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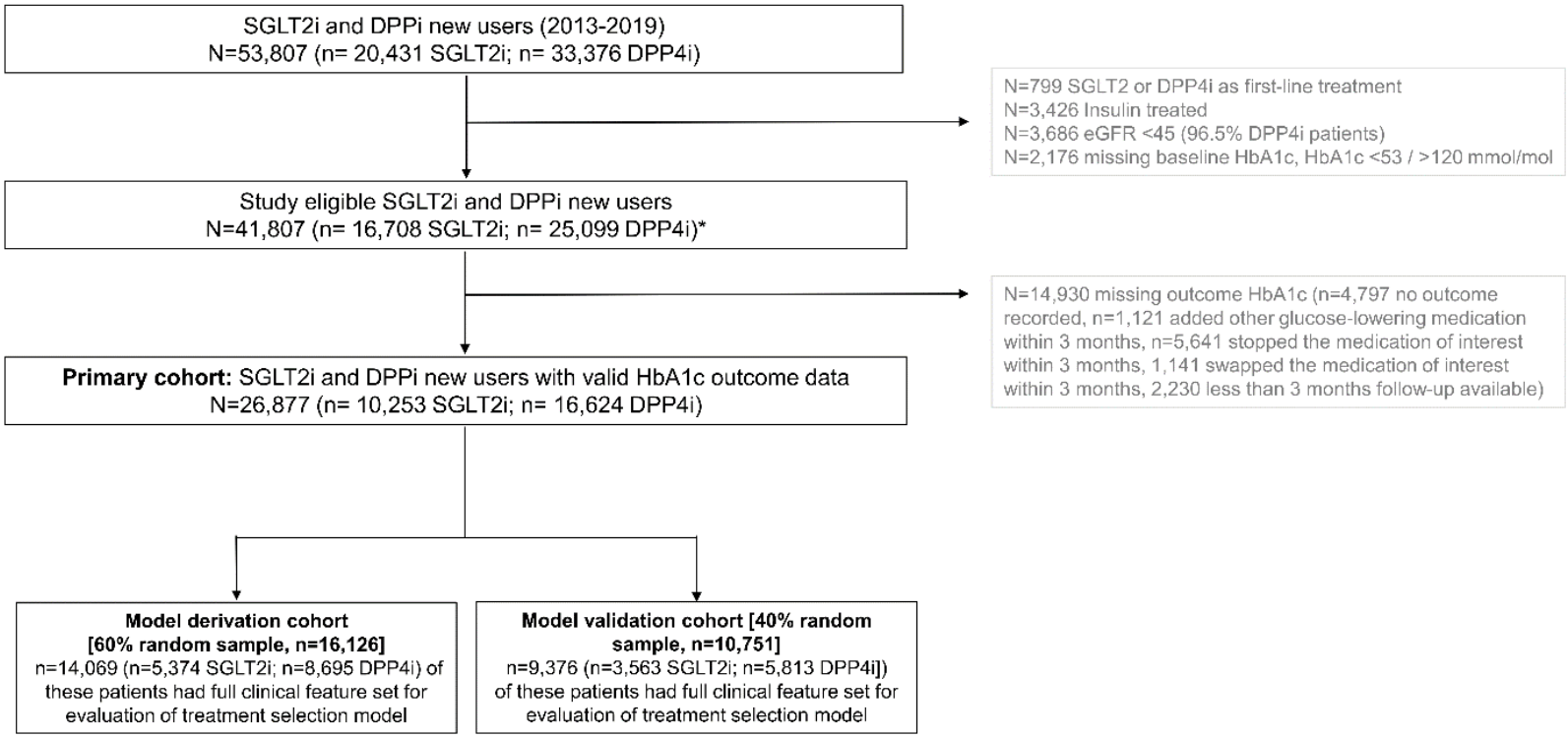
sFlowchart: CPRD patient flow and inclusion criteria for new users of SGLT2-inhibitor (SGLT2i) and DPP4-inhibitor (DPP4i) therapy



Baseline HbA1c defined as the closest HbA1c to drug initiation with –91/+7 days.

*For assessment of 6 month weight change, we followed the same procedures but included all patients with a baseline weight measure (within the 2 years prior to drug initiation) and outcome weight (closest weight to 6 month within 3-15 months, on unchanged glucose-lowering therapy), irrespective of whether they had an outcome HbA1c (n=20,065 [n= 7,842 SGLT2i, n=12,223 DPP4i). For assessment of treatment discontinuation, we included all patients with either 6 months of follow up time after drug initiation available, or 3 months of follow up time available after their last prescription (to confirm that the drug of interest was discontinued) (n=28,514 [n= 11,092 SGLT2i, n=17,422 DPP4i), irrespective of whether they had an outcome HbA1c

sTable 1: Baseline clinical characteristics by initiated drug class in clinical trial cohorts. Data are mean (SD) unless stated.

	CANTATA-D		CANTATA-D2		EMPA-REG MONO (BI 1245.20)	
	SGLT2-inhibitor (n=705) [Canagliflozin]	**DPP4-inhibitor (n=355) [Sitagliptin]**	**SGLT2-inhibitor (n=359) [Canagliflozin]**	**DPP4-inhibitor (n=356) [Sitagliptin]**	**SGLT2-inhibitor (n=505) [Empagliflozin]**	**DPP4-inhibitor (n=219) [Sitagliptin]**
Age (years)	55.2 (9.3)	55.4 (9.5)	56.5 (9.6)	56.6 (9.3)	54.3 (11.6)	55.1 (9.9)
Sex						
Female	382 (54.2)	187 (52.7)	161 (44.8)	151 (43.4)	173 (34.3)	82 (37.4)
Male	323 (45.8)	168 (47.3)	198 (55.2)	205 (57.6)	332 (65.7)	137 (62.6)
Ethnicity						
White	487 (69.1)	259 (73.0)	233 (64.9)	225 (63.2)	166 (32.9)	73 (33.3)
Asian	105 (14.9)	37 (10.4)	62 (17.3)	61 (17.1)	325 (64.4)	142 (64.8)
Black	27 (3.8)	12 (3.4)	42 (11.7)	42 (11.8)	10 (2.0)	3 (1.4)
Other	86 (12.2)	47 (13.2)	22 (6.1)	28 (7.9)	3 (0.6)	1 (0.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
HbA1c (mmol/mol)	63.3 (9.9)	63.1 (9.5)	65.1 (9.9)	65.4 (10.0)	68.2 (16.9)	62.2 (8.5)
BMI (kg/m^2)	31.9 (6.4)	32.0 (6.1)	31.5 (6.9)	31.7 (6.9)	28.3 (5.5)	28.2 (5.2)
eGFR (mL/min/1.3 m^2)	89.3 (18.2)	88.1 (18.8)	87.1 (18.1)	87.7 (20.3)	88.6 (19.2)	87.6 (17.4)
HDL-c (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)
Triglycerides (mmol/L)	2.1 (1.5)	2.0 (1.1)	2.0 (1.4)	1.9 (1.3)	2.2 (2.4)	2.2 (2.0)
ALT (IU/L)	29.1 (19.6)	28.5 (13.9)	27.8 (13.5)	27.8 (15.5)	31.4 (17.4)	31.9 (15.2)
Albumin (g/L)	41.0 (3.1)	41.1 (3.3)	40.9 (3.4)	40.9 (3.2)	45.2 (3.0)	45.5 (2.6)
Bilirubin (µmol/L)	8.7 (4.2)	8.8 (4.4)	8.2 (4.2)	8.3 (4.1)	10.0 (4.8)	9.8 (4.8)
Background therapy						
Metformin	705 (100.0)	355 (100.0)	359 (100.0)	356 (100.0)	0 (0.0)	0 (0.0)
Sulfonylurea	0 (0.0)	0 (0.0)	359 (100.0)	356 (100.0)	0 (0.0)	0 (0.0)
Thiazolidinedione	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DPP4-inhibitor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*other = α-glucosidase inhibitors, glucagon-like peptide-1 agonists, glinides

Values shown are mean (standard deviation) or n (%) for participants included in the mixed effects models and subsequent meta-analysis. This includes participants who were not insulin-treated and with at least one on-treatment HbA1c between randomisation and 6 months. EMPA-REG MONO/PIO/METSU: HbA1c measurements excluded after changes in study medication (including dose changes); EMPA-REG OUTCOME: HbA1c measurements excluded after changes in study medication (including dose changes) or changes in background medication (not including dose changes). Study medication (trial arm) is as randomised in all CANTATA trials, and as per actual study medication given in all other trials.

BMI, body mass index; DPP4-inhibitor, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin, type A1c; HDL-c, high-density lipoprotein cholesterol; SGLT2-inhibitor, sodium-glucose cotransporter-2 inhibitor.

	CANTATA-SU (n=939) [Canagliflozin]	**CANTATA-M (n=459) [Canagliflozin]**	**NCT01106651 (n=303) [Canagliflozin]**	**CANTATA-MSU (n=303) [Canagliflozin]**	**EMPA-REG PIO (n=321) [Empagliflozin]**	**EMPA-REG METSU (n=1,015) [Empagliflozin]**
Age (years)	55.9 (9.3)	53.8 (10.8)	64.1 (6.3)	56.7 (9.8)	54.5 (9.5)	55.5 (10.0)
Sex						
Female	460 (49.0)	257 (56.0)	138 (45.5)	142 (46.9)	161 (50.2)	456 (44.9)
Male	479 (51.0)	202 (44.0)	165 (54.5)	161 (53.1)	160 (49.8)	559 (55.1)
Ethnicity						
White	641 (6.8.3)	300 (65.4)	232 (76.6)	251 (82.8)	134 (41.7)	481 (47.4)
Asian	183 (19.5)	70 (15.3)	32 (10.6)	0 (0.0)	176 (54.8)	495 (48.8)
Black	34 (3.6)	34 (7.4)	19 (6.3)	16 (5.3)	10 (3.1)	25 (2.5)
Other	81 (8.6)	55 (12.0)	20 (6.6)	36 (11.9)	1 (0.3)	14 (1.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HbA1c (mmol/mol)	61.5 (8.5)	69.5 (15.2)	60.3 (8.6)	65.2 (10.1)	64.7 (9.4)	69.6 (16.3)
BMI (kg/m^2)	31.1 (5.3)	31.3 (6.3)	31.1 (4.5)	33.3 (6.3)	29.2 (5.6)	29.0 (5.5)
eGFR (mL/min/1.3 m^2)	90.6 (19.3)	88.5 (19.8)	77.8 (16.7)	89.9 (19.8)	85.8 (22.6)	89.2 (21.1)
HDL-c (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.3 (0.3)	1.3 (0.3)
Triglycerides (mmol/L)	2.1 (1.8)	2.1 (1.3)	1.8 (1.1)	2.2 (1.5)	1.8 (1.7)	1.9 (1.3)
ALT (IU/L)	28.9 (15.9)	28.6 (15.9)	26.2 (13.0)	28.9 (13.5)	23.6 (11.1)	28.2 (15.9)
Albumin (g/L)	42.2 (3.2)	41.1 (3.3)	40.9 (2.8)	40.9 (3.0)	44.6 (2.8)	45.2 (2.9)
Bilirubin (µmol/L)	8.8 (4.0)	9.4 (4.5)	8.7 (3.9)	8.7 (5.0)	8.7 (4.3)	9.2 (4.5)
Background therapy						
Metformin	939 (100.0)	0 (0.0)	278 (91.7)	303 (100.0)	245 (76.3)	1,015 (100.0)
Sulfonylurea	0 (0.0)	0 (0.0)	183 (60.5)	303 (100.0)	0 (0.0)	521 (51.3)
Thiazolidinedione	0 (0.0)	0 (0.0)	42 (13.7)	0 (0.0)	321 (100.0)	0 (0.0)
DPP4-inhibitor	0 (0.0)	0 (0.0)	32 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other*	0 (0.0)	0 (0.0)	17 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)

*other = α-glucosidase inhibitors, glucagon-like peptide-1 agonists, glinides

Values shown are mean (standard deviation) or n (%) for participants included in the mixed effects models and subsequent meta-analysis. This includes participants who were not insulin-treated and with at least one on-treatment HbA1c between randomisation and 6 months. EMPA-REG MONO/PIO/METSU: HbA1c measurements excluded after changes in study medication (including dose changes); EMPA-REG OUTCOME: HbA1c measurements excluded after changes in study medication (including dose changes) or changes in background medication (not including dose changes). Study medication (trial arm) is as randomised in all CANTATA trials, and as per actual study medication given in all other trials.

BMI, body mass index; DPP4-inhibitor, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin, type A1c; HDL-c, high-density lipoprotein cholesterol; SGLT2-inhibitor, sodium-glucose cotransporter-2 inhibitor.

