Supplementary Material

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# **Supplementary Methods 1. The CELOSIA database**

The CELOSIA database, from which this present study’s sample was extracted, includes all Swedish residents aged ≥18 years who were diagnosed with chronic kidney disease (CKD), heart failure (HF), or diabetes mellitus between January 1, 2000, and December 31, 2020. The database also includes a control population of 643 733 patients who were aged ≥18 years and registered as residents from Stockholm County between January 1, 2000, and December 31, 2020. This control population was randomly drawn from the total population of patients registered in Stockholm County during this time period.

Patients were identified from several sources with national coverage, including the Swedish Prescribed Drug Registry, the National Patient Registry, and the National Death Registry. Electronic health records with regional coverage were also used. The Swedish Prescribed Drug Registry logs each resident’s filled drug prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system.1 The National Patient Registry and the National Death Registry records diagnoses, surgical procedures, and causes of death using the International Classification of Diseases [ICD]2 system and the Nordic Medico-Statistical Committee Classification of Surgical Procedure system.3

A complete list of the ATC codes, ICD-10 codes, procedure codes, and laboratory values used to identify these patients is available in Table S1. Patients were required to have a 12-digit personal identity number, an identity number unique to all Swedish residents,4 enabling data to be linked between the different sources.

Patients with suspected de novo HF in Stockholm were matched 1:1 (2048:2048), based on age and sex, to other patients in Stockholm 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 of 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 CELOSIA database was initiated and sponsored by AstraZeneca and extracted to understand patients with signs, symptoms or diagnosed with heart failure in a real-world clinical situation across healthcare levels including primary-, specialist-, hospital outpatient-/inpatient care. This dataset has contributed to the understanding of prevalent heart failure patients, e.g., its prevalence,5 phenotypes,6 patient characteristics, comorbidities, treatment, risks, healthcare costs,5 and usefulness of initial ejection fraction phenotyping.7 The overall study design concept was written by AstraZeneca and the dedicated scientific committees, see above and the present study (REVOLUTION HF). REVOLUTION HF is the name of the study and does not represent the care given or its organization during the study period.

In Sweden, developed guidelines, locally/regionally adapted, for the management of suspected de novo HF are referred to as GENAST (Genomför EKG, Natriuretisk peptid vid Andfåddhet, Svullnad och/eller Trötthet), translated in English to IMMEDIATELY (Perform ECG, Natriuretic peptide, Breathlessness and or Tiredness).8 In brief, these guidelines are adapted to each region in Sweden and recommend that patients with NT-proBNP >2000 ng/L should be referred to echocardiography examination within 14 days, and patients with NT-proBNP 400–2000 ng/L within 30 days.8 By design, patients with NT-proBNP >300 ng/L were included. The >300 ng/L for data extraction was chosen as more inclusive than >400 ng/L, where echocardiography is recommended within 30 days.

# **Supplementary Methods 2. Identifying chronic kidney disease**

In addition to using International Classification of Diseases (ICD)-10 codes, laboratory measurements of creatinine-based estimated glomerular filtration rate (eGFR) and/or urine albumin-creatinine ratio (UACR), available in the electronic health records, were used to identify patients with chronic kidney disease according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines.9 Meaning, CKD was identified if a patient presented at least two abnormal eGFR measurements (<60 mL/min/1.73 m2) and/or two abnormal UACR measurements (≥3 g/mol), with the first and last measurements taken at least 90 days apart and where all measurements in between were abnormal. The revised Lund-Malmö equation was used to calculate eGFR from plasma creatinine, age and sex;10 and UACR was expressed in g/mol. The eGFR and UACR thresholds defining each stage of CKD according to KDIGO guidelines are detailed below:

|  |  |  |
| --- | --- | --- |
| **eGFR-defined stages** | | |
| **Stage** | **eGFR thresholds (mL/min/1.73 m2)** | **Abnormal** |
| 1 | ≥90 | No |
| 2 | 60–89 | No |
| 3a | 45–59 | Yes |
| 3b | 30–44 | Yes |
| 4 | 15–29 | Yes |
| 5 | GFR <15 | Yes |
| **Albuminuria-defined stages** | | |
| **Stage** | **UACR thresholds (g/mol)** | **Abnormal** |
| A1 | UACR <3 | No |
| A2 | UACR 3–30 | Yes |
| A3 | UACR >30 | Yes |

# **Supplementary Methods 3. Identifying hypertension**

In addition to using International Classification of Diseases (ICD)-10 code I10 to identify diagnoses of hypertension, blood pressure measurements available in the electronic health records were also used. Hypertension was identified if a patient’s systolic blood pressure and/or diastolic blood pressure measured >130 mmHg and/or >80 mmHg, respectively, in two separate examinations conducted at least 1 day apart.

# **Supplementary Methods 4. Defining the type of diabetes mellitus**

In addition to using International Classification of Diseases (ICD)-10 codes E10 and E11 to identify diagnoses of type 1 and type 2 diabetes, respectively, diabetes type was also defined in a series of steps detailed in the flowchart below. The starting point of the flowchart is the broader definition of diabetes mellitus (DM), ICD-10 codes E10-E14.



# **Supplementary Methods 5. Identifying echocardiography examinations**

Surgical codes for echocardiography (AF019, AF020, AF021, AF064) and electronic health records containing echocardiography results were used to identify if an echocardiography had been performed for each patient on or in the year following their index date. Owing to data availability, records of echocardiography were only attained for patients residing in Stockholm County.

