Received: 13 December 2021 | Revised: 7 March 2022 | Accepted: 20 March 2022

DOI: 10.1111/dom.14698

ORIGINAL ARTICLE

WILEY

Cost of healthcare utilization associated with incident cardiovascular and renal disease in individuals with type 2 diabetes: A multinational, observational study across 12 countries

Anna Norhammar MD[1,2] | Johan Bodegard MD[3] | Jan W. Eriksson MD[4] | Hermann Haller MD[5] | Gerard C. M. Linssen MD[6] | Amitava Banerjee MD[7,8] | Avraham Karasik MD[9] | Pavlos Mamouris PhD[10] | Navdeep Tangri MD[11] | Tiago Taveira-Gomes MD[12] | Aldo P. Maggioni MD[13,14] | Manuel Botana MD[15] | Marcus Thuresson PhD[16] | Suguru Okami PhD[17] | Toshitaka Yajima MD[17] | Takashi Kadowaki MD[18] | Kåre I. Birkeland MD[19] | CaReMe Cardiorenal Investigators

[1]Cardiology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden

[2]Capio St Görans Hospital, Stockholm, Sweden

[3]AstraZeneca, Oslo, Norway

[4]Department of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, Uppsala, Sweden

[5]Division of Nephrology, Hannover Medical School, Hannover, Germany

[6]Department of Cardiology, Hospital Group Twente, Almelo and Hengelo, The Netherlands

[7]Institute of Health Informatics, University College London, London, UK

[8]Department of Cardiology, University College London Hospitals, London, UK

[9]Maccabi Institute for Research and Innovation, Maccabi Healthcare Services, Tel Aviv, Israel

[10]Academic Center for General Practice, KU Leuven, Leuven, Belgium

[11]Department of Medicine and Community Health Sciences, University of Manitoba, Winnipeg, Canada

[12]Department of Community Medicine, Information and Decision in Health, Faculty of Medicine, University of Porto, Porto, Portugal

[13]ANMCO Research Centre, Florence, Italy

[14]Maria Cecilia Hospital, GVM Care and Research, Cotignola, Italy

Abstract

Aim: To examine how the development of cardiovascular and renal disease (CVRD) translates to hospital healthcare costs in individuals with type 2 diabetes (T2D) initially free from CVRD.

Methods: Data were obtained from the digital healthcare systems of 12 nations using a prespecified protocol. A fixed country-specific index date of 1 January was chosen to secure sufficient cohort disease history and maximal follow-up, varying between each nation from 2006 to 2017. At index, all individuals were free from any diagnoses of CVRD (including heart failure [HF], chronic kidney disease [CKD], coronary ischaemic disease, stroke, myocardial infarction [MI], or peripheral artery disease [PAD]). Outcomes during follow-up were hospital visits for CKD, HF, MI, stroke, and PAD. Hospital healthcare costs obtained from six countries, representing 68% of the total study population, were cumulatively summarized for CVRD events occurring during follow-up.

Results: In total, 1.2 million CVRD-free individuals with T2D were identified and followed for 4.5 years (mean), that is, 4.9 million patient-years. The proportion of individuals indexed before 2010 was 18% (n = 207 137); 2010-2015, 31% (361 175); and after 2015, 52% (609 095). Overall, 184 420 (15.7%) developed CVRD, of which cardiorenal disease was most frequently the first disease to develop (59.7%), consisting of 23.0% HF and 36.7% CKD, and more common than stroke (16.9%), MI (13.7%), and PAD (9.7%). The total cumulative cost for CVRD was US$1

[15]Endocrinology Service, Lucus Augusti University Hospital, Lugo, Spain

[16]Statisticon AB, Uppsala, Sweden

[17]AstraZeneca, Osaka, Japan

[18]Tranomon Hospital, Tokyo, Japan

[19]Department of Transplantation Medicine, Oslo University Hospital and University of Oslo, Oslo, Norway

Correspondence
Anna Norhammar, MD, Cardiology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden.
Email: anna.norhammar@ki.se

Funding information
This work was sponsored by AstraZeneca.

billion, of which 59.0% was attributed to cardiorenal disease, 3-, 5-, and 6-fold times greater than the costs for stroke, MI, and PAD, respectively.

Conclusion: Across all nations, HF or CKD was the most frequent CVRD manifestation to develop in a low-risk population with T2D, accounting for the highest proportion of hospital healthcare costs. These novel findings highlight the importance of cardiorenal awareness when planning healthcare.

KEYWORDS
cardiovascular disease, diabetic nephropathy, health economics, heart failure, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes affects almost 540 million individuals worldwide,[1] who are known to be burdened with co-morbidities like chronic kidney disease (CKD), heart failure (HF), coronary ischaemic disease, stroke, and peripheral artery disease (PAD) in addition to diabetes-related microvascular complications.[2,3] The majority (66%-72%) of the contemporary population with type 2 diabetes does not have a history of cardiovascular and renal disease (CVRD).[2,4,5] However, they are still considered to be at a high risk of cardiovascular disease according to guidelines and, therefore, require primary preventive risk management.[6-8] While atherosclerotic disease prevention is imperative and successfully managed today, individuals with type 2 diabetes still experience severe cardiorenal complications including HF and CKD, suggesting that a residual risk still persists and/or that there is a temporal change in disease burden.[2,4,9-11]

In order to develop health policy that directs resources to where the humanistic and societal burdens of such type 2 diabetes-related complications are greatest, there is a need to understand what forms of CVRD are most frequently the first to develop in a previously unaffected, low-risk population and which forms reoccur most often thereafter. In type 2 diabetes, incident HF and CKD reflects both an unmet clinical need[2] and a primary preventive treatment target for novel glucose-lowering drugs, particularly sodium-glucose co-transporter-2 inhibitors (SGLT2is). SGLT2is have, in both clinical trials[12-17] and a comparative effectiveness study,[18] been shown to reduce the risks of incident cardiorenal disease, HF, or CKD in type 2 diabetes and improved outcomes in patients with HF or CKD with or without type 2 diabetes.[19-22] Hence, the holistic cardiorenal disease definition is important to better understand the interchangeable relationship between HF and CKD,[23,24] improve treatment strategies,[8] and reduce the burden on healthcare providers.[25]

The aim of this study was to expand upon that research, detailing the incidence of CVRD in additional countries across North America, Europe, and Asia in a contemporary population with type 2 diabetes, initially free from CVRD. Additionally, in a multinational, real-world, clinical setting, this study aimed to determine the cost associated with such CVRD-related healthcare utilization.

2 | MATERIALS AND METHODS

The CArdioREnal and MEtabolic disease (CaReMe) cardiorenal study is a multinational, observational, descriptive study that utilized the unique features of available healthcare registries and the corresponding healthcare systems' secondary data from 12 countries across North America, Asia, and Europe: Belgium, Canada, England, Germany, Israel, Italy, Japan, The Netherlands, Norway, Portugal, Spain, and Sweden (Figure 1; supporting information, pages 4-11). A heat map describing the coverage of the registries and the availability of data is illustrated in Figure S1. A single prespecified protocol was used to collect data in each participating country. Only pseudo-anonymized patient data were collected, and thus there was not any direct patient or public involvement in the design, conduct, reporting, and dissemination of this study.

