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DIABETIC Medicine

RESEARCH ARTICLE

Epidemiology

Cardiovascular risk factors early in the course of treatment in people with type 2 diabetes without established cardiovascular disease: A population-based observational retrospective cohort study

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Abstract

Aims: To characterise the cardiovascular risk of people with type 2 diabetes without established cardiovascular disease but with risk factors, relative to those with established cardiovascular disease, to provide information on which patients could benefit from early use of glucose-lowering therapies that also reduce cardiovascular risk.

Methods: Data from people with type 2 diabetes initiating second-line glucose-lowering medication were retrieved from the UK Clinical Practice Research Datalink GOLD database and linked with Hospital Episode Statistics and Office for National Statistics (2001–2016). Cox proportional hazards models were used to estimate relative risks of major adverse cardiovascular events within groups defined by the presence of selected risk factors in people without versus with established cardiovascular disease.

Results: Of 53,182 individuals, 19.4% had established cardiovascular disease (i.e. a prior cardiovascular event). Over 5–7 years' follow-up, the rate of major adverse cardiovascular events was 14.0 and 49.6 events/1000 person-years without and with established cardiovascular disease, respectively (hazard ratio [HR] 0.28, 95% confidence interval [CI] 0.26, 0.29). Compared with a reference HR 1.0 for participants with established cardiovascular disease, estimated glomerular filtration rate <60 mL/min was the single factor associated with the highest risk of major adverse cardiovascular events (HR 0.75, 95% CI 0.70, 0.81) and mortality (HR 1.12, 95% CI 1.07, 1.18) in people with type 2 diabetes without established cardiovascular disease. The combination of chronic kidney disease with older age, smoking and/or dyslipidaemia was associated with a similarly high risk of cardiovascular events in people with type 2 diabetes and without cardiovascular disease compared with those having established cardiovascular disease.

Conclusions: These analyses provide important information to identify people who may benefit from primary prevention of cardiovascular disease. Modifiable cardiovascular risk factors should be controlled early in all individuals with type 2 diabetes (as well as in all individuals with cardiovascular disease).

KEYWORDS
cardiovascular disease, cardiovascular disease risk, risk factors, type 2 diabetes

1 | INTRODUCTION

Atherosclerotic cardiovascular disease is the leading cause of death in people with type 2 diabetes.[1] Diabetes confers a substantial independent risk for cardiovascular disease, and many people with type 2 diabetes have coexisting conditions and cardiovascular disease risk factors, such as hypertension, dyslipidaemia, obesity, chronic kidney disease and smoking.[1] Premature mortality is similar in people with type 2 diabetes, previous stroke, or previous myocardial infarction and any combination of these conditions is associated with multiplicative mortality risk.[2]

In people with type 2 diabetes and established cardiovascular disease or with risk factors for cardiovascular disease, a glucagon-like peptide-1 receptor agonist (GLP-1RA) or sodium–glucose cotransporter 2 inhibitor (SGLT2i) with proven cardiovascular benefit is recommended, added to metformin,[3,4] independent of glycaemic targets.[5] This is based on large cardiovascular outcome trials.[6–13] However, important knowledge gaps exist regarding people with type 2 diabetes and cardiovascular risk factors, but without established cardiovascular disease, early in their treatment course. Here, we describe the cardiovascular risk profile of people with type 2 diabetes who initiated second-line glucose-lowering medication (added to first-line pharmacotherapy) in a large UK primary care cohort. We compared outcomes in people without established cardiovascular disease (i.e. no prior cardiovascular event) to those in people with established cardiovascular disease (who had a previous event) to evaluate the effect of numbers and combinations of selected cardiovascular risk factors on the risk of major adverse cardiovascular events (MACE). The aim was to characterise the cardiovascular risk of subpopulations without established cardiovascular disease, relative to those with established cardiovascular disease, to provide information on which patients could benefit from receiving glucose-lowering therapies that reduce cardiovascular risk early in their type 2 diabetes treatment course.

Novelty statement

What is already known?

- People with established cardiovascular disease and type 2 diabetes are known to be a high-risk population, but few studies have evaluated cardiovascular risk and risk factors early in the course of diabetes treatment.

What has this study found?

- In this retrospective observational cohort study, people with type 2 diabetes and cardiovascular risk factors who were initiating second-line glucose-lowering medication had a high incidence of cardiovascular events. The risk of a major cardiovascular adverse event or death from any cause was greatest in people without established cardiovascular disease in the presence of moderate-to-severe chronic kidney disease. The combination of chronic kidney disease plus two other risk factors was associated with a risk for cardiovascular events that was not significantly different from that for people with established cardiovascular disease.

What are the clinical implications of the study?

- These findings highlight that modifiable cardiovascular risk factors, particularly chronic kidney disease, smoking and dyslipidaemia, should be controlled early in all individuals with type 2 diabetes (as well as in all individuals with cardiovascular disease).

2 | MATERIALS AND METHODS

2.1 | Data sources and population

A retrospective observational study was conducted using individual record data from the Clinical Practice Research Datalink GOLD database, derived from a UK-wide network of primary care practices.[14] Eligible participants had type 2 diabetes and were receiving both first- and second-line glucose-lowering pharmacotherapy during the follow-up period from 2001 to 2016 (Table S1). Outcomes data that could be linked to individuals were retrieved from Hospital Episode Statistics and the Office for National Statistics during the follow-up period.

