Heart failure and cardiomyopathies

Original research

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 629,624 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 169,518 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.

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,1–8 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 described 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 failure affecting up to 64 million people worldwide and its incidence is expected to rise with ageing populations and improved diagnostic methods.3

INTRODUCTION
Heart failure affects up to 64 million people worldwide and its incidence is expected to rise with ageing populations and improved diagnostic methods.3...
Heart failure and cardiomyopathies

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). 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

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<th>Belgium</th>
<th>Canada</th>
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Figure 1  Number of included patients with heart failure (HF) in each of the 11 participating countries.

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 (inpatient care). Green colour, Data available and utilized; Orange colour, Data not available.
Heart failure and cardiomyopathies

or hospital setting. 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.

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 |
| 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           | 1.13           | 1.43           | n/a            | 1.27           | 1.05           | 1.07           | 1.05           | 0.85 (1.25) 0.27  |
| No of patients with heart failure | 11 243         | 9 759           | 35 660         | 46 840         | 1 840          | n/a            | 103 182        | 74 055         | 282 579        |
| Broad definition (n) | 23 953         | n/a             | 67 369         | 76 561         | 36 81           | 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      | 12 8605        | 11 189 013    | 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

<table>
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<tr>
<th></th>
<th>Belgium</th>
<th>Canada</th>
<th>Germany*†</th>
<th>Israel</th>
<th>Italy</th>
<th>Norway</th>
<th>Spain</th>
<th>Sweden</th>
<th>Switzerland*</th>
<th>UK</th>
<th>Pooled baseline (95% CI)</th>
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<td><strong>No of patients</strong></td>
<td>2379</td>
<td>23 935</td>
<td>63 712</td>
<td>9759</td>
<td>67 369</td>
<td>76 561</td>
<td>3681</td>
<td>21 851</td>
<td>180 727</td>
<td>142 204</td>
<td>165 244</td>
</tr>
<tr>
<td><strong>Age (years) (mean (SD))</strong></td>
<td>72 (17)</td>
<td>75 (14)</td>
<td>75 (12)</td>
<td>74 (13)</td>
<td>78 (12)</td>
<td>74 (13)</td>
<td>78 (12)</td>
<td>75 (13)</td>
<td>74 (13)</td>
<td>74 (13)</td>
<td>75.2 (74.0 to 76.4)</td>
</tr>
<tr>
<td><strong>Women (%)</strong></td>
<td>932 (39)</td>
<td>11 993 (50)</td>
<td>27 892 (44)</td>
<td>36 881 (38)</td>
<td>33 987 (50)</td>
<td>30 746 (40)</td>
<td>21 711 (59)</td>
<td>10 261 (47)</td>
<td>77 791 (43)</td>
<td>5612 (40)</td>
<td>71 862 (43)</td>
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<table>
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<th><strong>NYHA functional classification (%)</strong></th>
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<th>II</th>
<th>III</th>
<th>IV</th>
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<tr>
<td>Age (years) (mean (SD))</td>
<td>72 (17)</td>
<td>75 (14)</td>
<td>75 (12)</td>
<td>74 (13)</td>
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<tr>
<td>Ischaemic heart disease (%)</td>
<td>1424 (60)</td>
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<td>8172 (45)</td>
<td>n/a</td>
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<td>Myocardial infarction (%)</td>
<td>883 (37)</td>
<td>7042 (29)</td>
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<td>n/a</td>
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<tr>
<td>Unstable angina (%)</td>
<td>9 (8)</td>
<td>6126 (26)</td>
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<td>n/a</td>
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<tr>
<td>Angina pectoris (%)</td>
<td>764 (32)</td>
<td>13 282 (55)</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Stroke (%)</td>
<td>428 (18)</td>
<td>4133 (17)</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Atial fibrillation/flutter (%)</td>
<td>1258 (53)</td>
<td>11 886 (50)</td>
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<td>n/a</td>
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<tr>
<td>Peripheral artery disease (%)</td>
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<td>2729 (11)</td>
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<td>n/a</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>865 (36)</td>
<td>10 549 (44)</td>
<td>n/a</td>
<td>n/a</td>
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<td>CKD diagnosis (%)</td>
<td>15 15 (64)</td>
<td>9766 (41)</td>
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<td>n/a</td>
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<td>Cancer (%)</td>
<td>439 (18)</td>
<td>2471 (14)</td>
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<td>Disease modifying HF drug treatment (%)</td>
<td>23 79 (100)</td>
<td>18 547 (77)</td>
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<td>RAAS inhibitor (%)</td>
<td>1445 (61)</td>
<td>13 827 (58)</td>
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<td>ACE inhibitor (%)</td>
<td>1368 (58)</td>
<td>9714 (38)</td>
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<td>ARB (%)</td>
<td>77 (3)</td>
<td>4653 (19)</td>
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<td>n/a</td>
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<td>Beta-blocker (%)</td>
<td>1914 (80)</td>
<td>13 541 (57)</td>
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<td>n/a</td>
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<td>MRA (%)</td>
<td>2077 (87)</td>
<td>2942 (12)</td>
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<td>n/a</td>
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<td>Sacubitril–valsartan (%)</td>
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<td>SGLT-2 (%)</td>
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<td>157 (2)</td>
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<td>Loop diuretics</td>
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<td>Nitrates (%)</td>
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<td>Warfarin (%)</td>
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<td>3331 (14)</td>
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<td>627 (26)</td>
<td>2782 (12)</td>
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**Heart failure and cardiomyopathies**

