension diagnosis prior to the date the date of index prescription (yes or no)
chronic_liver_disease	Chronic liver disease diagnosis prior to the date the date of index prescription (yes or no)
atrial_fibrillation	Atrial fibrillation diagnosis prior to the date the date of index prescription (yes or no)
ischaemic_heart_disease	Ischaemic heart disease diagnosis prior to the date the date of index prescription (yes or no)
metformin	Metformin prescribed within 90 days of index drug prescription (yes or no)
sulfonylurea	Sulfonylurea prescribed within 90 days of index drug prescription (yes or no)
sglt2[a]	Any SGLT2 inhibitor prescribed within 90 days of index drug prescription (yes or no)
pioglitazone	Pioglitazone prescribed within 90 days of index drug prescription (yes or no)
meglitinide	Meglitinide prescribed within 90 days of index drug prescription (yes or no)
ace	Any ACE inhibitor prescribed within 90 days of index drug prescription (yes or no)
statins	Any statin prescribed within 90 days of index drug prescription (yes or no)

Variable	Definition
antip	Any antiplatelet therapy prescribed within 90 days of index drug prescription (yes or no)
beta	Any beta-blocker prescribed within 90 days of index drug prescription (yes or no)
arb	Any ARB prescribed within 90 days of index drug prescription (yes or no)
drug_count	Number of different drug types prescribed within 90 days of index drug prescription
admi_count	Number of prior hospital admissions in the year before index prescription
consultation_count	Number of prior primary care appointments in the year before index prescription
prior_mace	Occurrence of a non-fatal myocardial infarction or non-fatal stroke event one year prior to the date of index prescription (yes or no)

[a]Select covariates were forced into the Cox proportional hazards regression model. All other covariates were considered for adjustment by the LASSO automatic feature selection tool.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; DPP4, dipeptidyl peptidase-4; HbA1c, haemoglobin A1C; HCRU, healthcare resource utilisation; LASSO, least absolute shrinkage selection operator; SGLT-2, sodium-glucose cotransporter-2; SLE, systemic lupus erythematosus.

Table S3. Incidence of first MACE[a] and all-cause death during among individuals with T2D at high or very high CV risk indexed on GLP-1RA, DPP4 inhibitor, or basal insulin treatment