	EMPA-REG OUTCOME (n=2,210) [Empagliflozin]	NCT00602472 (n=774) [Linagliptin]	NCT00621140 (n=326) [Linagliptin]	NCT00601250 (n=506) [Linagliptin]	NCT00622284 (n=759) [Linagliptin]
Age (years)	62.7 (8.8)	58.3 (9.9)	56.3 (10.1)	56.6 (10.0)	59.8 (9.4)
Sex					
Female	596 (27.0)	411 (53.1)	167 (51.2)	238 (47.0)	310 (40.8)
Male	1,614 (73.0)	363 (46.9)	159 (48.8)	268 (53.0)	449 (59.2)
Ethnicity					
White	1,472 (66.6)	367 (47.4)	171 (52.5)	381 (75.3)	645 (85.0)
Asian	629 (28.5)	395 (51.0)	155 (47.5)	111 (21.9)	93 (12.3)
Black	97 (4.4)	6 (0.8)	0 (0.0)	6 (1.2)	19 (2.5)
Other	12 (0.5)	6 (0.8)	0 (0.0)	8 (1.6)	2 (0.3)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HbA1c (mmol/mol)	63.4 (9.3)	65.5 (8.8)	63.7 (9.4)	64.8 (9.3)	60.5 (9.6)
BMI (kg/m^2)	29.7 (5.1)	28.4 (4.8)	29.0 (4.8)	29.9 (4.8)	30.2 (4.8)
eGFR (mL/min/1.3 m^2)	76.8 (20.5)	95.8 (22.9)	90.1 (22.4)	101.2 (29.9)	93.0 (22.5)
HDL-c (mmol/L)	1.2 (0.3)	1.2 (0.3)	1.2 (0.4)	1.2 (0.3)	1.2 (0.3)
Triglycerides (mmol/L)	1.9 (1.4)	2.1 (2.1)	1.9 (1.1)	2.0 (1.4)	1.9 (1.4)
ALT (IU/L)	26.1 (14.1)	27.2 (15.8)	25.7 (15.3)	27.2 (15.5)	27.8 (15.9)
Albumin (g/L)	44.8 (2.9)	45.3 (2.7)	45.1 (3.0)	44.8 (2.5)	44.8 (2.4)
Bilirubin (µmol/L)	8.6 (4.6)	9.3 (4.3)	10.7 (5.8)	9.0 (4.7)	9.0 (4.7)
Background therapy					
Metformin	1,819 (82.3)	774 (100.0)	0 (0.0)	506 (100.0)	759 (100.0)
Sulfonylurea	1,419 (64.2)	774 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Thiazolidinedione	125 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DPP4-inhibitor	324 (14.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other*	225 (10.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*other = α-glucosidase inhibitors, glucagon-like peptide-1 agonists, glinides

Values shown are mean (standard deviation) or n (%) for participants included in the mixed effects models and subsequent meta-analysis. This includes participants who were not insulin-treated and with at least one on-treatment HbA1c between randomisation and 6 months. EMPA-REG MONO/PIO/METSU: HbA1c measurements excluded after changes in study medication (including dose changes); EMPA-REG OUTCOME: HbA1c measurements excluded after changes in study medication (including dose changes) or changes in background medication (not including dose changes). Study medication (trial arm) is as randomised in all CANTATA trials, and as per actual study medication given in all other trials.

BMI, body mass index; DPP4-inhibitor, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin, type A1c; HDL-c, high-density lipoprotein cholesterol; SGLT2-inhibitor, sodium-glucose cotransporter-2 inhibitor.

sTable 2: Summary of clinical trial characteristics

a) Participant counts by study arm

	Trial	N SGLT2-inhibitor (final study cohorts) [1]					N DPP4-inhibitor (final study cohorts) [1]		
		Canagliflozin		Empagliflozin		Any SGLT2-i	Sitagliptin	Linagliptin	Any DPP4-i
		100mg	300mg	10mg	25mg		100mg	5mg	
1	**CANTATA-D (NCT01106677)**	352	353			705	355		355
2	**CANTATA-D2 (NCT01137812)**		359			359	356		356
3	**EMPA-REG MONO (BI1245.20; NCT01177813)**			214	291	505	219		219
4	**CANTATA-SU (NCT00968812)**	470	469			939			
5	**CANTATA-M (NCT01081834)**	229	230			459			
6	**Efficacy, Safety, and Tolerability of Canagliflozin vs. Placebo in the Treatment of Older Subjects… (NCT01106651)**	236	228			303			
7	**CANTATA-MSU (NCT01106625)**	149	154			303			
8	**EMPA-REG PIO (BI1245.19; NCT01210001)**			159	162	321			
9	**EMPA-REG METSU (BI1245.23; NCT01159600)**			434	581	1,015			
10	**EMPA-REG OUTCOME (BI1245.25; NCT01131676)**			1,100	1,110	2,210			
11	**Linagliptin in Combination With Metformin and a Sulfonylurea… (BI1218.18; NCT00602472)**							774	774
12	**Efficacy and Safety of Linagliptin vs. Placebo… (BI1218.16; NCT00621140)**							326	326
13	**Efficacy and Safety of Linagliptin vs. Placebo Added to Metformin Background Therapy… (BI1218.17; NCT00601250)**							506	506
14	**Efficacy and Safety of Linagliptin in Combination With Metformin (BI1218.20; NCT00622284)**							759	759

[1] Ns are participants included in the mixed effects models and subsequent meta-analysis. This includes participants who were not insulin-treated and with at least one on-treatment HbA1c between randomisation and 6 months (trials 3,8,9: HbA1c measurements excluded after changes in study medication (including dose changes); trial 10: HbA1c measurements excluded after changes in study medication (including dose changes) or changes in background medication (not including dose changes). Trials 1,2,4-7: treatment group is as randomised; trials 3,8-14: treatment group is actual study medication given.

DPP4-i(nhibitor), dipeptidyl-peptidase 4 inhibitor; SGLT2-i(nhibitor), sodium-glucose cotransporter-2 inhibitor

b) Clinical trial characteristics

	Trial	Trial type	Background therapy	Primary outcome(s)	Study time period	Inclusion criteria[1]
1	**CANTATA-D (NCT01106677) (1)**	Efficacy, placebo-controlled and active comparator	Immediate-release metformin monotherapy (≥2,000 mg/day, or ≥1,500 mg/day if unable to tolerate higher dose). (Participants on sulfonylurea in addition to metformin discontinued sulfonylurea.)	HbA1c change from baseline to 26 weeks	April 2010-August 2012	• Aged 18-80 • HbA1c ≥7% and ≤10.5% • Currently treated with metformin (maximum dose) alone or combined with sulfonylurea Exclusion: • Uncontrolled hyperglycaemia defined as repeated FPG ≥15.5mmol/L • Uncontrolled hypertension • eGFR <55mL/min (or <60 mL/min if based upon restriction in local label) or serum creatinine ≥124 μmol/L (men) or ≥115 μmol/L (women) • Treatment with PPAR-γ agonist, insulin, another SGLT2-inhibitor or any other antihyperglycaemic agents except metformin alone or with sulfonylurea within 12 weeks • Cardiovascular disease including MI, unstable angina, revascularisation procedure or cerebrovascular accident within 3 months • Severe hypoglycaemia episode within 6 months
2	**CANTATA-D2 (NCT01137812) (2)**	Efficacy, placebo-controlled and active comparator	Combined metformin and sulfonylurea at maximum- or near-maximum doses (adjusted pre-run in if not already at these doses)	HbA1c change from baseline to 52 weeks	June 2010-March 2012	• Aged 18+ • HbA1c ≥7% and ≤10.5% • Currently treated with metformin alone or combined with sulfonylurea Exclusion: • Uncontrolled hyperglycaemia defined as repeated FPG ≥16.7mmol/L • Uncontrolled hypertension • eGFR <55mL/min (or <60 mL/min if based upon restriction in local label) or serum creatinine ≥124 μmol/L (men) or ≥115 μmol/L (women) • Treatment with PPAR-γ agonist, insulin, another SGLT2-inhibitor or any other antihyperglycaemic agents except metformin and sulfonylurea within 12 weeks • History of cardiovascular disease • Severe hypoglycaemia episode within 6 months
3	**EMPA-REG MONO (BI1245.20; NCT01177813) (3)**	Efficacy, placebo-controlled and active comparator	None (drug-naïve)	HbA1c change from baseline to 24 weeks	August 2010-March 2012	• Aged 18+ (20+ in Japan only) • HbA1c ≥7% and ≤10% • BMI ≤45kg/m^2 • Drug-naïve to antihyperglycaemic agents Exclusion: • Uncontrolled hyperglycaemia after overnight fast during placebo run-in • eGFR <50mL/min at screening/placebo run-in • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks or any uncontrolled endocrine disorder except T2D • Treatment with anti-obesity medication/other treatment leading to unstable body weight • Any acute coronary syndrome], stroke, TIA within 3 months • Bariatric/other GI surgeries within 2 years • History of cancer • Any disorders causing haemolysis or unstable red blood cells

4	**CANTATA-SU (NCT00968812) (4)**	Efficacy, active comparator (sulfonylurea)	Immediate-release metformin monotherapy (≥2,000 mg/day, or ≥1,500 mg/day if unable to tolerate higher dose). (Participants on combined metformin and a second antihyperglycaemic agent (not TZD as per inclusion criteria) discontinued second agent.)	HbA1c change from baseline to 52 weeks	August 2009-December 2011 (core period) or January 2013 (52-week extension)	• Aged 18-80 • HbA1c ≥7% and ≤9.5% • BMI ≥22 and ≤45kg/m^2 • Currently treated with metformin (maximum dose) alone or combined with another antihyperglycaemic agent Exclusion: • Uncontrolled hyperglycaemia defined as repeated FPG ≥15mmol/L • History of active proliferative diabetic retinopathy • eGFR <55mL/min (or <60 mL/min if based upon restriction in local label) or serum creatinine ≥124 μmol/L (men) or ≥115 μmol/L (women) • Treatment with TZD within 16 weeks • Hereditary glucose-galactose malabsorption or primary renal glucosuria • Renal disease requiring immunosuppressive therapy within 12 months or a history of dialysis or renal transplant • Severe hypoglycaemia episode within 6 months
5	**CANTATA-M (NCT01081834) (5)**	Efficacy, placebo-controlled	None (participants on antihyperglycaemic agents as per inclusion criteria discontinued these)	HbA1c change from baseline to 26 weeks	March 2010-March 2012	• Aged 18-80 • Main study: HbA1c ≥7% and ≤10% on no antihyperglycaemic agent/HbA1c ≥6.5% and ≤9.5% on antihyperglycaemic agent monotherapy or combined low dose metformin and sulfonylurea; FPG ≤15mmol/L • High Glycaemic Substudy: HbA1c >10% and ≤12% and FPG ≤19.4mmol/L Exclusion: • eGFR <50mL/min • Treatment with PPAR-γ agonist, insulin, another SGLT2-inhibitor or any other antihyperglycaemic agents except as specified above within 12 weeks • Cardiovascular disease including MI, unstable angina, revascularisation procedure or cerebrovascular accident within 3 months • Hereditary glucose-galactose malabsorption or primary renal glucosuria • Severe hypoglycaemia episode within 6 months
6	**Efficacy, Safety, and Tolerability of Canagliflozin vs. Placebo in the Treatment of Older Subjects… (NCT01106651) (6)**	Efficacy, placebo-controlled	Any (usual care)	HbA1c change from baseline to 26 weeks	April 2010-November 2011 (core period) or June 2013 (78-week extension)	• Aged 55-80 (women at least 3 years postmenopausal) • HbA1c ≥7% and ≤10% • BMI ≥20 and ≤40kg/m^2 • Fasting fingerstick blood glucose ≥6.1mmol/L Exclusion: • Uncontrolled hyperglycaemia defined as repeated FPG ≥15mmol/L • Uncontrolled hypertension • eGFR <50mL/min • On metformin and serum creatinine ≥124 μmol/L (men) or ≥115 μmol/L (women) • Cardiovascular disease including MI, unstable angina, revascularisation procedure or cerebrovascular accident within 3 months • History of New York Heart Association Class III–IV cardiac disease • Severe hypoglycaemia episode within 6 months
7	**CANTATA-MSU (NCT01106625) (7)**	Efficacy, placebo-controlled	Combined metformin and sulfonylurea at maximum- or near-maximum doses (adjusted pre-run in if not already at these doses)	HbA1c change from baseline to 26 weeks	April 2010-April 2012	• Aged 18-80 • HbA1c ≥7% and ≤10.5% • Currently treated with combined metformin and sulfonylurea Exclusion: • Uncontrolled hyperglycaemia defined as repeated FPG ≥15mmol/L • Uncontrolled hypertension • eGFR <55mL/min (or <60 mL/min if based upon restriction in local label) or serum creatinine ≥124 μmol/L (men) or ≥115 μmol/L (women) • Treatment with any other antihyperglycaemic agents except metformin and sulfonylurea within 12 weeks • Severe hypoglycaemia episode within 6 months

