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Development of hypotension in patients newly diagnosed with heart failure in UK general practice: retrospective cohort and nested case–control analyses

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ABSTRACT

Objectives Hypotension is of particular relevance for patients with heart failure (HF), since almost all HF drugs cause lowering of blood pressure (BP) and it is associated with a poor prognosis. We aimed to investigate hypotension incidence and risk factors in patients with incident HF in the UK.

Design Retrospective cohort study including nested case–control analyses.

Setting The Health Improvement Network UK primary care database.

Participants 18 677 adult patients with incident HF during 2000–2005 were followed and cases of hypotension (systolic BP ≤90 mm Hg) were identified. Controls were age-matched, sex-matched and date-matched to cases (1:2).

Primary and secondary outcome measures We estimated hypotension incidence in the full study population and relevant subgroups (eg, sex and age). Potential risk factors for hypotension overall and for multiple versus single hypotensive episodes were evaluated using conditional logistic regression and unconditional regression models, respectively.

Results During a mean follow-up of 3.31 years, 2565 patients (13.7%) developed hypotension. The incidence of hypotension was 3.17 cases per 100 patient years (95% confidence interval (CI): 3.05–3.30), and was markedly increased in women aged 18–39 years (n=32; 17.72 cases per 100 patient-years; 95% CI: 9.69–29.73). Hypotension risk factors included high healthcare utilisation (proxy measure for HF severity and general comorbidity; eg, ≥10 primary care physician visits versus none, odds ratio (OR): 2.29; 95% CI: 1.34–3.90), previous hypotensive episodes (OR: 2.32; 95% CI: 1.84–2.92), renal failure and use of aldosterone antagonists, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Risk factors identified for hypotension generally overlapped with those for multiple versus single hypotensive episodes.

Conclusions Hypotension occurs frequently in patients with incident HF. Our findings may help identify patients most likely to benefit from close BP monitoring. The increased incidence of hypotension in young women with HF requires investigation.

Strengths and limitations of this study

- We have analysed hypotension incidence and risk factors in a large real-world cohort of patients with incident heart failure in UK primary care.
- Data are from The Health Improvement Network database, which has been extensively validated for use in pharmacoepidemiology.
- Since blood pressure is not systematically tested in routine clinical practice, we cannot rule out some detection bias.
- Due to the nature of data collection during routine clinical practice, we were unable to identify reliably the subgroup of cases with orthostatic hypotension, it was unclear if diagnoses of heart failure were made according to guidelines, and data on heart failure severity and ejection fraction were not complete for all patients.

INTRODUCTION

Almost all disease-modifying treatments for heart failure (HF) reduce blood pressure (BP),[1] and hypotension may also be caused by severe reductions in cardiac output.[2] Hypotension is therefore relevant in HF, and can prevent patients from receiving HF therapies.[3] In patients with HF and reduced ejection fraction (HFrEF), low BP is associated with poor prognosis.[4 5] However, it is unclear whether the poor outcomes in patients with HF and hypotension are caused by the hypotension itself or by the failure to meet guideline recommendations for therapy.[3]

Hypotension is generally defined as systolic BP (SBP) <90 mm Hg and/or diastolic BP <60 mm Hg,[6] and can be asymptomatic or symptomatic. Signs and symptoms of hypotension include dizziness or lightheadedness, syncope, lack of concentration, blurred vision, nausea, fatigue, general weakness, depression, pale skin, and palpitations.[2 6 7]

Patients with HF and hypotension are not well represented in clinical trials.[1] Major clinical trials of medications for chronic HFrEF

have commonly excluded patients with low SBP and/or symptoms of hypotension[1]; therefore, the incidence of hypotension in these studies may not reflect the real-world burden of disease. Population-based data on the incidence of hypotension and the role of risk factors in patients newly diagnosed with HF in routine clinical practice are sparse.

We therefore aimed to investigate the incidence of hypotension (both symptomatic and asymptomatic unless otherwise specified) and to identify risk factors for hypotension in patients newly diagnosed with HF in primary care in the UK.

METHODS

This study has a retrospective cohort design including nested case–control analyses using data from The Health Improvement Network primary care database (THIN) in the UK.

Data source

THIN is a primary care database of anonymised patient medical records in the UK, which is representative of the whole population in terms of age, sex, and geographic distribution.[8 9] The computerised information in THIN includes demographics, details from primary care physician (PCP) visits, diagnostic and treatment information from specialist referrals and hospital admissions, results of laboratory tests, prescriptions, and a free text section. The Read classification is used to code specific diagnoses as reasons for each consultation,[10] and a drug dictionary based on data from the Gemscript classification is used to record prescriptions.[11] THIN has been extensively validated for use in pharmacoepidemiology.[12]

Patient and public involvement

This research (which was based on anonymised patient records in THIN) was done without direct patient involvement. There was no patient input in the study design, interpretation of the results or drafting of the manuscript.

