Title

Outcomes in patients treated with loop diuretics without a diagnosis of heart failure: a retrospective cohort study.

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Abstract

Objective: Loop diuretics are commonly prescribed in the community, not always to patients with a recorded diagnosis of heart failure (HF). The rate of HF events in patients prescribed loop diuretics without a diagnosis of HF is unknown.

Methods: This was a propensity-matched cohort study using data from the Clinical Practice Research Datalink, Hospital Episode Statistics, and Office of National Statistics in the UK. Patients prescribed a loop diuretic without a diagnosis of HF (loop diuretic group) between January 1st 2010 and December 31st 2015 were compared to patients with HF (HF group) – analysis A; and patients with risk factors for HF (either ischaemic heart disease, or diabetes *and* hypertension – at-risk group) – analysis B. The primary endpoint was a HF event (a composite of presentation with HF symptoms, HF hospitalisation, HF diagnosis (analysis B only), and all-cause mortality).

Results: From a total population of 180,384 patients (78,968 in the loop diuretic group, 28,177 in the HF group, and 73,239 in the at-risk group), there were 59,694 patients, 22,352 patients, and 57,219 patients were in the loop diuretic, HF, and at-risk groups, respectively, after exclusion criteria were applied. After propensity matching for age, sex, and co-morbidities, patients in the loop diuretic group had a similar rate of HF events as those in the HF group (71.9% vs. 72.1%; hazard ratio (HR) 0.92 (95% confidence interval (CI) 0.90 – 0.94); P<0.001), and twice that of those in the at-risk group (59.2% vs. 35.7%; HR = 2.04 (95% CI 2.00 – 2.08); P<0.001).

Conclusions: Patients prescribed a loop diuretic without a recorded diagnosis of HF experience HF events at a rate comparable to that of patients *with* a recorded diagnosis of HF, many of these patients may have undiagnosed HF.

Key Messages

What is already known about the subject?

- The proportion of patients on primary care heart failure (HF) registers is much lower than expected from epidemiological data: there may be many patients missing from community HF registers. Furthermore, most patients only receive a diagnosis of HF after deteriorating to the point of requiring hospital admission; strategies to identify these missing patients may improve outcomes.

What are the new findings?

- Patients prescribed a loop diuretic without a recorded diagnosis of HF have an outcome profile similar to that of patients *with* a diagnosis of heart failure
- There were approximately three times as many patients prescribed a loop diuretic without a diagnosis of HF than were given a diagnosis of HF during the period January 2010 to December 2015.

How might these results change the focus of research or clinical practice?

- There are many medications that cannot be prescribed without first performing a blood test; mandating natriuretic peptide testing before prescribing a loop diuretic would be an easy-to-implement change in practice. Downstream testing may identify HF at an early stage of the disease.
- Establishing what proportion of patients taking a loop diuretic without a diagnosis of HF actually have underlying HF will allow for better planning of HF services and allow for adequate funding to support one of the biggest problems facing the modern NHS.

Introduction

Heart failure (HF)is a difficult diagnosis to make: symptoms are non-specific;[1] clinical signs difficult to elicit;[2] natriuretic peptide testing is insensitive;[3] and echocardiography is prone to errors in measurement.[4,5] Perhaps as a consequence, the true incidence and prevalence of HF is not clear.

Epidemiological studies report the prevalence as being between 1 and 7% of the general population.[6-10] The prevalence increases with age and affects more than 1 in 10 patients aged over 80.[11] However, in the UK, the prevalence of HF recorded in primary care HF registers is 0.9%.[12]

Loop diuretics are among the most commonly prescribed medications in primary care but they have few indications other than the treatment of venous congestion due to HF.[13] An audit of clinical practice found that the prevalence HF according to the register was much the same as the prevalence of loop diuretic prescription among patients who did not have a diagnosis of HF. Patients prescribed a loop diuretic without a diagnosis of HF had a rate of HF hospitalisation or all-cause death of 25% after 2 years.[14] It is possible a proportion of patients prescribed loop diuretics in the community have underlying HF.

We used data from the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES) admitted patient care (APC) records, and Office of National Statistics (ONS) death records to assess the frequency of HF-related events in patients prescribed a loop diuretic without a diagnosis of HF compared to patients *with* a diagnosis of HF. Loop diuretics may also be prescribed for other conditions associated with an increased risk of heart failure such as hypertension, or chronic kidney disease. Thus, in a second analysis, we also assessed the frequency of HF-related events in a control group of patients at-risk of developing HF to compare outcome profiles.

Methods

Data sources

The CPRD database contains anonymised longitudinal patient data on demographics, lifestyle, diagnoses, medications, investigations including blood tests, and referrals collected from primary care across the UK.[15]

Primary care electronic records were linked to the HES APC records and the ONS death records. HES APC and ONS death records are databases of all hospital admissions, and deaths, respectively, in the UK. The cause of each is ascribed an International Classification of Diseases 10 (ICD-10) code. Scientific approval for the present study was given by the CPRD Independent Scientific Advisory Committee. Ethics approval was given by the Hull York Medical School Ethics Committee (ref 21.28 - RECORD-HF).

