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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Suspected *de novo* heart failure in outpatient care: the REVOLUTION HF study

Lisa Anderson[1], Antoni Bayes-Genis [2], Johan Bodegård [3], Katrina Mullin[4], Stefan Gustafsson[5], Giuseppe M.C. Rosano [1,6,7,*], and Johan Sundström[8,9]

[1]Cardiovascular Clinical Academic Group, Molecular and Clinical Sciences Research Institute, St George's, University of London and St George's University Hospitals NHS Foundation Trust, London, UK; [2]Heart Institute, Hospital Universitari German Trias i Pujol, Universitat Autonoma de Barcelona, CIBERCV, Barcelona, Spain; [3]Cardiovascular Renal and Metabolism Evidence, BioPharmaceuticals Medical, AstraZeneca, Gothenburg, Sweden; [4]Cardiovascular, Renal and Metabolism Global Medical Affairs, BioPharmaceuticals Medical, AstraZeneca, Cambridge, UK; [5]Sence Research, Uppsala, Sweden; [6]Cardiology, San Raffaele Hospital Cassino, Cassino, Italy; [7]Department of Human Sciences and Promotion of Quality of Life, San Raffaele Open University of Rome, Rome, Italy; [8]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; and [9]The George Institute for Global Health, University of New South Wales, Sydney, Australia

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Abstract

Background and Aims Ambulatory patients presenting with signs or symptoms of heart failure (HF) should undergo natriuretic peptide testing. Rates of death, HF hospitalization, and healthcare costs were examined in patients thus identified with suspected *de novo* HF.

Methods This population-based study (REVOLUTION HF) encompassing two large healthcare regions in Sweden examined patients who presented to outpatient care for the first time between 1 January 2015 and 31 December 2020, who had a recorded sign (peripheral oedema) or symptom (dyspnoea) of HF, and whose N-terminal pro-B-type natriuretic peptide (NT-proBNP) measured >300 ng/L within ±30 days of that sign or symptom. Characteristics, outcomes, healthcare patterns, and healthcare costs for these patients were followed for 1 year. Comparisons were made with matched controls without history of HF, its signs, its symptoms, or elevated NT-proBNP.

Results Overall, 5942 patients (median age 78.7 years; 54% women) presented with suspected *de novo* HF. Within 1 year, 29% had received a HF diagnosis. Patients with suspected *de novo* HF had higher rates of all-cause death (11.7 vs. 6.5 events/100 person-years) and HF hospitalizations (12.5 vs. 2.2 events/100 person-years) than matched controls ($n = 2048$), with the highest event rates in the weeks after presentation. Rates were higher with higher NT-proBNP levels. Although some patients already used HF guideline-directed medical therapies for other indications, initiation of new medications was variable. Healthcare costs were higher in patients with suspected *de novo* HF than in matched controls, driven mostly by HF and chronic kidney disease.

Conclusions Patients with suspected HF and elevated NT-proBNP had high mortality and morbidity in the weeks after presentation, and accrued substantial healthcare costs, highlighting an urgent need for prompt identification, evaluation, and treatment of HF.

* Corresponding author. Email: giuseppe.rosano@gmail.com

Structured Graphical Abstract

Key Question

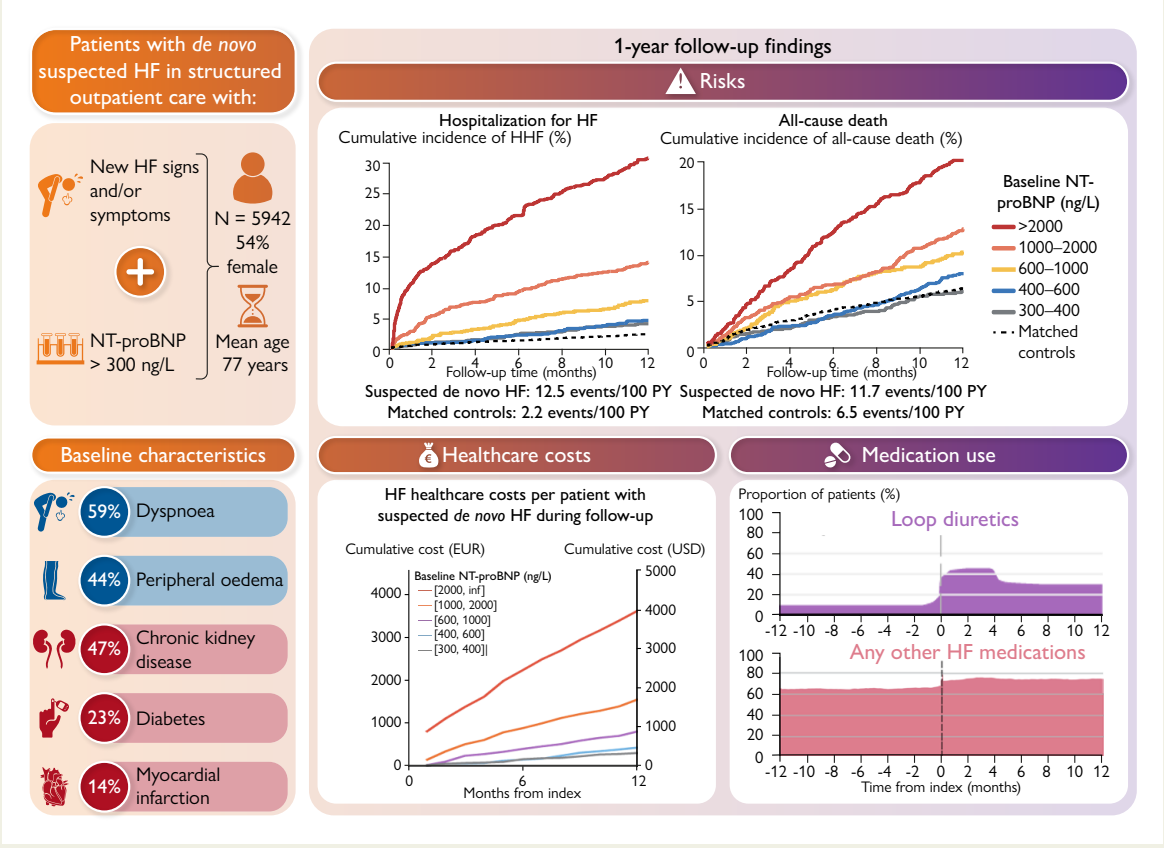
What are the characteristics, risk, cost, and medication use in patients presenting in outpatient care with a combination of heart failure (HF) signs (peripheral oedema) and/or symptoms (dyspnoea) and elevated NT-proBNP levels?

