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Prevalence, outcomes and costs of a contemporary, multinational population with heart failure

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ABSTRACT

Objective Digital healthcare systems could provide insights into the global prevalence of heart failure (HF). We designed the CardioRenal and Metabolic disease (CaReMe) HF study to estimate the prevalence, key clinical adverse outcomes and costs of HF across 11 countries.

Methods Individual level data from a contemporary cohort of 6 29 624 patients with diagnosed HF was obtained from digital healthcare systems in participating countries using a prespecified, common study plan, and summarised using a random effects meta-analysis. A broad definition of HF (any registered HF diagnosis) and a strict definition (history of hospitalisation for HF) were used. Event rates were reported per 100 patient years. Cumulative hospital care costs per patient were calculated for a period of up to 5 years.

Results The prevalence of HF was 2.01% (95% CI 1.65 to 2.36) and 1.05% (0.85 to 1.25) according to the broad and strict definitions, respectively. In patients with HF (broad definition), mean age was 75.2 years (95% CI 74.0 to 76.4), 48.8% (40.9–56.8%) had ischaemic heart disease and 34.5% (29.4–39.6%) had diabetes. In 51 442 patients with a recorded ejection fraction (EF), 39.1% (30.3–47.8%) had a reduced, 18.8% (13.5–24.0%) had a mildly reduced and 42.1% (31.5–52.8%) had a preserved left ventricular EF. In 1 69 518 patients with recorded estimated glomerular filtration rate, 49% had chronic kidney disease (CKD) stages III–V. Event rates were highest for cardiorenal disease (HF or CKD) and all cause mortality (19.3 (95% CI 11.3 to 27.1) and 13.1 (11.1 to 15.1), respectively), and lower for myocardial infarction, stroke and peripheral artery disease. Hospital care costs were highest for cardiorenal diseases.

Conclusions We estimate that 1–2% of the contemporary adult population has HF. These individuals are at significant risk of adverse outcomes and associated costs, predominantly driven by hospitalisations for HF or CKD. There is considerable public health potential in understanding the contemporary burden of HF and the importance of optimising its management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Few studies have assessed the burden of heart failure (HF) using both healthcare data from electronic healthcare records and national registries, and of those that have, highly selected patient populations that might not be representative of today's problem have been described.

WHAT THIS STUDY ADDS

⇒ This study shows that the contemporary prevalence of heart failure is 2% when a broad definition of HF was used and 1% when a strict definition was applied, similar across several countries.

⇒ The most frequent comorbidities were ischaemic heart disease and chronic kidney disease (CKD) stages III– V. Patients with HF have high risks of cardiorenal complications (HF or CKD) and all cause mortality.

⇒ Furthermore, hospital care costs were highest for cardiorenal diseases, higher than those stemming from atherosclerotic cardiovascular diseases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The cardiorenal burden, risks and costs in HF patients highlights an urgent need for improved risk management and an area that policy makers need to prioritise when planning healthcare for patients with HF.

INTRODUCTION

Heart failure affects up to 64 million people worldwide and its incidence is expected to rise with ageing populations and improved diagnostic methods.[1] Heart failure already places an enormous economic burden on healthcare systems, with Europe and the US each allocating 1–2% of their annual healthcare budgets towards it.[2]

Heart failure management is changing rapidly following pivotal clinical trials,[3–8] which are shaping treatment guidelines.[9–11] Consequently, the population with heart failure is also evolving quickly. Multinational studies of the characteristics and outcomes in persons with heart failure are scarce, often describing highly selected patient groups and likely unrepresentative of today's patient.[12–14] Hence there is a need for a comprehensive understanding of the contemporary patient with heart

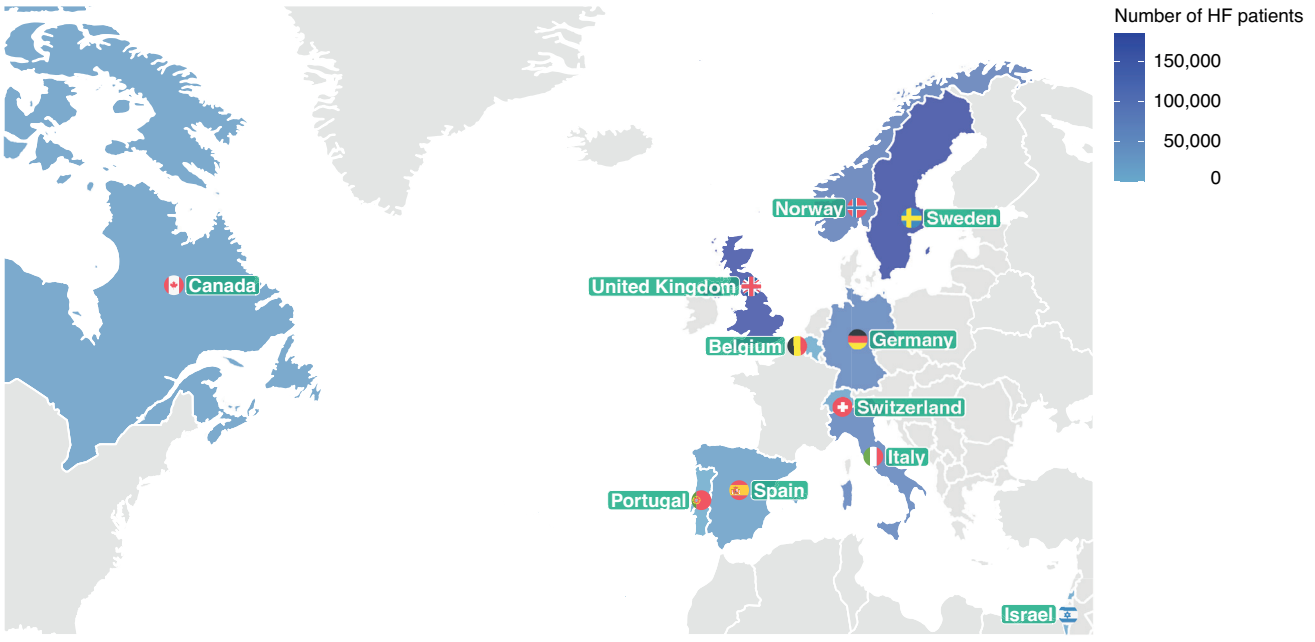

Figure 1 Number of included patients with heart failure (HF) in each of the 11 participating countries.

failure. The CardioRenal and Metabolic disease (CaReMe) Heart Failure study collected detailed contemporaneous data from healthcare systems in 11 nations to determine the prevalence of heart failure and to detail patient characteristics, risks and costs associated with heart failure across the participating countries.

MATERIALS AND METHODS

Study setting and data sources

The multinational, observational CaReMe study used data from healthcare registries, including patient records from routine clinical practice across Belgium, Canada, Germany, Israel, Italy, Norway, Portugal, Spain, Sweden, Switzerland, and the UK (figure 1).[14] A description of the data sources is provided in the online supplemental material (3–6) online supplemental material (pages 3–6). A heat map describing the coverage of the registries, data availability and healthcare level at which heart failure was identified is illustrated in figure 2. Permissions were obtained from ethics authorities before the start of the study in each participating country that required it. Approval numbers are available in the online supplemental materials (3-6).

Study population

To define the patient population, diagnoses of heart failure were searched for in all data available prior to the index date (online supplemental table S1). Prevalence was determined using a broad and a strict definition of heart failure. The broad definition included patients with a diagnosis of heart failure in a primary care

	Belgium			Canada			Germany			Israel			Italy			Norway			Portugal			Spain			Sweden			Switzerland			UK		
Level of care	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Registry coverage																																	
Nationwide full population																																	
Population with complete coverage																																	
Population with partial coverage																																	
Data available																																	
Electronic medical records																																	
Claims data																																	
Quality-of-care registry data																																	
Drug prescription data																																	
Laboratory data																																	
Health care cost data																																	
Cause-of-death registry data																																	
Death registry data																																	
Level of patient identification																																	

Figure 2 Description of data sources used across the participating countries. Data extractions are from the following levels of healthcare: (1) primary healthcare, (2) secondary healthcare (specialist or outpatient hospital care) and (3) tertiary healthcare (inhospital care). Green colour, Data available and utilized; Orange colour, Data not available.

or hospital setting.[15] The strict definition was restricted to patients with history of a hospital admission where heart failure was the main diagnosis, reflecting the prevalence of validated heart failure diagnoses.[15]

Index years and follow-up time

Three cohorts were formed in each country to describe: cohort 1 (cross sectional), the most contemporary patient characteristics; cohort 2 (longitudinal risks), 1 year event rates; and cohort 3 (longitudinal costs), hospital healthcare costs over a period of up to 5 years. All patients were indexed on 1 January in the year that their country of residence entered the study (online supplemental table S2). The index year varied between nations to ensure that the most recent data available in each participating country were used, and thus that the most contemporary patient populations were formed. For cohorts 2 and 3, indexing was adjusted to allow sufficient follow-up.

Baseline characteristics

In cohort 1, comorbidities and laboratory variables were searched for in all available data prior to the index, except for cancer, where diagnoses were identified in the 5 year period prior to the index. Medication use (renin–angiotensin–aldosterone system inhibitors, beta blockers, mineralocorticoid receptor antagonists, angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter 2 (SGLT-2) inhibitors) indicated by a filled drug prescription was searched for in the year prior to the index.