Study populations

All patients aged over 18 years of age contributing data to the CPRD between January 1st 2010 and December 31st 2015, who had been registered with their practice for at least 1 year, with records deemed acceptable by CPRD quality control, and approved for linkage to the HES APC and ONS death record datasets, were eligible for inclusion. The time frame was chosen to include the time when the National Institute for Health and Care Excellence (NICE) introduced a guideline for the diagnostic process for HF (2010),[16] and to allow the majority of patients to have at least 5 years of follow up prior to the peaks of the coronavirus pandemic in 2020-2021.

Patients were split into three groups: 1) patients prescribed a loop diuretic but who did not have a recorded diagnosis of HF (loop diuretic group); 2) patients with a new recorded

diagnosis of HF (HF group); and 3) patients with a new diagnosis of HF risk factors – ischaemic heart disease (IHD) or a diagnosis of diabetes in patients with a pre-existing diagnosis of hypertension, or vice versa (at-risk group).

Case identification

Read and ICD-10 code lists were generated from medical dictionary keyword searches, previously published literature,[6] and online clinical code repositories (appendix).[17] The index dates were the date of the first medication code for a loop diuretic, the date of the first Read or ICD-10 code for HF for the HF-group, and the date of the first Read code for IHD or the first Read code for diabetes in a patient with pre-existing hypertension (or vice versa) for the loop diuretic, HF, and at-risk groups respectively. [18]

Various exclusion criteria were applied to the three groups (figure 1). Patients with an existing Read or ICD-10 code for HF pre-dating 1st January 2010 (exclusion criteria 1-2), or a Read code specifically excluding HF before the index date (exclusion criterion 3), or whose date of death was prior to the index date (exclusion criterion 8) were excluded from all three groups.

Patients with a Read code for HF in the 3 months after the index date (exclusion criterion 4), or hospitalisation for HF or death within 1 month of the index date (exclusion criterion 5) were presumed to have clinically evident HF at the time of loop diuretic prescription and were excluded from the loop diuretic group. To ensure a fair comparison between the groups, patients who met exclusion criterion 5 were also excluded from the HF and at-risk groups.

Patients who underwent natriuretic peptide testing, echocardiography, or referral to cardiology out-patients within 3 months of the index date were presumed to have followed an appropriate diagnostic pathway and were excluded from the loop diuretic group (exclusion

158 criterion 6). Exclusion criterion 6 was also applied to the at-risk group on the assumption that
159 some patients who underwent investigations may have had HF.

160 Patients with Read codes for either aortic or mitral valve disease 3 months before or after the
161 index date were presumed to have HF due to valve disease and were excluded from the loop
162 diuretic group (exclusion criterion 7).

163 Finally, patients who were prescribed a loop diuretic before or on the index group were
164 excluded from the at-risk group (exclusion criterion 9).

165 We extracted from the primary care electronic record on: BMI, smoking status, common co-
166 morbidities, HF medications, presentation with HF symptoms before the index date
167 (peripheral oedema, breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, or fatigue),
168 natriuretic peptide testing, echocardiography referrals or results, and out-patient referrals.
169 Cause-specific hospitalisation data was extracted using linkage with HES APC record.
170 Cause-specific mortality was extracted from ONS death records.

171

172 *Statistical analysis*

173 We performed two separate comparisons: analysis A – loop diuretic group versus the HF
174 group; and analysis B – loop diuretic group versus the at-risk group. In analysis A, patients in
175 the loop diuretic group were matched with patients in the HF group using a propensity score
176 using age as a continuous variable, sex, and the presence of IHD, diabetes, hypertension, and
177 AF. The propensity score was calculated using a cumulative logit regression model. Matching
178 was on a 1:1 nearest neighbour basis, without replacement, with a calliper width of 0.2 of the
179 standard deviation of the logit of the propensity score.

In analysis B, patients in the study population were matched to patients in the at-risk group for age and sex. Matching was on a 1:1 nearest neighbour basis without replacement with exact matches only. Standardised mean difference and distribution plots were used to check the adequacy of the matching.

Two sensitivity analyses were performed: one for analysis A in which patients were matched for loop diuretic prescription as well as age, sex, and the presence of IHD, diabetes, hypertension, and AF; and one for analysis B in which patients were matched for the presence of IHD, diabetes, hypertension, and AF as well as age and sex.

Continuous data are presented as medians (1^{st} to 3^{rd} quartiles), categorical data are presented as numbers (%). Differences in baseline characteristics between un-matched groups, and matched groups was tested using independent t-tests for continuous variables and chi-squared tests for categorical variables.

Differences in outcome were assessed using uni- and multi-variable Cox regression models and Kaplan-Meier curves. The two-tailed level of statistical significance was set at <0.05. All statistical analysis was performed using SPSS Version 28.