	High CV risk			Very high CV risk		
	GLP-1RA	**DPP4 inhibitor**	**Basal insulin**	**GLP-1RA**	**DPP4 inhibitor**	**Basal insulin**
40–49 years	**n=750**	**n=450**	**n=1,066**	**n=2,220**	**n=1,168**	**n=1,940**
Composite MACE	75.7 (1.9, 422.0)	737.4 (270.6, 1,604.9)	676.5 (360.2, 1,156.8)	1,036.0 (743.5, 1,405.5)	2,282.9 (1,683.2, 3,026.8)	2,718.5 (2,199.4, 3,323.2)
Non-fatal MI	S	614.5 (199.5, 1,434.0)	208.1 (56.7, 532.9)	429.6 (250.2, 687.8)	1,522.0 (1,041.0, 2,148.5)	1,631.1 (1,235.4, 2,113.3)
Non-fatal stroke	75.7 (1.9, 422.0)	122.9 (3.1, 684.7)	364.2 (146.4, 750.5)	555.9 (348.4, 841.7)	856.1 (507.4, 1,353.0)	944.3 (650.0, 1,326.2)
CV-related death	S	S	104.1 (12.6, 375.9)	75.8 (15.6, 221.5)	237.8 (77.2, 555.0)	257.5 (117.8, 488.9)
All-cause death	227.2 (46.9, 664.1)	737.4 (270.6, 1,604.9)	1,352.9 (883.8, 1,982.3)	151.6 (55.6, 330.0)	570.7 (294.9, 997.0)	1,516.6 (1,136.1, 1,983.8)
50–59 years	**n=995**	**n=721**	**n=1,510**	**n=4,986**	**n=3,101**	**n=4,360**
Composite MACE	452.1 (195.2, 890.7)	1,084.2 (592.7, 1,819.1)	1,301.6 (906.6, 1,810.2)	1,544.4 (1,297.5, 1,824.6)	3,242.0 (2,789.3, 3,747.3)	3,666.5 (3,255.2, 4,115.3)
Non-fatal MI	282.5 (91.7, 659.3)	774.4 (371.4, 1,424.2)	632.2 (368.3, 1,012.2)	761.0 (591.0, 964.8)	1,771.6 (1,441.4, 2,154.7)	1,871.4 (1,581.1, 2,199.6)
Non-fatal stroke	169.5 (35.0, 495.4)	232.3 (47.9, 679.0)	632.2 (368.3, 1,012.2)	615.5 (463.7, 801.2)	1,275.6 (998.0, 1,606.3)	1,413.1 (1,162.5, 1,701.8)
CV-related death	56.5 (1.4, 314.8)	232.3 (47.9, 679.0)	185.9 (60.4, 433.9)	212.6 (128.0, 332.1)	531.5 (358.6, 758.7)	700.2 (527.5, 911.4)
All-cause death	621.6 (310.3, 1,112.2)	1,548.8 (946.1, 2,392.1)	1,971.0 (1,476.4, 2,578.1)	481.2 (348.3, 648.2)	1,718.5 (1,393.5, 2,096.4)	2,304.3 (1,980.8, 2,665.5)
60–69 years	**n=499**	**n=669**	**n=1,115**	**n=4,616**	**n=4,721**	**n=5,097**
Composite MACE	339.8 (70.1, 993.1)	1,330.7 (760.6, 2,161.0)	1,379.7 (909.2, 2,007.4)	2,234.8 (1,923.5, 2,582.0)	4,550.2 (4,108.1, 5,027.0)	4,722.9 (4,286.0, 5,192.2)
Non-fatal MI	113.3 (2.9, 631.1)	582.2 (234.1, 1,199.6)	459.9 (210.3, 873.0)	971.6 (770.4, 1,209.3)	2,339.8 (2,026.0, 2,688.4)	2,195.9 (1,901.4, 2,523.1)
Non-fatal stroke	226.5 (27.4, 818.4)	582.2 (234.1, 1,199.6)	868.7 (506.0, 1,390.8)	947.3 (748.8, 1,182.3)	1,846.0 (1,568.5, 2,158.4)	1,931.1 (1,655.6, 2,239.3)

