Renal outcomes in people with type 2 diabetes with and without albuminuria treated with SGLT-2 inhibitors and GLP-1 receptor agonists: target trial emulation

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ABSTRACT

OBJECTIVE

To compare the risk of renal deterioration under treatment with glucagon-like peptide-1 (GLP-1) receptor agonists or sodium-glucose contransporter-2 (SGLT-2) inhibitors versus other second line treatments in people with type 2 diabetes with and without albuminuria (albumin to creatinine ratio ≥30 mg/g).

DESIGN

Target trial emulation.

SETTINGS

Linkage of electronic health records and claims data from 10 health systems and two national health insurance plans—data from BESTMED (observational evaluation of second line therapy medications in diabetes) study.

PARTICIPANTS

People with type 2 diabetes and moderate cardiovascular risk and estimated glomerular filtration rate ≥45 mL/min/1.73 m^2 on metformin monotherapy who started treatment with a GLP-1 receptor agonist or SGLT-2 inhibitor, a sulfonylurea, or a dipeptidyl peptidase-4 (DPP-4) inhibitor after metformin between 2014 and 2022.

MAIN OUTCOME MEASURE

Deterioration of kidney function defined as doubling of serum creatinine or estimated glomerular filtration rate <15 mL/min/1.73 m^2.

RESULTS

Among 75 455 eligible people (61 583 (81.76%) without albuminuria), median age was 60 years (interquartile range 51-68), 36 231 (48%) were women, median haemoglobin A_{1c} was 7.8% (interquartile range 7.3-8.5%), and median estimated glomerular filtration rate was 92 mL/min/1.73 m^2 (interquartile range 77-102). People were followed for a median of 32 months (interquartile range 18-57). The estimated five year risk of the renal outcome was 2.4% (95% confidence interval 2.1% to 2.7%) for people taking GLP-1 receptor agonists or SGLT-2 inhibitors versus 2.1% (1.8% to 2.6%) for people taking DPP-4 inhibitors among those without albuminuria; and 3.2% (2.3% to 4.1%) versus 5.4% (4.2% to 6.7%), respectively, among people with albuminuria. The estimated five year risk ratio comparing the GLP-1 receptor agonist or SGLT-2 inhibitor group with the DPP-4 inhibitor group was 1.10 (95% confidence interval 0.90 to 1.38) among people without albuminuria and 0.60 (0.42 to 0.82) among people with albuminuria.

CONCLUSIONS

Compared with DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors reduce the risk of deterioration of renal function in people with albuminuria. Little evidence of renal benefit among people without albuminuria was observed over the study follow-up period.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose contransporter-2 (SGLT-2) inhibitors decrease the risk of chronic kidney disease progression in people with type 2 diabetes

Randomised trials that evaluated the effect of GLP-1 receptor agonists and SGLT-2 inhibitors on chronic kidney disease progression included a large proportion of people with moderately increased albuminuria and their findings may not be generalisable to a broader population

WHAT THIS STUDY ADDS

In people with type 2 diabetes and albuminuria, GLP-1 receptor agonists and SGLT-2 inhibitors had renoprotective effects

In people with type 2 diabetes and normoalbuminuria, sulfonylureas led to faster renal function decline

Introduction

Type 2 diabetes is becoming increasingly common in the United States and worldwide.[1 2] As the prevalence of type 2 diabetes grows, so does the burden of its many complications. People with type 2 diabetes have an increased risk of renal impairment, making diabetes the most common cause of chronic kidney disease.[3] Preventing kidney failure is therefore an important aspect of treating type 2 diabetes.[4]

Meta-analyses of randomised trials in people with type 2 diabetes have shown that glucagon-like peptide-1 (GLP-1) receptor agonists and sodium-glucose cotransporter-2 (SGLT-2) inhibitors decrease the risk of chronic kidney disease progression compared with placebo.[5 6] By contrast, randomised trials have shown no difference in progression of chronic kidney disease between dipeptidyl peptidase-4 (DPP-4) inhibitors and placebo.[7-10]

Some of the findings from these studies suggest that the renoprotective effects of GLP-1 receptor agonists and SGLT-2 inhibitors may be more pronounced among people with greater degrees of albuminuria.[11-13] Whether people without albuminuria taking GLP-

1 receptor agonists or SGLT-2 inhibitors experience a similar degree of protection from chronic kidney disease is not known.

A randomised trial designed to estimate the renoprotective effects of GLP-1 receptor agonists and SGLT-2 inhibitors separately in people without albuminuria would be resource intensive and may never be conducted. Therefore, we leveraged a multicentre observational study of people with type 2 diabetes to emulate a target trial of GLP-1 receptor agonists or SGLT-2 inhibitors (combined) versus other second line treatments after metformin in people without albuminuria. We emulated a target trial among people with albuminuria to benchmark the observational results with those from existing randomised trials. After benchmarking, we extended the inference by emulating a target trial in people without albuminuria. Because GLP-1 receptor agonists and SGLT-2 inhibitors are more likely to be prescribed to people at high cardiovascular risk, we restricted our analyses to those at moderate cardiovascular disease to reduce the possibility of confounding.

Methods

Target trials specification

The key elements of the protocol of the target trials (as specified in the TARGET reporting guideline[14]) are summarised in supplemental table 1. In the first target trial, people with albuminuria (defined as albumin to creatinine ratio ≥30 mg/g or equivalent) were eligible when they met the following criteria between 1 January 2014 and 1 January 2023: age ≥30 years; diagnosis of type 2 diabetes and no evidence of diabetes of any other type; haemoglobin A_{1c} between 7.0% and 11.0%; monotherapy with metformin for at least three months and no previous non-metformin outpatient diabetes treatment; moderate cardiovascular risk (defined as no history of diagnosis of atherosclerotic cardiovascular disease or hospital admission for heart failure and either men aged ≥35 years and women aged ≥45 years or men aged 30-34 and women aged 30-44 with hypertension, hyperlipidaemia, retinopathy, kidney disease, or neuropathy[15]); no metastatic cancer, end stage lung or liver disease or dementia, previous history of pancreatitis, medullary thyroid cancer or pyelonephritis, or estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2; at least 12 months of engagement with their health system or continuous enrolment at their health insurance plan (to ensure availability of historical information on baseline characteristics and to increase the probability of continued engagement); and a clinician's determination that a second type 2 diabetes drug needs to be started.

