

1 Title

2 **Loop diuretic utilisation with or without heart failure: impact on prognosis**

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1 Abstract

2 Background & Aims

3 Many patients are prescribed loop diuretics without a diagnostic record of heart failure. Little is
4 known about their characteristics and prognosis.

5 Methods

6 Glasgow regional health records (2009-2016) were obtained for adults with cardiovascular
7 disease or taking loop diuretics. Outcomes were investigated using Cox models with hazard
8 ratios adjusted for age, sex, socioeconomic deprivation, and co-morbid disease (adjHR).

9 Results

10 Of 198,898 patients (median age 65 years; 55% women), 161,935 (81%) neither took loop
11 diuretics nor had a diagnostic record of heart failure (reference group), 23,963 (12%) were
12 taking loop diuretics but had no heart failure recorded, 7,844 (4%) had heart failure recorded
13 and took loop diuretics and 5,156 (3%) had heart failure recorded but were not receiving loop
14 diuretics.

15 Five-year mortality was only slightly higher for heart failure in absence of loop diuretics (22%;
16 adjHR: 1.2 [95% CI 1.1-1.3]), substantially higher for those taking loop diuretics with no heart
17 failure recorded (40%; adjHR: 1.8 [95% CI 1.7-1.8]) and highest for heart failure treated with
18 loop diuretics (52%; adjHR: 2.2 [95% CI 2.0-2.2]).

19 Conclusions

20 For patients with **cardiovascular disease**, many are prescribed loop diuretics without a
21 diagnosis of heart failure being recorded. Mortality is more strongly associated with loop
22 diuretic use than with a heart failure record. The diagnosis of heart failure may be often missed,
23 or loop diuretic use is associated with other conditions with a prognosis similar to heart failure,
24 or inappropriate loop diuretic use increases mortality; all might be true.

25 INTRODUCTION

26 Heart failure (HF) is characterised by water and salt retention leading to congestion of
27 the systemic and pulmonary circulation and eventually to symptoms, such as exertional
28 breathlessness, and signs, such as peripheral oedema (1, 2). Guidelines on HF strongly
29 recommend loop diuretics for managing symptoms and signs of congestion (1, 3, 4), but loop

1 diuretics can also be used for resistant hypertension or managing congestion due to end-stage
2 kidney disease (1). For patients with HF, the development of congestion and the need for loop
3 diuretics to manage it are associated with an adverse prognosis (2). However, many patients
4 are prescribed loop diuretics but are not investigated for the underlying cause; if they relieve
5 symptoms and signs, they may mask a diagnosis of HF (1).

6 To find out how many patients are prescribed loop diuretics, how often this is
7 associated with a diagnosis of HF and whether prescribing loop diuretics is associated with an
8 adverse prognosis, electronic health records were obtained for patients in the Greater Glasgow
9 & Clyde region if they either had a diagnosis of coronary or peripheral arterial disease or HF or
10 were prescribed loop diuretics or medicines commonly prescribed for hypertension or
11 ventricular dysfunction.

12 METHODS

13 Data sources

14 In Scotland, every resident has free access to primary and secondary healthcare, and
15 free prescriptions through the National Health Service (NHS). Residents receive a unique
16 identification number, and all healthcare contacts and deaths are linked through this. For people
17 served by the NHS Greater Glasgow & Clyde Health Board, person-level pseudonymised
18 administrative data were obtained, including demographic data, primary care diagnostic
19 information; hospital admissions and associated diagnostic and procedural codes; community-
20 based prescriptions (5); and death records (Supplementary Table 3 for data sources). Any
21 haematology and biochemistry test results from primary and secondary care and reports of
22 electrocardiograms (ECGs) and echocardiograms were also obtained. Data extraction and

1 record linkage were performed by the West of Scotland Safe Haven service. Ethical approval
2 was given by the West of Scotland Safe Haven's Local Privacy Advisory Committee, reference
3 number GSH/18/CA/002.

4 **Study population.**

5 Patients were eligible for inclusion if they were alive and aged ≥ 18 years on 1st January
6 2012, had records available for ≥ 12 months and had a record of a diagnosis of coronary artery
7 disease (CAD), peripheral arterial disease or HF between 31st December 2009 and 31st
8 December 2011, or if, for any reason including hypertension, they were dispensed, angiotensin-
9 converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), beta-blockers,
10 mineralocorticoid receptor antagonists (MRA), or loop diuretics. Diagnoses were identified
11 using either the International Statistical Classification of Diseases and Related Health Problems,
12 10th Revision (ICD-10) in any position or primary care Read Codes, both with records going
13 back to the year 2000 (Supplementary Table 3). For patients who were included, primary and
14 secondary care diagnostic records were made available from the year 2000 onwards, although
15 prescribing data were not available before 31st December 2009. Medicines dispensed from
16 community pharmacies were identified using British National Formulary codes.

17 **Patient identification and categorisation**

18 Treatment with loop diuretics (Supplementary Table 7 for list) was defined as the first
19 occasion that loop diuretics were both prescribed and dispensed in two consecutive quarters
20 or if death occurred within 90 days of first prescription. HF was defined as a relevant diagnostic
21 record in either primary care (Read codes) or a hospitalisation discharge code in any of six
22 possible diagnostic positions (ICD-10 codes) from the year 2000 onwards. Code lists were
23 developed using previously published research (6) and through searching for the term 'heart

1 failure' in the NHS coding dictionary (Supplementary Table 4). Evidence of structural heart
2 disease was not required but relevant investigations are reported where available. Following
3 previous conventions (6), some patients (n = 627) were excluded because of uncertainty about
4 HF diagnosis date (Supplementary Table 5; Supplementary Figure 1). A first diagnosis of HF
5 during a fatal hospitalisation (1,093 deaths) was not counted as incident HF because of
6 diagnostic uncertainty and lack of information on in-hospital loop diuretic use.

7 Patients were classified on 31st December 2011 into one of four mutually exclusive
8 groups based on a prior record of HF at any time in the prior decade and recurrent dispensing
9 of loop diuretics in the prior 6 months, as: i) neither HF nor on loop diuretic, ii) loop diuretic
10 only, iii) HF only, or iv) HF on loop diuretics. Because the average age of patients in the
11 "neither" group was considerably younger than the other three groups, it was further divided
12 into those aged 18-59 years or ≥ 60 years.

13 Study outcomes

14 Patients were followed from 1st January 2012 until the 31st December 2016. Follow-up
15 was right censored on the date of the last available health record, including blood tests or other
16 investigations or dispensing, to avoid uncertainty about survival status if patients emigrated out
17 of the region as this would otherwise introduce an 'immortal' bias. The main outcome of
18 interest was 5-year all-cause mortality. The primary covariate of interest was group
19 membership defined by loop diuretic dispensing and HF diagnosis. The 5-year cumulative HF
20 incidence, loop diuretic initiation, cause-specific hospitalisation and mortality were also
21 investigated. Causes of hospitalisation were defined by the primary discharge code and mapped
22 onto twelve ICD-10 disease categories. Cause of death was defined from patient records and
23 classified as cardiovascular, neoplastic, infection, other, and unknown (Supplementary Table 9).

1 Patient characteristics

2 Baseline characteristics reported for 1st January 2012 included age, sex, ethnicity,
3 Scottish Index of Multiple Deprivation 2012 quintile, an area-based measurement of socio-
4 economic deprivation where lower numbers indicate higher levels of deprivation (see
5 supplementary materials) (7), co-morbidities, medication, blood tests, and, when available, the
6 results of ECGs and echocardiograms.

7 Co-morbidities in the decade prior to 1st January 2012 were identified from primary and
8 secondary care records, and included hypertension, diabetes mellitus, thyroid disease, atrial
9 fibrillation, or flutter (AF), CAD (including myocardial infarction), valve disease, peripheral
10 arterial disease, stroke, chronic obstructive pulmonary disease (COPD), cancer, liver disease,
11 and dementia. Diagnostic code lists were adapted from CALIBER phenotypes (8) and previously
12 published research (9) (Supplementary Table 6). Patients without a diagnostic record for a
13 specific disease were assumed to be free from that condition.