Outcome definitions

The primary outcome was time-to-first HF-related event which comprised of presentation to primary care with symptoms of HF, or hospitalisation with HF or all-cause mortality in analysis A; and presentation to primary care with symptoms of HF, or incident HF (new diagnosis of HF made in either primary or secondary care), or hospitalisation with HF, or all-cause mortality in analysis B. Secondary endpoints of time-to-first HF hospitalisation or all cause mortality; and time-to-first all-cause hospitalisation or all-cause mortality were also

assessed in both analyses. Patients were followed up until a first HF-event occurred or until 5 years.

Patient and public involvement

The Involve Hull patient and public involvement group provided written feedback on the study protocol during conception and prior to submission to the CPRD and guided plans for dissemination.

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Results

Of the 180,384 patients with either a first prescription of loop diuretics, or first diagnosis of either HF, IHD, hypertension or diabetes between 1st January 2010 and 31st of December 2015, 78,968 had a new loop diuretic prescription, 28,177 had a new diagnosis of HF, 32,701 had a new diagnosis of IHD, and 40,538 had a new diagnosis of diabetes in the context of pre-existing hypertension, or vice-versa. After application of exclusion criteria, 139,265 were used in the analyses comprising: 59,694 in the loop diuretic group, 22,352 in the HF group, and 57,219 in the at-risk group (figure 1).

Patient characteristics

225 Compared to patients with HF, patients taking a loop diuretic without a diagnosis of HF were
226 younger, more likely to be female (male sex 38% vs. 52%), and were less likely to have AF
227 (11% vs. 24%), CKD (20% vs. 30%), and IHD (15% vs. 30%) (p<0.001 for all). Furosemide
228 was the most commonly prescribed loop diuretic in both groups (table 1).

229 Compared to patients with HF risk factors, patients taking a loop diuretic without a diagnosis
230 of HF were older (74 vs. 64 years), more likely to be women (male sex 38% vs. 59%), and
231 were more likely to have either AF (11% vs. 4%) or CKD (20% vs. 12%) (p<0.001 for all).
232 (table 2).

Symptom burden

Only 1 in 5 patients in the loop diuretic group and the HF group had a presentation with HF symptoms to primary care in the month before their index date. Of those who had a recorded presentation prior to the index date, patients in the loop diuretic group were more likely to present with oedema (80% vs. 26%), and less likely to present with breathlessness (16% vs. 65%) than those in the HF group (p<0.001 for both) (table 1).

Outcome

Analysis A

In the propensity matched cohorts, during a median follow up of 65 (21 – 92) months, a HF-related event occurred in 71.9% of patients in the loop diuretic group and 72.1% of patients in the HF group. The proportion of patients presenting with a HF symptom was greater in the loop diuretic group (37.1% vs. 27.8%; P<0.001) but both hospitalisation with HF (1.9% vs.

4.0%; P<0.001) and all-cause mortality (55.6% vs. 61.2%; P<0.001) were more frequent in the HF group (table 3) (supplementary figure 1) (supplementary table 1).

Patients prescribed a loop diuretic without a recorded diagnosis of HF were only 6% less likely to experience a HF event compared to those with HF after adjustment for baseline characteristics (hazard ratio (HR) = 0.94 (95% confidence interval (CI) 0.92 – 0.96; P<0.001). (figure 2) (table 4).

The sensitivity analysis for analysis A found that HF events were significantly more likely in patients with a recorded diagnosis of HF compared to those taking a loop diuretic without a diagnosis of HF (supplementary tables 2 and 3). However, HF events were still very common in patients prescribed a loop diuretic without a recorded diagnosis of HF (69.3% vs. 73.7%; P<0.001).

All-cause hospitalisation or death occurred in 67.7% of patients in the loop diuretic group and 71.5% of patients in the HF group (P<0.001), although all-cause hospitalisation was more common in the loop diuretic group (27.5% vs. 23.0%; P<0.001) (supplementary figure 2) (table 3) (supplementary table 4).

Analysis B

In the propensity matched cohorts, during a median follow up of 89 (66 – 109) months, a HF-related event occurred in 59% of patients in the loop diuretic group and 36% of patients in the at-risk group (HR 2.04 (95% CI 2.00 – 2.08); P<0.001) (table 3).

Patients in the loop diuretic group were approximately twice as likely to experience a HF event compared to those in the at-risk group (un-adjusted HR = 2.04 (95% CI 2.00-2.08); P<0.001) (figure 3) (table 4) (supplementary figure 3) (supplementary table 1).

The sensitivity analysis for analysis B found an higher prevalence of HF events in both groups but similarly greater risk in patients in the loop diuretic group compared to the at-risk group (77.0% vs. 52.6%; P<0.001) (supplementary tables 2 and 3).

