**­Association between digoxin use and outcomes in patients with heart failure and reduced ejection fraction: an analysis from the Swedish Heart Failure Registry**

**Short title:** Digoxin and outcomes in heart failure with reduced ejection fraction

Chris J. Kapelios [1], Lars H. Lund [2], Lina Benson [3], Ulf Dahlström [4], Giuseppe MC Rosano [5], Paul J. Hauptman [6], Gianluigi Savarese [2]

[1] Department of Cardiology, Laiko General Hospital, Athens, Greece

[2] Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden

[3] Unit of Cardiology, Department of Medicine, Karolinska Institutet

[4] Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linköping University, Linkoping, Sweden

[5] Cardiovascular Clinical Academic Group St George's Hospitals NHS Trust University of London, Cranmer Terrace, London, United Kingdom; IRCCS San Raffaele, Pisana, Roma, Italy

[6] University of Tennessee Graduate School of Medicine, Knoxville TN

**Address for correspondence:**

Gianluigi Savarese, MD, PhD

Division of Cardiology, Department of Medicine

Karolinska Institutet

Karolinska University Hospital - Norrbacka S1:02

SE-17176 Stockholm, Sweden

E-mail. [gianluigi.savarese@ki.se](mailto:gianluigi.savarese@ki.se)

**Supplementary Material**

**Methods**

*Data sources*

The Swedish Heart Failure Registry (SwedeHF; www.swedeHF.se) is a national quality registry and has been previously described. Until April 2017, the only inclusion criterion was clinician-judged HF, and thereafter a diagnosis of HF according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, I13.2. Approximately 80 variables are recorded at discharge from hospital or after an outpatient clinic visit on a web-based case report form and entered into a database managed by the Uppsala Clinical Research Center ([www.ucr.uu.se](http://www.ucr.uu.se)). Both cardiology and non-cardiology inpatient wards and outpatient clinics enroll patients in SwedeHF. In 2019, 30.4% of the HF population in Sweden was registered in SwedeHF. All Swedish citizens have unique personal identification numbers that enable linking of disease-specific health registries and governmental health and statistical registries. For the current analysis, the SwedeHF database was linked with the Cause of Death Registry, which provided date of death, and the National Patient Registry (NPR), through which we obtained additional baseline comorbidities and the outcome HFH, defined according to ICD-10 codes (**Supplementary Table 1**). Additionally, Statistics Sweden (www.scb.se) provided socioeconomic characteristics, and the Dispensed Drug Registry (DDR) was used to obtain information on digoxin dispensation over time. For further information, see <https://kiheartfailure.github.io/shfdb3/>.

Establishment of the registry and this analysis were approved by a multi-site ethics committee.

**Statistical analyses**

*Missing data*

Multiple imputation (R-package mice; 10 imputed datasets generated) was used to handle missing values for variables included in multivariable models (marked in **Table 1)** for the overall population and for patients with and without AF. Digoxin use was not included in the imputation model. The outcome of first HF hospitalization (HFH)/death was included as the Nelson-Aalen estimator.

**Propensity score matching**

Propensity scores (PS) for digoxin use were separately calculated in each imputed dataset by a logistic regression model including all the variables highlighted in **Table 1** as covariates, and then averaged across the 10 imputed datasets for patients with and without AF. Digoxin users and non-users were then matched 1:1, with no replacement, based on the averaged PS using the nearest neighbor method where matching was allowed if the PS differed by 0.01 or less. The ability of the matching to balance baseline characteristics in digoxin users vs. non-users was assessed by standardized mean differences, with a value <0.10 considered as not significant. In the PS matched population, digoxin users and non-users were comparable for all the baseline characteristics included in the models.

**Consistency analysis**

Adjustments for PS as a covariate

Since PS matching reduces the sample size, Cox regression models were performed in the overall cohort adjusting for the PS as a continuous covariate rather than matching for the PS. The PS was modelled using a cubic spline with 4 degrees of freedom.

Crossover

In the main analysis, digoxin use was considered as at the baseline. As a consistency analysis digoxin was included as a time-dependent variable in the Cox regression models performed in the PS-matched populations. Patients treated with digoxin at baseline were assumed to be on digoxin until last dispensation + 3 months, independent of the time frame between the elapsed dispensations. In untreated patients, crossover was defined as a new digoxin dispensation in the DDR and thereafter in the same manner as for patients treated with digoxin at baseline. Therefore, patients with digoxin at baseline were allowed to cross over maximum once and patients without digoxin at baseline were allowed to cross over not more than twice.

Competing risk

In the PS-matched populations, the analyses for the outcome time to first HFH were also performed using a Fine and Gray sub-distributional hazards model where death was treated as a competing event.