# Supplementary Table S1 Inclusion criteria for the CELOSIA database from which the study sample was extracted

|  |  |
| --- | --- |
| **Inclusion criteria (any of)** | **Description** |
| ICD10: I50 | Heart failure |
| ICD10: I11.0 | Hypertensive heart disease with (congestive) heart failure |
| ICD10: I13.0 | Hypertensive heart and renal disease with (congestive) heart failure |
| ICD10: I13.2 | Hypertensive heart and renal disease with both (congestive) heart failure and renal failure |
| ICD10: I25.5 | Ischaemic cardiomyopathy |
| ICD10: I42.0 | Dilated cardiomyopathy |
| ICD10: I42.6 | Alcoholic cardiomyopathy |
| ICD10: I42.9 | Cardiomyopathy, unspecified |
| ICD10: I43.1 | Cardiomyopathy in metabolic diseases |
| ICD10: Z99.4 | Dependence on artificial heart |
| Procedure: FQA | Transplantation of heart |
| Procedure: FQB | Transplantation of heart and lung |
| Procedure: FPE26 | Implantation of transvenous cardiac pacemaker with biventricular electrodes |
| ATC: C01CX08 | Levosimendan |
| BNP >100ng/L | Laboratory value |
| NT-pro-BNP >300 ng/L | Laboratory value |
| ICD-10: E10.2 | Type I diabetes mellitus with renal complications |
| ICD-10: E11.2 | Type II diabetes mellitus with renal complications |
| ICD-10: E12.2 | Malnutrition-related diabetes mellitus with renal complications |
| ICD-10: E13.2 | Other specified diabetes mellitus with renal complications |
| ICD-10: E14:2 | Unspecified diabetes mellitus with renal complications |
| ICD-10: N08.3 | Glomerular disorders in diabetes mellitus |
| ICD-10: N17 | Acute renal failure |
| ICD-10: N18 | Chronic kidney failure |
| ICD-10: N19 | Unspecified kidney failure |
| ICD-10: I12.0 | Glomerular disorders in diabetes mellitus |
| ICD-10: I12.9 | Hypertensive renal disease without renal failure |
| ICD-10: I13.1 | Hypertensive heart and renal disease with renal failure |
| ICD-10: I13.9 | Hypertensive heart and renal disease, unspecified |
| ICD-10: Z49.1 | Extracorporeal dialysis |
| ICD-10: Z49.2 | Other dialysis |
| ICD-10: Z99.2 | Dependence on renal dialysis |
| Procedure: JAK10 | Laparotomy and insertion of peritoneal dialysis catheter |
| Procedure: TJA33 | Percutaneous introduction of peritoneal dialysis catheter |
| Procedure: TJA35 | Removal of peritoneal dialysis catheter |
| Procedure: DJ008 | Laparoscopic dialysis catheter insertion |
| Procedure: DR013 | Initiation of continuous ambulatory peritoneal dialysis (CAPD) |
| Procedure: DR014 | Haemodiafiltration (HDF) |
| Procedure: DR015 | Haemodialysis, acute |
| Procedure: DR016 | Haemodialysis, chronic |
| Procedure: DR017 | Haemofiltration |
| Procedure: DR023 | Peritoneal dialysis, acute |
| Procedure: DR024 | Peritoneal dialysis, chronic |
| Procedure: DR055 | Citrate dialysis |
| Procedure: DR056 | Heparin free dialysis |
| Procedure: DR060 | Home haemodialysis control |
| Procedure: DR061 | Home haemodialysis start |
| Procedure: KAS10 | Allogenic transplantation of kidney from cadaver donor |
| Procedure: KAS20 | Allogenic transplantation of kidney from living donor |
| Procedure: QF006 | Peritoneal dialysis |
| eGFR <60 mL/min/1.73 m2 | Laboratory value |
| U-albumin/creatinine ratio > 3 mg/mmol | Laboratory value |
| ICD-10: E10 | Type I diabetes mellitus |
| ICD-10: E11 | Type II diabetes mellitus |
| ICD-10: E12 | Malnutrition-related diabetes mellitus |
| ICD-10: E13 | Other specified diabetes mellitus |
| ICD-10: E14 | Unspecified diabetes mellitus |
| ATC: A10 | Drugs used in diabetes |
| HbA1c > 48 mmol/L | Laboratory value |

ATC=Anatomical Therapeutical Chemical. eGFR=estimated glomerular filtration rate. ICD=International Classification of Diseases.

# Supplementary Table S2 International Classification of Diseases-10 codes used to identify HF symptoms

|  |  |
| --- | --- |
| **Diagnosis** | **International Classification of Diseases-10 codes** |
| Dyspnoea | R06.0 |
| Peripheral oedema | R60 |

HF=heart failure.