14 In addition to ACEi, ARB, beta-blockers, MRA and loop diuretics, information on
15 calcium channel blockers, digoxin, thiazides and thiazide-related diuretics, aspirin, non-steroidal
16 anti-inflammatory drugs, lipid regulators, bronchodilators, thyroid medications, and
17 hypoglycaemic agents including insulin were reported. Patients were considered to be on these
18 medications if dispensed in the 180 days before 1st January 2012. Medicines were identified by
19 British National Formulary codes (Supplementary Table 7).

20 The most recent haemoglobin and estimated glomerular filtration rate (eGFR) measured
21 between 2010-2012 were reported. Anaemia was defined as <12.0 g/dL for women and <13.0

1 g/dL for men (10), and eGFR was calculated using the Chronic Kidney Disease-Epidemiology
2 Collaboration equation (11) without adjusting for ethnicity (12).

3 Measurements of left ventricular ejection fraction (LVEF) and left atrial diameter were
4 obtained from routinely available echocardiograms (if available) and heart rhythm and QRS
5 duration from ECGs. Results closest to a diagnosis of HF or initiation of loop diuretics were
6 chosen if there were multiple tests. LVEF was considered reduced if <50% and left atrium
7 dilated if >4.0 cm for men and >3.8 cm for women (13).

8 [Statistical analyses](#)

9 Patient characteristics are presented as numbers and percentages for categorical
10 variables and median with interquartile range (IQR) for continuous variables. Numbers and
11 percentages of complete records are displayed for variables with missing data. Percentages of
12 categorical variables refer to complete cases.

13 Prevalence was estimated within mid-year 2012 regional population estimates (14), using
14 sex-stratified, 5-year age bands as the denominator from ages 29 to >90 years.

15 Admission rates were calculated as the number of admissions per patient-year at risk
16 where the patient was at risk of being admitted (alive, not in hospital, and not lost to follow-
17 up). Allowance was made for the competing risk of death when estimating cumulative
18 incidences of initiating loop diuretics and incident HF.

19 A Cox proportional hazards regression model was used to assess between-group
20 differences in all-cause mortality with a robust sandwich-type estimator due to the potential
21 lack of statistical independence between chronic comorbidities (15). Due to the large sample
22 size and high statistical power to detect small departures from proportional hazards, the

1 proportional effects were visually checked using log-log plots. The model was adjusted for age,
2 as a continuous, linear value, kidney function using a penalised spline on eGFR with five knots
3 (Handling missing eGFR data in supplementary material), sex, Scottish Index of Multiple
4 Deprivation, and history of common, chronic conditions: hypertension, CAD, peripheral
5 arterial disease, diabetes mellitus, valve disease, AF, stroke, cancer, and dementia were selected
6 based on clinical expertise. Results are reported as hazard ratios (HR) with 95% confidence
7 intervals (CI). The estimated cumulative incidence of death due to cardiovascular disease,
8 infection, neoplasm, or other causes of death, and all-cause mortality after initiation of loop
9 diuretics or incident HF were also calculated from sub-distribution estimates.

10 Time-dependent covariates were used to assess the impact of disease progression on
11 morbidity and mortality. The dates of HF diagnosis and the start of repeated loop diuretic
12 dispensing were used to update loop diuretic/HF group. If both events occurred on the same
13 day, patients were classified as being on the combination to avoid immortal time bias (time-
14 dependent covariate analysis in supplementary material). Crude 5-year morbidity and mortality
15 rates were calculated using person-time at risk, where attributable time was allocated based on
16 time-dependent group status. All-cause mortality was modelled using Cox proportional hazards
17 and time-dependent covariates, using time-dependent comorbidity and loop diuretic/HF group
18 values and baseline age, sex, and Scottish Index of Multiple Deprivation.

19 Study findings are reported as advised by REporting of studies Conducted using
20 Observational Routinely-collected health Data recommendations (16). Data were prepared
21 using Microsoft SQL Server Management Studio (version 17.8.1), and statistical analyses were
22 performed using R (version 4.0.5). Relevant packages are listed in the supplementary material.

1 RESULTS

2 Of an estimated 982,385 adults in the NHS Greater Glasgow & Clyde region in 2012,
3 198,898 met the cohort inclusion criteria, which comprised more than half of all men aged >70
4 years and more than half of all women aged >75 years (Figure 1). The cohort included 161,935
5 (81%) patients who had no record of HF in the prior decade and had not been dispensed loop
6 diuretics in the prior 6 months (of whom 89,699 were aged ≥ 60 years), 23,963 (12%) who had
7 been dispensed loop diuretics but had no record of HF, 7,844 (4%) who had HF and were
8 dispensed loop diuretics, and 5,156 (3%) who had a record of HF but were not dispensed loop
9 diuretics. The estimated prevalence of HF for the population (including an estimated 0.3 million
10 people aged <18 years) was 1.0% overall, or 1.3% of the adult population (Figure 1).

11 People aged ≥ 60 years who neither had a diagnosis of HF nor were taking loop
12 diuretics, had a median age of 72 (IQR: 66–78) years and 54% were women. For these patients,
13 a history of hypertension (38%) and CAD (26%) were common and 20% had an eGFR <60
14 mL/min/1.73 m², 24% had anaemia, and 18% had diabetes mellitus (Table 1). COPD (10%),
15 stroke (8%), cancer (8%), AF (7%) and dementia (2%) were less commonly recorded (Table 1).
16 Of 77,029 patients who were never subsequently initiated on loop diuretics and did not
17 develop HF, LVEF was <50% in 443 (6%) of 7,221 patients with measurements and the left
18 atrium was dilated in 5,884 (46%) of 12,915 patients with measurements (Supplementary
19 Figures 3 and 4). More than two-thirds of patients were on an ACEi or ARB, 64% on lipid-
20 lowering agents, 45% on beta-blockers, 36% on calcium channel blockers, 35% on thiazides, and
21 45% on aspirin (Table 2). Patients aged 18-59 years who neither had HF recorded nor
22 dispensed loop diuretics had fewer co-morbidities than any of the other groups.

1 People dispensed loop diuretics but without a record of HF had a median age of 75
2 (IQR: 65–83) years, were predominantly women (70%), and many (44%) were in the most
3 socio-economically deprived quintile. Compared to those aged ≥ 60 years in the ‘neither’ group,
4 they had a similar prevalence of hypertension, diabetes mellitus, CAD, and myocardial
5 infarction, but more COPD (19%), AF (16%), and anaemia (36%). Although many patients had
6 an eGFR < 60 mL/min/1.73 m² (34%), it was rarely < 30 mL/min/1.73 m² (6%). Of the 31,872
7 patients who received loop diuretics at baseline or follow-up but never received a diagnosis of
8 HF, LVEF was $< 50\%$ in 509 (9%) of 5,409 patients with measurements and the left atrium was
9 dilated in 5,548 (57%) of 9,669 patients with measurements. Compared to patients in the
10 ‘neither’ group, patients were less likely to be prescribed ACEi or ARB or thiazide diuretics but
11 more likely to receive bronchodilators and oral anticoagulants. Few patients (15%) received
12 three or more anti-hypertensive agents (excluding loop diuretics), a criterion commonly used
13 to define resistant hypertension (17).

14 People with HF who were not dispensed loop diuretics were younger (median age 69
15 (IQR: 59–78) years) and predominantly men (68%). Compared to patients taking loop diuretics
16 without a diagnosis of HF, they had a high prevalence of CAD (75%) and myocardial infarction
17 (53%) and were less likely to have an eGFR < 60 mL/min/1.73 m² (20%). Of 5,608 patients who
18 had a diagnosis of HF at baseline or follow-up but who never received loop diuretics, LVEF was
19 $< 50\%$ in 381 (31%) of 1,212 patients with measurements and the left atrium was dilated in 1,112
20 (55%) of 2,022 patients with measurements. Compared to patients taking loop diuretics without
21 a diagnosis of HF, patients with HF only were more likely to receive an ACEi or ARB (77%),
22 beta-blockers (69%), lipid regulators (78%) and aspirin (66%) and less likely to receive
23 bronchodilators (16%).