Outcomes

Clinical outcomes

In cohort 2, 1 year hospital event rates per 100 patient years from index year were calculated for hospitalisations with a main diagnosis of heart failure, chronic kidney disease (including diagnoses of chronic, acute, unspecified, diabetic, hypertensive, glomerular, tubulo-intestinal or dialysis), myocardial infarction, stroke, peripheral artery disease and all cause death (online supplemental table S3).

Hospital healthcare costs

In cohort 3, the cumulative costs were calculated for each patient for a period of up to 5 years, including costs for all first and repeated hospitalisations. Costs were extracted from registered diagnose related groups that were weighted and calculated within each country (eg, the actual reimbursement claims to the local payer).

Statistical analysis

Analyses were performed separately in each country according to a prespecified common statistical analysis plan. Baseline characteristics were described using mean and SD for numerical variables, and frequencies and percentages for categorical variables. Random effect estimates were used when pooling data, assuming some heterogeneity between countries. The pooled estimates from the random effects models are presented with 95% CIs. Tau was used to describe this heterogeneity, which corresponds to the estimated SD in the underlying distribution of true results across participating countries. All analyses were conducted using R statistical software (R V.3.5.0). The meta-analyses of means and proportions were performed using meta-mean and metaprop functions, respectively, in the meta package, and tau was estimated using a restricted maximum-likelihood estimator.

Event rates

Event rates were calculated as events per 100 patient years based on time to first event, and patients were censored at death or 1 year after the index. Patients without an event were censored at the end of follow-up or when leaving the database. All analyses of the cumulative incidence are descriptive and formal comparisons between countries were not performed.

Hospital healthcare costs

Costs were summarised annually within each patient as the total cost per year per diagnosis, and then summarised further within country as the mean cost per patient per year. Costs were censored from death onwards, whereas patients leaving the database were not included in the denominator from the year after leaving the database. Results are presented separately for each country and there was no standardisation or formal comparisons between countries. All diagnoses were analysed independently from other diagnoses and hospitalisations, given that more than one of the targeted diagnoses contributes costs to each of the included diagnoses. Therefore, one cannot add the hospital healthcare costs of two diagnoses to form a combined cost.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study.

RESULTS

Prevalence of heart failure

In a background population of >32 million adults, the pooled prevalence of heart failure was 2.01% (95% CI 1.65 to 2.36) and 1.05% (95% CI 0.85 to 1.25) according to the broad and strict heart failure definitions, respectively (table 1). The highest prevalence (broad definition) was in Portugal (2.9%) and the lowest in the UK (1.4%). In countries with nationwide coverage

Table 1 Prevalence of heart failure in 32 million patients across multiple countries in Asia, Europe and North America, 2018–20

	Canada	Israel	Italy	Norway*	Portugal	Spain	Sweden*	UK	Total	Pooled prevalence (95% CI)	Tau
Prevalence of heart failure											
Broad definition (%)	2.26	n/a	1.54	1.84	2.86	1.88	2.22	1.44	1.77	2.01 (1.65 to 2.36)	0.48
Strict definition (%)	1.06	0.60	0.82	1.13	1.43	n/a	1.27	1.05	1.07	1.05 (0.85 to 1.25)	0.27
No of patients with heart failure											
Strict definition (n)	11 243	9759	35 660	46 840	1840	n/a	103 182	74 055	282 579		
Broad definition (n)	23 953	n/a	67 369	76 561	3681	21 851	180 727	165 244	539 386		
Background population >18 years (n)	1 060 153	1 622 570	4 363 833	4 153 579	128 605	1 189 003	8 147 081	11 496 448	32 161 272		

Broad definition of heart failure=numbers of patients with a registered heart failure diagnosis in any available healthcare records. Strict definition of heart failure=only patients hospitalised with heart failure as the main diagnosis.
*Countries with nationwide coverage of patients with heart failure and background populations. Background populations were estimated based on the coverage of the healthcare registries for countries in which this information was available.
Random effect estimates were used to calculate pooled values and tau describes the estimated SD of the underlying data across countries.
n/a, not available.

Table 2 Baseline characteristics of 629 440 contemporary patients with heart failure across 11 countries between 2018 and 2020

	Belgium	Canada	Germany*†	Israel	Italy	Norway	Portugal	Spain	Sweden	Switzerland*	UK	Pooled baseline (95% CI)	Tau
No of patients	2379	23 953	63 712	9759	67 369	76 561	3681	21 851	180 727	14 204	165 244	n/a	n/a
Index year	2018	2019	2019	2020	2018	2020	2019	2019	2019	2019	2020		
Age (years) (mean (SD))	72 (17)	75 (14)	75 (12)	74 (13)	78 (12)	74 (13)	78 (12)	78 (11)	75 (13)	74 (13)	74 (13)	75.2 (74.0 to 76.4)	2.00
Women (n (%))	932 (39)	11 993 (50)	27 892 (44)	3681 (38)	33 987 (50)	30 746 (40)	2171 (59)	10 261 (47)	77 791 (43)	5612 (40)	71 862 (43)	44.8 (41.1 to 48.6)	6.29
NYHA functional classification (n (%))													
I	101 (9)	n/a	2810 (5)	n/a	n/a	n/a	n/a	2781 (13)	n/a	436 (8)	8768 (32)	13.4 (3.8 to 23.0)	10.92
II	472 (43)	n/a	15 427 (27)	n/a	n/a	n/a	n/a	9716 (45)	n/a	1532 (27)	12 668 (47)	37.7 (29.0 to 46.4)	9.94
III	419 (38)	n/a	25 441 (45)	n/a	n/a	n/a	n/a	8172 (38)	n/a	2299 (40)	5427 (20)	36.2 (27.8 to 44.5)	9.48
IV	105 (10)	n/a	13 398 (23)	n/a	n/a	n/a	n/a	821 (4)	n/a	1446 (25)	358 (1)	12.7 (3.0 to 22.4)	11.10
Ischaemic heart disease (n (%))	1424 (60)	13 850 (58)	33 711 (53)	5812 (60)	19 720 (29)	41 933 (55)	1546 (42)	4769 (22)	87 152 (48)	n/a	70 379 (43)	48.8 (40.9 to 56.8)	12.16
Myocardial infarction (n (%))	883 (37)	7042 (29)	13 041 (20)	3132 (32)	7665 (11)	23 160 (30)	673 (18)	3130 (14)	62 768 (35)	n/a	45 022 (27)	25.5 (20.0 to 31.0)	8.84
Unstable angina (n (%))	9 (0)	6126 (26)	3399 (5)	299 (3)	2624 (4)	n/a	437 (12)	1034 (5)	20 255 (11)	n/a	5118 (3)	7.7 (2.7 to 12.7)	7.69
Angina pectoris (n (%))	764 (32)	13 282 (55)	2978 (5)	256 (3)	19 080 (28)	37 117 (48)	1296 (35)	1735 (8)	63 302 (35)	n/a	30 119 (18)	26.8 (15.6 to 38.1)	18.15
Stroke (n (%))	428 (18)	4133 (17)	5112 (8)	1147 (12)	7297 (11)	2298 (3)	466 (13)	2401 (11)	28 415 (16)	n/a	29 805 (18)	12.6 (9.6 to 15.6)	4.82
Atrial fibrillation/flutter (n (%))	1258 (53)	11 886 (50)	29 675 (47)	4144 (42)	20 655 (31)	39 544 (52)	1482 (40)	7246 (33)	95 330 (53)	n/a	67 552 (41)	44.1 (39.1 to 49.0)	7.97
Peripheral artery disease (n (%))	236 (10)	2729 (11)	6547 (10)	332 (3)	5115 (8)	7881 (10)	216 (6)	1050 (5)	14 010 (8)	n/a	11 985 (7)	7.8 (6.2 to 9.5)	2.62
Diabetes (n (%))	865 (36)	10 549 (44)	21 564 (34)	4868 (50)	25 103 (37)	16 039 (21)	1540 (42)	7371 (34)	45 134 (25)	3922 (28)	48 533 (29)	34.5 (29.4 to 39.6)	8.61
CKD diagnosis (n (%))	1515 (64)	9766 (41)	34 784 (55)	6146 (63)	11 082 (16)	21 398 (28)	898 (24)	6143 (28)	32 669 (18)	6389 (45)	60 331 (37)	38.0 (28.0 to 48.0)	16.91
Cancer (n (%))	439 (18)	3271 (14)	1798 (3)	2437 (25)	7665 (11)	19 637 (26)	956 (26)	2417 (11)	53 011 (29)	n/a	20 830 (13)	17.6 (12.2 to 22.9)	8.61
Disease modifying HF drug treatment (n (%))	2379 (100)	18 547 (77)	5529 (95)	9039 (93)	56 895 (84)	65 470 (86)	3020 (82)	19 407 (89)	163 686 (91)	n/a	150 758 (91)	88.7 (84.7 to 92.8)	6.56
RAAS inhibitor (n (%))	1445 (61)	13 827 (58)	5007 (86)	6697 (69)	43 575 (65)	50 879 (66)	1837 (50)	14 446 (66)	132 989 (74)	8409 (59)	117 198 (71)	65.8 (60.3 to 71.3)	9.36
ACE inhibitor (n (%))	1368 (58)	9174 (38)	2578 (44)	3488 (36)	23 926 (36)	30 913 (40)	1380 (37)	6840 (31)	74 681 (41)	5746 (40)	81 713 (49)	41.0 (36.8 to 45.3)	7.19
ARB (n (%))	77 (3)	4653 (19)	1938 (33)	3738 (38)	23 033 (34)	21 653 (28)	487 (13)	7606 (35)	62 741 (35)	3363 (24)	40 177 (24)	26.1 (19.8 to 32.5)	10.77
Beta blocker (n (%))	1914 (80)	13 541 (57)	4944 (85)	7940 (81)	36 842 (55)	56 186 (73)	1939 (53)	15 160 (69)	142 418 (79)	8823 (62)	113 060 (68)	69.3 (62.5 to 76.1)	11.46
MRA (n (%))	2077 (87)	2942 (12)	1878 (32)	3389 (35)	15 474 (23)	12 828 (17)	452 (12)	6816 (31)	50 363 (28)	n/a	40 299 (24)	30.2 (16.8 to 43.6)	21.59
Sacubitril–valsartan (n (%))	138 (6)	185 (1)	595 (10)	n/a	593 (1)	2678 (3)	41 (1)	1632 (7)	3887 (2)	509 (4)	5003 (3)	3.8 (1.9 to 5.7)	3.08
SGLT-2i (n (%))	39 (2)	568 (2)	268 (5)	840 (9)	499 (1)	2472 (3)	73 (2)	797 (4)	3677 (2)	164 (1)	3086 (2)	2.9 (1.6 to 4.2)	2.18
Other HF treatments (n (%))													
Loop diuretics	1360 (57)	12 548 (52)	4077 (70)	5948 (61)	37 532 (56)	34 688 (45)	1964 (53)	15 680 (72)	95 881 (53)	n/a	85 769 (52)	57.1 (52.0 to 62.3)	8.24
Digoxin	591 (25)	2095 (9)	8 (0)	556 (6)	6851 (10)	5221 (7)	n/a	1676 (8)	19 338 (11)	n/a	19 842 (12)	9.6 (5.3 to 13.9)	6.61
Device therapy*	n/a	1145 (5)	1021 (2)	1683 (17)	460 (1)	7429 (10)	n/a	1430 (7)	28 702 (16)	768 (5)	20 036 (12)	8.2 (4.3 to 12.1)	5.92
Nitrates (n (%))	77 (3)	2999 (13)	107 (2)	975 (10)	5805 (9)	10 177 (13)	443 (12)	2411 (11)	37 700 (21)	n/a	32 047 (19)	11.3 (7.5 to 15.0)	6.02
Warfarin (n (%))	648 (27)	3331 (14)	1108 (19)	834 (9)	11 107 (16)	9786 (13)	227 (6)	4096 (19)	39 739 (22)	n/a	26 196 (16)	16.0 (12.2 to 19.9)	6.15
Receptor P2Y12 antagonists (n (%))	627 (26)	2782 (12)	1563 (27)	2092 (21)	7636 (11)	7722 (10)	274 (7)	2137 (10)	15 040 (8)	n/a	22 768 (14)	14.7 (10.1 to 19.2)	7.32