# Supplementary Table S3 International Classification of Diseases-10 codes used to identify prevalent comorbidities of interest

|  |  |
| --- | --- |
| **Diagnosis** | **International Classification of Diseases-10 codes** |
| Myocardial infarction | I21–I22, I25.[26] |
| Unstable angina | I20.0 |
| Angina | I20.[189], I25.[15] |
| All stroke | I60–I66, G45 |
| Peripheral artery disease | I70–I72, I73.[19], I74, I77.[368], I79 |
| Hypertension | I10 |
| Valve disease | I05–I08, I34–I37, Z95.[2-4] |
| Atrial fibrillation | I48 |
| Myocarditis | I30–I33, I38–I41 |
| Chronic obstructive pulmonary disease | J44 |
| Asthma | J45 |
| Pulmonary emboli | I26 |
| Pneumonia | J12–J18 |
| Chronic kidney disease | E10.2, E11.2, E12.2, E13.2, E14.2, N08.3, N17–N19, I12.0, I12.9, I13.1, I13.9, Z49.[12], Z99.2 |
| Diabetes mellitus | E10–E14 |
| Diabetes mellitus, type 1 | E10 |
| Diabetes mellitus, type 2 | E11 |
| Gestational diabetes | O24.4 |
| Dialysis | Z49, Z99.2 |
| Cancer | C (excluding C44) |
| Breast cancer | C50 |
| Lymph cancer | C83.3, C85.1B, C83.9 |
| Leukaemia | C91–C95 |
| Chemo/radiation therapy | Z51.[01] |

# Supplementary Table S4 Anatomical Therapeutic Chemical codes used to identify medication use of interest

|  |  |
| --- | --- |
| **Medication** | **Anatomical Therapeutic Chemical codes** |
| Renin-angiotensin system inhibitors | C09 |
| Angiotensin converting enzyme inhibitors | C09[AB] |
| Angiotensin receptor blockers | C09C, C09D[AB] |
| Angiotensin receptor/neprilysin inhibitors | C09DX04 |
| Ivabradine | C01EB17 |
| Beta blockers | C07 |
| Mineralocorticoid receptor antagonists | C03DA |
| Sodium-glucose cotransport-2 inhibitors | A10BK, A10BD[15,16,19,20,21,23,24,25,27] |
| Loop diuretics | C03C |
| Digitalis | C01AA05 |
| Warfarin | B01AA |
| P2Y12 | B01AC[04,22,24] |
| Statins | C10AA, C10BA0[1–9], C10BA1[1–2],C10BX |
| Anti-diabetics | A10 |
| Insulin | A10A |
| Non-insulin | A10B |

# Supplementary Table S5 International Classification of Diseases-10 codes used to identify adverse outcomes of interest

|  |  |
| --- | --- |
| **Diagnosis** | **International Classification of Diseases-10 codes** |
| All-cause mortality | Any mortality coding |
| Cardiovascular mortality | I |
| Heart failure | I50 |
| Myocardial infarction | I21–I22 |
| Stroke | I60–I63 |
| Peripheral artery disease | I70–I72, I73.[19], I74, I77.[368], I79 |
| Chronic kidney disease | E10.2, E11.2, E12.2, E13.2, E14.2, N08.3, N17–N19, I12.0, I12.9, I13.1, I13.9, Z49.[12], Z99.2 |

# Supplementary Table S6 Characteristics of patients with suspected de novo HF stratified by the level of healthcare at which HF symptoms were diagnosed

