**Figure 1. Patients' Flowchart**

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**Table 1. Characteristics of patients in the total sample and according to benzodiazepine prescription.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Total sample** | **Benzodiazepine prescription** | | **P-value1** |
| **YES** | **NO** |
| **N = 2,139** | **N = 1,052** | **N = 1,087** |
| Time of follow-up, yrs. – median (25th-75th percentile) | 7.96  (4.02 – 12.59) | 8.23  (4.47 – 12.27) | 7.61  (3.41 – 12.99) | 0.16 |
| Sex (females) – n (%) | 599 (28.0) | 376 (35.7) | 223 (20.5) | <0.001 |
| Age, yrs. – median (25th-75th percentile) | 68.49  (58.33 – 76.21) | 68.53  (58.33 – 76.20) | 68.42  (58.32 – 76.30) | 0.76 |
| **Clinical HF variables** | | | | |
| Months since HF diagnosis –  median (25th-75th percentile) | 7 (1 – 42) | 8 (2 – 43) | 6 (1 – 41) | 0.17 |
| Ischemic etiology – n (%) | 1040 (48.6) | 499 (47.4) | 541 (49.8) | 0.28 |
| Baseline LVEF (<40 (HFrEF)) – n (%) | 1563 (73.1) | 761 (72.3) | 802 (73.8) | 0.45 |
| Baseline NYHA functional class — n (%) |  |  |  | 0.004 |
| I | 135 (6.3) | 48 (4.6) | 87 (8.0) |
| II | 1409 (65.9) | 698 (66.3) | 711 (65.4) |
| III | 571 (26.7) | 297 (28.2) | 274 (25.2) |
| IV | 24 (1.1) | 9 (0.9) | 15 (1.4) |
| Baseline NT-proBNP, pg/mL –  median (25th-75th percentile) | (N=1,491)  1680  (702 – 4070) | (N=753)  1706  (725 – 4228) | (N=738)  1623  (626 – 3915) | 0.13 |
| **Comorbidities** | | | | |
| Depressive symptoms at baseline, GDS≥1 – n (%) | 800 (37.4) | 507 (48.2) | 293 (27.0) | <0.001 |
| History of alcohol consumption – n (%) | 591 (27.6) | 248 (23.6) | 343 (31.6) | <0.001 |
| History of nicotine consumption – n (%) | 1348 (63.0) | 619 (58.8) | 729 (67.1) | <0.001 |
| Cancer — n (%) | 373 (17.4) | 198 (18.8) | 175 (16.1) | 0.10 |
| Diabetes mellitus — n (%) | 996 (46.6) | 482 (45.8) | 514 (47.3) | 0.50 |
| Hypertension — n (%) | 1452 (67.9) | 716 (68.1) | 736 (67.7) | 0.86 |
| Hypercholesterolemia — n (%) | 1276 (59.7) | 631 (60.0) | 645 (59.3) | 0.76 |
| Peripheral vasculopathy — n (%) | 540 (25.2) | 272 (25.9) | 268 (24.7) | 0.52 |
| COPD — n (%) | 466 (21.8) | 209 (19.9) | 257 (23.6) | 0.03 |
| Chronic renal failure — n (%) | 548 (25.6) | 278 (26.4) | 270 (24.8) | 0.40 |