2.1 | Study population

All individuals with type 2 diabetes and no record of any CVRD (Table S1) defined by signs and symptoms defined as HF, CKD (codes for chronic, acute, unspecified hypertensive, or diabetic kidney disease), stroke, transitory cerebrovascular ischaemic attack, myocardial infarction, unstable angina pectoris, angina pectoris, treatment with nitrates, coronary revascularization, atrial fibrillation, PAD, peripheral artery revascularization, and intermittent claudication were indexed (baseline) on 1 January in the year that their respective country of residence was entered into the study, with index years ranging from 2006 to 2017 (Table S2). Each country had its own index year to adapt to differences in structure between the registries of each participating nation; and to ensure, at minimum, 1 year of patient healthcare history while optimizing the length of follow-up and, subsequently, allowing for a sufficient number of CVRD events to occur in those low-risk individuals.

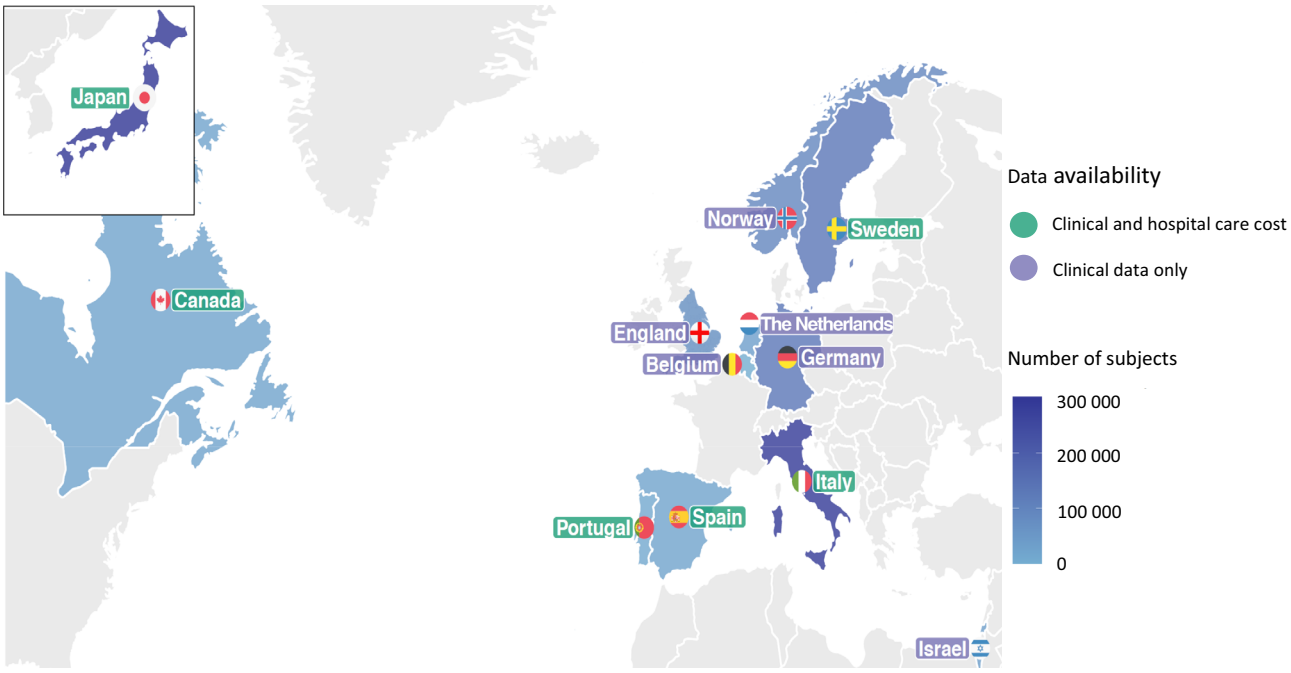

FIGURE 1 Countries and distribution of 1.2 million subjects with type 2 diabetes initially free from cardiovascular and renal disease

2.2 | CVRD outcomes

2.2.1 | Clinical outcomes

The CVRD outcome was defined by the following diseases or events: HF (including hypertensive HF), kidney disease (including diabetic nephropathy, acute kidney failure, CKD, unspecified kidney disease, diabetic kidney disease, and dialysis), stroke (including ischaemic and haemorrhagic stroke), myocardial infarction, PAD, peripheral artery revascularization, and intermittent claudication (Table S3).[2] In all countries, the first inpatient or outpatient diagnosis of any of the diseases or events listed above, registered between index (baseline) and the end of follow-up or death, represented the first CVRD outcome to occur. The presence of either HF or CKD as a first diagnosis can be summarized as cardiorenal disease,[8] derived from the well-defined cardiorenal syndrome.[23,26,27] Thus cardiorenal disease was described as a separate entity to the broader CVRD outcome. Additionally, HF and CKD were described, separately, as their own entities. If the first hospitalization was because of more than one of the diseases or events listed above, the diagnosis with the greatest importance was defined as the first form of CVRD to develop (i.e. the main [primary] diagnosis was considered more important than any secondary diagnoses).

2.2.2 | Hospital healthcare costs for CVRD outcomes

Hospital healthcare costs were extracted from data containing the actual cost of each individual visit as charged by the healthcare provider (e.g. the cost reflects the true reimbursement claim to the local payer). These hospital healthcare costs were cumulatively summarized from index through to the end of follow-up and, importantly, include costs for all first and all repeated events associated with the CVRD outcome. Hospital healthcare cost data were available in six of the 12 participating nations: Canada, Italy, Japan, Portugal, Spain, and Sweden.

2.3 | Statistical analysis

This study is descriptive and no formal hypothesis was tested and there were no comparisons between countries. All statistical analyses were performed in each country separately according to a prespecified statistical analysis plan. Baseline characteristics were described using standard statistical measures such as mean and standard deviation for numerical variables, and frequencies and percentages for categorical variables. The CVRD-free population with type 2 diabetes included in this study is described separately by country and overall, where the overall summary is weighted according to the number of individuals from each country.