All-cause hospitalisation or mortality occurred in 56% of patients in the loop diuretic group and 42% of patients in the at-risk group (P<0.001) (supplementary table 4) (supplementary figure 4)

Table 1 – Patient characteristics analysis A

Variable	Unmatched			Matched		
	Loop diuretic group Loop diuretic N=59694	**HF group** Heart failure N=22352	**p-value**	**Loop diuretic group** Loop diuretic N=22288	**HF group** Heart failure N=22288	**p-value**
Demographics						
Age (years)	74 (62 – 83)	77 (67 – 85)	<0.001	77 (67 – 84)	77 (67 – 85)	1.00
Sex (male) – N (%)	22575 (38)	13285 (52)	<0.001	11716 (53)	11680 (52)	0.74
BMI (m/kg^2)	27 (24 – 31)	27 (24 – 30)	0.001	27 (24 – 31)	27 (24 – 30)	0.65
Missing – N (%)	5563 (9)	1935 (9)	-	2106 (9)	1927(9)	-
Current Smoker – N (%)	15292 (26)	5680 (26)	0.01	5382 (24)	5670 (26)	<0.001
Ex-Smoker – N (%)	11354 (19)	4447 (20)		4900 (22)	4420 (20)	
Never Smoked – N (%)	32696 (55)	12040 (54)		11874 (54)	12013 (54)	
Missing – N (%)	352 (<1)	185 (<1)	-	132 (<1)	185 (<1)	-
HF Diagnosis Setting						
Primary care – N (%)	N/A	8575 (38)	-	-	8540 (38)	-
Secondary care – N (%)	N/A	13777 (62)		-	13748 (62)	
HF Symptoms 1 month before index date						
Any symptom – N (%)†	11584 (19)	1470 (17)	<0.001	4307 (19)	1467 (17)	<0.001
Oedema – N (%)‡	9281 (80)	382 (26)		3240 (75)	382 (27)	
Fatigue – N (%)‡	112 (1)	51 (3)		40 (1)	51 (3)	
Breathlessness – N (%)‡	1903 (16)	960 (65)		901 (21)	957 (65)	
Multiple symptoms – N (%)‡	288 (2)	77 (5)		126 (3)	77 (5)	
Co-morbidities						
Atrial fibrillation – N (%)	6481 (11)	5395 (24)	<0.001	4876 (22)	5333 (24)	<0.001
Chronic kidney disease – N (%)	12035 (20)	6635 (30)	<0.001	5005 (23)	6620 (30)	<0.001
COPD – N (%)	6752 (11)	3156 (14)	<0.001	2851 (13)	3144 (14)	<0.001
Diabetes mellitus – N (%)	10563 (18)	4983 (22)	<0.001	4408 (20)	4974 (22)	<0.001
Hypertension – N (%)	31173 (52)	12093 (54)	<0.001	12013 (54)	12061 (54)	0.65

Ischaemic heart disease – N (%)	9071 (15)	6650 (30)	<0.001	5995 (27)	6588 (30)	<0.001
Stroke – N (%)	5443 (9)	2881 (13)	<0.001	2639 (12)	2869 (13)	<0.001
≥3 of the above – N (%)	24257 (41)	12643 (57)	<0.001	11361 (51)	12580 (56)	0.003
Medications						
ACEI or ARB – N (%)	21515 (36)	11707 (52)	<0.001	8917 (40)	11667 (52)	<0.001
Beta-blocker – N (%)	7831 (13)	7854 (35)	<0.001	4197 (19)	7820 (35)	<0.001
MRA – N (%)	2236 (4)	2361 (11)	<0.001	899 (4)	2352 (11)	<0.001
Loop diuretic – N (%)	59694 (100)	11045 (49)	<0.001	22288 (100)	11009 (49)	-
Furosemide – N (%)	57927 (97)	11022 (92)	<0.001	21568 (97)	10189 (93)	<0.001
Bumetanide – N (%)	1711 (3)	814 (8)		700 (3)	809 (7)	
Torasemide – N (%)	56 (<1)	11 (<1)		20 (<1)	11 (<1)	

Legend

† - as a percentage of those with Read code at index date in control group 1 (diagnosed with HF in primary care); ‡ - as a percentage of those who had recorded symptoms 1 month before the index date

