Supplementary materials

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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Supplementary tables

Table S1 Factors showing non-significant associations with the development of hypotension in patients newly diagnosed with heart failure

	Controls (n=5012)		Cases with hypotension (n=2551)			
	n	**%**	**n**	**%**	**OR***	**95%CI**
Lifestyle factors						
Alcohol, units/week						
None	1094	21.4	541	21.2	1	–
1–2	1535	30.1	818	32.1	1.08	0.93 to 1.25
3–15	1235	24.2	650	25.5	1.08	0.92 to 1.26
16–24	244	4.8	124	4.9	1.20	0.92 to 1.57
≥25	291	5.7	113	4.4	0.88	0.67 to 1.15
Unknown	703	13.8	305	12.0	0.92	0.77 to 1.11
Smoking status						
Non-smoker	1596	31.3	792	31.0	1	–
Smoker	751	14.7	368	14.4	1.05	0.89 to 1.25
Ex-smoker	2614	51.2	1336	52.4	0.97	0.86 to 1.10
Unknown	141	2.8	55	2.2	0.83	0.59 to 1.19

Cardiovascular comorbidities†						
Cerebrovascular disease	955	18.7	490	19.2	1.12	0.98 to 1.28
Ischaemic stroke	503	9.9	264	10.3	1.18	0.99 to 1.40
TIA	483	9.5	239	9.4	1.04	0.87 to 1.25
Haemorrhagic stroke	50	1.0	27	1.1	1.28	0.77 to 2.13
DVT or PE	570	11.2	320	12.5	1.13	0.96 to 1.33
Atrial fibrillation	1712	33.6	924	36.2	0.99	0.88 to 1.11
PAD (lower limb)	632	12.4	335	13.1	1.05	0.90 to 1.23
Other specific comorbidities†						
Proteinuria	370	7.3	178	7.0	0.95	0.77 to 1.16
Hyperthyroidism	128	2.5	91	3.6	1.32	0.99 to 1.77
Rheumatoid arthritis	217	4.3	105	4.1	0.93	0.71 to 1.20
Anxiety	861	16.9	445	17.4	1.01	0.88 to 1.16
Parkinson disease	83	1.6	46	1.8	1.18	0.79 to 1.77
Cardiovascular drugs‡						
Digoxin	1071	21.0	573	22.5	0.88	0.77 to 1.01
Anticoagulants§	1218	23.9	732	28.7	1.00	0.89 to 1.14
Antiplatelets	2678	52.5	1379	54.1	1.02	0.89 to 1.16
Antiarrhythmics	631	12.4	345	13.5	1.15	0.97 to 1.36
Statins	2631	51.6	1462	57.3	1.03	0.90 to 1.18

Other drugs‡						
Antibiotics	949	18.6	566	22.2	1.16	0.99 to 1.36
NSAIDs (not coxibs)	263	5.2	115	4.5	1.02	0.80 to 1.31
Coxibs	52	1.0	27	1.1	1.08	0.65 to 1.81
Oral and inhaled steroids	952	18.7	501	19.6	1.11	0.96 to 1.27
DMARDs	106	2.1	55	2.2	1.08	0.76 to 1.54
Immunosuppressants	31	0.6	19	0.7	1.28	0.69 to 2.38
Anxiolytics	139	2.7	83	3.3	0.94	0.69 to 1.28
Drugs for Parkinson disease	83	1.6	47	1.8	1.09	0.73 to 1.61
Levothyroxine	465	9.1	294	11.5	1.18	0.99 to 1.40
PDE5 inhibitors	31	0.6	13	0.5	0.91	0.44 to 1.87

*The OR was adjusted for primary care physician visits, use of antihypertensive medications (thiazides and related diuretics, loop diuretics, aldosterone antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers and beta-blockers), hypertension, renal failure, ischaemic heart disease and valvular cardiac disease.

†The reference category was absence of the corresponding comorbidity.

‡Current use (0–30 days before the index date) was compared with never use as the reference category.

§Anticoagulants included both oral and parenteral anticoagulants (vitamin K antagonists, non-vitamin K antagonist oral anticoagulants and low molecular weight heparins).

CI, confidence interval; coxib, cyclooxygenase-2 inhibitor; DMARD, disease-modifying anti-rheumatic drug; DVT, deep vein thrombosis; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PAD, peripheral arterial disease; PDE5, phosphodiesterase 5; PE, pulmonary embolism; TIA, transient ischaemic attack.