2.3.1 | Manifestation of clinical outcomes

The first incidence of CVRD among the initially CVRD-free individuals with type 2 diabetes was analysed, accounting for competing risk of other events and death. Those who did not develop CVRD during the study period were censored at the end of follow-up, or when leaving the database. The results are presented separately by

TABLE 1 Baseline characteristics of each cohort with type 2 diabetes, initially free of cardiovascular and renal disease, from 12 countries

	All CVRD-free T2D patients	Belgium	Canada	England	Germany	Israel	Italy	Japan	The Netherlands	Norway	Portugal	Spain	Sweden
Index year	n/a	2006	2009	2010	2014	2007	2017	2016	2012	2010	2017	2013	2007
Study duration, y	n/a	10	9	9	4	12	2	3	6	6	3	7	10
Number of patients	1 177 407	3224	27 164	66 412	136 635	39 011	295 940	299 965	36 903	94 683	13 190	26 542	137 738
Total follow-up time, patient-years	4 857 173	27 305	250 174	511 372	514 213	380 399	575 311	768 430	169 754	477 442	31 545	90 242	1 060 986
Age, y (SD)	65 (13)	61 (14)	55 (14)	60 (13)	66 (12)	58 (11)	67 (12)	68 (12)	67 (12)	61 (15)	64 (NA)	67 (12)	64 (12)
Females, *n* (%)	543 645 (46)	1700 (53)	14 533 (54)	30 950 (47)	61 203 (45)	18 715 (48)	144 517 (49)	124 306 (41)	18 340 (50)	46 623 (49)	5564 (42)	12 688 (48)	64 506 (47)
CVD prevention, *n* (%)	816 711 (69)	1643 (51)	15 868 (58)	56 133 (85)	111 496 (82)	30 739 (79)	180 853 (61)	182 275 (61)	33 003 (89)	69 007 (73)	7480 (57)	21 822 (82)	106 392 (77)
Low-dose aspirin, *n* (%)	277 376 (24)	706 (22)	2483 (9)	23 514 (35)	7778 (6)	18 082 (46)	110 735 (37)	32 169 (11)	7595 (21)	30 050 (32)	1085 (8)	2470 (9)	40 709 (30)
Statins, *n* (%)	514 860 (44)	1052 (33)	8291 (31)	47 176 (71)	44 447 (33)	24 121 (62)	142 156 (48)	101 924 (34)	24 760 (67)	45 123 (48)	5057 (38)	11 964 (45)	58 789 (43)
Antihypertensives (%)	525 149 (45)	1622 (50)	13 205 (49)	39 192 (59)	94 501 (69)	20 353 (52)	16 855 (6)	149 173 (50)	24 107 (65)	56 539 (60)	5837 (44)	17 738 (67)	86 027 (62)
ACE inhibitors (%)	280 849 (24)	830 (26)	6440 (24)	27 196 (41)	59 644 (44)	15 764 (40)	85 929 (29)	14 736 (5)	n/a	17 377 (18)	2857 (22)	8252 (31)	41 824 (30)
ARBs, *n* (%)	344 665 (29)	406 (13)	4462 (16)	9167 (14)	33 264 (24)	3455 (9)	119 022 (40)	104 459 (35)	n/a	32 220 (34)	838 (6)	7858 (30)	29 514 (21)
Beta blockers, *n* (%)	262 274 (22)	1089 (34)	2581 (10)	8161 (12)	54 315 (40)	9261 (24)	78 571 (27)	27 536 (9)	13 231 (36)	23 284 (25)	1306 (10)	3992 (15)	38 947 (28)
LOOP diuretics, *n* (%)	125 851 (11)	183 (6)	730 (3)	3514 (5)	14 587 (11)	683 (2)	45 926 (16)	25 020 (8)	3854 (10)	9002 (10)	531 (4)	4300 (16)	17 521 (13)
MRA, *n* (%)	22 239 (2)	118 (4)	187 (1)	418 (1)	1997 (1)	248 (1)	6546 (2)	4128 (1)	1109 (3)	1375 (1)	121 (1)	1380 (5)	4612 (3)
Metformin, n (%)	725 526 (62)	1333 (41)	11 771 (43)	54 180 (82)	98 046 (72)	22 636 (58)	220 787 (75)	88 841 (30)	29 000 (79)	70 813 (75)	6695 (51)	17 770 (67)	103 654 (75)
Sulphonylurea, *n* (%)	303 633 (26)	917 (28)	3943 (15)	23 530 (35)	24 648 (18)	10 580 (27)	59 157 (20)	75 970 (25)	13 950 (38)	33 535 (35)	1542 (12)	8546 (32)	47 315 (34)
DPP-4i, *n* (%)	212 048 (18)	0 (0)	69 (0)	2229 (3)	29 130 (21)	0 (0)	14 076 (5)	154 933 (52)	1917 (5)	1279 (1)	2337 (18)	6078 (23)	0 (0)
SGLT2i, *n* (%)	10 374 (1)	0 (0)	0 (0)	0 (0)	1122 (1)	0 (0)	181 (0)	8786 (3)	0 (0)	0 (0)	285 (2)	0 (0)	0 (0)
GLP-1RA, *n* (%)	16 467 (1)	0 (0)	0 (0)	977 (1)	3037 (2)	0 (0)	5098 (2)	6000 (2)	485 (1)	360 (0)	136 (1)	374 (1)	0 (0)
Meglitinides, *n* (%)	70 696 (6)	217 (7)	201 (1)	467 (1)	3353 (2)	1871 (5)	36 707 (12)	17 808 (6)	39 (0)	249 (0)	44 (0)	1082 (4)	8658 (6)
Thiazolidinediones, *n* (%)	58 133 (5)	145 (4)	707 (3)	9102 (14)	215 (0)	2416 (6)	6405 (2)	25 566 (9)	1032 (3)	4074 (4)	55 (0)	222 (1)	8194 (6)
Acarbose, *n* (%)	73 521 (6)	3 (0)	46 (0)	202 (0)	1288 (1)	2162 (6)	12 378 (4)	54 354 (18)	45 (0)	642 (1)	95 (1)	316 (1)	1990 (1)
Insulin, *n* (%)	225 769 (19)	575 (18)	607 (2)	8399 (13)	29 648 (22)	3561 (9)	31 724 (11)	80 267 (27)	10 220 (28)	14 986 (16)	715 (5)	5158 (19)	39 909 (29)

All numbers in parenthesis are percentage if not stated otherwise.

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CVD, cardiovascular disease; CVRD, cardiovascular and renal disease; DPP-4i, dipeptidyl-peptidase-4 inhibitors; GLP-1RA, glucagon-like peptide-1 receptor agonist; LOOP, Loop diuretics; MRA, Mineralocorticoid receptor antagonist; n/a, not applicable; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitors; T2D, type 2 diabetes.