8	**EMPA-REG PIO (BI1245.19; NCT01210001) (8)**	Efficacy, placebo-controlled	Pioglitazone alone or in combination with metformin	HbA1c change from baseline to 24 weeks (for any background therapy and for pioglitazone + metformin subset)	September 2010-April 2012	• Aged 18+ • BI1245.19: HbA1c ≥7% and ≤10%; BI1245.23: ≤11% for randomised arm, >11% for open-label arm • BMI ≤45kg/m^2 • Current treatment matches trial background therapy Exclusion: • Uncontrolled hyperglycaemia after overnight fast during placebo run-in • eGFR <30mL/min at screening/placebo run-in • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks or any uncontrolled endocrine disorder except T2D • Treatment with anti-obesity medication/other treatment leading to unstable body weight • MI, stroke, TIA within 3 months • Bariatric/other GI surgeries within 2 years • History of cancer • Any disorders causing haemolysis or unstable red blood cells
9	**EMPA-REG METSU (BI1245.23; NCT01159600) (9)**	Efficacy, placebo-controlled	Immediate-release metformin (≥1500mg/day or maximum dose) alone or in combination with sulfonylurea (≥half maximum dose)	HbA1c change from baseline to 24 weeks	July 2010-February 2012	
10	**EMPA-REG OUTCOME (BI1245.25; NCT01131676) (10)**	CV outcomes, placebo-controlled	Any (usual care)	Time to first occurrence of 3-point MACE (composite of CV death, non-fatal MI, and non-fatal stroke)	July 2010-April 2015	• Aged 18+ • HbA1c ≥7% and ≤10%, or ≥7% and ≤9% if drug-naïve • BMI ≤45kg/m^2 • High cardiovascular risk defined as ≥1 of the following (all >2 months prior): history of MI; evidence of single-vessel or multi-vessel coronary artery disease; unstable angina with evidence of single- or multi-vessel coronary artery disease; history of stroke (ischemic or hemorrhagic); occlusive peripheral artery disease Exclusion: • Uncontrolled hyperglycaemia after overnight fast during placebo run-in • eGFR <30mL/min at screening/placebo run-in • Planned cardiac surgery or angioplasty within 3 months • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks or any uncontrolled endocrine disorder except T2D • Treatment with anti-obesity medication/other treatment leading to unstable body weight • Acute coronary syndrome, stroke, TIA within 2 months • Bariatric/other GI surgeries within 2 years • History of cancer • Any disorders causing haemolysis or unstable red blood cells
11	**Linagliptin in Combination With Metformin and a Sulfonylurea… (BI1218.18; NCT00602472) (11)**	Efficacy, placebo-controlled	Combined metformin (≥1500mg/day or maximum dose) and sulfonylurea (maximum dose)	HbA1c change from baseline to 24 weeks	February 2008-May 2009	• Aged 18-80 • HbA1c ≥7% and ≤10% • BMI ≤40kg/m^2 • Current treatment matches trial background therapy Exclusion: • Renal failure, or renal impairment defined as serum creatinine ≥1.5 mg/dL • Treatment with TZD, GLP-1 analogue, or insulin within 3 months • Treatment with anti-obesity drugs (sibutramine, rimonabant, orlistat) within 3 months • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks • MI, stroke, TIA within 6 months • Dehydration • Current acute or chronic metabolic acidosis
12	**Efficacy and Safety of Linagliptin vs. Placebo… (BI1218.16; NCT00621140) (12)**	Efficacy, placebo-controlled	None (participants on antihyperglycaemic agents as per inclusion criteria discontinued these)	HbA1c change from baseline to 24 weeks	February 2008-May 2009	• Aged 18-80 • HbA1c ≥6.5% and ≤9%, or ≥7% and ≤10% if treatment-naïve Exclusion: • Treatment with >1 oral antidiabetic agent within 10 weeks • Treatment with TZD, GLP-1 analogue, or insulin within 3 months • Treatment with anti-obesity drugs (sibutramine, rimonabant, orlistat) within 3 months

						• Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks • MI, stroke, TIA within 6 months
13	**Efficacy and Safety of Linagliptin vs. Placebo Added to Metformin Background Therapy… (BI1218.17; NCT00601250) (13)**	Efficacy, placebo-controlled	Metformin monotherapy (≥1500mg/day or maximum dose). (Participants on an additional oral antidiabetes agents as per inclusion criteria discontinued these.)	HbA1c change from baseline to 24 weeks	January 2008-May 2009	• Aged 18-80 • HbA1c ≥6.5% and ≤9% if undergoing wash-out of previous medication, or ≥7% and ≤10% otherwise • BMI ≤40kg/m^2 • Currently treated with metformin (maximum dose) alone or combined with another oral antidiabetes agent Exclusion: • Renal failure or renal impairment • Treatment with TZD, injectable GLP-1 analogue, or insulin within 3 months • Treatment with anti-obesity drugs (sibutramine, rimonabant, orlistat) within 3 months • Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks • MI, stroke, TIA within 6 months • Unstable or acute congestive heart failure • Dehydration • History of acute or chronic metabolic acidosis • Hereditary galactose intolerance
14	**Efficacy and Safety of Linagliptin in Combination With Metformin (BI1218.20; NCT00622284) (14)**	Efficacy, placebo-controlled and active comparator (sulfonylurea)	Metformin monotherapy (≥1500mg/day or maximum dose). (Participants on an additional oral antidiabetes agents as per inclusion criteria discontinued these.)	HbA1c change from baseline to 52 weeks	February 2008-December 2010	• Aged 18-80 • HbA1c ≥6% and ≤9% if treated with metformin and another oral antidiabetes agent,, or ≥6.5% and ≤10% if treated with metformin alone • BMI ≤40kg/m^2 • Currently treated with metformin (maximum dose) alone or combined with another oral antidiabetes agent Exclusion: • Renal failure or renal impairment • Treatment with TZD, GLP-1 analogue, or insulin within 3 months • MI, stroke, TIA within 6 months

[1] All trials:
• Diagnosis of Type 2 diabetes mellitus
• Background therapy as stated in table and unchanged for up to 12 weeks prior to randomisation (varies between trials)
Exclusion:
• (Symptoms of) Type 1 diabetes mellitus or other type of diabetes mellitus
• Contraindications (according to local market) to assigned background or study medications
• Liver disease defined by elevated ALT, AST and/or alkaline phosphatase
• Nursing or pregnant women; or premenopausal women of child bearing potential either intending to become pregnant during the trial period and/or not practicing an acceptable method of birth control
• History of alcohol or drug abuse
• Participation in another trial with an investigational drug within preceding 30 days
• Any other clinical condition that would jeopardise patient safety while participating in this clinical trial

BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HbA1c, glycated haemoglobin, type A1c; MACE, major adverse cardiovascular event; MI, myocardial infarction; PPAR-γ, peroxisome proliferator-activated receptor gamma; SGLT2-i(nhibitor), sodium-glucose cotransporter-2 inhibitor; T2D, Type 2 diabetes; TIA, transient ischaemic attack; TZD, thiazolidinedione.

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sTable 3: Associations between clinical features and baseline HbA1c adjusted 6 month HbA1c response for SGLT2-inhibitor and DPP4-inhibitor treatment

a) CPRD routine clinical data (primary cohort, n=26,877). Data underlying Figure 2a. Estimates are derived from separate models for each clinical feature. N's represent the number of patients included in the model for each clinical feature. Each model was adjusted for baseline HbA1c-by-drug interaction, number of glucose-lowering drug classes ever prescribed, number of current glucose-lowering treatments, and month of HbA1c outcome measurement.

	SGLT2-inhibitor	**DPP4-inhibitor**
	Beta coefficient (95%CI)	**Beta coefficient (95%CI)**
Male Sex (n=26,877)	-1.39 (-1.92;-0.86)	-0.40 (-0.82;0.02)
Current age per year (n=26,877)	0.27 (-0.02;0.56)	-1.86 (-2.05;-1.66)
Diabetes Duration per year (n=26,877)	0.41 (0.12;0.70)	-1.12 (-1.33;-0.91)
eGFR per 1 mL/min/1.3 m^2 (n=26,877)	-0.81 (-1.10;-0.52)	1.45 (1.25;1.64)
BMI per 1 kg/m^2 (n=26,877)	-0.21 (-0.47;0.05)	0.96 (0.75;1.17)
HDL-c per 1 mmol/L (n=26,877)	0.62 (0.36;0.89)	-0.39 (-0.60;-0.19)
Triglycerides per 1 mmol/L (n=26,877)	0.05 (-0.24;0.33)	0.99 (0.78;1.21)
ALT per 1 IU/L (n=26,877)	-1.42 (-1.70;-1.14)	0.57 (0.35;0.78)
Albumin per 1 g/L (n=26,877)	-0.59 (-0.85;-0.32)	0.16 (-0.05;0.37)
Bilurubin per 1 µmol/L (n=26,877)	-1.01 (-1.27;-0.75)	-0.40 (-0.61;-0.20)

b) Clinical trial data (meta-analysis of 14 clinical trials). Data underlying Figure 2b. For each clinical feature, estimates are derived from random effects meta-analysis of beta coefficients estimated separately in each trial. I^2 represents the fraction of variance that is due to heterogeneity across the trials. N's represent the number of patients in the included in the model for each clinical feature.

i) Meta-analysis

	SGLT2-inhibitor			DPP4-inhibitor		
	Beta coefficient (95%CI)	**I^2**	**N**	**Beta coefficient (95%CI)**	**I^2**	**N**
Male Sex	-1.05 (-1.63;-0.47)	70.3%	7,119	-0.20 (-0.60;0.20)	0.0%	3,295
Current age per SD change	0.76 (0.60;0.92)	0.0%	7,117	0.12 (-0.10;0.33)	0.8%	3,295
Diabetes Duration per SD change	NA	NA	NA	NA	NA	NA
eGFR per SD change	-0.82 (-0.96;-0.68)	1.04%	7,104	0.01 (-0.16;0.18)	0.0%	3,226
BMI per SD change	0.09 (-0.14;0.33)	40.7%	7,116	0.70 (0.41;0.99)	21.3%	3,295
HDL-c per SD change	0.55 (0.38;0.73)	23.5%	7,054	-0.08 (-0.26;0.11)	0.0%	3,166
Triglycerides per SD change	0.15 (0.00;0.29)	0.0%	7,067	0.56 (0.36;0.76)	0.0%	3,166
ALT per SD change	-0.79 (-1.02;-0.55)	43.1%	7,027	0.43 (0.13;0.73)	40.4%	3,130
Albumin per SD change	-0.84 (-1.12;-0.56)	47.0%	7,079	-0.57 (-0.86,-0.28)	0.0%	3,184
Bilurubin per SD change	-0.52 (-0.74;-0.29)	36.2%	6,981	-0.26 (-0.65;0.13)	65.6%	3,166

ii) Individual trials

	CANTATA-D						CANTATA-D2						EMPA-REG MONO					
	SGLT2-inhibitor (n=705) [Canagliflozin]			DPP4-inhibitor (n=355) [Sitagliptin]			SGLT2-inhibitor (n=359) [Canagliflozin]			DPP4-inhibitor (n=356) [Sitagliptin]			SGLT2-inhibitor (n=505) [Empagliflozin]			DPP4-inhibitor (n=219) [Sitagliptin]		
	Beta	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**
Male sex	-0.120	0.460	705	0.634	0.641	355	-0.978	0.648	359	-0.160	0.652	356	-1.639	0.714	505	-0.785	0.822	219
Current age	0.728	0.254	705	-0.149	0.347	355	0.720	0.348	359	-0.008	0.369	356	0.802	0.308	504	0.030	0.418	219
eGFR	-0.826	0.236	702	-0.053	0.321	353	-0.539	0.344	356	-0.062	0.304	354	-0.424	0.334	504	0.482	0.433	219
BMI	0.260	0.232	703	0.464	0.345	355	0.618	0.300	359	0.566	0.306	356	-0.316	0.403	505	1.288	0.496	219
HDL-c	0.316	0.229	700	0.202	0.358	353	0.756	0.315	358	0.210	0.315	354	1.271	0.287	498	0.026	0.347	218
Triglycerides	0.086	0.217	704	0.724	0.341	354	-0.296	0.298	358	0.556	0.320	355	-0.270	0.291	498	0.376	0.351	218
ALT	-0.577	0.245	699	-0.245	0.377	351	-0.332	0.382	354	1.029	0.356	354	-0.694	0.364	500	0.473	0.454	218
Albumin	-0.741	0.291	699	-0.286	0.393	351	-0.675	0.378	355	-0.280	0.396	354	-0.342	0.457	502	-1.717	0.600	218
Bilirubin	0.016	0.282	684	-0.469	0.382	346	-0.265	0.401	343	0.795	0.413	344	-0.870	0.356	502	-1.335	0.410	218

	CANTATA-SU (n=939) [Canagliflozin]			CANTATA-M (n=459) [Canagliflozin]			NCT01106651 (n=303) [Canagliflozin]			CANTATA-MSU (n=303) [Canagliflozin]			EMPA-REG PIO (n=321) [Empagliflozin]			EMPA-REG METSU (n=1,015) [Empagliflozin]		
	Beta	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**
Male sex	-1.267	0.371	939	0.034	0.624	459	-0.619	0.567	303	-0.953	0.596	303	0.123	0.757	321	-1.949	0.415	1,015
Current age	0.599	0.206	939	0.907	0.298	459	0.806	0.463	303	0.644	0.314	303	1.000	0.411	321	0.696	0.218	1,015
eGFR	-0.671	0.183	937	-1.042	0.302	457	-0.390	0.321	301	-0.610	0.281	301	-0.962	0.313	321	-0.809	0.187	1,015
BMI	-0.380	0.228	939	0.018	0.325	459	0.214	0.414	302	-0.050	0.305	303	0.497	0.447	321	0.519	0.248	1,015
HDL-c	0.702	0.178	935	0.252	0.323	454	0.437	0.298	302	0.528	0.320	302	0.090	0.361	320	0.621	0.198	1,001
Triglycerides	0.130	0.176	938	0.324	0.303	459	0.230	0.303	303	0.138	0.270	302	0.595	0.381	320	-0.252	0.203	1,001
ALT	-0.844	0.203	929	-0.702	0.355	454	-0.429	0.344	301	-0.396	0.345	300	-1.043	0.450	319	-0.900	0.227	997
Albumin	-0.626	0.234	932	-0.296	0.376	455	-0.674	0.401	301	-0.731	0.393	301	-0.759	0.548	320	-1.634	0.285	1,004
Bilirubin	-0.166	0.243	918	-0.972	0.348	446	-0.370	0.379	290	-0.310	0.311	289	-0.534	0.448	320	-1.023	0.239	1,003