Table S2 Association of current use of subtypes of diuretics and CCBs (0–30 days before the index date) with development of hypotension in patients newly diagnosed with heart failure

	Controls (n=5012)		Cases with hypotension (n=2551)			
	n	**%**	**n**	**%**	**OR***	**95% CI**
Diuretics						
Thiazides and related diuretics	455	8.9	164	6.4	0.97	0.79 to 1.20
Loop diuretics	3359	65.8	2007	78.7	1.31	1.10 to 1.55
Aldosterone antagonists	747	14.6	864	33.9	2.54	2.23 to 2.90
CCBs						
Dihydropyridines	777	15.2	248	9.7	0.70	0.59 to 0.83
Non-dihydropyridines						
Verapamil	59	1.2	24	0.9	0.87	0.52 to 1.47
Diltiazem	300	5.9	128	5.0	0.92	0.73 to 1.17

*The OR (current use versus never use) was adjusted for primary care physician visits, use of antihypertensive medications (thiazides and related diuretics, loop diuretics, aldosterone antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, CCBs and beta-blockers), hypertension, renal failure, ischaemic heart disease and valvular disease.

CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio.

Table S3. Association of current cardiovascular drug use (0–30 days before the index date) with development of hypotension in patients newly diagnosed with heart failure, stratified by duration of treatment.

	Controls (n=5012)		**Cases with hypotension (n=2551)**			
	n	**%**	**n**	**%**	**OR***	**95% CI**
Cardiovascular drugs						
Thiazides and related diuretics						
<30 days	54	1.1	29	1.1	0.90	0.55 to 1.50
1–3 months	65	1.3	22	0.9	0.75	0.44 to 1.28
>3–12 months	112	2.2	51	2.0	1.16	0.80 to 1.69
>1 year	224	4.4	62	2.4	0.98	0.71 to 1.34
Loop diuretics						
<30 days	284	5.6	188	7.4	1.66	1.29 to 2.14
1–3 months	455	8.9	258	10.1	1.29	1.03 to 1.63
>3–12 months	1030	20.2	613	24.0	1.29	1.06 to 1.56
>1 year	1590	31.2	948	37.2	1.25	1.04 to 1.50
Aldosterone antagonists						
<30 days	103	2.0	138	5.4	3.06	2.30 to 4.06

1–3 months	134	2.6	186	7.3	2.97	2.31 to 3.81
>3–12 months	267	5.2	292	11.4	2.31	1.91 to 2.81
>1 year	243	4.8	248	9.7	2.32	1.88 to 2.86
ACE inhibitors						
<30 days	147	2.9	121	4.7	2.68	1.87 to 3.83
1–3 months	189	3.7	112	4.4	1.96	1.38 to 2.78
>3–12 months	413	8.1	245	9.6	1.65	1.27 to 2.14
>1 year	660	12.9	361	14.2	1.74	1.36 to 2.22
ARBs						
<30 days	54	1.1	40	1.6	1.52	0.97 to 2.38
1–3 months	67	1.3	49	1.9	1.68	1.10 to 2.57
>3–12 months	233	4.6	123	4.8	1.39	1.07 to 1.82
>1 year	515	10.1	244	9.6	1.21	0.98 to 1.50
CCBs						
<30 days	81	1.6	35	1.4	0.90	0.59 to 1.39
1–3 months	107	2.1	32	1.3	0.64	0.42 to 0.97
>3–12 months	289	5.7	104	4.1	0.77	0.60 to 0.99
>1 year	653	12.8	227	8.9	0.77	0.65 to 0.93
Beta-blockers						
<30 days	118	2.3	112	4.4	1.89	1.41 to 2.55

1–3 months	172	3.4	144	5.6	1.49	1.15 to 1.93
>3–12 months	464	9.1	279	10.9	1.12	0.93 to 1.35
>1 year	1214	23.8	620	24.3	1.00	0.86 to 1.15
Nitrates						
<30 days	193	3.8	127	5.0	1.30	1.00 to 1.69
1–3 months	134	2.6	88	3.4	1.04	0.76 to 1.42
>3–12 months	270	5.3	191	7.5	1.29	1.03 to 1.61
>1 year	597	11.7	386	15.1	1.25	1.05 to 1.49
Digoxin						
<30 days	80	1.6	62	2.4	1.25	0.86 to 1.80
1–3 months	132	2.6	73	2.9	0.75	0.54 to 1.04
>3–12 months	314	6.2	184	7.2	0.90	0.73 to 1.12
>1 year	545	10.7	254	10.0	0.85	0.71 to 1.01
Anticoagulants†						
<30 days	87	1.7	59	2.3	1.40	1.06 to 1.86
1–3 months	149	2.9	98	3.8	0.91	0.71 to 1.18
>3–12 months	361	7.1	236	9.3	1.10	0.92 to 1.31
>1 year	621	12.2	339	13.3	0.97	0.83 to 1.13
Antiplatelets						
<30 days	204	4.0	125	4.9	1.23	0.94 to 1.60

1–3 months	290	5.7	149	5.8	0.97	0.77 to 1.23
>3–12 months	734	14.4	417	16.3	1.09	0.92 to 1.29
>1 year	1449	28.4	686	26.9	0.95	0.82 to 1.10
Antiarrhythmics						
<30 days	48	0.9	41	1.6	1.89	1.18 to 3.02
1–3 months	67	1.3	34	1.3	1.10	0.69 to 1.75
>3–12 months	172	3.4	102	4.0	1.17	0.88 to 1.56
>1 year	344	6.7	168	6.6	1.04	0.83 to 1.30
Statins						
<30 days	165	3.2	114	4.5	1.40	1.06 to 1.86
1–3 months	257	5.0	128	5.0	0.91	0.71 to 1.18
>3–12 months	682	13.4	408	16.0	1.10	0.92 to 1.31
>1 year	1527	29.9	809	31.8	0.97	0.83 to 1.13

*The OR (current use by duration versus never use [reference category]) was adjusted for primary care physician 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 disease.

