BMJ Open

Treatment and prescribing trends of antihypertensive drugs in 2.7 million UK primary care patients over 31 years: a population-based cohort study

Julie Rouette [1,2] Emily G. McDonald,[3,4] Tibor Schuster,[1,5] James M. Brophy [1,6,7] Laurent Azoulay [1,2,8]

ABSTRACT

Objectives To describe the prescribing trends of antihypertensive drugs in primary care patients and assess the trajectory of antihypertensive drug prescriptions, from first-line to third-line, in patients with hypertension according to changes to the United Kingdom (UK) hypertension management guidelines.

Design Population-based cohort study.

Setting and participants We used the UK Clinical Practice Research Datalink, an electronic primary care database representative of the UK population. Between 1988 and 2018, we identified all adult patients with at least one prescription for a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, beta-blocker or calcium channel blocker (CCB).

Primary and secondary outcome measures We estimated the period prevalence of patients with antihypertensive drug prescriptions for each calendar year over a 31-year period. Treatment trajectory was assessed by identifying patients with hypertension newly initiating an antihypertensive drug, and treatment changes were defined by a switch or add-on of a new class. This cohort was stratified before and after 2007, the year following important changes to UK hypertension management guidelines.

Results The cohort included 2 709 241 patients. The prevalence of primary care patients with antihypertensive drug prescriptions increased from 7.8% (1988) to 21.9% (2018) and was observed for all major classes except thiazide diuretics. Patients with hypertension initiated thiazide diuretics (36.8%) and beta-blockers (23.6%) as first-line drugs before 2007, and ACE inhibitors (39.9%) and CCBs (31.8%) after 2007. After 2007, 17.3% were not prescribed guideline-recommended first-line agents. Overall, patients were prescribed a median of 2 classes (IQR 1–2) after first-line treatment.

Conclusion Nearly one-quarter of primary care patients were prescribed antihypertensive drugs by the end of the study period. Most patients with hypertension initiated guideline-recommended first-line agents. Not all patients, particularly females, were prescribed recommended agents however, potentially leading to suboptimal cardiovascular outcomes. Future research should aim to better understand the implication of this finding.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of the Clinical Practice Research Datalink (CPRD) allowed for the inclusion of 2.7 million primary care patients and a 31-year follow-up period.

⇒ We conducted a detailed analysis of the antihypertensive drugs prescribed in patients with hypertension, up to the third-line, capturing changes in the pharmacological management of hypertension over time.

⇒ The CPRD captures prescriptions issued by general practitioners and does not capture dispensing information.

⇒ The first-ever prescription might not have been captured for some patients, although the use of a 1-year look-back period should have minimised this limitation.

INTRODUCTION

Antihypertensive drugs are commonly prescribed drugs, with a prevalence ranging between 8% and 35% of the adult population.[1–6] There are five major classes, comprised of thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers and calcium channel blockers (CCBs). These classes have been approved for several years, with ARBs being the latest first-line class introduced in the market in 1995.[7]

Despite a long-standing prescribing history, the prescription prevalence of antihypertensive drugs over time has not been comprehensively evaluated. Further, evidence suggests that sex differences may exist in the prescription of different antihypertensive drug classes in primary care settings.[8] Changes to hypertension management over time have also led to earlier treatment initiation in the disease course, and in younger patients.[9] To better understand these issues, there is a need for large country-specific studies describing the different patient subgroups being prescribed

these drugs and the changes in antihypertensive treatment over time.

Additionally, although guidelines have been published on the pharmacological treatment of patients with hypertension, few studies have investigated the application of these guidelines in real-world clinical practice. This gap in the literature is important because in the United Kingdom (UK) specifically, thiazide diuretics and beta-blockers were recommended first-line treatment in early guidelines, and gradually replaced by ACE inhibitors, ARBs and CCBs in later guidelines.[10–15] A comprehensive assessment is thus needed to capture the treatment trajectory of patients with hypertension over time and identify potential gaps and inequities in best practice management of hypertension.

Therefore, the aims of this population-based study were to describe the long-term prescribing trends of antihypertensive drugs in UK primary care patients and define the trajectory of antihypertensive drug prescriptions, from first-line to third-line, in primary care patients with hypertension.

METHODS
Data source
This study was conducted using the UK Clinical Practice Research Datalink (CPRD) Gp OnLine Data (GOLD), a large primary care database of electronic medical records representative of the UK population.[16 17] The CPRD contains demographic information, anthropometric data such as body mass index (BMI), and lifestyle variables such as smoking. Medical diagnoses, laboratory test results, procedures and specialist referrals are recorded using Read codes, and prescriptions details are recorded using the British National Formulary (BNF) dictionary.[17]

Patient records provided by the general practices are assessed for quality through the Quality and Outcomes Framework, with lifestyle variables such as smoking, blood pressure, BMI, and alcohol intake having over 70% completeness in the CPRD.[18] The CPRD has also been shown to be representative of the UK population for age, sex, ethnicity and BMI distribution,[17] and diagnoses have been shown to have high sensitivity and specificity.[19]

Study population
Using the CPRD, we first identified a cohort of patients at least 18 years of age and registered with a general practice between 1 January 1988 and 31 December 2018. Cohort entry was defined as the patient's start of registration with the general practice, the date the general practice met data quality standards, or 1 January 1988, whichever came later. End of follow-up was defined as the patient's end of registration with the general practice, death from any cause, or 31 December 2018, whichever came first. Within this cohort, we identified patients who received at least one antihypertensive drug prescription during the study period, with no restrictions on specific comorbidities as these drugs can be prescribed for different

indications. These drugs consisted of all those available in the UK during the study period and included thiazide and thiazide-like diuretics, ACE inhibitors, ARBs, beta-blockers, CCBs, other diuretics (loop diuretics, potassium-sparing diuretics, other diuretics), and other agents (alpha-blockers, alpha agonists, direct-acting vasodilators, centrally acting agents, ganglion-blocking agents, direct renin inhibitors and combination pills) (BNF codes in online supplemental table 1).

Statistical analyses
Period prevalence of patients with antihypertensive drug prescriptions
We first estimated the period prevalence of primary care patients prescribed antihypertensive drugs, overall and stratified by antihypertensive drug class, in each calendar year of the study period. Period prevalence was calculated by dividing the number of patients who were prescribed an antihypertensive drug by the total number of patients in the CPRD in each calendar year during the study period. Second, we assessed the period prevalence among patient subgroups, including by sex and age (18–39, 40–59, 60–79, ≥80 years), and by indications of use (hypertension, heart failure, coronary heart disease, diabetes and chronic kidney disease). The latter was calculated by dividing the number of patients with a given indication and a prescription for a specific antihypertensive drug class by the total number of patients prescribed any antihypertensive drug with that indication. This analysis was conducted to describe the patient population with these specific conditions. Finally, we estimated the number of antihypertensive drug classes prescribed to primary care patients over the study period overall, by sex, and by age group, to better understand changes in treatment intensity over time in primary care.

Characteristics of patients initiating a first-ever antihypertensive drug
To better understand the patient population initiating antihypertensive drugs, we identified all patients aged 18 and above with a first prescription for an antihypertensive drug between 1 January 1988 and 31 December 2018. Cohort entry corresponded to the date of the first-ever antihypertensive drug prescription in monotherapy in the patient's medical record. For this analysis, all patients were required to have at least 1 year of medical history in the CPRD before cohort entry. This was necessary to ascertain first-ever status and to have a sufficient look-back period to capture clinically relevant characteristics. Patient characteristics were described overall (1988–2018) and by decades (1988–1999, 2000–2009, 2010–2018). The following characteristics were captured at cohort entry: age, sex, BMI, smoking status, systolic and diastolic blood pressure (last measurement before cohort entry); and measured ever before: diagnoses of hypertension, heart failure, coronary heart disease, peripheral vascular disease, stroke, arrhythmias, atrial fibrillation, stable

angina, myocardial infarction, diabetes, and chronic kidney disease.