Table 2 – Patient characteristics analysis B

	Unmatched			Matched		
	Loop diuretic group Loop diuretic N=59694	**At-risk group** HF risk factors N=57219	**p-value**	**Loop diuretic group** Loop diuretic N=39339	**At-risk group** HF risk factors N=39339	**p-value**
Demographics						
Age (years)	74 (62 – 83)	64 (54 – 72)	<0.001	68 (58 – 76)	68 (58 – 76)	1.00
Sex (male) – N (%)	22575 (38)	33771 (59)	<0.001	17226 (44)	17226 (44)	1.00
BMI (m/kg^2)	27 (24 – 31)	28 (25 – 31)	<0.001	28 (24 – 32)	27 (25 – 31)	<0.001
Missing – N (%)	5563 (9)	2686 (5)		2576 (7)	1781 (5)	
Current Smoker – N (%)	15292 (26)	17168 (30)	<0.001	12524 (32)	10886 (28)	<0.001
Ex-Smoker – N (%)	11354 (19)	9679 (17)		6599 (17)	6131 (16)	
Never Smoked – N (%)	32696 (55)	30101 (53)		20013 (51)	22097 (56)	
Missing – N (%)	352 (<1)	271 (<1)		203 (<1)	225 (<1)	
Co-morbidities						
Atrial fibrillation – N (%)	6481 (11)	2250 (4)	<0.001	3414 (9)	1855 (5)	<0.001
Chronic kidney disease – N (%)	12035 (20)	6818 (12)	<0.001	6445 (16)	5897 (15)	<0.001
COPD – N (%)	6752 (11)	3306 (6)	<0.001	4686 (12)	2604 (7)	<0.001
Diabetes mellitus – N (%)	10563 (18)	37544 (66)	<0.001	7391 (19)	26130 (66)	<0.001
Hypertension – N (%)	31173 (52)	44026 (77)	<0.001	19828 (50)	31082 (79)	<0.001
Ischaemic heart disease – N (%)	9071 (15)	23844 (42)	<0.001	5484 (14)	16289 (41)	<0.001
Stroke – N (%)	5443 (9)	4155 (7)	<0.001	2905 (7)	3207 (8)	<0.001
$\geq$3 of the above – N (%)	24257 (41)	44531 (78)	<0.001	14639 (37)	31476 (80)	<0.001
Medications						
ACEI or ARB – N (%)	21515 (36)	29314 (51)	<0.001	14111 (36)	19503 (50)	<0.001
Beta-blocker – N (%)	7831 (13)	12133 (21)	<0.001	4848 (12)	7992 (20)	<0.001
MRA – N (%)	2236 (4)	475 (1)	<0.001	1685 (4)	325 (1)	<0.001

Legend

Abbreviations used: BMI – body mass index; HF – heart failure; COPD – chronic obstructive pulmonary disease; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist

Table 3 – Outcomes in analyses A and B

Analysis A							
	Loop diuretic group N=22288	**HF group N=22288**	**p-value**	**Univariable Cox regression**		**Multivariable Cox regression**	
				HR	**p-value**	**HR**	**p-value**
HF event	**16037 (71.9)**	**16078 (72.1)**	**0.67**	0.92 (0.90 – 0.94)	**<0.001**	0.94 (0.92 – 0.96)	**<0.001**
HF symptom in primary care	*8279 (37.1)*	*6205 (27.8)*	*<0.001*	-	-	-	-
HF hospitalisation	*427 (1.9)*	*893 (4.0)*	*<0.001*	-	-	-	-
All-cause mortality	*12404 (55.6)*	*13659 (61.2)*	*<0.001*	-	-	-	-
HF hospitalisation or all-cause mortality	**12541 (56.3)**	**14074 (63.1)**	**<0.001**	0.76 (0.75 – 0.78)	<0.001	0.74 (0.72 – 0.76)	<0.001
HF hospitalisation	*427 (1.9)*	*893 (4.0)*	*<0.001*	-	-	-	-
All-cause mortality	*12404 (55.6)*	*13659 (61.2)*	*<0.001*	-	-	-	-
All-cause hospitalisation or all-cause mortality	**15091 (67.7)**	**15941 (71.5)**	**<0.001**	0.84 (0.82 – 0.86)	<0.001	0.83 (0.81 – 0.85)	<0.001
All-cause hospitalisation	*6137 (27.5)*	*5136 (23.0)*	*<0.001*	-	-	-	-
All-cause mortality	*12404 (55.6)*	*13659 (61.2)*	*<0.001*	-	-	-	-
Analysis B							
	Loop diuretic group N=39339	**At-risk group N=39339**	**p-value**	**Univariable Cox regression**		**Multivariable Cox regression**	
				HR	**p-value**	**HR**	**p-value**
Incident HF	**1497 (3.8)**	**608 (1.5)**	**<0.001**	**-**	**-**	**-**	**-**
Primary care	*1216 (81.2)*	*473 (77.8)*	*0.07*	**-**	**-**	**-**	**-**
Secondary care†	*281 (18.8)*	*135 (22.2)*		**-**	**-**	**-**	**-**
Investigations and referrals for suspected HF‡	**4055 (10.3)**	**2556 (6.5)**	**<0.001**	**-**	**-**	**-**	**-**
Natriuretic peptide testing	*1913 (4.8)*	*674 (1.7)*	*<0.001*	**-**	**-**	**-**	**-**
Echocardiography	*654 (1.7)*	*433 (1.1)*	*<0.001*	**-**	**-**	**-**	**-**
Out-patient cardiology referral	*2226 (5.6)*	*1718 (4.4)*	*<0.001*	**-**	**-**	**-**	**-**
HF event	**23303 (59.2)**	**14059 (35.7)**	**<0.001**	2.04 (2.00 – 2.08)	P<0.001	1.69 (1.62 – 1.76)	P<0.001
Presentation with HF symptom in primary care	*14148 (35.9)*	*7798 (19.8)*	*<0.001*				
Incident HF	*1497 (3.8)*	*608 (1.5)*	*<0.001*				
All-cause mortality	*15023 (38.1)*	*8247 (20.9)*	*<0.001*				
HF hospitalisation or all-cause mortality	**15206 (38.6)**	**8328 (21.1)**	**<0.001**	2.06 (2.01 – 2.12)	**<0.001**	1.86 (1.77 – 1.95)	**<0.001**