Study cohort and case ascertainment

Our initial HF cohort comprised all patients in THIN aged 1–89 years between 1 January 2000 and 31 December 2005 with a first ever diagnosis of HF, excluding those with first diagnosis of HF recorded at death or post-mortem. Patients with HF were identified by automated computer searches for HF Read codes, and a semi-automatic review of patient records was undertaken to obtain data on symptoms, signs and diagnostic tests. At the time of diagnosis, approximately half (54.1%) of the patients were ambulatory and managed by a PCP only, while 27.3% were referred to a consultant and 18.6% had a related hospitalisation.[13] In a random sample of the HF cohort (n=200), 84% had the diagnosis of incident HF validated by their PCP via a questionnaire.[13] From this cohort, we selected individuals aged 18–89 years and excluded those with a record of cancer before the entry date (the date of the initial diagnosis of HF), leaving a final study cohort of 18 677 patients newly diagnosed with HF. All study cohort members were followed from their entry date until the earliest occurrence of one of the following endpoints: first recorded episode of hypotension, reaching 90 years of age, death, cancer, or the end of the study period (May 2016). We defined hypotension as SBP ≤90 mm Hg recorded during follow-up, with or without symptoms. We focused on systolic hypotension, since SBP rather than diastolic BP is frequently used as the decision criterion in clinical trials[1] and observational studies[3] and SBP is more strongly associated with outcome than diastolic BP in observational studies.[5] The date when hypotension was detected was marked as the index date.

Patients with noticeable symptoms usually associated with hypotension (listed in the Introduction), recorded within 7 days before or after the index date, were classified as symptomatic cases. We also ascertained the number of patients with multiple episodes of hypotension during follow-up (we required ≥7 days between different episodes).

Data collection

For the cohort analyses, we obtained information on age and hospital/referral status at the time of HF diagnosis (start date), sex, and hypotension antecedents (ie, episodes of hypotension at any time prior to the start date using the same operational definition as for case ascertainment).

For case–control analyses, we obtained information on body mass index (BMI) and lifestyle factors (smoking status and weekly alcohol consumption) at any time before the index date, and healthcare utilisation (number of PCP visits, referrals and hospitalisations) in the year before the index date. We also extracted information on a range of comorbidities (infections in the 3 months before the index date; anaemia, depression, anxiety and sleep disorders in the year before the index date; and other comorbidities at any time before the index date). Renal function in THIN was ascertained by searching for serum creatinine measurements recorded at any time before the index date and taking the closest valid serum creatinine value. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[14] Information on the use of prescribed medications was determined between the start date and the index date and classified into four mutually exclusive time windows: current use (most recent prescription lasted until the index date or ended in the 30 days before the index date); recent use (finished between 31 and 365 days before the index date); past use (finished more than 365 days before the index date); and never use (no recorded use at any time between the start date and index date). We also analysed the effect of treatment duration (<30 days, 1–3 months, >3–12 months, and >1 year) on the risk of hypotension in current users of cardiovascular drugs. Furthermore, we assessed the risk of hypotension in treatment-naïve current users of

angiotensin-converting enzyme (ACE) inhibitors (overall and according to treatment duration). We considered ACE inhibitor users to be treatment-naïve if they had ≥1 year between the last prescription written before the start date and the first prescription after the start date.

Statistical analyses

Cohort analyses for hypotension

We estimated the incidence rate (95% confidence interval (CI)) of hypotension in the cohort of patients newly diagnosed with HF overall and stratified by sex, age group, hospital/referral status at HF diagnosis, and hypotension antecedents. The risk of hypotension (hazard ratio (HR)) associated with sex and age was estimated by Cox regression modelling adjusted by age or sex as well as calendar year, PCP visits in the year before the start date, smoking, alcohol consumption, prior history of ischaemic heart disease, atrial fibrillation, peripheral venous disease, valvular disease, arterial hypertension, hyperlipidaemia, diabetes, renal failure, prior hypotension, and use of diuretics, beta-blockers, ACE inhibitors, angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs; all variables measured at the start date). Kaplan-Meier curves of patients stratified by hypotension antecedents were compared using the log-rank test.