The three treatment strategies of interest are initiation of a GLP-1 receptor agonist (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide, or tirzepatide) or an SGLT-2 inhibitor (canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin); initiation of a sulfonylurea (glimepiride, glipizide, or glyburide); or initiation of a DPP-4 inhibitor (alogliptin, linagliptin, saxagliptin, or sitagliptin). All SGLT-2 inhibitors, sulfonylureas, and DPP-4 inhibitors were administered orally. All GLP-1 receptor agonists were administered subcutaneously except semaglutide, which could be administered both subcutaneously and orally. People must have started exactly one of these drugs and subsequently could continue or discontinue them at their discretion. In a variation of this target trial, treatment strategies of starting GLP-1 receptor agonists and SGLT-2 inhibitors were considered separately.

The outcome was deterioration of kidney function—defined as doubling of baseline serum creatinine or eGFR <15 mL/min/1.73 m^2. We also considered the outcome of progression to severely increased albuminuria (albumin to creatinine ratio ≥300 mg/g) proteinuria. For this outcome, we added the eligibility criterion of "no severely increased albuminuria."

Follow-up of eligible people started at assignment (index date) and ended at the outcome, loss to follow-up (12 months without healthcare encounters, vital signs, or lab measurements, or loss of membership with the health insurance plan), or study end (1 July 2023). The causal contrast of interest was the intention-to-treat effect, defined as the total effect.[16]

For the intention-to-treat analysis, we compared the five year cumulative incidence (referred to as risk) of the outcome between treatment strategies using ratios and differences. Risks can be estimated non-parametrically by the Kaplan-Meier estimator or parametrically through a pooled logistic regression model[17] for the monthly probability of the outcome with the following covariates: month of follow-up (modelled as a quadratic polynomial); indicators for treatment strategy; and product ("interaction") terms between month and the treatment indicators.

The primary analysis compared treatment strategies among people with albuminuria (defined as albumin to creatinine ratio ≥30 mg/g or equivalent). We included prespecified prognostic factors as covariates in the model, with the risk estimates standardised to the distribution of these factors. Subgroup analyses were conducted by sex, age, baseline haemoglobin A_{1c}, and baseline eGFR. Non-parametric bootstrapping with 500 resamples was used to calculate 95% confidence intervals (CIs) for all estimates. The second target trial was identical to the first except that eligibility was restricted to people without albuminuria.

Target trial emulation

We emulated the above target trials using data from the BESTMED (observational evaluation of second line therapy medications in diabetes) study, which comprised people who were treated at one of 10 health systems or had their health insurance at one of two national health insurance plans in the US. People who had data at more than one study site were identified using a privacy preserving linkage solution[18] and their records were merged.

Information on patients' baseline characteristics, analytical covariates, and outcomes was obtained

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Table 1 | Baseline characteristics of eligible people without albuminuria (BESTMED Consortium, 2014-23)

Characteristics	Overall	DPP-4 inhibitors	SGLT-2 inhibitors or GLP-1 receptor agonists	Sulfonylureas	SMD (GLP-1 receptor agonists or SGLT-2 inhibitors *v* DPP-4 inhibitors)	SMD (sulfonylureas *v* DPP-4 inhibitors)
No of eligible people	61 583 (100)	11 458 (18.6)	21 330 (34.6)	28 795 (46.8)	—	—
Age (years), median (IQR)	59 (51-67)	60 (52-67)	57 (50-65)	61 (52-69)	0.175	0.089
Female sex	29 615 (48.1)	5620 (49.0)	10 735 (50.3)	13 260 (46.0)	0.026	0.06
Race	—	—	—	—	0.046	0.373
Asian	1239 (2.0)	220 (1.9)	365 (1.7)	654 (2.3)	—	—
Black	4639 (7.5)	836 (7.3)	1444 (6.8)	2359 (8.2)	—	—
Other	2175 (3.5)	405 (3.5)	624 (2.9)	1146 (4.0)	—	—
White	30 498 (49.5)	4831 (42.2)	9013 (42.3)	16 654 (57.8)	—	—
No information	23032 (37.4)	5166 (45.1)	9884 (46.3)	7982 (27.7)	—	—
Ethnicity	—	—	—	—	0.037	0.363
Hispanic	3137 (5.1)	527 (4.6)	872 (4.1)	1738 (6.0)	—	—
Non-Hispanic	34 895 (56.7)	5689 (49.7)	10 360 (48.6)	18 846 (65.4)	—	—
No information	23 551 (38.2)	5242 (45.7)	10 098 (47.3)	8211 (28.5)	—	—
Private health insurance	51 105 (83.0)	9880 (86.2)	18 802 (88.1)	22 423 (77.9)	0.057	0.219
Social deprivation index percentile	—	—	—	—	0.069	0.031
1-30	18 206 (32.9)	3065 (31.9)	6737 (34.4)	8404 (32.2)	—	—
31-60	16 382 (29.6)	2768 (28.8)	5803 (29.6)	7811 (29.9)	—	—
61-100	20 695 (37.4)	3767 (39.2)	7055 (36.0)	9873 (37.8)	—	—
Haemoglobin A_{1c} (%), median (IQR)	7.8 (7.3-8.5)	7.7 (7.3-8.4)	7.8 (7.3-8.5)	7.8 (7.4-8.6)	0.054	0.105
eGFR (mL/min/1.73 m^2), median (IQR)	92 (78-102.4)	91.9 (77.8-102.4)	93.3 (79.5-103.3)	91.1 (77-101.6)	0.078	0.045
Stage of chronic kidney disease*	—	—	—	—	0.069	0.034
Stage 2	24947 (40.5)	4657 (40.6)	8295 (38.9)	11 995 (41.7)	—	—
Stage 3a	3403 (5.5)	650 (5.7)	970 (4.5)	1783 (6.2)	—	—
Low density lipoprotein cholesterol (mg/dL), median (IQR)	90 (70-113)	89 (70-112)	89 (69-113)	90 (71-113)	0.002	0.021
Hospital admission in previous three months	1419 (2.3)	308 (2.7)	449 (2.1)	662 (2.3)	0.038	0.025
Body mass index	—	—	—	—	0.352	0.166
<30	6933 (11.3)	1321 (11.5)	1887 (8.8)	3725 (12.9)	—	—
30.0-34.9	8648 (14.0)	1406 (12.3)	2912 (13.7)	4330 (15.0)	—	—
≥35.0	22 422 (36.4)	3356 (29.3)	9499 (44.5)	9567 (33.2)	—	—
No information	23 580 (38.3)	5375 (46.9)	7032 (33.0)	11 173 (38.8)	—	—
Hypertension	48 474 (78.7)	9132 (79.7)	16810 (78.8)	22 532 (78.2)	0.022	0.036
Heart failure	3466 (5.6)	601 (5.2)	1238 (5.8)	1627 (5.7)	0.024	0.018
Charlson comorbidity index ≥5	1372 (2.2)	238 (2.1)	520 (2.4)	614 (2.1)	0.024	0.004