Finally, as recent evidence has shown an increase in beta-blocker prescriptions for non-cardiovascular conditions over time,[20] we described the distribution of this drug class in patients with a first-ever and ever prescription.

Treatment trajectory

We also assessed the treatment trajectory among patients initiating a first-line antihypertensive drug in monotherapy before and after 1 January 2007. This dichotomisation was based on the June 2006 pharmacological update of the 2004 National Institute for Health and Care Excellence (NICE) guidelines on hypertension in primary care.[13 14] These guidelines newly recommended ACE inhibitors (or ARBs if ACE inhibitors are not well tolerated) as the preferred first-line treatment in younger patients rather than beta-blockers.

For this analysis, we identified patients initiating a first-line antihypertensive drug with evidence of hypertension before cohort entry. Evidence of hypertension was defined by either a diagnosis of hypertension before cohort entry or by at least three elevated systolic (≥140 mm Hg) or diastolic (≥90 mm Hg) blood pressure measurements in the year before cohort entry.[21] Patients were followed from their initial first-line treatment to subsequent treatment lines up to the third-line. A change in treatment line was defined by a patient switching a drug class to a new drug class or adding on a new drug class. End of follow-up was defined as the last prescription date on record. At each treatment line, we captured the new drug class and calculated the median number of days between each treatment change (from the date of the first prescription of the first-line drug to the date of the first prescription of the second-line drug, and so on).

Finally, to describe treatment intensity, we calculated the number of antihypertensive drug classes prescribed after failure on first-line monotherapy treatment over the study period. All analyses were performed with SAS V.9.4 (SAS Institute).

Patient and public involvement

Patients and the public were not involved in the design and implementation of the study (as this study involved the use of secondary data), or in dissemination plans.
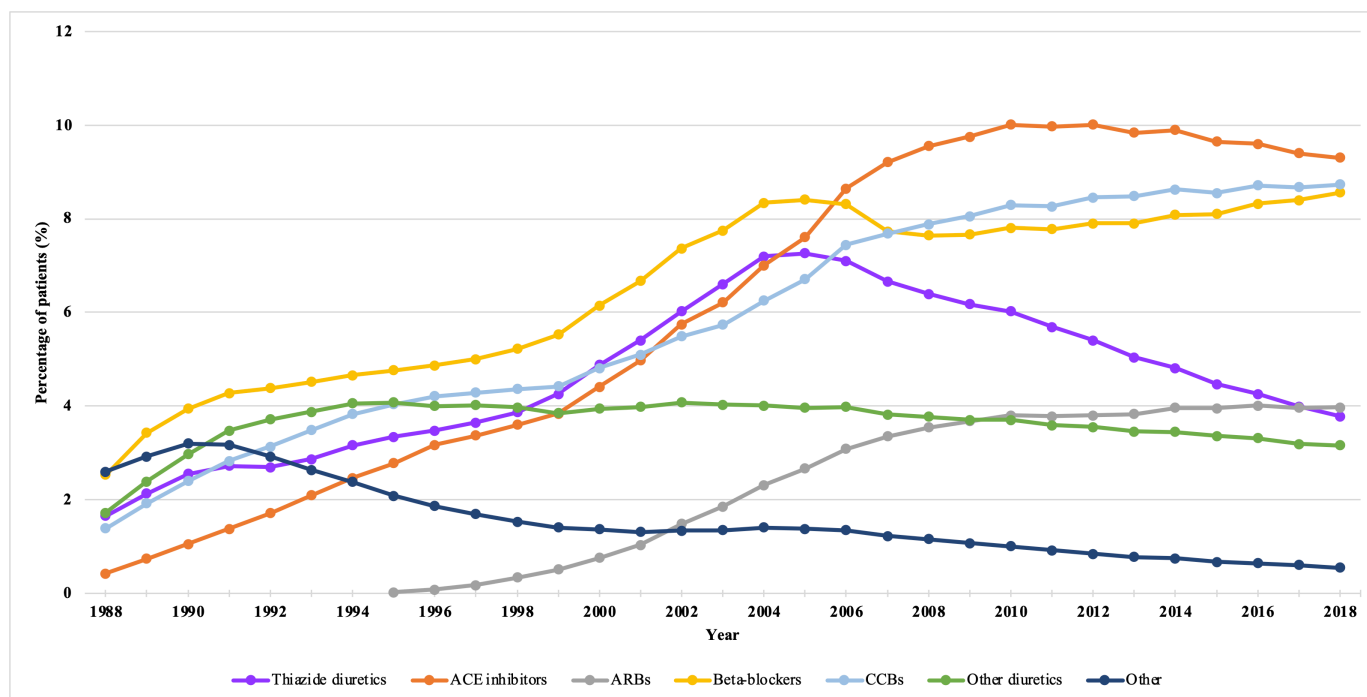
RESULTS

Period prevalence of patients with antihypertensive drug prescriptions

Within a cohort of 11 417 758 primary care patients, 2 709 241 patients were prescribed at least one antihypertensive drug during the study period. Overall, the prevalence of patients with antihypertensive drug prescriptions increased from 7.8% in 1988 to 21.9% in 2018, and has remained relatively steady since 2006 (figure 1). By the end of the study period, 51.0% of patients were prescribed two or more antihypertensive drug classes.

Figure 2 presents the period prevalence for each antihypertensive drug class during the study period. Between 1988 and 2018, the prevalence increased for ACE inhibitors (0.4% vs 9.3%), CCBs (1.4% vs 8.7%) and beta-blockers (2.6% vs 8.6%). The prevalence of patients prescribed ARBs modestly increased from 0% in 1995 (the year ARBs entered the UK market) to 4.0% in 2018. For thiazide diuretics, the prevalence decreased from a peak of 7.3% in 2005 to 3.8% in 2018. In 2018, ACE inhibitors represented 24.5% of all antihypertensive drug prescriptions, followed by CCBs (22.9%), beta-blockers (22.5%), ARBs (10.4%), thiazide diuretics (9.9%), other diuretics
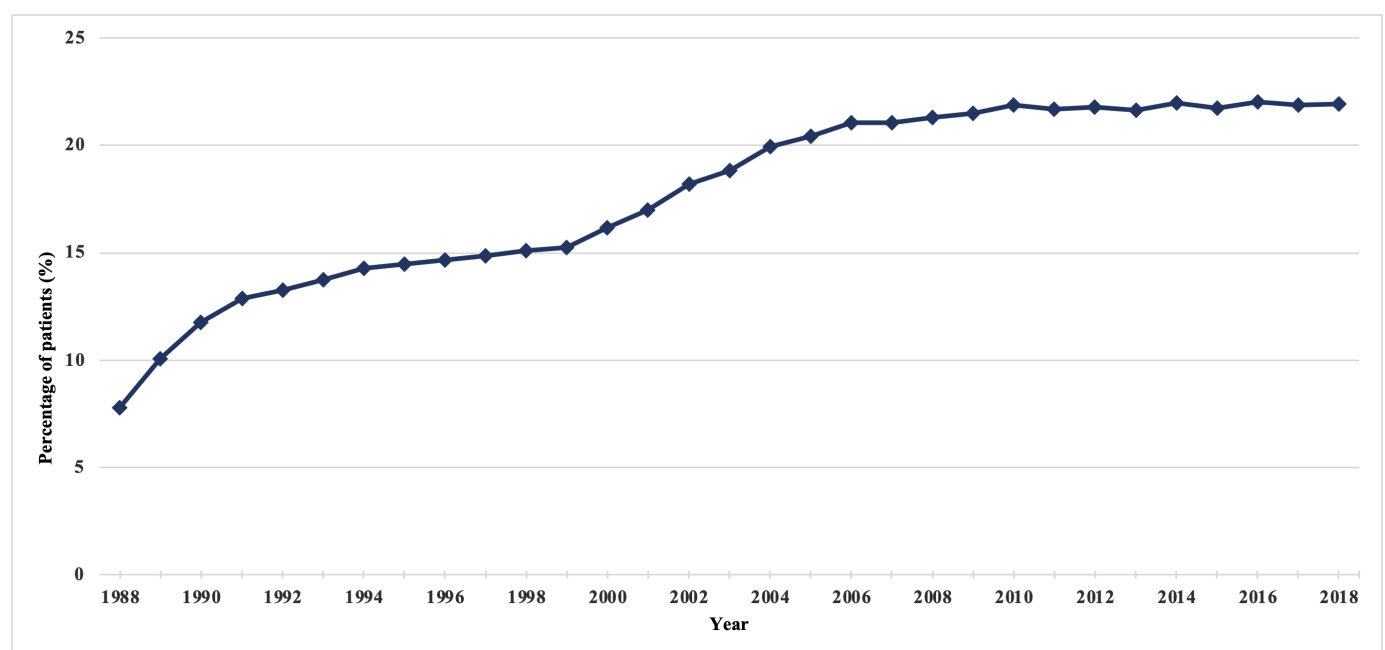
Figure 1 Overall period prevalence of primary care patients with antihypertensive drug prescriptions.