|  |  |  |  |
| --- | --- | --- | --- |
|  | **All patients** | **Primary care** | **Specialist outpatient care** |
| **N (%)** | 5942 | 3933 (66.2) | 2009 (33.8) |
| **Age, years, median (IQR)** | 78.7 (71.9–85.0) | 80.1 (73.5–86.1) | 75.8 (68.8–82.2) |
| **Women, n (%)** | 3207 (54.0) | 2142 (54.5) | 1065 (53.0) |
| **HF symptoms and signs** |  |  |  |
| Dyspnoea, n (%) | 3480 (58.6) | 1831 (46.6) | 1649 (82.1) |
| Peripheral oedema, n (%) | 2630 (44.3) | 2240 (57.0) | 390 (19.4) |
| NT-pro-BNP, ng/L, median (IQR) | 723 (438–1550) | 725 (439–1535) | 722 (436–1580) |
| NT-pro-BNP levels, n (%) |  |  |  |
| 300–400 ng/L | 1155 (19.4) | 761 (19.3) | 394 (19.6) |
| 400–600 ng/L | 1316 (22.1) | 876 (22.3) | 440 (21.9) |
| 600–1000 ng/L | 1215 (20.4) | 796 (20.2) | 419 (20.9) |
| 1000–2000 ng/L | 1172 (19.7) | 806 (20.5) | 366 (18.2) |
| >2000 ng/L | 1084 (18.2) | 694 (17.6) | 390 (19.4) |
| **Comorbidities, n (%)** |  |  |  |
| Ischaemic heart disease | 1359 (22.9) | 851 (21.6) | 508 (25.3) |
| ASCVD | 2372 (39.9) | 1546 (39.3) | 826 (41.1) |
| MI | 817 (13.7) | 497 (12.6) | 320 (15.9) |
| Stroke | 1011 (17.0) | 700 (17.8) | 311 (15.5) |
| PAD | 599 (10.1) | 385 (9.8) | 214 (10.7) |
| Hypertension | 4881 (82.1) | 3237 (82.3) | 1644 (81.8) |
| Atrial fibrillation | 1898 (31.9) | 1282 (32.6) | 616 (30.7) |
| Valvular disease | 593 (10.0) | 374 (9.5) | 219 (10.9) |
| Myocarditis | 342 (5.8) | 244 (6.2) | 98 (4.9) |
| COPD | 723 (12.2) | 435 (11.1) | 288 (14.3) |
| Asthma | 634 (10.7) | 412 (10.5) | 222 (11.1) |
| Pulmonary emboli | 213 (3.6) | 115 (2.9) | 98 (4.9) |
| Type 1 diabetes | 95 (1.6) | 60 (1.5) | 35 (1.7) |
| Type 2 diabetes | 1251 (21.1) | 848 (21.6) | 403 (20.1) |
| Any cancer | 1538 (25.9) | 939 (23.9) | 599 (29.8) |
| Cancer treatment | 125 (2.1 ) | 45 (1.1) | 80 (4.0) |
| **CKD diagnosis or laboratory, n (%)** |  |  |  |
| Diagnosis | 820 (13.8) | 564 (14.3) | 256 (12.7) |
| KDIGO-confirmed CKD (eGFR <60 mL/min/1.73m2 and UACR ≥3 g/mol) | 2766 (46.5) | 1977 (50.3) | 789 (39.3) |
| **Laboratory measurements, median (IQR)** |  |  |  |
| SBP, mmHg | 140 (130–155) | 140 (130–152) | 142 (130–160) |
| DBP, mmHg | 80 (70–85) | 80 (70–85) | 80 (70–88) |
| Body mass index, kg/m2 | 26.1 (23.1–29.9) | 26.1 (22.9–30.0) | 26.2 (23.4–29.7) |
| HbA1c, mmol/mol | 41.0 (37.0–49.0) | 41.0 (37.0–49.0) | 41.0 (37.0–49.0) |
| eGFR, mL/min/1.73m2 | 59.2 (47.2–70.6) | 58.1 (46.3–69.2) | 61.6 (49.7–74.3) |
| UACR, g/mol | 2.0 (0.6–8.4) | 1.9 (0.6–8.0) | 2.1 (0.8–11.7) |
| P-creatinine, µmol/L | 82.0 (68.0–102.0) | 83.0 (68.0–102.8) | 80.0 (67.0–100.0) |
| Haemoglobin, g/L | 129 (118–141) | 129 (118–141) | 129 (117–140) |
| Potassium, mmol/L | 4.1 (3.9–4.4) | 4.2 (3.9–4.4) | 4.1 (3.8–4.4) |
| Sodium, mmol/L | 140 (138–142) | 140 (138–142) | 140 (138–142) |
| **Medication use, n (%)** |  |  |  |
| RASi | 2827 (47.6) | 1843 (46.9) | 984 (49.0) |
| ACEi | 1471 (24.8) | 1001 (25.5) | 470 (23.4) |
| ARB | 1473 (24.8) | 913 (23.2) | 560 (27.9) |
| SGLT2i | 33 (0.6) | 16 (0.4) | 17 (0.8) |
| Beta blockers | 3014 (50.7) | 1950 (49.6) | 1064 (53.0) |
| MRA | 222 (3.7) | 130 (3.3) | 92 (4.6) |
| Loop diuretics | 1088 (18.3) | 667 (17.0) | 421 (21.0) |
| Nitrates | 638 (10.7) | 377 (9.6) | 261 (13.0) |
| Warfarin | 740 (12.5) | 513 (13.0) | 227 (11.3) |
| P2Y12i | 373 (6.3) | 193 (4.9) | 180 (9.0) |
| Statins | 2250 (37.9) | 1468 (37.3) | 782 (38.9) |
| All anti-diabetic | 992 (16.7) | 664 (16.9) | 328 (16.3) |
| Insulin | 460 (7.7) | 298 (7.6) | 162 (8.1) |
| Non-insulin | 775 (13.0) | 531 (13.5) | 244 (12.1) |

Characteristics of patients with suspected de novo HF as of the index date and that patient-cohort stratified by whether they received symptom diagnoses in primary care or specialist outpatient care. ACEi=angiotensin converting enzyme inhibitor. ARB=angiotensin receptor blocker. ASCVD=atherosclerotic cardiovascular disease. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. DBP=diastolic blood pressure. eGFR=estimated glomerular filtration rate. HF=heart failure. KDIGO=Kidney Disease: Improving Global Outcomes. MI=myocardial infarction. MRA=mineralocorticoid receptor antagonist. PAD=peripheral artery disease. RASi=renin-angiotensin system inhibitor. SBP=systolic blood pressure. SGLT2i=sodium-glucose cotransporter-2 inhibitor. UACR=urinary albumin-creatinine ratio.

# Supplementary Table S7 Characteristics of the patients with suspected de novo HF from Stockholm County and the matched controls