A two-sided p-value of <0.05 was considered statistically significant. All analyses were performed using R version 4.0.2 (R Core Team 2019). The R code for data handling and statistical analyses are available at https://github.com/KIHeartFailure/digoxinhfref

**Results**

**Overall population with heart failure with reduced ejection fraction (HFrEF)**

**A) Digoxin use over time**

In the overall population with HFrEF, the use of digoxin over time showed a reverse U shape, starting with an annual use rate below 7.5% in 2006, peaking at approximately 9.2% in 2011-12 and declining to 7.5% in 2018 (**Supplementary Figure 1**).

**B) Patient characteristics according to digoxin use**

**Supplementary Table 2** reports baseline characteristics in the overall population. Overall, digoxin users were older with more severe HF (i.e. higher New York Heart Association [NYHA] class, longer HF duration, more often registered as inpatients, lower left ventricular ejection fraction [LVEF], higher N-terminal pro-brain natriuretic peptide [NT-proBNP], lower blood pressure [BP]) compared with digoxin non-users. A majority of patients receiving digoxin had a history of atrial fibrillation [AF] (92% vs. 44% among non-users). Consistently, patients receiving digoxin had higher heart rates. Except for valvular heart disease, liver disease and chronic obstructive pulmonary disease, most comorbidities (hypertension, peripheral vascular disease, ischemic heart disease, anemia, chronic kidney disease) were less likely among digoxin users. Finally, digoxin users were more likely to receive beta-blockers (BBs), mineralocorticoid receptor antagonists (MRAs) and diuretics, but less likely to be followed in a HF nurse-led clinic or hospital care compared with non-users.

**C) Independent predictors of digoxin use**

In multivariable regression models independent associations between patient characteristics and the likelihood of receiving digoxin were assessed. Predictors of digoxin use in the overall population were female sex, younger age, more severe HF (i.e. longer history of HF, higher NYHA class, inpatient registration, mean BP ≤90 mmHg, LVEF <30%), heart rate >70 bpm, no history of hypertension or ischemic heart disease or anemia, history of AF, diabetes and chronic obstructive pulmonary disease, better renal function (estimated glomerular filtration rate >60 vs 30-60 ml/min/1.73m2), no use of RASi, but higher use of diuretics, BBs and MRAs, and lack of referral to HF-nurse led clinic (**Supplementary Figure 2**).

**Supplementary Table 1. Variable definitions**

|  |  |
| --- | --- |
| **Variable** | **Definition** |
| **Medical history** |  |
| Atrial fibrillation | Diagnosis in SwedeHF (history of atrial fibrillation or ECG showing atrial fibrillation) or in NPR (ICD-10 code: I48). |
| Anaemia | Haemoglobin <120 g/l in females and <130 g/l in males |
| COPD | Diagnosis in NPR (ICD-10 codes: J40-J44) |
| Diabetes mellitus | Diagnosis in SwedeHF or in NPR (ICD-10 codes: E10-E14) |
| Dilated cardiomyopathy | Diagnosis in SwedeHF or in NPR (ICD-10 code: I420) |
| Hypertension | Diagnosis in SwedeHF or in NPR (ICD-10 codes:I10-I15) |
| Peripheral artery disease | Diagnosis in NPR (ICD-10 codes: I70-I73) |
| Ischaemic heart disease | Diagnosis in SwedeHF or in NPR (ICD-10 codes: I20-I25; procedure codes: FNG, FNA, FNB, FNC, FND, FNE, FNF, FNH, Z951, Z955). |
| Cancer within the last 3 years | Diagnosis in NPR within 3 years prior to the registrations in SwedeHF (ICD-10 codes: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97) |
| Stroke/transient ischaemic attack | Diagnosis in NPR (I61-I64, G458, G459, I639) |
| Valvular disease | Diagnosis in SwedeHF or in NPR (ICD-10 codes: A520, I05-I08, I091, I098, I34-I39, Q230-Q233, Z952, Z954) |
| Dementia | Diagnosis in NPR (ICD-10 codes: F00, F01, F02, F03, F04) |
| **Outcomes** |  |
| CV mortality | Main diagnosis in Causes of Death register (ICD-10 codes: I00-I99) |
| Hospitalization for heart failure | Main diagnosis in NPR (ICD-10 codes: I50, I42, I43, I255, K761, I110, I130, I132, J81) |

NPR: National Patient Register; ICD: International Classification of Diseases; COPD: Chronic obstructive pulmonary disease.