Nested case–control analysis of hypotension

Individuals with an incident episode of hypotension (SBP ≤90 mm Hg) were cases. To select controls for each case, we performed a search on the index date for two individuals in the cohort of patients newly diagnosed with HF who were age-matched and sex-matched to the case. For 14 cases two matched controls could not be found; these 14 cases were therefore excluded from the analysis. We thus selected 5102 control patients. As this sampling method allows the control group to include future cases, there were 763 patients who were cases as well as being controls on a date before the occurrence of hypotension.

We computed odds ratios (OR) and 95% CI for the association of hypotension with potential risk factors using conditional logistic regression models, adjusted for healthcare utilisation and cardiovascular comedication and comorbidity.

In a secondary analysis, we ran unconditional regression models comparing cases who had multiple episodes of hypotension during the follow-up with cases who had only one episode of hypotension (considered as controls for this analysis). The multivariable regression model included the following variables: sex, age, PCP visits within the year before the index date, and the time interval between the start date and the index date.

RESULTS

Characteristics of patients with HF who developed hypotension

In the HF cohort (n=18 677), 2565 patients (13.7%) developed ≥1 episode of hypotension over a mean ±standard deviation follow-up period of 3.31±3.97 years (median: 3.12 years; interquartile range: 0.96–6.86). Most of the cases were male (table 1), and 69.6% were aged ≥70 years at the index date (mean age: 73.3±10.8 years). Also, 1041 (40.6%) of the cases had recurrent hypotension during follow-up (mean number of recurrent episodes: 2.79±3.08), and 288 (11.2%) had symptomatic hypotension. The most common symptoms were dizziness related (table 1).

Table 1 Characteristics of patients newly diagnosed with heart failure who developed hypotension

	Cases with hypotension (n=2565)	
	n	%
Sex		
Male	1640	63.9
Female	925	36.1
Age, years		
18–39	28	1.1
40–49	53	2.1
50–59	204	8.0
60–69	496	19.3
70–79	949	37.0
≥80	835	32.6
Hypotension-related symptoms	288	11.2
Dizziness, giddiness, unsteadiness, lightheadedness	105	4.1
Fainting, syncope, collapse, blackout	52	2.0
Nausea, vomiting, malaise	50	1.9
Fatigue, drowsiness, tiredness, asthenia, lethargy	41	1.6
Depression, low mood	14	0.5
General weakness	12	0.5
Pale skin	5	0.2
Palpitations	9	0.4
Prior hypotension	219	8.5
1 episode	163	6.4
2–4 episodes	45	1.8
≥5 episodes	11	0.4
Recurrent hypotension episodes during follow-up	1041	40.6
1 recurrent episode	485	18.9
2 recurrent episodes	189	7.4
3–5 recurrent episodes	246	9.6
6–9 recurrent episodes	84	3.3
≥10 recurrent episodes	37	1.4

Incidence rate of hypotension

The rates of overall and symptomatic hypotension in the HF cohort were 3.17 and 0.36 cases per 100 patient-years,

Table 2 Incidence of hypotension in patients newly diagnosed with HF

	Cases with hypotension (n=2565)	Person-time (years)	Incidence of hypotension per 100 patient-years*	95% CI
Overall hypotension	2565	80 840	3.17	3.05 to 3.30
Symptomatic hypotension only	288	80 840	0.36	0.32 to 0.40
Hospital/referral status at HF diagnosis				
Hospitalisation for HF	1263	45 683	4.05	3.71 to 4.42
Specialist referral	800	22 754	3.52	3.28 to 3.77
Primary care	502	12 403	2.76	2.61 to 2.92
Hypotension antecedents				
No	2346	78 881	2.97	2.86 to 3.10
≥1 episodes	219	1959	11.18	9.79 to 12.76

*Incidence rates are presented for overall (symptomatic and asymptomatic) hypotension unless otherwise specified.
CI, confidence interval; HF, heart failure.

respectively (table 2). Hypotension was recorded during the first year of follow-up in 789 cases (30.8%), yielding a rate of 5.04 cases per 100 patients in the first year after diagnosis of HF (95% CI: 4.70–5.40). The incidence rate of hypotension was relatively constant in all age groups in men, whereas in women the rate was highest in those aged 18–39 years (figure 1). Mean SBP within the 3 months before the start date was 117 mm Hg and 144 mm Hg in women aged 18–39 years and ≥40 years, respectively.

We observed a higher incidence rate in patients who were HF-hospitalised at the start date compared with those who were referred to a specialist or managed only by the PCP (table 2). The incidence rate was also significantly higher in patients with versus without hypotension antecedents (table 2). The increased rate in patients with hypotension antecedents was relatively constant over the duration of follow-up and became more pronounced with increasing number of hypotension antecedents (figure 2).