Key Finding

In this population-based study encompassing two large healthcare regions in Sweden, patients who presented with suspected de novo HF had higher rates of all-cause mortality and hospitalization for HF, and higher healthcare costs than matched controls. Healthcare costs were high and driven mostly by cardiorenal complications. Rates of new medication initiation, HF diagnosis and echocardiography use were variable.

Take Home Message

There is an urgent need for the effective identification, evaluation and treatment of patients who present in outpatient care with a combination of HF signs and/or symptoms and elevated NT-proBNP levels.



Baseline characteristics, risks, healthcare costs, medication use, and healthcare patterns among patients with suspected *de novo* HF (REVOLUTION HF). HF, heart failure; HHF, hospitalization for heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PY, person-years.

Keywords *De novo* heart failure • Peripheral oedema • Dyspnoea • NT-proBNP testing • Echocardiography • SGLT2i

Introduction

The burden of heart failure (HF) is rising with an ageing global population and improved diagnosis,[1] increasing the financial costs of a condition that already places a substantial burden on healthcare systems.[2] Earlier detection and treatment of HF is needed to improve its outcomes and ease this burden.

Earlier detection might be achieved by improved identification and evaluation of patients in outpatient care who present with a combination of HF symptoms and signs, and elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).[3] One proposed strategy is to refer these patients for echocardiography to identify a structural and/or functional cardiac abnormality and refine treatment.[3] For such a strategy to be reasonable, however, the subsequent incidence of

HF, costs of healthcare, and mortality in that population would need to be substantial. They are currently unknown.

We therefore characterized a contemporary, population-based cohort of ambulatory patients identified in outpatient care with suspected *de novo* HF, as indicated by the presentation of HF symptoms including dyspnoea or signs such as peripheral oedema, in combination with an elevated NT-proBNP. We also investigated their morbidity, mortality, healthcare patterns, and healthcare costs thereafter to inform care strategies.

Methods

Data sources

The REVOLUTION HF study was set in Sweden, which has a comprehensive, nationwide public healthcare system that each resident can access with a minor co-payment for healthcare visits, hospitalizations, and medications.[4] Residents have a unique personal identification number (person-ID),[5] which is mandatory for all administrative purposes, including any contact with the healthcare system and filling of drug prescriptions. Thus, providing a basis for complete population-wide medical history. In Sweden, the GENAST (Genomför EKG, Natriuretisk peptid vid Andfåddhet, Svullnad och/eller Trötthet) guidelines (English acronym: IMMEDIATELY [Perform ECG, Natriuretic peptide, Breathlessness and/or Tiredness]) have been developed for the management of suspected *de novo* HF and are locally/regionally adapted.[6]

Patients aged >18 years were identified in outpatient care, inclusive of primary and specialist outpatient care, and linked using the person-ID with data from the Swedish Prescribed Drug Register, the Cause of Death Register, the National Patient Register, and from several data sources with extensive regional coverage, including electronic health records.[2] More details of the database from which data were extracted can be viewed in Supplementary data online, *Methods S1* and *Table S1*.

This study conformed with the principles outlined in the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (approval numbers 2020-03850 and 2020-06716). Given the nature of the study, informed consent was not required.

Patients

For characterization of patients with suspected *de novo* HF, we identified relevant patients residing in two of Sweden's largest regions, Stockholm County and Skåne County, where records of NT-proBNP were available. For comparisons of outcomes, medication use, and healthcare costs, patients with suspected *de novo* HF from Stockholm County, being the only region that could offer matched controls, were matched with the general population of Stockholm County.

We defined patients with suspected *de novo* HF as ambulatory patients who presented in primary and specialist outpatient care with a first recorded diagnosis code for a sign (peripheral oedema) or symptom (dyspnoea) of HF (see Supplementary data online, *Table S2*), coded in any position (primary or secondary) between 1 January 2015 and 31 December 2020, and whose NT-proBNP measured >300 ng/L within ±30 days of that sign or symptom coding. Most NT-proBNP measures were taken on the same day as the first recorded diagnosis code for a sign or symptom (see Supplementary data online, *Figure S1*). By design, the cut-off of >300 ng/L for data extraction (and inclusion criterion) was chosen as more inclusive than >400 ng/L, where echocardiography is recommended within 30 days.[6] The index date was the first day on which a diagnosis code for a sign or symptom of HF and an elevated NT-proBNP measurement were both on record for a given patient. Patients with suspected *de novo* HF were excluded if they had a HF diagnosis at any time before index. Patients with an inpatient admission at or between the sign or symptom recording and NT-proBNP measurement recording were excluded, as were patients with an inpatient admission within 24 h after the index. There was no exclusion for inpatient visits prior to the initial NT-proBNP test or sign or symptom coding (whichever occurred first).

Patients with suspected *de novo* HF were matched, based on age and sex, to other patients who also visited the same level of outpatient care (i.e. primary care or specialist outpatient care) for any reason except for HF during the year of the index date for the patient with suspected *de novo* HF. The date that the matched control visited outpatient care was considered their index date. The matched controls could not have had a HF diagnosis before index, though patients with undiagnosed HF may be present.

The patients with suspected *de novo* HF and the matched controls had to be registered residents of Stockholm County or Skåne County for at least 18 months prior to the index date, and could not have been hospitalized within 24 h after the outpatient care visit. Not included in this study are 6957 patients who had their sign or symptom of HF recorded in outpatient care but had an inpatient care episode within the 24 h thereafter, or the 2337 patients who had their sign or symptom registered in inpatient care.

Baseline characteristics

All diagnoses in any position in primary care, outpatient secondary care, and/or inpatient care up until the index date were used to identify prevalent comorbidities in each patient and the matched controls (see Supplementary data online, *Table S3*). In addition to diagnostic coding, laboratory and blood pressure measurements in electronic health records were used to identify the prevalence of chronic kidney disease (see Supplementary data online, *Methods S2*) and hypertension (see Supplementary data online, *Methods S3*) in each cohort. Similarly, additional methods were used to define the type of diabetes (1 or 2) in those with the condition (detailed in Supplementary data online, *Methods S4*). Laboratory measurements were also used to establish clinical profiles of each cohort. The most recent single measurement within 2 years prior to the index date was used. Medication use by each patient and the matched controls was based on data available 1 year prior to the index (see Supplementary data online, *Table S4*).