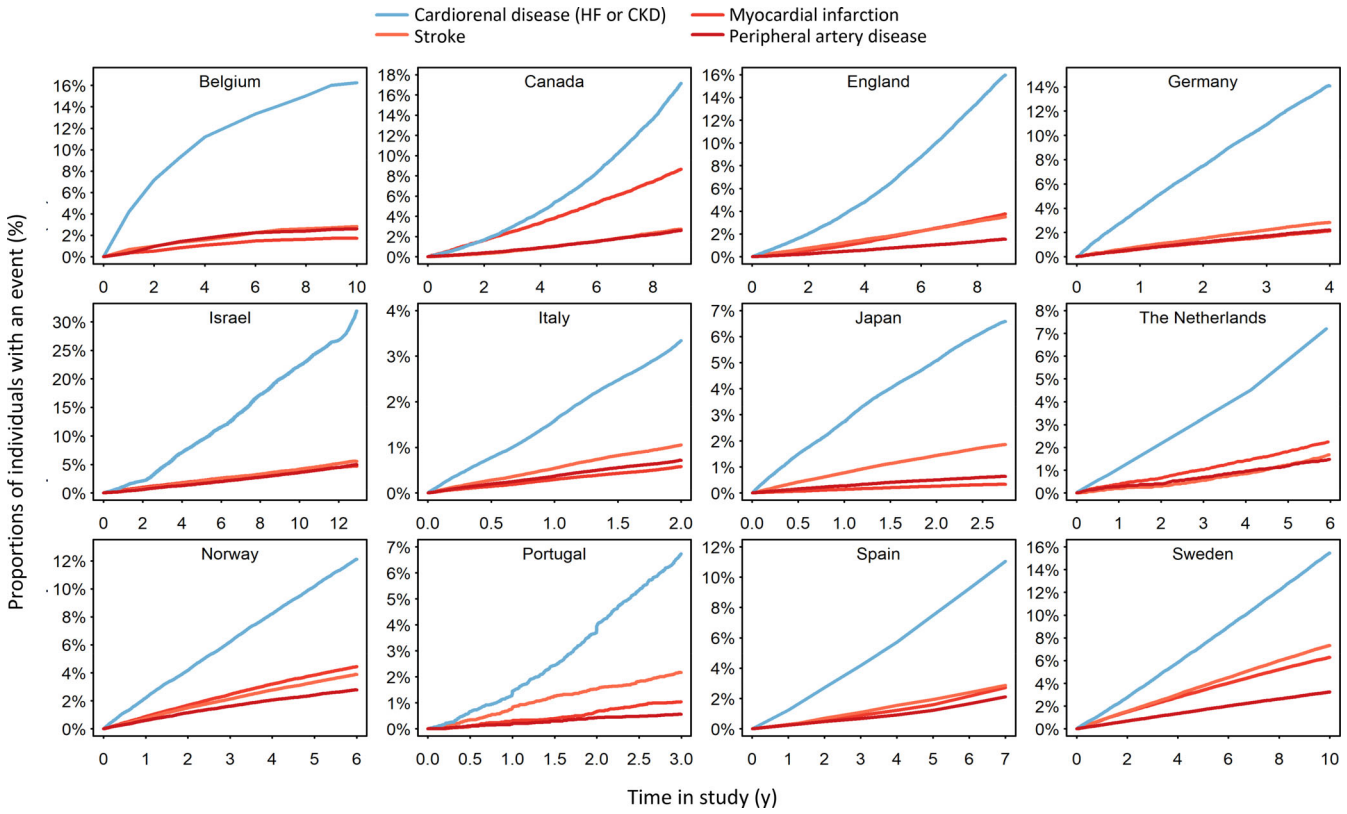

FIGURE 2 Cumulative incidence of cardiovascular and renal disease (184 420 [15.7%]) in 1 177 407 individuals with type 2 diabetes, initially free from any prior cardiovascular and renal disease, from 12 countries. CKD, chronic kidney disease; HF, heart failure

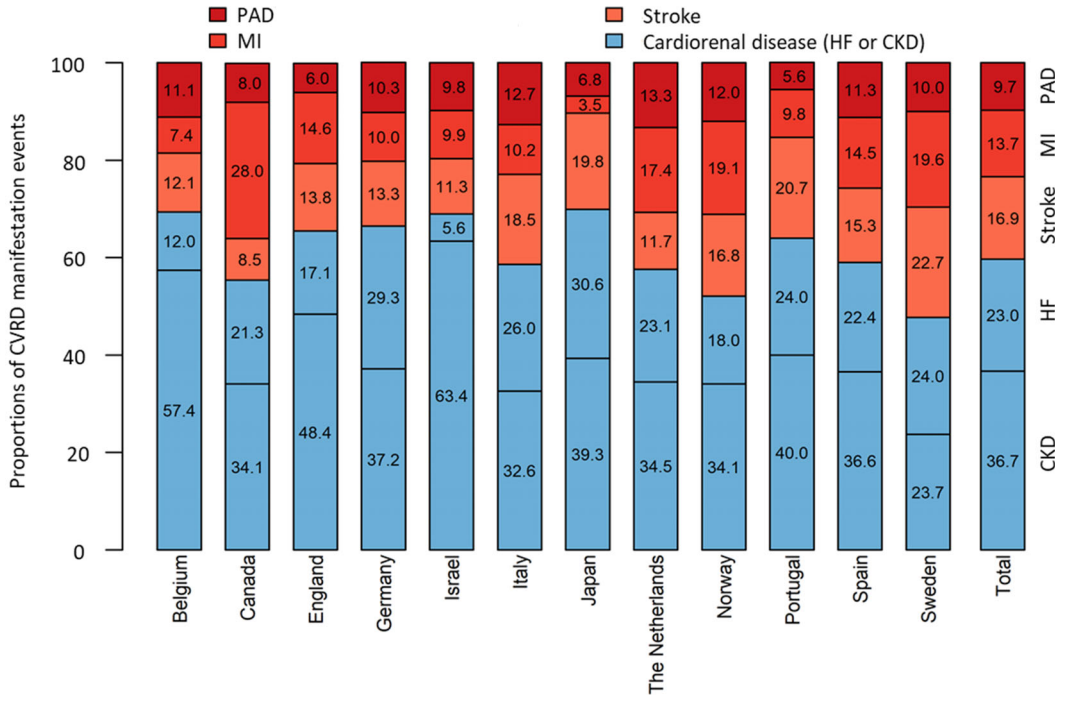

FIGURE 3 Detailed proportions of all incident cardiovascular and renal disease (CVRD) manifestations (184 420 [15.7%]) in 1 177 407 individuals with type 2 diabetes, initially free from any prior CVRD, across 12 countries. CKD, chronic kidney disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease

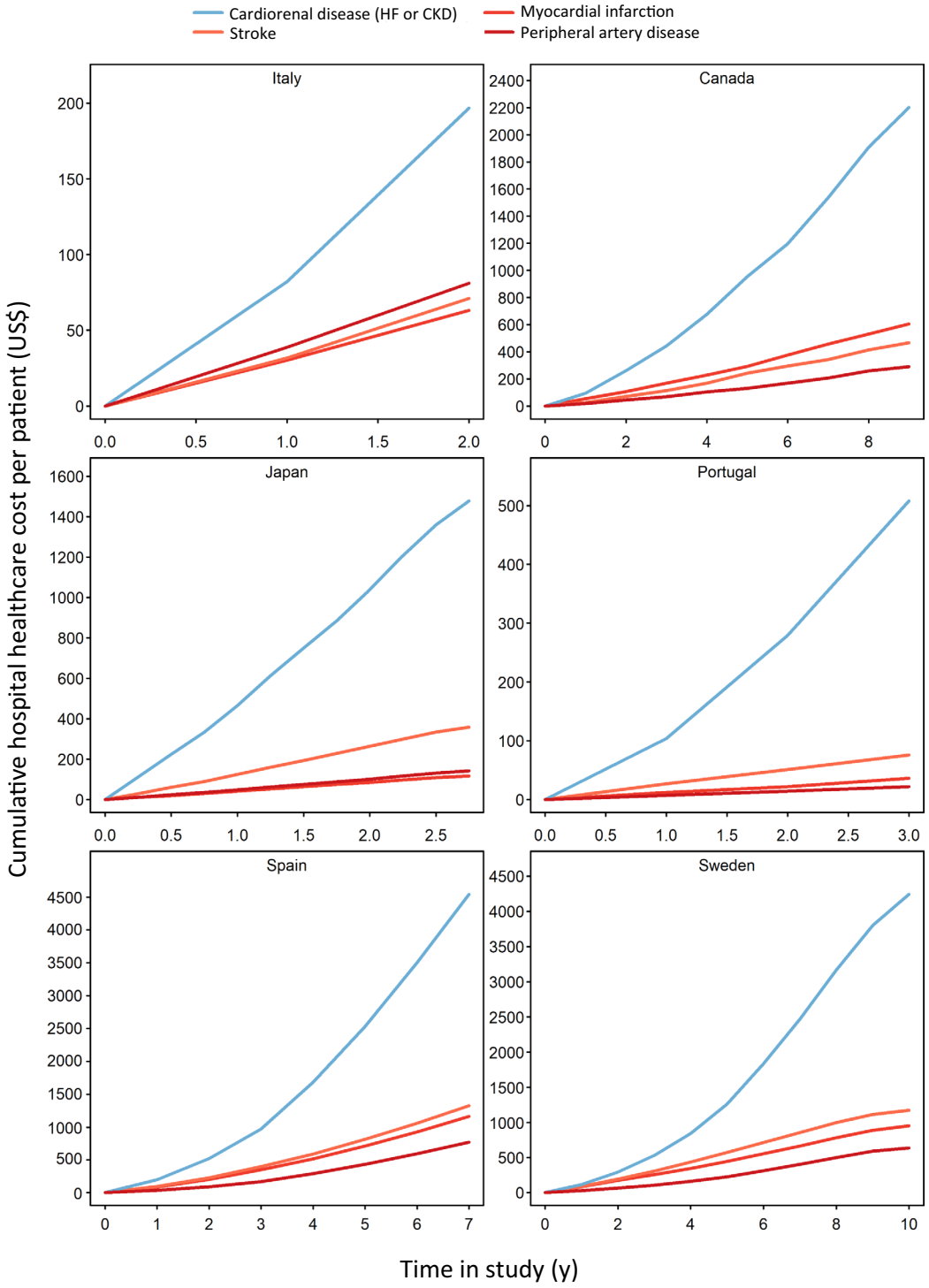

FIGURE 4 Cumulative hospital healthcare costs including the first and repeated cardiovascular and renal disease (CVRD) in individuals with type 2 diabetes, initially free from any prior CVRD, from six countries. CKD, chronic kidney disease; HF, heart failure

country in cumulative incidence plots (i.e. the proportion of individuals with a CVRD event over time) and by description of the relative proportion of event types among individuals who experienced a CVRD event during follow-up. All analyses of the cumulative incidence are descriptive and formal analyses between countries were not performed.

2.3.2 | Hospital healthcare costs

Hospital healthcare costs were first summarized annually within each individual as the total cost per year per diagnosis and then summarized further within each country as the mean cost per individual per year for each participating nation with available cost data. Hospital

healthcare costs were censored from death onwards, whereas individuals leaving the database were not included in the denominator from the year after they left the database. Results are presented separately for each country and no formal comparisons between countries were performed. All diagnoses were analysed independently from other diagnoses and, thus, hospitalizations because of more than one of the targeted CVRD diagnoses contribute hospital healthcare costs to each of the included diagnoses. Therefore, one cannot add the hospital healthcare costs of two diagnoses to form a combined cost. For the purpose of currency conversion to US$, US$1 equalled 0.77 Canadian dollars, 1.13 Euros, 8.56 Swedish krona, and 108.59 Japanese yen. All analyses were conducted using R statistical software (R version 3.5.0).

3 | RESULTS

In total, 1 177 407 CVRD-free individuals with type 2 diabetes were identified and followed for an average of 4.5 years, a total of 4.9 million patient-years. The proportion of that population indexed before 2010, during 2010-2015, and after 2015 was 18% (207 137 individuals), 31% (361 175), and 52% (609 095), respectively. The mean age ranged from 55 to 68 years and individuals in Germany, Italy, Japan, the Netherlands, and Spain were, in general, somewhat older than in the other countries (Table 1). Use of antidiabetic and cardiovascular risk-lowering therapies varied slightly between cohorts. The use of one or more cardiovascular preventive treatments was common, even in this initially CVRD-free cohort (51% to 89%).

Cardiorenal disease (HF or CKD) was consistently the most frequent disease to develop first, increasing early on during the follow-up period across all countries (Figures 2 and S2). Of the 1 177 407 CVRD-free individuals with type 2 diabetes, 184 420 (15.7%) developed CVRD during 4.5 years (mean) of follow-up. Of the potential CVRD outcomes, cardiorenal disease (59.7%), consisting of HF (23.0%) and CKD (36.7%), was the most common to develop first; 4-fold more common than stroke (16.9%) and myocardial infarction (13.7%), and 6-fold more common than PAD (9.7%) (Figure 3). These findings were similar in countries with a short follow-up (Italy [2 years], Japan [2.5], and Portugal [3]) and those with a longer follow-up (Sweden [10], England [10], and Israel [12]).

3.1 | Hospital healthcare costs

In 800 539 CVRD-free individuals with type 2 diabetes (68.0% of the entire study population) from the six countries with available hospital healthcare cost data (Italy, Canada, Japan, Portugal, Spain, and Sweden), patterns of initial CVRD development (Figure 2) and proportions of cumulative incident CVRD (Figure 3) were similar to that across the six countries without available hospital healthcare cost data. The cumulation of hospital healthcare cost (Figure 4) followed the same pattern as that of the cumulation of incident CVRD (Figure 2). Costs for cardiorenal disease (HF or CKD) hospital healthcare were consistently higher compared with costs related to atherosclerotic cardiovascular diseases (stroke, myocardial infarction,