	EMPA-REG OUTCOME (n=2,210) [Empagliflozin]			NCT00602472 (n=770) [Linagliptin]			NCT00621140 (n=326) [Linagliptin]			NCT00601250 (n=506) [Linagliptin]			NCT00622284 (n=759) [Linagliptin]		
	Beta	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**	**Beta**	**SE**	**n**
Male sex	-2.390	0.329	2,210	0.279	0.438	774	-0.860	0.768	326	-0.490	0.563	506	-0.428	0.363	759
Current age	0.861	0.173	2,209	-0.146	0.228	774	-0.082	0.397	326	0.121	0.293	506	0.495	0.196	759
eGFR	-1.061	0.134	2,210	0.117	0.182	744	0.320	0.333	311	0.048	0.183	486	-0.174	0.150	759
BMI	-0.187	0.187	2,210	1.099	0.292	774	1.331	0.519	326	0.254	0.379	506	0.476	0.243	759
HDL-c	0.444	0.148	2,184	-0.362	0.212	751	-0.099	0.303	298	-0.044	0.269	473	-0.067	0.171	719
Triglycerides	-0.014	0.156	2,184	0.713	0.200	760	0.806	0.429	296	0.561	0.293	469	0.323	0.186	714
ALT	-1.346	0.166	2,174	0.519	0.230	739	1.007	0.444	299	0.429	0.319	460	0.135	0.195	709
Albumin	-1.286	0.202	2,210	-0.659	0.307	762	-0.331	0.529	308	-0.861	0.436	470	-0.455	0.300	721
Bilirubin	-0.605	0.163	2,186	-0.292	0.248	759	-0.534	0.342	308	-0.224	0.300	470	0.105	0.198	721

Mixed effects model results used for the trial meta-analysis

Beta, SE and n are the beta coefficients, standard error of the means and number of participants from mixed effects models of the association between individual clinical features and HbA1c outcome within each trial arm*. These models included patient-level random effects and adjusted for baseline HbA1c. Clinical features were standardised to CPRD means and standard deviations, so that beta coefficients represent the change in outcome HbA1c in mmol/mol per standard deviation change in the clinical feature (ALT and triglycerides values were logged prior to inclusion in the model). Diabetes duration was not available (except in categorised form) in any of the trial data.

Using notation from the nlme R package, the mixed models were of the form:
[outcome HbA1c] ~ factor([time point]) + [baseline HbA1c] + [clinical feature of interest] + factor([SGLT2-inhibitor dose]), random = ~ [time point] | [patient ID]

Outcome HbA1c: on-therapy HbA1c values up to 6 months post-randomisation. EMPA-REG MONO/PIO/METSU: HbA1c measurements excluded after changes in study medication (including dose changes); EMPA-REG OUTCOME: HbA1c measurements excluded after changes in study medication (including dose changes) or changes in background medication (not including dose changes).

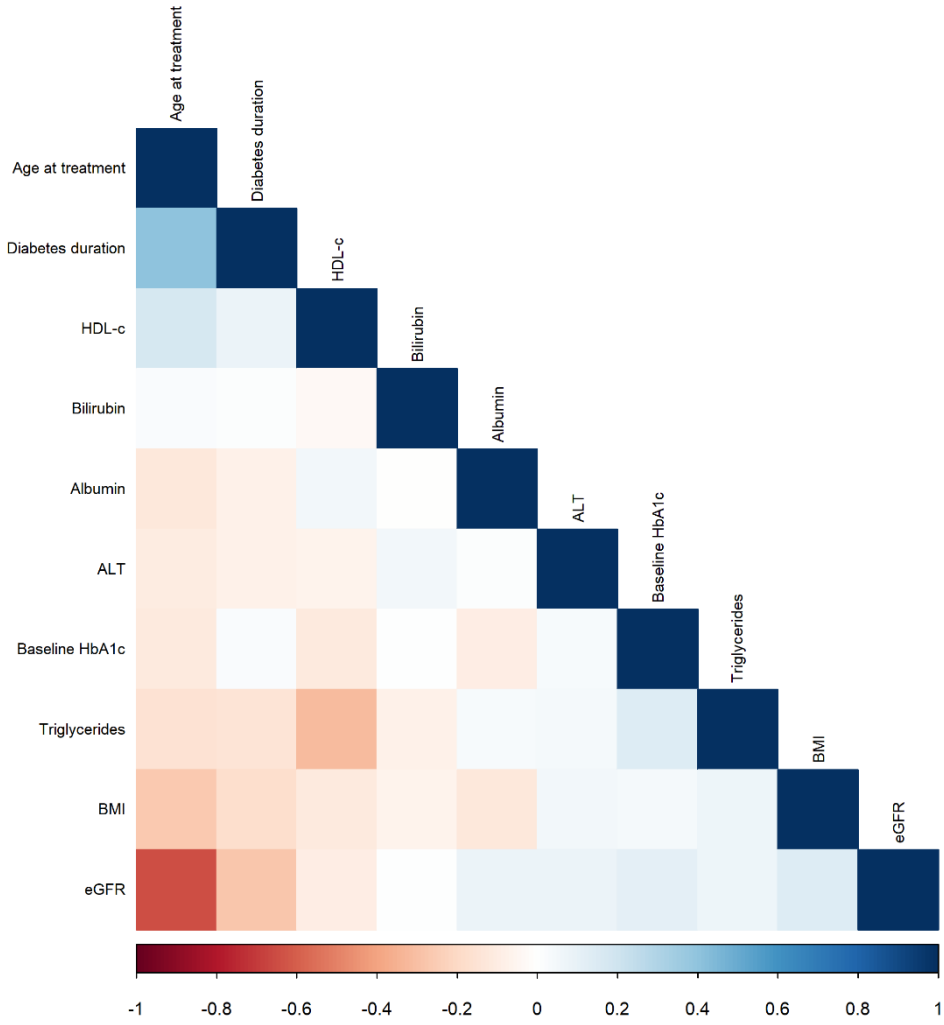
Time point: time point post-randomisation at which the outcome HbA1c was measured (1 for the first time point post-randomisation in a trial, 2 for the second etc.).

Total number of observations per model was > n as individuals have multiple on-therapy HbA1c values up to 6 months post-randomisation). Participants who were insulin-treated were not included in the analysis.

*Study medication (trial arm) is as randomised in all CANTATA trials, and as per actual study medication given in all other trials.

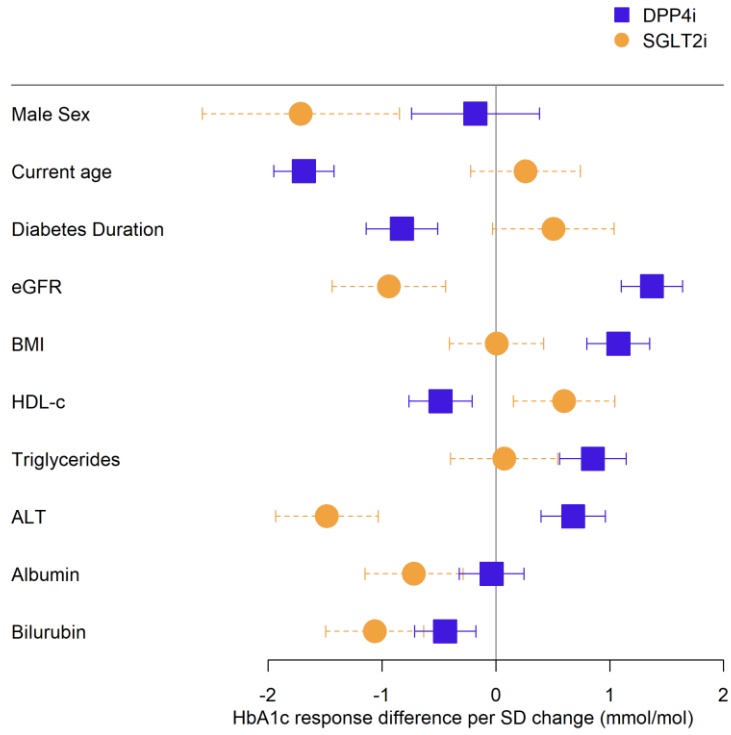
BMI, body mass index; DPP4-inhibitor, dipeptidyl-peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin, type A1c; HDL-c, high-density lipoprotein cholesterol; SGLT2-inhibitor, sodium-glucose cotransporter-2 inhibitor.

sFigure 1: Correlation matrix for all predictor variables assessed in CPRD

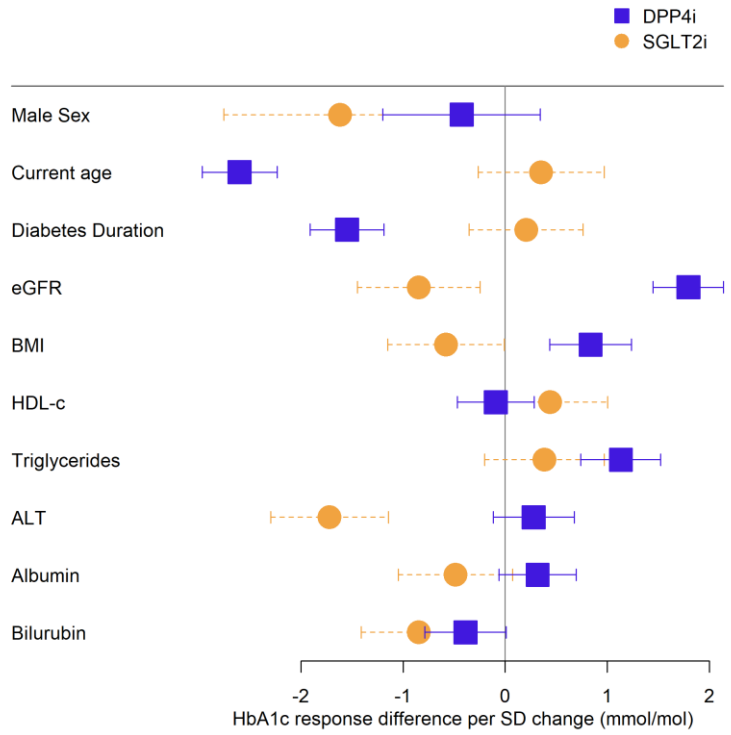


sFigure 2: Sensitivity analysis for associations between clinical features and baseline HbA1c adjusted 6-month HbA1c response for SGLT2-inhibitor and DPP4-inhibitor treatment. Negative estimates represent an association between a higher value of the clinical feature and greater HbA1c improvement, positive estimates represent an association between a higher value of the clinical feature and lesser HbA1c improvement.

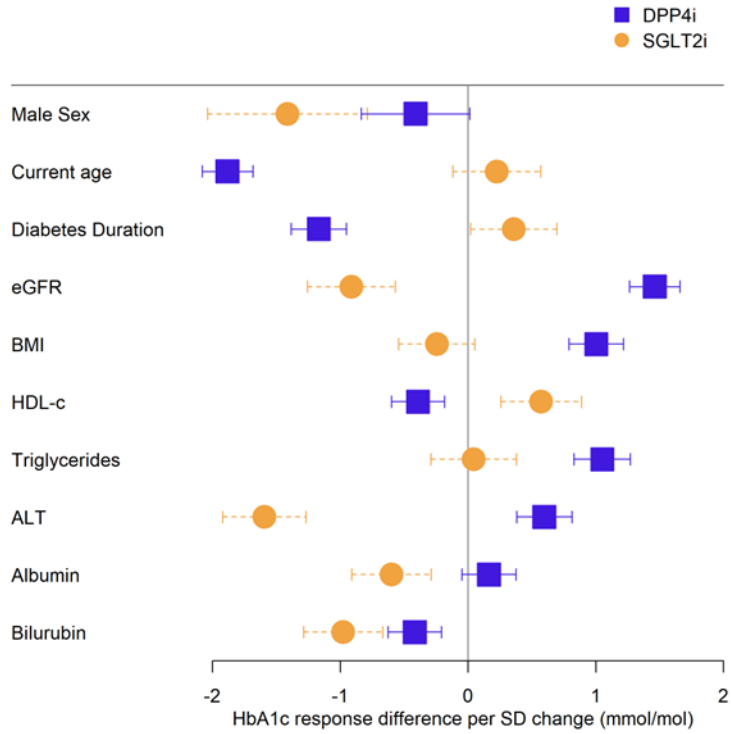
a) Patients on background metformin monotherapy (n=12,421)



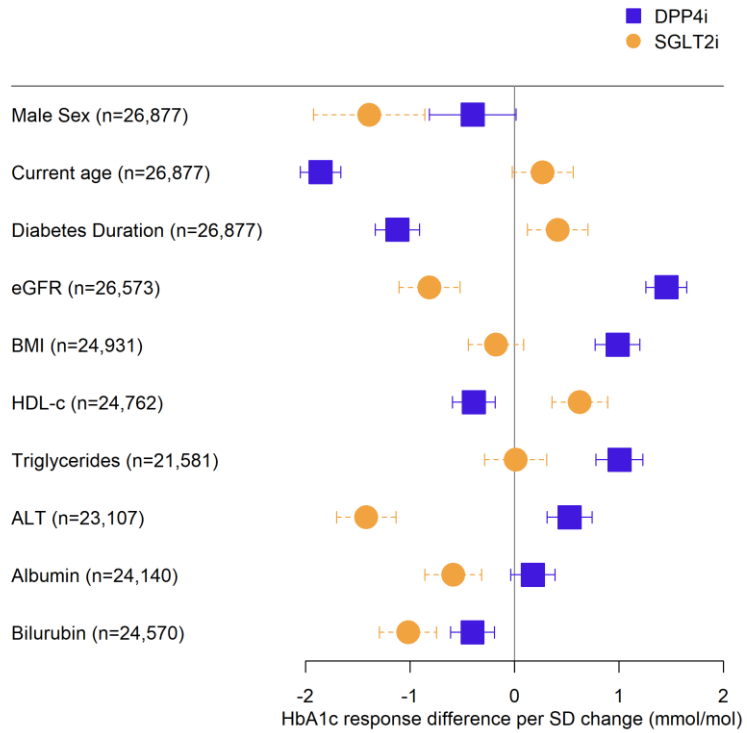
b) Patients on background metformin + sulfonylurea dual-therapy (n=7,579)



c) Excluding patients initiating SGLT2i whilst treated with DPP4i (n=2,712) or initiating DPP4i whilst treated with SGLT2i (n=361) [final cohort n=23,804]



d) Using only biomarker values recorded in the 12 months (rather than 24 months) prior to the date of drug initiation



sTable 4: Baseline clinical characteristics by initiated drug class for model derivation and validation sets in CPRD. Data are mean (SD) unless stated.