Risk factors for development of hypotension

Cohort analysis

Men had a significantly higher risk of developing hypotension than women (HR: 1.41; 95% CI: 1.29–1.54), and the risk of hypotension increased with decreasing age (HR (18–39 vs ≥80 years]: 1.72; 95% CI: 1.19–2.48).

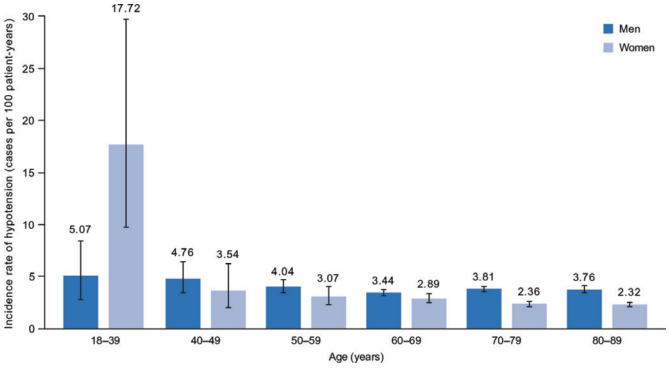

Figure 1 Incidence of hypotension in patients newly diagnosed with heart failure, stratified by age and sex.

Nested case–control analysis

We observed a significantly increased risk of hypotension in patients with high healthcare utilisation (table 3). Patients who were overweight (BMI: 25–29.99 kg/m^2) or obese (BMI: ≥30 kg/m^2) had a lower likelihood of hypotension than patients with normal BMI (20–24.99 kg/m^2). There were no significant associations with other lifestyle factors (online supplementary table S1).

Of the examined cardiovascular comorbidities (table 3 and online supplementary table S1), hypotension antecedents, ischaemic heart disease, valvular cardiac disease and hyperlipidaemia were associated with an increased risk of hypotension. As expected, hypertension was associated with a markedly decreased risk of hypotension. Renal failure was an independent predictor of hypotension, with the risk of hypotension increasing with decreasing eGFR. Other non-cardiovascular comorbidities including infections (respiratory and genitourinary), hypothyroidism, anaemia, liver disease, chronic obstructive pulmonary disease, depression, and dementia were associated with an increased risk of hypotension, and diabetes was associated with a decreased risk (table 3).

Of the evaluated cardiovascular medications (table 3 and online supplementary table S1–2), aldosterone antagonists, ACE inhibitors and ARBs were associated with the largest increases in the risk of hypotension (current versus never use). Current use of CCBs was associated with a reduced risk of hypotension. In current users of cardiovascular drugs, the period of greatest risk was generally the first month of treatment (online supplementary table S3). The effect of treatment duration was particularly marked in treatment-naïve current users of ACE inhibitors. Of the evaluated non-cardiovascular drugs (table 3 and online supplementary table S1), antidepressants and opioids were associated with an increased risk of