HF hospitalisation	*334 (0.8)*	*145 (0.4)*	*<0.001*				
All-cause mortality	*15023 (38.1)*	*8247 (20.9)*	*<0.001*				
All-cause hospitalisation or all-cause mortality	20328 (51.6)	13415 (34.0)	**<0.001**	1.87 (1.81 – 1.94)	<0.001	1.69 (1.63 – 1.75)	<0.001
All-cause hospitalisation	*7483 (19.0)*	*6918 (17.5)*	*<0.001*				
All-cause mortality	*15023 (38.1)*	*8247 (20.9)*	*<0.001*				

Legend

† - First diagnosis of HF made after hospitalisation; different to HF hospitalisation as an endpoint. ‡ - occurring after 3 month exclusion window.

Abbreviations used: HF – heart failure

Table 4 - Uni- and multivariable Cox regression for heart failure events in analyses A and B

Variable	Analysis A					Analysis B				
	Univariable			Multivariable		Univariable			Multivariable	
	HR (95% CI)	χ^2 (Wald)	P-value	HR (95% CI)	P-value	HR (95% CI)	χ^2 (Wald)	P-value	HR (95% CI)	P-value
Loop diuretic group (vs. HF group)	0.92 (0.90 – 0.94)	26	<0.001	0.94 (0.92 – 0.96)	<0.001					
Loop diuretic group (vs. at-risk group)						2.04 (2.00 – 2.08)	4442	<0.001	1.69 (1.62 – 1.76)	<0.001
Age - per year older	1.04 (1.04 – 1.04)	5938	<0.001	1.04 (1.04 – 1.04)	<0.001	1.04 (1.04 – 1.04)	8106	<0.001	1.04 (1.03 – 1.04)	<0.001
Sex (female vs. male)	1.00 (0.91 – 1.02)	0	0.90			1.09 (1.07 – 1.11)	67	<0.001		
BMI – per m/kg^2 increment	0.99 (0.98 – 0.99)	223	<0.001			0.98 (0.98 – 098)	396	<0.001		
Smoker (vs. ex- or never)	1.06 (1.02 – 1.09)	100	<0.001	1.20 (1.16 – 1.24)	<0.001	0.99 (0.96 – 1.02)	1	0.35		
Atrial fibrillation (vs. no atrial fibrillation)	1.27 (1.24 – 1.30)	343	<0.001	1.03 (1.01 – 1.06)	0.01	1.59 (1.53 – 1.65)	575	<0.001	1.15 (1.09 – 1.22)	<0.001
CKD (vs. no CKD)	1.52 (1.48 – 1.55)	1261	<0.001	1.13 (1.10 – 1.16)	<0.001	1.55 (1.51 – 1.59)	1279	<0.001	1.14 (1.09 – 1.18)	<0.001
COPD (vs. no COPD)	1.96 (1.91 – 2.02)	2176	<0.001	1.70 (1.65 – 1.76)	<0.001	3.46 (3.37 – 3.55)	8485	<0.001	2.55 (2.44 – 2.66)	<0.001
Diabetes (vs. no diabetes)	1.15 (1.12 – 1.17)	112	<0.001	1.14 (1.11 – 1.17)	<0.001	0.69 (0.68 – 0.71)	1227	<0.001		
Hypertension (vs. no hypertension)	1.27 (1.24 – 1.30)	459	<0.001			0.92 (0.90 – 0.94)	73	<0.001		
IHD (vs. no IHD)	1.22 91.19 – 1.25)	286	<0.001			0.71 (0.67 – 0.75)	135	<0.001	0.92 (0.86 – 0.98)	0.01
Stroke or TIA (vs. no stroke or TIA)	1.41 (1.37 – 1.46)	489	<0.001	1.14 (1.10 – 1.17)	<0.001	1.57 (1.52 – 1.62)	760	<0.001	1.15 (1.10 – 1.21)	<0.001
ACEI or ARB (vs. no ACEI or ARB)	1.05 (1.03 – 1.08)	23	<0.001	0.91 (0.89 – 0.93)	<0.001	0.93 (0.91 – 0.94)	60	<0.001		
Beta-blocker (vs. no beta-blocker)	0.98 (0.96 – 1.01)	2	0.15			0.99 (0.96 – 1.01)	1	0.25		
MRA (vs. no MRA)	1.24 (1.19 – 1.29)	109	<0.001	1.18 (1.13 – 1.23)	<0.001	1.83 (1.73 – 1.93)	481	<0.001	1.18 (1.05 – 1.32)	0.004