2.2 | CVD risk determination and clinical characteristics at the index date

The index date was defined as that of the first prescription of second-line glucose-lowering therapy. This was chosen to capture the early type 2 diabetes population. Established cardiovascular disease was defined as any record prior to the index date of a cardiovascular disease-related Read Code in the GOLD database (including codes for acute myocardial infarction, acute coronary syndrome, coronary revascularisation and other arterial revascularisation procedures, stroke and transient ischemic attack, heart failure, aortic aneurysm and peripheral artery disease) (Table S2). Information on clinical characteristics was collected from participant records at the index date. Cardiovascular risk factor values included the last value in the year prior to the index date.

To identify people with type 2 diabetes at high cardiovascular risk, the presence of nine selected risk factors was assessed based on known risk levels and modified guideline recommendations: sex (male),[15] age (>65 years),[4,15] obesity (body mass index ≥30 kg/m^2),[16] hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg),[4] dyslipidaemia (total cholesterol >6.2 mmol/L [>240 mg/dL]),[4,17] current smoking,[15] hyperglycaemia (glycated haemoglobin [HbA_{1c}] ≥58 mmol/mol [≥7.5%]),[18] diabetes duration (the time since diagnosis) ≥5 years[4] and chronic kidney disease that was at least moderate (estimated glomerular filtration rate <60 mL/min, henceforth referred to as chronic kidney disease).[4,19] Total cholesterol was chosen as this is routinely measured in UK primary care and is the pay-for-performance target. Estimated glomerular filtration rate was calculated using the Cockcroft–Gault formula: (140 − age [years] × weight [kg] × 1.23 for men or 1.03 for women)/serum creatinine (μmol/L).

The type and total number of different types of cardiovascular medication and first- and second-line glucose-lowering medication prescribed before the index date were calculated and categorised by class to further characterise the population.

2.3 | Endpoints assessed during follow-up

The following cardiovascular-related endpoints were assessed over the follow-up period: (1) 3-point MACE, a composite of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke; (2) expanded MACE, 3-point MACE plus hospitalisation for angina, hospitalisation for HF or coronary revascularisation (also evaluation of individual expanded MACE components); and (3) all-cause mortality. International Classification of Diseases, 10th Revision codes and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures version 4 codes from Hospital Episode Statistics and the Office for National Statistics were used to identify the following: cardiovascular mortality, acute myocardial infarction, stroke, hospitalisation for unstable angina, hospitalisation for heart failure, coronary revascularisation and all-cause mortality (Table S3).

2.4 | Statistical analyses

Demographics and clinical characteristics were reported as *n* (%) and mean ± standard deviation for participants with/without cardiovascular disease respectively.

Statistical analyses were performed using SAS version 7.1. Time to first in-study event of 3-point MACE, expanded MACE and all-cause mortality were analysed by a Cox proportional hazards model comparing outcomes in participants without established cardiovascular disease to those in participants with established cardiovascular disease. MACE outcomes were recorded from the time of first prescription of second-line glucose-lowering therapy. Individuals were censored at the first occurrence of either the end of their personal follow-up, end of follow-up of their primary care practice, end of Hospital Episode Statistics coverage, end of Office for National Statistics coverage or death. All analyses were adjusted for the calendar year at index date by including this as a continuous variable in the model. Effect estimates for participants without established cardiovascular disease were reported as hazard ratios (HR) with 95% CI against a reference value of 1.0 for participants with established cardiovascular disease.

Similar analyses were performed comparing outcomes in participants without cardiovascular disease versus with cardiovascular disease, categorising participants without cardiovascular disease according to baseline risk defined by the following (Table S4):

1. According to the actual number of the nine selected risk factors
2. As high risk according to the respective nine selected individual risk factors
3. As high risk according to two- and three-way combinations of the nine selected individual risk factors.

Participants with missing values on one or more of the nine selected risk factors were excluded from these analyses. However, to explore the effect of missing data, an analysis of outcomes according to individual risk factors was also performed via multiple imputation using fully conditional specification (also known as imputation by chained equations or sequential generalised regression). The variables included were the nine selected risk factors (male sex, age >65 years, body mass index ≥30 kg/m^2, hypertension, dyslipidaemia, current smoking, hyperglycaemia, diabetes duration ≥5 years and chronic kidney disease) plus history of cardiovascular disease, calendar year, and incidence of and time to 3-point MACE, expanded MACE and all-cause mortality. Twenty datasets were imputed using PROC MI in SAS. Results were combined by PROC MIANALYZE.

3 | RESULTS

Of 464,253 patients in the GOLD database with type 2 diabetes-related codes, 17,057 were excluded to avoid alternative diabetes diagnoses (Table S1). Between 2001 and 2016, 90,838 type 2 diabetes patients in the database had at least one prescription of second-line glucose-lowering therapy within 120 days of the last prescription of first-line glucose-lowering therapy. Of these, 53,182 were people aged ≥18 years with sufficient follow-up data that could be cross-linked in Hospital Episode Statistics and the Office for National Statistics. There was a high rate of missing data for cholesterol, body mass index, HbA_{1c} and estimated glomerular filtration rate (Table 1).