1 Patients with a diagnosis of HF who were also treated with loop diuretics had a median
2 age of 77 (IQR: 68–83) years, similar to other patients treated with loop diuretics, and 50%
3 were women. Compared to patients taking loop diuretics without a diagnosis of HF, they were
4 more likely to have a history of hypertension (52%), diabetes (29%), CAD (67%), myocardial
5 infarction (40%), valve disease (20%), AF (45%), COPD (28%), and anaemia (45%). Many patients
6 had an eGFR <60 mL/min/1.73 m² (48%), but it was rarely <30 mL/min/1.73 m² (9%). Of the
7 14,938 patients with a diagnosis of HF at baseline or follow-up who also received loop diuretics,
8 LVEF was <50% in 1,701 (40%) of 4,279 patients with measurements and the left atrium was
9 dilated in 5,545 (74%) of 7,518 patients with measurements. Compared to patients taking loop
10 diuretics without a record of HF, they were more likely to receive an ACEi or ARB (74%),
11 beta-blockers (64%), digoxin (23%), and oral anticoagulants (29%), and less likely to receive
12 calcium channel blockers (22%), but only a minority were on MRA (15%).

13 [Initiation of loop diuretics and incident heart failure during follow-up.](#)

14 Over the following 5 years, for patients in the ‘neither’ group aged ≥60 years, 9,706
15 (10.8%) started taking loop diuretics, of whom only 12.6% subsequently had HF recorded
16 (Figure 2). A further 2,951 (3.3%) patients received a diagnosis of HF, of whom 1,728 (58.7%)
17 were later initiated on loop diuretics. Overall, 4,191 (4.7%) were diagnosed with HF before or
18 after initiation of loop diuretics. For patients initially in the ‘neither’ group and aged ≥60 years
19 (all of whom had evidence of or were receiving treatment for cardiovascular disease), 14,062
20 (15.7%) died over the following 5 years without receiving a diagnosis of HF or being dispensed
21 loop diuretics. Of those initiated on loop diuretics who did not receive a diagnosis of HF, 2,640
22 (27.2%) subsequently died, and of those initiated on loop diuretics who did receive a diagnosis
23 of HF, 1,040 (35.0%) subsequently died (Figure 3 and Supplementary Figure 7). A similar

1 pattern, although at much lower rates, was observed for patients with cardiovascular disease
2 aged 18-59 years (Figure 2). Very few deaths (5.7%) occurred within 90 days of first loop
3 diuretic prescription that might have prevented appropriate, timely investigation.

4 Of 23,963 patients taking loop diuretics at baseline but without a diagnosis of HF, only
5 2,635 (11.0%) subsequently received a HF diagnosis of whom 1,375 (52.2%) died; 8,266 (34.5%)
6 died without first getting a HF diagnosis (Figure 2). Of 5,156 patients with HF not receiving loop
7 diuretics at baseline, only 1,119 (21.7%) were later initiated on loop diuretics of whom 325
8 (29.0%) died; 812 (15.7%) patients died without being dispensed loop diuretics. For those with
9 HF taking loop diuretics at baseline, mortality was 52.3% (Figure 2).

10 In the overall cohort, 54.4% of deaths were preceded by initiation of loop diuretics or a
11 diagnosis of HF (Supplementary Figure 16). The most common source of new HF diagnosis was
12 hospitalisations. Loop diuretic initiation without a diagnosis of HF generally occurred in primary
13 care (55.0% of initiations) with no secondary care contact (ward or clinic) in the prior 30 days.

14 Hospitalisations

15 Compared to patients aged ≥ 60 years who did not have HF and were not taking loop diuretics,
16 rates of hospital admission per patient-year at risk were higher for those taking loop diuretics
17 whether or not they had a diagnosis of HF (Figure 4). In the 5 years after 1st January 2012,
18 39,341 (54.5%) patients in the 'neither' group aged 18-59 had at least one admission, with
19 131,664 admissions in all (0.4 per patient-year at risk) and 66,124 (73.7%) patients in the
20 'neither' group aged ≥ 60 years had 261,793 admissions (0.7 per patient-year at risk). Patients
21 taking loop diuretics who did not have HF at baseline had 91,361 admissions over 5 years (1.0
22 per person-year at risk, with 19,884 [83.0%] having at least one admission). Patients with HF
23 who were not dispensed loop diuretic had 18,317 admissions over 5 years (0.8 per person-year

1 at risk, with 4,063 [78.8%] having at least one admission). Patients with HF taking loop diuretics
2 had 34,120 admissions over 5 years (1.3 per person-year at risk, with 6,842 [87.2%] having at
3 least one admission) (Figure 4). However, only a minority of admissions for all groups of
4 patients was attributed to cardiovascular disease and an even smaller proportion to HF. Time-
5 dependent analysis showed that rates of admissions increased based on updated HF and loop
6 diuretic status (Supplementary Figures 12 and 13), especially for cardiovascular and infection-
7 related admissions.

8 Mortality

9 For mortality, the proportional hazards assumption was not met for the first 14 days,
10 but this applied to only 328 deaths (0.9% of all deaths). Accordingly, proportional hazards were
11 considered a reasonable summary of between-group differences. Using the entire “neither”
12 loop diuretics nor HF group as reference, the adjusted HR (which includes age) for 5-year all-
13 cause mortality for those dispensed loop diuretics without a diagnosis of HF was 1.8 (95% CI:
14 1.7-1.8), for those with HF who were not dispensed loop diuretics was 1.2 (95% CI: 1.1-1.3),
15 and for HF treated with loop diuretics was 2.1 (95% CI: 2.0-2.2) (Figure 5). In the absence of
16 loop diuretics, thiazide diuretics were not associated with adverse outcomes. Applying time-
17 dependent covariates increased the strength of the association between loop diuretics and
18 mortality, especially for patients with HF (Supplementary Figure 14).

19 Using baseline loop diuretic/HF classification, all-cause and cardiovascular mortality at
20 five years for patients who had neither HF nor were prescribed loop diuretics and were aged
21 <60 years were, respectively, 3.3% and 0.8%, and for those ≥ 60 years 20.2% and 5.8%, for
22 patients with a diagnosis of HF who were not taking loop diuretics it was 22.1% and 8.2%, for
23 those dispensed loop diuretics without a HF diagnosis it was 40.2% and 12.1% and for those

1 with HF taking loop diuretics 52.3% and 22.6% (Figure 2; and Supplementary Figures 8 and 9,
2 and Table 12). There were similar rates of deaths due to neoplasms for each of these three
3 groups (Supplementary Figures 8 and 15).

4 Of 23,963 patients in the loop diuretic-only group, 6,506 (79.9% women) were included
5 solely because they were dispensed loop diuretics without meeting other criteria. Of these, 643
6 had a history of CAD or peripheral arterial disease before 31st December 2009. Of the
7 remaining 5,863, 2,251 (38.4%) died. This compares with an all-cause mortality of 40.2% (7,013
8 deaths) in the remaining 17,457 patients who were included because they had cardiovascular
9 disease or were prescribed other medications.

10 DISCUSSION

11 This analysis suggests that for patients with a broad range of cardiovascular diseases,
12 mortality is more closely associated with taking loop diuretics than with a diagnosis of HF, even
13 after adjusting for age and other risk factors (Structured Graphical Abstract). The estimated
14 prevalence of HF amongst adults in Glasgow of 1.3% is consistent with data from elsewhere in
15 the United Kingdom (6) but many more patients (3.2%) were dispensed loop diuretics. Only
16 one in four patients treated with loop diuretics had a diagnostic record of HF, and only 11.0%
17 were subsequently diagnosed with HF over the following 5 years. The prognosis of patients
18 treated with loop diuretics, even without a diagnosis of HF, was substantially worse than that of
19 patients with HF who were not receiving loop diuretics. Indeed, patients with a diagnosis of HF
20 who were not receiving loop diuretics had only a slightly worse prognosis than patients aged
21 ≥ 60 years with a broad range of other cardiovascular problems. Patients with HF who were
22 treated with loop diuretics had the worst prognosis. Hospitalisation rates were also higher for
23 patients taking loop diuretics with or without a diagnosis of HF, although the primary reason

1 was usually for conditions other than cardiovascular disease for all patient groups. In summary,
2 patients dispensed loop diuretics constitute a much larger healthcare problem than patients
3 with a diagnostic record of HF, which might be explained by substantial under-diagnosis or
4 under-recording of HF (1). This has serious implications for HF epidemiology and health service
5 capacity to manage it. Patients with cardiovascular disease treated with loop diuretics are at
6 high risk even if they do have no record of HF, which should alert clinicians to consider the
7 need for further investigation and treatment.

