Association between antihypertensive treatment and hospitalisation or death due to falls according to sex, ethnicity, and social deprivation status: an observational cohort study in English primary care electronic health-care records

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Summary

Background Antihypertensive therapy is associated with an increased risk of adverse events, such as falls, in older patients and those with increasing levels of frailty. This study aimed to explore the association between antihypertensive treatment and serious adverse events in other patient subgroups in primary care according to sex, ethnicity, and socioeconomic status.

Methods This retrospective observational cohort study used routinely collected primary care data from England, UK, in the Clinical Practice Research Datalink Aurum database between Jan 1, 1998, and Dec 31, 2018. Patients aged 40 years or older, without previous antihypertensive prescriptions, and with a systolic blood pressure reading of 130–179 mm Hg were included. The main outcome was first hospitalisation or death from a fall within 10 years of follow-up. Exposure was defined as the first antihypertensive prescription within 12 months after inclusion. Cox regression models adjusted for propensity scores were developed in sex, ethnicity, and socioeconomic status subgroups, and absolute risk differences were calculated.

Findings 2 614 330 patients were included in the analyses, of whom 337 742 (12·9%) were in the exposed group and 2 276 588 were in the non-exposed group. Median age in the non-exposed group was 53 years (IQR 46–63); 1 141 885 (50·2%) were female and 1 134 703 (49·8%) were male; 1 120 659 (49·2%) were White, 561 427 (24·7%) were of mixed or other ethnicity, 64 377 (2·8%) were Black, and 53 338 (2·3%) were south Asian. In the exposed group, median age was 61 years (51–71); 166 639 (49·3%) were female and 171 103 (50·7%) were male; 196 432 (58·2%) were White, 66 460 (19·7%) were of mixed or other ethnicity, 13 668 (4·0%) were Black, and 10 948 (3·2%) were south Asian. The median follow-up time was 7·0 years (IQR 2·9–10·0). The main outcome of falls was observed in 110 874 patients (4·2% of the total population; 23 925 [7·1%] in the exposed group and 86 949 [3·8%] in the non-exposed group). The association between antihypertensive medication and hospitalisation or death due to falls was similar for both sexes (adjusted hazard ratio [aHR] 1·09 [95% CI 1·06–1·12] for male patients and 1·10 [1·07–1·12] for female patients). The associations (aHRs) in the different ethnicity groups were 1·32 (95% CI 1·13–1·53) in Black patients, 1·22 (1·05–1·41) in south Asian patients, 1·47 (1·29–1·66) in patients of mixed or other ethnicity, and 1·05 (1·03–1·07) in White patients. The most deprived group had an aHR of 1·02 (95% CI 0·99–1·06) and the least deprived group had an aHR of 1·16 (1·12–1·21). The absolute risk difference was low for all subgroups (≤12 events per 10 000 patients per year).

Interpretation All subgroups of patients with antihypertensive prescriptions had an increased risk of hospitalisation or death due to falls versus those who were unexposed. No significant difference in risk of falls was observed based on sex, ethnicity, or social deprivation; therefore, no distinction should be made among these groups when considering the harms of antihypertensives in individual treatment decisions in primary care.

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Introduction

Antihypertensive drugs are among the most commonly prescribed medications in primary care and are important components of preventive strategies to reduce morbidity and mortality from cardiovascular disease.[1,2] Nearly a quarter of primary care patients in the UK are prescribed antihypertensive treatment.[3] Initiating antihypertensive treatment often commits patients to long-term or even lifelong medication. Therefore, assessing the benefits and risks of treatment in primary care is essential.[4] In recent years, these benefits and risks have been shown to differ among patient subgroups; specifically, the risk of adverse