Outcomes

Adverse outcomes (all-cause and cardiovascular mortality; and hospitalizations with a primary diagnosis of HF, myocardial infarction, stroke, peripheral artery disease, or chronic kidney disease) were monitored for the year following the index date (see Supplementary data online, *Table S5*). Only hospitalizations with a main diagnosis of the adverse outcomes listed above were used and described as the number of events per 100 person-years. The time to a diagnosis of HF was presented using Kaplan–Meier curves.

Healthcare patterns

For the patients in Stockholm County, procedure codes for echocardiography (see Supplementary data online, *Methods S5*) and electronic health records containing echocardiography results were used to identify if an echocardiography had been performed for each patient on or during the year following their index date. The time to an echocardiography was presented using Kaplan–Meier curves.

The proportions of patients and matched controls using loop diuretics, renin-angiotensin system (RAS) inhibitors, mineralocorticoid receptor antagonists (MRAs), beta blockers, and/or sodium-glucose cotransporter 2 (SGLT2) inhibitors on any given day throughout the year prior to and the year following the index date were assessed. A patient was considered using a medication of interest on any given day if, on that day, it was calculated that they had a supply of that medication from a recently filled prescription. The number of days that the supply would last was calculated as the number of available doses of the given medication divided by the number of times daily the medication was prescribed. A grace period extended the supply duration by 25% to allow for inconsistencies in medication use (e.g. sporadic days on which medication was not taken).

Healthcare costs

The average cumulative cost of specialist outpatient care and inpatient care each month over a 12-month period beginning the day after the index date

was calculated separately for HF, chronic kidney disease, myocardial infarction, stroke, and peripheral artery disease. Diagnoses in any position (primary or secondary) were used. A standard 30-day month was used for all 12 months. Costs were expressed in euros and United States dollars (conversion rates: Swedish krona to euros, 0.089; Swedish krona to United States dollars, 0.097), and were based on diagnostic-related group costs in specialist outpatient care and inpatient care data from the Swedish patient registry, using the 2021 cost table. The average cost per patient for each condition of interest was calculated using the following formula:

$$\text{Average cost} = \frac{(\text{Cost of visit} \times \text{Proportion of days within the time period of interest})}{\text{Number of patients who could be followed until end of given month}}$$

Statistical methods

A Cox proportional hazards model was used to estimate the relative hazard of all-cause mortality and HF hospitalization for different combinations of age, sex, and NT-proBNP level. The model was fit adjusting for NT-proBNP, age, and sex: rcs(NT-proBNP) + rcs(age) + sex + rcs(NT-proBNP):rcs(age) + rcs(NT-proBNP):sex, in which 'rcs()' is a restricted cubic spline with three knots. Relative hazards were extracted from the model using a woman aged 78.7 years with NT-proBNP measuring 723 ng/L as the reference, representing a median individual to which all other covariate combinations were compared. The competing risk of death on healthcare patterns was investigated using a combined outcome of time to HF diagnosis, echocardiography examination, or all-cause death. Analyses were performed using *R* (version 3.6.0).

Results

Patient characteristics

In total, 5942 patients (median age 78.7 years; 54% women) with suspected *de novo* HF were identified in primary (66.2%) and specialist outpatient care (33.8%; *Table 1* and Supplementary data online, *Tables S6* and *S7*). Of those, 59% presented with dyspnoea, 44% with peripheral oedema, and 2.8% with both; median NT-proBNP was 723 ng/L. At presentation, 82% of patients had hypertension, nearly half had chronic kidney disease, 40% had atherosclerotic cardiovascular disease, nearly one-third had atrial fibrillation, nearly half were treated with RAS inhibitors, and just over half were treated with beta blockers (*Table 1*). When stratified by NT-proBNP levels, the prevalence of most comorbidities increased as NT-proBNP levels increased (see Supplementary data online, *Table S8*).

Morbidity and mortality

Rates of all-cause death (11.7 vs. 6.5 events per 100 person-years), HF hospitalizations (12.5 vs. 2.2 events per 100 person-years), and the combined outcome of HF hospitalizations or all-cause death (22.3 vs. 8.4 events per 100 person-years) were substantially higher in patients with suspected *de novo* HF than in the matched controls (*Figure 1*). There were notable associations of NT-proBNP levels (*Figure 1*) and age (see Supplementary data online, *Figure S2A–C*, with corresponding 95% confidence intervals [CI] presented in panels D–F) with the incidence of each outcome. Detailed causes of death are presented in Supplementary data online, *Figure S3*. Other causes of mortality included chronic ischaemic heart disease, myocardial infarction, and cancer. Approximately one-third of hospitalizations for HF in patients with NT-proBNP >1000 ng/L occurred within 6 weeks from the index date. Risk of HF hospitalization or death increased markedly with increasing NT-proBNP up to around 2000 ng/L (see Supplementary data online, *Figure S2*). Above this, the risks increased more slowly. Risks according to healthcare level were generally similar when comparing primary and specialist outpatient care, though the risk of all-cause death was slightly higher among patients visiting specialist outpatient care (see Supplementary data online, *Figure S4*). The differences in event rates for HF hospitalizations or death compared with matched controls were 1.3 (95% CI −.9 to 3.3) for NT-proBNP 300–400 ng/L, 3.1 (95% CI .9 to 5.4) for 400–600 ng/L, 7.7 (95% CI 5.4 to 10.4) for 600–1000 ng/L, 14.9 (95% CI 12.3 to 17.6) for 1000–2000 ng/L, and 33.2 (95% CI 30.1 to 36.5) for >2000 ng/L. Results for other outcomes are reported in Supplementary data online, *Figure S5*. Rates of all-cause death and HF hospitalizations in Skåne vs. Stockholm regions were 12.5 vs. 10.3 and 10.7 vs. 16.1 events per 100 person-years, respectively.