Data are numbers (%) unless stated otherwise.
Stage of chronic kidney disease: stage 2: eGFR 60-89 mL/min/1.73 m^2; stage 3a: eGFR 45-59 mL/min/1.73 m^2.
DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; IQR=interquartile range; SGLT-2=sodium-glucose contransporter-2; SMD=standardised mean difference.

from electronic health records of participating health systems and claims data of participating health insurance plans (combined with electronic health records and laboratory data of their data partners; table 1 and table 2). People without urine albumin measurements were included in the group without albuminuria (because we expected most people to fall into this category). Information on drugs was obtained from prescription records (healthcare delivery organisations) and prescription fills (health insurance plans).

Statistical analysis

The five year risk of the renal outcome was estimated as described for the target trial. The pooled logistic regression models included the following baseline covariates: participant demographics (age, sex, health insurance); community factors (proportion treated with brand name *v* generic anticoagulants by site; social deprivation index[19] by zip code); month of study entry; laboratory values (haemoglobin A_{1c}, eGFR, low density lipoprotein cholesterol); excess weight (based on body mass index ≥35 or ICD (international classification of diseases) code indicating class 2-3 obesity); number of non-diabetes drugs taken as a representation of the patient's comorbidity load; number of outpatient visits in the year before the index date; number of distinct laboratory tests in the previous year; hospital admission in the previous three months; heart failure; advanced liver fibrosis (fibrosis-4 score >2.67[20]); Charlson comorbidity index; and treatment with systemic glucocorticoids, statins, and anti-platelet drugs. Supplemental table 7 describes these variables and the methods used to address missing data. DPP-4 inhibitors were chosen as the reference treatment strategy because randomised trials have shown no difference in chronic kidney disease progression between DPP-4 inhibitors and placebo.[7-10]

We also conducted several sensitivity analyses. To explore the impact of confounding adjustment on our estimates, we obtained estimates adjusted for age only. We also investigated the impact of competing events by censoring people when they experienced the competing event (death from any cause). To estimate the effects on

Table 2 | Baseline characteristics of eligible people with albuminuria (BESTMED Consortium, 2014-23)

Characteristics	Overall	DPP-4 inhibitors	SGLT-2 inhibitors or GLP-1 receptor agonists	Sulfonylureas	SMD (SGLT-2 inhibitors or GLP-1 receptor agonists *v* DPP-4 inhibitors)	SMD (sulfonylureas *v* DPP-4 inhibitors)
No of eligible people	13 872 (100)	2296 (16.6)	4720 (34)	6856 (49.4)	—	—
Age (years), median (IQR)	61 (52-69)	61 (53-70)	59 (50-67)	62 (53-70)	0.232	0.004
Female sex	6616 (47.7)	1129 (49.2)	2339 (49.6)	3148 (45.9)	0.008	0.065
Race	—	—	—	—	0.042	0.311
Asian	479 (3.5)	80 (3.5)	145 (3.1)	254 (3.7)	—	—
Black	1192 (8.6)	200 (8.7)	429 (9.1)	563 (8.2)	—	—
Other	805 (5.8)	126 (5.5)	246 (5.2)	433 (6.3)	—	—
White	8247 (59.5)	1217 (53.0)	2574 (54.5)	4456 (65.0)	—	—
No information	3149 (22.7)	673 (29.3)	1326 (28.1)	1150 (16.8)	—	—
Ethnicity	—	—	—	—	0.068	0.299
Hispanic	904 (6.5)	117 (5.1)	316 (6.7)	471 (6.9)	—	—
Non-Hispanic	9642 (69.5)	1480 (64.5)	3001 (63.6)	5161 (75.3)	—	—
No information	3326 (24.0)	699 (30.4)	1403 (29.7)	1224 (17.9)	—	—
Private health insurance	10 686 (77.0)	1794 (78.1)	3884 (82.3)	5008 (73.0)	0.104	0.119
Social deprivation index percentile	—	—	—	—	0.039	0.022
1-30	4367 (33.8)	671 (32.9)	1554 (34.6)	2142 (33.5)	—	—
31-60	3685 (28.5)	578 (28.3)	1268 (28.2)	1839 (28.7)	—	—
61-100	4882 (37.7)	793 (38.8)	1673 (37.2)	2416 (37.8)	—	—
Haemoglobin A_{1c} (%), median (IQR)	7.8 (7.4-8.6)	7.8 (7.3-8.5)	7.8 (7.4-8.7)	7.9 (7.4-8.6)	0.095	0.091
eGFR (mL/min/1.73 m^2), median (IQR)	90.2 (74.5-102.4)	90 (74.1-101.8)	91.6 (75.5-103.3)	89.4 (73.9-101.6)	0.091	0.007
Stage of chronic kidney disease*	—	—	—	—	0.074	0.038
Stage 2	5667 (40.9)	923 (40.2)	1865 (39.5)	2879 (42.0)	—	—
Stage 3a	1213 (8.7)	222 (9.7)	368 (7.8)	623 (9.1)	—	—
Low density lipoprotein cholesterol (mg/dL), median (IQR)	86.90 (67-110)	84 (66-108)	87 (65-111)	87 (68-110)	0.035	0.055
Hospital admission in previous three months	425 (3.1)	66 (2.9)	162 (3.4)	197 (2.9)	0.032	<0.001
Body mass index	—	—	—	—	0.321	0.172
<30	1781 (12.8)	319 (13.9)	509 (10.8)	953 (13.9)	—	—
30.0-34.9	2235 (16.1)	324 (14.1)	748 (15.8)	1163 (17.0)	—	—
≥35.0	5683 (41.0)	780 (34.0)	2240 (47.5)	2663 (38.8)	—	—
No information	4173 (30.1)	873 (38.0)	1223 (25.9)	2077 (30.3)	—	—
Hypertension	11 756 (84.7)	1991 (86.7)	4019 (85.1)	5746 (83.8)	0.045	0.082
Heart failure	961 (6.9)	148 (6.4)	330 (7.0)	483 (7.0)	0.022	0.024
Charlson comorbidity index ≥5	605 (4.4)	130 (5.7)	227 (4.8)	248 (3.6)	0.038	0.097