**Supplementary Table 2. Baseline characteristics of patients stratified by digoxin use in the overall and matched population**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Overall population** | | | **Matched population** | | | | |
| Missing (%) | **No digoxin** | **Digoxin** | **p** | | Missing (%) | **No digoxin** | **Digoxin** | **p** |
| n |  | 35,472 | 6,984 |  | |  | 6,874 | 6,874 |  |
| Male gender† | 0.0 | 25298 (71.3) | 4816 (69.0) | <0.001 | | 0.0 | 4815 (70.0) | 4763 (69.3) | 0.344 |
| Age, years | 0.0 | 73.0 [64.0, 81.0] | 74.0 [65.0, 81.0] | 0.002 | | 0.0 | 74.0 [66.0, 81.0] | 74.0 [65.0, 81.0] | 0.085 |
| Age≥75 years† | 0.0 | 16349 (46.1) | 3337 (47.8) | 0.010 | | 0.0 | 3356 (48.8) | 3314 (48.2) | 0.484 |
| Outpatients† | 0.0 | 20088 (56.6) | 3303 (47.3) | <0.001 | | 0.0 | 3323 (48.3) | 3280 (47.7) | 0.473 |
| Year of inclusion† | 0.0 |  |  | <0.001 | | 0.0 |  |  | 0.970 |
| . 2005-2010 |  | 12273 (34.6) | 3117 (44.6) |  | |  | 3031 (44.1) | 3022 (44.0) |  |
| . 2011-2015 |  | 13390 (37.7) | 2519 (36.1) |  | |  | 2491 (36.2) | 2505 (36.4) |  |
| . 2016-2018 |  | 9809 (27.7) | 1348 (19.3) |  | |  | 1352 (19.7) | 1347 (19.6) |  |
| Children† | 0.0 | 29199 (82.3) | 5746 (82.3) | 0.947 | | 0.0 | 5613 (81.7) | 5657 (82.3) | 0.340 |
| Living alone | 0.3 | 16185 (45.8) | 3357 (48.2) | <0.001 | | 0.3 | 3300 (48.2) | 3295 (48.1) | 0.919 |
| Education level† | 2.0 |  |  | 0.447 | | 2.1 |  |  | 0.617 |
| Compulsory |  | 15102 (43.5) | 2987 (43.7) |  | |  | 2997 (44.6) | 2946 (43.7) |  |
| Secondary |  | 13973 (40.2) | 2702 (39.5) |  | |  | 2625 (39.0) | 2660 (39.5) |  |
| University |  | 5677 (16.3) | 1151 (16.8) |  | |  | 1102 (16.4) | 1128 (16.8) |  |
| Income above median \*\*† | 0.3 | 17644 (49.9) | 3549 (50.9) | 0.110 | | 0.3 | 3481 (50.8) | 3480 (50.8) | 0.972 |
| BMI, kg/m2 | 39.8 | 26.3 [23.3, 29.8] | 25.9 [23.1, 29.6] | <0.001 | | 41.1 | 26.3 [23.3, 29.8] | 25.9 [23.1, 29.6] | 0.004 |
| BMI≥30 kg/m2 † | 39.8 | 5259 (24.5) | 957 (23.3) | 0.119 | | 41.1 | 977 (24.1) | 945 (23.4) | 0.432 |
| HF history≥ 6m † | 2.1 | 16100 (46.4) | 3581 (52.1) | <0.001 | | 1.8 | 3589 (53.2) | 3517 (52.0) | 0.177 |
| NYHA class† | 26.4 |  |  | <0.001 | | 26.7 |  |  | 0.864 |
| I |  | 2504 (9.6) | 357 (6.9) |  | |  | 352 (7.1) | 355 (7.0) |  |
| II |  | 12483 (47.8) | 2308 (44.6) |  | |  | 2195 (44.0) | 2270 (44.6) |  |
| III |  | 10227 (39.2) | 2303 (44.5) |  | |  | 2232 (44.7) | 2266 (44.5) |  |
| IV |  | 876 (3.4) | 209 (4.0) |  | |  | 212 (4.2) | 202 (4.0) |  |
| SBP, mmHg | 1.8 | 123.0 [110.0, 140.0] | 120.0 [110.0, 135.0] | <0.001 | | 1.9 | 120.0 [110.0, 135.0] | 120.0 [110.0, 135.0] | 0.993 |
| DBP, mmHg | 1.7 | 72.0 [65.0, 80.0] | 72.0 [65.0, 80.0] | 0.734 | | 1.8 | 73.0 [65.0, 80.0] | 72.0 [65.0, 80.0] | 0.161 |
| MBP, mmHg | 1.7 | 90.0 [81.7, 100.0] | 90.0 [80.0, 98.3] | <0.001 | | 1.8 | 90.0 [80.3, 98.3] | 90.0 [80.0, 98.3] | 0.470 |
| MBP>90 mmHg † | 1.7 | 16680 (47.8) | 3124 (45.5) | 0.001 | | 1.8 | 3048 (45.2) | 3089 (45.8) | 0.514 |
| Duration AF, days | 51.6 | 536.0 [43.0, 1908.5] | 467.0 [35.0, 2004.5] | 0.064 | | 12.8 | 425.0 [33.0, 1812.8] | 473.0 [36.0, 2006.5] | 0.010 |
| ECG, % | 2.1 |  |  | <0.001 | | 1.7 |  |  | <0.001 |
| Sinus rhythm |  | 22047 (63.5) | 1203 (17.5) |  | |  | 2018 (29.8) | 1196 (17.7) |  |
| AF |  | 8857 (25.5) | 4972 (72.5) |  | |  | 3915 (57.9) | 4876 (72.2) |  |
| Paced/other |  | 3816 (11.0) | 687 (10.0) |  | |  | 829 (12.3) | 681 (10.1) |  |
| HR, bpm | 2.6 | 72.0 [63.0, 83.0] | 78.0 [68.0, 90.0] | <0.001 | | 2.7 | 76.0 [68.0, 88.0] | 78.0 [68.0, 90.0] | <0.001 |
| HR≥ 70 bpm† | 2.6 | 18081 (52.3) | 4472 (66.1) | <0.001 | | 2.7 | 4387 (65.3) | 4388 (65.9) | 0.424 |
| Current smoker † | 20.7 | 4091 (14.5) | 707 (12.9) | 0.003 | | 21.9 | 673 (12.6) | 684 (12.7) | 0.805 |