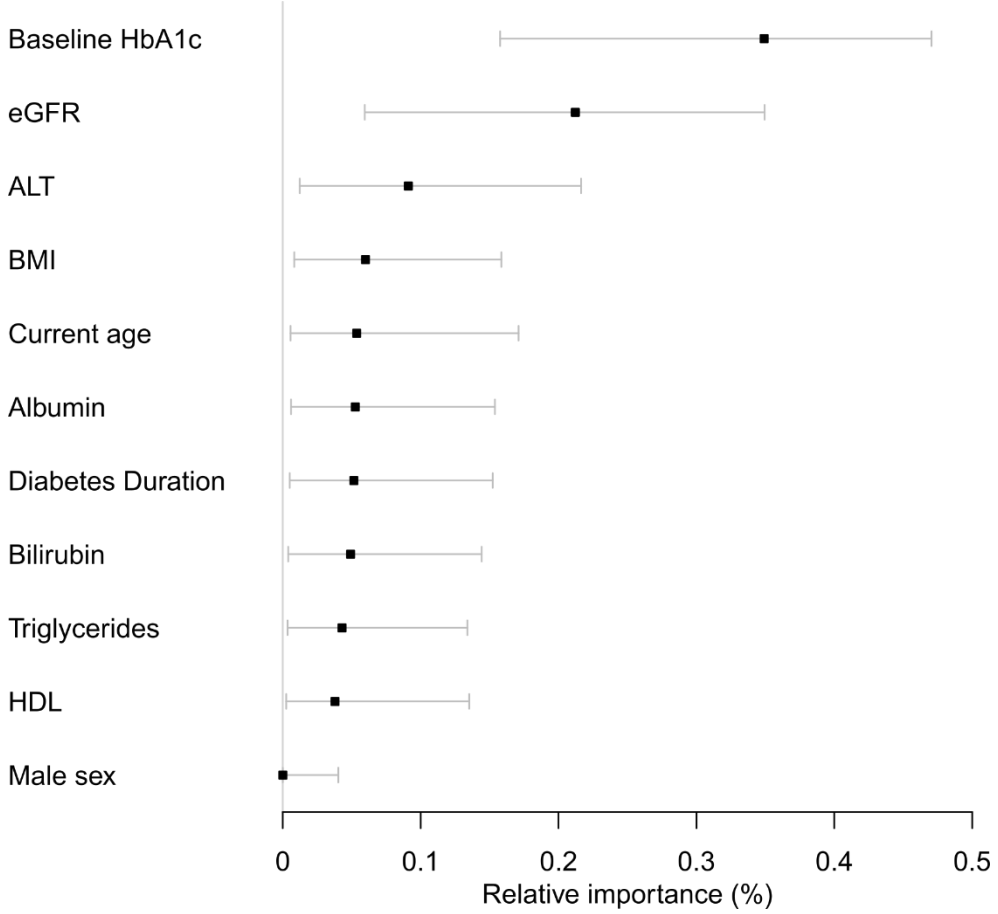
	Derivation set			Validation set		
	DPP4-inhibitor (n=9,974)	**SGLT2i (n=6,152)**	**SMD†**	**DPP4-inhibitor (n=6,650)**	**SGLT2i (n=4,101)**	**SMD†**
Age (years) [mean SD]	63.8 (10.8)	60.0 (9.2)	0.385	64.0 (10.8)	60.1 (9.1)	0.39
Duration of diabetes (years) [mean SD]	8.0 (5.3)	8.5 (5.1)	0.090	7.9 (5.3)	8.6 (5.2)	0.131
Sex						
Female	6240 (62.6)	3862 (62.8)	0.004	4119 (61.9)	2640 (64.4)	0.05
Male	3734 (37.4)	2290 (37.2)		2531 (38.1)	1461 (35.6)	
Ethnicity						
White	4849 (48.6)	2822 (45.9)	0.063	3240 (48.7)	1971 (48.1)	0.082
Asian	383 (3.8)	228 (3.7)		267 (4.0)	126 (3.1)	
Black	124 (1.2)	65 (1.1)		92 (1.4)	34 (0.8)	
Mixed / Other	94 (0.9)	56 (0.9)		64 (1.0)	34 (0.8)	
Missing	4524 (45.4)	2981 (48.5)		2987 (44.9)	1936 (47.2)	
DPP4i type						
Alogliptin	1155 (11.6)		NA	802 (12.1)		NA
Linagliptin	2013 (20.2)			1318 (19.8)		
Saxagliptin	1292 (13.0)			915 (13.8)		
Sitagliptin	5450 (54.6)			3575 (53.8)		
Vildagliptin	64 (0.6)			40 (0.6)		
SGLT2i type						
Canaglifozin		947 (15.4)	NA		641 (15.6)	NA
Dapagliflozin		3513 (57.1)			2348 (57.3)	
Empagliflozin		1692 (27.5)			1112 (27.1)	
Number of glucose-lowering drug classes ever prescribed						
1	4456 (44.7)	1322 (21.5)	0.846	2899 (43.6)	876 (21.4)	0.841
2	4173 (41.8)	1906 (31.0)		2851 (42.9)	1281 (31.2)	
3	1141 (11.4)	1837 (29.9)		760 (11.4)	1190 (29.0)	
4+	204 (2.0)	1087 (17.7)		140 (2.1)	754 (18.4)	
Number of other current glucose-lowering drugs						
0	573 (5.7)	163 (2.6)	0.542	374 (5.6)	123 (3.0)	0.554
1	5850 (58.7)	2505 (40.7)		3852 (57.9)	1612 (39.3)	
2	3429 (34.4)	2817 (45.8)		2341 (35.2)	1884 (45.9)	
3+	122 (1.2)	667 (10.8)		83 (1.2)	482 (11.8)	

	Derivation set			Validation set		
	DPP4-inhibitor (n=9,974)	**SGLT2i (n=6,152)**	**SMD†**	**DPP4-inhibitor (n=6,650)**	**SGLT2i (n=4,101)**	**SMD†**
Background therapy						
Metformin	8828 (88.5)	5577 (90.7)	0.070	5839 (87.8)	3719 (90.7)	0.093
Sulfonylurea	3743 (37.5)	2371 (38.5)	0.021	2577 (38.8)	1610 (39.3)	0.010
DPP4-inhibitor	NA	1619 (26.3)	NA	NA	1093 (26.7)	
SGLT2-inhibitor	214 (2.1)	NA	NA	147 (2.2)	NA	
Thiazolidinedione	232 (2.3)	197 (3.2)	0.053	190 (2.9)	142 (3.5)	0.035
GLP1-receptor agonist	38 (0.4)	383 (6.2)	0.331	18 (0.3)	267 (6.5)	0.350
Baseline biomarkers [mean (SD)]						
HbA1c (mmol/mol)*	73.1 (13.6)	76.7 (14.1)	0.266	73.0 (13.2)	77.3 (14.3)	0.313
BMI (kg/m^2)	32.3 (6.4)	34.5 (6.6)	0.331	32.4 (6.4)	34.2 (6.4)	0.285
eGFR (mL/min/1.3 m^2)	83.3 (17.3)	88.8 (14.8)	0.346	82.9 (17.3)	88.8 (14.5)	0.370
HDL-c (mmol/L)	1.2 (0.3)	1.1 (0.3)	0.154	1.2 (0.3)	1.1 (0.3)	0.145
Triglycerides (mmol/L)	2.2 (1.5)	2.4 (1.6)	0.085	2.2 (1.6)	2.4 (1.6)	0.066
ALT (IU/L)	32.9 (33.5)	35.9 (33.0)	0.088	34.9 (71.9)	37.6 (49.0)	0.044
Albumin (g/L)	42.2 (4.0)	42.2 (4.0)	0.006	42.3 (4.0)	42.2 (4.0)	0.027
Bilurubin (µmol/L)	10.1 (5.2)	9.8 (5.0)	0.050	9.9 (4.9)	9.8 (5.1)	0.025
Cardiovascular disease [n (%)]						
Atherosclerotic cardiovascular disease**	2020 (20.3)	985 (16.0)	0.11	1294 (19.5)	661 (16.1)	0.087
Heart failure	316 (3.2)	125 (2.0)	0.071	219 (3.3)	88 (2.1)	0.071
Cardiovascular disease (CVD) risk***						
SCORE 10-year CVD risk [%; mean (SD)]	1.81 (2.04)	1.18 (1.29)	0.372	1.82 (1.99)	1.19 (1.26)	0.375
High or very high CVD risk (SCORE ≥5%) [n (%)]	639 (6.9)	111 (1.9)	0.244	428 (6.9)	75 (1.9)	0.242
Renal disease [n (%)						
Chronic kidney disease (CKD****	1331 (13.3)	288 (4.7)	0.306	926 (13.9)	188 (4.6)	0.327
SGLT2-inhibitor eligible due to CVD or CKD status [n (%)]	3282 (32.9)	1297 (21.1)	0.269	2193 (33.0)	887 (21.6)	0.257
HbA1c outcome						
Outcome HbA1c (mmol/mol) [mean SD]	65.1 (16.3)	65.0 (14.4)	0.007	65.1 (16.0)	65.3 (14.5)	0.007
Month of outcome HbA1c measure	6.4 (2.7)	6.3 (2.6)	0.040	6.4 (2.7)	6.3 (2.5)	0.033

Footnotes: †Standardized mean difference: ≥0.1 is a metric for a meaningful imbalance.

**Composite of history of: myocardial infarction, stroke, ischaemic heart disease, peripheral artery disease, revascularisation. ***Systematic COronary Risk Evaluation (SCORE), excluding patients with a history of myocardial infarction. Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003 ****eGFR <60 mL/min/1.3 m^2 and/or urinary albumin to creatinine ratio >30 mg/g

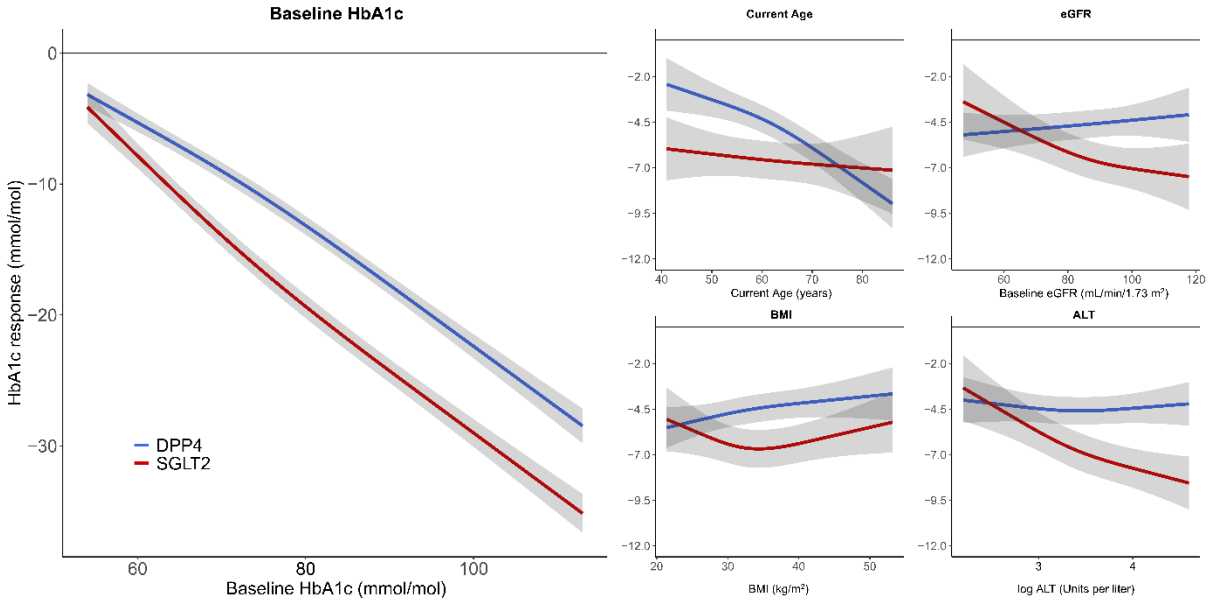
sFigure 3: Relative feature importance for treatment selection between SGLT2-inhibitor and DPP4-inhibitor treatment, for all clinical features in multivariable analysis in routine clinical data. Feature importance reflects the proportion of chi-squared explained by drug-by-covariate interaction terms for each clinical feature, as these represent differential treatment effects for the two therapies. Model estimated from complete case analysis of 12,034 CPRD patients with full clinical feature set available in the primary care record. Bars represent bootstrapped 95% confidence intervals.



sTable 5: Full treatment selection model equation. Drugclass = “SGLT2” or “DPP4” (factor variable), prehba1cmmol = baseline HbA1c, drugline = number of current and previous therapies (including therapy initiated), ncurrtx = number of current glucose-lowering therapies, hba1cmonth = month of HbA1c outcome measure, egfr_ckdepi = eGFR (CKD-EPI equation), prealtlog = Alanine aminotransferase (logged), prebmi = BMI, agetx = current age. To predict achieved 6 month HbA1c for a patient initiating second-line treatment (e.g. after metformin), set drugline == 2, ncurrtx == 1, hba1cmonth == 6, and input patient-specific values of other clinical features.