Healthcare patterns

Of patients with suspected *de novo* HF, 29% had received a diagnosis of HF within 1 year from the index date (*Figure 2A*). Of the patients who were diagnosed with HF by the end of follow-up, 37% received their diagnosis in inpatient care. The coverage of registered echocardiograms in these routine healthcare registries was incomplete to an unknown extent. Within 1 year, 57% of patients with NT-proBNP >2000 ng/L and 41% of those with NT-proBNP ≤2000 ng/L had been admitted to inpatient care for any cause. The median time to an echocardiogram for those that had one during a 1-year follow-up was 40 days (*Figure 2B*). The time to echocardiography varied with NT-proBNP and age. The combined outcome of HF diagnosis, echocardiography, or all-cause death showed a similar pattern (see Supplementary data online, *Figure S6*). Healthcare patterns according to healthcare level were similar comparing primary and specialist outpatient care (see Supplementary data online, *Figure S7*).

The proportions of patients with suspected *de novo* HF that used RAS inhibitors, MRAs, and/or beta blockers increased subtly following the index date in comparison with, e.g. loop diuretics that increased several-fold. The proportion that used any guideline-directed medical therapy for HF increased from ∼60% to ∼80% shortly after the identification of signs or symptoms of HF and an elevated NT-proBNP (*Figure 3A*). The most distinct change was in the proportion of patients who used loop diuretics, which rapidly increased fivefold (from ∼10% to ∼50%), especially for those with oedema. Approximately 40% of those patients discontinued use approximately 4 months later. Treatment patterns according to healthcare level were similar when comparing primary care and specialist outpatient care (see Supplementary data online, *Figure S8*). Patients with NT-proBNP >2000 ng/L were more likely to be prescribed loop diuretics than those with NT-proBNP <2000 ng/L (see Supplementary data online, *Figure S9*). The difference between patients with NT-proBNP >2000 ng/L and <2000 ng/L was less pronounced for RAS inhibitors, MRAs, and beta blockers.

The proportions of matched controls who used these medications changed little from the year prior to the year after the index date (*Figure 3B*). The number of patients and matched controls who used SGLT-2 inhibitors at any time was negligible.

Healthcare costs

Costs of specialist outpatient care and inpatient care for HF in patients with suspected *de novo* HF rose steeply immediately following the index date in those whose NT-proBNP measured >1000 ng/L (see Supplementary data online, *Figure S10*). Costs were mainly driven by care for cardiorenal complications (HF or chronic kidney disease), while costs of care for atherosclerotic cardiovascular diseases were substantially lower (*Figure 4*).

Table 1 Characteristics of patients with suspected *de novo* heart failure and matched controls

	Patients with suspected *de novo* HF	Matched controls
N	5942	2048
Age, years, median (IQR)	78.7 (71.9–85.0)	77.2 (70.1–83.9)
Women, *n* (%)	3207 (54.0)	1087 (53.1)
HF signs and symptoms		
Dyspnoea, *n* (%)	3480 (58.6)	NA
Peripheral oedema, *n* (%)	2630 (44.3)	NA
Dyspnoea and peripheral oedema, *n* (%)	168 (2.8)	NA
NT-proBNP, ng/L, median (IQR)	723 (438–1550)	NA
NT-pro-BNP levels, *n* (%)		
300–400 ng/L	1155 (19.4)	NA
400–600 ng/L	1316 (22.1)	NA
600–1000 ng/L	1215 (20.4)	NA
1000–2000 ng/L	1172 (19.7)	NA
>2000 ng/L	1084 (18.2)	NA
Level of outpatient care, *n* (%)		
Primary care	3933 (66.2)	NA
Specialist care	2009 (33.8)	NA
Comorbidities, *n* (%)		
Ischaemic heart disease	1359 (22.9)	321 (15.7)
ASCVD	2372 (39.9)	590 (28.8)
Myocardial infarction	817 (13.7)	146 (7.1)
Stroke	1011 (17.0)	282 (13.8)
Peripheral artery disease	599 (10.1)	114 (5.6)
Hypertension	4881 (82.1)	1629 (79.5)
Atrial fibrillation	1898 (31.9)	264 (12.9)
Valvular disease	593 (10.0)	100 (4.9)
Myocarditis	342 (5.8)	33 (1.6)
COPD	723 (12.2)	179 (8.7)
Asthma	634 (10.7)	247 (12.1)
Pulmonary emboli	213 (3.6)	43 (2.1)
Type 1 diabetes	95 (1.6)	12 (0.6)
Type 2 diabetes	1251 (21.1)	325 (15.9)
Any cancer	1538 (25.9)	413 (20.2)
CKD diagnosis or laboratory, *n* (%)		
Diagnosis	820 (13.8)	140 (6.8)
KDIGO-confirmed CKD (eGFR <60 mL/min/1.73 m^2 and UACR ≥3 g/mol)	2766 (46.5)	481 (23.5)
Laboratory measurements, median (IQR)		
SBP, mmHg	140 (130–155)	139 (128–151)
Body mass index, kg/m^2	26.1 (23.1–29.9)	24.7 (22.1–27.8)
eGFR, mL/min/1.73 m^2	59.2 (47.2–70.6)	63.2 (53.3–73.5)

Continued

Table 1 *Continued*

	Patients with suspected *de novo* HF	Matched controls
Medication use, *n* (%)		
RASi	2827 (47.6)	853 (41.7)
SGLT2i	33 (0.6)	13 (0.6)
Beta blockers	3014 (50.7)	599 (29.2)
MRA	222 (3.7)	40 (2.0)
Loop diuretics	1088 (18.3)	159 (7.8)
Warfarin	740 (12.5)	159 (7.8)
Statins	2250 (37.9)	589 (28.8)

Characteristics of patients with suspected *de novo* HF and the matched controls as of the index date.
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HF, heart failure; KDIGO, Kidney Disease: Improving Global Outcomes; MRA, mineralocorticoid receptor antagonist; NA, not applicable; RASi, renin-angiotensin system inhibitor; SBP, systolic blood pressure; SD, standard deviation; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Costs of care for cardiorenal diseases and atherosclerotic diseases were negligible in the matched controls.