Random effect estimates were used to calculate pooled values and tau describes the estimated SD of underlying data across countries.
*Patients identified following a first hospitalisation for heart failure in a specified time period in Germany and Switzerland due to data availability, during 2019 and 2015–2019, respectively
†Laboratory and drug treatment data from one hospital, Leipzig Heart Centre, Leipzig, Germany.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; HF, heart failure; MRA, mineralocorticoid receptor antagonist; n/a, not available; NYHA, New York Heart Association; RAAS, renin–angiotensin–aldosterone system inhibitor; SGLT-2i, sodium–glucose cotransporter 2 inhibitors.

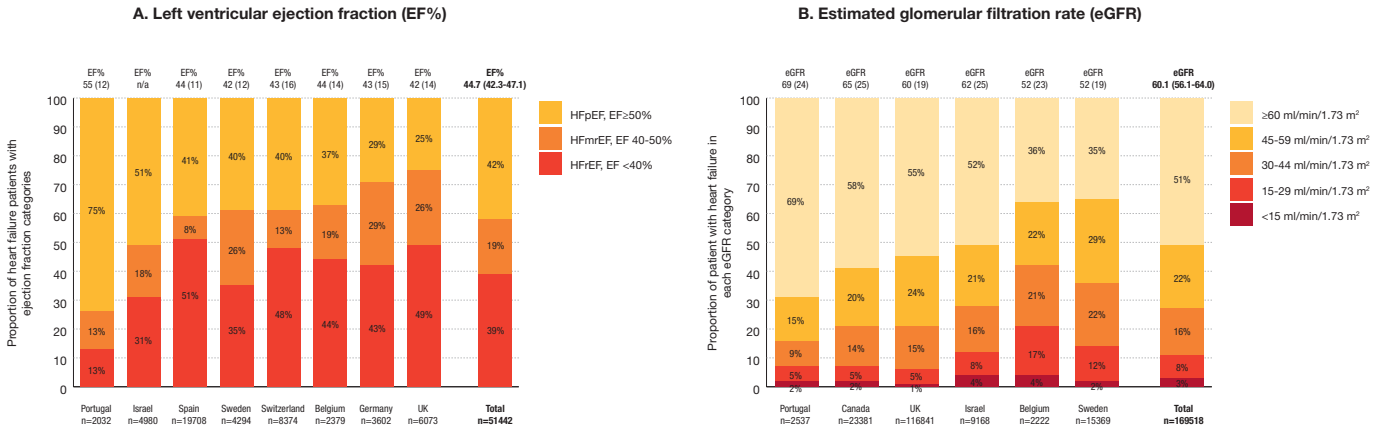

Figure 3 Baseline measurements of left ventricular ejection fraction (n=51 422) and estimated glomerular filtration rate (eGFR, n=1 69 518) across participating countries from data sources including these variables. (A) The proportion of 51 442 patients with heart failure and reduced (HFrEF), mildly reduced (HFmrEF) and preserved (HFpEF) left ventricular ejection fraction. Mean (SD) ejection fraction (EF%) is shown for each country on top of each bar. (B) The 1 69 518 patients with heart failure and a recorded eGFR value. Mean (SD) eGFR is shown for each country on top of each bar. Chronic kidney disease defined as eGFR <60 mL/min/1.73 m^2.

(Norway and Sweden), the prevalence of heart failure (broad definition) was 1.8% and 2.2%, respectively.

Baseline characteristics

A total of 6 29 440 patients with prevalent heart failure (broad definition) were identified between 2018 and 2020 (mean age 75.2 years (95% CI 74.0 to 76.4); 44.8% (95% CI 41.1 to 48.6) women; 48.8% (95% CI 40.9 to 56.8) had ischaemic heart disease; 44.1% (95% CI 39.1 to 49.0) had atrial fibrillation; and 34.5% (95% CI 29.4 to 39.6) had diabetes) (table 2). Most patients (74%) had a New York Heart Association (NYHA) class II or class III functional classification, whereas NYHA class I (13%) and class IV (13%) were less frequent. Regarding disease modifying medical treatment, 65.8% (95% CI 60.3 to 671.3) of patients were being treated with renin–angiotensin–aldosterone system inhibitors, 69.3% (95% CI 62.5 to 76.1) with beta blockers and 30.2% (95% CI 16.8 to 43.6) with mineralocorticoid receptor antagonists. Of the novel heart failure medications, 3.8% (95% CI 1.9 to 5.7) of patients were treated with angiotensin receptor–neprilysin inhibitors and 2.9% (95% CI 1.6 to 4.2) with SGLT-2 inhibitors. Device treatment was registered in 8.2% (95% CI 4.3–12.1) of patients.

Baseline left ventricular ejection fraction and estimated glomerular filtration rate

Measured left ventricular ejection fraction and estimated glomerular filtration rate (eGFR) were reported in 51 442 and 1 69 518 patients, respectively, representing 20% and 62% of patients with available electronic health records (online supplemental table S4). Left ventricular ejection fraction was reduced in 39.1% (95% CI 30.3 to 47.8), mildly reduced in 18.8% (95% CI 13.5 to 24.0) and preserved in 42.1% (95% CI 31.5 to 52.8) of those patients (figure 3A and online supplemental table S5). Of the 1 69 518 patients with a measured eGFR value, 49% had chronic kidney disease, stages III–V (eGFR of <60 mL/min/1.73 m^2; figure 3B and online supplemental table S5).

Event rates and hospital healthcare costs

Patterns of events per 100 patient years in persons with prevalent heart failure were similar across countries, and highest for cardiorenal disease (19.3 events (95% CI 11.3 to 27.2)) and all cause mortality (13.10 events (95% CI 11.1 to 15.1)) (table 3). When the components of cardiorenal disease were assessed separately, event rates for heart failure and chronic kidney disease were 15 and 6 events per 100 patients years, respectively. Events per 100 patient years for myocardial infarction (2.7 events (95% CI 1.3 to 3.9)), stroke (1.8 events (95% CI 1.2 to 2.5)) and peripheral artery disease (1.4 events (95% CI 0.8 to 2.0)) were lower, with similar incidence patterns between countries. During the first year, 13.1% died. Hospital healthcare costs were available from six countries covering 462 825 (74%) patients in the population. Baseline and cumulative costs were highest for heart failure, followed by chronic kidney disease. In comparison, costs for atherosclerotic cardiovascular diseases were lower (figure 4 and online supplemental table S6).