†Anticoagulants included both oral and parenteral anticoagulants (vitamin K antagonists, non-vitamin K antagonist oral anticoagulants and low molecular weight heparins).

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CI, confidence interval; OR, odds ratio.

Table S4 Association of patient characteristics and cardiovascular medication use with the likelihood of having multiple episodes (rather than a single episode) of hypotension after a new diagnosis of heart failure

	Controls (patients with 1 episode of hypotension, n=1520)		Cases (patients with > 1 episode of hypotension, n=1031)			
	n	**%**	**n**	**%**	**OR***	**95% CI**
Demographics						
Sex						
Male	908	59.7	728	70.6	1.45	1.22 to 1.72
Female	612	40.3	303	29.4	1	
Age, years						
18–49	25	1.7	43	4.2	3.33	1.97 to 5.63
50–59	84	5.5	119	11.5	2.85	2.06 to 3.95
60–69	268	17.6	228	22.1	1.85	1.46 to 2.34
70–79	555	36.5	394	38.2	1.58	1.29 to 1.93
≥80	588	38.7	247	24.0	1	
Time interval from start date to index date, years†						
<1	413	27.2	365	35.4	3.26	2.01 to 5.29

1–<2	199	13.1	183	17.8	3.58	2.16 to 5.93
2–<5	453	29.8	282	27.4	2.53	1.56 to 4.12
5–<10	363	23.9	178	17.3	2.09	1.27 to 3.44
≥10	92	6.1	23	2.2	1	
BMI, kg/m^2						
11–19.99	104	6.8	51	4.9	0.70	0.48 to 1.02
20–24.99	384	25.3	307	29.8	1	
25–29.99	475	31.2	342	33.2	0.86	0.70 to 1.07
≥30	421	27.7	249	24.2	0.68	0.54 to 0.86
Unknown	136	8.9	82	8.0	0.72	0.52 to 1.00
Comorbidities‡						
Prior hypotension	77	5.1	133	12.9	2.27	1.67 to 3.07
1 episode	63	4.2	92	8.9	1.96	1.39 to 2.76
≥2 episodes	11	0.7	33	3.2	3.59	1.92 to 6.69
Hypertension	840	55.3	415	40.3	0.65	0.55 to 0.77
Ischaemic heart disease	976	64.2	712	69.1	1.23	1.03 to 1.47
Myocardial infarction	548	36.1	461	44.7	1.32	1.12 to 1.56
Unstable angina	139	9.1	130	12.6	1.60	1.23 to 2.08
Atrial fibrillation	548	36.1	376	36.5	1.16	0.97 to 1.38
Hyperlipidaemia	454	29.9	346	33.6	1.26	1.05 to 1.50

Anaemia	328	21.6	139	13.5	0.68	0.54 to 0.85
Proteinuria	123	8.1	55	5.3	0.67	0.48 to 0.94
Renal failure§						
No (eGFR >60 mL/min/1.73 m^2)	407	26.8	300	29.1	1	
eGFR 45–59 mL/min/1.73 m^2	236	15.5	106	10.3	0.88	0.65 to 1.17
eGFR 30–44 mL/min/1.73 m^2	392	25.8	243	23.6	1.14	0.90 to 1.45
eGFR <30 mL/min/1.73 m^2	364	23.9	284	27.5	1.26	1.00 to 1.58
eGFR not recorded	121	8.0	98	9.5	0.97	0.70 to 1.35
Cardiovascular drug use‖						
Aldosterone antagonists	463	30.5	401	38.9	1.37	1.15 to 1.64
ACE inhibitors	943	62.0	722	70.0	1.56	1.24 to 1.97
CCBs	263	17.3	135	13.1	0.70	0.55 to 0.88
Beta-blockers	653	43.0	502	48.7	1.28	1.06 to 1.53
Anticoagulants	403	26.5	329	31.9	1.35	1.12 to 1.62
Other drug use‖						
Antidiabetics	276	18.2	156	15.1	0.76	0.61 to 0.95

*****Odds ratios adjusted for sex, age, primary care physician visits in the year before the index date (date of occurrence of hypotension) and the time interval between the start date (date of heart failure diagnosis) and the index date.

†Mean ± standard deviation time from the start date (new diagnosis of heart failure) to the index date (first recorded episode of hypotension during follow-up) was 3.71±3.34 years for controls and 2.73±2.80 for cases.

‡Reference category was 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.

‖Values are given for current drug use (0–30 days before the index date) versus never use.

ACE, angiotensin-converting enzyme; BMI, body mass index; CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.