Of the 53,182 individuals included in the analyses, 10,313 (19%) had established cardiovascular disease or a cardiovascular disease-related procedure and 42,869 (81%) did not have cardiovascular disease (Table 1). The most common first cardiovascular disease diagnoses/procedures were myocardial infarction (36%), coronary revascularisation (25%) and heart failure (21%) (Table S5).

Compared with those with cardiovascular disease, people without cardiovascular disease were younger (61 vs. 70 years), had shorter diabetes duration (3.5 vs. 4.2 years) and had higher body mass index (31.8 vs. 30.5 kg/m^2), systolic/diastolic blood pressure (136/80 vs. 135/76 mmHg), total cholesterol (4.7 vs. 4.4 mmol/L), HbA_{1c} levels (74 vs. 72 mmol/mol [8.9% vs. 8.7%]) and estimated glomerular filtration rate (108 vs. 82 mL/min), but lower frequency of chronic kidney disease (estimated glomerular filtration rate <60 mL/min) (13% vs. 31%) (Table 1).

Most participants (99% with and 85% without cardiovascular disease) were receiving at least one cardiovascular medication at index date, mostly lipid-lowering drugs, hypertension/heart failure medication and/or antiplatelet drugs (Table 1). Of those with cardiovascular disease, 88% were receiving at least three cardiovascular medications compared with 42% of those without cardiovascular disease. The most common first-line glucose-lowering treatment for both groups was metformin (68%–78%), with sulphonylureas (48%–51%) most frequently added as second-line treatment (Table 1). Second-line treatment with GLP-1RA (0.5%–0.8%) and SGLT2i (0.3%–0.7%) was uncommon.

Compared with those with cardiovascular disease, the cardiovascular-related endpoints occurred at around one-quarter to one-third of the rate in individuals without cardiovascular disease. Over the follow-up period, the incidence rate of 3-point MACE was 14.0 events per 1000 person-years in those without cardiovascular disease (mean follow-up 6.6 years) compared with 49.6 events per 1000 person-years in people with cardiovascular disease (mean follow-up 5.6 years) (HR for people without cardiovascular disease vs. with cardiovascular disease: 0.28, 95% CI 0.26, 0.29; Table S6). The incidence rate of the expanded MACE endpoint was 22.6 events per 1000 person-years in people without cardiovascular disease (mean follow-up 6.4 years) compared with 93.1 events per 1000 person-years in those with cardiovascular disease (mean follow-up 4.8 years) (HR 0.24, 95% CI 0.23, 0.25), with hospitalisation for heart failure the most common individual component (10.2 and 50.7 events per 1000 person-years, respectively; HR 0.20, 95% CI 0.19, 0.21; Table S6). In total, 16.9% of people without cardiovascular disease died (mean follow-up 6.8 years), while 41.0% of those with cardiovascular disease died (mean follow-up 6.0 years) (HR 0.35, 95% CI 0.34, 0.37; Table S6).

Compared with those with cardiovascular disease, the risk of 3-point MACE in those without cardiovascular disease increased with an increasing number of risk factors (Figure 1). People without cardiovascular disease had a median (range) of 3 (0–8) of the selected nine cardiovascular risk factors. The risk of 3-point MACE associated with the presence of a minimum number and

TABLE 1 Demographic and clinical characteristics of individuals with type 2 diabetes without and with established cardiovascular disease prior to index date (first prescription of second-line glucose-lowering therapy)

	People with type 2 diabetes without established CVD, *N* = 42,869 (81%)		**People with type 2 diabetes with established CVD, *N* = 10,313 (19%)**	
	n	**Mean ± SD or *n* (%)**	***n***	**Mean ± SD or *n* (%)**
Age, years	42,869	61 ± 13	10,313	70 ± 11
BMI, kg/m^2	38,311	31.8 ± 6.6	8932	30.5 ± 5.8
SBP, mmHg	41,238	136 ± 16	10,021	135 ± 18
DBP, mmHg	41,237	80 ± 10	10,021	76 ± 10
Total cholesterol, mmol/L	38,376	4.7 ± 1.2	9235	4.4 ± 1.1
High density lipoprotein, mmol/L	31,909	1.2 ± 0.3	7364	1.1 ± 0.3
HbA_{1c}, mmol/L	37,999	74 ± 20	9076	71 ± 20
HbA_{1c}, %	37,999	8.9 ± 1.9	9076	8.7 ± 1.8
Diabetes duration, years	42,869	3.5 ± 3.6	10,313	4.2 ± 4.1
eGFR, mL/min	35,781	108 ± 47	8414	82 ± 37
Selected risk factors used in further analyses, *n* (%)				
Male sex	42,869	23,897 (56)	10,313	6965 (68)
Age >65 years	42,869	15,415 (36)	10,313	6795 (66)
Obesity: BMI ≥30 kg/m^2	38,311	21,493 (56)	8932	4332 (48)
Hypertension: SBP ≥140 mmHg or DBP ≥90 mmHg	41,238	18,743 (45)	10,021	4243 (42)
Dyslipidaemia: total cholesterol >6.2 mmol/L (>240 mg/dL)	38,376	3759 (10)	9235	535 (5.8)
Current smoking	42,402	7018 (17)	10,222	1591 (16)
Hyperglycaemia: HbA_{1c} (58 mmol/mol) (≥7.5%)	37,999	31,292 (82)	9076	6984 (77)
Diabetes duration ≥5 years	42,869	11,161 (26)	10,313	3403 (33)
CKD at least moderate: eGFR <60 mL/min	35,781	4521 (13)	8414	2594 (31)
Number of different cardiovascular medications, *n* (%)				
0		6438 (15)		109 (1.1)
1		8948 (21)		296 (2.9)
2		9317 (22)		811 (7.9)
3		8155 (19)		1631 (16)
4		5870 (14)		2664 (26)
5		2997 (7.0)		2805 (27)
≥6		1144 (2.7)		1997 (19)
Cardiovascular medications, *n* (%)				
Lipid-regulating drugs	42,869	28,288 (66)	10,313	8740 (85)
Hypertension and heart failure drugs	42,869	22,106 (52)	10,313	7813 (76)
Antiplatelets	42,869	12,891 (30)	10,313	7906 (77)
Diuretics	42,869	12,046 (28)	10,313	5291 (51)
Nitrates, calcium channel blockers, other anti-anginals	42,869	11,264 (26)	10,313	5835 (57)