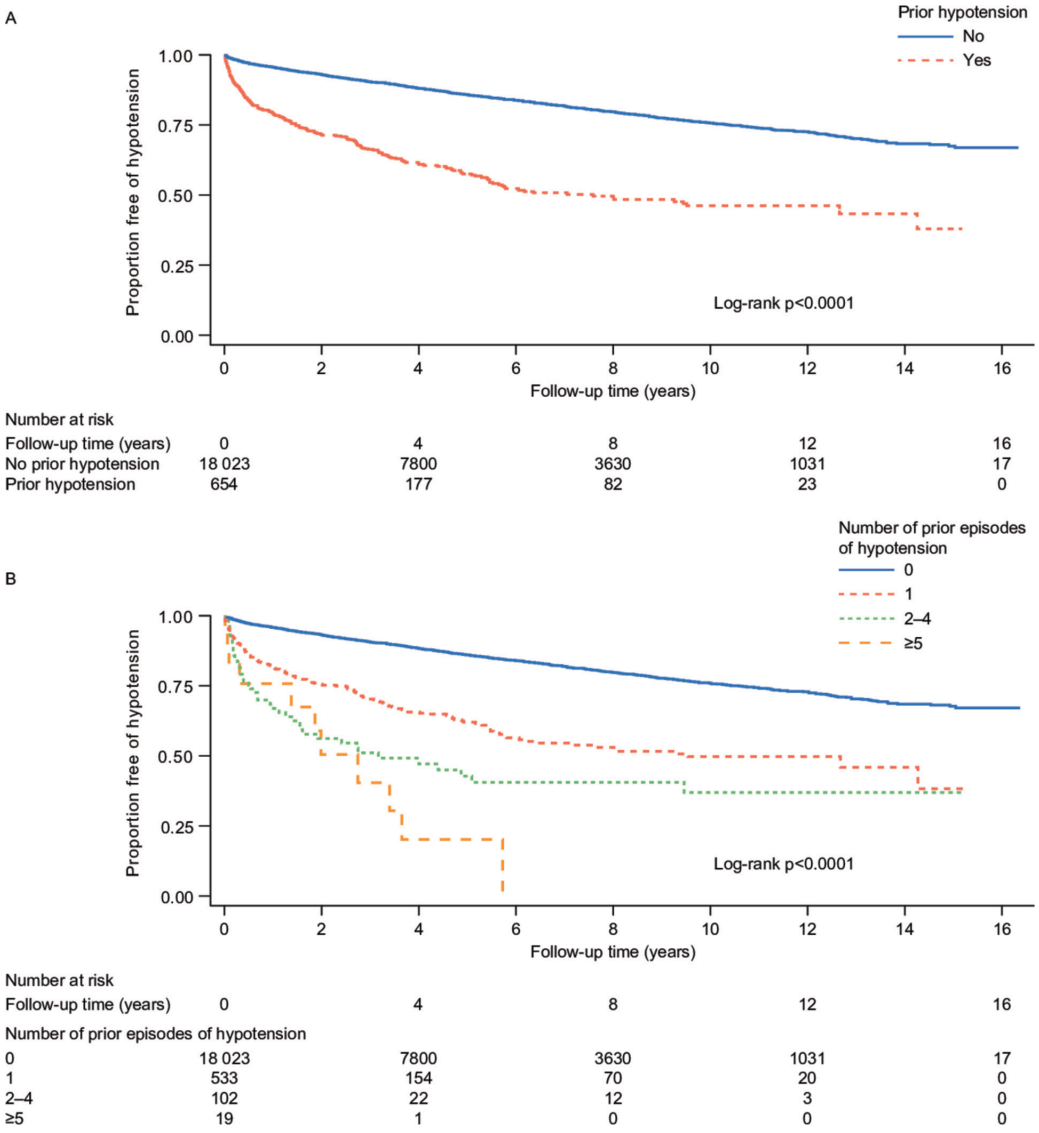

Figure 2 Kaplan–Meier estimates for development of hypotension in patients newly diagnosed with heart failure, stratified by (A) occurrence of hypotension before the heart failure diagnosis and (B) number of hypotension episodes before the heart failure diagnosis.

hypotension, and antidiabetic medications were associated with a decreased risk.

Secondary analysis: risk factors for multiple versus single episodes of hypotension

Male sex, young age, and hypotension antecedents (before entering the study) were important predictors of developing multiple versus single episodes of hypotension (online supplementary table S4). Obese patients were less likely than patients with normal BMI to develop multiple episodes of hypotension. Patients with ischaemic heart disease were at increased risk and patients with hypertension, anaemia or proteinuria were at decreased risk of having multiple episodes of hypotension. Significant associations between medication use and the risk of multiple episodes of hypotension are shown in online supplementary table S4.

DISCUSSION

Our analysis of a large, validated primary care database showed that hypotension occurs frequently in patients newly diagnosed with HF in the UK, and identified several patient characteristics associated with the development of hypotension.

Much of the available data on hypotension in patients with HF stems from clinical trials. However, clinical trials of HF drugs often excluded patients with low SBP and/or symptomatic hypotension,[1] those with severe comorbidities such as severe renal failure,[15 16] or those with late-stage HF. Consequently, lower incidences of hypotension could be expected in contemporary clinical trials compared with real-world clinical practice.[1]

In key successful clinical trials in chronic HFrEF, post-randomisation hypotension occurred in 0%–20% of patients in the control groups. The definition of

Table 3 Factors significantly associated with the development of hypotension in patients newly diagnosed with heart failure