8 The observation that loop diuretics are associated with an adverse prognosis in the
9 absence of HF is not unique to Glasgow. International trials of AF (18), and type 2 diabetes
10 mellitus (19) show that patients treated with loop diuretics often do not carry a diagnosis of HF
11 but have worse outcomes than those with a diagnostic label of HF who are not treated with
12 loop diuretics; those with both HF and loop diuretics consistently have the worst outcome. A
13 study of patients with AF from England found that those receiving loop diuretics but no record
14 of HF had a prognosis similar to those with HF recorded (20).

15 Current criteria used to define HF are not robust, relying heavily on symptoms and
16 signs such as breathlessness and ankle swelling, that lack specificity and may not be obvious until
17 HF is severe, requiring the patients to be hospitalised (1, 6, 21-23). In the current analysis, few
18 patients initiated on loop diuretics without a diagnosis of HF had measured natriuretic peptides
19 or an echocardiogram to support or exclude a diagnosis of HF. However, many patients had
20 hypertension, diabetes mellitus, anaemia, AF, and impaired kidney function, common
21 comorbidities that may cause or exacerbate HF. The diagnosis of HF in the presence of a
22 preserved LVEF is especially difficult when other reasons for symptoms and signs exist, such as
23 lung or kidney disease (24). Many patients treated with loop diuretics who were not given a

1 diagnosis of HF were older women and had left atrial dilation, consistent with the demographic
2 profile and diagnosis of HF with preserved ejection fraction. AF may also cause left atrial
3 dilation, but if it leads to symptoms and signs of congestion requiring treatment with loop
4 diuretics, it may also be considered to have caused HF. Such diagnostic uncertainties might
5 explain why many patients are treated with loop diuretics but are not diagnosed with HF.

6 About half of patients had been hospitalised in the year before initiation of loop
7 diuretics, and many others attended hospital out-patients, usually for non-cardiovascular
8 conditions. A few patients treated with loop diuretics had end-stage kidney disease, and some
9 will have received loop diuretics for the treatment of resistant hypertension, but neither
10 indication for loop diuretics appeared to account for their widespread use (3). On general
11 medical and surgical wards, loop diuretics may have been initiated for symptoms and signs of
12 HF, but appropriate investigations not done or not recorded in patients' medical records (25).
13 When loop diuretics are listed as hospital discharge medications, primary care physicians may
14 automatically repeat the prescription, trusting that their hospital colleagues have investigated
15 appropriately. Patients admitted with, for example, respiratory infections, may receive both
16 antibiotics and loop diuretics due to diagnostic uncertainty. Even if antibiotics are responsible
17 for the success of treatment, loop diuretics may be continued long-term because no one
18 decided to stop them.

19 Current consensus guidelines state that symptoms and signs of congestion are essential
20 diagnostic criteria for HF (21), and strongly recommend loop diuretics for their treatment (4).
21 In the current analysis, many patients with a diagnostic label of HF were not treated with loop
22 diuretics. These patients had often had myocardial infarctions, had reduced LVEF and were
23 prescribed renin-angiotensin system inhibitors and beta-blockers. The relatively favourable

1 prognosis of patients with HF who were not treated with loop diuretics may reflect the
2 effective deployment of guideline-recommended therapies that prevent or reverse the
3 development of congestion, rendering treatment with loop diuretics unnecessary. However, the
4 decision not to initiate loop diuretics suggests that these patients had few or no symptoms or
5 signs of congestion, and may not have fulfilled current guideline criteria for a diagnosis of HF.

6 That there is an association between taking loop diuretics and an adverse prognosis in
7 patients with HF is not surprising (26). Loop diuretics are used to treat symptoms and signs of
8 congestion, which is associated with more severe cardiac and renal dysfunction and a higher
9 mortality. For patients with severe congestion, loop diuretics are almost certainly life-saving in
10 the short term, but the longer-term adverse consequences, including activation of
11 neuroendocrine systems, electrolyte disturbances and increased calcium excretion, might
12 increase morbidity and mortality (27-29). The overall prognosis of patients taking loop diuretics
13 will reflect the average prognosis for each of the diverse reasons for their use. Patients who
14 received loop diuretics for ankle swelling in the absence of serious underlying disease might
15 have a good prognosis, and therefore, for other patients within this diverse group, it must be
16 much worse. It is also possible that prognosis is driven primarily by problems other than HF,
17 such as lung disease or cancer, for which loop diuretics might do more harm than good.
18 Further research is required to determine how often loop diuretic prescription is simply a
19 bystander marker of a poor outcome or associated with symptoms and signs due to cardiac
20 dysfunction; in other words, HF.

21 **Strengths and limitations**

22 Administrative health records were accessed for a region encompassing 23% of the
23 Scottish population (14) including all community-based prescriptions and blood tests from 2010

1 onwards and primary care diagnosis and reasons for hospital admissions from the year 2000
2 onwards. However, some important variables were unavailable, including height, weight,
3 smoking habit, blood pressure, dose, and dose frequency. Unlike many other large
4 administrative datasets (8, 30, 31), a large sample of echocardiographic and ECG results were
5 available. However, many more tests may have been done at the “bedside” without results
6 being entered into electronic records. In future, accessing patients’ case notes may be possible
7 to retrieve this information. Information on in-hospital prescribing of interventions such as
8 intravenous loop diuretic use was not available.

9 The cohort was defined with a broad, though incomplete, set of cardiovascular diseases,
10 missing those with conditions such as AF, valvular disease, or venous thromboembolism.
11 However, any patient dispensed an ACEi, ARB, MRA, beta-blocker, or loop diuretic would still
12 have been included. This might have influenced the risk of the reference group but will not have
13 the relative amongst groups.

14 Hypertension was probably under-reported, given the high prescription rates for ACEi,
15 ARB, calcium channel blockers, and thiazide diuretics. However, the prevalence of diabetes and
16 percentage of patients on hypoglycaemic therapy and the prevalence of COPD and percentage
17 on bronchodilators were similar, suggesting that these are useful pharmaco-epidemiological
18 markers of disease (32, 33), just as loop diuretics might be for symptoms and signs of HF.

19 Research using administrative health records is reliant on clinical coding. In an audit of Scottish
20 hospitalisation records, the ‘I50’ code for HF was judged to be correct >90% of the time but
21 missed a diagnosis of HF in 22% of cases (34). Death certificates are probably fairly accurate for
22 classifying deaths as cardiovascular or due to cancer but may be less reliable for further
23 specifying causes such as HF or sudden death.

1 In conclusion, this analysis suggests that in patients with a broad range of cardiovascular
2 diseases, mortality is more strongly associated with use of loop diuretics than with a diagnosis
3 of HF, but amongst those treated with loop diuretics, a diagnosis of HF is associated with a
4 worse prognosis. Either the diagnosis of HF is often missed, which may result in the withholding
5 of evidence-based treatment of HF, or loop diuretic use is associated with other conditions
6 with a prognosis similar to HF, or inappropriate loop diuretic use increases mortality; all might
7 be true and contribute to poor outcomes. Nevertheless, treatment with loop diuretics provides
8 a simple, reliably-collected, objective marker of patients at increased risk of hospitalisation and
9 death. The proportion of patients on loop diuretics undergoing investigation for HF could be
10 used to audit the quality of diagnostic care in clinical practice. When a clinician encounters a
11 patient treated with loop diuretics, this should trigger a review of the patient's medical records
12 to ensure that appropriate investigations have been done, such as measurement of natriuretic
13 peptides or cardiac imaging, to exclude serious cardiac pathology.

14

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17 the National Health Service as part of their care and support.

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20

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27

28

1

2 Legends

3 Graphical abstract: Description of the observational cohort for adults with cardiovascular (CV)
4 disease in the Greater Glasgow & Clyde Health Board, including patient characteristics, a
5 breakdown into distinct groups based on loop diuretic (LD) and heart failure (HF) status at
6 baseline, and 5-year mortality statistics. CV disease, neoplasm, infection, and other causes of
7 mortality were reported per patient-year at risk. Cox proportional hazards ratios (HR) and
8 95% confidence intervals were reported adjusting for age, sex, socioeconomic deprivation, and
9 ten chronic comorbidities.

10 Figure 1: Greater Glasgow & Clyde population classified by sex, age group, repeat prescription
11 of loop diuretics (LD), and by a diagnosis of heart failure (HF), based on the mid-year
12 population estimate for 2012.

13 Figure 2: Transition diagrams show how many patients started in each of the four groups (left
14 most boxes) and how many experienced subsequent events between 1st January 2012 through
15 31st December 2016. Percentages in the boxes are calculated with the baseline group size as the
16 denominator, while transitions are calculated based on those eligible for each transition.