| Atrial fibrillation† | 0.0 | 15699 (44.3) | 6420 (91.9) | <0.001 | | 0.0 | 6348 (92.3) | 6310 (91.8) | 0.243 |
| Diabetes† | 0.0 | 9533 (26.9) | 1841 (26.4) | 0.383 | | 0.0 | 1818 (26.4) | 1815 (26.4) | 0.969 |
| Hypertension† | 0.0 | 21229 (59.8) | 3891 (55.7) | <0.001 | | 0.0 | 3898 (56.7) | 3864 (56.2) | 0.570 |
| COPD† | 0.0 | 4198 (11.8) | 884 (12.7) | 0.055 | | 0.0 | 882 (12.8) | 863 (12.6) | 0.645 |
| Stroke† | 0.0 | 4748 (13.4) | 976 (14.0) | 0.194 | | 0.0 | 993 (14.4) | 965 (14.0) | 0.510 |
| IHD† | 0.0 | 20394 (57.5) | 3185 (45.6) | <0.001 | | 0.0 | 3261 (47.4) | 3172 (46.1) | 0.133 |
| PAD † | 0.0 | 3128 (8.8) | 508 (7.3) | <0.001 | | 0.0 | 510 (7.4) | 504 (7.3) | 0.870 |
| Valve disease† | 0.0 | 5944 (16.8) | 1340 (19.2) | <0.001 | | 0.0 | 1380 (20.1) | 1328 (19.3) | 0.274 |
| Cancer† | 0.0 | 4657 (13.1) | 915 (13.1) | 0.966 | | 0.0 | 900 (13.1) | 900 (13.1) | 1.000 |
| Liver disease† | 0.0 | 702 (2.0) | 171 (2.4) | 0.013 | | 0.0 | 163 (2.4) | 165 (2.4) | 0.955 |
| ICD/CRT† | 1.2 | 3029 (8.6) | 603 (8.7) | 0.850 | | 1.1 | 635 (9.3) | 594 (8.7) | 0.231 |
| EF<30%† | 0.0 | 16823 (47.4) | 3770 (54.0) | <0.001 | | 0.0 | 3715 (54.0) | 3679 (53.5) | 0.549 |
| Hemoglobin, gr/l | 3.4 | 135.0 [122.0, 146.0] | 137.0 [125.0, 149.0] | <0.001 | | 2.7 | 136.0 [124.0, 148.0] | 137.0 [125.0, 149.0] | <0.001 |
| Anemia† | 3.4 | 10939 (32.0) | 1812 (26.7) | <0.001 | | 2.7 | 1840 (27.5) | 1800 (26.9) | 0.445 |
| GFR, ml/min/1.73m2 | 1.2 | 63.7 [46.3, 81.9] | 64.7 [49.2, 81.3] | <0.001 | | 1.1 | 63.9 [47.0, 80.2] | 64.5 [49.0, 81.3] | 0.003 |
| GFR † | 1.2 |  |  | <0.001 | | 1.1 |  |  | 0.352 |
| . 30-60 |  | 12868 (36.7) | 2564 (37.2) |  | |  | 2604 (38.3) | 2541 (37.4) |  |
| . ≥60 |  | 19502 (55.6) | 4031 (58.4) |  | |  | 3877 (57.0) | 3944 (58.1) |  |
| . ≤30 |  | 2677 (7.6) | 304 (4.4) |  | |  | 326 (4.8) | 304 (4.5) |  |
| NT-ProBNP, pg/ml | 48.3 | 2820.0 [1185.5, 6356.0] | 3456.0 [1776.0, 6811.5] | <0.001 | | 51.8 | 3365.0 [1670.0, 6736.5] | 3452.0 [1770.0, 6805.0] | 0.290 |
| NT-proBNP above median † | 48.3 | 9143 (49.0) | 1828 (55.8) | <0.001 | | 51.8 | 1872 (55.5) | 1812 (55.8) | 0.865 |
| Serum potassium | 19.4 | 4.2 [3.9, 4.5] | 4.2 [3.9, 4.5] | 0.001 | | 23.6 | 4.2 [3.9, 4.5] | 4.2 [3.9, 4.5] | 0.464 |
| Serum potassium groups † | 19.4 |  |  | 0.032 | | 23.6 |  |  | 0.670 |
| . normakalemia |  | 26951 (92.9) | 4871 (93.2) |  | |  | 4963 (92.8) | 4806 (93.2) |  |
| . hypokalemia |  | 1108 (3.8) | 218 (4.2) |  | |  | 233 (4.4) | 218 (4.2) |  |
| . hyperkalemia |  | 941 (3.2) | 137 (2.6) |  | |  | 154 (2.9) | 135 (2.6) |  |
| Beta-Blocker † | 0.3 | 32286 (91.3) | 6550 (94.1) | <0.001 | | 0.4 | 6406 (93.6) | 6440 (94.0) | 0.441 |
| RASi† | 1.3 | 31906 (91.0) | 6239 (90.7) | 0.398 | | 1.5 | 6143 (90.6) | 6134 (90.6) | 1.000 |
| MRA† | 0.6 | 12815 (36.3) | 2918 (42.2) | <0.001 | | 0.7 | 2910 (42.6) | 2847 (41.8) | 0.349 |
| Diuretics† | 0.4 | 26526 (75.1) | 5833 (83.8) | <0.001 | | 0.5 | 5727 (83.9) | 5724 (83.6) | 0.692 |
| Statins† | 0.4 | 18576 (52.6) | 2775 (39.9) | <0.001 | | 0.5 | 2789 (40.8) | 2759 (40.3) | 0.619 |
| Nitrates † | 0.5 | 4526 (12.8) | 763 (11.0) | <0.001 | | 0.6 | 776 (11.4) | 759 (11.1) | 0.676 |
| ASA† | 0.5 | 17613 (49.9) | 1726 (24.9) | <0.001 | | 0.6 | 1708 (25.0) | 1721 (25.2) | 0.744 |
| Anticoagulant† | 0.4 | 13421 (38.0) | 5273 (75.8) | <0.001 | | 0.4 | 5175 (75.6) | 5166 (75.5) | 0.921 |
| FU in HF clinic† | 4.9 | 21915 (64.8) | 3840 (58.4) | <0.001 | | 5.6 | 3795 (58.3) | 3797 (58.7) | 0.641 |
| FU location† | 3.9 |  |  | 0.017 | | 4.6 |  |  | 0.397 |
| . Hospital |  | 25952 (76.0) | 4934 (74.3) |  | |  | 4837 (73.5) | 4862 (74.4) |  |
| . Primary care |  | 7390 (21.6) | 1524 (23.0) |  | |  | 1553 (23.6) | 1495 (22.9) |  |
| . Other |  | 827 (2.4) | 179 (2.7) |  | |  | 194 (2.9) | 176 (2.7) |  |