Figure 2 Period prevalence of primary care patients with antihypertensive drug prescriptions, stratified by drug class. ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CCBs, calcium channel blockers.

(8.3%) and other antihypertensive drugs (1.4%). Treatment intensity increased during the study period (online supplemental figure 1), with patients being prescribed a median of 1 drug class (IQR 1–2, maximum 7) in 1988 to 2 (IQR 1–2, maximum 7) in 2018. During the study period, female patients were more likely than male patients to be prescribed only one class (52.5% vs 45.3% in 2018, respectively) (online supplemental figure 2A,B). Patients aged 60 and over were increasingly more likely to be prescribed two or more classes (online supplemental figure 3A–D).

Online supplemental figure 4A–G presents the period prevalence for males and females by age groups. Female patients were consistently more likely to be prescribed thiazide diuretics compared with male patients throughout the study period. In contrast, male patients were more likely to be prescribed ACE inhibitors than females, across all age groups. Similarly, males were more commonly prescribed CCBs during the study period, except for the youngest (18–39 years old) and oldest (80+) age groups. Finally, the prevalence of patients aged 18–39 years with beta-blocker prescriptions increased from 0.3% in 1988 to 1.9% for males and to 4.0% for females in 2018.

Online supplemental figures 5–9 show the prevalence of antihypertensive drugs for patients with hypertension, heart failure, coronary heart disease, diabetes and chronic kidney disease, respectively, to describe the patient population with these conditions. In patients with hypertension, the prevalence of patients with beta-blocker and thiazide diuretic prescriptions was highest from 1988 until 2005–2006, when the 2004 guideline and the 2006 pharmacological update began primarily recommending

ACE inhibitors and CCBs for the management of hypertension (online supplemental figure 5).[13 14] In patients with heart failure, the most prevalent drug classes were diuretics (since 1988), ACE inhibitors (since 1992) and beta-blockers (since 2003) (online supplemental figure 6). Beta-blockers were contraindicated for chronic heart failure until the publication of guidelines in 1997[22] after which the prevalence rose rapidly, becoming the most prevalent class by the end of the study period. Patients with coronary heart disease and type 2 diabetes showed a similar pattern, with the highest prevalence for ACE inhibitors, beta-blockers and CCBs, particularly after 2000 (online supplemental figures 7,8). Finally, among patients with chronic kidney disease, the prevalence of patients with ACE inhibitors, CCBs, beta-blockers and loop diuretics was highest for most of the study period, however with a sharp decline for loop diuretics in 2006 coinciding with the publication of the Quality and Outcomes Framework for chronic kidney disease in England and the UK chronic kidney disease management guidelines (online supplemental figure 9).

Characteristics of patients initiating a first-ever antihypertensive drug

There were 1 425 542 patients initiating a first-ever antihypertensive drug prescription in monotherapy during the study period (online supplemental figure 10); 44.6% of those were males, and the mean age was 55.4 years (SD: 17.2).

Table 1 describes the characteristics of patients initiating first-ever antihypertensive drugs, overall and by drug class, during the study period. Beta-blockers represented

Table 1 Baseline characteristics of primary care patients with a first-ever antihypertensive drug prescription between 1 January 1988 and 31 December 2018

	Thiazide diuretics	ACE inhibitors	ARBs	Beta-blockers	CCBs	Other diuretics	Other*	Total
Total	202 856 (14.9)	237 923 (17.5)	17 846 (1.3)	494 333 (36.4)	196 485 (14.5)	157 994 (11.6)	52 632 (3.9)	1 360 069
Males, n (%)	75 317 (37.1)	149 293 (62.7)	10 731 (60.0)	201 755 (40.1)	103 536 (52.7)	60 632 (38.4)	5353 (10.2)	606 617 (44.6)
Mean age, years (SD)	63.2 (14.5)	55.3 (13.0)	57.0 (13.4)	45.9 (16.7)	61.5 (14.1)	65.9 (17.7)	53.5 (12.0)	55.4 (17.2)
Mean BMI, kg/m² (SD)	27.7 (5.4)	29.4 (6.0)	28.8 (5.8)	26.2 (5.4)	27.5 (5.4)	27.6 (6.8)	26.8 (5.3)	27.4 (5.8)
Smoking status								
Current	54 949 (27.1)	58 332 (24.5)	4212 (23.6)	155 440 (31.4)	46 474 (23.6)	43 226 (27.4)	15 851 (30.1)	378 484 (27.8)
Never	94 945 (46.8)	114 852 (48.3)	8808 (49.4)	227 370 (46.0)	94 175 (47.9)	64 733 (41.0)	23 968 (45.5)	628 851 (45.2)
Past	32 981 (16.3)	57 318 (24.0)	3830 (21.5)	74 052 (15.0)	46 490 (23.6)	28 990 (18.3)	7668 (14.6)	251 329 (18.5)
Unknown	19 981 (9.8)	7421 (3.1)	996 (5.6)	37 471 (7.6)	9346 (4.8)	21 045 (13.3)	5145 (9.8)	101 405 (7.5)
Mean blood pressure, mm Hg (SD)								
Systolic	160.9 (22.9)	156.6 (20.0)	157.1 (20.9)	133.5 (22.0)	157.4 (23.5)	136.4 (19.4)	133.0 (20.1)	146.0 (24.8)
Diastolic	91.3 (12.2)	92.3 (12.3)	92.2 (12.1)	80.7 (12.2)	89.9 (13.0)	79.2 (10.1)	80.4 (10.9)	85.7 (13.3)
Hypertension††	144 530 (71.2)	181 752 (76.4)	13 668 (76.6)	113 052 (22.9)	133 362 (67.9)	22 232 (14.1)	11 388 (21.6)	619 984 (45.6)
Year of initiation, n (%)								
1988–1993	10 748 (5.3)	2683 (1.1)	0	20 137 (4.1)	6182 (3.1)	11 944 (7.6)	5463 (10.4)	57 157 (4.2)
1994–1999	37 126 (18.3)	11 124 (4.7)	588 (3.3)	60 356 (12.2)	16 230 (8.3)	28 427 (18.0)	7424 (14.1)	161 275 (11.9)
2000–2005	105 496 (52.0)	51 364 (21.6)	7514 (42.1)	142 009 (28.7)	32 484 (16.5)	46 137 (29.2)	15 888 (30.2)	400 892 (29.5)
2006–2011	41 214 (20.3)	107 238 (45.1)	6174 (34.6)	131 472 (26.6)	68 823 (35.0)	41 638 (26.4)	14 726 (28.0)	411 285 (30.2)
2012–2018	8272 (4.1)	65 514 (27.5)	3570 (20.0)	140 359 (28.4)	72 766 (37.0)	29 848 (18.9)	9131 (17.3)	329 460 (24.2)
Medical history, n (%)‡‡								
Heart failure	1107 (0.5)	3024 (1.3)	100 (0.6)	1234 (0.2)	403 (0.2)	9852 (6.2)	269 (0.5)	15 989 (1.2)
Coronary heart disease §	19 310 (9.5)	25 597 (10.8)	1457 (8.2)	46 243 (9.4)	24 899 (12.7)	17 680 (11.2)	2344 (4.5)	137 530 (10.1)
Peripheral vascular disease	4233 (2.1)	5751 (2.4)	316 (1.8)	3877 (0.8)	6913 (3.5)	5781 (3.7)	482 (0.9)	27 353 (2.0)
Stroke	5090 (2.5)	8577 (3.6)	396 (2.2)	4395 (0.9)	5079 (2.6)	5766 (3.6)	449 (0.9)	29 752 (2.2)
Arrythmias	3768 (1.9)	5343 (2.2)	379 (2.1)	27 442 (5.6)	6756 (3.4)	9326 (5.9)	512 (1.0)	53 526 (3.9)
Atrial fibrillation	2676 (1.3)	3916 (1.6)	271 (1.5)	19 669 (4.0)	4214 (2.1)	7977 (5.0)	292 (0.6)	39 015 (2.9)
Stable angina	3246 (1.6)	5233 (2.2)	279 (1.6)	19 313 (3.9)	8912 (4.5)	4627 (2.9)	412 (0.8)	42 022 (3.1)
Myocardial infarction	1446 (0.7)	6873 (2.9)	262 (1.5)	11 846 (2.4)	2930 (1.5)	3755 (2.4)	175 (0.3)	27 287 (2.0)
Diabetes	21 707 (10.7)	80 306 (33.8)	4503 (25.2)	59 012 (11.9)	32 154 (16.4)	20 901 (13.2)	7221 (13.7)	225 813 (16.6)
Chronic kidney disease	1991 (1.0)	11 522 (4.8)	686 (3.8)	4707 (1.0)	6018 (3.1)	4428 (2.8)	444 (0.8)	29 796 (2.2)