Data are numbers (%) unless stated otherwise.
Stage of chronic kidney disease: stage 2: eGFR 60-89 mL/min/1.73 m^2; stage 3a: eGFR 45-59 mL/min/1.73 m^2.
DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; IQR=interquartile range; SGLT-2=sodium-glucose contransporter-2; SMD=standardised mean difference.

components of the composite outcome, we redefined the outcome as doubling of serum creatinine. We also analysed the impact of an acute (and often transient) decrease in eGFR that could be observed soon after starting some of the study drugs, such as SGLT-2 inhibitors,[21] by excluding events in the first six months after starting a study drug. Additionally, to explore other measures of progression of kidney disease, we conducted an analysis where the primary outcome was development of severely increased albuminuria (albumin to creatinine ratio ≥300mg/g). Finally, to explore the impact of classifying people without albumin measurements in the no albuminuria group, we required laboratory confirmation of no albuminuria to be classified in that group.

All statistical analyses were performed in R v4.4.0. This study was approved by the institutional review boards of all participating institutions.

Patient and public involvement

Patient members of the BESTMED study stakeholder advisory board, Robert Hottin, Neal Lindeman, and A K M Wara, highlighted the need for information on renal outcomes to help inform the choice of type 2 diabetes drugs among people with moderate cardiovascular risk. They provided input to the study questions, analyses, results, and interpretation. They have agreed to help us with dissemination of our findings. This work uses data collected by the health systems and health insurance plans participating in the BESTMED study as part of patient care and support.

Results

People without albuminuria

Of 61 583 eligible people (supplemental figure 1), 21 330 (34.6%) started GLP-1 receptor agonists or SGLT-2 inhibitors, 28 795 (46.8%) sulfonylureas, and 11 458 (18.6%) DPP-4 inhibitors. Compared with DPP-4 inhibitors, the difference in median values for those taking GLP-1 receptor agonists or SGLT-2 inhibitors did not exceed three years for age, 0.1% for haemoglobin A_{1c}, 2 mL/min/1.73 m^2 for eGFR, and 1 mm Hg for systolic blood pressure among people without albuminuria (table 1).

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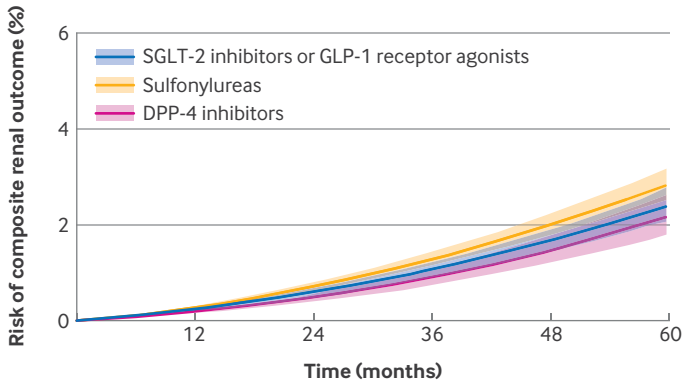

Fig 1 | Estimated risk of composite renal outcome by treatment group among people without baseline albuminuria (BESTMED Consortium, 2014-23). DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose contransporter-2

Over a median follow-up of 32 months (interquartile range 18-58), 783 (1.3%) people experienced the renal outcome; 1805 (2.9%) died and 20 028 (32.5%) were lost to follow-up (after a median of 27 months; interquartile range 17-44). The estimated five year risk (95% CI) of the outcome was 2.4% (2.1% to 2.7%) for GLP-1 receptor agonists or SGLT-2 inhibitors, 2.8% (2.5% to 3.2%) for sulfonylureas, and 2.1% (1.8% to 2.6%) for DPP-4 inhibitors (fig 1). Compared with DPP-4 inhibitors, the estimated five year risk ratio (95% CI) was 1.10 (0.90 to 1.38) for GLP-1 receptor agonists or SGLT-2 inhibitors and 1.31 (1.11 to 1.58) for sulfonylureas (table 3). The estimated five year risk for GLP-1 receptor agonists and SGLT-2 inhibitors had largely overlapping confidence intervals (supplemental table 2). The estimated five year risk (95% CI) of developing severely increased albuminuria was 1.6% (1.3% to 1.9%) for GLP-1 receptor agonists or SGLT-2 inhibitors, 2.2% (2.0% to 2.6%) for sulfonylureas, and 2.0% (1.7% to 2.4%) for DPP-4 inhibitors (supplemental table 15).