	High CV risk			Very high CV risk		
	GLP-1RA	**DPP4 inhibitor**	**Basal insulin**	**GLP-1RA**	**DPP4 inhibitor**	**Basal insulin**
CV-related death	S	249.5 (51.5, 729.2)	204.4 (55.7, 523.3)	461.5 (326.6, 633.5)	870.1 (683.2, 1,092.3)	1,070.4 (868.0, 1,305.8)
All-cause death	453.1 (123.5, 1,160.1)	2,079.3 (1,345.6, 3,069.4)	4,803.3 (3,881.6, 5,878.0)	1,251.0 (1,021.1, 1,517.2)	3,080.5 (2,718.8, 3,477.0)	4,667.7 (4,233.4, 5,134.4)
70–79 years	**n=117**	**n=456**	**n=619**	**n=2,113**	**n=5,313**	**n=4,525**
Composite MACE	1,927.6 (525.2, 4,935.5)	1,743.9 (953.4, 2,925.9)	3,145.4 (2,151.5, 4,440.4)	2,818.2 (2,305.0, 3,411.6)	6,440.4 (5,932.8, 6,979.8)	7,040.3 (6,460.0, 7,658.8)
Non-fatal MI	S	747.4 (274.3, 1,626.7)	786.4 (339.5, 1,549.4)	1,395.7 (1,042.4, 1,830.3)	2,667.2 (2,344.3 to 3,022.2)	2,623.9 (2,274.5, 3,011.7)
Non-fatal stroke	1,445.7 (298.1, 4,225.0)	622.8 (202.2, 1,453.4)	1,572.7 (898.9, 2,554.0)	1,154.1 (835.3, 1,554.6)	2,678.1 (2,354.5 to 3,033.7)	3,221.4 (2,832.9, 3,648.3)
CV-related death	481.9 (12.2, 2,685.0)	498.3 (135.8, 1,275.7)	1,179.5 (609.5, 2,060.4)	510.0 (307.0, 796.4)	1,973.3 (1,697.0 to 2,281.8)	2,078.3 (1,768.8, 2,426.5)
All-cause death	963.8 (116.7, 3,481.7)	5,107.1 (3,664.9, 6,928.3)	9,829.5 (7,997.7, 11,955.3)	1,610.4 (1,228.9, 2,072.9)	6,700.6 (6,182.7 to 7,250.4)	8,729.0 (8,081.4, 9,414.6)
≥80 years	**n=15**	**n=233**	**n=331**	**n=247**	**n=3,960**	**n=3,053**
Composite MACE	9,235.2 (1,118.4, 33,360.7)	5,761.6 (3,566.6, 8,807.3)	3,694.0 (2,224.1, 5,768.7)	7,876.1 (5,421.5, 11,061.0)	11,381.9 (10,557.1, 12,254.0)	11,803.3 (10,843.3, 12,825.5)
Non-fatal MI	4,617.6 (116.9, 25,727.6)	1,920.5 (772.2, 3,957.1)	777.7 (211.9, 1,991.2)	2,864.0 (1,479.9, 5,002.9)	4,084.6 (3,596.7, 4,620.1)	3,602.4 (3,081.3, 4,186.5)
Non-fatal stroke	4,617.6 (116.9, 25,727.6)	2,194.9 (947.6, 4,324.9)	1,555.4 (671.5, 3,064.7)	3,580.0 (2,003.7, 5,904.7)	4,375.2 (3,869.7, 4,928.3)	4,916.3 (4,304.0, 5,591.3)
CV-related death	S	2,743.6 (1,315.7, 5,045.7)	2,138.7 (1,067.6, 3,826.7)	2,864.0 (1,479.9, 5,002.9)	4,924.1 (4,386.9, 5,508.9)	5,530.8 (4,880.1, 6,244.1)
All-cause death	9,235.2 (1,118.4, 33,360.7)	12,620.8 (9,240.0, 16,834.3)	14,776.2 (11,642.0, 18,494.6)	5,012.1 (3,102.5, 7,661.5)	15,353.5 (14,393.1, 16,361.1)	17,736.7 (16,555.3, 18,980.2)

Values are reported as incidence per 100,000 person-years (95% CI). Definitions for high and very high CV risk are provided in Figure S1. Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with

basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors.

[a]Composite MACE (non-fatal MI, non-fatal stroke, or CV-related death) and its individual components.

CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular events; S, suppressed (n<5); T2D, type 2 diabetes.

Table S4. Cox proportional hazards models for time-to-first MACE[a] and all-cause death in individuals with T2D at high or very high CV risk

Outcome	Comparison	Events	Unadjusted difference		Adjusted[b]	
			HR (95% CI)	p value	HR (95% CI)	p value
High CV risk						
Composite MACE	DPP4 inhibitor	56	ref	-	ref	-
	GLP-1RA	11	0.21 (0.11, 0.40)	<0.001	0.45 (0.20, 1.00)	0.0506
	Basal insulin	94	ref	-	ref	-
	GLP-1RA	11	0.21 (0.11, 0.39)	<0.001	0.33 (0.16, 0.68)	0.0025
Non-fatal MI	DPP4 inhibitor	28	ref	-	ref	-
	GLP-1RA	S	0.19 (0.07, 0.50)	<0.001	0.28 (0.09, 0.870	0.0274
	Basal insulin	31	ref	-	ref	-
	GLP-1RA	S	0.29 (0.11, 0.75)	0.0108	0.42 (0.14, 1.25)	0.1186
Non-fatal stroke	DPP4 inhibitor	19	ref	-	ref	-
	GLP-1RA	S	0.34 (0.14, 0.85)	0.0207	0.74 (0.22, 2.46)	0.6283
	Basal insulin	52	ref	-	ref	-
	GLP-1RA	S	0.21 (0.09, 0.48)	<0.001	0.36 (0.14, 0.93)	0.0359
CV-related death	DPP4 inhibitor	15	ref	-	ref	-
	GLP-1RA	S	Could not be determined	-	Could not be determined	-
	Basal insulin	23	ref	-	ref	-
	GLP-1RA	S	Could not be determined	-	Could not be determined	-
All-cause death	DPP4 inhibitor	109	ref	-	ref	-
	GLP-1RA	13	0.13 (0.07, 0.23)	<0.001	0.28 (0.14, 0.55)	<0.001
	Basal insulin	229	ref	-	ref	-
	GLP-1RA	13	0.10 (0.06, 0.18)	<0.001	0.32 (0.16, 0.60)	<0.001