DISCUSSION

From a contemporary routine clinical practice setting that included a background population of approximately 32 million people, this study characterised more than 600 000 patients with heart failure using digital healthcare registries in 11 countries, and estimated the total cost of heart failure in healthcare systems across Europe, Israel and North America. The prevalence of heart failure varied between 1% and 2%, dependent on whether a strict or broad definition of heart failure was applied. Those with heart failure had numerous comorbidities, with ischaemic heart disease and chronic kidney disease stages III–V being higher than previously reported. Despite large heterogeneity in phenotypes of heart failure between countries, mainly explained by variations in the data sources, similar event rates and cost patterns from heart failure were observed. Modern treatment with angiotensin receptor–neprilysin inhibitors, SGLT-2 inhibitors and devices was generally still low. Most healthcare costs were attributable to cardiorenal events, higher than those stemming from atherosclerotic cardiovascular diseases, illustrating high rates of repeated heart failure events and mortality following heart failure. Patients with heart failure were also at high risk of death (13% died after 1 year).

Prevalence of heart failure

The prevalence of heart failure (1–2%) is consistent with several European focused cohort studies conducted over the past two decades.[16] However, as recently highlighted, heart failure often goes undiagnosed, and thus its prevalence could be as high as

Table 3 One year event rates per 100 patient years in a contemporary multinational population with prevalent heart failure

	Belgium	Canada	Germany*	Israel	Italy	Norway	Portugal	Spain	Sweden	UK	Pooled event rates (95% CI)	Tau
Cardiorenal disease	n/a	4735 (21.9)	10974 (18.6)	1243 (13.3)	14017 (23.5)	7848 (11.8)	128 (13.3)	8846 (48.8)	14106 (8.8)	8750 (13.1)	19.3 (11.3 to 27.2)	12.09
Heart failure	256 (19.7)	2918 (13.5)	9722 (16.6)	770 (8.2)	9987 (16.1)	6343 (9.5)	107 (11.1)	6512 (37.2)	12271 (7.6)	6869 (10.2)	15.0 (9.5 to 20.4)	8.75
Chronic kidney disease	251 (19.1)	1817 (8.4)	1280 (2.2)	482 (5.2)	1531 (2.3)	1996 (2.9)	38 (4.0)	2334 (11.5)	2425 (1.5)	2644 (3.8)	6.0 (2.7 to 9.4)	5.40
Myocardial infarction	113 (8.1)	517 (2.4)	652 (1.1)	67 (0.7)	1401 (2.1)	1541 (2.3)	21 (2.2)	1060 (5.0)	2289 (1.4)	1320 (1.9)	2.7 (1.4 to 3.9)	2.06
Stroke	45 (3.1)	375 (1.7)	579 (1.0)	56 (0.6)	1699 (2.6)	282 (0.4)	18 (1.9)	765 (3.6)	2784 (1.7)	1368 (2.0)	1.8 (1.2 to 2.4)	1.02
Peripheral artery disease	51 (3.5)	284 (1.3)	1619 (2.8)	65 (0.7)	846 (1.3)	933 (1.4)	1 (0.1)	445 (2.1)	1331 (0.8)	451 (0.6)	1.4 (0.8 to 2.0)	0.98
All cause death	172 (10.7)	2649 (12.1)	n/a	1115 (11.9)	n/a	7920 (11.6)	114 (11.9)	2677 (13.1)	21966 (13.2)	13869 (19.9)	13.1 (11.1 to 15.1)	2.89

Values are number of events (event rate per 100 patient years).
Random effect estimates were used to calculate pooled values, and tau describes the estimated SD of the underlying data across countries. High heart failure event rates in Spain is partly explained by physicians being prone to admit a patient earlier instead of ambulatory outpatient clinic follow-up.
*Patients identified following a first hospitalisation for heart failure in a specified time period in Germany and Switzerland due to data availability, during 2019 and 2015–2019, respectively.
†Countries with inhospital mortality death only.
n/a, not available.

4%.[16] By applying a broader definition of heart failure, it can be expected that not only a higher prevalence would be estimated than that using the strict definition, but also increased discrepancy between countries. The recent European Heart Failure Atlas Survey also found variations in prevalence between countries (1.2–3.9%),[16] potentially due to varying reporting practices and diagnostic tools, variation in the population's average age and, perhaps more importantly, differences in the clusters of risk factors.

A population burdened by comorbidities

The average age (75 years) of the patients in this study was higher than that of the populations included in several randomised clinical trials and cohort studies focused on heart failure.[4–8] Although the burden of comorbidities differed between countries, this study demonstrated that overall, around 50% of patients had ischaemic heart disease, one third had diabetes and about 50% had eGFR verified stage III–V chronic kidney disease (eGFR <60 mL/min/1.73 m^2), of which most (78%) were stage IIIa or stage IIIb. This indicates that contemporary patients with heart failure in clinical practice are generally older and burdened with more comorbidities than previously reported in single country studies (routine healthcare settings) that are now ageing.[11 13 17] This might partly be explained by a general trend of increasing survival, highlighting the importance of access to contemporary data to better understand the current population with heart failure.

Cardiorenal syndrome (heart failure and chronic kidney disease) has been associated with a substantially higher mortality risk than atherosclerotic cardiovascular diseases.[18 19] This study reports a high prevalence of cardiorenal syndrome. The highest hospitalisation rates after the first year were related to cardiorenal causes, further emphasising the deleterious interaction between heart failure and chronic kidney disease, and highlighting the importance of detecting chronic kidney disease in patients with heart failure.[19]

Heart failure phenotypes

The overall distribution of heart failure with reduced (39%), mildly reduced (19%) and preserved (42%) left ventricular ejection fraction (HFrEF, HFmrEF and HFpEF, respectively) in routine clinical practice differs from other studies with highly selected populations in terms of HFrEF (56–60%) and HFpEF (16–23%),[20 21] but is consistent with reports of increasing proportions of HFpEF in ageing populations.[1 16] For instance, HFrEF is often reported to be more common in populations with acute heart failure.[22] However, HFpEF or HFmrEF were most common (61%) phenotypes in the present study where data were collected in a routine clinical setting (at any healthcare level, both primary and hospital care, and not following an acute hospitalisation for heart failure). Proportions varied between countries, with higher incidences of HFpEF in countries with older populations, variations that might also be explained by how patients were referred or diagnosed (eg, availability of cardiologist examinations, accuracy of echocardiography measurements etc).

Risks

Event rates for heart failure and mortality were higher in this study compared with those reported by recent clinical trials in heart failure with reduced and preserved heart failure.[4–8] This might be explained by a population identified in clinical practice, which was older in age, versus those formed in randomised

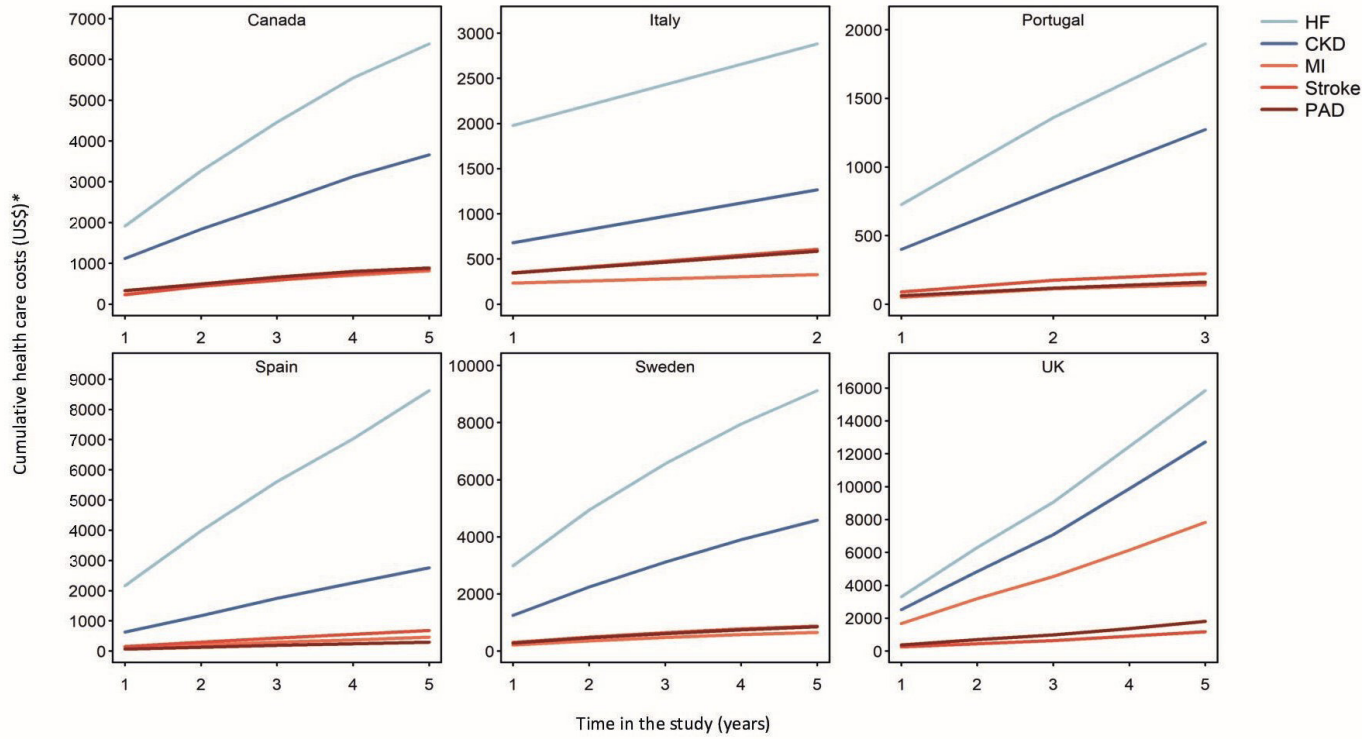

Figure 4 Cumulative hospital healthcare costs per patient in 3 62 825 patients with heart failure (HF) from six countries. Hospital healthcare cost data were available from Canada, Italy, Portugal, Spain, Sweden and the UK. Costs are in US$ per patient at index and cumulatively over a period of up to 5 years (from 2014 in Sweden, the UK and Canada; from 2015 in Spain; from 2017 in Portugal; and from 2018 in Italy). The x axis is the number of years (year 0 to 1 almost not illustrated). *For the purpose of currency conversion to US Dollars, US$1=0.77 Canadian Dollars, 1.13 Euros and 8.56 Swedish Krona. Fixed currency rates were used and variations over time were not accounted for. CKD, chronic kidney disease; MI, myocardial infarction; PAD, peripheral artery disease.