17 Reasons for transitions include diagnosis of heart failure (HF), initiation of loop diuretics (LD),
18 or death during follow-up.

19 Figure 3

20 (A) Estimation of the cumulative initiation of loop diuretics for patients not already taking loop
21 diuretics at baseline and the competing risk of all-cause mortality.

1 (B) Estimation of the cumulative incidence of a diagnosis of heart failure for patients who did
2 not have heart failure at baseline and the competing risk of all-cause mortality.

3 LD, loop diuretics; HF, heart failure

4 Figure 4: 5-year event rates by patient-year at risk.

5 (A) Hospital admission rate classified by the primary admission reason and baseline group
6 determined by the presence or absence of a repeat prescription loop diuretics (LD) and a
7 diagnosis of heart failure (HF). Rates were adjusted by patient-year at risk for those eligible (i.e.,
8 not already in hospital or dead) to be admitted. The total number of admissions (n) per group
9 are reported above each column. Supplementary Figures 12 and 13 show similar data with the
10 loop diuretic/HF group as a time-dependent covariate.

11 (B) All-cause mortality classified by the underlying cause of death and the baseline group
12 determined by the presence or absence of a repeat prescription of loop diuretic (LD) and a
13 diagnosis of heart failure (HF) adjusted for patient-year at risk where the patient was under
14 follow-up. Patients were censored at the last medical contact (blood test, prescription, etc.)
15 date to account for patients who moved out of the region). The total number of deaths (n) per
16 group are reported above each column. Supplementary Figure 14 shows similar data with loop
17 diuretic/HF group as a time-dependent covariate.

18 Figure 5: 5-year survival analysis from 1st January 2012 through end of follow-up classified by
19 baseline group according to use of loop diuretics (LD) and diagnosis of heart failure (HF).

20 (A) Kaplan-Meier curves to compare survival patterns by baseline group.

1 (B) Forest plot of hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality
2 by baseline group. The model was adjusted for age, sex, Scottish Index of Multiple Deprivation,
3 a history of hypertension, coronary artery disease, peripheral arterial disease, diabetes mellitus,
4 valve disease, atrial fibrillation or flutter, stroke, cancer, dementia, and the closest eGFR in the
5 prior 2 years.

6 **Pre-registered clinical trial number**

7 Not applicable.

9 **Ethical approval statement**

10 Ethical approval was given via the NHS GG&C's Local Privacy Advisory Committee, reference
11 number GSH/18/CA/002.

12 **Data availability statement**

13 The data and study materials will not be made available to other researchers. However, the analysis
14 code is available on GitHub (<https://github.com/jocelynfriday/CharactersticsAndPrognosisOfLD>),
15 individual-level datasets can be requested for use in other research studies through an application to
16 NHS West of Scotland Safe Haven (<https://www.researchdata.scot/safe-haven-services>), and aggregated
17 data are provided in the supplementary material.

18 **Conflict of interest statement**

19 Nothing to declare.

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27

1 Third party permissions are not applicable. The authors declare that all illustrations and figures
2 in the manuscript are entirely original and do not require reprint permission.

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4

ACCEPTED MANUSCRIPT

- 1 Table I. Baseline demographics, co-morbidities, and blood tests for the study population classified by prescription of loop-diuretics
 2 (LD) and diagnosis of heart failure (HF)

| variable | Neither (18-59 yrs) | Neither (≥ 60 yrs) | LD Only | HF Only | Both: LD + HF |
|--|------------------------|-----------------------|--------------|--------------|------------------|
| n | 72,236 | 89,699 | 23,963 | 5,156 | 7,844 |
| Age (years) | 50 (41 - 55) | 72 (66 - 78) | 75 (65 - 83) | 69 (59 - 78) | 77 (68 - 83) |
| Under 60 years of age | 72,236 (100%) | 0 (0%) | 3,903 (16%) | 1,358 (26%) | 810 (10%) |
| Sex | | | | | |
| Women | 38,838 (54%) | 48,184 (54%) | 16,775 (70%) | 1,670 (32%) | 3,959 (50%) |
| Men | 33,398 (46%) | 41,515 (46%) | 7,188 (30%) | 3,486 (68%) | 3,885 (50%) |
| Ethnicity | | | | | |
| White | 44,164 (61%) | 70,461 (79%) | 20,660 (86%) | 4,425 (86%) | 7,151 (91%) |
| Missing | 25,182 (35%) | 17,302 (19%) | 2,902 (12%) | 577 (11%) | 523 (7%) |
| Other | 2,890 (4%) | 1,936 (2%) | 401 (2%) | 154 (3%) | 170 (2%) |
| Scottish Index of Multiple Deprivation | | | | | |
| 1 (most deprived) | 30,476 (42%) | 31,527 (35%) | 10,525 (44%) | 2,258 (44%) | 3,457 (44%) |
| 2 | 13,046 (18%) | 16,252 (18%) | 4,524 (19%) | 917 (18%) | 1,529 (19%) |
| 3 | 9,857 (14%) | 11,914 (13%) | 3,236 (14%) | 613 (12%) | 1,021 (13%) |
| 4 | 8,170 (11%) | 11,904 (13%) | 2,636 (11%) | 582 (11%) | 898 (11%) |
| 5 (least deprived) | 10,687 (15%) | 18,102 (20%) | 3,042 (13%) | 786 (15%) | 939 (12%) |
| HF in hospital records | N/A | N/A | N/A | 3,702 (72%) | 6,806 (87%) |
| Co-morbidities * | | | | | |
| H/o Hypertension | 14,728 (20%) | 34,038 (38%) | 9,110 (38%) | 2,312 (45%) | 4,104 (52%) |
| Diabetes mellitus | 8,824 (12%) | 16,222 (18%) | 4,858 (20%) | 952 (18%) | 2,303 (29%) |
| Thyroid disease | 709 (1%) | 2,013 (2%) | 1,083 (5%) | 194 (4%) | 502 (6%) |
| CAD (including MI) | 7,432 (10%) | 23,638 (26%) | 7,390 (31%) | 3,860 (75%) | 5,266 (67%) |
| Myocardial infarction | 3,420 (5%) | 7,916 (9%) | 2,485 (10%) | 2,734 (53%) | 3,157 (40%) |
| Valve disease | 323 (0%) | 1,338 (1%) | 1,139 (5%) | 507 (10%) | 1,570 (20%) |
| Atrial fibrillation/ flutter | 1,021 (1%) | 6,390 (7%) | 3,819 (16%) | 1,284 (23%) | 3,638 (45%) |

| | | | | | |
|---|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Peripheral arterial disease | 623 (1%) | 2,431 (3%) | 923 (4%) | 291 (6%) | 670 (9%) |
| Stroke | 1,668 (2%) | 7,177 (8%) | 2,385 (10%) | 609 (12%) | 1,183 (15%) |
| Chronic obstructive pulmonary disease | 3,321 (5%) | 8,636 (10%) | 4,616 (19%) | 895 (17%) | 2,203 (28%) |
| Liver disease [⊕] | 376 (1%) | 293 (0%) | 385 (2%) | 23 (0%) | 64 (1%) |
| Cancer | 1,383 (2%) | 7,308 (8%) | 2,280 (10%) | 417 (8%) | 796 (10%) |
| Dementia | 28 (<1%) | 1,995 (2%) | 1,195 (5%) | 143 (3%) | 456 (6%) |
| Blood results [○] | | | | | |
| Patient-record of eGFR | 57,305 (79%) | 83,815 (93%) | 22,575 (94%) | 4,962 (96%) | 7,656 (98%) |
| eGFR | 99 (90 - 106) | 78 (64 - 88) | 71 (52 - 85) | 81 (64 - 92) | 61 (43 - 79) |
| eGFR 30 - 59 | 1,061 (2%) | 15,469 (18%) | 6,419 (28%) | 886 (18%) | 3,004 (39%) |
| eGFR <30 | 231 (<1%) | 1,134 (1%) | 1,330 (6%) | 121 (2%) | 707 (9%) |
| Patient-record of haemoglobin | 49,507 (69%) | 69,406 (77%) | 21,125 (88%) | 4,427 (86%) | 7,295 (93%) |
| Haemoglobin: Women | 13.3 (12.5 - 14.0) | 12.9 (12.0 - 13.8) | 12.6 (11.5 - 13.6) | 12.6 (11.6 - 13.6) | 12.2 (11.1 - 13.3) |
| Haemoglobin: Men | 14.9 (14.0-15.7) | 14.1 (13.0 - 15.1) | 13.3 (11.9 - 14.5) | 14.1 (13.0 - 15.1) | 13.2 (11.7 - 14.4) |
| Anaemic [◇] | 5,872 (12%) | 16,735 (24%) | 7,696 (36%) | 1,220 (28%) | 3,247 (45%) |
| <p>Data are frequencies (%) for categorical values or median (1st - 3rd quartile) for continuous values. * History of a coded record on or before 1st January 2012 [⊕] Defined by the presence of liver fibrosis, sclerosis, or cirrhosis [○] Based on the most recent value in the two years before 1st January 2012 [◇] Using the World Health Organization's definition of anaemia eGFR = estimated glomerular filtration rate in mL/min/1.73 m² using CKD-EPI equation¹¹ Haemoglobin in g/dL</p> | | | | | |
| H/o hypertension, History of hypertension; CAD, coronary artery disease; MI, myocardial infarction; | | | | | |