Legend

All variables with univariable associations with a heart failure event with P<0.1 (an arbitrary cut off) were included in the multivariable analysis. Variables that were entered into the multivariable model but that were not associated with outcome in multivariable analysis were not recorded. Variables included

in the multivariable model for analysis A were: age; BMI; smoker (vs. ex- or never); atrial fibrillation (vs. no atrial fibrillation); CKD (vs. no CKD); COPD (vs. no COPD); diabetes (vs. no diabetes); hypertension (vs. no hypertension); IHD (vs. no IHD); stroke or TIA (vs. no stroke or TIA); ACEI or ARB (vs. no ACEI or ARB); MRA (vs. no MRA). Variables included in the multivariable model for analysis B were: age; BMI; sex (female vs. male); atrial fibrillation (vs. no atrial fibrillation); CKD (vs. no CKD); COPD (vs. no COPD); diabetes (vs. no diabetes); hypertension (vs. no hypertension); IHD (vs. no IHD); stroke or TIA (vs. no stroke or TIA); ACEI or ARB (vs. no ACEI or ARB); MRA (vs. no MRA). Abbreviations used: BMI – body mass index; CKD – chronic kidney disease; COPD – chronic obstructive pulmonary disease; IHD – ischaemic heart disease; TIA – transient ischaemic attack; ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; MRA – mineralocorticoid receptor antagonist.

Discussion

Using a large, representative sample of patients in primary care, we found that patients who are prescribed a loop diuretic but who do not have a recorded diagnosis of HF have a high rate of HF-related events: similar to that of those with a confirmed diagnosis of HF, and nearly twice that of age- and sex-matched patients with risk factors for developing HF. During the 5 year index period of our study (2010-2015), there were over twice as many patients prescribed a loop diuretic without a recorded diagnosis of HF than were given a formal diagnosis of HF. Contrasting the results of analysis A to analysis B, patients prescribed a loop diuretic are far more similar to patients with a recorded diagnosis HF in terms of symptom burden and outcome than they are to patients with risk factors for HF: undiagnosed or "un-coded" heart failure may account for many of the loop diuretic prescriptions.

Patients prescribed a loop diuretic without a diagnosis of HF

The demographics of patients prescribed a loop diuretic without a recorded diagnosis of HF, and those with a recorded HF in this study are similar to those of patients with HF and a normal ejection fraction (HeFNEF): the majority were female, aged over 70 with multiple co-morbidities; of which, AF, CKD and hypertension were the most common, while IHD was uncommon.[19,20]

While we cannot infer what proportion of patients in the loop diuretic group had underlying HF as a cause of their symptoms, as a group they were more likely than patients *with* HF to present to their GP with symptoms, and only marginally less likely to be admitted to hospital or die.

Defining heart failure

The benefits of establishing a diagnosis of HF for the individual are numerous: in the case of HF with a reduced ejection fraction (HeFREF), there are multiple medical and device treatments which can enormously reduce the chance of serious morbidity, and prolong life.[21] In the case of HeFNEF, which may account for approximately half of all HF diagnoses,[22] treatment with sodium glucose co-transporter 2 inhibitors can reduce morbidity related to HF.[23,24] Regardless of HF phenotype, establishing a diagnosis provides clarity to the patient, and removes clinical uncertainty for the non-specialist which may prevent delays to treatment.[25]

The benefits of establishing a diagnosis of HF for the wider community are also numerous: having a proper understanding of the epidemiology of heart failure is essential for planning health care services. Establishing the diagnosis in the community is associated with lower healthcare costs and better clinical outcomes.[26] However, the proportion of patients who receive their HF diagnosis in the community is decreasing;[26-28], the most recent data suggest that up to 80% of patients receive their diagnosis only after hospitalisation with HF.[28] This may be due to the requirement for preliminary investigations prior to specialist referral in order to make a diagnosis, leading to uncertainty before a diagnosis is confirmed or refuted. Potentially compounding the problem are the diverse and complex diagnostic criteria, particularly for HeFNEF.[1]

The symptoms of congestion are often, quite reasonably, treated before a definitive diagnosis is made. However, very few of the patients prescribed a loop diuretic had had appropriate investigations during 10 years' follow up. In contrast, the majority of patients with a diagnosis of HF have some form of investigation or referral before a diagnosis is made, regardless of the setting in which it is made.[28]

Can we rely on coding?