*Other antihypertensive drugs.
†Defined as a recorded diagnosis of hypertension or at least three elevated systolic (≥140) or diastolic (≥90) blood pressure readings in the year before cohort entry.
‡Non-mutually exclusive categories.
§Includes stable ischaemic heart disease (chronic coronary syndrome), carotid artery disease (carotid stenosis) and peripheral artery disease.
ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; CCBs, calcium channel blockers.

the most commonly initiated drugs (36.4%), followed by ACE inhibitors (17.5%). Males were more likely to receive ACE inhibitors, ARBs and CCBs (62.7%, 60.0% and 52.7%, respectively), while females were more likely to receive thiazide diuretics, beta-blockers, other diuretics and other antihypertensive drugs (62.9%, 59.9%, 61.6%, 89.8%, respectively). The majority of prescriptions in the 'Other antihypertensive drugs' category (71.3%) were for clonidine hydrochloride 0.025 mg tablets.

Most patients initiating a thiazide diuretic, ACE inhibitor, ARB and CCB had evidence of hypertension (71.2%, 76.4%, 76.6% and 67.9%, respectively). In contrast, patients initiating a beta-blocker, other diuretics and other antihypertensive drugs were less likely to have evidence of hypertension (22.9%, 14.1% and 21.6%, respectively). The majority of first-ever beta-blocker prescriptions were for propranolol (online supplemental table 2).

Online supplemental tables 3–5 describe the characteristics of patients initiating a first-ever antihypertensive drug by decade (1988–1999, 2000–2009, 2010–2018). Between the first and the third decades, there was an overall increase in the proportion of patients diagnosed with diabetes (8.9% vs 21.3%) and chronic kidney disease (0.3% vs 3.6%), as well as hypertension for ACE inhibitors (71.4% vs 78.2%), CCBs (44.2% vs 73.8%) and other diuretics (10.6% vs 16.8%).

Treatment trajectory

The trajectory analysis included a total of 619 984 patients with hypertension, comprised of 317 210 patients initiating a first-line antihypertensive drug in the pre-2007 cohort and 302 774 patients in the post-2007 cohort. Online supplemental tables 6,7 present the baseline characteristics of these patients. Patients in the pre-2007 cohort were slightly older than the post-2007 cohort (60.5 years, SD: 18.3) vs 58.1 years, SD: 14.0) and had a higher pretreatment mean systolic (166.2 mm Hg, SD: 17.9 vs 161.1 mm Hg, SD: 16.5) and diastolic blood pressure (94.9 mm Hg, SD: 10.6 vs 93.4 mm Hg, SD: 10.7). In the post-2007 cohort, female patients were less likely to be prescribed a UK guideline-recommended first-line agent such as ACE inhibitors (38.4%), ARBs (40.0%) or CCBs (45.9%). In the pre-2007 cohort, 79.4% of patients switched to or added-on a new antihypertensive drug in contrast to 53.2% of patients in the post-2007 cohort (online supplemental table 8).

Figure 3 presents the treatment trajectory of patients initiating an antihypertensive drug before 1 January 2007. In this cohort, thiazide diuretics (36.8%) and beta-blockers (23.6%) were the most common first-line drugs. Among patients with first-line thiazide diuretic prescriptions, ACE inhibitors and beta-blockers were the most common second-line treatment (26.9% and 25.6%, respectively). Among patients with first-line beta-blocker prescriptions, thiazide diuretics and ACE inhibitors were the most common second-line treatment (23.7% and 22.6%, respectively). Treatment trajectory details for ARBs and 'Others' are in online supplemental figure 11.

The median number of days between treatment changes was 186 days (IQR 47–870) for first-line thiazide diuretics and 319 days (IQR 59–1211) for first-line beta-blockers (online supplemental figure 12).

Figure 4 presents the treatment trajectory after 1 January 2007. The most common first-line drugs were ACE inhibitors (39.9%) and CCBs (31.8%). A total of 17.3% of patients were not prescribed a guideline-recommended first-line agent. Among patients with first-line ACE inhibitor prescriptions, CCBs were the most common second-line drugs (25.5%). Similarly, among patients with first-line CCB prescriptions, ACE inhibitors were the most common second-line drugs (30.9%). Treatment trajectory details for ARBs and 'Others' are in online supplemental figure 13. The median number of days before starting second-line treatment was 182 days (IQR 63–654) for ACE inhibitors and 114 days (IQR 39–468) for CCBs (online supplemental figure 14).

The median number of antihypertensive drug classes prescribed after failure on first-line treatment was 2 (IQR 1–2, maximum 7). Over time, the percentage of patients prescribed two classes after failure on first-line treatment increased from 35.9% in 1989 to 45.8% in 2018. Similarly, patients with three classes increased from 9.8% in 1990 to 16.2% in 2018 (online supplemental figure 15).

DISCUSSION
Principal findings

In this large population-based study, the prevalence of patients prescribed antihypertensive drugs increased during the study period but has remained relatively steady since 2006, with 21.9% of primary care patients receiving antihypertensive drugs by the end of the study period. The prescription prevalence was highest for ACE inhibitors (24.5%), CCBs (22.9%) and beta-blockers (22.5%). Beta-blockers were most prevalent in females and in youngest and oldest patients. Most patients with hypertension initiated guideline-recommended first-line agents, with thiazide diuretics and beta-blockers representing the most common first-line drugs before 2007 (36.8% and 23.6%, respectively) and ACE inhibitors and CCBs after 2007 (39.9% and 31.8%, respectively). Fewer females initiated recommended first-line agents.