(Continues)

TABLE 1 (Continued)

	People with type 2 diabetes without established CVD, *N* = 42,869 (81%)		People with type 2 diabetes with established CVD, *N* = 10,313 (19%)	
	n	**Mean ± SD or *n* (%)**	***n***	**Mean ± SD or *n* (%)**
Beta blockers	42,869	7529 (18)	10,313	5015 (49)
Anticoagulants and protamine	42,869	1558 (3.6)	10,313	1569 (15)
Positive inotropic drugs	42,869	1007 (2.3)	10,313	1311 (13)
Anti-arrhythmic drugs	42,869	857 (2.0)	10,313	543 (5.3)
Fibrinolytics	42,869	5 (<0.1)	10,313	1 (<0.1)
Sympathomimetics	42,869	2 (<0.1)	10,313	1 (<0.1)
First-line glucose-lowering treatment, *n* (%)				
Biguanides	42,869	33,433 (78)	10,313	7037 (68)
Sulphonylureas	42,869	7960 (19)	10,313	2776 (27)
Glitazones	42,869	292 (0.7)	10,313	74 (0.7)
Insulin	42,869	800 (1.9)	10,313	333 (3.2)
GLP-1RAs	42,869	11 (<0.1)	10,313	0
DPP-4 inhibitors	42,869	148 (0.3)	10,313	47 (0.5)
SGLT2is	42,869	9 (<0.1)	10,313	0
Glinides	42,869	60 (0.1)	10,313	14 (0.1)
α-glucosidase inhibitors	42,869	42 (0.1)	10,313	10 (0.1)
Oral combinations[a]	42,869	114 (0.3)	10,313	22 (0.2)
Second-line glucose-lowering treatment, *n* (%)				
Biguanides	42,869	6981 (16)	10,313	2264 (22)
Sulphonylureas	42,869	21,737 (51)	10,313	4966 (48)
Glitazones	42,869	5448 (13)	10,313	1023 (10)
Insulin	42,869	1827 (4.3)	10,313	784 (7.6)
GLP-1RAs	42,869	342 (0.8)	10,313	47 (0.5)
DPP-4 inhibitors	42,869	4281 (10)	10,313	838 (8.1)
SGLT2is	42,869	290 (0.7)	10,313	34 (0.3)
Glinides	42,869	307 (0.7)	10,313	90 (0.9)
α-glucosidase inhibitors	42,869	127 (0.3)	10,313	42 (0.4)
Oral combinations[b]	42,869	1529 (3.6)	10,313	225 (2.2)

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; *n*, number of individuals with data available; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

[a]Oral combinations containing DPP-4 inhibitors or glitazones.

[b]Oral combinations containing DPP-4 inhibitors, glitazones or SGLT2is.

an actual number of selected cardiovascular risk factors is shown in Figure 1, and for expanded MACE and all-cause mortality in Tables S7 and S8. Demographic and clinical characteristics were generally similar for people without cardiovascular disease and complete data (included in the analyses), and those with missing data (excluded from the analyses), except for hypertension and dyslipidaemia (higher among people with missing data) and diabetes duration ≥5 years (higher among people with complete data) (Table S9).

The risks of 3-point MACE, expanded MACE and all-cause mortality by selected risk factors are shown in Table 2 (using multiple imputation to account for missing data) and Table S10 (with missing data excluded). Compared with a reference HR of 1.0 for participants with established cardiovascular disease, chronic kidney disease (estimated