Outcome	Comparison	Events	Unadjusted difference		Adjusted[b]	
			HR (95% CI)	p value	HR (95% CI)	p value
Very high CV risk						
Composite MACE	DPP4 inhibitor	1,626	ref	-	ref	-
	GLP-1RA	450	0.33 (0.29, 0.36)	<0.001	0.67 (0.60, 0.76)	<0.001
	Basal insulin	1,425	ref	-	ref	-
	GLP-1RA	450	0.36 (0.32, 0.40)	<0.001	0.77 (0.68, 0.87)	<0.001
Non-fatal MI	DPP4 inhibitor	715	ref	-	ref	-
	GLP-1RA	211	0.35 (0.30, 0.41)	<0.001	0.65 (0.54, 0.78)	<0.001
	Basal insulin	595	ref	-	ref	-
	GLP-1RA	211	0.41 (0.35, 0.48)	<0.001	0.76 (0.63, 0.91)	0.003
Non-fatal stroke	DPP4 inhibitor	657	ref	-	ref	-
	GLP-1RA	186	0.34 (0.29, 0.40)	<0.001	0.64 (0.53, 0.78)	<0.001
	Basal insulin	595	ref	-	ref	-
	GLP-1RA	186	0.36 (0.31, 0.43)	<0.001	0.75 (0.62, 0.91)	0.00385
CV-related death	DPP4 inhibitor	486	ref	-	ref	-
	GLP-1RA	82	0.20 (0.16, 0.25)	<0.001	0.87 (0.66, 1.14)	0.312
	Basal insulin	414	ref	-	ref	-
	GLP-1RA	82	0.23 (0.18, 0.29)	<0.001	1.22 (0.93, 1.60)	0.152
All-cause death	DPP4 inhibitor	1,626	ref	-	ref	-
	GLP-1RA	209	0.15 (0.13, 0.18)	<0.001	0.42 (0.36, 0.50)	<0.001
	Basal insulin	1,586	ref	-	ref	-
	GLP-1RA	209	0.15 (0.13, 0.18)	<0.001	0.47 (0.40, 0.56)	<0.001

Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. In the high-risk cohorts, full case data were available for 2,045 individuals indexed on GLP-1RAs (75.5% of cohort), 2,200 individuals indexed on DPP4 inhibitors (82.3% of cohort), and 3,710 individuals indexed on basal insulin (71.0% of cohort). In the very-high-risk cohorts, full case data were available for 13,062 individuals indexed on GLP-1RAs (88.9% of cohort), 16,100 individuals indexed on DPP4 inhibitors (87.2% of cohort), and 15,553 individuals indexed on basal insulin (79.9% of cohort).

[a]Composite MACE (non-fatal MI, non-fatal stroke, and CV-related death) and its individual components; [b]Covariates for adjustment were selected using the LASSO automatic feature selection tool. The following variables were forced into the model: age, gender, prior MACE, time since diabetes diagnosis, SGLT-2 inhibitor use, BMI, and prior treatment with DPP4 inhibitors.