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-2, sodium-glucose co-transporter 2 inhibitors.
Heart failure and cardiomyopathies

Figure 3  Baseline measurements of left ventricular ejection fraction (EF%) and estimated glomerular filtration rate (eGFR, n=1 695 18) across participating countries from data sources including these variables. (A) The proportion of 51 442 patients with heart failure and reduced (HFrEF) and preserved (HfPEF) left ventricular ejection fraction. Mean (SD) ejection fraction (EF%) is shown for each country on top of each bar. (B) The 1 695 18 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 629 440 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 67.3) 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 agonists. Of the novel heart failure medications, 3.8% (95% CI 1.9 to 5.7) of patients were treated with angiotensin receptor–neprilsin 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 1 695 18 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 1 695 18 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–neprilsin 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. However, as recently highlighted, heart failure often goes undiagnosed, and thus its prevalence could be as high as...
Heart failure and cardiomyopathies

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

<table>
<thead>
<tr>
<th>Pooled event rates</th>
<th>(95% CI)</th>
<th>Tau</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>10.9%</td>
<td>2.32</td>
</tr>
<tr>
<td>Canada</td>
<td>12.3%</td>
<td>1.91</td>
</tr>
<tr>
<td>Germany*</td>
<td>11.3%</td>
<td>2.28</td>
</tr>
<tr>
<td>Israel</td>
<td>9.6%</td>
<td>1.77</td>
</tr>
<tr>
<td>Norway</td>
<td>12.8%</td>
<td>2.18</td>
</tr>
<tr>
<td>Portugal</td>
<td>11.0%</td>
<td>1.93</td>
</tr>
<tr>
<td>Spain</td>
<td>10.8%</td>
<td>2.08</td>
</tr>
<tr>
<td>Sweden</td>
<td>10.5%</td>
<td>1.91</td>
</tr>
<tr>
<td>UK</td>
<td>10.7%</td>
<td>2.09</td>
</tr>
</tbody>
</table>

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) 65 (0.9) 1699 (2.6) 765 (0.6) 18 (1.9) 323 (1.6) 291 (1.5) 313 (1.9) 1.8 (1.2 to 2.4) 1.02
Peripheral artery disease: 51 (3.9) 284 (1.3) 1619 (2.8) 65 (0.7) 846 (1.3) 923 (1.4) 114 (1.9) 267 (1.3) 2196 (1.2) 13869 (19.9) 131 (1.1) 15.1 2.89

Values are number of events (event rate per 100 patient years). Random effect estimates were used to calculate pooled event rate estimates.

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. 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 m²), 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. 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. 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.

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 HFP EF, respectively) in routine clinical practice differs from other studies with highly selected populations in terms of HFrEF (56–60%) and HFP EF (16–23%), but is consistent with reports of increasing proportions of HFpEF in ageing populations. For instance, HFrEF is often reported to be more common in populations with acute heart failure. However, HFP EF 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 HFP EF 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. This might be explained by a population identified in clinical practice, which was older in age, versus those formed in randomised...
Heart failure and cardiomyopathies


clinical trials, indirectly highlighting the need for clinical trials in an older, more representative, patient population.

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 cardio-renal 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 and updated guidelines. 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. 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.

