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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

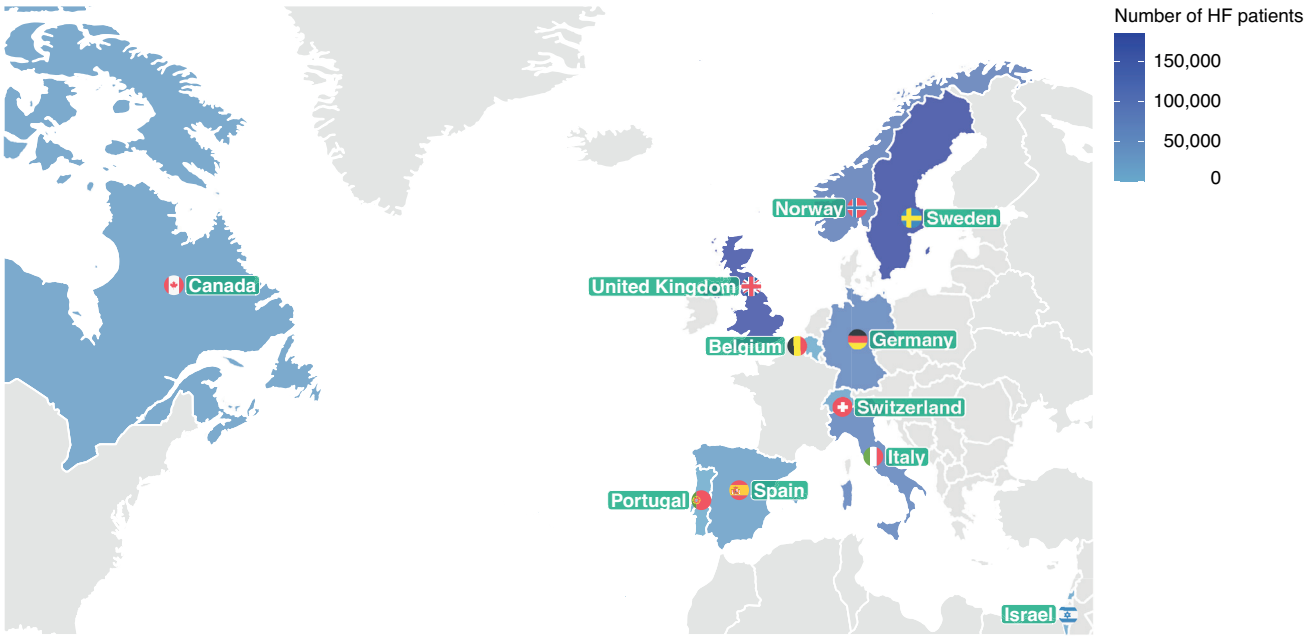

Figure 1 Number of included patients with heart failure (HF) in each of the 11 participating countries.

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.