Comparison with previous studies

Although previous studies have described prescribing trends of antihypertensive drugs in UK primary care practices, these trends were reported for specific patient populations, indications, drug classes, or over short time periods.[7 23–37] As such, there was a gap in the literature for a comprehensive assessment of the prescribing practices in primary care settings over time. In our study, 8% of adult primary care patients were prescribed antihypertensive drugs in 1988 and increasing to 22% by the end of the study period. Similarly, other countries and jurisdictions have reported an overall prevalence ranging between 8% and 35% in adult populations, with an increase over
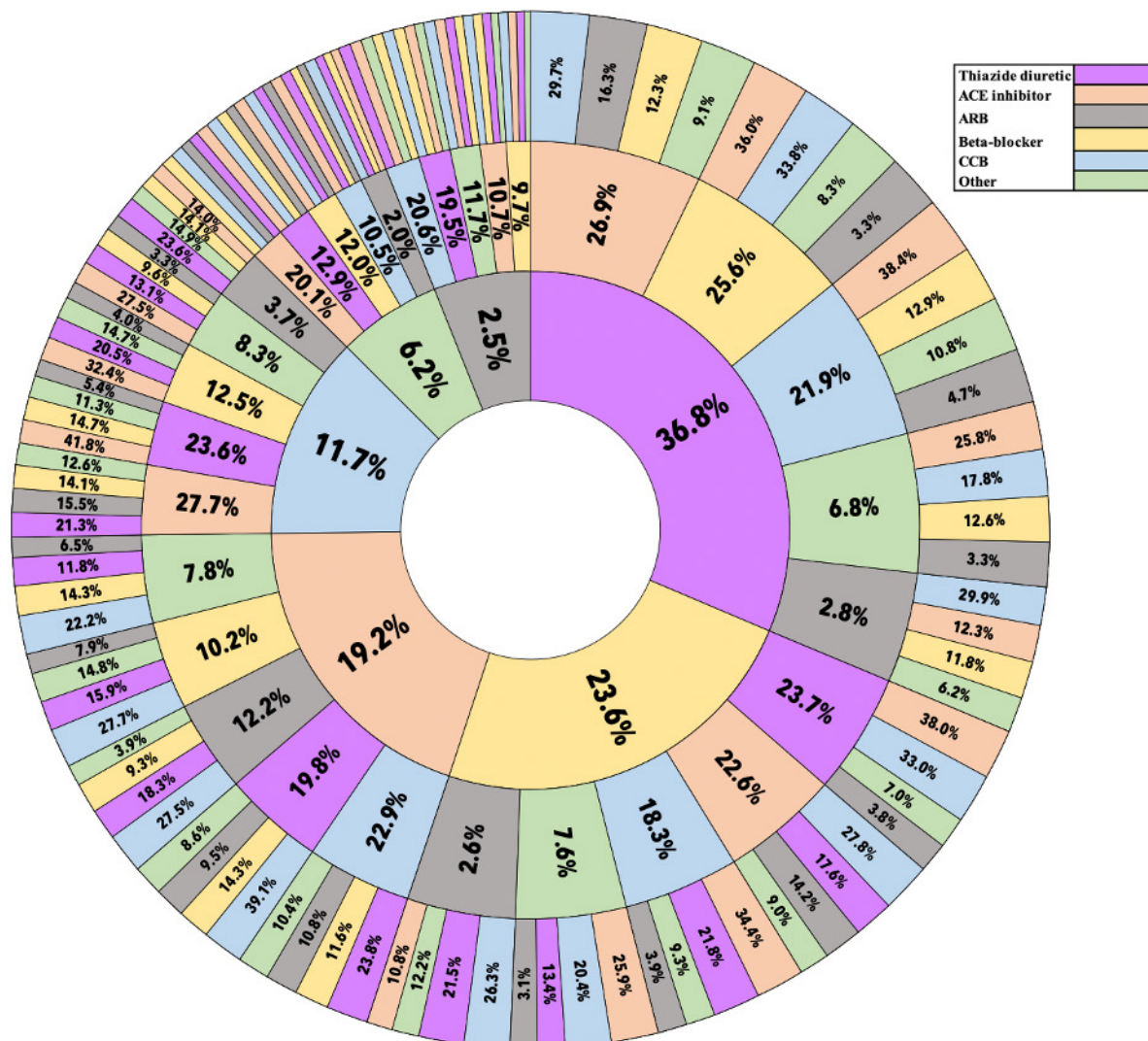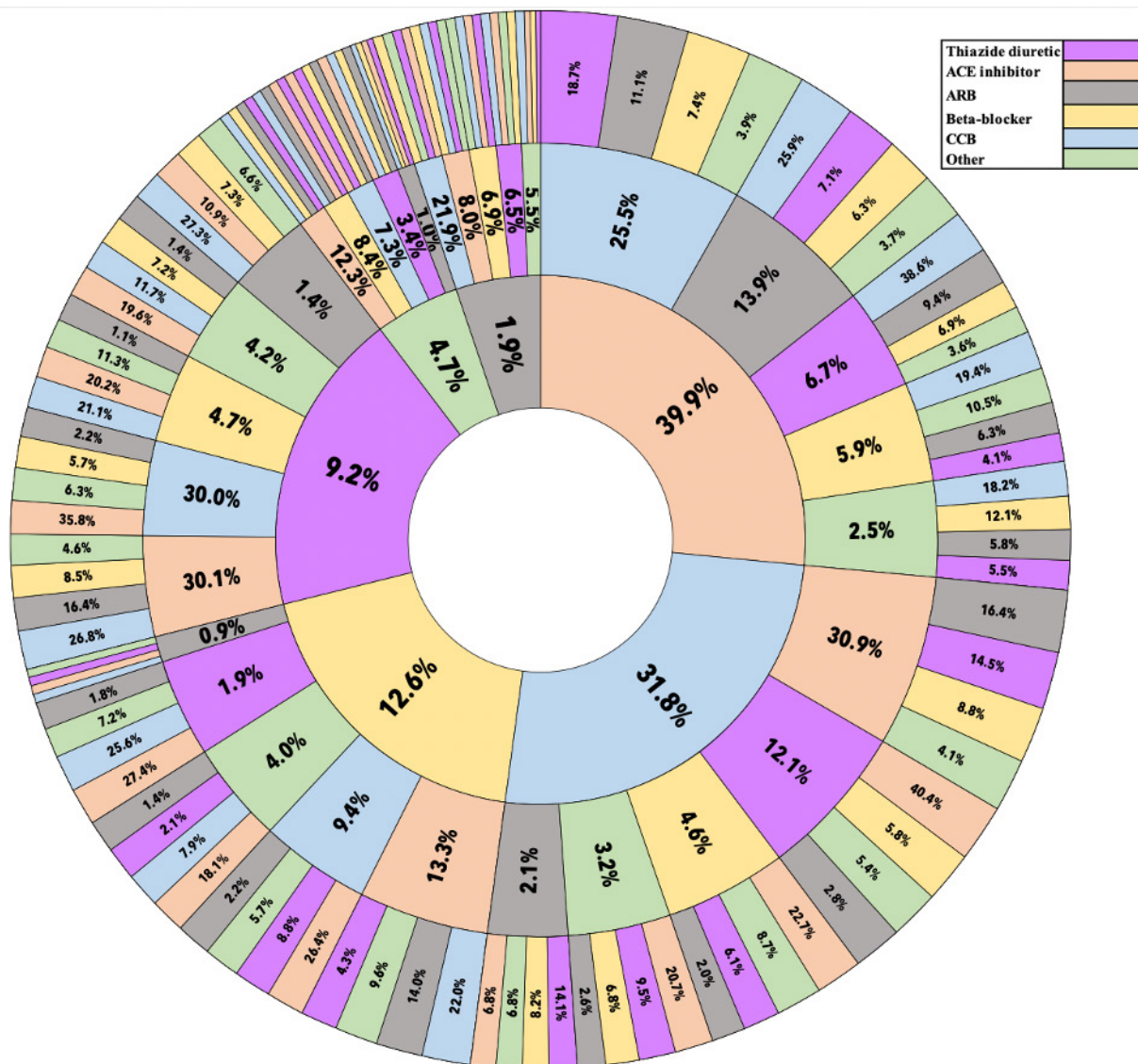
Figure 3 Treatment trajectory of primary care patients with hypertension with a first-ever antihypertensive drug prescription before 1 January 2007. [a]Each concentric circle represents a treatment line. Percentages do not reach 100% as only patients who switched to or added-on a new drug class are included. Fewer patients were prescribed first-line ARBs and 'Other' antihypertensive drugs, resulting in thinner slices for these two classes. As such, details of third-line results for ARB and 'Other' are in online supplemental figure 11 to better visualise the results. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

time.[1–5 38] A large pooled analysis of 104 million primary care individuals found that the age-standardised prevalence of hypertension doubled between 1990 and 2019 in primary care patients aged 30–79.[39] Countries such as Canada, Peru and the UK (in women only) reported the lowest prevalence of hypertension, representing less than 25% of its primary care population.[39] Hypertension treatment was highest in Canada, South Korea and Iceland, representing over 70% of patients with hypertension, but reported to be only 47% in the UK.