*Categorical variables are presented with n (%) and tested with chi-square test and continuous variables with median [q1-q3] and tested with Mann-Whitney U test.*

*AF: atrial fibrillation; ASA: acetylsalicylic acid; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; ECG: electrocardiogram; EF: ejection fraction; FU: follow-up; GFR: glomerular filtration rate; HF: heart failure; HR: heart rate; ICD/CRT: intra-cardiac defibrillator/cardiac resynchronization therapy; IHD: ischemic heart disease; MBP: mean blood pressure; MRA: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal pro-brain natriuretic peptide (NT-proBNP); NYHA: New York Heart Association; RASi: renin-angiotensin system inhibitors (angiotensin converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor/neprilysin inhibitors); PAD: peripheral artery disease; SBP: systolic blood pressure*

*\* Income above median for each year*

*† Included in the multiple imputation model (although not necessarily imputed if there is no missing data) and logistic/cox models.*

**Supplementary Table 3. Baseline characteristics of patients with HFrEF with and without history of AF stratified by digoxin use in the matched population**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **History of AF** | | | **No History of AF** | | | |
| Missing (%) | **No digoxin** | **Digoxin** | **p** | Missing (%) | **No digoxin** | **Digoxin** | **p** |
| n |  | 6288 | 6288 |  |  | 560 | 560 |  |
| Male gender† | 0.0 | 4380 (69.7) | 4382 (69.3) | 0.985 | 0.0 | 365 (65.2) | 368 (65.7) | 0.900 |
| Age, years | 0.0 | 74.0 [67.0, 81.0] | 74.0 [66.0, 81.0] | 0.088 | 0.0 | 69.0 [59.0, 77.0] | 69.0 [59.0, 78.0] | 0.688 |
| Age≥75 years† | 0.0 | 3132 (49.8) | 3109 (49.4) | 0.695 | 0.0 | 182 (32.5) | 197 (35.2) | 0.377 |
| Outpatients† | 0.0 | 3044 (48.4) | 3018 (48.0) | 0.655 | 0.0 | 261 (46.6) | 250 (44.6) | 0.549 |
| Year of inclusion† | 0.0 |  |  | 0.443 | 0.0 |  |  | 0.757 |
| . 2005-2010 |  | 2576 (41.0) | 2643 (42.0) |  |  | 365 (65.2) | 354 (63.2) |  |
| . 2011-2015 |  | 2395 (38.1) | 2368 (37.7) |  |  | 126 (22.5) | 136 (24.3) |  |
| . 2016-2018 |  | 1317 (20.9) | 1277 (20.3) |  |  | 69 (12.3) | 70 (12.5) |  |
| Children† | 0.0 | 5207 (82.8) | 5209 (82.8) | 0.981 | 0.0 | 435 (77.7) | 427 (76.2) | 0.619 |
| Living alone | 0.3 | 3012 (48.1) | 3014 (48.0) | 1.000 | 0.3 | 274 (49.2) | 273 (49.0) | 1.000 |
| Education level† | 1.9 |  |  | 0.971 | 3.0 |  |  | 0.670 |
| Compulsory |  | 2701 (43.8) | 2698 (43.7) |  |  | 237 (43.3) | 241 (44.7) |  |
| Secondary |  | 2433 (39.4) | 2423 (39.3) |  |  | 231 (42.2) | 230 (42.7) |  |
| University |  | 1039 (16.8) | 1048 (17.0) |  |  | 79 (14.4) | 68 (12.6) |  |