clinical trials, indirectly highlighting the need for clinical trials in an older, more representative, patient population.[4–8]

Hospital healthcare costs in a population with heart failure

The cumulative costs analyses account for repeated events, rather than the time to first event. This provided the capacity to demonstrate that, over a 5 year period, hospital healthcare costs in patients with heart failure were mainly driven by cardiorenal events, and to a lesser extent by atherosclerotic cardiovascular disease events, further highlighting the need for improved cardiorenal prevention and management.

Observational data collected from contemporary, real world, routine, clinical practice settings at all healthcare levels are of increasing importance given that heart failure management is rapidly changing due to paradigm shifting trials[3–8] and updated guidelines.[9–11] Hence real time understanding of the characteristics of patients with heart failure, as well as its burden and treatment, in routine real world clinical practice is warranted to understand unmet clinical needs and the current implementation of new guidelines.[23 24] For instance, it displays a truer comorbidity pattern of patients in need of intensified prevention, and thus informs how healthcare resources could be optimised. Further, it illustrates more realistic patterns and event rates resulting from heart failure than does the clinical trial setting, including more per protocol follow-up or disease specific registries where patients are often selected based on hospitalisation for heart failure. Moreover, data from the present study have been collected by all types of healthcare professionals interacting with patients with heart failure, and not only in a cardiology setting. Indeed, event rates in the present study were also higher than those in the most recent HFrEF trials, as discussed above. Finally, for researchers planning and interpreting clinical trial findings, the understanding of differences in characteristics and event rates across countries might be important to acknowledge if unexpected heterogeneity is seen in relation to treatment effects.[25]

This study used digital healthcare data to characterise over 600 000 patients with heart failure who were in routine clinical care. The recorded diagnoses for heart failure and chronic kidney disease used in that protocol have been validated previously, demonstrating high sensitivity and specificity (online supplemental material (3–6)).

Despite the strengths of this study, the findings should be interpreted with caution. The generalisability of our results to populations with very different circumstances in terms of race, resources or care is unknown. The prevalence of heart failure was not obtained in three of the 11 participating countries since estimation of the background population was missing. However, the robustness of the findings were supported by their consistency across heterogenous data sources (figure 2), representative population data (all countries) and different ethnicities (American, Asian and European; figure 1). Undetected and unreported heart failure in patients was not possible to assess in this study and might therefore underestimate the true prevalence. This study only assessed outcomes requiring hospital care, which might have also underestimated event rates with less severe conditions (eg, those managed in primary care). Some variables were not available in the registries (eg, ejection fraction (available in 20% of the population), eGFR (available in 62%), hypertension history, diabetes duration, body mass index,

smoking, alcohol consumption, diet, physical activity, stress, socioeconomic and environmental factors), limiting the descriptive capacity of this study. Further, data sources were limited to high income countries.

Although hospital healthcare costs were obtained in six out of the 11 participating countries, the available data covers 74% of the total population with heart failure, providing an indication of what healthcare costs could amount to across all countries in the analysis. It was assumed that the national healthcare and reimbursement structure specifics would affect different diseases similarly, and that within country ranking of costs for different diseases would therefore be possible. Renal replacement therapy costs were handled differently in different countries and this is likely to affect some within country rankings; notably, rankings were nonetheless quite similar between countries. However, ultimately, total healthcare costs are likely to be underestimated in this study as most costs are attributed to hospital care and do not account for non-hospital related costs (eg, primary care, drugs, indirect disease burden (eg, sick leave), etc).

CONCLUSION

In this contemporary population from a routine clinical practice setting, the prevalence of heart failure was 1–2% in Europe, Canada and Israel. Of these, more than half (>60%) had mildly reduced or preserved heart failure and almost half showed signs of kidney failure. These individuals are at significant risk of adverse outcomes and associated costs, predominantly driven by hospitalisations for heart failure or chronic kidney disease. With rapidly improving treatments for heart failure, there is considerable public health potential in understanding the contemporary burden of heart failure and the importance of optimising its management.

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Contributors All authors participated in the research design. MT performed the data management and statistical analyses for all countries after discussion with all authors. Statistical analyses were separately performed in Belgium, Canada, Germany, Israel, Italy, Norway, Portugal, Spain, Sweden and the UK. All authors participated in data interpretation and in writing the manuscript. AN, ABo and JB drafted the first manuscript with further adjustments from all authors. All authors took final responsibility in the decision to submit for publication. JB is the guarantor of this work and, as such, had full access to all the data in the study takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1 Savarese G, Lund LH, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden. Global public health burden of heart failure. *Card Fail Rev* 2017;03:7–11.
2 Stewart S, Jenkins A, Buchan S, *et al*. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail* 2002;4:361–71.
3 Solomon SD, McMurray JJV, Claggett B, *et al*. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med* 2022;387:1089–98.
4 McMurray JJV, Packer M, Desai AS, *et al*. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med Overseas Ed* 2014;371:993–1004.
5 McMurray JJV, Solomon SD, Inzucchi SE, *et al*. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019;381:1995–2008.
6 Packer M, Anker SD, Butler J, *et al*. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020;383:1413–24.
7 Anker SD, Butler J, Filippatos G, *et al*. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med* 2021;385:1451–61.
8 Heidenreich PA, Bozkurt B, Aguilar D. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2022;2022:e895–1032.
9 McDonagh TA, Metra M, Adamo M. Esc guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;2021:3599–726.
10 McDonald M, Virani S, Chan M, *et al*. CCS/CHFS heart failure guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol* 2021;37:531–46.
11 Conrad N, Judge A, Tran J, *et al*. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;391:572–80.
12 Seferović PM, Vardas P, Jankowska EA, *et al*. The Heart Failure Association Atlas: heart failure epidemiology and management statistics 2019. *Eur J Heart Fail* 2021;23:906–14.
13 Gerber Y, Weston SA, Redfield MM, *et al*. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015;175:996–1004.
14 Sundström J, Bodegard J, Bollmann A, *et al*. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2·4 million patients from 11 countries: the CaReMe CKD study. *Lancet Reg Health Eur* 2022;20:100438.
15 Ingelsson E, Arnlöv J, Sundström J, *et al*. The validity of a diagnosis of heart failure in a hospital discharge register. *Eur J Heart Fail* 2005;7:787–91.
16 Rosano GMC, Seferovic P, Savarese G, *et al*. Impact analysis of heart failure across European countries: an ESC-HFA position paper. *ESC Heart Fail*;26.
17 Lindmark K, Boman K, Olofsson M, *et al*. Epidemiology of heart failure and trends in diagnostic work-up: a retrospective, population-based cohort study in Sweden. *Clin Epidemiol* 2019;11:231–44.
18 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;22:1607–18.
19 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:e840–78.
20 Chioncel O, Lainscak M, Seferovic PM, *et al*. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC heart failure long-term registry. *Eur J Heart Fail* 2017;19:1574–85.
21 Savarese G, Settergren C, Schrage B, *et al*. Comorbidities and cause-specific outcomes in heart failure across the ejection fraction spectrum: a blueprint for clinical trial design. *Int J Cardiol* 2020;313:76–82.
22 Chioncel O, Mebazaa A, Harjola V-P, *et al*. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC heart failure long-term registry. *Eur J Heart Fail* 2017;19:1242–54.
23 Savarese G, Bodegard J, Norhammar A, *et al*. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). *Eur J Heart Fail* 2021;23:1499–511.
24 Savarese G, Kishi T, Vardeny O, *et al*. Heart failure drug Treatment-Inertia, titration, and discontinuation: a multinational observational study (evolution HF). *JACC Heart Fail* 2022.
25 Lam CSP, Ferreira JP, Pfarr E, *et al*. Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial. *Eur Heart J* 2021;42:4442–51.