The prevalence of patients with ACE inhibitor and CCB prescriptions has increased steadily over the last three decades, while it has decreased sharply for thiazide diuretics since 2005. Similarly, a previous UK study reported a decrease in the number of thiazide diuretic prescriptions between 2010 and 2016/2017.[24] Changes in UK hypertension treatment guidelines, notably in 2004

when ACE inhibitors and CCBs were newly recommended as first-line treatment for hypertension along with thiazide diuretics and beta-blockers,[13] may have contributed to this decline. Indeed, this decreasing trend was also seen in our findings specific to patients with hypertension. As thiazide diuretics have been associated with lower treatment adherence compared with ACE inhibitors, ARBs and CCBs,[40–42] this could have led clinicians to favour other classes with higher adherence. Indeed, we observed a shorter number of days between treatment changes in patients with thiazide diuretic prescriptions relative to other drugs. Concerningly, as we consistently observed more female patients being prescribed thiazide diuretics throughout the study period, lower treatment adherence could lead to suboptimal blood pressure control in women.

Figure 4 Treatment trajectory of primary care patients with hypertension with a first-ever antihypertensive drug prescription after 1 January 2007. [a]Each concentric circle represents a treatment line. Percentages do not reach 100% as only patients who switched to or added-on a new drug class are included. Fewer patients were prescribed first-line ARBs and 'Other' antihypertensive drugs, resulting in thinner slices for these two classes. As such, details of third-line results for ARB and 'Other' are in online supplemental figure 13 to better visualise the results. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

A large 2020 systematic review and meta-analysis of sex differences in cardiovascular medication prescriptions in primary care patients found that women were 27% more likely to be prescribed thiazide diuretics but less likely to be prescribed ACE inhibitors (pooled prevalence ratio 0.83%, 95% CI 0.78 to 0.89).[8] Over the study period, our study consistently showed a higher prevalence of female patients with thiazide diuretic prescriptions and a lower prevalence with ACE inhibitor prescriptions compared with male patients, similar to previous large studies of primary care patients.[43 44] This sex difference may perhaps be explained by dissimilar presentations of cardiovascular symptoms, or different reporting of adverse events in men compared with women.[45 46] Indeed, a 2019 systematic review of adverse reactions to heart failure drugs

showed that cough and angioedema were reported more frequently in women treated with ACE inhibitors than men.[47] These factors may in turn be reflected in the clinical decisions leading to prescribing practices. Nonetheless, further research should focus on better understanding these sex differences in prescribing practices.

Our results also showed an age and sex difference in beta-blockers prescriptions. Beta-blockers were the first-ever drug class for 36.4% of the cohort and were predominantly prescribed in the youngest patients, primarily females, and without evidence of hypertension or other cardiovascular indications. After 2010, when beta-blockers were no longer recommended as first-line therapy for hypertension in the UK,[14] beta-blockers still constituted nearly 41% of first-ever drugs. Notably, the prevalence

of patients aged 18–39 with a beta-blocker prescription increased over time, most markedly since 2007. Similarly, between 1999–2000 and 2011–2012, a US study found a nearly eightfold increase in the prevalence of adults aged 20–39 with non-cardioselective beta-blocker prescriptions.[1] Our study also showed that the majority of those first-ever prescriptions were for propranolol. Indeed, a recent study reported a 2.5-fold increase in the prevalence of propranolol prescriptions for anxiety in UK primary care practices between 2003 and 2018, with a higher incidence for female patients and patients aged <45 years old.[20] This increase in prescriptions may correspond to the increase in the recording of anxiety symptoms and diagnoses in female and younger patients in recent years.[48] Although propranolol is licensed for use in anxiety symptoms management,[49] there is currently limited evidence of their long-term effectiveness and safety[50 51] and no specific recommendations exist from NICE regarding its use in anxiety.[52] Further, the UK Healthcare Safety Investigation Branch recently informed of a potential risk of propranolol toxicity in overdose, reporting a 33% increase in deaths potentially associated with propranolol overdose between 2012 and 2017.[52] Our study also found a sharp increase in patients aged 80 and over with beta-blocker prescriptions, representing the largest age group with prescriptions for this class. Beta-blockers, and specifically non-cardioselective beta-blockers such as propranolol, have been associated with increased risk of fall in the elderly.[53] Together, these findings warrant further investigation to understand the benefits and safety of beta-blockers, especially propranolol.

National guidelines recommend select first-line agents for antihypertensive treatment. Published by the British Hypertension Society in 1989, the first guideline recommended thiazide diuretics and beta-blockers as first-line treatments.[10] At that time, ACE inhibitors and CCBs were new agents with limited evidence of their efficacy. Similar recommendations were made in subsequent guidelines,[11 12] although ACE inhibitors, CCBs, alpha-blockers and later, ARBs could be considered potential options. As more evidence became available from randomised controlled trials and hypertension treatment became more complex,[54–71] NICE and the British Hypertension Society published four new guidelines and updates (2004, 2006, 2011, 2019) recommending ACE inhibitors and CCBs as first-line agents and introducing treatment choice based on age and ethnicity.[13–15 72] Our findings showed that patients treated after 2007 were younger and had lower mean blood pressure measurements than those treated before 2007. This is consistent with recent improvements in hypertension management which have led to the earlier treatment of patients, those younger in age, and those with lower initial blood pressure. However, much remains to be done. Previous studies showed that patients initiating an ACE inhibitor or a CCB had similar reductions in blood pressure, regardless of age,[73 74] suggesting that treatment choice based on indications rather than age might be more important.

The treatment trajectories reported in our study reflected the UK hypertension management guidelines published during the study period, with thiazide diuretics and beta-blockers being the most common first-line agents in the pre-2007 cohort and ACE inhibitors and CCBs in the post-2007 cohort. Similarly, one UK study found that diuretics and beta-blockers were prescribed in 54% of patients between 1993–1997.[23] More recently, another UK study found that 69.7% of patients initiated an ACE inhibitor or CCB between 2006 and 2014.[75] In our study however, 17.3% of patients were not prescribed a guideline-recommended first-line agent after 2007 and female patients were less likely to be prescribed an ACE inhibitor, ARB or CCB, which are currently guideline-recommended first-line agents. Further, 19.5% of patients were prescribed three or more antihypertensive drug classes after failure on first-line monotherapy, with some patients being prescribed up to seven classes. These findings suggest that some patients may be less likely to receive first-line agents and more likely to be overprescribed antihypertensive drugs, potentially leading to less effective blood pressure control and higher risk of adverse effects. These gaps and inequities in best practice management of hypertension should be further investigated. Further, studies should investigate which specific treatment trajectory optimises cardiovascular outcomes in patients with hypertension.