	Controls (n=5102)		Cases with hypotension (n=2551)			
	n	%	n	%	OR*	95% CI
Lifestyle factors						
BMI (kg/m^2)						
11–19.99	221	4.3	155	6.1	1.20	0.94 to 1.54
20–24.99	1137	22.3	691	27.1	1	–
25–29.99	1701	33.3	817	32.0	0.76	0.66 to 0.88
≥30	1560	30.6	670	26.3	0.64	0.55 to 0.74
Unknown	483	9.5	218	8.5	0.73	0.59 to 0.90
Healthcare utilisation						
PCP visits†						
0–3	105	2.1	17	0.7	1	–
4–9	771	15.1	208	8.2	1.32	0.76 to 2.30
≥10	4226	82.8	2326	91.2	2.29	1.34 to 3.90
Referrals†						
None	1022	20.0	355	13.9	1	–
1–3	1900	37.2	873	34.2	1.20	1.02 to 1.41
≥4	2180	42.7	1323	51.9	1.41	1.20 to 1.65
Hospitalisations†						
None	3487	68.3	1409	55.2	1	–
≥1	1615	31.7	1142	44.8	1.53	1.37 to 1.71
Cardiovascular comorbidities‡						
Hypotension antecedents	160	3.1	210	8.2	2.32	1.84 to 2.92
1 episode	131	2.6	155	6.1	2.09	1.61 to 2.71
≥2 episodes	29	0.5	55	2.1	3.31	2.06 to 5.34
Ischaemic heart disease	2940	57.6	1688	66.2	1.36	1.22 to 1.53
Myocardial infarction	1519	29.8	1009	39.6	1.35	1.20 to 1.52
Stable angina	1671	32.8	967	37.9	1.14	1.01 to 1.28
Unstable angina	363	7.1	269	10.5	1.25	1.03 to 1.52
Valvular cardiac disease	612	12.0	378	14.8	1.19	1.03 to 1.38
Hyperlipidaemia	1419	27.8	800	31.4	1.15	1.02 to 1.30
Hypertension	3080	60.4	1255	49.2	0.59	0.52 to 0.66
Other specific comorbidities‡						
Renal failure§						
No (eGFR >60 mL/min/1.73 m^2)	1816	35.6	707	27.7	1	–
eGFR 45–59 mL/min/1.73 m^2	1324	26.0	648	25.4	1.16	1.00 to 1.33
eGFR 30–44 mL/min/1.73 m^2	1005	19.7	635	24.9	1.44	1.23 to 1.68
eGFR <30 mL/min/1.73 m^2	439	8.6	342	13.4	2.01	1.66 to 2.43
eGFR not recorded	518	10.2	219	8.6	1.23	0.99 to 1.52
Diabetes	1334	26.1	642	25.2	0.85	0.75 to 0.96
Infections¶						
Respiratory	497	9.7	2962	11.6	1.31	1.12 to 1.52
Genitourinary	114	2.2	91	3.6	1.64	1.21 to 2.23
Hypothyroidism	508	10.0	318	12.5	1.18	1.00 to 1.39
Anaemia¶	215	4.2	151	5.9	1.35	1.07 to 1.71

Continued

Table 3 Continued

	Controls (n=5102)		Cases with hypotension (n=2551)			
	n	%	n	%	OR*	95% CI
Liver disease	127	2.5	82	3.2	1.36	1.00 to 1.85
COPD	968	19.0	512	20.1	1.18	1.03 to 1.36
Depression¶	214	4.2	159	6.2	1.61	1.28 to 2.03
Dementia	117	2.3	77	3.0	1.55	1.12 to 2.16
Cardiovascular drugs**						
Diuretics††	3741	73.3	2138	83.8	1.49	1.24 to 1.80
Aldosterone antagonists	747	14.6	864	33.9	2.54	2.23 to 2.90
ACE inhibitors	2906	57.0	1665	65.3	1.68	1.44 to 1.95
ARBs	869	17.0	456	17.9	1.33	1.12 to 1.58
CCBs††	1130	22.1	398	15.6	0.77	0.67 to 0.89
Beta-blockers	1968	38.6	1155	45.3	1.14	1.01 to 1.29
Nitrates	1194	23.4	792	31.0	1.24	1.08 to 1.43
Other drugs**						
Antidepressants	740	14.5	484	19.0	1.36	1.18 to 1.57
Opioids	592	11.6	372	14.6	1.24	1.06 to 1.45
Antidiabetics	934	18.3	432	16.9	0.79	0.68 to 0.91

*The OR was adjusted for PCP visits, use of antihypertensive medications (thiazides and related diuretics, loop diuretics, aldosterone antagonists, ACE inhibitors, ARBs, CCBs, and beta-blockers), hypertension, renal failure, ischaemic heart disease, and valvular cardiac disease.
†Healthcare utilisation in the year before the index date was assessed.
‡The reference category was the absence of the corresponding comorbidity.
§Renal function was ascertained by searching for serum creatinine measurements any time before the index date and taking the closest valid serum creatinine value. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.
¶Anaemia and depression were assessed in the year before the index date and infections in the 3 months before the index date.
**Current use (0–30 days before the index date) was compared with never use as the reference category.
††Other subtypes of diuretics (thiazide and loop diuretics) and subtypes of CCBs (dihydropyridines and non-dihydropyridines (verapamil and diltiazem)) are presented in online supplementary table S2.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; PCP, primary care physician.

hypotension differed between the trials and BP monitoring was inconsistent.[1] However, the overall frequency of hypotension observed in our study (13.7%) lies well within this range.