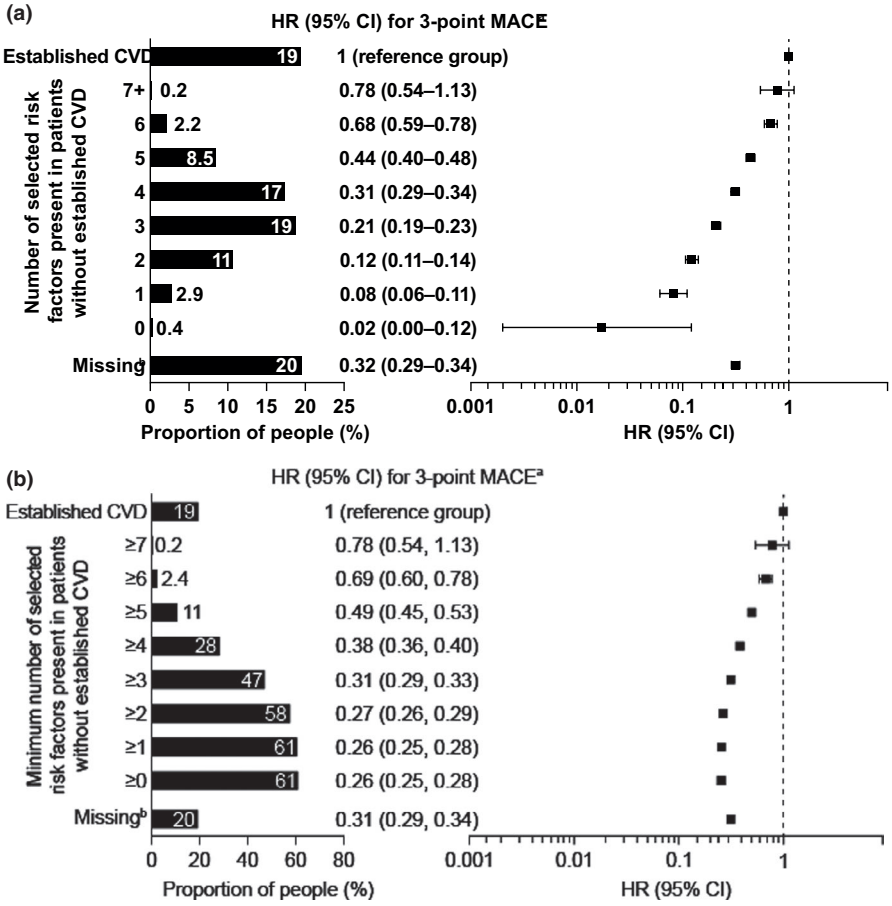

FIGURE 1 (a) Risk of 3-point MACE associated with the actual number of selected cardiovascular risk factors present; (b) Risk of 3-point MACE associated with the minimum number of selected cardiovascular risk factors present (patients with missing data were excluded).

[a]HR adjusted for calendar year of first prescription of second-line glucose-lowering therapy (index date). bPeople with missing data for one or more risk factors.

Risk calculated for people with non-missing covariates.

Abbreviations: CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events

glomerular filtration rate <60 ml/min) was the single selected risk factor associated with the highest risk of 3-point MACE and expanded MACE in people without established cardiovascular disease (HR 0.75, 95% CI 0.70, 0.81 and 0.59, 95% CI 0.56, 0.63, respectively) followed by older age (HR 0.53, 95% CI 0.51, 0.56 and 0.46, 95% CI 0.44, 0.48, respectively), longer diabetes duration (HR 0.34, 95% CI 0.32, 0.37 and 0.30, 95% CI 0.28, 0.31, respectively), dyslipidaemia (HR 0.32, 95% CI 0.29, 0.35 and 0.26, 95% CI 0.24, 0.29, respectively) and hypertension (HR 0.32, 95% CI 0.31, 0.34 and 0.28, 95% CI 0.27, 0.29, respectively) (Table 2). Chronic kidney disease was also the single selected risk factor associated with the highest all-cause mortality; the HR of 1.12 (95% CI 1.07, 1.18) indicates that risk of death in people with type 2 diabetes and chronic kidney disease is potentially greater than for those with cardiovascular disease (Table 2). The second highest risk factor for death was older age (crude HR 0.78, 95% CI 0.75, 0.81). Exclusion rather than imputation of missing data had little effect on the three main adverse endpoints (Table S10, Figure 2). However, the association with adverse outcomes in people with chronic kidney disease was somewhat weaker for 3-point MACE and all-cause mortality.

For combinations of two selected risk factors associated with a risk of 3-point MACE in people without versus with cardiovascular disease, chronic kidney disease plus one other risk factor gave HRs of approximately 0.8, comparable to the reference risk of 1.0 in the cardiovascular disease group when missing data were excluded (Figure 2). This was similar for all-cause mortality (data not shown). Other combinations of two risk factors, such as obesity plus hyperglycaemia or obesity plus male sex, were associated with the lowest risk of adverse endpoints (data not shown).

For risk factors other than chronic kidney disease in people without cardiovascular disease, the double combination of risk factors associated with the highest HR for 3-point MACE compared with participants with cardiovascular disease (reference HR 1.0), were older age and dyslipidaemia (crude HR 0.70, 95% CI 0.59, 0.83), and older age and smoking (crude HR 0.55, 95% CI 0.47, 0.65) (data not shown). Similarly, in the absence of chronic kidney disease, the double combinations associated with the highest HR for all-cause mortality were older age plus smoking (crude HR 0.88, 95% CI 0.80, 0.98), and older age plus dyslipidaemia (crude HR 0.87, 95% CI 0.76, 0.99) (data not shown). In the absence of chronic kidney disease, the triple risk factor combinations associated with the highest HR for 3-point MACE and all-cause mortality were older age, dyslipidaemia, plus smoking; and older age, male sex, plus dyslipidaemia (data not shown).