Strengths and limitations of the study

Our study has several strengths. First, with the inclusion of 2.7 million patients, it is the largest and most comprehensive study to date on the prescribing trends of antihypertensive drugs, presenting trends by drug class, sex, age group and comorbidities. Second, the 31-year study period provides the most extended follow-up to date and captures major changes in UK treatment guidelines over time. Third, this study describes the treatment trajectory of antihypertensive drugs from first- through third-line, providing a detailed picture of the treatment lines used in the management of patients with hypertension along with the duration of each of these treatment lines. Finally, the CPRD has been shown to be representative of the UK population and undergoes regular data quality checks to ensure its validity.[17]

Our study also has limitations. First, as the CPRD represents prescriptions issued by general practitioners, prescriptions from specialists are not captured in the database. However, in the UK, most patients treated with antihypertensive drugs are managed by general practitioners.[76 77] Second, the CPRD captures prescriptions rather than dispensing information. Therefore, it is possible that some patients may not fill a prescription or adhere to the prescription. However, our study focused on the prescription rather than use of antihypertensive drugs. Third, for the treatment trajectory cohort, the analysis was limited to patients with a recorded diagnosis of hypertension through a robust algorithm. However, it is possible that some patients were not captured by this

definition, leading to an underestimation of the number of patients included in the cohort. However, there is no evidence suggesting that these patients would differ by antihypertensive drug class. Fourth, some antihypertensive drugs may have been prescribed for indications other than hypertension. However, we captured the first-ever antihypertensive drug prescription after a diagnosis of hypertension, therefore minimising the likelihood that the prescriptions were indicated for other comorbidities. Finally, it is possible that we might not have captured the first-ever prescription for some patients.

In summary, nearly one-quarter of primary care patients were prescribed antihypertensive drugs by the end of the study period, with half of those concomitantly receiving two or more classes. Beta-blockers were most prevalent in females and in both the youngest and oldest patients, although this class is associated with potential adverse events. Most patients with hypertension initiated a thiazide diuretic or beta-blocker before 2007 and an ACE inhibitor or CCB after 2007. These prescribing patterns mirror the changes in hypertension management guidelines during the study period. However, fewer females initiated recommended first-line agents, potentially leading to suboptimal cardiovascular outcomes. Future studies should investigate these gaps and inequities, as well as which specific treatment trajectory optimises cardiovascular outcomes in patients with hypertension.

Author affiliations
[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[2]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Montreal, Quebec, Canada
[3]Division of General Internal Medicine, McGill University Health Centre, Montreal, Quebec, Canada
[4]Department of Experimental Medicine, McGill University, Montreal, Quebec, Canada
[5]Department of Family Medicine, McGill University, Montreal, Quebec, Canada
[6]Division of Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada
[7]Departmenf of Medicine, McGill University, Montreal, Quebec, Canada
[8]Gerald Bronfman Department of Oncology, McGill University, Montreal, Quebec, Canada

influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

ORCID iDs
Julie Rouette http://orcid.org/0000-0003-3882-0998
James M. Brophy http://orcid.org/0000-0001-8049-6875
Laurent Azoulay http://orcid.org/0000-0001-5162-3556

REFERENCES
1 Kantor ED, Rehm CD, Haas JS, *et al*. Trends in prescription drug use among adults in the United States from 1999-2012. *JAMA* 2015;314:1818–31.
2 Jung M, Choo E, Lee S. Comprehensive trends and patterns of antihypertensive prescriptions using a nationwide claims database in Korea. *Clin Epidemiol* 2020;12:963–75.
3 Health survey for England 2016: prescribed medicines (2017).
4 Sundbøll J, Adelborg K, Mansfield KE, *et al*. Seventeen-Year nationwide trends in antihypertensive drug use in Denmark. *Am J Cardiol* 2017;120:2193–200.
5 Cois A, Ehrlich R. Antihypertensive treatment and blood pressure trends among South African adults: a repeated cross-sectional analysis of a population panel survey. *PLoS One* 2018;13:e0200606.
6 Garies S, Hao S, McBrien K, *et al*. Prevalence of hypertension, treatment, and blood pressure targets in Canada associated with the 2017 American College of cardiology and American heart association blood pressure guidelines. *JAMA Netw Open* 2019;2:e190406.
7 Blak BT, Mullins CD, Shaya FT, *et al*. Prescribing trends and drug budget impact of the Arbs in the UK. *Value Health* 2009;12:302–8. 10.1111/j.1524-4733.2008.00423.xMar-Apr.
8 Zhao M, Woodward M, Vaartjes I, *et al*. Sex Differences in Cardiovascular Medication Prescription in Primary Care: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2020;9:e014742.

9 Gu Q, Burt VL, Dillon CF, *et al*. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National health and nutrition examination survey, 2001 to 2010. *Circulation* 2012;126:2105–14.

10 Swales JR LE, Coope JR, Pocock SJ, *et al*. Treating mild hypertension. *BMJ* 1989;298:694–8.

11 Sever P, Beevers G, Bulpitt C, *et al*. Management guidelines in essential hypertension: report of the second Working Party of the British hypertension Society. *BMJ*. 1993;306:983–7. Apr 10.

12 Ramsay L, Williams B, Johnston G, *et al*. Guidelines for management of hypertension: report of the third Working Party of the British hypertension Society. *J Hum Hypertens* 1999;13:569–92.

13 National Institute for Clinical Excellence. *Clinical guideline 18. Hypertension - management of hypertension in adults in primary care*, 2004.

14 National Collaborating Centre for Chronic Conditions. *Hypertension: management in adults in primary care: pharmacological update*, 2006.

15 National Institute for Health and Clinical Excellence. *Hypertension: clinical management of primary hypertension in adults (update) (clinical guideline 127*, 2011.

16 Bhaskaran K, Forbes HJ, Douglas I, *et al*. Representativeness and optimal use of body mass index (BMI) in the UK clinical practice research Datalink (CPRD). *BMJ Open* 2013;3:e003389.

17 Herrett E, Gallagher AM, Bhaskaran K, *et al*. Data resource profile: clinical practice research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.

18 Gillam SJ, Siriwardena AN, Steel N. Pay-For-Performance in the United Kingdom: impact of the quality and outcomes framework: a systematic review. *Ann Fam Med* 2012;10:461–8.

19 Herrett E, Thomas SL, Schoonen WM, *et al*. Validation and validity of diagnoses in the general practice research database: a systematic review. *Br J Clin Pharmacol* 2010;69:4–14.

20 Archer C, MacNeill SJ, Mars B, *et al*. Rise in prescribing for anxiety in UK primary care between 2003 and 2018: a population-based cohort study using clinical practice research Datalink. *Br J Gen Pract* 2022. doi:10.3399/BJGP.2021.0561. [Epub ahead of print: 31 Jan 2022].

21 Denaxas SC, George J, Herrett E, *et al*. Data resource profile: cardiovascular disease research using linked bespoke studies and electronic health records (caliber). *Int J Epidemiol* 2012;41:1625–38.

22 Remme WC JGF. The treatment of heart failure. Task force of the Working group on heart failure of the European Society of cardiology. *Eur Heart J* 1997;18:736–53.

23 Walley T, Duggan AK, Haycox AR, *et al*. Treatment for newly diagnosed hypertension: patterns of prescribing and antihypertensive effectiveness in the UK. *J R Soc Med* 2003;96:525–31.

24 McNally RJ, Morselli F, Farukh B, *et al*. A review of the prescribing trend of thiazide-type and thiazide-like diuretics in hypertension: a UK perspective. *Br J Clin Pharmacol* 2019;85:2707–13.

25 Mahmoudpour SH, Asselbergs FW, Souverein PC, *et al*. Prescription patterns of angiotensin-converting enzyme inhibitors for various indications: a UK population-based study. *Br J Clin Pharmacol* 2018;84:2365–72.

26 Calvert MJ, Shankar A, McManus RJ, *et al*. Evaluation of the management of heart failure in primary care. *Fam Pract* 2009;26:145–53.

27 Shah SM, Carey IM, DeWilde S, *et al*. Trends and inequities in beta-blocker prescribing for heart failure. *Br J Gen Pract* 2008;58:862–9.

28 Uijl A, Vaartjes I, Denaxas S, *et al*. Temporal trends in heart failure medication prescription in a population-based cohort study. *BMJ Open* 2021;11:e043290.

29 Baker A, Chen L-C, Elliott RA, *et al*. The impact of the 'Better Care Better Value' prescribing policy on the utilisation of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for treating hypertension in the UK primary care setting: longitudinal quasi-experimental design. *BMC Health Serv Res* 2015;15:367.