| Income above median \*\*† | 0.3 | 3227 (51.5) | 3204 (51.1) | 0.661 | 0.5 | 245 (44.0) | 252 (45.2) | 0.718 |
| BMI, kg/m2 | 40.9 | 26.3 [23.3, 29.8] | 25.9 [23.1, 29.7] | 0.002 | 46.2 | 25.9 [22.7, 29.4] | 24.9 [22.2, 28.4] | 0.050 |
| BMI≥30 kg/m2 † | 40.9 | 894 (24.1) | 883 (23.7) | 0.683 | 46.2 | 65 (21.7) | 59 (19.51 | 0.571 |
| HF history≥ 6m † | 2.0 | 3214 (52.3) | 3156 (51.1) | 0.198 | 1.4 | 345 (62.7) | 364 (65.7) | 0.333 |
| NYHA class† | 27.0 |  |  | 0.986 | 24.2 |  |  | 0.747 |
| I |  | 313 (6.9) | 319 (6.9) |  |  | 37 (8.8) | 34 (8.0) |  |
| II |  | 2056 (45.3) | 2096 (45.1) |  |  | 165 (39.1) | 160 (37.5) |  |
| III |  | 1991 (43.9) | 2056 (44.3) |  |  | 198 (46.9) | 204 (47.8) |  |
| IV |  | 174 (3.8) | 174 (3.7) |  |  | 22 (5.2) | 29 (6.8) |  |
| SBP, mmHg | 1.8 | 120.0 [110.0, 135.0] | 120.0 [110.0, 135.0] | 0.580 | 2.0 | 120.0 [104.0, 130.0] | 115.0 [100.0, 130.0] | 0.230 |
| DBP, mmHg | 1.8 | 75.0 [65.0, 80.0] | 74.0 [65.0, 80.0] | 0.029 | 1.8 | 70.0 [60.0, 80.0] | 70.0 [60.0, 80.0] | 0.301 |
| MBP, mmHg | 1.8 | 90.0 [81.7, 100.0] | 90.0 [81.3, 99.2] | 0.155 | 1.8 | 85.0 [76.7, 93.8] | 83.3 [76.7, 93.6] | 0.275 |
| MBP>90 mmHg † | 1.8 | 2909 (47.1) | 2898 (46.9) | 0.870 | 1.8 | 171 (31.1) | 174 (31.6) | 0.897 |
| Duration AF, days | 5.2 | 383.0 [29.0, 1783.5] | 480.0 [37.0, 2013.5] | <0.001 | - | - | - | - |
| ECG, % | 1.7 |  |  | <0.001 | 2.5 |  |  | - |
| Sinus rhythm |  | 1522 (24.6) | 723 (11.7) |  |  | 484 (88.2) | 468 (86.2) |  |
| AF |  | 3860 (62.5) | 4856 (78.5) |  |  | 0 (0.0) | 0 (0.0) |  |
| Paced/other |  | 798 (12.9) | 605 ( 9.8) |  |  | 65 (11.8) | 75 (13.8) |  |
| HR, bpm | 2.8 | 77.0 [68.0, 88.0] | 78.0 [68.0, 90.0] | <0.001 | 3.4 | 73.0 [64.0, 82.0] | 73.0 [65.0, 83.0] | 0.586 |
| HR≥ 70 bpm† | 2.8 | 4088 (66.7) | 4060 (66.6) | 0.985 | 3.4 | 307 (56.1) | 302 (56.4) | 0.963 |
| Current smoker † | 22.5 | 586 (12.1) | 604 (12.3) | 0.770 | 20.4 | 82 (18.2) | 76 (17.2) | 0.765 |
| Diabetes† | 0.0 | 1607 (25.6) | 1613 (25.7) | 0.919 | 0.0 | 187 (33.4) | 196 (35.0) | 0.614 |
| Hypertension† | 0.0 | 3635 (57.8) | 3606 (57.3) | 0.613 | 0.0 | 307 (54.8) | 319 (57.0) | 0.508 |
| COPD† | 0.0 | 785 (12.5) | 791 (12.6) | 0.893 | 0.0 | 74 (13.2) | 72 (12.9) | 0.929 |
| Stroke† | 0.0 | 935 (14.9) | 902 (14.3) | 0.419 | 0.0 | 67 (12.0) | 61 (10.9) | 0.639 |
| IHD† | 0.0 | 2848 (45.3) | 2850 (45.3) | 0.986 | 0.0 | 307 (54.8) | 319 (57.0) | 0.508 |
| PAD † | 0.0 | 448 (7.1) | 460 (7.3) | 0.705 | 0.0 | 47 (8.4) | 45 (8.0) | 0.913 |
| Valve disease† | 0.0 | 1216 (19.3) | 1194 (19.0) | 0.634 | 0.0 | 142 (25.4) | 134 (23.9) | 0.627 |
| Cancer† | 0.0 | 846 (13.5) | 826 (13.1) | 0.618 | 0.0 | 88 (15.7) | 71 (12.7) | 0.171 |
| Liver disease† | 0.0 | 143 (2.3) | 139 (2.2) | 0.857 | 0.0 | 23 (4.1) | 25 (4.5) | 0.883 |