Discussion

Patients who presented to primary or specialist outpatient care with suspected *de novo* HF identified by HF signs or symptoms and elevated NT-proBNP levels had a very high risk of all-cause mortality and hospitalization for HF, and accrued substantial healthcare costs mainly owing to care for cardiorenal disease (*Structured Graphical Abstract*). Despite extensive early testing with NT-proBNP, long delays to HF diagnosis and documented echocardiogram exist and this is reflected in the variable initiation of evidence-based HF medications. These observations point to an important opportunity for more aggressive identification and work-up of patients in outpatient care that present with a combination of HF signs, symptoms, and elevated NT-proBNP levels.

Patients with suspected *de novo* heart failure have a high risk of adverse outcomes

Patients with suspected *de novo* HF had multiple comorbidities, including cardiovascular diseases, chronic kidney disease, type 2 diabetes, and cancer; albeit at a lower prevalence than that in contemporary patients with a first-time diagnosis of HF.[7] On average, levels of NT-proBNP were also lower in those with suspected *de novo* HF than in those with a first-time diagnosis.[7] As NT-proBNP levels reached >2000 ng/L, the characteristics of patients with suspected *de novo* HF were increasingly similar to those of patients with a first-time HF diagnosis, and 64% of patients with an NT-proBNP >2000 ng/L were diagnosed with HF at any care level within 1 year.[7] When considering the very high risks associated with suspected *de novo* HF, it should be acknowledged that the included patients were those who had an NT-proBNP measured rapidly and, to a large extent, received appropriate treatment. Hence, the risks in patients who did not get this care may be even higher. Notably, also among those with documented high NT-proBNP (and signs or symptoms of HF), a large proportion remained undiagnosed with HF or were diagnosed after long delays, likely contributing to the observed absence of, and delays in initiation of, HF medications and the ensuing very high risks observed.

Although adverse events increased with increasing NT-proBNP, event rates were highest in the days following presentation regardless of NT-proBNP level. The risk of all-cause mortality and hospitalization for HF was highest in patients with the highest NT-proBNP level, with approximately one-third of all hospitalizations for HF recorded during follow-up occurring in the first 4–6 weeks following the identification of signs and/or symptoms of HF and an NT-proBNP >2000 ng/L.

HF was the most prominent cause of mortality, closely followed by ischaemic heart disease, acute myocardial infarction, lung cancer, and prostate cancer. While cardiovascular disease seemed to be the most prominent cause of death, the actual proportion of patients who died from cardiovascular disease was very low due to the wide array of causes of mortality. This population had a high prevalence of comorbidities and a high incidence of inpatient admissions in the year before index, and was therefore likely to be at higher risk than the general primary care population.

Opportunities for improved care of patients with suspected *de novo* heart failure

Despite early NT-proBNP testing and prescription of diuretics, 37% of patients presenting in the community and receiving a diagnosis of HF within 1-year follow-up received that diagnosis in inpatient care. More patients will have presented directly to the hospital (or have been admitted within a day and not included in this analysis) so the true proportion of patients with HF diagnosed in the hospital setting will be higher. These findings are in line with previous research from the UK reporting that approximately 80% of all *de novo* HF diagnoses were made during emergency hospitalization for HF, despite approximately 50% of these patients having reported symptoms of HF to their general practitioner in the 5 years prior to presentation.[8–12]

The 2018 National Institute for Health and Care Excellence guidelines,[13] recently endorsed by a clinical consensus statement from the European Society of Cardiology, recommended that all patients with signs or symptoms of HF should have an echocardiogram within 6 weeks (those with NT-proBNP between 400 and 2000 ng/L) or 2 weeks (those with NT-proBNP >2000 ng/L), from the date of measurement.[3] The median time to an echocardiogram in patients with suspected *de novo* HF that