TABLE 2 Risk of endpoints associated with selected risk factors after multiple imputation to account for missing data

	3-point MACE	Expanded MACE	All-cause mortality
	HR (95% CI)	HR (95% CI)	HR (95% CI)
With established CVD	1 (reference group)	1 (reference group)	1 (reference group)
Without established CVD: selected risk factors			
CKD at least moderate: eGFR <60 mL/min	0.75 (0.70, 0.81)	0.59 (0.56, 0.63)	1.12 (1.07, 1.18)
Older age: >65 years[a]	0.53 (0.51, 0.56)	0.46 (0.44, 0.48)	0.78 (0.75, 0.81)
Longer diabetes duration: ≥5 years[a]	0.34 (0.32, 0.37)	0.30 (0.28, 0.31)	0.43 (0.41, 0.46)
Dyslipidaemia: total cholesterol >6.2 mmol/L (> 240 mg/dL)	0.32 (0.29, 0.35)	0.26 (0.24, 0.29)	0.33 (0.30, 0.36)
Hypertension: SBP ≥140 mmHg or DBP ≥90 mmHg	0.32 (0.31, 0.34)	0.28 (0.27, 0.29)	0.39 (0.37, 0.40)
Current smoking	0.31 (0.28, 0.33)	0.25 (0.23, 0.26)	0.37 (0.35, 0.39)
Male sex[a]	0.28 (0.27, 0.30)	0.24 (0.23, 0.26)	0.34 (0.33, 0.36)
Hyperglycaemia: HbA_{1c} ≥ 7.5% (58 mmol/mol)	0.27 (0.26, 0.29)	0.24 (0.23, 0.25)	0.34 (0.33, 0.36)
Obesity: BMI ≥30 kg/m^2	0.25 (0.23, 0.26)	0.23 (0.22, 0.24)	0.28 (0.27, 0.30)

Note: HRs and associated CIs calculated via multiple imputation using fully conditional specification. Twenty multiply imputed datasets were analysed for each of the nine selected risk factors.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; SBP, systolic blood pressure.

[a]No data were missing so no imputation was done.

4 | DISCUSSION

A large proportion of people with type 2 diabetes without established cardiovascular disease were at high cardiovascular risk and a large proportion (17%) died over the 6.4 years of follow-up. When missing data were accounted for by multiple imputation, the risk of death in people with chronic kidney disease was similar or even greater than for those with established cardiovascular disease (mean follow-up 4.8 years). Additionally, risk factors such as obesity, hypertension and dyslipidaemia were more common in those without cardiovascular disease than those with cardiovascular disease, possibly due to a greater focus on prevention in people with previous events. These findings highlight the need to control cardiovascular risk factors early in the course of type 2 diabetes in all individuals, and emphasise the need to identify people who may particularly benefit from treatments known to reduce cardiovascular risk.

Even relatively early in the treatment course of type 2 diabetes, approximately one-fifth of people had established cardiovascular disease. Many of these were receiving at least three cardiovascular medications, almost half were hypertensive and half had obesity. Furthermore, mean HbA_{1c} levels were 74 mmol/mol [8.9%] at second-line glucose-lowering therapy initiation, indicating delayed treatment intensification. Current guidelines recommend modifying treatment regularly (3–6 months) if HbA_{1c} remains above target.[3,14] Sulphonylureas were the most-prescribed second-line treatment, whereas GLP-1RA or SGLT2i use was low. As the study retrieved records from 2001 to 2016, infrequent use of newer agents is not unexpected. Were the study to be extended up to the present, we might anticipate an increase in the use of GLP-1RAs and SGLT2is with proven cardiovascular benefit as second-line therapy, in line with recent recommendations.[3–5] The current study showed high post-index rates of 3-point MACE, expanded MACE, and all-cause mortality (50–93 events per 1000 person-years) in people with cardiovascular disease, demonstrating the need for glucose-lowering treatments that reduce cardiovascular risk and approaches to reduce cardiovascular risk factors, such as hypertension, dyslipidaemia and obesity.

Assessment of cardiovascular disease risk according to the actual number of risk factors in people without cardiovascular disease showed that risk increased with the number of risk factors present, with people having seven or more risk factors having a risk of 3-point MACE and all-cause mortality similar to that of the reference group. The risk of cardiovascular disease in people without previous cardiovascular disease was also assessed according to the presence of the minimum number of selected cardiovascular risk factors present and showed a similar pattern. Some single risk factors were associated with