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Patients with suspected de novo HF** | **Matched controls from general population** | **Matched controls from outpatient care** |
| **N** | 2048 | 2048 | 2048 |
| **Age, years, median (IQR)** | 77.4 (70.2–83.9) | 77.2 (70.0–83.9) | 77.2 (70.1–83.9) |
| **Women, n (%)** | 1087 (53.1) | 1087 (53.1) | 1087 (53.1) |
| **HF signs and symptoms** |  |  |  |
| Dyspnoea, n (%) | 1329 (64.9) | NA | NA |
| Peripheral oedema, n (%) | 739 (36.1) | NA | NA |
| NT-proBNP, ng/L median (IQR) | 727 (439–1640) | NA | NA |
| NT-pro-BNP levels, n (%) |  |  |  |
| 300–400 ng/L | 406 (19.8) | NA | NA |
| 400–600 ng/L | 425 (20.8) | NA | NA |
| 600–1000 ng/L | 421 (20.6) | NA | NA |
| 1000–2000 ng/L | 395 (19.3) | NA | NA |
| >2000 ng/L | 401 (19.6) | NA | NA |
| **Comorbidities, n (%)** |  |  |  |
| Ischemic heart disease | 447 (21.8) | 275 (13.4) | 321 (15.7) |
| ASCVD | 792 (38.7) | 514 (25.1) | 590 (28.8) |
| Myocardial infarction | 264 (12.9) | 134 (6.5) | 146 (7.1) |
| Stroke | 323 (15.8) | 239 (11.7) | 282 (13.8) |
| Peripheral artery disease | 220 (10.7) | 97 (4.7) | 114 (5.6) |
| Hypertension | 1917 (93.6) | 1510 (73.7) | 1629 (79.5) |
| Atrial fibrillation | 632 (30.9) | 224 (10.9) | 264 (12.9) |
| Valvular disease | 183 (8.9) | 82 (4.0) | 100 (4.9) |
| Myocarditis | 65 (3.2) | 39 (1.9) | 33 (1.6) |
| COPD | 270 (13.2) | 157 (7.7) | 179 (8.7) |
| Asthma | 231 (11.3) | 181 (8.8) | 247 (12.1) |
| Pulmonary emboli | 74 (3.6) | 37 (1.8) | 43 (2.1) |
| Type 1 diabetes | 40 (2.0) | 10 (0.5) | 12 (0.6) |
| Type 2 diabetes | 473 (23.1) | 305 (14.9) | 325 (15.9) |
| Any cancer | 537 (26.2) | 361 (17.6) | 413 (20.2) |
| **CKD diagnosis or laboratory, n (%)** |  |  |  |
| Diagnosis | 289 (14.1) | 135 (6.6) | 140 (6.8) |
| KDIGO-confirmed CKD (eGFR <60 mL/min/1.73m2 and UACR ≥3 g/mol) | 903 (44.1) | 471 (23.0) | 481 (23.5) |
| **Laboratory measurements, median (IQR)** |  |  |  |
| SBP, mmHg | 140 (128–160) | 137 (126-150) | 139 (128–151) |
| Body mass index, kg/m2 | 26.0 (23.1–29.9) | 24.9 (22.1-28.1) | 24.7 (22.1–27.8) |
| eGFR, mL/min/1.73m2 | 61.1 (49.0–73.0) | 62.5 (52.1-73.3) | 63.2 (53.3–73.5) |
| **Medication use, n (%)** |  |  |  |
| RASi | 1068 (52.1) | 787 (38.4) | 853 (41.7) |
| SGLT2i | 9 (0.4) | 9 (0.4) | 13 (0.6) |
| Beta blockers | 1086 (53.0) | 566 (27.6) | 599 (29.2) |
| MRA | 60 (2.9) | 36 (1.8) | 40 (2.0) |
| Loop diuretics | 60 (2.9) | 129 (6.3) | 159 (7.8) |
| Warfarin | 246 (12.0) | 86 (4.2) | 159 (7.8) |
| Statins | 750 (36.6) | 578 (28.2) | 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. RASi=renin-angiotensin system inhibitor. SBP=systolic blood pressure. SGLT2i=sodium-glucose cotransporter-2 inhibitor.