SUPPLEMENTARY MATERIAL

Contents

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Data Sources

The study consists of data from nationwide cohort studies including patients with heart failure (HF) from Belgium, Canada, Germany, Israel, Italy, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom to obtain a study population of appropriate coverage. Countries within the Europe and Canada region and associated data sources were selected based on quality, representativeness, and availability. Hence, within each country, all available sources were scrutinized and interrogated for the research purpose. The properties of registries vary country to country (e.g., access to primary- and hospital care [Belgium, Canada, Israel, Italy, Portugal, Spain and United Kingdom] versus hospital care only [Germany, Norway and Switzerland], full population data (Norway and Sweden), representative population data [all countries]. Each country is represented by a national scientific committee. Additionally, a single, pre-specified protocol was implemented within each country, ensuring that data collection procedures were consistent between nations despite inherent differences between the various healthcare registries. The initiative is sponsored by AstraZeneca. A description of the respective databases is provided below.

Belgium

The Belgian retrospective data analysis study "CORDIS-HF" was set-up in order to collect baseline descriptive data (demographics, medication use, medical history, lab values) and cardiovascular /renal outcomes from Belgian HF patients. The study used the electronic medical records obtained from HF patients in a representative cardiology centre in Belgium (Cardiovascular Centre OLV Hospital Aalst, Dr.Marc Vanderheyden).

LynxCare, a data processor according to the GDPR (acting solely on the instructions of the hospital), obtained the study data through their data mining and natural language processing solution 'CareMonitor' whereby structured, semi-structured and unstructured reports (e.g., free text in clinical notes) are automatically processed and pre-defined datapoints are extracted and coded. These pre-defined datapoints are detected by using computational linguistic techniques and comprehensive clinical ontologies, scientifically validated (like SNOMED CT). LynxCare is an accredited data partner of the European Health Data Network and stores the data compliant to the OMOP Common Database Model, enabling the participation in other international research. This process has proven a 90% accuracy on a patient level for the datapoints defined, contingent on the inclusion of the datapoint in the clinical file. The result of this study is a pseudonymized research database compliant with the European Health Data Network requirements to be used by the hospital for the duration of the project for answering study questions, improving clinical insights and outcomes for the patients and can be a source for future research projects (conditionally to subsequent EC approvals). For the hospital, the source data is visualised in a comprehensive dashboard and can be consulted on the database level. All extracted concepts can be easily verified using the traceback functionality that shows the initial source were the data is extracted from LynxCare.

Canada

We conducted a retrospective cohort analysis using administrative health databases housed at the Repository at the Manitoba Centre for Health Policy (MCHP) at the University of Manitoba. The Repository holds population-wide de-identified health information for Manitoba residents. All databases are de-identified but contain a scrambled personal health identification number (PHIN) that allows linking unique individuals across databases. Demographics and vital status information were obtained from the Manitoba Health Insurance Registry. Medication information was obtained from the Drug Program Information Network (DPIN) database. Diagnostic and procedural information from all hospitalizations was determined using the Hospital Discharge Abstracts (CIHI-DAD). Laboratory data was obtained from the Diagnostic Services of Manitoba database which captures laboratory measures from hospital and community laboratories in Manitoba.

This study was approved by the University of Manitoba Health Research Ethics Board (ethics file number HS223414 (H2019:454)). The results and conclusions are those of the authors and no official endorsement by Manitoba Health was intended or should be inferred. Data used in this study are from the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health, Seniors, and Active Living, Vital Statistics, and Shared Health Diagnostic Services.

Germany

The "HELIOS-HF" study database includes HF patient information from administrative data covering approximately 86 Helios group hospitals. The Helios hospital group operates metropolitan and regional acute care hospitals ranging from basic to maximum care, outpatient clinics, and prevention centres across Germany (https://www.helios-gesundheit.de/). Patients have free choice of healthcare providers independent of insurance status. Helios hospitals provide inpatient care to about 1.2 million patients annually that corresponds to about 7% of all hospitalizations in Germany. The German Diagnosis Related Groups (G-DRG) system is used for hospital

reimbursement in Germany since 2004 and is subject to encoded diagnoses (International Statistical Classification of Diseases, German Modification; ICD-10 GM) and procedures (German procedure classification; OPS). This obligatory documentation and accounting system is specified and regulated in detail by mandatory coding instructions and requires the coding of a main diagnosis for all in-hospital cases reflecting the underlying cause for hospital admission. Up to 15% of the codes are controlled – and corrected if required – by specialized physicians ("Medizinischer Dienst der Krankenversicherung") independently from health insurances and hospitals. Administrative data provides information on basic characteristics (age, gender), the encoded main and secondary diagnoses at hospital discharge, type of hospital admission and type of hospital discharge. EMR data contains additional information (including used medication and laboratory results) for the sub-cohort of patients from the Heart Center Leipzig. The data are arranged on a case-by-case basis and can only be assigned to the specific patient within one unique hospital. There are no cross-links between hospitals regarding cases of individual patients.

Israel

Data from the Maccabi Healthcare Services (MHS) were used for this study. MHS is the second largest primary healthcare insurer and provider in Israel. This health maintenance organization (HMO) serves 25% of the total population in Israel, with approximately 2.2 million members. Since 1999, information on member–MHS interactions have been recorded in a large central computerized database. The database includes beyond demographic and administrative data, information on hospitalizations, emergency department, physician, outpatient specialist, and home healthcare visits. Additionally, purchases of medications and other aids, laboratory tests, imaging, and paramedical services such as nursing care, physiotherapy, social workers, and dietary consultations, patients' socioeconomic status and health care utilization are all captured. Comorbidities are gathered in MHS chronic disease registries (diabetes mellitus, hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and specific cardiovascular disease registry). Specific diagnoses including cerebrovascular accident, transient ischemic attack, myocardial infarction, peripheral vascular disease and atrial fibrillation were also available. Israel is well-represented by this database, though Maccabi patients are slightly younger, less heterogeneous, and have a slightly better higher income compared to the country as a whole.[1]

Italy

The database held by ReS Foundation (Fondazione ReS Ricerca e Salute) captures different administrative data sources, including Hospital Discharge Records (inpatient data, including causes of hospitalisation and associated costs), drug prescription, outpatient visits, and exemption codes for chronic diseases. Such data are reimbursement claims for the National Health System, which provides every resident in Italy with a public health insurance. The database is covering over 7 million patients aged 18 or older retrieved from several Regions across the whole Country, corresponding to more than 10% of the total Italian population. Subjects in the ReS database have been shown to have similar characteristics compared to demographics of the National Institute of Statistics (ISTAT) regarding the general census population.

Norway

The study database includes patient information from three linked national Norwegian registries with full coverage of the Norwegian population: the Norwegian Prescription Database (July 2004 to April 2020) covering all filled drug prescriptions using ATC codes; the Norwegian Cause of Death Registry (1958 to April 2020[2]; and the Norwegian Patient Register covering all open patient clinic visit diagnoses and all hospital discharge diagnoses for the years 2008 to 2020. Diagnoses are recorded according to the ICD-system. Data linkage was performed by the Norwegian Institute of Public Health.

The study was approved by the Regional Ethics Committee, Helse Sør-Øst (reference numbers 2015/1337/REK sør-øst A and 11744) and was authorized by the Norwegian Data Inspectorate (Datatilsynet). The linked database was separately managed by Statisticon AB (Uppsala, Sweden).

Portugal

The Unidade de Saude Local de Matosinhos EPE (USLM-EPE) is an integrated public medical care centre comprising both primary, secondary and tertiary healthcare. It fully serves the population of Matosinhos region, a urban area, that amounts to approximately 175.000 patients. Data was collected and anonymised by the hospital IT department from multiple healthcare systems used to provide everyday care both in hospital and primary care. The study was approved by the Ethics Committee and the Data Protection Officer of USLM-EPE. This was a secondary data study and data were fully anonymized and dissociated from patients. Therefore, according to Portuguese regulation, there was no need for collecting informed consent from the patients.

Spain

Observational cohort study, comprising cross-sectional and longitudinal retrospective analyses using secondary data captured in electronic health records from seven Spanish regions. Data sources were provided by BIG-PAC®. BIG-PAC is an electronic database that integrates information from primary and specialist care medical records. This database has been validated as an information source for studies of epidemiology, therapeutic adaptation and health/non-healthcare resource use. It has been demonstrated its representativeness of the Spanish population. This study was approved by the Investigation Ethics Committee of Consorci Sanitari from Terrassa on 16th December 2019. This was a secondary data study and data were fully anonymized and dissociated from patients. Therefore, according to Spanish regulation, there was no need for providing informed consent.

Sweden

The study database includes patient information from three linked national Swedish registries with full coverage of the Swedish population: the Prescribed Drug Register (July 2005 to December 2018) covering all filled drug prescriptions using the Anatomical Therapeutic Chemical (ATC) codes; the Cause of Death Registry (1987 to 2018); and the National Patient Registry covering all open patient clinic visit diagnoses for 2001 to 2018 and all hospital discharge diagnoses for the years 1987–2018.[3] Diagnoses are recorded according to the ICD-system and has been shown to be of high validity.[4] All three registers are held by the Swedish National Board of Health and Welfare (NBHW), who also performed the data linkage by using unique personal identification numbers.[5]
The study was approved by the Stockholm Regional Ethics Committee (reference numbers 2020-05714 and 2013/2206-31), with data linkage performed by the Swedish National Board of Health and Welfare. The linked database was separately managed by Statisticon AB (Uppsala, Sweden).