BMI, body mass index; CI, confidence interval; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; LASSO, least absolute shrinkage selection operator; MACE, major adverse cardiovascular event; MI, myocardial infarction; ref, reference; S, suppressed (n<5); SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

Table S5. All-cause HCRU-related outcomes and costs in secondary care among individuals with T2D at high or very high CV risk, indexed on GLP-1RA, DPP4 inhibitor, or basal insulin treatment

	High CV risk			Very high CV risk		
	GLP-1RA n=2,709	**DPP4 inhibitor n=2,673**	**Basal insulin n=5,225**	**GLP-1RA n=14,692**	**DPP4 inhibitor n=18,461**	**Basal insulin n=19,477**
Hospitalisations						
n (%)	956 (35.3)	1,195 (44.7)	2,327 (44.5)	6,460 (44.0)	11,866 (64.3)	11,912 (61.2)
Length of stay, bed days per person per year						
Mean (SD)	1.1 (7.5)	4.4 (18.0)	4.9 (19.4)	1.8 (9.0)	9.9 (26.7)	8.3 (24.2)
Median (min–max)	0.0 (0.0–219.7)	0.0 (0.0–246.9)	0.0 (0.0–305.6)	0.0 (0.0–311.5)	0.0 (0.0–365.2)	0.0 (0.0–356.8)
Outpatient appointments						
n (%)	2,035 (75.1)	2,147 (80.3)	4,296 (82.2)	12,017 (81.8)	16,450 (89.1)	17,307 (88.9)
Cost per person per year, £						
Inpatient						
Mean (SD)	786 (2,832)	1,716 (5,043)	2,182 (6,667)	1,198 (3,369)	3,743 (7,941)	3,612 (8,189)
Median (min–max)	0 (0–70,456)	0 (0–101,578)	0 (0–99,413)	0 (0–90,358)	676 (0–167,349)	545 (0–249,056)
Outpatient						
Mean (SD)	614 (1,093)	823 (1,981)	974 (1,725)	776 (1,365)	1,270 (2,060)	1,306 (2,068)
Median (min–max)	304 (0–25,794)	395 (0–68,475)	489 (0–32,849)	417 (0–72,733)	757 (0–79,062)	745 (0–58,155)

Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors.

CV, cardiovascular; DPP4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCRU, healthcare resource utilisation; SD, standard deviation; T2D, type 2 diabetes.

Table S6. Generalised linear regression models for all-cause HCRU outcomes and costs in secondary care among individuals with T2D at high or very high CV risk

Outcome	Comparison	Mean[a]	Unadjusted difference		Adjusted[b]	
			Est (95% CI)	p value	Est (95% CI)	p value
High CV risk						
Number of hospitalisations	DPP4 inhibitor	1.4	ref	-	ref	-
	GLP-1RA	0.8	−0.59 (−0.71, −0.48)	<0.001	−0.20 (−0.33, −0.07)	0.0031
	Basal insulin	1.7	ref	-	ref	-
	GLP-1RA	0.8	−0.91 (−1.03, −0.80)	<0.001	−0.06 (−0.13, 0.01)	0.0823
Length of hospitalisations, number of bed days	DPP4 inhibitor	5.1	ref	-	ref	-
	GLP-1RA	1.6	−3.49 (−4.35, −2.76)	<0.001	−0.76 (−1.23, −0.28))	0.0017
	Basal insulin	5.5	ref	-	ref	-
	GLP-1RA	1.6	−3.96 (−4.61, −3.37)	<0.001	−0.24 (−0.49, 0.01))	0.0625
Number of outpatient appointments	DPP4 inhibitor	9.7	ref	-	ref	-
	GLP-1RA	7.6	−2.14 (−2.80, −1.50)	<0.001	−1.34 (−2.05, −0.62)	<0.001
	Basal insulin	11.3	ref	-	ref	-
	GLP-1RA	7.6	−3.69 (−4.26, −3.13)	<0.001	−2.12 (−2.95, −1.28)	<0.001
Total cost, £	DPP4 inhibitor	5,215	ref	-	ref	-
	GLP-1RA	3,755	−1,460.79 (−1,811.80, −1,118.34)	<0.001	−817.63 (−1,114.92, −520.34)	<0.001
	Basal insulin	5,727	ref	-	ref	-
	GLP-1RA	3,755	−1,972.48 (−2,284.75, −1,659.87)	<0.001	−462.36 (−701.01, −223.70)	<0.001