Full model equation
31.321954+0.64204609* prehba1cmmol-8.5439347e-05*pmax(prehba1cmmol-59,0)^3+0.00012815908*pmax(prehba1cmmol-71.000008,0)^3-4.2719731e-05*pmax(prehba1cmmol-94.999992,0)^3+33.896175*(drugclass=="SGLT2")+4.3479453*(drugline=="3")+7.7707306*(drugline=="4")+9.8519056*(drugline=="5")-6.0952285*(ncurrtx=="1")-8.4474283*(ncurrtx=="2")-10.076309*(ncurrtx=="3")+0.01458388* egfr_ckdepi+6.5992202e-07*pmax(egfr_ckdepi-61.712658,0)^3-1.6584462e-06*pmax(egfr_ckdepi-87.730606,0)^3+9.9852416e-07*pmax(egfr_ckdepi-104.9258,0)^3-0.59830102* prealtlog+0.38060553*pmax(prealtlog-2.7080502,0)^3-0.75191225*pmax(prealtlog-3.3672958,0)^3+0.37130672*pmax(prealtlog-4.0430513,0)^3+0.090509535* prebmi-0.00016688487*pmax(prebmi-25.700001,0)^3+0.00027814137*pmax(prebmi-32.099998,0)^3-0.0001112565*pmax(prebmi-41.700001,0)^3-0.093145764* agetx-9.4518092e-05*pmax(agetx-49,0)^3+0.00018228489*pmax(agetx-62,0)^3-8.77668e-05*pmax(agetx-76,0)^3-0.62516011* hba1cmonth+0.0042770662*pmax(hba1cmonth-4,0)^3-0.012831199*pmax(hba1cmonth-10,0)^3+0.0085541324*pmax(hba1cmonth-13,0)^3+(drugclass=="SGLT2")*(-0.26397744* prehba1cmmol+0.0002001556*pmax(prehba1cmmol-59,0)^3-0.00030023353*pmax(prehba1cmmol-71.000008,0)^3+0.00010007793*pmax(prehba1cmmol-94.999992,0)^3)+(drugclass=="SGLT2")*(-0.10243175* egfr_ckdepi+1.8080869e-05*pmax(egfr_ckdepi-61.712658,0)^3-4.5438926e-05*pmax(egfr_ckdepi-87.730606,0)^3+2.7358057e-05*pmax(egfr_ckdepi-104.9258,0)^3)+(drugclass=="SGLT2")*(-2.4219094* prealtlog+0.24680001*pmax(prealtlog-2.7080502,0)^3-0.48757028*pmax(prealtlog-3.3672958,0)^3+0.24077028*pmax(prealtlog-4.0430513,0)^3)+(drugclass=="SGLT2")*(-0.25565408* prebmi+0.00099460814*pmax(prebmi-25.700001,0)^3-0.0016576797*pmax(prebmi-32.099998,0)^3+0.00066307158*pmax(prebmi-41.700001,0)^3)+(drugclass=="SGLT2")*(0.061244729* agetx+0.00010509417*pmax(agetx-49,0)^3-0.00020268161*pmax(agetx-62,0)^3+9.758744e-05*pmax(agetx-76,0)^3)

sFigure 4: Visualisation of non-linear associations for continuous clinical variables in the full multivariable treatment selection model (as reported in sTable 3). Predictions are scaled to: baseline HbA1c 58, mean value of other continuous covariates and baseline defaults of other features: number of current and previous therapies (including therapy initiated) = 2, number of current glucose-lowering therapies = 1, month of HbA1c outcome measure = 6, eGFR = 87.9, Alanine aminotransferase (logged) = 3.33, BMI = 32.1, current age = 62.



sTable 6: Model performance statistics for predicting HbA1c outcome

a) Internal validation (CPRD derivation cohort, n=14,069). Model outcome is 6 month HbA1c.

	Apparent performance (95%CI)	Average optimism*	Final model optimism corrected performance (95%CI)*
R^2	0.294 (0.278, 0.310)	0.0026	0.29 (0.27, 0.31)
Root mean square error (mmol/mol)	12.91	-0.02	12.93 (12.69, 13.18)
Calibration slope	1.00 (0.98, 1.03)	0.0033	0.997 (0.995, 0.998)
Calibration-in-the-large (intercept) (mmol/mol)	-0.06 (-1.74, 1.62)	-0.2128	0.21 (0.18, 0.32)

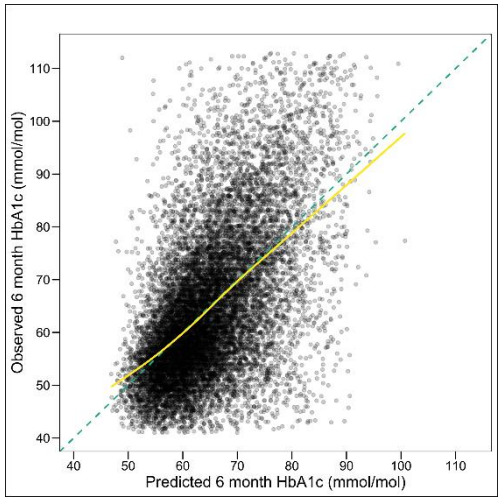
*Optimism corrected performance estimated from 1000 bootstraps with replacement

b) External validation. Model outcome is 6 month HbA1c.

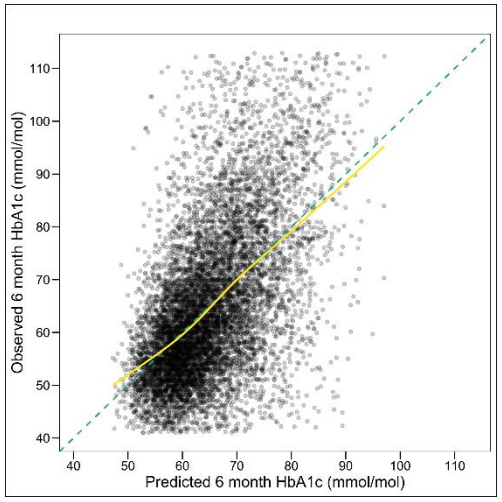
	CPRD validation cohort (n=9,376)	CANTATA D/D2 trials (n=1,755)	BI1245.20 trial (n=630)
R^2	0.29 (0.27, 0.31)	0.28 (0.24, 0.33)	0.26 (0.20, 0.34)
Root mean square error (mmol/mol)	13.2	9.1	8.5
Calibration slope	1.02 (0.99, 1.05)	0.94 (0.88, 1.02)	1.06 (0.93, 1.20)
Calibration-in-the-large (intercept) (mmol/mol)	-1.2 (-3.3, 0.9)	-1.0 (-5.1, 3.1)	-6.1 (-14.0, 1.8)

sFigure 5: Assessment of calibration between model predicted HbA1c 6 month outcome and observed HbA1c in derivation and validation cohorts

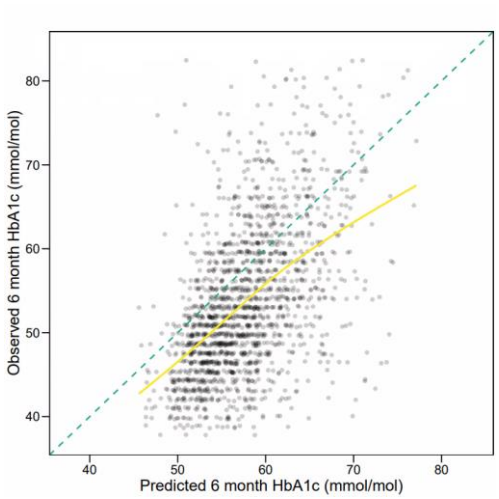
a) CPRD derivation cohort (n=14,069)



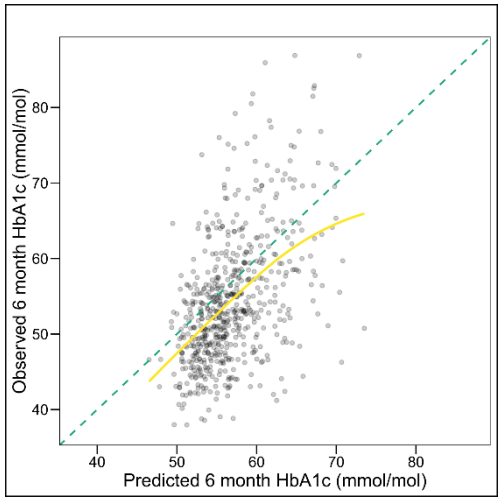
b) CPRD validation cohort (n=9,376)



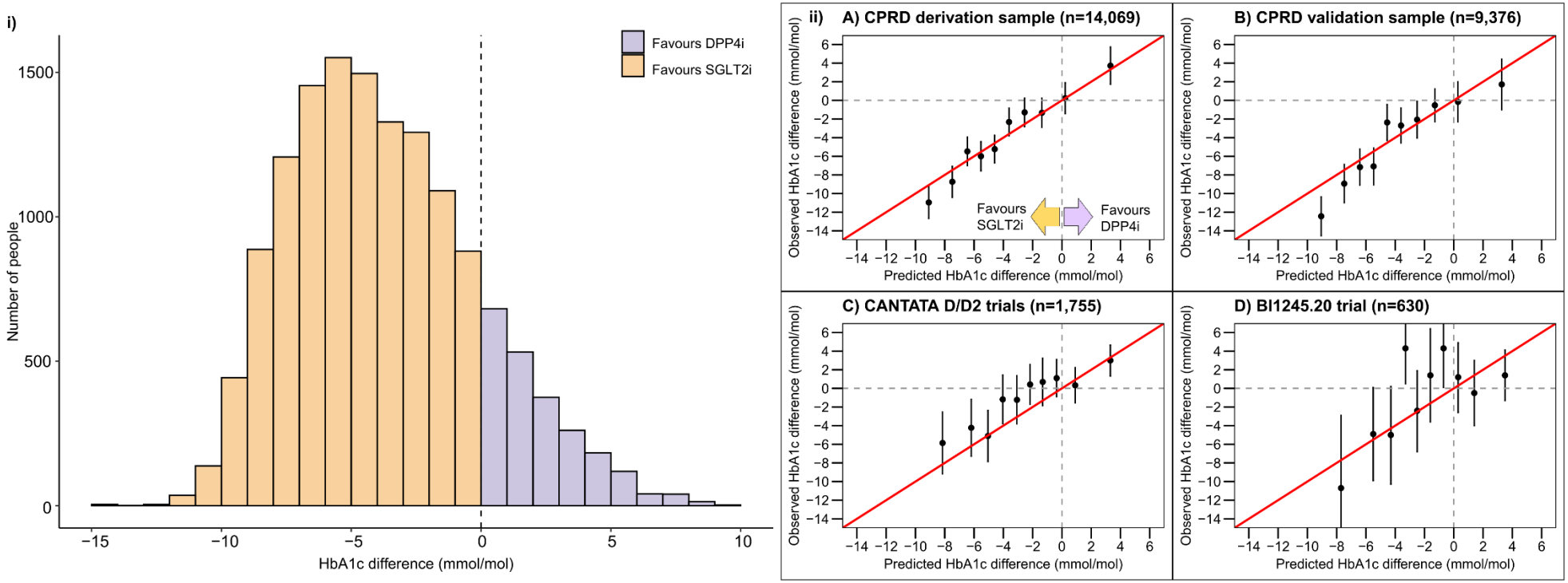
c) CANTATA D/D2 trials (n=1,755)



d) BI1245.20 trial (n=630)