| ICD/CRT† | 1.1 | 527 (8.5) | 506 (8.1) | 0.499 | 1.1 | 81 (14.7) | 88 (15.8) | 0.652 |
| EF<30%† | 0.0 | 3285 (52.2) | 3258 (51.8) | 0.198 | 0.0 | 420 (75.0) | 408 (72.9) | 0.454 |
| Hemoglobin, gr/l | 3.0 | 137.0 [124.0, 148.0] | 138.0 [125.0, 150.0] | <0.001 | 1.1 | 133.0 [121.0, 145.0] | 132.0 [120.0, 144.0] | 0.428 |
| Anemia† | 3.0 | 1598 (26.2) | 1614 (26.4) | 0.816 | 1.1 | 188 (34.1) | 193 (34.6) | 0.903 |
| GFR, ml/min/1.73m2 | 1.2 | 63.6 [47.1, 79.0] | 64.1 [48.8, 80.6] | 0.003 | 0.5 | 68.6 [50.2, 86.0] | 68.1 [50.2, 87.5] | 0.918 |
| GFR † | 1.2 |  |  | 0.711 | 0.5 |  |  | 0.700 |
| . 30-60 |  | 2409 (38.7) | 2370 (38.2) |  |  | 179 (32.1) | 178 (32.0) |  |
| . ≥60 |  | 3554 (57.1) | 3564 (57.4) |  |  | 354 (63.4) | 347 (62.4) |  |
| . ≤30 |  | 259 (4.2) | 273 (4.4) |  |  | 25 (4.5) | 31 (5.6) |  |
| NT-ProBNP, pg/ml | 51.6 | 3365.0 [1701.0, 6771.5] | 3462.0 [1811.5, 6770.8] | 0.231 | 54.0 | 3365.0 [1701.0, 6771.5] | 3462.0 [1811.5, 6770.8] | 0.231 |
| NT-proBNP above median † | 51.6 | 1729 (55.6) | 1682 (56.4) | 0.550 | 54.0 | 3386.0 [1235.0, 6370.0] | 3350.0 [1277.2, 7495.0] | 0.515 |
| Serum potassium | 23.0 | 4.2 [3.9, 4.4] | 4.2 [3.9, 4.5] | 0.165 | 30.7 | 4.2 [3.9, 4.4] | 4.2 [4.0, 4.5] | 0.061 |
| Serum potassium groups † | 23.0 |  |  | 0.863 | 30.7 |  |  | 0.376 |
| . normakalemia |  | 4564 (92.9) | 4446 (93.2) |  |  | 371 (92.1) | 346 (92.8) |  |
| . hypokalemia |  | 221 (4.5) | 204 (4.3) |  |  | 21 (5.2) | 13 (3.5) |  |
| . hyperkalemia |  | 126 (2.6) | 122 (2.6) |  |  | 11 (2.7) | 14 (3.8) |  |
| Beta-Blocker † | 0.3 | 5947 (95.0) | 5921 (94.4) | 0.159 | 0.4 | 483 (86.2) | 494 (89.0) | 0.191 |
| RASi† | 1.3 | 5640 (90.7) | 5613 (90.6) | 0.852 | 1.6 | 499 (90.2) | 498 (90.7) | 0.868 |
| MRA† | 0.7 | 2555 (40.9) | 2549 (40.9) | 1.000 | 1.0 | 302 (54.3) | 295 (53.3) | 0.792 |
| Diuretics† | 0.5 | 5230 (83.7) | 5233 (83.5) | 0.774 | 0.5 | 479 (85.7) | 473 (85.2) | 0.893 |
| Statins† | 0.5 | 2789 (40.8) | 2759 (40.3) | 0.619 | 0.4 | 257 (45.9) | 268 (48.3) | 0.459 |
| Nitrates † | 0.6 | 673 (10.8) | 663 (10.6) | 0.816 | 0.8 | 91 (16.3) | 96 (17.3) | 0.718 |
| ASA† | 0.6 | 1407 (22.5) | 1418 (22.7) | 0.778 | 0.7 | 307 (55.0) | 301 (54.3) | 0.865 |
| Anticoagulant† | 0.4 | 5037 (80.4) | 4976 (79.4) | 0.164 | 0.9 | 163 (29.3) | 164 (29.7) | 0.938 |
| FU in HF clinic† | 5.8 | 3561 (60.1) | 3499 (59.1) | 0.313 | 6.6 | 278 (53.4) | 279 (53.1) | 0.994 |
| FU location† | 4.7 |  |  | 0.937 | 5.7 |  |  | 0.497 |
| . Hospital |  | 4447 (74.0) | 4431 (74.1) |  |  | 406 (77.0) | 399 (75.4) |  |
| . Primary care |  | 1399 (23.3) | 1395 (23.3) |  |  | 106 (20.1) | 108 (20.4) |  |
| . Other |  | 161 (2.7) | 154 (2.6) |  |  | 15 (2.8) | 22 (4.2) |  |