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2

1 Table 2. Baseline age and concurrent medications for the study population classified by prescription of loop-diuretics (LD) and
 2 diagnosis of heart failure (HF)

| variable | Neither (18-59 yrs) | Neither (≥60yrs) | LD Only | HF Only | Both: LD + HF |
|-----------------------------|---------------------|------------------|--------------|--------------|---------------|
| n | 72,236 | 89,699 | 23,963 | 5,156 | 7,844 |
| Age (years) | 50 (41 - 55) | 72 (66 - 78) | 75 (65 - 83) | 69 (59 - 78) | 77 (68 - 83) |
| Medication** | | | | | |
| ACEi or ARB | 34,436 (48%) | 60,624 (68%) | 11,638 (49%) | 3,992 (77%) | 5,769 (74%) |
| ACEi | 27,746 (38%) | 45,540 (51%) | 8,498 (35%) | 3,320 (64%) | 4,572 (58%) |
| ARB | 7,459 (10%) | 16,406 (18%) | 3,687 (15%) | 785 (15%) | 1,465 (19%) |
| Beta-blocker | 27,941 (39%) | 40,555 (45%) | 8,512 (36%) | 3,542 (69%) | 5,054 (64%) |
| MRA | 462 (1%) | 600 (1%) | 971 (4%) | 173 (3%) | 1,179 (15%) |
| Calcium channel blockers | 12,901 (18%) | 32,213 (36%) | 7,516 (31%) | 1,220 (24%) | 1,737 (22%) |
| Diltiazem/Verapamil | 1,045 (1%) | 3,872 (4%) | 1,801 (8%) | 254 (5%) | 351 (4%) |
| Dihydropyridine | 11,907 (16%) | 28,485 (32%) | 5,784 (24%) | 982 (19%) | 1,403 (18%) |
| Digoxin | 115 (0%) | 1,461 (2%) | 1,792 (7%) | 366 (7%) | 1,772 (23%) |
| Thiazide‡ | 11,151 (15%) | 31,103 (35%) | 1,499 (6%) | 591 (11%) | 307 (4%) |
| NSAIDs | 12,962 (18%) | 11,559 (13%) | 3,289 (14%) | 430 (8%) | 441 (6%) |
| Low dose aspirin | 12,091 (17%) | 40,474 (45%) | 10,727 (45%) | 3,383 (66%) | 4,409 (56%) |
| Oral anticoagulant | 646 (1%) | 4,114 (5%) | 2,789 (12%) | 722 (14%) | 2,253 (29%) |
| Lipid regulator | 21,382 (30%) | 57,287 (64%) | 13,975 (58%) | 3,999 (78%) | 5,743 (73%) |
| Bronchodilators | 6,691 (9%) | 11,580 (13%) | 5,988 (25%) | 839 (16%) | 2,108 (27%) |
| Thyroid medications | 3,375 (5%) | 8,360 (9%) | 3,218 (13%) | 350 (7%) | 949 (12%) |

| | | | | | |
|---|-------------|--------------|-------------|-----------|-------------|
| Hypoglycaemic Agents | 8,049 (11%) | 13,689 (15%) | 4,390 (18%) | 694 (13%) | 1,862 (24%) |
| Insulin† | 2,085 (3%) | 2,030 (2%) | 1,196 (5%) | 146 (3%) | 650 (8%) |
| Other hypoglycaemic agents | 6,781 (9%) | 12,771 (14%) | 3,798 (16%) | 626 (12%) | 1,515 (19%) |
| <p>Data are frequencies (%) for categorical values or median (1st – 3rd quartile) for continuous values.</p> <p>** A prescription dispensed 180 days before through 1st January 2012</p> <p>‡ Thiazide or thiazide-related medications</p> <p>† either alone or in combination with another agent</p> <p>ACEi, angiotensin-converting-enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; and NSAIDs, non-steroidal anti-inflammatory drugs.</p> | | | | | |