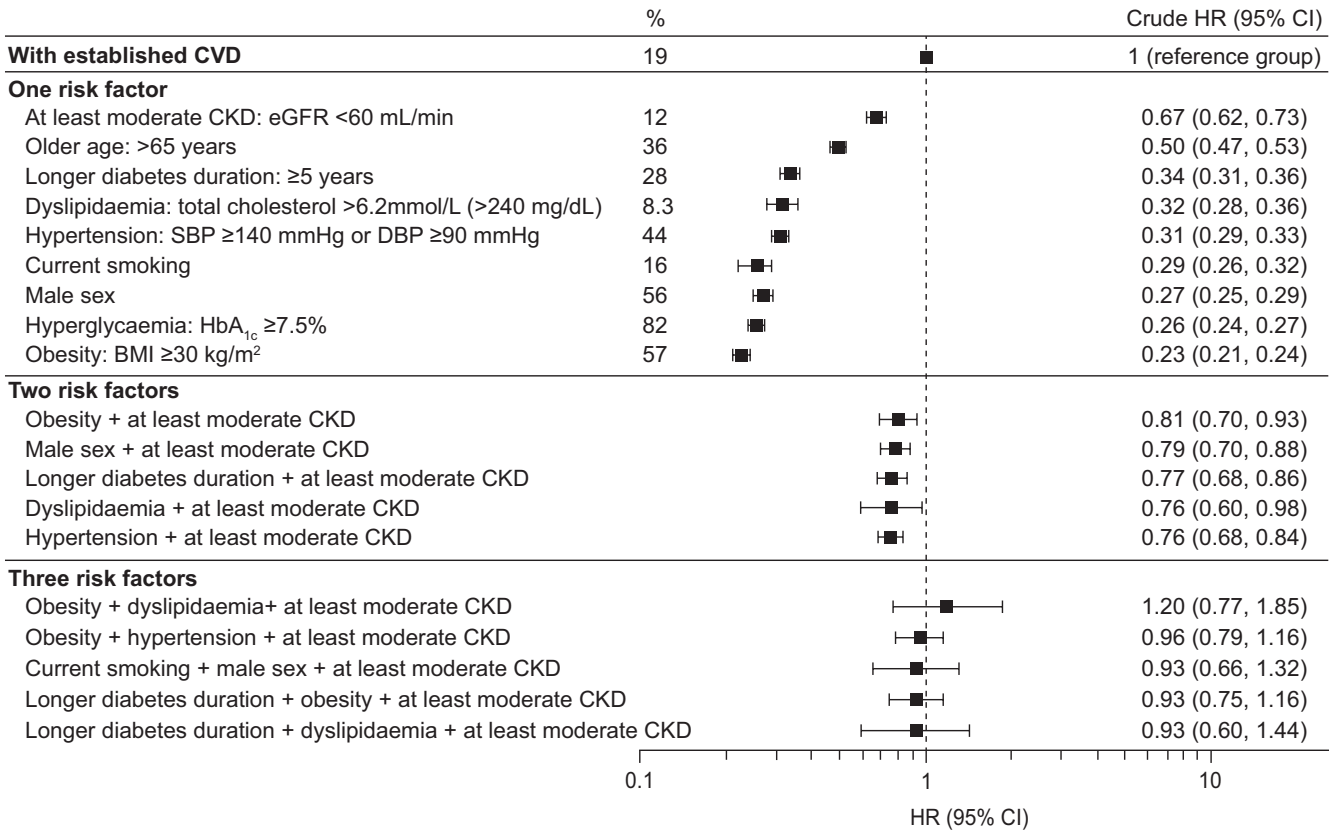

FIGURE 2 Risk of 3-point MACE by selected risk factors and combinations of selected risk factors associated with the highest risk (top 5) among people with type 2 diabetes without established CVD (patients with missing data were excluded).

People with missing data for one or more risk factors were excluded. HR adjusted for calendar year of first prescription of second-line glucose-lowering therapy (index date).

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HR, hazard ratio; MACE, major adverse cardiovascular events; SBP, systolic blood pressure

substantially higher risk of adverse outcomes than others. Chronic kidney disease (estimated glomerular filtration rate <60 mL/min) was the single selected risk factor associated with the highest risk of adverse outcomes, and was common with or without established cardiovascular disease (31% and 13%, respectively). These findings are in line with another Clinical Practice Research Datalink analysis showing that nephropathy and other microvascular diseases significantly affect future cardiovascular disease risk in people with type 2 diabetes in a cumulative manner.[20] International recommendations state that for individuals with type 2 diabetes and chronic kidney disease, with or without cardiovascular disease, the use of an SGLT2i shown to reduce the progression of chronic kidney disease should be considered.[3] If SGLT2is are contraindicated or not preferred, a GLP-1RA shown to reduce the progression of chronic kidney disease should be considered.

For people without chronic kidney disease, combinations of older age, dyslipidaemia, smoking and male sex appeared to be associated with a risk of MACE and all-cause mortality nearing that of those with cardiovascular disease. Strategies for smoking cessation and intensification of lipid-lowering drugs should be encouraged in these high-risk populations. However, it should be noted that patients with established cardiovascular disease were on average 9 years older than those without. Given that the risk of stroke doubles each decade after the age of 55,[21,22] age would have had a potentially disproportionate (and unavoidable) effect on the event rates in people with established cardiovascular disease.

A strength of the present study is that it provides a comprehensive representation of the cardiovascular risk profile of people with type 2 diabetes initiating second-line glucose-lowering treatment who are likely to be largely managed in primary care. Around the time of the analysis, Clinical Practice Research Datalink GOLD included approximately 4.4 million currently registered individuals, around 6.9% of the UK population, who are broadly representative of the UK general population in terms of age, sex and ethnicity.[14]

A potentially major limitation is that an appreciable amount of data for selected risk factors were missing, particularly for measurements of total cholesterol, body mass index, HbA_{1c} and estimated glomerular filtration rate, which are known to be predictors of poor outcomes in cardiovascular and other diseases. Although individuals with missing data were excluded from the association analyses, a sensitivity analysis using multiple imputation suggested that missing data did not appear to greatly affect the overall findings. In the UK, the Quality and Outcomes Framework that was initiated in 2004 has greatly reduced the amount of missing data in general practice databases and, had we only included patients from 2004 onwards, it is likely that this would have reduced the amount of missing data.