There is sparse real-world evidence on the incidence of hypotension in patients with HF. In a Russian study of 199 patients with chronic HF followed for 24 months, arterial hypotension (BP ≤100/60 mm Hg) was identified in 6.5% of the patients based on measurements taken during medical visits, but this proportion rose to 65.8% when based on 24 hour BP monitoring (with hypotension defined as daytime BP ≤100/60 mm Hg or nocturnal BP ≤85/47 mm Hg).[17] In a US-based retrospective observational study of 104 patients with HF who began treatment with spironolactone, 7% developed hypotension (defined as SBP <90 mm Hg and a decrease in SBP by >15% from pre-treatment baseline).[18]

Our data showed that beta-blockers, ACE inhibitors, ARBs and aldosterone antagonists – drugs with well-known effects on BP[19] – are positively associated with hypotension in patients with HF. Beta-blockers are expected to lower BP owing to their vasodilatory effects,[16] but were associated with only a slightly increased risk of hypotension in our study. The increased risk of hypotension associated with ACE inhibitors, ARBs or aldosterone agonists results from blockade of the renin–angiotensin–aldosterone system: ACE inhibitors reduce levels of angiotensin II and ARBs block signalling of angiotensin II via the angiotensin I receptor (thus reducing vasoconstriction and sodium chloride reabsorption), while aldosterone antagonists reduce sodium reabsorption and potassium secretion in distal tubules.[20] Hypotension was one of the most common adverse events in two pivotal trials of the ACE inhibitor enalapril in HF,[21 22] and ARBs are as likely as ACE inhibitors to cause hypotension.[23] Both ACE inhibitors and ARBs were associated with a <2-fold increased risk of hypotension in our study (current versus never use), and we found a greater increase in risk associated

with aldosterone antagonists (2.5-fold). A meta-analysis of 16 randomised controlled trials involving 31 429 patients with HF also showed that addition of ARBs to conventional therapy (including ACE inhibitors) significantly increased the rate of hypotension compared with placebo (rate ratio: 1.63; 95% CI: 1.30 to 2.62),[24] consistent with the association of increasing neurohormonal blockade with an increased risk of hypotension.[1 20] However, in contrast to our findings, the meta-analysis showed only a non-significant increase in the rate of hypotension with addition of aldosterone antagonists to conventional therapy (rate ratio: 1.35; 95% CI: 0.78–2.41). In the meta-analysis, the incidence of hypotension per 100 patient-years was 4.49 (95% CI: 3.34– 6.66), 3.66 (95% CI: 2.07–6.12) and 2.71 (95% CI: 2.11–3.30) in patients receiving ARBs, aldosterone antagonists and placebo, respectively.[24] We found a decreased risk of hypotension associated with CCB use; this is likely to be due to confounding by indication, because CCBs are usually indicated for hypertension. Although certain HF treatments are associated with an increased risk of hypotension, the previously reported benefits of these treatments (even in patients with low SBP)[3] must also be considered; careful up-titration to target doses with adjustment of other medications and management of comorbidities may help to optimise the benefit/risk balance.[25]

The incidence of hypotension in younger women (aged 18–39 years) with HF was much higher than the overall incidence in our study (figure 1). To the best of our knowledge, this has not been described before. While this result should be interpreted cautiously based on the small number of women in this age group (n=32), it is interesting to note that the same group also showed an elevated risk of ischaemic cerebrovascular events in a previous investigation of this HF cohort,[26] and that orthostatic hypotension was identified as a risk factor for stroke in a meta-analysis of observational studies.[27] This finding thus deserves further evaluation.

In patients with HF, BP decreases with advancing pump failure; hypotension can thus be a sign of advanced or severe HF.[25] In our study, the severity of HF could not be measured directly, but different types of healthcare utilisation were assessed as proxy measures for HF severity and showed a clear positive association with hypotension.