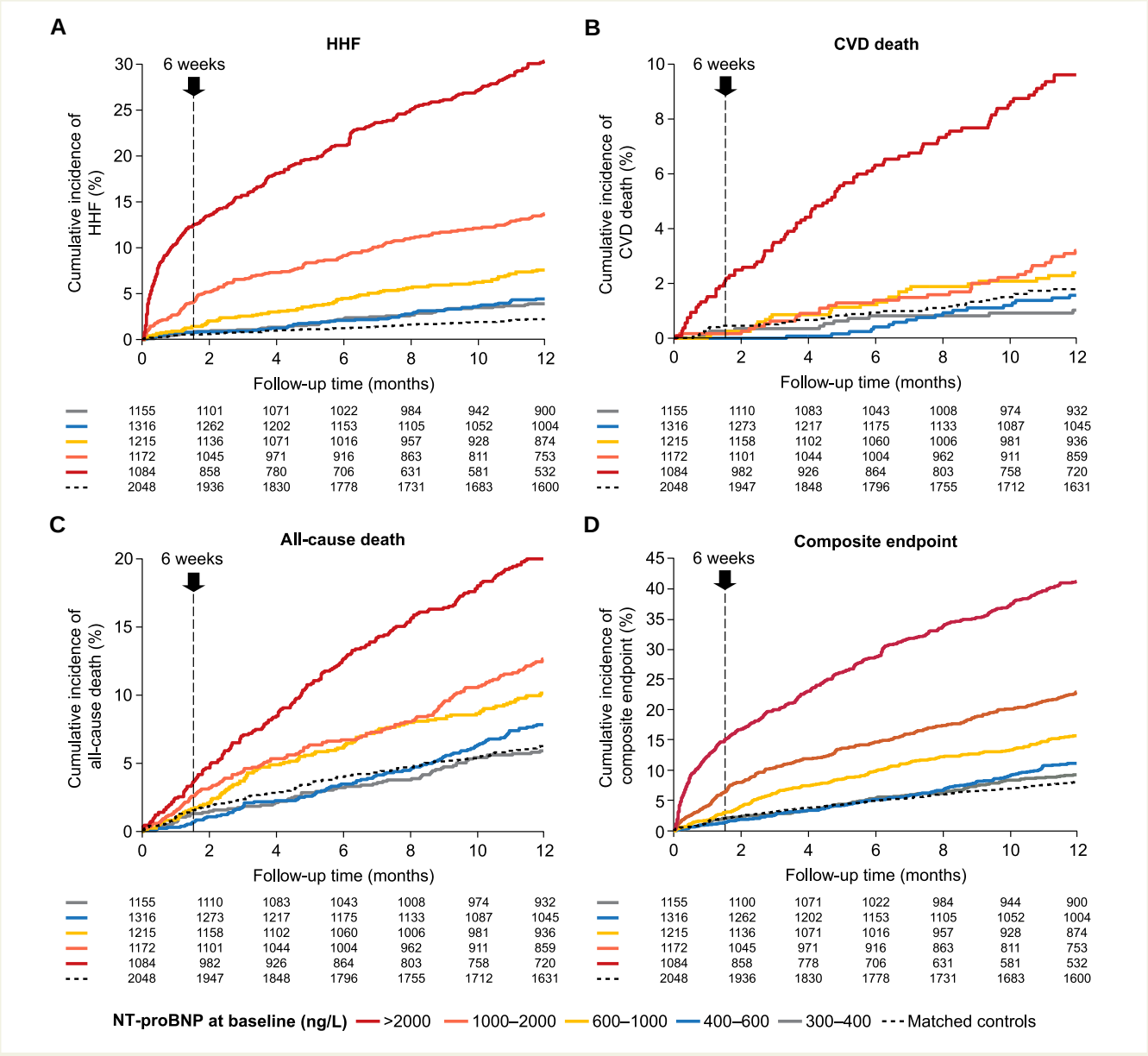


Figure 1 The cumulative incidence of (*A*) hospitalization for heart failure, (*B*) death related to cardiovascular disease, (*C*) all-cause death, and (*D*) the composite endpoint of hospitalization for heart failure and/or all-cause death in patients with suspected *de novo* heart failure, stratified by N-terminal pro-B-type natriuretic peptide thresholds, during the year following the identification of signs and symptoms of heart failure. Numbers at risk for each timepoint are detailed. CVD, cardiovascular disease; HF, heart failure; HHF, hospitalization for heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide

could be followed for 1 year was 40 days. Given that the study period predates this statement, it could have been expected that the care for patients would not have met these recommendations. That said, the use of natriuretic peptides as a diagnostic tool for HF has been endorsed in HF guidelines for over two decades, but with variable uptake in community-based care centres.[3] Because this study did not have access to an unknown number of echocardiography results (for example, those from bedside echocardiograms and other undocumented examinations), however, these findings should be interpreted with caution.

Considering that diagnoses of HF slowly increased throughout follow-up, the limited increase in the use of guideline-directed medical therapies for HF (other than loop diuretics) could have been expected. Pharmaceutical treatment for HF should usually be initiated only once HF has been diagnosed after echocardiography (and preferably by a specialist), and should be defined for HF diagnosis by echocardiogram and phenotype included (i.e. preserved, mildly reduced, or reduced ejection fraction). Indeed, a share of false-positive elevations in NT-proBNP is also likely, e.g. owing to a variety of conditions (including NT-proBNP production by non-cardiac cancer cells).[14]

A diagnosis of HF and phenotyping with echocardiography may be significantly delayed owing to a lack of resources, and yet there is a very high risk of adverse outcomes while a patient waits for an echocardiogram. Thus, a low threshold may be warranted for initiating guideline-directed medical therapy for HF until a confirmatory echocardiogram can be

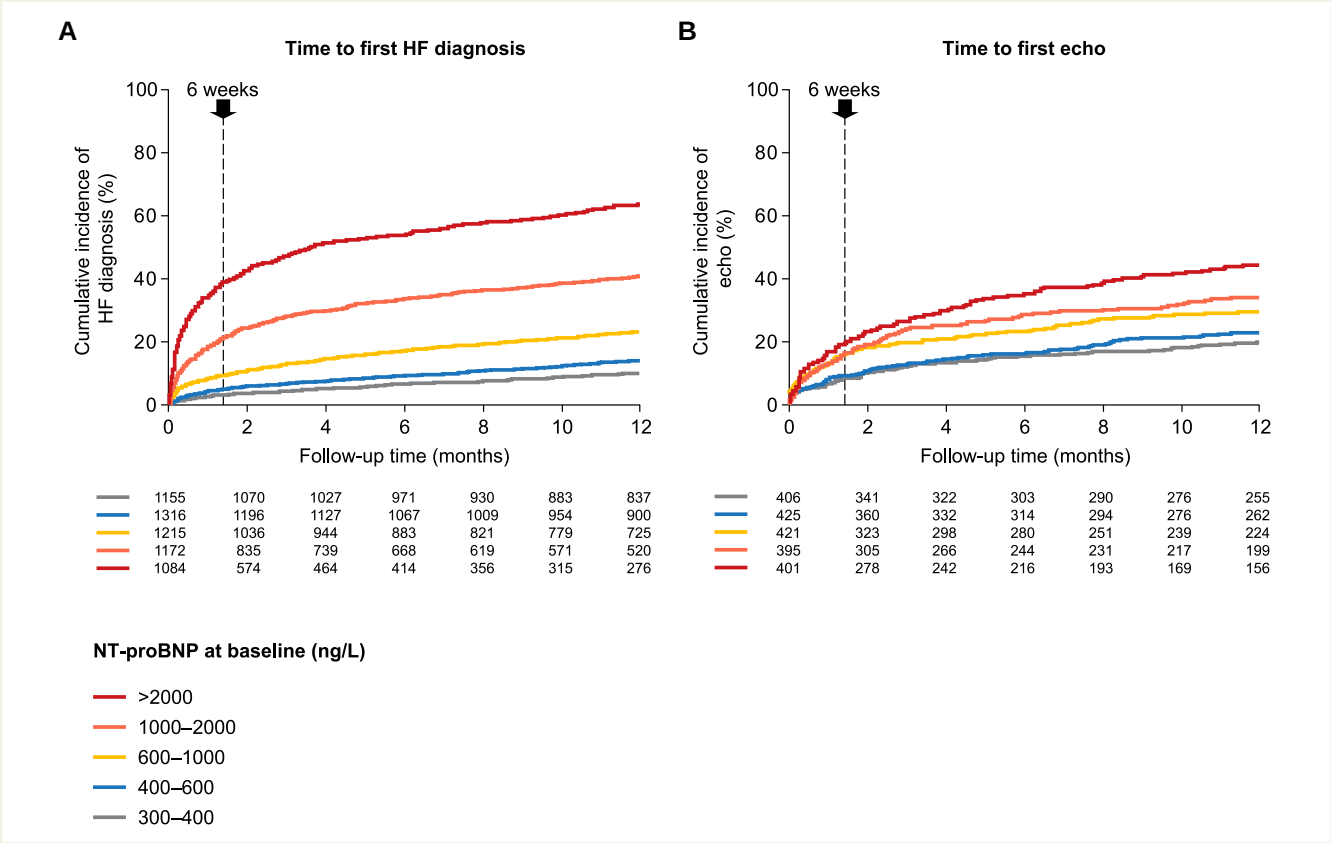


Figure 2 The time to (*A*) a first diagnosis of heart failure and (*B*) the first echocardiogram in patients with suspected *de novo* heart failure following the identification of the condition's signs and symptoms. Patients are stratified by N-terminal pro-B-type natriuretic peptide thresholds. Numbers at risk for each timepoint are detailed. Time to first echo data only available in Stockholm County. HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide

performed. This is particularly the case for those with the highest likelihood of an HF diagnosis and of HF admission, i.e. those with the most elevated NT-proBNP.[3] In a recent study following incident HF diagnosis, using the same data source as the present study, we showed that one out of four patients had an echocardiogram registered in such a way that it could be extracted for this study. This represents an unknown fraction of all echocardiograms performed in these patients.[15]

Despite clinical findings of suspected HF, 70% were not diagnosed within the first year. This can be explained by several factors: first, echocardiographic examinations were limited/delayed within the first year; second, the initial signs/symptoms were perceived as congestion and managed with loop diuretics without planned echocardiographic examination due to high age, or comorbidities like atrial fibrillation, chronic obstructive pulmonary disease, or short life expectancy; third, echocardiographic examination was not registered; and fourth, echocardiographic examination was negative for HF.

A recent clinical consensus statement from the Heart Failure Association of the ESC suggests validated NT-proBNP cut-points to 'rule in' or 'rule out' *de novo* HF diagnosis in the outpatient setting.[3] In this analysis, we present evidence of immediate risk of death and hospitalization of HF in this patient population in outpatient care. Given the rapid onset of benefit demonstrated with SGLT2 inhibitors regardless of ejection fraction, where delays are expected for an echocardiogram to be performed, a possible option would be to consider initiation of at least this pillar of HF therapy to manage the high risk of these patients. Should eventual echocardiogram not confirm HF, the safety profile of SGLT2 inhibitors is well established in patients without HF. Furthermore, 51% of patients may be eligible for SGLT2 inhibitors based on other indications such as type 2 diabetes (21%) and/or chronic kidney disease (47%). Recent clinical trial data also demonstrate the efficacy of novel MRAs in patients with HF and a left ventricular ejection fraction ≥40%,[16] regardless of baseline SGLT2 inhibitor use,[17] thus suggesting that non-steroidal MRAs could also be considered for early initiation, prior to ejection fraction measurement.

Healthcare costs for patients with suspected *de novo* heart failure

A large proportion (over one-third) of all costs attributed to hospitalizations for cardiorenal complications and atherosclerotic cardiovascular disease outcomes during follow-up were due to HF healthcare. Hospitalizations for chronic kidney disease also contributed substantially to healthcare costs. Consistent with recent studies of contemporary patients with an HF diagnosis,[2,18] this emphasizes the need to improve the identification and management of both HF and chronic kidney disease in patients presenting with HF, rather than focusing on HF alone, to realize the potential of easing the economic burden resulting from the care of these patients.

Strengths and limitations

This study had access to health registries and electronic health records that contained information about most healthcare and medication use by residents in two of Sweden's largest regions, representing