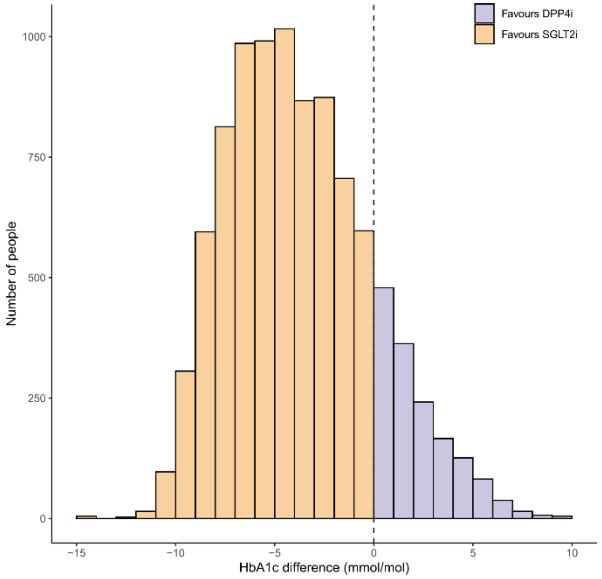


sFigure 6: Treatment selection model performance. i) Distribution of the predicted individualised treatment effect of SGLT2-inhibitor treatment compared to DPP4-inhibitor treatment in the CPRD derivation sample (n=14,069) [left panel]. Negative values reflect a predicted glucose-lowering treatment benefit on SGLT2-inhibitor treatment, positive values reflect a predicted treatment benefit on DPP4-inhibitor treatment. **ii) Calibration between observed and predicted treatment effects, by decile of predicted treatment effect [right panel], in a) CPRD derivation sample (n=14,069); b) CPRD validation sample (n=9,376); c) CANTATA D/D2 trials (n=1,755); d) BI1245.20 trial (n=630).** In CPRD, estimates are adjusted for clinical features in the treatment selection model (to improve precision and control for potential differences in covariate balance within subgroups). Trial estimates are unadjusted**.**

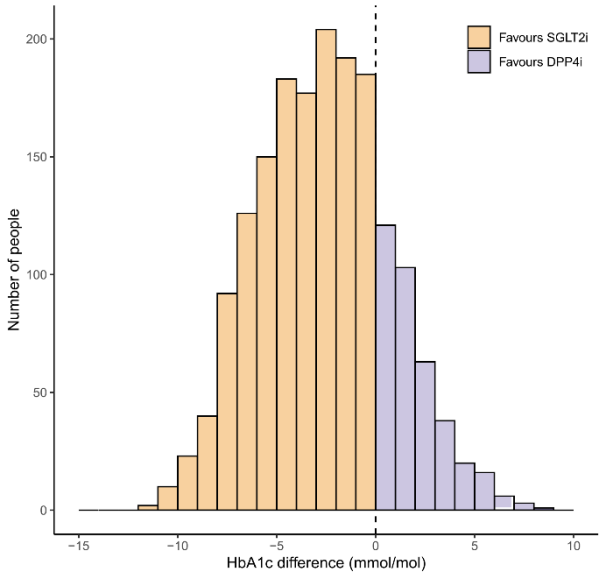


sFigure 7: Distribution of the predicted individualised treatment effect of SGLT2-inhibitor treatment compared to DPP4-inhibitor treatment in validation cohorts. Negative values reflect a predicted glucose-lowering treatment benefit on SGLT2-inhibitor treatment, positive values reflect a predicted treatment benefit on DPP4-inhibitor treatment.

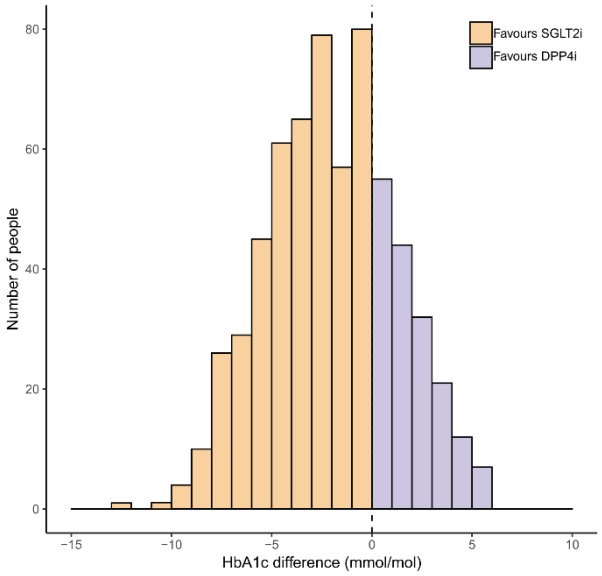
a) CPRD validation cohort (n=9,376)



b) CANTATA D/D2 trials (n=1,755)



c) BI1245.20 trial (n=630)



sTable 7: Observed treatment effects across subgroups defined by clinical cut-offs of predicted treatment effects (data underlying Figure 4). In CPRD, estimates are adjusted for clinical features in the treatment selection model (to improve precision and control for potential differences in covariate balance within subgroups). Trial data estimates are unadjusted**.**

a) CPRD validation sample (n=9,376).

	Observed treatment difference (mmol/mol; negative favours SGLT2i)				
Predicted HbA1c difference	**N patients**	**Treatment difference**	**Lower CI**	**Upper CI**	**p-value**
Overall	9,376	-4.7	-5.4	-4.2	<0.001
Subgroup					
SGLT2i benefit by any mmol/mol	7,848	-5.4	-6.0	-4.7	<0.001
SGLT2i benefit by ≥5 mmol/mol	3,733	-8.8	-9.8	-7.8	<0.001
SGLT2i benefit by 3-5 mmol/mol	1,939	-2.7	-4.1	-1.4	<0.001
SGLT2i benefit by 0-3 mmol/mol	2,136	-0.8	-2.0	0.5	0.22
DPP4i benefit by any mmol/mol	1,528	0.5	-1.5	2.4	0.62
DPP4i benefit by 0-3 mmol/mol	1,094	0.1	-2.1	2.4	0.92
DPP4i benefit by ≥3 mmol/mol	434	2.0	-2.3	6.3	0.36

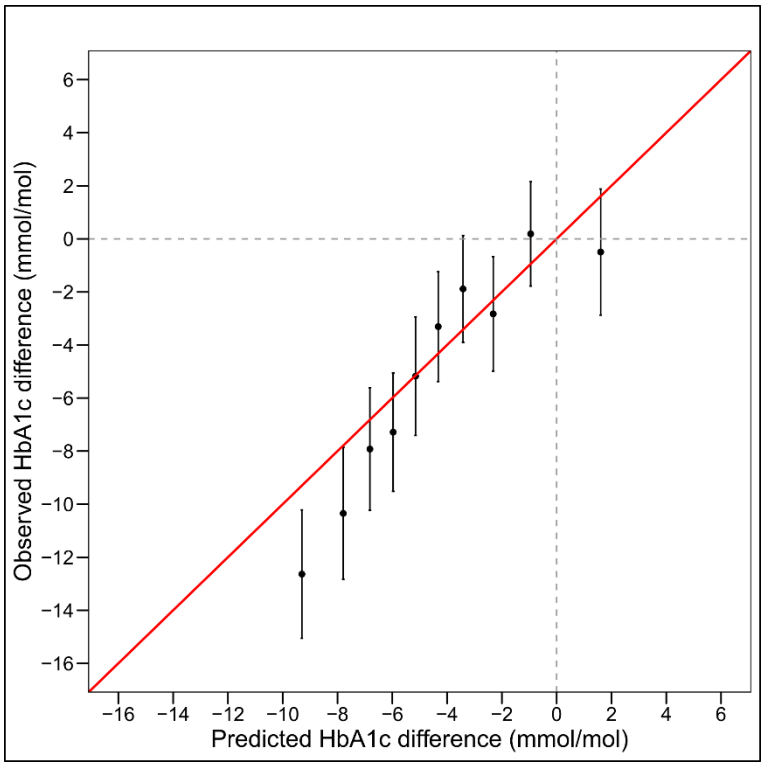
b) CANTATA-D and CANTATA-D2 clinical trial participants (n=1,755).

	Observed treatment difference (mmol/mol; negative favours SGLT2i)				
Predicted HbA1c difference	**N patients**	**Treatment difference**	**Lower CI**	**Upper CI**	**p-value**
Overall	1,755	-1.4	-2.2	-0.6	0.003
Subgroup					
SGLT2i benefit by any mmol/mol	1,384	-2.2	-3.2	-1.3	<0.001
SGLT2i benefit by ≥5 mmol/mol	443	-5.8	-7.7	-3.9	<0.001
SGLT2i benefit by 3-5 mmol/mol	360	-2.0	-3.8	-0.2	0.03
SGLT2i benefit by 0-3 mmol/mol	581	0.6	-0.7	1.8	0.37
DPP4i benefit by any mmol/mol	371	1.4	0.1	2.6	0.03
DPP4i benefit by 0-3 mmol/mol	287	0.9	-0.5	2.4	0.18
DPP4i benefit by ≥3 mmol/mol	84	2.3	-0.8	5.3	0.14

c) BI1245.20 clinical trial participants (n=630).

	Observed treatment difference (mmol/mol; negative favours SGLT2i)				
Predicted HbA1c difference	**N patients**	**Treatment difference**	**Lower CI**	**Upper CI**	**p-value**
Overall	630	-1.1	-2.6	0.5	0.19
Subgroup					
SGLT2i benefit by any mmol/mol	459	-1.9	-3.8	0.1	0.06
SGLT2i benefit by ≥5 mmol/mol	117	-6.6	-11.0	-2.2	0.003
SGLT2i benefit by 3-5 mmol/mol	126	-1.1	-4.6	2.4	0.54
SGLT2i benefit by 0-3 mmol/mol	216	0.9	-1.5	3.4	0.46
DPP4i benefit by any mmol/mol	171	1.5	-0.7	3.7	0.17
DPP4i benefit by 0-3 mmol/mol	131	1.3	-1.3	3.9	0.32
DPP4i benefit by ≥3 mmol/mol	40	2.6	-1.6	6.8	0.22

sFigure 8: Calibration between observed and predicted treatment effects, by decile of predicted treatment effect [right panel], in the CPRD validation sample excluding 2,518 individuals with established atherosclerotic heart disease, heart failure, chronic kidney disease, or SCORE risk ≥5% (n=6,858)



sTable 8: Validation of 12 month HbA1c: Observed treatment effects across subgroups defined by clinical cut-offs of predicted treatment effects. Estimates are unadjusted**.**

a) CANTATA-D and CANTATA-D2 clinical trial participants (n=1,775). 20 additional participants included who had an HbA1c outcome recorded post but not prior to 6 months.

	Observed treatment difference (mmol/mol; negative favours SGLT2i)				
Predicted HbA1c difference	**N patients**	**Treatment difference**	**Lower CI**	**Upper CI**	**p-value**
Overall	1,775	-2.4	-3.4	-1.4	<0.001
Subgroup					
SGLT2i benefit by any mmol/mol	1,399	-3.4	-4.6	-2.3	<0.001
SGLT2i benefit by ≥5 mmol/mol	446	-6.4	-8.6	-4.2	<0.001
SGLT2i benefit by 3-5 mmol/mol	365	-3.8	-5.9	-1.7	<0.001
SGLT2i benefit by 0-3 mmol/mol	588	0.5	-2.1	1.1	0.54
DPP4i benefit by any mmol/mol	376	0.7	-0.8	2.2	0.34
DPP4i benefit by 0-3 mmol/mol	291	0.3	-1.4	2.0	0.70
DPP4i benefit by ≥3 mmol/mol	85	1.8	-1.3	4.8	0.25

b) BI1245.20 clinical trial participants (n=630).

	Observed treatment difference (mmol/mol; negative favours SGLT2i)				
Predicted HbA1c difference	**N patients**	**Treatment difference**	**Lower CI**	**Upper CI**	**p-value**
Overall	630	-2.1	-3.7	-0.4	0.01
Subgroup					
SGLT2i benefit by any mmol/mol	459	-1.9	-3.8	0.1	0.06
SGLT2i benefit by ≥5 mmol/mol	117	-7.6	-12.0	-3.3	<0.001
SGLT2i benefit by 3-5 mmol/mol	126	-2.5	-6.2	1.3	0.20
SGLT2i benefit by 0-3 mmol/mol	216	-0.2	-2.8	2.4	0.88
DPP4i benefit by any mmol/mol	171	0.9	-1.8	3.5	0.52
DPP4i benefit by 0-3 mmol/mol	131	0.9	-2.2	4.0	0.53
DPP4i benefit by ≥3 mmol/mol	40	0.7	-4.7	6.0	0.80

sTable 9: 6 month weight change and risk of treatment discontinuation, across subgroups defined by clinical cut-offs of predicted treatment benefit, in CPRD routine clinical data

a) **Estimates of 6 month weight change.** Estimates include all patients with valid baseline data for glucose-lowering treatment selection model and with weight outcome recorded between 3 and 15 months after drug initiation, on unchanged glucose-lowering therapy. Estimates are adjusted for baseline weight, the number of currently prescribed glucose-lowering treatments, and the number of glucose-lowering drug classes ever prescribed.