| BMI, kg/m2 — median (25th–75th percentile) | 26.97  (24.17–30.28) | 26.83  (23.92 – 29.94) | 27.12  (24.39 – 30.49) | 0.04 |
| **Baseline Functionality** | | | | |
| Barthel index — median (25th–75th percentile) | 100 (95 – 100) | 100 (90 – 100) | 100 (95 – 100) | 0.006 |
| OARS — median (25th–75th percentile) | 14 (12 – 14) | 14 (11 – 14) | 14 (12 – 14) | 0.20 |
| Pfeiffer test — median (25th–75th percentile) | 0 (0 – 1) | 0 (0 – 1) | 0 (0 – 1) | 0.69 |
| Frailty syndrome – n (%) | 668 (31.2) | 375 (35.6) | 293 (27.0) | <0.001 |
| **Medical Treatment** | | | | |
| Antidepressants – n (%) | 697 (32.6) | 531 (50.5) | 166 (15.3) | <0.001 |
| ACE inhibitors or ARBs– n (%) | 1824 (85.3) | 899 (85.5) | 925 (85.1) | 0.81 |
| Beta-blockers— n (%) | 1891 (88.4) | 945 (89.8) | 946 (87.0) | 0.04 |
| Loop diuretics – n (%) | 1910 (89.3) | 954 (90.7) | 956 (87.9) | 0.04 |
| Thiazide diuretics – n (%) | 657 (30.7) | 364 (34.6) | 293 (27.0) | <0.001 |
| Aldosterone antagonists – n (%) | 1273 (59.5) | 678 (64.4) | 595 (54.7) | <0.001 |
| Hydralazine – n (%) | 757 (35.4) | 399 (37.9) | 358 (32.9) | 0.02 |
| Nitrates – n (%) | 1064 (49.7) | 556 (52.9) | 508 (46.7) | 0.005 |
| Digoxin – n (%) | 790 (36.9) | 425 (40.4) | 365 (33.6) | 0.001 |
| Calcium antagonists – n (%) | 432 (20.2) | 238 (22.6) | 194 (17.8) | 0.006 |
| Ivabradine – n (%) | 366 (17.1) | 188 (17.9) | 178 (16.4) | 0.36 |
| Amiodarone – n (%) | 520 (24.3) | 283 (26.9) | 237 (21.8) | 0.006 |
| Acenocumarol – n (%) | 1014 (47.4) | 534 (50.8) | 480 (44.2) | 0.002 |
| Antiplatelet – n (%) | 1278 (59.7) | 647 (61.5) | 631 (58.0) | 0.10 |
| Statins – n (%) | 1560 (72.9) | 798 (75.9) | 762 (70.1) | 0.003 |
| Oral antidiabetics – n (%) | 813 (38.0) | 418 (39.7) | 395 (36.3) | 0.11 |
| Insulin – n (%) | 604 (28.2) | 310 (29.5) | 294 (27.0) | 0.21 |
| **Changes during the first year of follow-up** | | | | |
| LVEF, % of change between baseline  and 1st year of follow-up —  median (25th–75th percentile) | (N=1,420)  +6 (0 – +15) | (N=755)  +5 (0 - +14) | (N=665)  +6 (0 - +15) | 0.44 |
| NYHA functional class, change  between baseline and 1st year of  follow-up — n (%) | (N=1,545) | (N=818) | (N=727) | 0.14 |
| Improvement | 329 (21.3) | 185 (22.6) | 144 (19.8) |
| Stability | 1056 (68.3) | 541 (66.1) | 515 (70.8) |
| Worsening | 160 (10.4) | 92 (11.2) | 68 (9.4) |