People with albuminuria

Of 13 872 eligible people (supplemental figure 1), 4720 (34.0%) started GLP-1 receptor agonists or SGLT-2 inhibitors, 6856 (49.4%) sulfonylureas, and 2296 (16.6%) DPP-4 inhibitors. Compared with DPP-4 inhibitors, the difference in median values for those taking GLP-1 receptor agonists or SGLT-2 inhibitors did not exceed two years for age, 0.1% for haemoglobin A_{1c}, 2 mL/min/1.73 m^2 for eGFR, and 2 mm Hg for systolic blood pressure among people with albuminuria (table 2). Most people (12 595, 90.1%) had moderately increased albuminuria (albumin to creatinine ratio 30-299 mg/g).

Over a median follow-up of 32 months (interquartile range 18-56), 349 (2.5%) people experienced the renal outcome; 571 (4.1%) died and 3773 (27.2%) were lost to follow-up (after a median of 27 months; interquartile range 17-45). The estimated five year risk (95% CI) of the outcome was 3.2% (2.3% to 4.1%) for GLP-1 receptor agonists or SGLT-2 inhibitors, 4.6% (3.9% to 5.2%) for sulfonylureas, and 5.4% (4.2% to 6.7%) for DPP-4 inhibitors (fig 2). Compared with DPP-4 inhibitors, the estimated five year risk ratio (95% CI) was 0.60 (0.42 to 0.82) for GLP-1 receptor agonists or SGLT-2 inhibitors and 0.85 (0.69 to 1.10) for sulfonylureas (table 3). The estimated five year risks were similar for people with eGFR <60 mL/min/1.73 m^2 (fig 2). Estimated five year risks for GLP-1 receptor agonists and SGLT-2 inhibitors had largely overlapping confidence intervals (supplemental table 2). The estimated five year risk (95% CI) of developing severely increased albuminuria was 8.6% (7.1% to 10.1%) for GLP-1 receptor agonists or SGLT-2 inhibitors, 9.8% (8.7% to 10.9%) for sulfonylureas, and 10.6% (9.0% to 12.4%) for DPP-4 inhibitors (supplemental table 15).

Sensitivity analyses

In models adjusted only for age, estimated five year risk (95% CI) of the renal outcome was 2.4% (2.1% to 2.7%) for GLP-1 receptor agonists or SGLT-2 inhibitors, 2.8% (2.5% to 3.2%) for sulfonylureas, and 2.1% (1.8% to 2.6%) for DPP-4 inhibitors among people without albuminuria; and 3.2% (2.3% to 4.1%) for GLP-1 receptor agonists or SGLT-2 inhibitors, 4.6% (3.9% to 5.2%) for sulfonylureas, and 5.4% (4.2% to 6.7%)

Table 3 | Estimated five year risk of composite renal outcome by treatment group (BESTMED Consortium, 2014-23)

Treatment group	No of eligible people	No of events	Five year risk, % (95% CI)	Risk difference, % (95% CI)	Risk ratio (95% CI)
With albuminuria					
DPP-4 inhibitors	2296	78	5.4 (4.2 to 6.7)	Reference	Reference
GLP-1 receptor agoinsts or SGLT-2 inhibitors	4720	57	3.2 (2.3 to 4.1)	-2.18 (-3.54 to -0.81)	0.60 (0.42 to 0.82)
Sulfonylureas	6856	214	4.6 (3.9 to 5.2)	-0.82 (-1.92 to 0.45)	0.85 (0.69 to 1.10)
Without albuminuria					
DPP-4 inhibitors	11 458	130	2.1 (1.8 to 2.6)	Reference	Reference
GLP-1 receptor agonists or SGLT-2 inhibitors	21 330	171	2.4 (2.1 to 2.7)	0.23 (-0.24 to 0.69)	1.10 (0.90 to 1.38)
Sulfonylureas	28 795	482	2.8 (2.5 to 3.2)	0.66 (0.28 to 1.09)	1.31 (1.11 to 1.58)

CI=confidence interval; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose contransporter-2.

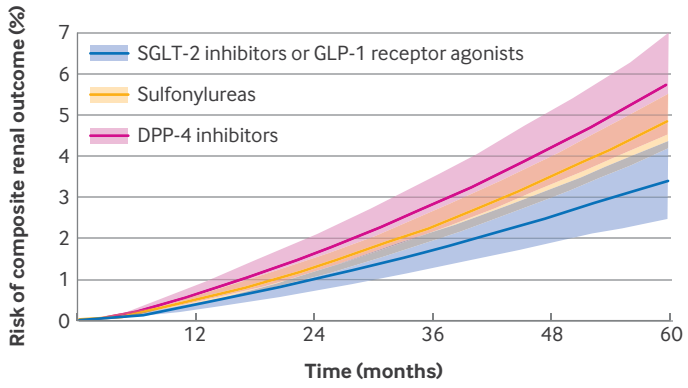

Fig 2 | Estimated risk of composite renal outcome by treatment group among people with baseline albuminuria (BESTMED Consortium, 2014-23). DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose contransporter-2

for DPP-4 inhibitors among people with albuminuria (supplemental table 3). Estimates were similar in the other sensitivity analyses (supplemental tables 4, 5, 6, and 9). Risk differences across subgroups defined by sex, age, eGFR, and haemoglobin A_{1c} had largely overlapping confidence intervals (fig 3 and fig 4).

Discussion

Principal findings

In this nationwide observational study of people with type 2 diabetes at moderate cardiovascular risk, we studied the renal effects of GLP-1 receptor agonists or SGLT-2 inhibitors in those with and without albuminuria separately. We estimated that GLP-1 receptor agonists or SGLT-2 inhibitors reduce the risk of renal deterioration in people with albuminuria, but we found little indication of renal benefit among people without albuminuria.