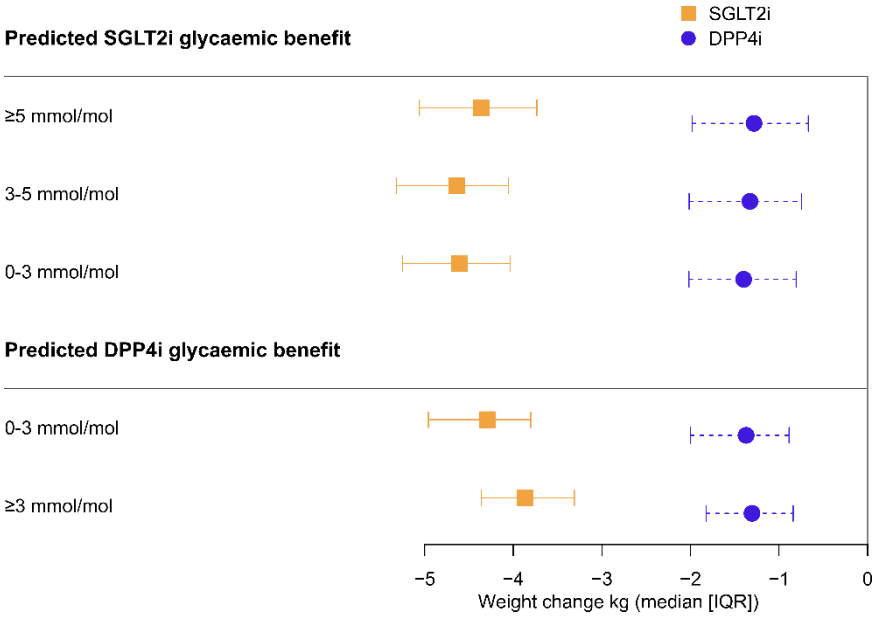
		Weight change kg (Median [IQR])	
Predicted HbA1c difference	**N patients**	**SGLT2**	**DPP4**
Overall	15,627	-3.7 (-4.3, -3.2)	-1.0 (-1.6, -0.5)
Subgroup			
SGLT2i benefit by any mmol/mol	13,212	-3.8 (-4.4, -3.3)	-1.0 (-1.6, -0.5)
SGLT2i benefit by ≥5 mmol/mol	6,407	-3.9 (-4.5, -3.4)	-1.0 (-1.6, -0.4)
SGLT2i benefit by 3-5 mmol/mol	3,239	-3.9 (-4.6, -3.4)	-1.0 (-1.6, -0.5)
SGLT2i benefit by 0-3 mmol/mol	3,566	-3.7 (-4.3, -3.2)	-1.1 (-1.6, -0.6)
DPP4i benefit by any mmol/mol	2,415	-3.0 (-3.5, -2.4)	-0.9 (-1.5, -0.5)
DPP4i benefit by 0-3 mmol/mol	1,763	-3.2 (-3.7, -2.7)	-1.0 (-1.5, -0.5)
DPP4i benefit by ≥3 mmol/mol	652	-2.4 (-3.0, -1.9)	-0.8 (-1.3, -0.4)

b) **Estimates of treatment discontinuation within 6 months.** Estimates include all patients with valid baseline data for glucose-lowering treatment selection model and with 3 additional months of follow up to confirm treatment was truly discontinued. Estimates are adjusted for the number of currently prescribed glucose-lowering treatments, and the number of glucose-lowering drug classes ever prescribed.

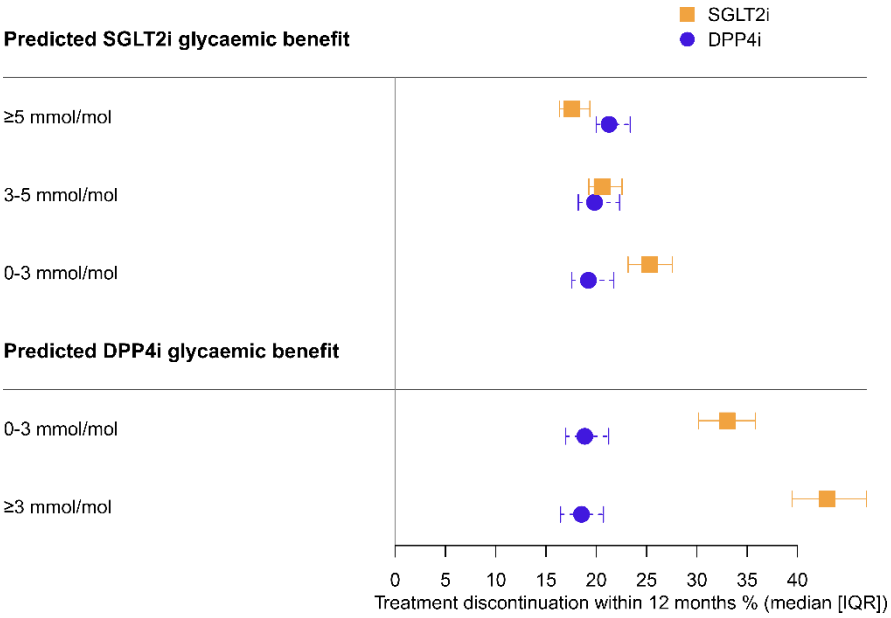
		Treatment discontinuation % (Median [IQR])	
Predicted HbA1c difference	**N patients**	**SGLT2**	**DPP4**
Overall	28,514	16.1 (13.5, 20.3)	14.4 (12.9, 16.7)
Subgroup			
SGLT2i benefit by any mmol/mol	23,992	15.2 (13.2, 17.9)	14.4 (12.9, 16.7)
SGLT2i benefit by ≥5 mmol/mol	11,730	13.2 (12.1, 14.8)	14.4 (13.0, 16.7)
SGLT2i benefit by 3-5 mmol/mol	5,761	15.6 (14.4, 17.5)	14.2 (12.8, 16.7)
SGLT2i benefit by 0-3 mmol/mol	6,431	19.0 (17.3, 21.3)	14.2 (12.8, 16.7)
DPP4i benefit by any mmol/mol	4,592	26.8 (23.4, 31.0)	14.8 (12.9, 16.8)
DPP4i benefit by 0-3 mmol/mol	3,249	25.0 (22.5, 27.7)	14.7 (12.8, 16.8)
DPP4i benefit by ≥3 mmol/mol	1,343	33.1 (29.7, 36.9)	14.9 (13.0, 16.9)

sFigure 9: Sensitivity analysis for 12 month weight change and risk of treatment discontinuation, across subgroups defined by clinical cut-offs of predicted treatment benefit, in CPRD routine clinical data

a) **Weight change at 12 months (n=11,298).** Estimates include all patients with valid baseline data for glucose-lowering treatment selection model and with weight outcome recorded between 9 and 15 months after drug initiation, on unchanged glucose-lowering therapy. Estimates are adjusted for baseline weight, the number of currently prescribed glucose-lowering treatments, and the number of glucose-lowering drug classes ever prescribed.



b) **Risk of treatment discontinuation within 12 months (n=23,739.** Estimates include all patients with valid baseline data for glucose-lowering treatment selection model and with 3 additional months of follow up to confirm treatment was truly discontinued. Estimates are adjusted for the number of currently prescribed glucose-lowering treatments, and the number of glucose-lowering drug classes ever prescribed.



sTable 10: Clinical characteristics of subgroups in CPRD defined by predicted HbA1c differences between therapies (n=36,454 with valid data to fit the model).

	Predicted HbA1c benefit subgroup				
	SGLT2i ≥5 mmol/mol	**SGLT2i 3-5 mmol/mol**	**SGLT2i 0-3 mmol/mol**	**DPP4i 0-3 mmol/mol**	**DPP4i ≥3 mmol/mol**
n	**14860 (40.8%)**	**7332 (20.1%)**	**8245 (22.6%)**	**4203 (11.5%)**	**1814 (5.0%)**
Clinical characteristics [median (IQR)]					
Age (years)	55.0 (50.0, 61.0)	62.0 (57.0, 67.0)	68.0 (62.0, 73.0)	73.0 (69.0, 78.0)	79.0 (75.0, 84.0)
Duration of diabetes (years)	6.1 (3.4, 9.5)	7.6 (4.3, 11.3)	8.6 (5.1, 12.5)	9.9 (6.1, 14.0)	11.5 (7.5, 15.9)
Male sex (n [%])	9892 (66.6)	4551 (62.1)	4827 (58.5)	2259 (53.7)	935 (51.5)
HbA1c (mmol/mol)	80.2 (72.0, 91.0)	70.0 (64.0, 79.0)	66.0 (61.0, 74.0)	64.0 (59.0, 70.0)	61.0 (57.0, 66.0)
BMI (kg/m^2)	34.1 (30.7, 38.3)	32.1 (28.7, 36.6)	30.8 (27.7, 35.0)	29.2 (26.1, 33.2)	26.5 (24.0, 30.0)
eGFR (mL/min/1.3 m^2)	97 (89, 104)	88 (77, 96)	79 (68, 89)	68 (59, 79)	59 (51, 68)
HDL-c (mmol/L)	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)	1.1 (1.0, 1.3)	1.2 (1.0, 1.4)	1.3 (1.1, 1.5)
Triglycerides (mmol/L)	2.1 (1.5, 3.0)	1.9 (1.4, 2.7)	1.8 (1.3, 2.5)	1.7 (1.2, 2.3)	1.5 (1.1, 2.1)
ALT (IU/L)	37.0 (27.0, 52.0)	28.0 (21.0, 38.0)	24.0 (18.0, 33.0)	19.0 (15.0, 25.0)	15.0 (12.0, 20.0)
Albumin (g/L)	43.0 (40.0, 45.0)	42.0 (39.0, 45.0)	42.0 (39.0, 45.0)	42.0 (39.0, 45.0)	41.0 (38.0, 44.0)
Bilirubin (µmol/L)	9.0 (7.0, 12.0)	9.0 (6.0, 12.0)	9.0 (6.0, 12.0)	9.0 (6.0, 12.0)	8.8 (6.0, 11.0)
Cardiovascular disease [n (%)]					
Atherosclerotic cardiovascular disease*	1806 (12.2)	1321 (18.0)	1909 (23.2)	1132 (26.9)	619 (34.1)
Heart failure	240 (1.6)	187 (2.6)	319 (3.9)	215 (5.1)	152 (8.4)
Cardiovascular disease (CVD) risk**					
10-year CVD risk (SCORE) [median (IQR)]	0.45 (0.21, 0.89)	0.97 (0.47, 1.73)	1.68 (0.88, 2.78)	2.68 (1.67, 4.21)	4.41 (2.95, 6.41)
High / very high CVD risk (SCORE ≥5%) [n (%)]	9 (0.1)	72 (1.1)	422 (5.5)	653 (16.9)	655 (41.0)
Chronic kidney disease (CKD)***	257 (1.7)	185 (2.5)	560 (6.8)	788 (18.7)	712 (39.3)
SGLT2-inhibitor eligible due to CVD or CKD status [n (%)]	2125 (14.3)	1605 (21.9)	2650 (32.1)	2101 (50.0)	1360 (75.0)
Treatment received [n (%)]					
SGLT2-inhibitor	7399 (49.8%)	4173 (56.9%)	2888 (35.0%	925 (22.0%)	205 (11.3%)
DPP4-inhibitor	7461 (50.2%)	3159 (43.1%)	5357 (65.0%)	3278 (78.0%)	1609 (88.7%)

Predicted 6 month outcomes by therapy [median (IQR)]										
Therapy	DPP4i	SGLT2i	DPP4i	SGLT2i	DPP4i	SGLT2i	DPP4i	SGLT2i	DPP4i	SGLT2i
HbA1c change (mmol/mol)	-8.5 (-13.2, -4.7)	-15.7(-20.8,-11.4)	-5.6 (-9.7, -2.2)	-9.7 (-13.8, -6.1)	-4.8 (-8.7, -1.6)	-6.5 (-10.4, -3.2)	-5.1 (-8.6, -1.8)	-3.8 (-7.4, -0.4)	-5.2 (-8.4, -1.6)	-0.4 (-4.0, 3.4)
Weight change (KG)	-0.9 (-1.5, -0.4)	-3.8 (-4.4, -3.3)	-1.0 (-1.6, -0.5)	-3.9 (-4.5, -3.4)	-1.0 (-1.6, -0.5)	-3.7 (-4.2, -3.2)	-0.9 (-1.5, -0.5)	-3.1 (-3.7, -2.6)	-0.8 (-1.3, -0.4)	-2.4 (-2.9, -1.9)
Treatment discontinuation (%)	14.4 (13.0, 16.7)	13.3 (12.1, 14.9)	14.2 (12.8, 16.7)	15.6 (14.4, 17.6)	14.2 (12.8, 16.7)	19.1 (17.3, 21.4)	14.8 (12.8, 16.8)	25.1 (22.6, 28.0)	14.9 (13.0, 16.9)	33.4 (29.8, 37.3)

*Composite of history of: myocardial infarction, stroke, ischaemic heart disease, peripheral artery disease, revascularisation. **Systematic COronary Risk Evaluation (SCORE), excluding patients with a history of myocardial infarction. Derived using equations from Conroy RM, Pyörälä K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987-1003. ***eGFR <60 mL/min/1.3 m^2 and/or urinary albumin to creatinine ratio >30 mg/g

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TRIPOD checklist

TRIPOD Checklist: Prediction Model Development

Section/Topic	Item	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	4
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6, Table 1, appendix 7-12
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6-7
	5b	Describe eligibility criteria for participants.	6-7
	5c	Give details of treatments received, if relevant.	6
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	Report any actions to blind assessment of the outcome to be predicted.	6-7
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	6-7
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	6-7
Sample size	8	Explain how the study size was arrived at.	6, 8
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7-8
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	7-10
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7-10
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8-10
Risk groups	11	Provide details on how risk groups were created, if done.	8-10
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Appendix P.2
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1 Appendix P.4-6
Model development	14a	Specify the number of participants and outcome events in each analysis.	11-13
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	Figure 2
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Appendix P.23
	15b	Explain how to the use the prediction model.	13
Model performance	16	Report performance measures (with CIs) for the prediction model.	8-10
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	15-16
Interpretation	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	14,16
Implications	20	Discuss the potential clinical use of the model and implications for future research.	14,16
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	13, 18
Funding	22	Give the source of funding and the role of the funders for the present study.	10, 17

We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.