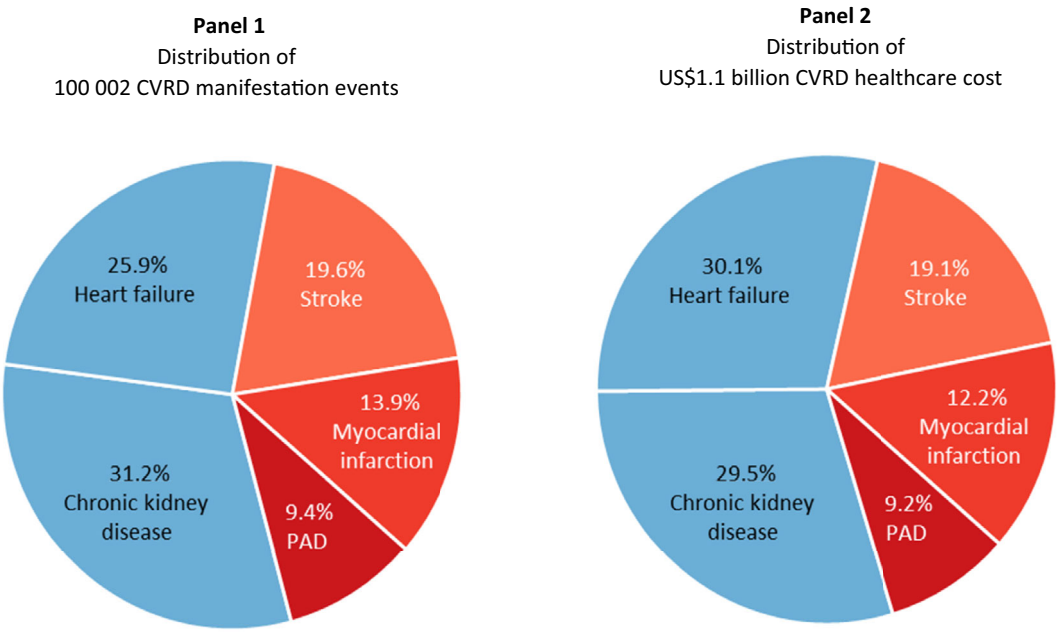

FIGURE 5 Cardiorenal disease manifestation and associated hospital healthcare costs compared with atherosclerotic cardiovascular disease during follow-up of 800 539 cardiovascular and renal disease (CVRD)-free individuals with type 2 diabetes in six countries with available hospital healthcare cost data: Italy, Canada, Japan, Portugal, Spain, and Sweden. Panel 1 shows the distribution of first CVRD event manifestations. Panel 2 shows the distribution of total cumulative healthcare costs for all first and repeated events associated with CVRD hospital events. PAD, peripheral artery disease

and PAD; Figure 4). Notably, in countries with a longer follow-up of 7-10 years, such as Canada, Spain, and Sweden, costs for cardiorenal disease hospital healthcare increased progressively, while the increase in costs for myocardial infarction, stroke, and PAD were more linear (Figure 4). The detailed cumulative hospital healthcare costs during follow-up for the separate components of CVRD are described in Table S6.

The proportions for the incidence of each form of CVRD (Figure 5, Panel 1) were similar to the distribution of total hospital healthcare costs for those diseases (Figure 5, Panel 2). Of the US $1 090 129 146 in total hospital healthcare cost, 59.0% (US $643 338 774) was attributed to cardiorenal disease; 3-, 5-, and 6-fold more costly than stroke (US$208 million), myocardial infarction (US$133 million), and PAD (US$100 million), respectively.

4 | DISCUSSION

In this large population-based study including approximately 1.2 million individuals with type 2 diabetes from 12 countries and different ethnic populations across North America, Asia, and Europe, cardiorenal disease (i.e. HF or CKD) was consistently the most frequent form of CVRD (60%) to develop first in this initially CVRD-free population. Relative to other forms of CVRD, cardiorenal disease was associated with the highest hospital healthcare costs (59%), with 3-, 5-, and 6-fold higher costs than those resulting from stroke, myocardial infarction, and PAD, respectively. These findings were remarkably similar between countries with a short follow-up (2-4 years) and those with a longer follow-up (10-12 years), showing a robustness in the data with its consistency throughout different time periods and changes in guidelines, treatment strategies, and healthcare structures.

In similar research that covered half of the countries included in this study,[2] cardiorenal disease was also consistently the most frequent disease to first develop in a population with type 2 diabetes initially free of CVRD. This prominence in cardiorenal disease could partly be explained by the role of type 2 diabetes as a central risk factor for both HF and kidney disease.[28,29] Importantly, this study builds upon previous research by, to the best of our knowledge, detailing for the first time in a contemporary setting that cardiorenal disease is associated with higher hospital healthcare costs over time compared with atherosclerotic cardiovascular diseases. These results emphasize the importance of conducting clinical cardiorenal risk assessment, in addition to microvascular and atherosclerotic cardiovascular risk management (prevention of microvascular and macrovascular diseases), to prevent the costly and burdensome complications of type 2 diabetes.[8,30]

In a large study, Rawshani et al. reported that sufficient risk factor management could significantly reduce or even eliminate the excess risk of atherosclerotic cardiovascular disease.[31] However, the substantial excess risk associated with HF was not completely eliminated with traditional risk factor management. This excess risk might account for the increased incidence of HF in the present study, given that, with a mix of aetiologies in diabetes, the risk of HF is less impacted by traditional risk management (e.g. statins, low-dose aspirin, and antihypertensives) than that of myocardial infarction, for example. Ischaemic cardiomyopathy is generally considered to be the most common cause of HF in diabetes. However, in our uniquely 'low-risk' population, no such studies on aetiology have been reported. Hence, compared with the general hospitalized HF patient largely burdened with prior coronary ischaemic diagnoses, one could speculate if the importance of other co-morbidities, such as hypertensive and renal involvement, or a pure diabetic cardiomyopathy, might be greater in our low-risk population with type 2 diabetes. The increased incidence in HF could also be explained by a comparatively recent increase in the awareness of HF with preserved systolic function, which is especially associated with co-morbidities commonly seen in diabetes, such as hypertension, atrial fibrillation, obesity, and renal disease. Whatever the mechanisms behind the excess risk of HF despite effective, preventive treatment of lipids, hypertension, glucose control, and albuminuria, there is indeed an unmet preventive clinical need in individuals with type 2 diabetes.[31] Because the majority of individuals with type 2 diabetes are free of CVRD,[2] improved prevention of HF and CKD is of critical importance and can be expected to have a significant impact on future healthcare utilization.[8,25,31]

Recent evidence detailing the association between cardiorenal disease and mortality supports the findings from this study,[2] stressing an urgent need for improved preventive treatment strategies. Furthermore, episodes of HF have been shown to increase the risk of CKD progression by up to 3-fold. Declining kidney function also leads to worse HF, suggesting a strong interplay between these complications. This highlights that any interventions should be designed to elicit benefits for both components of cardiorenal disease, rather than one or the other. It has been reported that novel glucose-lowering drugs like SGLT2is have strong and consistent effects, reducing cardiorenal risk in individuals with type 2 diabetes without established CVRD.[15,18] Subsequently, SGLT2is may contribute to an improved primary preventive strategy and clinical practice, complementing important, traditional atherosclerotic cardiovascular disease risk factor management in type 2 diabetes.[8]