Of note, the Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease equations are increasingly preferred to the Cockcroft–Gault formula used here to calculate estimated glomerular filtration,[23] but the former is not widely used in the UK (or at least was not during the timeframe of data collection). It includes the variable of race, which was sparsely recorded in the current dataset.

Some risk factors may have been measured more accurately than others and this may have impacted the findings. The most frequent event in the established cardiovascular disease group was hospitalisation for heart failure, which is consistent with other observations.[24] Heart failure may occur due to causes other than cardiovascular disease,[25] but people with heart failure were included in the established cardiovascular disease group to avoid overestimation of overall cardiovascular disease risk in those without cardiovascular disease. Although the definition of established cardiovascular disease in this study was based on people who had experienced a cardiovascular event, people without a previous cardiovascular event can also have increased cardiovascular risk. Some misclassification may have occurred due to undiagnosed cardiovascular disease event in the group without established cardiovascular disease. Although total cholesterol was chosen as a risk factor because it is routinely measured in UK primary care, many guidelines and cardiovascular risk trials focus on low-density lipoprotein cholesterol, and this may have provided a better risk assessment.

In total, 42,805 of the 53,182 participants identified were included in the analysis. The aim was not to examine causal relationships, but rather which risk factors and risk factor combinations were most strongly associated with cardiovascular disease on its own. The selected risk factors were chosen based on their known causal relationship with cardiovascular disease. We acknowledge that chance associations are likely, which is a limitation of analyses of the type reported here.

Approximately 70% of participants were taking sulfonylureas either as first- or second-line treatment. Since the time the data were collected, sulfonylureas have been associated with an increased risk of cardiovascular events and mortality.[26] However, the randomised CAROLINA trial showed no increase in cardiovascular risk with the sulfonylurea glimepiride compared with the dipeptidyl peptidase-4 inhibitor linagliptin.[27] Dipeptidyl peptidase-4 inhibitors are considered neutral with respect to cardiovascular effect.[3–5] Current recommendations advocate the use of a GLP-1RA or SGLT2i with proven cardiovascular benefit in patients with type 2 diabetes who are at increased cardiovascular risk.[3–5] In the current analysis, the time that participants remained on their prescribed second-line glucose-lowering therapy was not considered.

Although the study required a minimum of 1 year of data, the established cardiovascular disease definition covered any record of a cardiovascular disease-related Read Code in the database prior to the index date and therefore minimised bias in terms of overestimating risk assessment of the risk factor only group. Most participants had long-term data available, but there remains the possibility of overestimation of risk for those with a short disease history.

In conclusion, we found a high prevalence of cardiovascular disease among people with type 2 diabetes relatively early during their treatment course, and there is a high level of unmet need with regard to risk factor management. We identified risk factors (chronic kidney disease, older age, smoking and dyslipidaemia) that may help stratify those with type 2 diabetes without cardiovascular disease who are at particularly high risk of cardiovascular events, so that efforts to control modifiable risk factors and glucose-lowering therapies that reduce cardiovascular risk can be targeted appropriately. Modifiable cardiovascular risk factors should be controlled early in all individuals with type 2 diabetes (as well as in all individuals with cardiovascular disease).

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CONFLICTS OF INTEREST

KK has served as a consultant for and received speaker fees from Amgen, AstraZeneca, Bayer, Berlin-Chemie AG/Menarini Group, Boehringer Ingelheim, Eli Lilly,

Merck Sharp & Dohme, NAPP, Novartis, Novo Nordisk, Roche, Sanofi-Aventis and Servier; has served on an advisory board for AstraZeneca, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis; and has received grants in support of investigator and investigator-initiated trials from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis and Servier. CLH, LLNH and JSP are employees and shareholders of Novo Nordisk A/S, Denmark. EM is a shareholder of Novo Nordisk A/S, Denmark and was an employee at the time of the study. RBN is an employee of Novo Nordisk A/S, Denmark. SCB received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi-Aventis; has received funding for the development of educational programs from Medscape; has provided expert advice for All-Wales Medicines Strategy Group and National Institute for Health and Care Excellence UK; and is a shareholder of Glycosmedia.

AUTHOR CONTRIBUTIONS

LLNH and RBN were involved in the design, analysis, interpretation and writing of the manuscript. KK, CLH, EM, RBN, JSP and SCB were involved in the design, interpretation and writing of the manuscript. All authors interpreted the data and participated in writing the article, with the support of medical writing services provided by the funder. The medical writer developed the article under the guidance of the authors. All authors read and approved the submitted version of the article. LLNH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

STATEMENT OF ASSISTANCE

All authors were involved in designing the study. Data were analysed by the sponsor (Novo Nordisk A/S, Denmark). The manuscript was drafted by the authors with medical writing and editorial support, funded by the sponsor. All authors had access to the study results, actively contributed to all drafts of the manuscript and made the decision to submit the manuscript for publication. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the study to the protocol.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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