Comparison with other studies

Our estimates are compatible with those from randomised trials that analysed renal outcomes in people treated with SGLT-2 inhibitors and GLP-1 receptor agonists and included a large proportion of people with albuminuria ≥30 mg/g. For trials of SGLT-2 inhibitors, this proportion ranged from 53% in EMPA-REG OUTCOME to 100% in CREDENCE and DAPA-CKD,[12 22 23] and for trials of GLP-1 receptor agonists from 35% in REWIND to 97% in FLOW.[11 24 25] Several trials found greater benefits for people with a larger degree of albuminuria.[11-13] Our findings suggest that the renal benefits shown in these studies for new type 2 diabetes drugs—GLP-1 receptor agonists and SGLT-2 inhibitors—do not extend to people without albuminuria.

Other previously published observational studies and meta-analyses have found renal benefits among people with type 2 diabetes and no albuminuria treated with SGLT-2 inhibitors.[26 27] However, differences in study design (eg, a comparator group that included sulfonylureas found to be linked to excess renal risk in this analysis; and inclusion of people starting study drugs as a third or fourth type 2 diabetes agent) and definitions of albuminuria (eg, ≥200 mg/g *v* ≥30 mg/g in this analysis) do not allow a direct comparison between the study findings.

Clinical implications

Historically, albuminuria was thought to be the primary mechanism for renal impairment in diabetic kidney disease[28] because renal reabsorption of albumin escaped from the glomerular filter leads to tubulo-interstitial atrophy, fibrosis, and renal function loss.[29] However, more recent studies found no albuminuria in approximately a third of people with diabetes and reduced eGFR,[30] which likely involves renal lesions outside the glomerulus (eg, interstitium and vasculature).[31]

Prevention of deterioration of kidney function in people without albuminuria remains a challenge. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been shown to improve renal outcomes only among people with severely increased albuminuria[32 33] and have not been found to have an advantage over other antihypertensive agents in those with normoalbuminuric kidney disease.[34] Finerenone, a non-steroidal mineralocorticoid receptor antagonist that decreases progression of kidney disease in people with type 2 diabetes, has not been tested in those without albuminuria.[35] Further research is needed to identify treatments that can prevent progression of kidney disease in the large population of people with type 2 diabetes and normoalbuminuria.

Our study also found an increased risk of renal deterioration among people without albuminuria treated with sulfonylureas (compared with DPP-4 inhibitors). Little is currently known about the impact of sulfonylureas on renal function. Several observational studies found that people treated with sulfonylureas experienced faster renal deterioration than those treated with metformin.[36 37] However, because metformin was recommended as first line treatment for type 2 diabetes when these studies were conducted, it is possible that people in the sulfonylurea group were qualitatively different from those in the metformin group in ways that could not be measured using study data, potentially confounding the results. Furthermore, previous studies focusing on the impact of sulfonylureas on renal function among people with normoalbuminuria are lacking.

Strengths and limitations of the study

The present study has two key strengths. The use of electronic health records allowed us to characterise people using rich clinical data. Quality and completeness of data were further augmented by linkage of patient records between study sites. Additionally, the study explicitly emulated a target trial—an approach that minimises common sources of bias in observational analyses.[38]

Owing to the absence of randomisation, residual confounding cannot be excluded. However, baseline

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Treatment group	No of eligible people	No of events	Five year risk, % (95% CI)	Risk ratio (95% CI)	Risk difference, % (95% CI)
Overall	61 583	783			
DPP-4 inhibitors	11 458	130	2.1 (1.8 to 2.6)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	21 330	171	2.4 (2.1 to 2.7)	1.10 (0.90 to 1.38)	0.23 (-0.24 to 0.69)
Sulfonylureas	28 795	482	2.8 (2.5 to 3.2)	1.31 (1.11 to 1.58)	0.66 (0.28 to 1.09)
Sex					
Female					
DPP-4 inhibitors	5620	73	2.5 (2.0 to 3.1)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	10 735	109	3.0 (2.4 to 3.6)	1.22 (0.91 to 1.61)	0.54 (-0.25 to 1.31)
Sulfonylureas	13 260	286	3.6 (3.1 to 4.3)	1.45 (1.17 to 1.83)	1.12 (0.50 to 1.78)
Male					
DPP-4 inhibitors	5838	57	1.9 (1.5 to 2.4)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	10 595	62	1.8 (1.4 to 2.2)	0.97 (0.68 to 1.33)	-0.06 (-0.72 to 0.51)
Sulfonylureas	15 535	196	2.1 (1.7 to 2.5)	1.10 (0.86 to 1.42)	0.20 (-0.30 to 0.66)
Age (years)					
<65					
DPP-4 inhibitors	7641	66	1.8 (1.3 to 2.2)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	15 680	113	1.9 (1.6 to 2.3)	1.09 (0.82 to 1.44)	0.15 (-0.36 to 0.66)
Sulfonylureas	17 563	250	2.4 (2.0 to 2.8)	1.34 (1.08 to 1.67)	0.60 (0.17 to 1.02)
≥65					
DPP-4 inhibitors	3817	64	3.1 (2.3 to 3.9)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	5650	58	3.3 (2.5 to 4.1)	1.06 (0.76 to 1.50)	0.18 (-0.84 to 1.29)
Sulfonylureas	11 232	232	3.6 (3.0 to 4.2)	1.14 (0.92 to 1.52)	0.44 (-0.29 to 1.30)
Baseline HbA1c (%)					
<8					
DPP-4 inhibitors	6713	73	2.0 (1.6 to 2.5)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	12 096	88	2.0 (1.6 to 2.4)	0.96 (0.73 to 1.29)	-0.07 (-0.66 to 0.50)
Sulfonylureas	15 718	259	2.6 (2.2 to 3.1)	1.30 (1.05 to 1.63)	0.61 (0.10 to 1.13)
≥8					
DPP-4 inhibitors	4745	57	2.3 (1.7 to 2.9)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	9234	83	3.0 (2.4 to 3.7)	1.29 (0.95 to 1.80)	0.68 (-0.15 to 1.55)
Sulfonylureas	13 077	223	3.0 (2.5 to 3.6)	1.31 (1.01 to 1.78)	0.71 (0.03 to 1.34)
Baseline eGFR (mL/min/1.73 m²)					
<60					
DPP-4 inhibitors	650	7	2.1 (1.0 to 3.8)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	970	16	3.8 (2.0 to 6.3)	1.77 (0.79 to 4.27)	1.64 (-0.62 to 4.16)
Sulfonylureas	1783	43	3.2 (2.2 to 4.9)	1.52 (0.84 to 3.51)	1.11 (-0.52 to 2.89)
≥60					
DPP-4 inhibitors	10 808	123	2.2 (1.9 to 2.7)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	20 360	155	2.3 (1.9 to 2.7)	1.01 (0.82 to 1.27)	0.03 (-0.44 to 0.53)
Sulfonylureas	27 012	439	2.8 (2.5 to 3.2)	1.24 (1.04 to 1.50)	0.54 (0.10 to 0.95)