4.1 | Strengths and limitations

To the best of our knowledge, this study is the first to report clinical cardiorenal disease development and subsequent hospital healthcare costs in individuals with type 2 diabetes across several continents and ethnicities. Using available diagnoses (including signs and symptoms) and treatments that indicate ischaemic coronary diseases, cerebral ischaemia, diagnoses of peripheral ischaemic symptoms, HF, atrial fibrillation (representing a risk of incident HF), and a wide diagnostic selection of CKD, this study was able to include a CVRD-free population that is representative of the majority of individuals with type 2 diabetes.[2,4] Remarkably, findings were consistent across all participating nations, despite differences in ethnicity and the structure of healthcare systems, variations in the index dates for each country, and

changes in treatment guidelines, showing the robust nature of the data. Hospital healthcare costs also include the costs of the first and all repeated CVRD events requiring hospitalization during follow-up (e.g. healthcare costs for all HF admissions and readmissions were added in the cumulative calculation). The diagnoses used for CKD in this study have previously been validated, showing a high positive predictive value for diagnoses set in hospital visits (outpatient and inpatient visits), outpatient visits, and primary care visits (Figures S4, S5, and S6, respectively).[2,18]

Despite the large size of the study, its findings should be interpreted within the context of several potential limitations. Data sources vary in terms of treatment-level coverage (primary or hospital care) and the proportions of the population covered might have, subsequently, resulted in an insufficient amount of information to confirm that individuals with type 2 diabetes are truly free of CVRD at index. The remarkable robustness of CVRD manifestation and its associated trends in hospital healthcare cost are, however, supported by observation in a diversity of registry properties and healthcare systems across the participating nations (Figure S1). Examples of significant differences in registry properties are access to primary and hospital healthcare (Belgium, Canada, Germany, Israel, Italy, The Netherlands, Portugal, Spain, and the England) versus hospital-only healthcare (Japan, Norway, and Sweden), full population data (Norway and Sweden), representative population data (all countries) and, finally, different ethnicities (American, Asian, and European). Only outcomes requiring hospital care were used, which might have underestimated less severe conditions (e.g. those that are managed in primary care). Given that costs for primary care health were not accounted for, the estimated healthcare costs may also be underestimated. However, prior studies have shown that the majority (75%) of healthcare costs are attributed to hospital care, while only 25% may be attributable to primary care.[32] Validation of HF diagnoses from hospital care has been evaluated in previous research, but not in a CVRD-free type 2 diabetes population, such as that in the present study. The registries lack numerous variables, which might have influenced the results (e.g. diabetes duration, hypertension duration, body mass index, laboratory records, proteinuria measurements, measurements of cardiac function, smoking status, alcohol intake, diet, physical activity, stress, and environmental factors). Given that CKD is generally symptom free in its early phases and that a diagnosis relies on having measured albuminuria or estimated glomerular filtration rate, the incidence of CKD might be underestimated. Type of kidney disease was not available in all countries and, for example, patients with full recovery after an acute kidney injury might have contributed to the CKD manifestation findings. However, acute kidney injury and CKD are closely interconnected syndromes where CKD is a risk factor for acute kidney injury, acute kidney injury a risk factor for development of CKD, and both CKD and acute kidney injury are risk factors for cardiovascular disease.[33] Hence, the likelihood of acute kidney injury leading to an overestimation of CKD manifestation in this population is probably low. Hospital healthcare costs could only be obtained in six of the 12 countries. However, these cohorts could be judged representative of the wider population, still covering 68% of the total CVRD-free population with type 2 diabetes (800 539 of 1 177 407 individuals) across North America, Asia, and Europe, each with similar characteristics and incidences of CVRD to those of the entire study cohort. Although the majority of healthcare costs are attributed to hospital care that is registered for claim purposes, other related costs for cardiovascular/antidiabetic drugs, indirect disease burden (e.g. sick leave), and primary care costs were not addressed in the present study. Therefore, it is expected that the cost of healthcare utilization has been underestimated. In some countries (Portugal and Spain), complete coverage of all patient-related hospital care costs for procedures like dialysis or peripheral amputations was lacking, whereas coverage was complete in other registries that are nationwide (Sweden), statewide (Canada), and full population (Japan and England).

Future research on cardiorenal manifestation in this large group of younger and comparatively low-risk individuals with type 2 diabetes is encouraged to address questions not assessed in the present study (e.g. the impact of the duration of diabetes and/or hypertension, and the influence of classic risk factors [systolic blood pressure, cholesterol levels, and smoking]).

In conclusion, this large multinational study showed that cardiorenal disease was consistently the most frequent form of CVRD to develop first in an initially CVRD-free population of 1.2 million individuals with type 2 diabetes. Additionally, cardiorenal disease was associated with higher hospital healthcare costs than those for atherosclerotic cardiovascular diseases. These results further emphasize the existence of an unmet clinical need, a need to implement modern, evidence-based preventive strategies that reduce the incidence of cardiorenal disease and ease the substantial burden that these complications of type 2 diabetes impose at a humanistic and societal level.

ACKNOWLEDGEMENTS

MT researched data and reviewed/edited the manuscript. AN, JB, JWE, HH, GCML, AB, AK, PM, NT, TTG, APM, MB, SO, TY, TK, and KIB contributed to the discussion and reviewed/edited the manuscript and researched data. We are grateful to Prof. Ron Herings, Louise Lemmens, Fernie Penning, Urban Olsson, Prof. Geert Goderis, C. Melzer Cohen, Letizia Dondi, Ruiqi Zhang, Elena Garal-Pantaler, Marc Pignot, and Jetty Overbeek for statistical support; and Marco Gnesi, Maya Greenblom, Beatriz Palacios, Miren Sequera, Julia Blanco, Isabelle Fovel, Jonathan Edwin, Dörte Andersson, Wendy Beekman-Hendriks, Stijn Gijsbers, Susanna Jerström, and Helena Goike at AstraZeneca for logistic support and valuable comments on the manuscript. The authors thank Jordan Loader PhD, of Sence, Uppsala, Sweden, for providing medical writing support/editorial support, which was funded by AstraZeneca, Stockholm, Sweden, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). Data from the Norwegian Cause of Death Registry, the Norwegian Prescription Database, and the Norwegian Patient Register have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian patient register is intended, nor should be inferred. This work was sponsored by AstraZeneca.