Outcome	Comparison	Mean[a]	Unadjusted difference		Adjusted[b]	
			Est (95% CI)	p value	Est (95% CI)	p value
Very high CV risk						
Number of hospitalisations	DPP4 inhibitor	2.9	ref	-	ref	-
	GLP-1RA	1.2	−1.66 (−1.74, −1.59)	<0.001	−0.76 (−0.89, −0.63)	<0.001
	Basal insulin	3.1	ref	-	ref	-
	GLP-1RA	1.2	−1.83 (−1.91, −1.75)	<0.001	−0.28 (−0.36, −0.20)	<0.001
Length of hospitalisations, number of bed days	DPP4 inhibitor	11.7	ref	-	ref	-
	GLP-1RA	2.7	−9.00 (−9.54, −8.49)	<0.001	−2.85 (−3.23, −2.48)	<0.001
	Basal insulin	9.9	ref	-	ref	-
	GLP-1RA	2.7	−7.20 (−7.66, −6.76)	<0.001	−1.33 (−1.62, −1.03)	<0.001
Number of outpatient appointments	DPP4 inhibitor	15.1	ref	-	ref	-
	GLP-1RA	9.9	−5.19 (−5.52, −4.86)	<0.001	−2.67 (−3.08, −2.27)	<0.001
	Basal insulin	15.6	ref	-	ref	-
	GLP-1RA	9.9	−5.73 (−6.06, −5.39)	<0.001	−1.93 (−2.30, −1.56)	<0.001
Total cost, £	DPP4 inhibitor	9,135	ref	-	ref	-
	GLP-1RA	5,014	−4,121.53 (−4,320.02, −3,925.25)	<0.001	−1,493.31 (−1,651.98, −1,334.65)	<0.001
	Basal insulin	8,769	ref	-	ref	-
	GLP-1RA	5,014	−3,755.67 (−3,945.09, −3,568.02)	<0.001	−1,009.82 (−1,156.05, −863.58)	<0.001

Definitions for high and very high CV risk are provided in Figure S1. Drug groups are based on the indexed drug. GLP-1RA cohorts included any individuals prescribed GLP-1RAs. DPP4 inhibitor cohorts included individuals prescribed combined treatment with DPP4 inhibitors and basal insulin. Basal insulin cohorts included individuals prescribed combined treatment with basal insulin and any oral antidiabetic therapy, other than GLP-1RAs or DPP4 inhibitors. In the high-risk cohorts, full case data were available for 2,045 individuals indexed on GLP-1RAs (75.5% of cohort), 2,200 individuals indexed on DPP4 inhibitors (82.3% of cohort), and 3,710 individuals indexed on basal insulin (71.0% of cohort). In the very-high-risk cohorts, full case data were available for 13,062 individuals indexed on GLP-1RAs (88.9% of cohort), 16,100 individuals indexed on DPP4 inhibitors (87.2% of cohort), and 15,553 individuals indexed on basal insulin (79.9% of cohort).

[a]Per person mean during follow up (not annualised); [b]Covariates for adjustment were selected using the LASSO automatic feature selection tool. The following variables were forced into the model: age, gender, follow-up duration, time since diabetes diagnosis, SGLT-2 inhibitor use, BMI, and prior treatment with DPP4 inhibitors.

BMI, body mass index; CI, confidence interval; CV, cardiovascular; DPP4, dipeptidyl peptidase-4; Est, estimated; GLP-1RA, glucagon-like peptide-1 receptor agonist; HCRU, healthcare resource utilisation; LASSO, least absolute shrinkage selection operator; ref, reference; SGLT-2, sodium-glucose cotransporter-2; T2D, type 2 diabetes.

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