# Supplementary Table S8 Characteristics of the patients with suspected de novo HF stratified by NT-proBNP levels

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **300–400 ng/L** | **400–600 ng/L** | **600–1000 ng/L** | **1000–2000 ng/L** | **>2000 ng/L** |
| **N (%)** | 1155 | 1316 | 1215 | 1172 | 1084 |
| **Age, years, median (IQR)** | 76.6 (70.1–82.8) | 77.8 (71.0–84.0) | 78.8 (71.9–84.7) | 79.7 (72.8–85.8) | 81.1 (74.6–87.8) |
| **Women, n (%)** | 680 (58.9) | 754 (57.3) | 670 (55.1) | 580 (49.5) | 523 (48.2) |
| **HF signs and symptoms** |  |  |  |  |  |
| Dyspnoea, n (%) | 671 (58.1) | 750 (57.0) | 705 (58.0) | 678 (57.8) | 676 (62.4) |
| Peripheral oedema, n (%) | 513 (44.4) | 602 (45.7) | 536 (44.1) | 529 (45.1) | 450 (41.5) |
| NT-proBNP, ng/L median (IQR) | 345 (323–371) | 480 (438–534) | 755 (664–862) | 1410 (1180–1643) | 3377 (2498–5348) |
| **Comorbidities, n (%)** |  |  |  |  |  |
| Ischaemic heart disease | 221 (19.1) | 277 (21.0) | 291 (24.0) | 291 (24.8) | 279 (25.7) |
| ASCVD | 386 (33.4) | 492 (37.4) | 502 (41.3) | 505 (43.1) | 487 (44.9) |
| Myocardial infarction | 128 (11.1) | 164 (12.5) | 162 (13.3) | 186 (15.9) | 177 (16.3) |
| Stroke | 150 (13.0) | 202 (15.3) | 217 (17.9) | 222 (18.9) | 220 (20.3) |
| Peripheral artery disease | 98 (8.5) | 132 (10.0) | 106 (8.7) | 123 (10.5) | 140 (12.9) |
| Hypertension | 902 (78.1) | 1053 (80.0) | 999 (82.2) | 1001 (85.4) | 926 (85.4) |
| Atrial fibrillation | 134 (11.6) | 237 (18.0) | 384 (31.6) | 587 (50.1) | 556 (51.3) |
| Valvular disease | 66 (5.7) | 104 (7.9) | 113 (9.3) | 147 (12.5) | 163 (15.0) |
| Myocarditis | 54 (4.7) | 59 (4.5) | 73 (6.0) | 76 (6.5) | 80 (7.4) |
| COPD | 154 (13.3) | 159 (12.1) | 137 (11.3) | 143 (12.2) | 130 (12.0) |
| Asthma | 151 (13.1) | 149 (11.3) | 124 (10.2) | 120 (10.2) | 90 (8.3) |
| Pulmonary emboli | 48 (4.2) | 54 (4.1) | 43 (3.5) | 30 (2.6) | 38 (3.5) |
| Type 1 diabetes | 26 (2.3) | 19 (1.4) | 18 (1.5) | 20 (1.7) | 12 (1.1) |
| Type 2 diabetes | 249 (21.6) | 256 (19.5) | 252 (20.7) | 264 (22.5) | 230 (21.2) |
| Any cancer | 275 (23.8) | 323 (24.5) | 324 (26.7) | 324 (27.6) | 292 (26.9) |
| **CKD diagnosis or laboratory, n (%)** |  |  |  |  |  |
| Diagnosis | 115 (10.0) | 168 (12.8) | 130 (10.7) | 170 (14.5) | 237 (21.9) |
| KDIGO-confirmed CKD (eGFR <60 mL/min/1.73m2 and UACR ≥3 g/mol) | 453 (39.2) | 584 (44.4) | 528 (43.5) | 582 (49.7) | 619 (57.1) |
| **Laboratory measurements, median (IQR)** |  |  |  |  |  |
| SBP, mmHg | 141 (130–160) | 140 (130–155) | 140 (126–156) | 140 (127–152) | 140 (127–155) |
| Body mass index, kg/m2 | 26.6 (23.3–30.4) | 26.1 (23.4–29.9) | 26.5 (23.0–30.1) | 26.1 (23.2–30.2) | 25.3 (22.6–29.0) |
| eGFR, mL/min/1.73m2 | 62.8 (51.2–73.3) | 61.1 (49.1–72.8) | 60.2 (49.4–72.2) | 58.4 (46.0–68.3) | 52.6 (39.8–64.0) |
| **Medication use, n (%)** |  |  |  |  |  |
| RASi | 511 (44.2) | 624 (47.4) | 567 (46.7) | 604 (51.5) | 521 (48.1) |
| SGLT2i | 8 (0.7) | 8 (0.6) | ≤5 | 11 (0.9) | ≤5 |
| Beta blockers | 461 (39.9) | 557 (42.3) | 626 (51.5) | 707 (60.3) | 663 (61.2) |
| MRA | 35 (3.0) | 51 (3.9) | 53 (4.4) | 36 (3.1) | 47 (4.3) |
| Loop diuretics | 173 (15.0) | 214 (16.3) | 194 (16.0) | 235 (20.1) | 272 (25.1) |
| Warfarin | 49 (4.2) | 90 (6.8) | 149 (12.3) | 228 (19.5) | 224 (20.7) |
| Statins | 425 (36.8) | 492 (37.4) | 455 (37.4) | 474 (40.4) | 404 (37.3) |