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Research in context

Evidence before this study

This study is based on previous publications by the STRATIFY team on the harms of antihypertensive treatment, which include a systematic review on antihypertensives and adverse events (Albasri et al, 2021) and a cohort study on the association between antihypertensives and serious adverse events by age and frailty (Sheppard et al, 2023). In these studies, the risk of adverse events 10 years after starting new antihypertensive treatment in frail and older adults was notably increased, and the number needed to harm approached the number needed to treat. The current study aimed to explore this association between antihypertensive treatment and serious adverse events in subgroups under-represented in research to help uncover health inequities. These underserved communities, such as people from minority ethnic groups and socioeconomically deprived backgrounds, are disproportionally affected by hypertension and hypertension-mediated complications. In these populations, therefore, there might be a greater need for antihypertensive management tailored to individual needs.

Added value of this study

This was a large, nationally representative cohort of community-dwelling patients in England, UK. The study cohort allowed for analyses of small (minority) subgroups, with the smallest subgroup still comprising more than 60 000 patients. Focusing specifically on commonly under-represented and under-reported patient groups in a large cohort will help our understanding of whether health inequities exist.

Implications of all the available evidence

Although the burden of hypertension disproportionately affects those from underserved communities, our results should reassure physicians that the potential harms of antihypertensive therapy are low, and safety concerns should not preclude treatment in any patient group, including those typically under-represented in trials and underserved in care in the communities that were studied in this analysis.

events, such as falls, is higher among older patients and those with increasing levels of frailty.[5,6] By contrast, evidence for the management of hypertension, specifically the harms of treatment, in minority ethnic groups, socioeconomically deprived patient groups, and sex-specific management, is currently scarce.[7]

Certain minority ethnic patient groups have been reported to experience higher rates of hypertension and hypertension-mediated complications, probably due to a combination of pathophysiology, socioeconomic status, response to antihypertensive drugs due to pharmacogenetic variants, or other yet unknown factors.[7–10] Similarly, socioeconomically deprived individuals have a higher risk of developing hypertension due to an interaction between mutually reinforcing factors, such as education, occupation, diet, and income.[11] Furthermore, important sex-specific differences exist in hypertension epidemiology and management and, historically, women are under-represented in hypertension clinical trials.[12,13] Additionally, women have been reported to be more likely to experience adverse effects from antihypertensives.[12–14] Focusing specifically on these commonly under-represented and under-reported patient groups will help our understanding of whether health inequities exist and whether treatment plans should be tailored to individual needs when managing hypertension.[7,10]

This study aimed to explore the association between antihypertensive treatment and serious adverse events, such as falls, particularly in clinically relevant and under-represented patient subgroups (minority ethnic groups, people from socioeconomically deprived backgrounds, and women), in a large nationally representative cohort from primary care in England, UK.

Methods

Study design and setting

We designed a large observational cohort study using retrospective data from primary care. The design and methods have been described elsewhere.[5] Data were extracted from the Clinical Practice Research Datalink (CPRD) database, an ongoing dynamic database containing pseudonymised data from UK primary care electronic healthcare records. In CPRD, to ensure representativeness, consent is based on an opt-out system. For this study, the CPRD Aurum dataset was used, which covered around 13% of the population in England, UK, in 2018 and is broadly representative.[15] This study adhered to the RECORD guideline.[16] CPRD data have ongoing ethical approval for research use, subject to scientific review and approval; the current study was approved by the CPRD ISAC Committee (protocol 19_042).

Study population

Data were extracted from patient records between Jan 1, 1998, and Dec 31, 2018 (study start and end dates). Inclusion criteria were: age 40 years or older, registration at an up-to-standard general practice (records met quality standards for research), linkage to hospital data, no previous antihypertensive treatment, and at least one systolic blood pressure reading of 130–179 mm Hg. Patients with a systolic blood pressure reading of 180 mmHg or higher were excluded because antihypertensive treatment is deemed indicated in this population regardless of adverse event risk.[7] Patients entered the cohort after their first systolic blood pressure reading. Exposure to antihypertensive treatment was defined by having a prescription for