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GDS, Geriatric Depression Scale; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fraction of the B-type Natriuretic Peptide; NYHA, New York Heart Association; OARS, Instrumental Activities Section of the Duke University Scale.

1 P-values were determined using Pearson χ2 test for categorical variables and the Mann–Whitney U test for continuous variables, as all of them had a non-normal distribution.

**Table 2. Variables included in the Cox proportional hazard analysis of mortality in patients with chronic HF.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Univariate analyses** | | | **Multivariate analysis** | | |
|  | **HR** | **95% CI** | **P value** | **HR** | **95% CI** | **P value** |
| **Benzodiazepine prescription** | 0.84 | 0.75 – 0.95 | 0.005 | 0.85 | 0.75 – 0.97 | 0.01 |
| **Demographic variables** | | | | | | |
| Sex (Males) | 1.12 | 0.98 – 1.27 | 0.10 | 1.25 | 1.07 – 1.46 | 0.006 |
| Age | 1.06 | 1.06 – 1.07 | <0.001 | 1.04 | 1.04 – 1.05 | <0.001 |
| **Clinical HF variables** | | | | | | |
| Months since HF diagnosis | 1.00 | 1.00 – 1.00 | <0.001 | 1.00 | 1.00 – 1.00 | 0.001 |
| Ischemic aetiology | 1.33 | 1.18 – 1.50 | <0.001 | 1.50 | 1.30 – 1.72 | <0.001 |
| Baseline LVEF | 1.01 | 1.01 – 1.01 | <0.001 | --- | --- | --- |
| Baseline NYHA functional class | 2.07 | 1.88 – 2.29 | <0.001 | 1.39 | 1.23 – 1.56 | <0.001 |
| **Comorbidities** | | | | | | |
| Depressive symptoms at baseline (GDS-4 ≥ 1) | 1.28 | 1.13 – 1.45 | <0.001 | 1.15 | 1.00 – 1.31 | 0.05 |
| History of alcohol consumption | 0.84 | 0.73 – 0.97 | 0.02 | 1.20 | 1.03 – 1.40 | 0.02 |
| History of nicotine consumption | 0.87 | 0.77 – 0.98 | 0.02 | --- | --- | --- |
| Cancer | 1.24 | 1.06 – 1.44 | 0.007 | --- | --- | --- |
| Diabetes mellitus | 1.40 | 1.24 – 1.58 | <0.001 | 1.41 | 1.19 – 1.68 | <0.001 |
| Hypertension | 1.38 | 1.21 – 1.57 | <0.001 | --- | --- | --- |
| Hypercholesterolemia | 0.91 | 0.81 – 1.03 | 0.13 | --- | --- | --- |
| Chronic renal failure | 1.85 | 1.61 – 2.11 | <0.001 | 1.25 | 1.07 – 1.45 | 0.004 |
| COPD | 1.74 | 1.52 – 1.99 | <0.001 | 1.31 | 1.14 – 1.51 | <0.001 |
| Peripheral vasculopathy | 1.71 | 1.50 – 1.95 | <0.001 | 1.29 | 1.13 – 1.48 | <0.001 |
| BMI | 0.97 | 0.96 – 0.98 | <0.001 | 0.97 | 0.96 – 0.99 | <0.001 |
| **Baseline functionality** | | | | | | |
| Barthel Index | 0.97 | 0.97 – 0.97 | <0.001 | 0.99 | 0.98 – 0.99 | <0.001 |
| OARS | 0.87 | 0.85 – 0.88 | <0.001 | --- | --- | --- |
| Pfeiffer test | 1.29 | 1.22 – 1.36 | <0.001 | --- | --- | --- |
| Frailty syndrome | 1.67 | 1.48 – 1.89 | <0.001 | --- | --- | --- |
| **Treatments throughout follow-up** | | | | | | |
| Antidepressants | 0.96 | 0.85 – 1.09 | 0.52 | --- | --- | --- |
| ACE inhibitors or ARBs | 0.35 | 0.30 – 0.41 | <0.001 | 0.63 | 0.53 – 0.75 | <0.001 |
| Beta-blockers | 0.34 | 0.29 – 0.40 | <0.001 | 0.58 | 0.48 – 0.70 | <0.001 |
| Loop diuretics | 2.12 | 1.63 – 2.76 | <0.001 | 1.39 | 1.05 – 1.84 | 0.02 |
| Thiazide diuretics | 1.70 | 1.51 – 1.91 | <0.001 | 1.32 | 1.16 – 1.50 | <0.001 |
| Aldosterone antagonists | 0.81 | 0.72 – 0.91 | 0.001 | 0.84 | 0.74 – 0.96 | 0.01 |
| Hydralazine | 1.59 | 1.41 – 1.79 | <0.001 | --- | --- | --- |
| Nitrates | 1.63 | 1.44 – 1.84 | <0.001 | --- | --- | --- |
| Digoxin | 1.10 | 0.98 – 1.25 | 0.11 | --- | --- | --- |
| Calcium antagonists | 0.90 | 0.78 – 1.04 | 0.16 | 0.86 | 0.74 – 0.99 | 0.04 |
| Ivabradine | 0.58 | 0.48 – 0.71 | <0.001 | 0.74 | 0.60 – 0.91 | 0.004 |
| Amiodarone | 1.23 | 1.08 – 1.40 | 0.002 | --- | --- | --- |
| Acenocumarol | 0.92 | 0.82 – 1.04 | 0.19 | --- | --- | --- |
| Antiplatelet | 0.96 | 0.84 – 1.08 | 0.48 | --- | --- | --- |
| Statins | 0.52 | 0.46 – 0.59 | <0.001 | 0.56 | 0.48 – 0.66 | <0.001 |
| Oral antidiabetics | 0.85 | 0.75 – 0.96 | 0.008 | 0.73 | 0.62 – 0.85 | <0.001 |
| Insulin | 1.52 | 1.34 – 1.72 | <0.001 | 1.25 | 1.07 – 1.47 | 0.005 |

Analysis was adjusted in a backward step conditional Cox proportional hazard analysis.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GDS, Geriatric Depression Scale; HF, heart failure; HR, Hazard Ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association