Clinical and Laboratory data Sweden (CELOSIA HF dataset)

The study population in the CELOSIA HF dataset comprises all patients in Stockholm with a recorded diagnosis of heart failure in the Stockholm Regional Healthcare Data Warehouse (called VAL) between January 2013 to June 2018 (Stockholm with its 2.4 million citizens accounts for 24% of the Swedish population). VAL includes information on all contacts with healthcare financed by Region Stockholm and data from primary care, secondary care and hospitalizations are included. Diagnoses are recorded according to the ICD system. Data on prescription drugs are coded according to the ATC system. VAL also contains demographic information on patient age, sex, migration status and death. For the study population, we included data on diagnoses, clinical procedures, demographics, and drug utilization for the period of January 2003 to June 2018. From Electronic Health Records, we included data on clinical measurements and results from laboratory tests for the period of January 2003 to June 2018 (with limited data in the earlier years and increasing over time).

The study was approved by the Ethical Review Authority (reference number 2020-03850). The CELOSIA HF dataset was separately managed by Sence Research AB (Uppsala, Sweden).

Switzerland

All patients with heart failure who were admitted at Bern University Hospital (Inselspital), Switzerland- a large tertiary cardiology center- between January 2015 and January 2020, were eligible for the present study. The clinical data warehouse at the Inselspital contains administrative and medical data of all patients from the department of cardiology and the heart failure division. Among other data, demographic and clinical characteristics, information on hospitalizations, comorbidities, implantable cardiac devices, heart failure and diabetes medication, laboratory data, and survival status is obtained. Demographic and clinical characteristics included age, sex, body mass index, NYHA functional class and left ventricular ejection fraction. Comorbidities included were chronic kidney disease, type 2 diabetes mellitus; cardiac devices included implantable cardioverter defibrillator, pacemaker and cardiac resynchronization therapy. Laboratory data consisted of lipid profile, HbA1c, iron, estimated glomerular filtration, and N-terminal-pro hormone BNP. The presence of cardiac devices, mainly ICD and CRT, was extracted using Swiss surgical classification (CHOP) codes. Medication information was obtained using ATC codes. Survival status was assessed by linking with the national mortality record. Information about the diagnosis was obtained based on the International Statistical Classification of Diseases and Related Health Problems 10th version, ICD. Survival status was assessed by linking with the national mortality record.

The study was approved for quality assurance by the Ethics Committee of the Canton Bern approved the study (KEK-Nr. Req-2020-00980). Data sharing is partly restricted as the original dataset contains de-identifying sets of coded diagnoses on patient level. Further data requests can be sent to Dr. Dominique Furrer (hc.lesni@rerruf.euqinimod), the director of the institutional data access at the Insel Data Science Center, University Hospital of Bern, Berne, Switzerland.

United Kingdom

Data Source: The Clinical Practice Research Datalink (CPRD) is a real-world research service supporting retrospective and prospective public health and clinical studies.[6] CPRD database contains de-identified patient data sourced from a sample of general practitioner (GP) practices that use either the Vision or EMIS software systems contributing to the CPRD GOLD or CPRD Aurum primary care databases, respectively.[7] These de-identified databases containing primary care data have been individually linked to secondary care and other health- and area-based datasets. The April 2020 release of both CPRD GOLD and CPRD Aurum were analysed. To avoid duplicate patient records, the 'Vison to EMIS Migrators' file was used to remove practices from CPRD GOLD where these overlap with the Aurum records. CPRD GOLD included 19 million individuals (with acceptable quality medical records) from 1987 onwards, from whom data were actively being collected for 3.1 million patients (4.7% of the population of UK). In addition, the CPRD GOLD database collects data from the four countries of the UK, with 22% of contributing practices located in England at the time of this study, 8% in Northern Ireland, 45% in Scotland and 25% in Wales. CPRD Aurum included 32 million individuals with complete reliable data spanning from 1 January 1995, from whom data were being actively collected for 11.1 million patients (17% of the population of UK). The CPRD Aurum database is more recently established, and at the time of this study (April 2020 release) drew on data collected from general practices in England mainly (99%), using the EMIS practice system. The databases include diagnoses, issued drug prescriptions, clinical measures taken within the general practice, lab tests and referrals to specialist care, and have been linked to national secondary care databases (e.g., Hospital Episode Statistics, HES with detailed hospitalisation information on hospital admissions episodes in UK) as well as deprivation and death registration (Office for National Statistics, ONS) data. The ONS mortality data was used to identify the specific cause of death outcomes. Hospitalisation information and specialist care notes are generally recorded by the general practitioner into the primary care patient records. Patients in CPRD are broadly representative of the UK general population.[7,8]

Study population: The study population comprised patients with heart failure diagnosis registered in CPRD GOLD and CPRD Aurum practices in the UK, including patients in research active practices and in those eligible for linkage to HES data. HF patients aged 18 years or older who had contributed data between 1 Jan 2007 and 30 April 2020 were included in this ecological study. Patients met the eligibility criteria for broad definition of prevalence estimates if they had a HF diagnosis (Read/SNOMED-CT) codes documented on or before the 1 January 2020 and were alive and registered in a CPRD practice on that date. Denominator data consisted of the count of all acceptable patients who were alive and registered at a CPRD contributing practice on 1 January 2020. Patients met the eligibility criteria for the strict definition of prevalence if they had an ICD-10 code for HF diagnosis documented on or before the 1 January 2019 and were alive and registered in a CPRD practice contributing linkage data to HES on that date. Denominator data consisted of the count of all acceptable patients who were alive and registered at a CPRD contributing practice with eligible linkage to HES on 1 January 2019. The latest available linked dataset for HES linkage at the time of this study (Set 18) was used for the analysis. A sub-cohort of patients with ICD-10 code in primary position for HF diagnosis in the HES-linked dataset and actively registered in the practices on 1 January 2018 was used to describe the 1-year year event rates. HES data were from practices in England only.

Ethics: This overall study protocol was approved by the Independent Scientific Advisory Committee (ISAC) of CPRD; protocol reference number: 19_264AR3. This study is based in part on data from the Clinical Practice Research Datalink (CPRD) obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. The data is provided by patients and collected by the National Health Service as part of patient care and support. This CPRD study also used data from the Office for National Statistics and Hospital Episode Statistics. The interpretation and conclusions contained in this study are those of the authors alone.

Table S1: Comorbidity definitions

Disease	ICD-8	ICD-9	ICD 10	Surgical code/medication
CVRD (includes all codes below)				
Myocardial infarction	410.9, 410.99	410	I21-I22, I25.2, I25.6	
CABG		414.02-07, V45.81-82		Surgical by-pass codes
PCI with stent				Peripheral intervention codes
Unstable angina		411	I20.0	
Angina pectoris	4193, 4139	413, 414.0	I20.1, I20.8, I20.9, I25.1, I25.5	Nitrates: C01DA
Heart failure (total)	425.99, 427.09–427.19, 427.99, 428.99	428	I50, I11.0, I13.0, I13.2	
Heart failure			I50	
Heart failure - hypertensive			I11.0, I13.0, I13.2	
CKD (total)	581.00–582.09, 583	585, 583.81, 250D	N17-N19, I12.0-I12.9, I13.1, I13.2, N08.3, E10.2, E11.2, E12.2, E13.2, E14.2, Z49, Z99.2	Dialysis and kidney transplantation codes
CKD - Acute			N17	
CKD - Chronic			N18	
CKD - Unspecified			N19	
CKD - Diabetic			E10.2, E11.2, E12.2, E13.2, E14.2, N08.3	
CKD - Hypertensive			I12.0-I12.9, I13.1, I13.2	
CKD - Dialysis			Z49, Z99.2	Daily codes
Atrial fibrillation	427.93, 427.94	427.3	I48	
Stroke		430-438, V125	I60-I66, G45	
Hemorrhagic	43000-43099, 43100, 43108–43190, 43198-43199	430-432	I60-I62	
Ischemic	43200–43299, 43309–43399, 43409-43499	433-434, 436	I63	
Transitory ischemic attack	43509-43599	V12.5, 435	G45	
Peripheral artery disease	440.20–440.30	440/441/444	I70.2, I73.9, I74.2-9	Revascularization codes, upper/lower extremities
Dialysis			Z49, Z99.2	
Cancer	140.0–204.4	140-239	C00-C99	

CVRD, cardiovascular renal disease. CABG, coronary artery bypass graft. PCI, percutaneous coronary intervention. CKD, chronic kidney disease.

Table S2: Index dates for the cohorts

	Cohort 1: Most contemporary baseline date	**Cohort 2:** 1-year event rate baseline date	**Cohort 3:** 5-year cost analysis baseline date
Belgium	2018-01-01	2018-01-01	n/a
Canada	2019-01-01	2018-01-01	2014-01-01
Germany	First HHF during 2019	n/a	n/a
Israel	2020-01-01	2019-01-01	n/a
Italy	2018-01-01	2018-01-01	2018-01-01
Norway	2020-01-01	2019-01-01	n/a
Portugal	2019-01-01	2018-01-01	2017-01-01
Spain	2019-01-01	2019-01-01	2015-01-01
Sweden	2019-01-01	2018-01-01	2014-01-01
Switzerland	First HHF during 2015-2019	n/a	n/a
UK	2020-01-01	2018-01-01	2014-01-01

Table S3: Outcomes

Variable	Definition	Comment
All-cause death	Death of any cause	
Cardiovascular death	Death with any "I" diagnosis as underlying cause of death	Only in countries with cause of death registry
Myocardial infarction	I21, I22	
Stroke	I60-I63	
Heart failure	I50, I11.0, I13.0, I13.2	
CKD	N17-N19, I12.0-I2.9, I13.1, I13.2, N08.3, E10.2, E11.2, E12.2, E13.2, E14.2, Z49, Z99.2 + procedure codes	
PAD	I70.2, I73.9, I74.2-9	

CKD, chronic kidney disease. PAD, peripheral artery disease.