We found that only 1 in 5 patients who were prescribed a loop diuretic or were given a diagnosis of HF were coded as having an attendance with symptoms of HF in the month prior to the index date (including on the index date itself), which seems surprising and may represent absent coding. General practitioners (GPs) in the UK are financially incentivised via Quality Outcomes Framework to keep and maintain a register of patients within their practice population with a HF diagnosis.[12] While absent coding may account for some of the "missing" patients in our analysis, this may only affect a minority of patients.[14]

Estimates of the prevalence of HF in community settings varying greatly depending on the methods of diagnosis, and the populations studied.[6-11] Using clinical coding in the general population, the prevalence of HF in the UK is estimated as 1.4%.[6] If even a small proportion of patients prescribed a loop diuretic had underlying HF, regardless of whether it was *clinically* recognised by the clinician, using clinical coding to estimate prevalence would be an underestimation. Consequently, planning for and funding of HF services is unlikely to be adequate.

Clinical implications

The widespread use of loop diuretics without further investigations is an impediment to a timely diagnosis of heart failure. There are many cardiovascular medications which require blood tests (renal function or serum electrolyte concentrations, for example) to be checked prior to initiation. We believe that mandating measurement of natriuretic peptide concentrations prior to initiation of loop diuretics is necessary, clinically appropriate, straightforward to implement, and may improve care.

Patients with HF are being missed at present and, as a consequence, potentially not receiving life prolonging and symptom relieving medication. The wider health care economy is not receiving the benefits of early appropriate treatment that reduces the risk of hospitalisation and which would improve our understanding of HF epidemiology, allowing better planning and funding of HF services. A nationwide effort to review all patients currently taking loop diuretics without a diagnosis of HF may find many patients with a treatable condition who stand to gain much from their diagnosis.

Limitations

We had incomplete clinical information in the available electronic health records. Absent coding may account for the majority of missed diagnoses in patients prescribed a loop diuretic without a diagnosis of HF.[14] If this finding is generalizable to the data from the CPRD, our findings are all the more important. If the absence of a clinical code does not mean the absence of the disease, then epidemiological reports using electronic data are destined to under-estimate prevalence. However, the positive predictive value of a diagnosis recorded in CPRD being clinically present is approximately 89%.[29]

It is likely that some patients in the loop diuretic group would have been prescribed a loop diuretic for the treatment of other causes of peripheral oedema such as hypoalbuminaemia, lymphoedema, or venous stasis – the pattern of symptoms before the index date were notably different for those in the loop diuretic group compared to those in the HF group.

We acknowledge a degree of immortal time bias affecting patients in the HF group. Although 50% of patients were recorded as being on a loop diuretic at the time of the heart failure diagnosis, approximately 25% were taking a loop diuretic *before* the diagnosis was made (25% started a loop diuretic at the same time as the heart failure diagnosis).

Although we used propensity matching and multi-variable Cox-regression analyses we cannot account for unmeasured clinical variables that may confound the results.

Conclusion

Patients who are prescribed a loop diuretic without a recorded diagnosis of heart failure are at high risk of HF-related events over long term follow up. Many patients in the community may have unrecognised HF. This has profound implications for our understanding of HF epidemiology.

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Contributorship

JJC, IS, SJL, ALC conceived the project. JJC and IS performed data cleansing and analysis. JC and JT were responsible for data handling and governance. JJC, SJL, AF, IS and ALC drafted the manuscript.

Competing interests

None.

Figure Legends

Figure 1

Title: Cohort flow diagram and exclusion criteria

Caption: Abbreviations used: CPRD – clinical practice research datalink; IHD – ischaemic heart disease; DM – diabetes mellitus; HTN – hypertension; HF – heart failure.

Figure 2

Title: Risk of HF event in patients taking a loop diuretic without a diagnosis of HF (loop diuretic group) compared to those with a HF diagnosis (HF group)

Caption: Abbreviations used: HF – heart failure; HR – hazard ratio

Figure 3

Title: Risk of HF event in patients taking a loop diuretic without a diagnosis of HF (loop diuretic group) compared to patients with HF risk factors (at-risk group)

Caption: Abbreviations used: HF – heart failure; HR – hazard ratio

Supplementary Figure 1

Title: Risk of HF hospitalisation or all-cause mortality in patients taking a loop diuretic without a diagnosis of HF (loop diuretic group) compared to those with a HF diagnosis (HF group)

Caption: Abbreviations used: HF – heart failure; HR – hazard ratio

Supplementary figure 2

Title: Risk of all-cause hospitalisation or mortality in patients taking a loop diuretic without a diagnosis of HF (loop diuretic group) compared to those with a HF diagnosis (HF group)

Caption: Abbreviations used: HF – heart failure; HR – hazard ratio

Supplementary figure 3

Title: Risk of HF hospitalisation or all-cause mortality in patients taking a loop diuretic without a diagnosis of HF (loop diuretic group) compared to patients with HF risk factors (at-risk group)

Caption: Abbreviations used: HF – heart failure; HR – hazard ratio

Supplementary figure 4

Title: Risk of all-cause hospitalisation or mortality in patients taking a loop diuretic without a diagnosis of HF (loop diuretic group) compared to patients with HF risk factors (at-risk group)

Caption: Abbreviations used: HF – heart failure; HR – hazard ratio

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