CONFLICT OF INTEREST

AN has received honoraria from MSD, Astra Zeneca, Eli Lilly, Boehringer Ingelheim, and Novo Nordisk. TK: grants: Asahi Mutual Life Insurance Co., Boehringer Ingelheim Japan, Daiichi Sankyo Company Limited, Kowa Pharmaceutical Co. Ltd, Mitsubishi Tanabe Pharma Corporation, MSD K.K., Novo Nordisk Pharma Ltd, Sanofi K.K., and Takeda Pharmaceutical Company Limited; and lecture/other fees: AstraZeneca K.K., Astellas Pharma Inc., Boehringer Ingelheim Japan, Daiichi Sankyo Company Limited, Eli Lilly Japan K.K., Kowa Pharmaceutical Co. Ltd, Kyowa Hakko Kirin Co. Ltd, Mitsubishi Tanabe Pharma Corporation, MSD K.K., Ono Pharmaceutical Co. Ltd, Sanofi K.K., Sumitomo Dainippon Pharma Co. Ltd, Sanwa Kagaku Kenkyusho Co. Ltd, Taisho Pharmaceutical Co. Ltd, and Takeda Pharmaceutical Company Limited. AB reports research funding from AstraZeneca. AK reports grants and consulting fees from AstraZeneca, Novo Nordisk, Merck, and Boehringer Ingelheim. PM: none declared. NT has received consulting fees from Boehringer Ingelheim, Eli Lilly, Otsuka, and AstraZeneca; research grants from AstraZeneca, including support for the present study; research grants from Janssen and Tricida; and consulting fees and stock options from Tricida, PulseData, and Mesentech. TTG has received grants from AstraZeneca and for lectures and consulting from AstraZeneca, Bial, Merck Sharp & Dohme, and Daiichi Sankyo. APM reports receiving fees for serving on study committees from Novartis, Bayer, and Fresenius. MB has received lecture and other fee honoraria from Janssen, Astra Zeneca, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, and Sanofi. KIB has received grants to his institution from AstraZeneca for this study and for lectures and consulting from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, and Merck Sharp & Dohme. JB holds a full-time position at AstraZeneca as an epidemiologist. JWE has received honoraria or research grants from AstraZeneca, NovoNordisk, Bayer, Sanofi, and MSD. HH has received lecture fees and travel expenses from Alexion, Baxter, NovoNordisk, Noxxon, Janssen, and AstraZeneca. GCML: no competing interests. MT is employed by an independent statistical consultant company, Statisticon AB, Uppsala, Sweden, of which AstraZeneca Nordic-Baltic is a client. SO: full-time employee of AstraZeneca. TY: full-time employee of AstraZeneca.

AUTHOR CONTRIBUTIONS

All authors participated in the research design. MT performed the data management and statistical analyses for all countries after discussion with all authors. All authors participated in data interpretation and in writing the manuscript. All authors took final responsibility for the decision to submit for publication. MT guarantees the statistical analyses. JB is the guarantor of the study taking the full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14698.

DATA AVAILABILITY STATEMENT

The data sources utilized in the present are all underlying local, ethical and privacy restrictions for data transfer abroad or into public domain limiting data availability on request.

ORCID

Johan Bodegard https://orcid.org/0000-0001-5423-3967
Jan W. Eriksson https://orcid.org/0000-0002-2639-9481
Suguru Okami https://orcid.org/0000-0003-4402-0209
Kåre I. Birkeland https://orcid.org/0000-0003-3002-6933

REFERENCES

1. Magliano DJ, Boyko EJ, Karuranga S, et al. *IDF Diabetes Atlas 2021*. 10th ed. Brussels, Belgium: International Diabetes Federation; 2021.
2. Birkeland KI, Bodegard J, Eriksson JW, et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: A large multinational cohort study. *Diabetes Obes Metab*. 2020;22(9):1607-1618.
3. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract*. 2019;157:107843.
4. Pylypchuk R, Wells S, Kerr A, et al. Cardiovascular risk prediction in type 2 diabetes before and after widespread screening: a derivation and validation study. *Lancet*. 2021;397(10291):2264-2274.
5. Sicras-Mainar A, Sicras-Navarro A, Palacios B, et al. Epidemiology and resource use in Spanish type 2 diabetes patients without previous cardiorenal disease: CaReMe Spain study summary. *Endocrinología Diabetes y Nutrición*. 2021; in press.
6. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Rev Esp Cardiol*. 2016;69(10):939.
7. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S125-S150.
8. Handelsman Y, Anderson JE, Ballantyne C, et al. *DCRM multiplicinary practice recommendations for the management of diabetes, cardiorenal and metabolic diseases*. New Orleans, Louisiana, United States of America: Diabetes Cardiorenal & Metabolism Institute; 2021.
9. Ceriello A, Catrinoiu D, Chandramouli C, et al. Heart failure in type 2 diabetes: current perspectives on screening, diagnosis and management. *Cardiovasc Diabetol*. 2021;20(1):218.
10. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. *N Engl J Med*. 2014;370(16):1514-1523.
11. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. *Lancet Diabetes Endocrinol*. 2016;4(6):537-547.
12. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
13. Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation*. 2019;140(9):739-750.
14. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus: results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation*. 2018;138(5):458-468.
15. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
16. Mosenzon O, Wiviott SD, Cahn A, et al. Effects of dapagliflozin on development and progression of kidney disease in patients with type

2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol*. 2019;7(8):606-617.
17. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139(22):2528-2536.
18. Birkeland KI, Bodegard J, Banerjee A, et al. Lower cardiorenal risk with sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes without cardiovascular and renal diseases: A large multinational observational study. *Diabetes Obes Metab*. 2021;23(1):75-85.
19. McMurray JJV, Solomon SD, Inzucchi SE. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381(21):1995-2008.
20. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383(15):1436-1446.
21. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383(15):1413-1424.
22. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385(16):1451-1461.
23. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement From the American Heart Association. *Circulation*. 2019;139(16):e840-e878.
24. Braunwald E. Diabetes, heart failure, and renal dysfunction: the vicious circles. *Prog Cardiovasc Dis*. 2019;62(4):298-302.
25. McEwan P, Morgan AR, Boyce R, et al. Cardiorenal disease in the United States: future health care burden and potential impact of novel therapies. *J Manag Care Spec Pharm*. 2022;28(4):415-424.
26. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527-1539.
27. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med*. 2008;34(5):957-962.
28. Avery CL, Loehr LR, Baggett C, et al. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol*. 2012;60(17):1640-1646.
29. Nichols GA, Gullion CM, Koro CE, Ephross SA, Brown JB. The incidence of congestive heart failure in type 2 diabetes: an update. *Diabetes Care*. 2004;27(8):1879-1884.
30. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227-3337.
31. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2018;379(7):633-644.
32. Nathanson D, Sabale U, Eriksson JW, et al. Healthcare cost development in a type 2 diabetes patient population on glucose-lowering drug treatment: a nationwide observational study 2006-2014. *Pharmacoecon Open*. 2018;2(4):393-402.
33. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371(1):58-66.

SUPPORTING INFORMATION

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

How to cite this article: Norhammar A, Bodegard J, Eriksson JW, et al. Cost of healthcare utilization associated with incident cardiovascular and renal disease in individuals with type 2 diabetes: A multinational, observational study across 12 countries. *Diabetes Obes Metab*. 2022;1-11. doi:10.1111/dom.14698