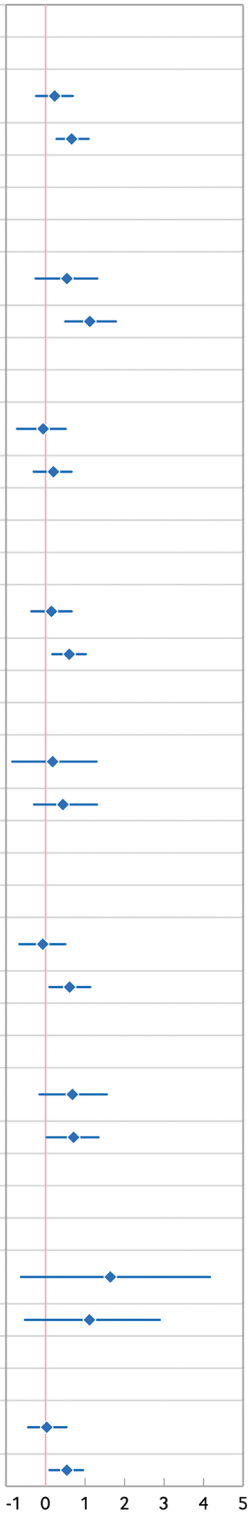

Fig 3 | Subgroup analyses for estimated risk of composite renal outcome among people without baseline albuminuria (BESTMED Consortium, 2014-23). CI=confidence interval; DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; HBA1c=haemoglobin A_{1c}; SGLT-2=sodium-glucose contransporter-2

characteristics of people were similar across treatment groups, even before confounding adjustment, making it less likely that important unmeasured confounders exist. Additionally, people at high cardiovascular risk were not included to reduce the risk of confounding owing to channeling of people to different drug classes

Treatment group	No of eligible people	No of events	Five year risk, % (95% CI)	Risk ratio (95% CI)	Risk difference, % (95% CI)
Overall	13 872	349			
DPP-4 inhibitors	2296	78	5.4 (4.2 to 6.7)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	4720	57	3.2 (2.3 to 4.1)	0.60 (0.42 to 0.82)	-2.18 (-3.54 to -0.81)
Sulfonylureas	6856	214	4.6 (3.9 to 5.2)	0.85 (0.69 to 1.10)	-0.82 (-1.92 to 0.45)
Sex					
Female					
DPP-4 inhibitors	1129	36	5.5 (3.8 to 7.6)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	2339	35	4.1 (2.9 to 5.8)	0.75 (0.49 to 1.14)	-1.38 (-3.58 to 0.68)
Sulfonylureas	3148	120	5.8 (4.6 to 7.4)	1.06 (0.76 to 1.54)	0.32 (-1.69 to 2.21)
Male					
DPP-4 inhibitors	1167	42	5.2 (3.5 to 6.8)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	2381	22	2.3 (1.3 to 3.5)	0.45 (0.24 to 0.78)	-2.83 (-4.83 to -0.86)
Sulfonylureas	3708	94	3.6 (2.9 to 4.4)	0.70 (0.51 to 1.01)	-1.53 (-3.20 to 0.06)
Age (years)					
<65					
DPP-4 inhibitors	1352	44	4.6 (3.3 to 6.2)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	3191	35	2.5 (1.7 to 3.3)	0.54 (0.34 to 0.83)	-2.13 (-4.01 to -0.59)
Sulfonylureas	3883	102	3.5 (2.8 to 4.4)	0.76 (0.55 to 1.03)	-1.14 (-2.65 to 0.12)
≥65					
DPP-4 inhibitors	944	34	6.9 (4.8 to 9.9)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	1529	22	5.0 (3.0 to 7.5)	0.73 (0.40 to 1.21)	-1.86 (-5.24 to 1.05)
Sulfonylureas	2973	112	6.6 (5.1 to 8.5)	0.96 (0.70 to 1.39)	-0.30 (-2.70 to 2.03)
Baseline HbA1c (%)					
<8					
DPP-4 inhibitors	1310	44	5.6 (4.1 to 7.5)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	2563	30	3.1 (2.1 to 4.6)	0.55 (0.34 to 0.86)	-2.53 (-4.54 to -0.63)
Sulfonylureas	3705	114	4.2 (3.4 to 5.2)	0.75 (0.56 to 1.03)	-1.42 (-3.23 to 0.13)
≥8					
DPP-4 inhibitors	986	34	5.5 (3.6 to 8.1)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	2157	27	3.3 (2.0 to 4.5)	0.59 (0.32 to 0.98)	-2.25 (-5.24 to -0.06)
Sulfonylureas	3151	100	5.1 (3.9 to 6.5)	0.92 (0.64 to 1.35)	-0.42 (-2.63 to 1.44)
Baseline eGFR (mL/min/1.73 m²)					
<60					
DPP-4 inhibitors	222	15	9.9 (5.0 to 18.9)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	368	6	5.1 (1.2 to 11.3)	0.51 (0.11 to 1.41)	-4.88 (-14.32 to 2.46)
Sulfonylureas	623	22	8.2 (4.8 to 13.2)	0.82 (0.39 to 1.62)	-1.78 (-10.04 to 3.40)
≥60					
DPP-4 inhibitors	2074	63	4.9 (3.7 to 6.3)	1 (reference)	0 (reference)
SGLT-2 inhibitors or GLP-1 receptor agonists	4352	51	3.2 (2.3 to 4.1)	0.65 (0.44 to 0.95)	-1.72 (-3.37 to -0.21)
Sulfonylureas	6233	192	4.4 (3.7 to 5.2)	0.90 (0.70 to 1.18)	-0.50 (-1.78 to 0.69)