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,
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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Acknowledgements This study is the result of the contributions from many collaborating investigators, statisticians and project managers from all participating countries, for which we are deeply grateful. We thank the scientific and statistical support from the CaReMe Heart Failure Investigator group, Imke Masuy, LynxCare Clinical Research, Leuven; Monika Beles, Cardiovascular Center, Onze-Lieve-Vrouwe Ziekenhuis Aalst, Aalst; Sebastian König PhD, Heart Center Leipzig at University of Leipzig and Leipzig Heart Institute, Leipzig; Vincent Pellissier PhD and Anne Nitsche, Leipzig Heart Institute; Leipzig; Cheli Melzer Cohen MD PhD, Maccabi Institute for Research and Innovation, Maccabi Healthcare Services, Tel Aviv; Letizia Dondì MSc, Fondazione Re's Ricerca e Salute, Casalvecchio di Rienzo, Bologna; and Birkerd MD PhD, Oslo University Hospital and University of Oslo, Oslo; Cristina Gawina MD PhD, Department of Cardiology, Hospital Pedro Hispano USLM; Roberto Alcazar MD, University Hospital Infantia Leonor, Madrid; Antonio Hormigo MD, Primary Care Center Puerta Blanca, Malaga; Nicolás Manito MD, University Hospital Bellvitge, Hospital de Llobregat, Barcelona; Ian W Eriksson MD PhD, Department of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, Uppsala; Thomas Cars PhD, SENCE Research AB, Uppsala; Valentina Gonzalez-Jaramillo MD MSc and Professor Taulant Muka MD PhD, Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern; Ruigi Zhang PhD and Jil Billy Maman PhD, Medical and Scientific Affairs, BioPharmaceuticals Medical, AstraZeneca, Cambridge. The study would not have been possible without the valuable management and support from Isabelle Fovel, Eef Vandendriessche, Zarha Vermeulen PhD and Marieke Dijkema MD PhD, AstraZeneca, Brussels; Navid Shohri Fard, Amgen, Cambridge; KanyiPhyli PhD, AstraZeneca, Ontario; Antoine Piéchal and Marie-Hélène, AstraZeneca, Hamburg; Maya Greenbloom, AstraZeneca, Tel Aviv; Marco Gnesi PhD, Francesca Pluchinotta MD and Lavinia Narici, AstraZeneca, Milan; Mário Almeida, Hugo Martinho and Filipe Bernardo, AstraZeneca, Lisbon; Carlos Escobar Cerventas MD, University Hospital La Paz, Madrid; Beatriz Palacios PhD and Luis Varela MD, AstraZeneca, Madrid; Peter Langer, AstraZeneca, Bern. Special thanks to Susanna Jerström and Helena Goike PhD, AstraZeneca Nordic, Södertälje, for international coordination and publication support. The authors thank Jordan Loader PhD of Sence, Uppsala, Sweden, for providing medical writing support/editorial support, which was funded by AstraZeneca, Stockholm, Sweden, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). All authors are guarantors of the manuscript. Data from the Norwegian Patient Register, Norwegian Cause of Death Registry, and Norwegian Prescription Database have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian patient register is intended nor should be inferred.

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, Canada, Germany, Israel, Italy, Norway, Portugal, Spain, Sweden and the UK. All authors participated in data interpretation and in writing the manuscript. AN, AB, JD 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 and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding This work was sponsored by AstraZeneca. AstraZeneca, JB, supported the design, interpretation of results, writing of the manuscript and publication of this study together with the investigators. Study management and data extraction was coordinated by AstraZeneca in all countries.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by countries where applicable. Canada: the study was approved by the University of Manitoba Health Research Ethics Board (ethics file number HS23414 (H2019-454)). Norway: the study was approved by the Regional Ethics Committee, Helse Sør-Øst (reference Nos 2015/1337/REK sør-est A and 11744) and was authorised by the Norwegian Data Inspectorate (Datatilsynet). Portugal: the study was approved by the ethics committee and the Data Protection Officer of USLM-EPE. Spain: the study was approved by the Investigation Ethics Committee of Consorci Sanitari from Terrassa. Sweden: the study was approved by the Stockholm Regional Ethics Committee (reference Nos 2020-05714 and 2013/2206-31); the study was also approved by the Ethical Review Authority (reference No 2020-03850). Switzerland: the study was approved for quality assurance by the ethics committee of the Canton Bern study (KEK-Nr: Req-2020-00980). UK: the overall study protocol was approved by the Independent Scientific Advisory Committee (ISAC) of CPRD; protocol reference No 19_264AR3; this was a secondary data study and data were fully anonymised and dissociated from patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data sources used in the present are all underlying local, ethical and privacy restrictions for data transfer abroad or into public domain, limiting data availability on request. Therefore, the data that support the findings of this study are not available on request.

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