30 Gulliford MC, Charlton J, Latinovic R. Trends in antihypertensive and lipid-lowering therapy in subjects with type II diabetes: clinical effectiveness or clinical discretion? *J Hum Hypertens* 2005;19:111–7.

31 Phillips K, Subramanian A, Thomas GN, *et al*. Trends in the pharmacological management of atrial fibrillation in UK general practice 2008-2018. *Heart* 2022;108:517-522.

32 Allen C, Donegan K. The impact of regulatory action on the co-prescribing of renin-angiotensin system blockers in UK primary care. *Pharmacoepidemiol Drug Saf* 2017;26:858–62.

33 Jameson K, Jick S, Hagberg KW, *et al*. Prevalence and management of chronic kidney disease in primary care patients in the UK. *Int J Clin Pract*. 2014;68:1110–21. Sep.

34 Lee S, Shafe ACE, Cowie MR. Uk stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the general practice research database. *BMJ Open* 2011;1:e000269.

35 Hardoon SL, Whincup PH, Petersen I, *et al*. Trends in longer-term survival following an acute myocardial infarction and prescribing of evidenced-based medications in primary care in the UK from 1991: a longitudinal population-based study. *J Epidemiol Community Health* 2011;65:770–4.

36 MacDonald TM, Morant SV, Mozaffari E. Treatment patterns of hypertension and dyslipidaemia in hypertensive patients at higher and lower risk of cardiovascular disease in primary care in the United Kingdom. *J Hum Hypertens* 2007;21:925–33.

37 Kalra PR, Morley C, Barnes S, *et al*. Discontinuation of beta-blockers in cardiovascular disease: UK primary care cohort study. *Int J Cardiol* 2013;167:2695–9.

38 Hemmelgarn BR, Chen G, Walker R, *et al*. Trends in antihypertensive drug prescriptions and physician visits in Canada between 1996 and 2006. *Can J Cardiol* 2008;24:507–12.

39 NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. *Lancet* 2021;398:957–80.

40 Kurdi AI, Chen L-C, Elliott RA. Exploring factors associated with patients' adherence to antihypertensive drugs among people with primary hypertension in the United Kingdom. *J Hypertens*. 2017;35:1881–90. Sep.

41 Elliott WJ, Plauschinat CA, Skrepnek GH, *et al*. Persistence, adherence, and risk of discontinuation associated with commonly prescribed antihypertensive drug monotherapies. *J Am Board Fam Med* 2007;20:72–80.

42 Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med* 2012;125:882–7.

43 Qvarnström M, Wettermark B, Ljungman C, *et al*. Antihypertensive treatment and control in a large primary care population of 21 167 patients. *J Hum Hypertens* 2011;25:484–91.

44 Jiao T, Platt RW, Douros A, *et al*. Prescription patterns for the use of antihypertensive drugs for primary prevention among patients with hypertension in the United Kingdom. *Am J Hypertens* 2022;35:42–53.

45 Rydberg DM, Mejyr S, Loikas D, *et al*. Sex differences in spontaneous reports on adverse drug events for common antihypertensive drugs. *Eur J Clin Pharmacol* 2018;74:1165–73.

46 Jochmann N, Stangl K, Garbe E, *et al*. Female-Specific aspects in the pharmacotherapy of chronic cardiovascular diseases. *Eur Heart J* 2005;26:1585–95.

47 Bots SH, Groepenhoff F, Eikendal ALM, *et al*. Adverse Drug Reactions to Guideline-Recommended Heart Failure Drugs in Women: A Systematic Review of the Literature. *JACC Heart Fail* 2019;7:258–66.

48 Archer C, Turner K, Kessler D, *et al*. Trends in the recording of anxiety in UK primary care: a multi-method approach. *Soc Psychiatry Psychiatr Epidemiol* 2022;57:375-386.

49 British National Formulary. Propranolol hydrochloride. Available: https://bnf.nice.org.uk/drug/propranolol-hydrochloride.html

50 Steenen SA, van Wijk AJ, van der Heijden GJMG, *et al*. Propranolol for the treatment of anxiety disorders: systematic review and meta-analysis. *J Psychopharmacol* 2016;30:128–39.

51 Baldwin DS, Anderson IM, Nutt DJ, *et al*. Evidence-Based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British association for psychopharmacology. *J Psychopharmacol* 2014;28:403–39.

52 Healthcare Safety Investigation Branch. *Potential under-recognized risk of harm from the use of propranolol*, 2020.

53 Ham AC, van Dijk SC, Swart KMA, *et al*. Beta-Blocker use and fall risk in older individuals: original results from two studies with meta-analysis. *Br J Clin Pharmacol* 2017;83:2292–302.

54 ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002;288:2981–97.

55 Dahlöf B, Sever PS, Poulter NR, *et al*. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian cardiac outcomes Trial-Blood pressure lowering arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895–906.

56 Zanchetti A, Crepaldi G, Bond MG, *et al*. Different effects of antihypertensive regimens based on fosinopril or hydrochlorothiazide with or without lipid lowering by pravastatin on progression of asymptomatic carotid atherosclerosis: principal

results of PHYLLIS--a randomized double-blind trial. *Stroke* 2004;35:2807–12.

57 Julius S, Kjeldsen SE, Weber M, *et al*. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the value randomised trial. *Lancet* 2004;363:2022–31.

58 Cohn JN, Tognoni G. Valsartan heart failure trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–75.

59 Dahlöf B, Devereux RB, Kjeldsen SE, *et al*. Cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (life): a randomised trial against atenolol. *Lancet* 2002;359:995–1003.

60 Young JB, Dunlap ME, Pfeffer MA, *et al*. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. *Circulation* 2004;110:2618–26.

61 Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, *et al*. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145–53.

62 Fox KM, EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet* 2003;362:782–8.

63 Konstam MA, Neaton JD, Dickstein K, *et al*. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. *Lancet* 2009;374:1840–8.

64 , Yusuf S, Teo KK, *et al*, ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358:1547–59.

65 Jamerson K, Weber MA, Bakris GL, *et al*. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417–28.

66 Beckett NS, Peters R, Fletcher AE, *et al*. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–98.

67 Pitt B, Zannad F, Remme WJ, *et al*. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. randomized Aldactone evaluation study Investigators. *N Engl J Med* 1999;341:709–17.

68 Pitt B, Remme W, Zannad F, *et al*. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–21.

69 Zannad F, McMurray JJV, Krum H, *et al*. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;364:11–21.

70 Packer M, Fowler MB, Roecker EB, *et al*. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. *Circulation* 2002;106:2194–9.

71 Poole-Wilson PA, Swedberg K, Cleland JGF, *et al*. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the carvedilol or metoprolol European trial (comet): randomised controlled trial. *Lancet* 2003;362:7–13.

72 National Institute for Health and Clinical Excellence. Hypertension in adults: diagnosis and management, 2019. Available: https://www. nice.org.uk/guidance/ng136

73 Sinnott S-J, Douglas IJ, Smeeth L, *et al*. First line drug treatment for hypertension and reductions in blood pressure according to age and ethnicity: cohort study in UK primary care. *BMJ* 2020;371:m4080.

74 Blood Pressure Lowering Treatment Trialists' Collaboration, Turnbull F, Neal B, *et al*. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *BMJ* 2008;336:1121–3.

75 Marinier K, Macouillard P, de Champvallins M, *et al*. Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension: a propensity score-matched cohort study in the UK clinical practice research Datalink. *Pharmacoepidemiol Drug Saf* 2019;28:1572–82.

76 Boffa RJ, Constanti M, Floyd CN, *et al*. Hypertension in adults: summary of updated NICE guidance. *BMJ* 2019;367:l5310.

77 Mejzner N, Clark CE, Smith LF, *et al*. Trends in the diagnosis and management of hypertension: repeated primary care survey in South West England. *Br J Gen Pract*. 2017;67:e306–13. 10.3399/bjgp17X690461May.