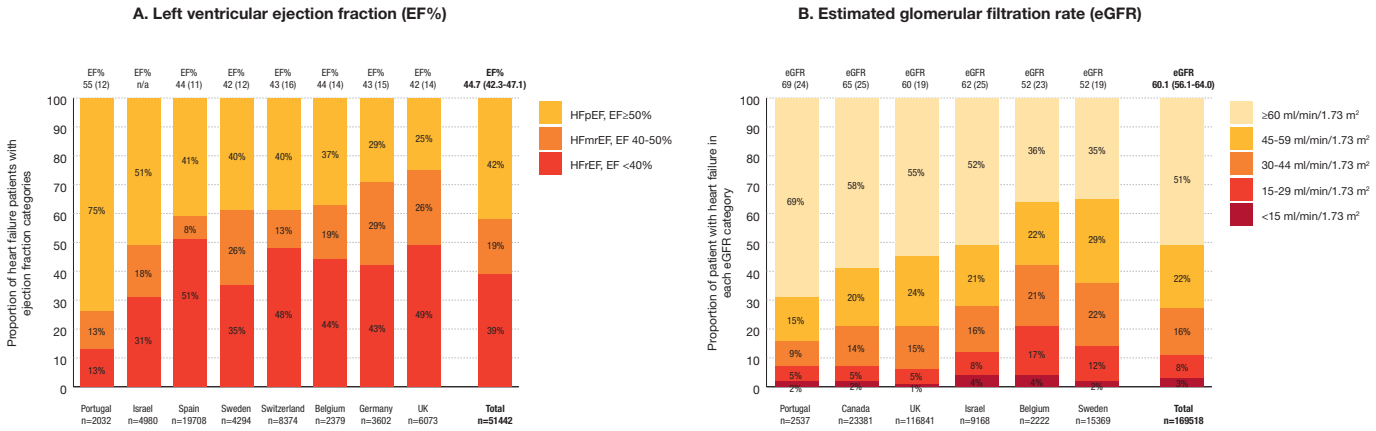

Figure 3 Baseline measurements of left ventricular ejection fraction (n=51 422) and estimated glomerular filtration rate (eGFR, n=1 69 518) across participating countries from data sources including these variables. (A) The proportion of 51 442 patients with heart failure and reduced (HFrEF), mildly 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

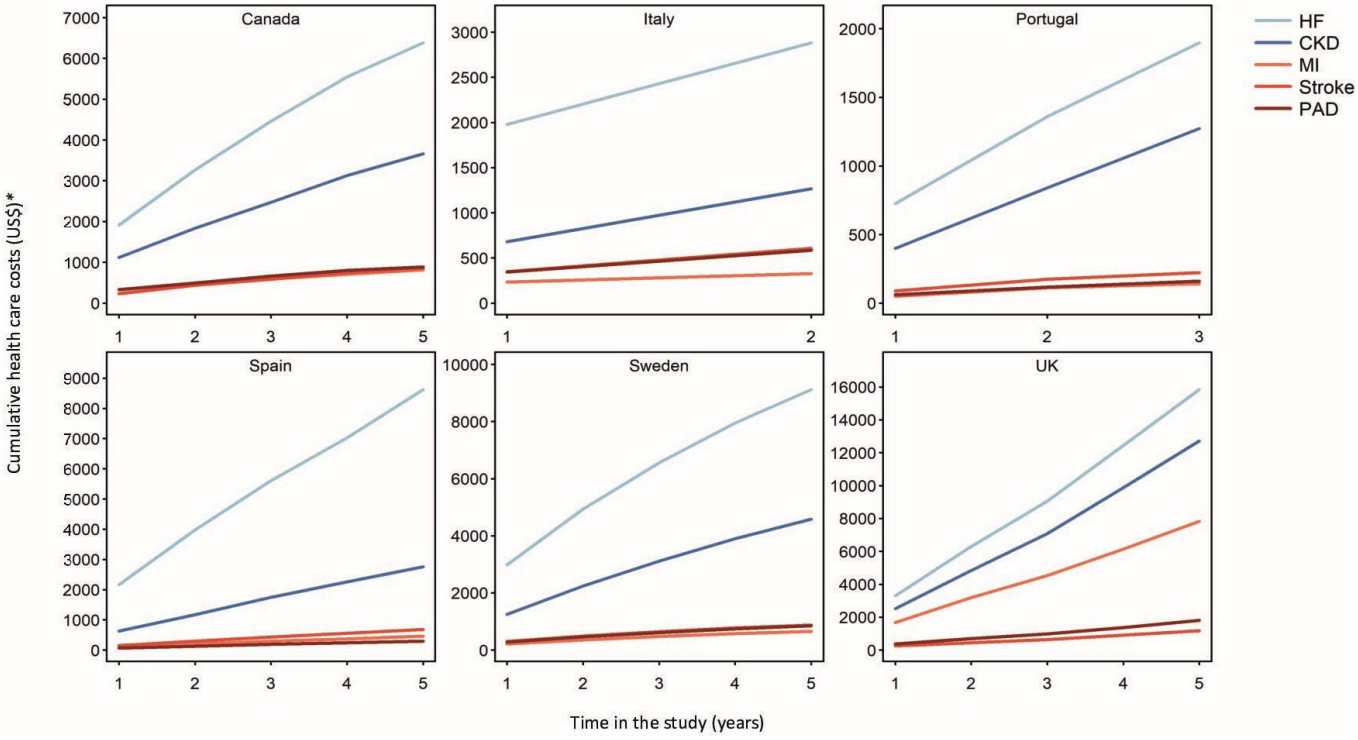

Figure 4 Cumulative hospital healthcare costs per patient in 3 62 825 patients with heart failure (HF) from six countries. Hospital healthcare cost data were available from Canada, Italy, Portugal, Spain, Sweden and the UK. Costs are in US$ per patient at index and cumulatively over a period of up to 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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