antihypertensives in the 12 months after cohort entry. The index date (baseline) was set at the end of this exposure period. The 12-month exposure period was chosen to eliminate immortal time bias and to account for delays in general practice prescribing, including the need for multiple blood pressure readings before treatment initiation. Patients were thereafter followed up for up to 10 years. Patients exited the cohort on the study end date (Dec 31, 2018), or when they transferred out of a registered general practice, died, or experienced any of the outcomes of interest, whichever came first. The process of cohort entry, exposure period, index date, and cohort exit is visualised for clarification in the appendix (p 2). Records were linked at a patient level to Office for National Statistics (ONS) death registration data, Hospital Episode Statistics (HES) Admitted Patient Care data, and Index of Multiple Deprivation (IMD) 2015 data, applying the same study start and end dates. The datasets for the current analyses were constructed in November, 2024.

Outcomes

The main outcome of this study was first hospitalisation or death after a primary diagnosis of a fall within 10 years of follow-up. Additional outcomes were hospitalisation or death after a primary diagnosis of each of the following: hypotension, syncope, fracture, or acute kidney injury. Outcomes were captured in ONS and HES data. For mortality data from ONS death registration data, we extracted both all-cause mortality and cause-specific data. We used HES Admitted Patient Care data to extract the hospital admission records. All the cause-specific outcomes were defined based on both the primary diagnosis in the HES Admitted Patient Care and the ONS death registration data using prespecified ICD-9 and ICD-10 codes. Data collection and outcome definitions methods were consistent across all outcomes. A full list of codes is provided in the appendix (pp 3–8).

Variables

Exposure was defined as any antihypertensive prescription in the 12 months after cohort entry. Patients in the cohort without antihypertensive prescription within 12 months were included as non-exposed individuals. Starting antihypertensive treatment was defined as any prescription of the following drug classes: ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazides and thiazide-like diuretics, β blockers, α blockers, and other antihypertensives (ie, vasodilators, direct renin inhibitors, and centrally acting antihypertensives). A full list of British National Formulary codes is available online.

In CPRD Aurum, gender and sex are categorised into two groups: male and female. They correspond to biologically male and biologically female sex, respectively.

Ethnicity is coded into eleven categories in CPRD Aurum and HES. It is based on self-reported ethnicity details provided by patients: Bangladeshi, Black African, Black Caribbean, Black other, Chinese, Indian, mixed, other, other Asian, Pakistani, and White. For this study, the original categories were combined into four groups to account for small numbers: Black (Black African, Black Caribbean, or Black other), mixed or other (Chinese, mixed, other, or other Asian), south Asian (Bangladeshi, Indian, or Pakistani), and White.

Socioeconomic status was assessed using the IMD. We used IMD 2015 in our study, which was linked to CPRD Aurum.[17] IMD is a composite measure derived from several domains of socioeconomic deprivation: income, employment, education and skills, health, housing, crime, access to services, and living environment. The IMD scores were divided into five categories (quintiles): IMD 1 contains individuals who are the least socially deprived, and IMD 5 contains individuals who are the most socially deprived.

Covariates were chosen based on literature, treatment guidelines, and expert opinion.[5,7] They included patient demographics, smoking, BMI, alcohol consumption, frailty, relevant disease history and comorbidities, previous history of the outcomes of interest, and other prescriptions, including medicines related to cardiovascular risk management (ie, anticoagulants and antiplatelets) and falls risk (ie, opioids, benzodiazepines, antidepressants, and anticholinergics). A list of all covariates is provided in the appendix (pp 11–12). Read Codes and Medcode for all covariates are provided online.