Table S4: Coverage of EF% and eGFR in data sources

Proportion of patients with registered ejection fraction (EF) or estimated glomerular filtration rate (eGFR) with available electronic medical records (EMR) containing laboratory data

	Population with available EMR	EF registration	%
Portugal	3681	2032	55 %
Israel	9759	4980	51 %
Spain	21851	19708	90 %
Sweden	28116	4294	15 %
Switzerland	14204	8374	59 %
Belgium	2379	2379	100 %
UK	165244	6073	4 %
Total	**245234**	**47840**	**20 %**

	Population with available EMR	eGFR registration	%
Portugal	3681	2537	69 %
Canada	29953	2338	8 %
UK	165244	116841	71 %
Israel	9759	9168	94 %
Belgium	2379	2222	93 %
Sweden	28116	15369	55 %
Total	**239132**	**148475**	**62 %**

Proportion of patients with registered ejection fraction (EF) or estimated glomerular filtration rate (eGFR) with *and without* available electronic medical records (EMR) containing laboratory data

	Total HF population	EF	%
Portugal	3681	2032	55 %
Israel	9759	4980	51 %
Spain	21851	19708	90 %
Sweden	180727	4294	2 %
Switzerland	14204	8374	59 %
Belgium	2379	2379	100 %
UK	165244	6073	4 %
Norway	76561	0	0 %
Italy	67396	0	0 %
Total	**541802**	**47840**	**9 %**

	Total HF population	eGFR	%
Portugal	3681	2537	69 %
Canada	29953	2338	8 %
UK	165244	116841	71 %
Israel	9759	9168	94 %
Belgium	2379	2222	93 %
Sweden	180727	15369	9 %
Norway	76561	0	0 %
Italy	67396	0	0 %
Total	**535700**	**148475**	**28 %**

Table S5: Baseline EF% and eGFR

	Belgium	Canada	Germany*	Israel	Portugal	Spain	Sweden	Switzerland	UK	Total	Random effects estimate (95%CI)	τ^2
Ejection fraction, mean (SD)	44 (14)	n/a	43 (15)	n/a	55 (12)	44 (11)	42 (12)	43 (16)	42 (14)	44 (13)	44.7 (41.3-48.1)	4.61
≥50%	891 (37)	n/a	1,041 (29)	2,536 (51)	1,516 (75)	8,123 (41)	1,704 (40)	3,322 (40)	1,498 (25)	20,631 (40)	42.1 (31.5-52.8)	15.31
>40 - <50%	445 (19)	n/a	1,029 (29)	888 (18)	256 (13)	1,553 (8)	1,103 (26)	1,057 (13)	1,599 (26)	7,930 (15)	18.8 (13.5-24.0)	7.51
≤40%	1,043 (44)	n/a	1,532 (43)	1,553 (31)	260 (13)	10,032 (51)	1,487 (35)	3,995 (48)	2,976 (49)	22,878 (44)	39.1 (30.3-47.8)	12.63
eGFR, mean (SD)	52 (23)	65 (25)	62 (24)	62 (25)	69 (24)	n/a	52 (19)	n/a	60 (19)	60 (21)	60.1 (54.5-65.7)	6.99
≥60	811 (36)	13,615 (58)	n/a	4,746 (52)	1,753 (69)	n/a	5,421 (35)	n/a	64,492 (55)	90,838 (54)	51.0 (40.6-61.5)	13.05
<60	1,411 (64)	9,766 (42)	n/a	4,422 (48)	784 (31)	n/a	9,948 (65)	n/a	52,349 (45)	78,680 (46)	49.0 (38.5-59.4)	13.05
45-59	481 (22)	4,716 (20)	n/a	1,882 (21)	377 (15)	n/a	4,510 (29)	n/a	27,905 (24)	39,871 (24)	21.8 (17.9-25.6)	4.74
30-44	470 (21)	3,205 (14)	n/a	1,502 (16)	228 (9)	n/a	3,311 (22)	n/a	17,580 (15)	26,296 (16)	16.1 (12.3-19.9)	4.70
15-29	380 (17)	1,272 (5)	n/a	710 (8)	122 (5)	n/a	1,773 (12)	n/a	5,665 (5)	9,922 (6)	8.5 (4.7-12.4)	4.83
<15	80 (4)	573 (2)	n/a	328 (4)	57 (2)	n/a	354 (2)	n/a	1,199 (1)	2,591 (2)	2.5 (1.7-3.3)	0.94

SD, Standard deviation. EF%, left ventricular ejection fraction. eGFR, estimated glomerular filtration rate, ml/min/1.73 m^2. *eGFR <60 ml/min/1.73 m^2. CKD, chronic kidney disease defined as eGFR <60 ml/min/1.73 m^2.
UK, United Kingdom.

Table S6: Detailed Hospital health care costs (US$) per patient.

	Year 1	Year 2	Year 3	Year 4	Year 5
Canada					
Cardiovascular and renal disease					
Cardiorenal disease					
Heart failure	3719	4563	5450	6464	7280
Chronic kidney disease	2104	3473	5299	7073	11023
Atherosclerotic cardiovascular disease					
Myocardial infarction	3908	4962	6150	7172	7913
Stroke	261	349	468	557	650
Peripheral artery disease	602	724	940	1108	1229
Italy					
Cardiovascular and renal disease					
Cardiorenal disease					
Heart failure	700	1038	n/a	n/a	n/a
Chronic kidney disease	100	195	n/a	n/a	n/a
Atherosclerotic cardiovascular disease					
Myocardial infarction	177	244	n/a	n/a	n/a
Stroke	128	226	n/a	n/a	n/a
Peripheral artery disease	101	193	n/a	n/a	n/a
Portugal					
Cardiovascular and renal disease					
Cardiorenal disease					
Heart failure	867	1597	2142	2626	3074
Chronic kidney disease	468	868	1196	1551	1914
Atherosclerotic cardiovascular disease					
Myocardial infarction	43	101	146	191	217
Stroke	510	885	947	1015	1050
Peripheral artery disease	94	138	180	225	271
Spain					
Cardiovascular and renal disease					
Cardiorenal disease					
Heart failure	2161	3982	5603	7028	8618
Chronic kidney disease	625	1173	1750	2258	2752
Atherosclerotic cardiovascular disease					
Myocardial infarction	107	203	289	366	457
Stroke	152	290	435	553	677
Peripheral artery disease	69	123	185	238	297
Sweden					
Cardiovascular and renal disease					
Cardiorenal disease					
Heart failure	2983	4933	6561	7954	9114
Chronic kidney disease	1250	2245	3119	3899	4586
Atherosclerotic cardiovascular disease					
Myocardial infarction	209	360	482	576	654
Stroke	298	487	643	772	879
Peripheral artery disease	274	461	607	742	848
United Kingdom					
Cardiovascular and renal disease					
Cardiorenal disease					
Heart failure	3303	6297	9060	12454	15831
Chronic kidney disease	2505	4841	7074	9872	12721
Atherosclerotic cardiovascular disease					
Myocardial infarction	1672	3184	4532	6144	7816
Stroke	245	440	633	899	1174
Peripheral artery disease	359	688	979	1355	1807

SD, Standard deviation. The holistic cardiorenal disease definition (heart failure or chronic kidney disease)[9] is important to better understand the interchangeable relationship between these conditions, [10,11] improve treatment strategies,[12] and reduce the burden on healthcare providers.[13,14]

References

1. Vigen R, Maddox TM, Allen LA. Aging of the United States population: impact on heart failure. *Curr Heart Fail Rep* 2012; **9**(4): 369-74.
2. Norwegian Cause of Death Registry. https://www.fhi.no/en/hn/health-registries/cause-of-death-registry/ (accessed 9th of February 2017).
3. Norhammar A, Bodegard J, Nystrom T, Thuresson M, Eriksson JW, Nathanson D. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. *Diabetologia* 2016; **59**(8): 1692-701.
4. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450.
5. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; **24**(11): 659-67.
6. CPRD. Clinical Practice Research Datalink. https://cprd.com/home (accessed 9 Feb 2021.
7. Dedman D, Lunn D, Booth H, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. 2019.
8. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015; **44**(3): 827-36.
9. Schechter M, Melzer Cohen C, Yanuv I, et al. Epidemiology of the diabetes-cardio-renal spectrum: a cross-sectional report of 1.4 million adults. *Cardiovasc Diabetol* 2022; **21**(1): 104.
10. Braunwald E. Diabetes, heart failure, and renal dysfunction: The vicious circles. *Prog Cardiovasc Dis* 2019; **62**(4): 298-302.
11. 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-e78.
12. Handelsman Y, Anderson JE, Bakris GL, et al. DCRM Multispecialty Practice Recommendations for the management of diabetes, cardiorenal, and metabolic diseases. *J Diabetes Complications* 2022; **36**(2): 108101.
13. 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): 415-24.

14. 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; **24**(7): 1277-87.