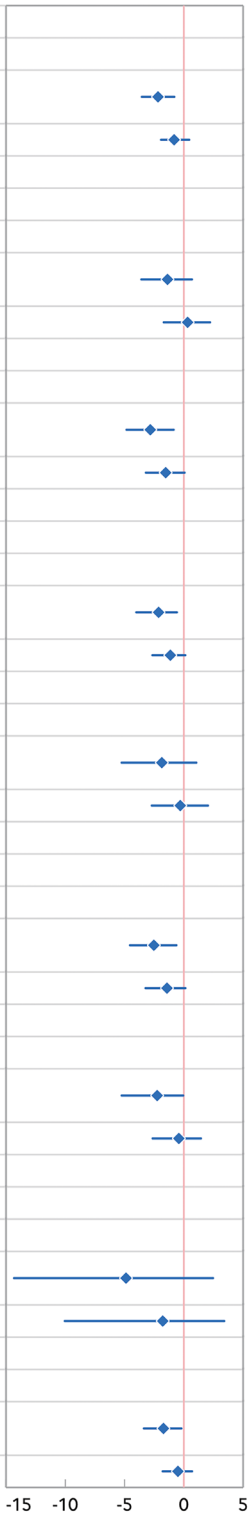

Fig 4 | Subgroup analyses for estimated risk of composite renal outcome among people with baseline albuminuria (BESTMED Consortium, 2014-23). CI-confidence interval; DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; HBA1c=haemoglobin A_{1c}; SGLT-2=sodium-glucose contransporter-2

because of the established clinical benefits of GLP-1 receptor agonists and SGLT-2 inhibitors. Information on duration of diabetes was not available. However, age and haemoglobin A_{1c}—both indirect indicators of duration of diabetes—were similar across treatment arms, likely because the study cohort was limited to

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people on metformin monotherapy starting a second type 2 diabetes agent. Information on non-prescription drugs (eg, non-steroidal anti-inflammatory drugs) was not available for analysis.

Most people who started treatment with GLP-1 receptor agonists or SGLT-2 inhibitors had a relatively short period of follow-up (median 23 months, interquartile range 14-40), and therefore study findings may not apply to longer periods of observation. When using development of severely increased albuminuria as the outcome, we found little difference in the estimated effect of GLP-1 receptor agonists or SGLT-2 inhibitors between people with versus without baseline albuminuria. This finding is likely because of de novo albuminuria in the group without baseline albuminuria. Analysis of eGFR trajectories, which we could not conduct, might have provided further insights into the changes in renal function over time. Most of the primary outcome events were doubling of serum creatinine rather than eGFR <15 mL/min/1.73 m^2 and the study results should be interpreted accordingly.

Some of the additional risk factors for kidney disease (eg, high density lipoprotein cholesterol, triglycerides, and pretreatment eGFR slopes) were not included in the analysis. The study findings might not be generalisable to populations with different levels of access to healthcare, or different racial or ethnic distribution, from those in our study population. However, our study drew on a large US population and included people with a broad range of renal function and proteinuria, which augments its generalisability to a wide population of people with diabetes.

Conclusions

In summary, we estimated that, compared with DPP-4 inhibitors, GLP-1 receptor agonists or SGLT-2 inhibitors slowed the decrease in renal function in people with type 2 diabetes with moderately increased albuminuria, but not in those without albuminuria, over the study follow-up period. Sulfonylureas led to faster decline in renal function in people with type 2 diabetes and normoalbuminuria. These results underscore the importance of considering albuminuria when making treatment decisions for people with type 2 diabetes at risk of declining renal function.

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Contributors: AT, LCP, and MAH were responsible for the study concept and design. Acquisition, analysis, and interpretation of the data were carried out by AT, LCP, EH, RMC, AD, SG, MCL, VN, EP, VW, and MAH. The manuscript was drafted by AT, LCP, MAH, and EH. Statistical analysis was performed by LCP and EH. Manuscript was critically reviewed by RMC, AD, SG, MCL, MEM, VN, EP, VW, AFK, and MAH. Funding was obtained by AT. Supervision was carried out by AT. AT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Transparency: The corresponding author (AT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: After publication, the results will be freely available both to stakeholders and to the broader public. To ensure broad dissemination, we will issue press releases jointly with Mass General Brigham and coauthors' institutions and share findings via social media (eg, X, LinkedIn). By leveraging these channels, we aim to reach a diverse audience, including patients, care givers, clinicians, policy makers, and other stakeholders, and contribute to informed decision making in treatment of type 2 diabetes.

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Ethical approval: This study was approved by the institutional review boards of all participating institutions (protocol No 2021P001171 at Mass General Brigham) and the requirement for informed consent was waived.

Data sharing: Patient-level information is not available owing to the institutional restrictions by the study sites. Both code sets used to define study variables and the analytical programme code used to perform the analysis are publicly available at Harvard Dataverse at https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/VMRQO8.

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Supplementary file: Supplemental figures and tables