We identified hypotension antecedents, ischaemic heart disease and hyperlipidaemia as risk factors for hypotension. These findings are consistent with results from the Organised Programme to Initiate Lifesaving Treatment in Hospitalised Patients with HF (OPTIMIZE-HF) registry[5] and the Efficacy of Vasopressin Antagonism in HF Outcome Study with Tolvaptan (EVEREST)[19] and Candesartan in HF: Assessment of Reduction in Mortality and Morbidity (CHARM)[28] clinical trials, in which ischaemic aetiology, hypercholesterolaemia and discontinuation due to hypotension were more common in patients with lower SBP. We also found a reduced risk of hypotension in patients with diabetes or receiving antidiabetic medication and in patients with hypertension; again, these results are consistent with the known association between diabetes and hypertension[29] and results from the EVEREST trial in patients with HF, in which diabetes and hypertension were less common in patients with lower SBP.[19] Male sex and young age were associated with an increased risk of hypotension in our study; the proportion of men also increased with decreasing SBP in OPTIMIZE-HF, EVEREST and CHARM, and age decreased with decreasing SBP in EVEREST and CHARM.[5 19 28] Obese or overweight patients in our study were less likely to develop hypotension than patients of normal weight, consistent with the well-known association between obesity and hypertension[30] and data from the general population suggesting that thinner individuals are more likely to have hypotension.[31] Hypotension has been associated with cognitive impairment in several previous studies[32] and was associated with dementia in our analysis. Orthostatic hypotension is also a symptom of Parkinson disease,[33] but we found no significant association between Parkinson disease and hypotension in patients with HF. We observed an increased risk of hypotension in patients with recent depression. Depression is a common clinical problem among patients with HF and has been associated with poor HF outcomes.[34] Furthermore, we found that hypotension during follow-up was related to other intervening medical events, such as anaemia. Other studies in patients with advanced HF showed that those with lower haemoglobin levels had lower blood pressure.[35 36] Several comorbidities, both cardiovascular and non-cardiovascular, have shown a statistically significant association with hypotension in patients with newly diagnosed HF; however, these associations may not reflect causal effects.

The risk factors we identified for hypotension generally overlapped with those for multiple versus single episodes of hypotension.

Limitations

Detection of hypotension depends on BP monitoring frequency,[17] thus we cannot rule out some detection bias. BP is not systematically recorded in routine clinical practice; however, any misclassification would be non-differential. On the other hand, as shown by study data, healthcare utilisation within the year before the index date was greater among cases than controls, which could increase the likelihood of having BP measured and therefore the possibility of having a hypotension episode detected. Nonetheless, the impact of this on hypotension ascertainment, if any, might be small, as the mean number of recorded BP measures within the year prior to the index date was only slightly higher in cases than in controls (3.5 vs 3.0). During the follow-up of patients in the HF cohort overall, all cases and most non-cases (86.3%) had at least one SBP value recorded between the first HF diagnosis date and the stop date. The mean number of BP records per patient was 11.8 for non-cases and 12.9 for cases.

Due to the nature of data collection during routine clinical practice, we were unable to identify reliably the

subgroup of cases with orthostatic hypotension. Data on HF severity were not complete for all patients. Therefore, we were only able to adjust for severity indirectly using healthcare utilisation as a proxy measure for overall comorbidity. Data on ejection fraction were also not systematically recorded, preventing us from differentiating between HFrEF and HF with preserved ejection fraction. It is unclear if diagnoses of HF were made according to guidelines,[37 38] because diagnostic test results are not systematically recorded in the database.

CONCLUSIONS

In a real-world cohort of 18 677 patients newly diagnosed with HF in the UK, the incidence of hypotension was 3.17 cases per 100 patient-years, and the risk was higher in men than in women. Patients with greater healthcare utilisation (a proxy measure for HF severity and general comorbidity) were at increased risk of developing hypotension, as were those with specific comorbidities including renal failure, ischaemic heart disease, hyperlipidaemia and anaemia, patients with hypotension antecedents and those taking certain medications including aldosterone antagonists, ACE inhibitors and ARBs. As our study is a population-based study in UK primary care with few exclusion criteria, our results should be generalisable to the broader UK population of patients with incident HF. The risk factors identified in this study may help to identify patients most likely to benefit from close BP monitoring. The markedly increased risk of hypotension (as well as ischaemic cerebrovascular events in a previous analysis)[26] in the small group of young women with HF deserves further evaluation.

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Patient consent for publication Not required. This study involved the use of anonymised patient medical records, which contained no information that could reasonably be used to identify people.

Ethics approval Data collection for THIN was approved by the South East Multicentre Research Ethics Committee (MREC) in 2003. The study protocol was approved by an independent Scientific Review Committee (reference number 16THIN086).

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