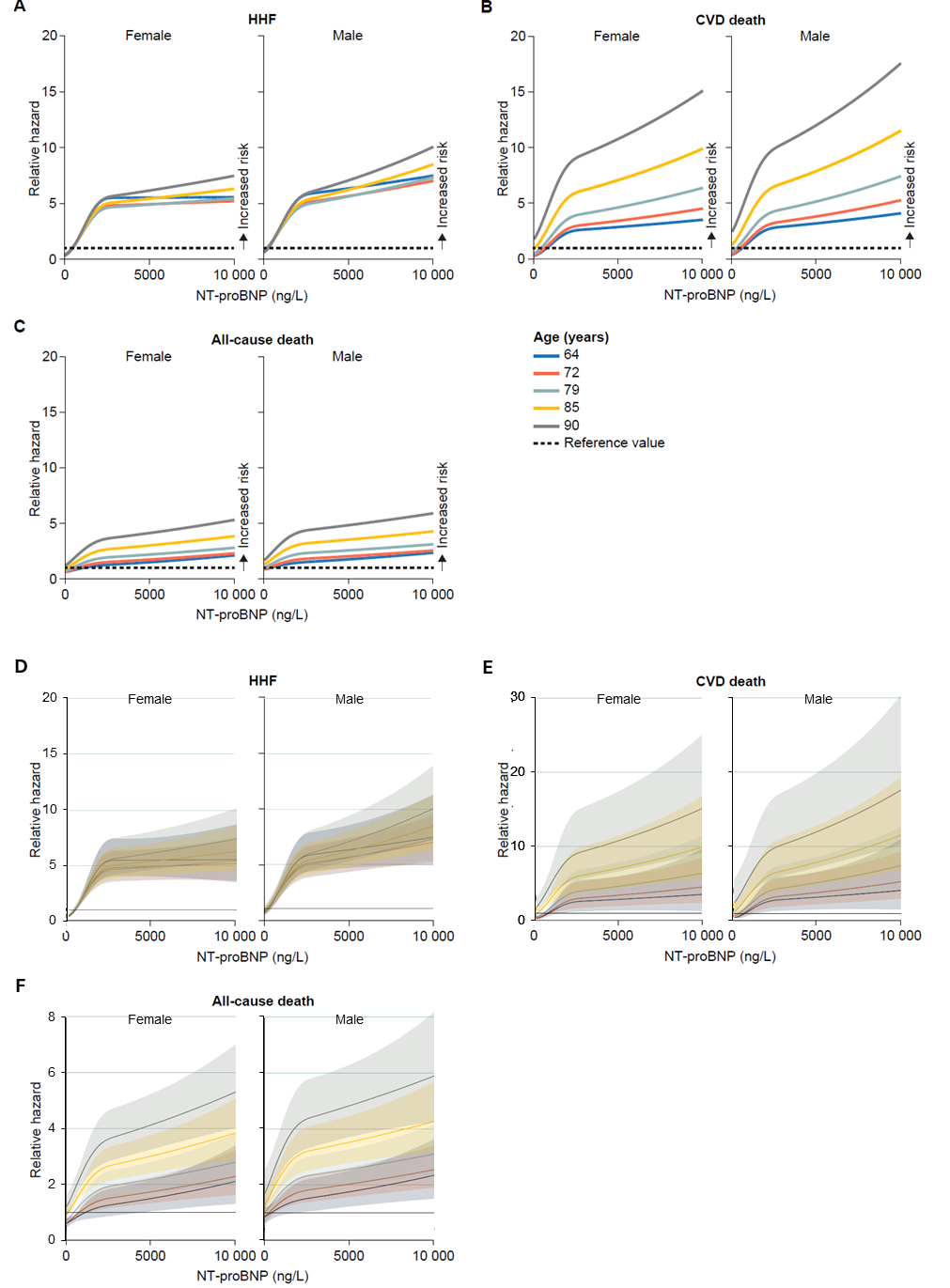
Characteristics of patients with suspected de novo HF and the matched controls as of the index date. ASCVD=atherosclerotic cardiovascular disease. CKD=chronic kidney disease. COPD=chronic obstructive pulmonary disease. eGFR=estimated glomerular filtration rate. HF=heart failure. KDIGO=Kidney Disease: Improving Global Outcomes. MRA=mineralocorticoid receptor antagonist. RASi=renin-angiotensin system inhibitor. SBP=systolic blood pressure. SGLT2i=sodium-glucose cotransporter-2 inhibitor.

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# Supplementary Figure S1 The distribution of NT-pro-BNP measurements in patients with suspected de novoHF following the identification of HF symptoms.

HF=heart failure.



# Supplementary Figure S2 The relative hazard of (A) hospitalization for HF (HHF), (B) death related to cardiovascular disease (CVD death), and (C) all-cause death as NT-proBNP levels increase in patients with suspected de novo HF stratified by age and sex, during the year following the identification of signs and symptoms of HF. The same data represented as spline curves with confidence intervals in panels (D), (E) and (F).

HF=heart failure.

A graph with many different colored dots

Description automatically generated with medium confidence

# Supplementary Figure S3 Causes of mortality during 1-year follow-up of patients with suspected de novo HF.

Labelled causes of mortality are those recorded for ≥1/50 patients. An additional 19.5% of those who died within 1 year had an unknown cause of death (no diagnosis). The most common ICD10 chapter was cardiovascular (I:26.8%), followed by cancer (C:21.6%). Within the cardiovascular chapter, the most common three-character diagnosis was HF followed by ischemic heart disease and myocardial infarction. COPD=chronic obstructive pulmonary disease. HF=heart failure. ICD=International Classification of Diseases.

A graph of a disease

Description automatically generated with medium confidence

# Supplementary Figure S4 The cumulative incidence of hospitalization for HF (HHF), death related to cardiovascular disease (CVD death), and all-cause death in (A) patients with suspected de novo HF and (B) the matched controls.

HF=heart failure.

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# Supplementary Figure S5 Absolute risk differences of outcomes by NT-proBNP levels compared with matched controls.

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# Supplementary Figure S6 The time to the composite endpoint of first diagnosis of HF, first echocardiogram and/or all-cause death in patients with suspected de novoHF following the identification of the condition’s signs or symptoms.

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# Supplementary Figure S7 The time to the composite endpoint of a first diagnosis of HF, first echocardiogram and/or all-cause death in patients with suspected de novo HF following the identification of the condition’s signs and symptoms in (A) primary care and (B) specialist outpatient care. Patients are stratified by NT-proBNP thresholds.

HF=heart failure.

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# Supplementary Figure S8 Use of guideline-directed medical therapies for HF before and after index date in (A) patients with suspected de novo HF and (B) the matched controls.