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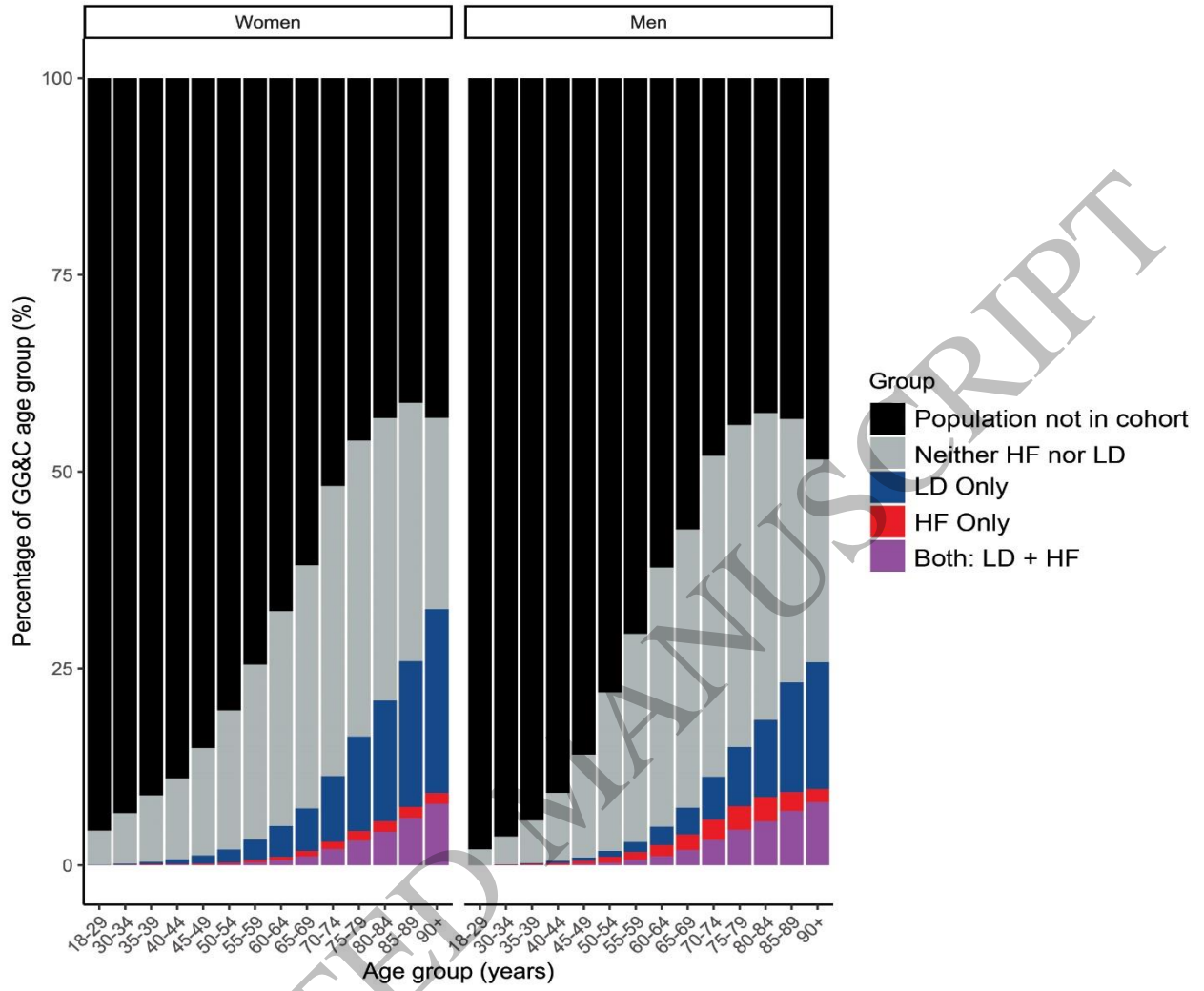
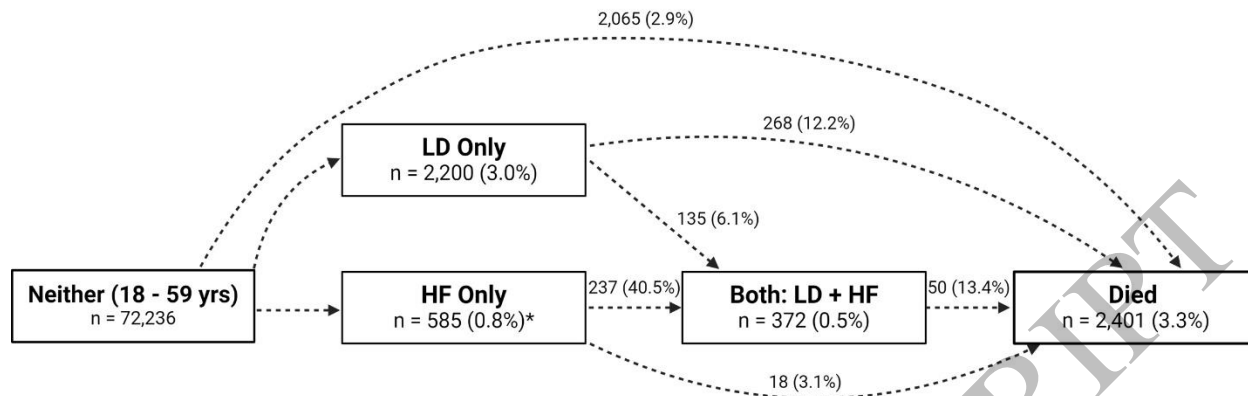
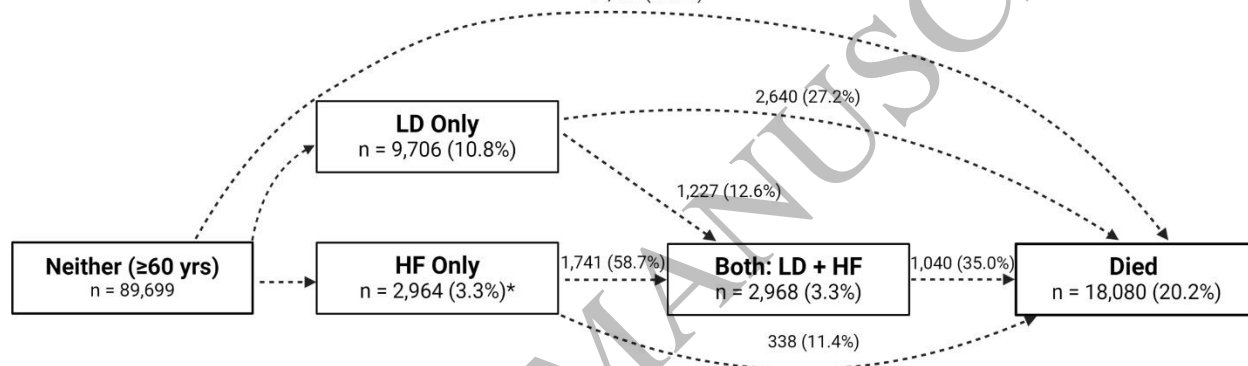


Figure 1
559x510 mm (x DPI)

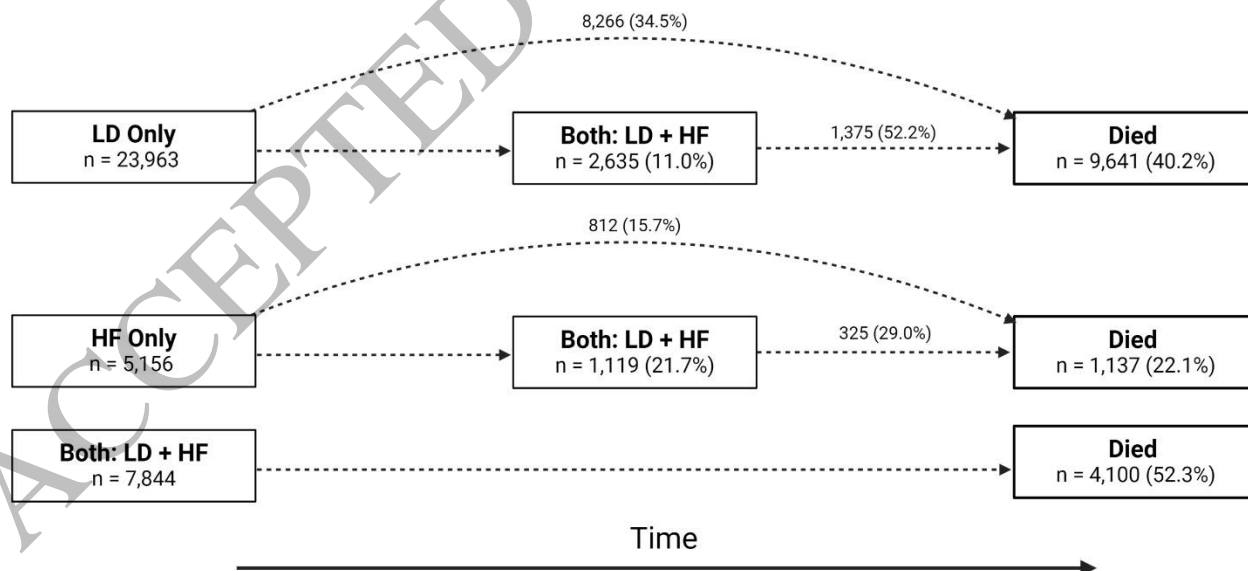
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* Includes ≤ 6 with both LD and HF recorded on the same day, none of whom died



* Includes 13 with both LD and HF recorded on the same day, of whom ≤ 6 died



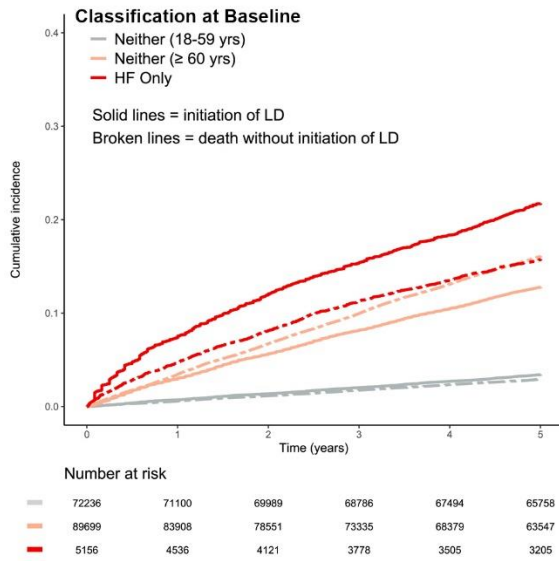
Time



Figure 2
461x559 mm (x DPI)