*Categorical variables are presented with n (%) and tested with chi-square test and continuous variables with median [q1-q3] and tested with Mann-Whitney U test.*

*AF: atrial fibrillation; ASA: acetylsalicylic acid; BMI: body mass index; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; ECG: electrocardiogram; EF: ejection fraction; FU: follow-up; GFR: glomerular filtration rate; HF: heart failure; HR: heart rate; ICD/CRT: intra-cardiac defibrillator/cardiac resynchronization therapy; IHD: ischemic heart disease; MBP: mean blood pressure; MRA: mineralocorticoid receptor antagonists; NT-proBNP: N-terminal pro-brain natriuretic peptide (NT-proBNP); NYHA: New York Heart Association; RASi: renin-angiotensin system inhibitors (angiotensin converting enzyme inhibitors, angiotensin receptor blockers or angiotensin receptor/neprilysin inhibitors); PAD: peripheral artery disease; SBP: systolic blood pressure*

*\* Income above median for each year*



**Supplementary Figure 1. Use of digoxin over time in the overall population with heart failure with reduced ejection fraction.**



**Supplementary Figure 2. Independent predictors of digoxin use in the overall population with heart failure with reduced ejection fraction.** ACE-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNi: angiotensin receptor-neprilysin inhibitor; CRT/ICD: cardiac resynchronization therapy/intracardiac defibrillator; COPD: chronic obstructive pulmonary disease;eGFR: estimated glomerular filtration rate; EF: ejection fraction; HF: heart failure; MAP: mean arterial pressure; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association Class.