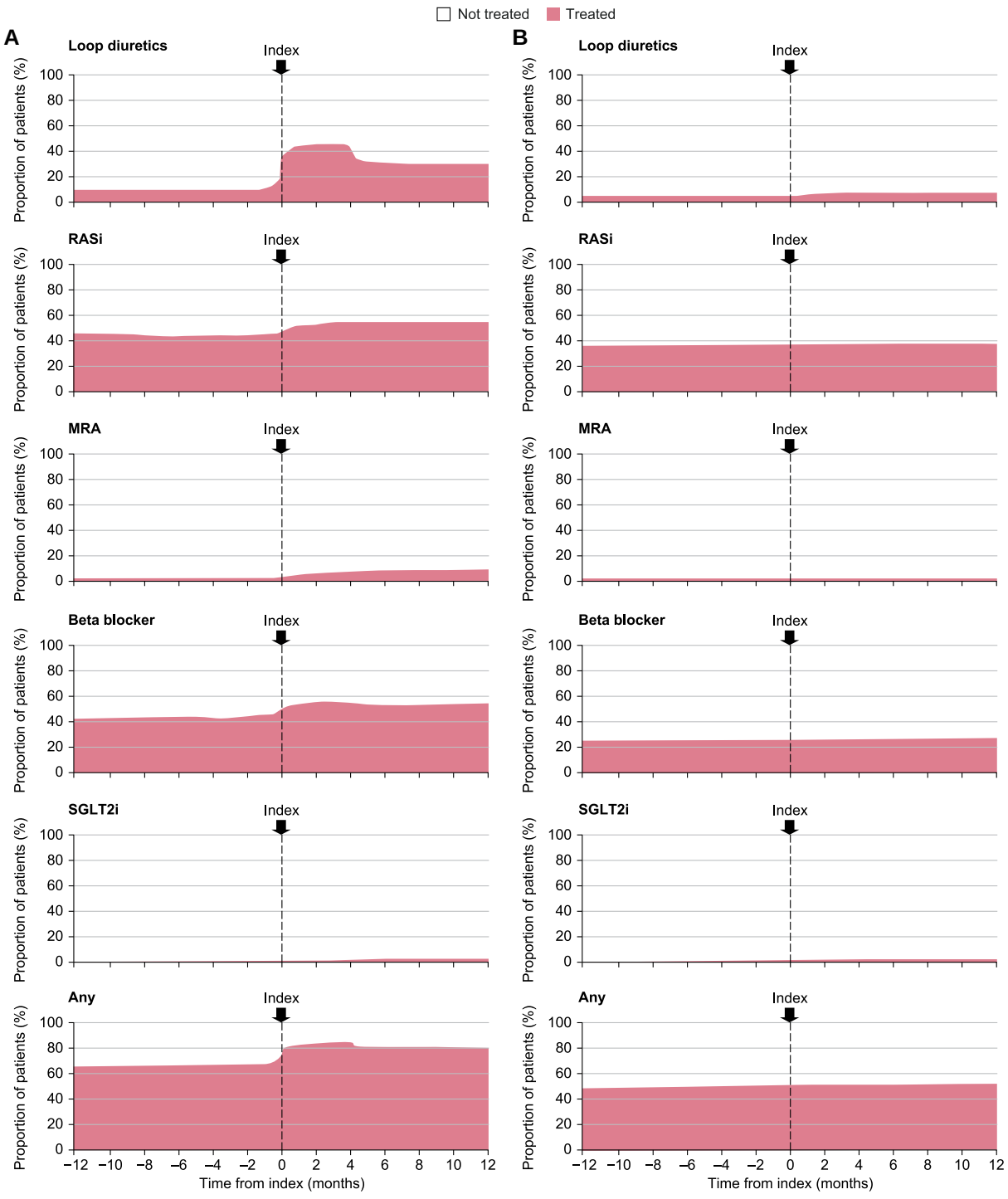


Figure 3 Use of guideline-directed medical therapies for heart failure before and after index date in (*A*) patients with suspected *de novo* heart failure and (*B*) the matched controls. MRA, mineralocorticoid receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor

approximately one-third of the national population. In Sweden, each resident has a unique person-ID that is used consistently across all levels of public and private healthcare. This identification number makes it possible to extract complete data for all healthcare use, dispensed drugs, and deaths from nationwide registries with full coverage. Moreover, the Swedish Cause of Death Register has complete coverage of all Swedish residents and is based on mandatory death reporting without exceptions. Despite its strength in its capacity to identify and characterize patients relevant to the study aims and to detail their healthcare thereafter, several limitations must be acknowledged.

Although the available data sources detail most incidences of healthcare, not all echocardiography recordings were available (for example,

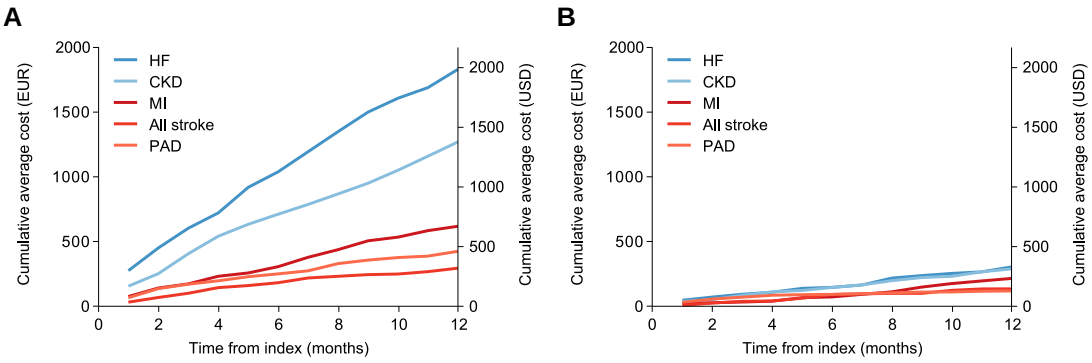


Figure 4 The average cumulative cost of specialized outpatient care and inpatient care each month during the 12-month period following the index date for (*A*) patients with suspected *de novo* heart failure and (*B*) the matched controls. Each month is a standardized 30-day month and costs are expressed in euros and Unites States dollars. CKD, chronic kidney disease; HF, heart failure; MI, myocardial infarction; PAD, peripheral artery disease

those from bedside echocardiograms and other examinations documented outside the reach of this data extraction). Additionally, records of echocardiography were only attained for patients residing in Stockholm County. Finally, a significant proportion die early before having the chance of echocardiography. Collectively, this did not allow for conclusions to be made regarding the timing of echocardiography examinations. The proportion of false positives is unknown; those in this population with suspected *de novo* HF that were confirmed to not have HF are indistinguishable from those that had HF but were not diagnosed with it.

For the Stockholm region, we have high coverage of diagnoses recorded in primary care. However, we capture only about 50% of the laboratory measurements from primary care. This limitation in data collection may partially explain the differences observed between the Stockholm region and the Skåne region. Matched controls were only available from Stockholm County. If patients with suspected *de novo* HF were only selected from Stockholm County, the event rates would have been even higher for HF hospitalizations, but comparable for all-cause death.

This study did not assess whether or not characteristics, rates of adverse outcomes, healthcare, and costs of healthcare varied between patients with suspected *de novo* HF from different socioeconomic backgrounds or ethnicities. Additionally, the study population was derived from two of the largest regions in Sweden. While this study's findings may be generalized to the wider Swedish population, it is unknown if they can be generalized to other nations where healthcare systems can differ considerably. By design, analyses were limited to patients with NT-proBNP ≥300 ng/L, and comparisons with patients with NT-proBNP <300 ng/L are beyond the scope of this analysis. In one of the regions included in the present study (Stockholm), a project was implemented during 2012–17 to improve the organization of HF healthcare.[6] The project led to increased referrals, improved treatment, and reduced risk of death and HF readmissions. Since this project preceded and partly overlapped with the timeframe of the present study, it might have partly impacted the results reported here.

Conclusions

Patients presenting in outpatient care with suspected *de novo* HF (signs or symptoms and elevated NT-proBNP levels) had a very high risk of adverse outcomes in the first weeks after presentation. Thereafter, they accrued high healthcare costs for both HF and chronic kidney disease, but there was limited initiation of HF treatment. These findings highlight a need for urgent identification, evaluation, and treatment of patients who present in outpatient care with a combination of signs or symptoms of HF and elevated NT-proBNP levels.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

A.B.G. has participated in advisory boards and/or lectured for Abbott, AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics, and Vifor Pharma. J.B. and K.M. are employed by AstraZeneca. J.S. reports stock ownership in Anagram Kommunikation AB and Symptoms Europe AB. All other authors have nothing to disclose.

Data Availability

Data sources utilized in this project are subject to ethical and privacy restrictions in Sweden. Therefore, the data that support the findings of this study are not available on request.

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Ethical Approval

This study conforms with the principles outlined in the Declaration of Helsinki and was approved by the Swedish Ethical Review Authority (approval numbers 2020-03850 and 2020-06716). Given the nature of the study, informed consent was not required.

Pre-registered Clinical Trial Number

Not applicable.

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