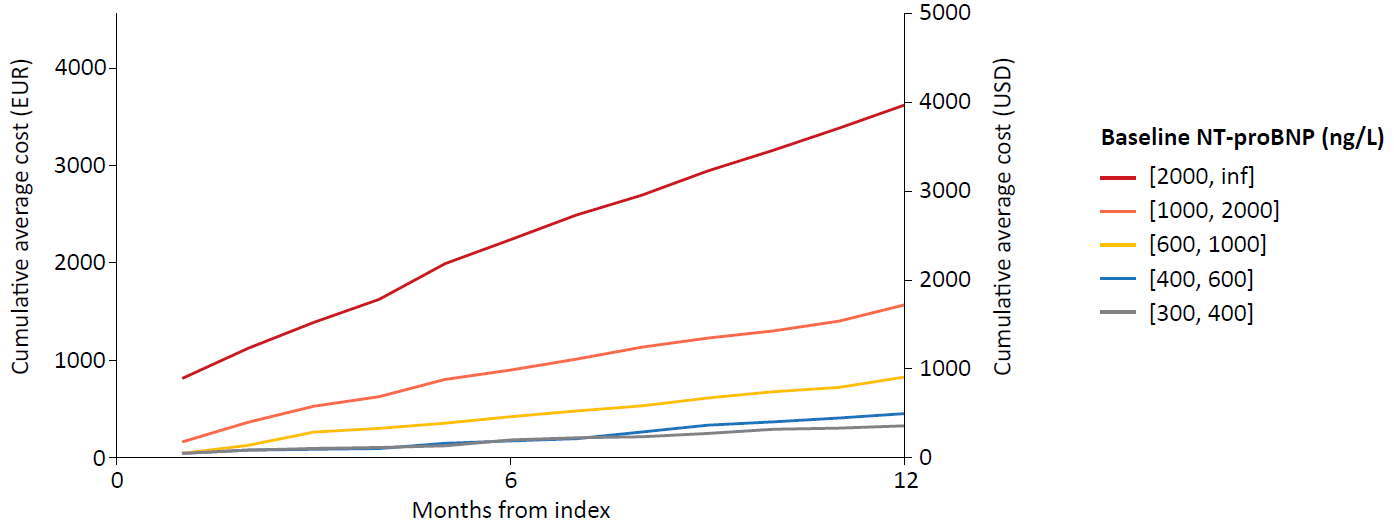
HF=heart failure. MRA=mineralocorticoid receptor antagonist. RASi=renin-angiotensin system inhibitor. SGLT2i=sodium-glucose cotransporter-2 inhibitor.

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# Supplementary Figure S9 Use of guideline-directed medical therapies for HF before and after index date in patients with suspected de novo HF treated in (A) primary care and (B) specialist outpatient care stratified by NT‑proBNP level.

HF=heart failure. MRA=mineralocorticoid receptor antagonist. RASi=renin-angiotensin system inhibitor. SGLT2i=sodium-glucose cotransporter-2 inhibitor.



# Supplementary Figure S10 HF healthcare costs for patients with suspected de novo HF during follow-up.

Shown is the average cumulative cost of specialized outpatient care and inpatient care for HF each month during the 12-month period following the index date for patients with suspected de novoHF, stratified by NT-proBNP thresholds. Each month is a standardized 30-day month and costs are expressed in euros and United States dollars (USD).

HF=heart failure.

# References

1. World Health Organization WHO collaborating centre for drug statistics methodology. ATC/DDD index 2017. <https://www.whocc.no/> (19 June 2023)

2. World Health Organization International classification of disease and related health problems. <http://www.who.int/classifications/icd/en/> (19 June 2023)

3. Nordic Medico-Statistical Committee NOMESCO classification of surgical procedures. 2010. <https://norden.diva-portal.org/smash/get/diva2:970547/FULLTEXT01.pdf> (19 June 2023)

4. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;**24**:659–667. doi: 10.1007/s10654-009-9350-y

5. Norhammar A, Bodegard J, Vanderheyden M, Tangri N, Karasik A, Maggioni AP, et al. Prevalence, outcomes and costs of a contemporary, multinational population with heart failure. *Heart* 2023;**109**:548–556. doi: 10.1136/heartjnl-2022-321702

6. Sundstrom J, Arnlov J, Karayiannides S, Bodegard J, Ersmark K, Gustafsson S, et al. Heart failure outcomes by left ventricular ejection fraction in a contemporary region-wide patient cohort. *ESC Heart Fail* 2024;**11**:1377–1388. doi: 10.1002/ehf2.14685

7. Christersson M, Gustafsson S, Lampa E, Almstedt M, Cars T, Bodegård J, et al. Usefulness of Heart Failure Categories Based on Left Ventricular Ejection Fraction. *Journal of the American Heart Association* 2024;**13**:e032257. doi: 10.1161/JAHA.123.032257

8. Matan D, Lofstrom U, Corovic Cabrera C, Eriksson B, Ekstrom M, Hage C, et al. Reorganization of heart failure management and improved outcome - the 4D HF Project. *Scand Cardiovasc J* 2021;**55**:1–8. doi: 10.1080/14017431.2020.1820075

9. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. *Kidney Int* 2014;**85**:49–61. doi: 10.1038/ki.2013.444

10. Nyman U, Grubb A, Larsson A, Hansson LO, Flodin M, Nordin G, et al. The revised Lund-Malmo GFR estimating equation outperforms MDRD and CKD-EPI across GFR, age and BMI intervals in a large Swedish population. *Clin Chem Lab Med* 2014;**52**:815–824. doi: 10.1515/cclm-2013-0741