1
2
3
4

(A) Initiation of loop diuretics



(B) Diagnosis of heart failure

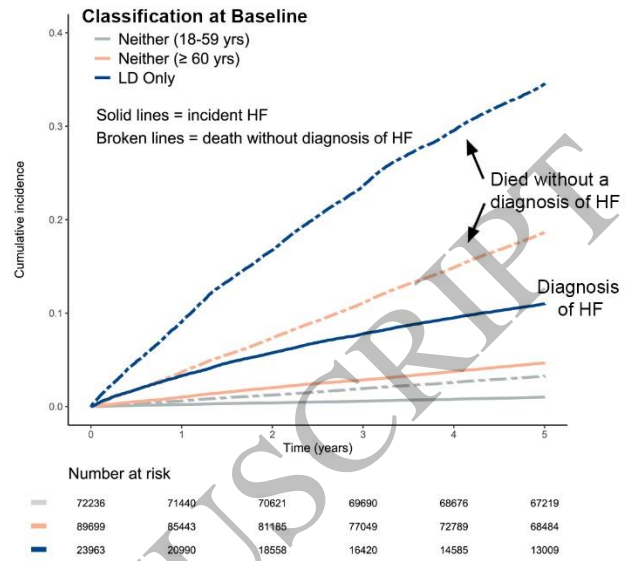
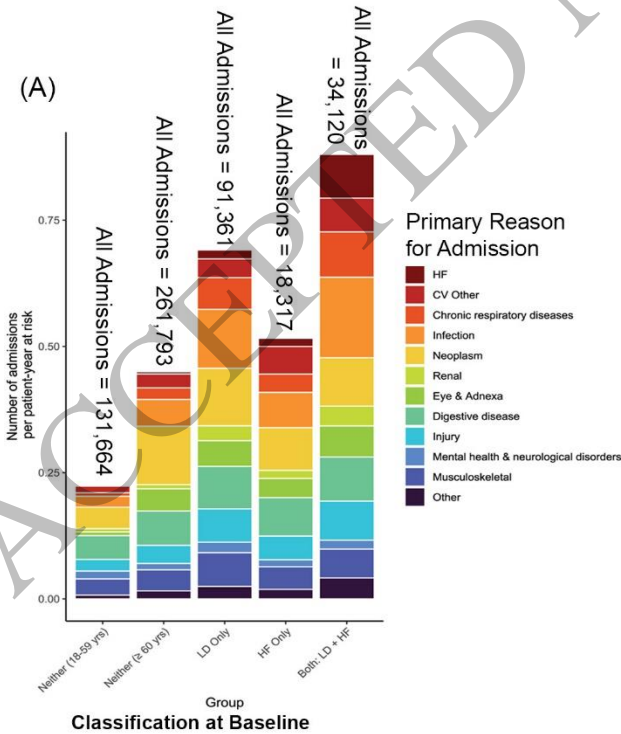


Figure 3
559x277 mm (x DPI)

1
2
3
4
5

(A)



(B)

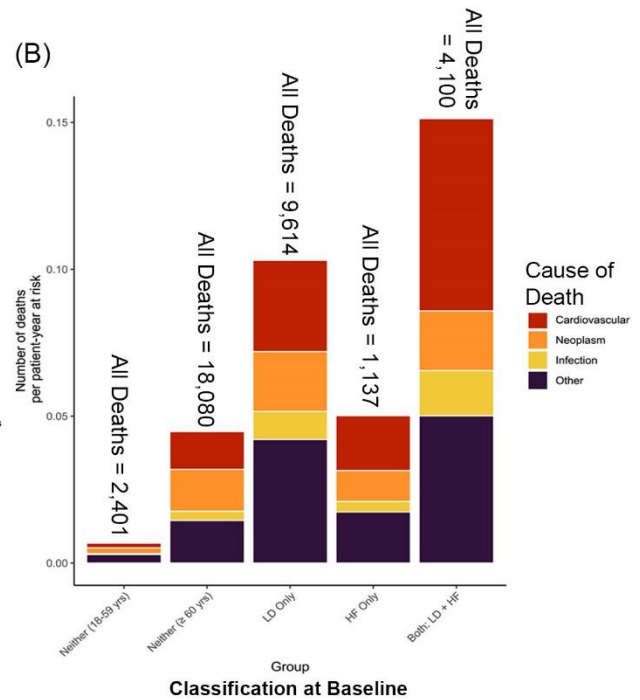
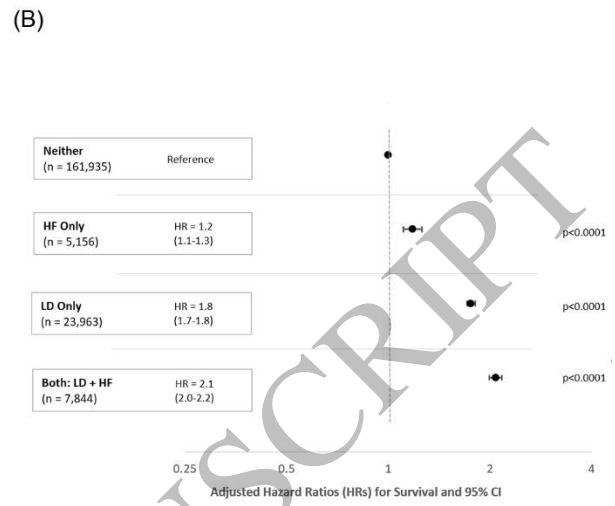
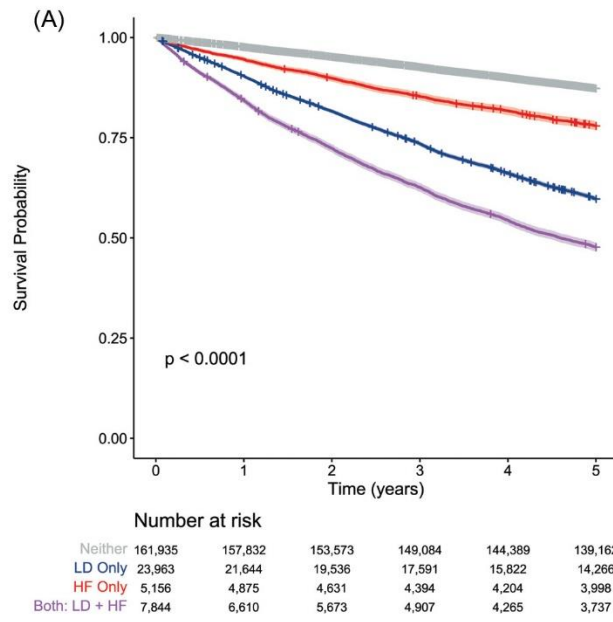


Figure 4
556x344 mm (x DPI)

6
7
8

1



2

3

4

Figure 5
534x279 mm (x DPI)

ACCEPTED MANUSCRIPT

Key question

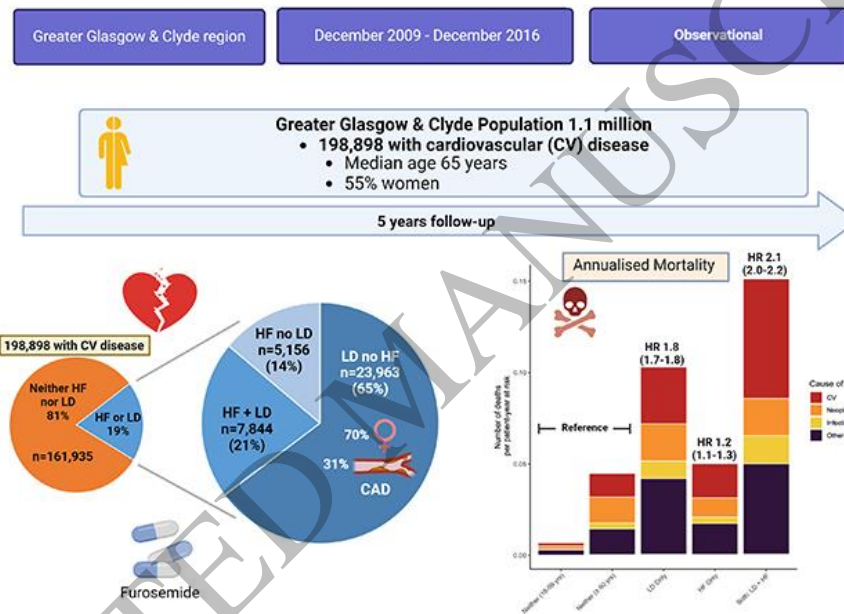
What is the prevalence, nature and prognosis of people treated with loop diuretics with or without a diagnostic record of heart failure; and what about patients with heart failure who are not treated with loop diuretics?

Key finding

Of 198,898 people with cardiovascular disease, 16% were receiving loop diuretics, of whom only 25% had a diagnostic record of heart failure. Mortality was more strongly associated with the use of loop diuretics than with a record of heart failure.

Take-home message

Either the diagnosis of heart failure was often missed, or other conditions with a poor prognosis led to use of loop diuretics, or inappropriate diuretic use increased mortality. Patients prescribed loop diuretics should be carefully reviewed and, potentially, investigated further



1
2
3
4

Structured Graphical Abstract
107x130 mm (x DPI)