Statistical analysis

Baseline characteristics were reported using descriptive statistics, with categorical variables as numbers with percentages and continuous variables as means with SDs or medians with IQRs. Propensity scores were generated by developing a multivariable logistic regression model. This model predicted the likelihood of antihypertensive treatment prescription based on individual variables (possible confounders). The following variables were included in the propensity score model (appendix pp 11–12): age, sex, ethnicity, smoking status (non-smoker, ex-smoker, or current smoker), alcohol consumption (non-drinker, unknown units, <1 unit per day, 1–2 units per day, 3–6 units per day, ≥7 units per day), IMD, BMI, blood pressure, previous history of the main and additional outcomes, frailty index, medical history (stroke, myocardial infarction, heart failure, transient ischaemic attack, peripheral vascular disease, angina, coronary artery bypass graft, chronic kidney disease, diabetes, atrial fibrillation, and cancer), and other medication prescriptions (statins, antiplatelets or anticoagulants, anticholinergics, antidepressants, benzodiazepines, and opioids). The individual likelihoods (propensity scores) were subsequently used in models to examine the association between antihypertensive treatment and the outcomes of interest.[18,19] Because of computational considerations, including running time, continuous variables were categorised. BMI was categorised as: low weight (<18·5 kg/m^2), normal (≥18·5 kg/m^2 to <25 kg/m^2), overweight (≥25 kg/m^2 to <30 kg/m^2), obese (≥30 kg/m^2 to <35 kg/m^2), and very obese

See Online for appendix

For **Read Codes and Medcodes of covariates** see https://github.com/jamessheppard48/STRATIFY-BP/tree/Causal-inference-project/CPRD%20AURUM

For the **full list of drug codes** see https://github.com/jamessheppard48/STRATIFY-BP/tree/Causal-inference-project/CPRD%20AURUM

(≥35 kg/m^2). Frailty index was categorised as: fit (≤0·12), mild frailty (>0·12 to ≤0·24), moderate frailty (>0·24 to ≤0·36), and severe frailty (>0·36). Systolic blood pressure was categorised as <140 mm Hg, 140–159 mm Hg, or 160–169 mm Hg, and diastolic blood pressure was categorised as <80 mm Hg, 80–89 mm Hg, or 90–149 mm Hg.

The propensity score model was evaluated using four methods: estimating discrimination (c-statistic), constructing a calibration plot, visualising propensities for exposed and non-exposed patients in a density plot, and propensity score matching. Then, covariate balance was compared using standardised mean differences between propensity score before and after matching. Matching was based on a propensity score 1:1 matching of exposed and non-exposed individuals using the nearest-neighbour method (with calliper size restricted to 0·2). A standardised mean difference of less than 0·1 was considered an acceptable balance.

For the main analysis, a time-to-event modelling approach was chosen using Cox regression models adjusted only for propensity scores. A maximum of 10 years of follow-up was chosen to examine the association between antihypertensive treatments and the prespecified main and additional outcomes.[5] Model assumptions were checked by inspecting survival curves and Schoenfeld residuals for the main exposure and main outcome. After confirming that the assumptions were met, absolute risk differences were calculated using the method by Austin.[20] Confidence intervals were obtained through bootstrapping with 100 repetitions.[20] Results were stratified for sex, ethnicity, and IMD quintiles and per outcome. All eligible patients from the study population were included in the analyses, and no matching was used in the main analyses. As a post-hoc sensitivity analysis, the analyses were repeated in a subset of patients aged 80 years or older, because this group has been shown to experience the most harm from antihypertensive treatment.[5] Additionally, post-hoc interaction analyses were done to estimate differences between subgroups (sex, ethnicity, and IMD quintiles). Sample size calculations were published previously and resulted in a prespecified sample size of at least 88 380 patients and 4634 events, assuming an increase of 10% in the rate of each adverse event with treatment, and an event rate of at least 0·5% per year in the non-exposed group, with 90% power and an α of 0·05.[5] All analyses were done in R (version 4.4.1) with packages *mice*, *rms*, *survival*, *survminer*, and *forester*.

Missing data were imputed using multiple imputations by chained equation.[21,22] There were five variables with missing values: ethnicity (20·2% missing), IMD (9·7% missing), smoking status (6·1% missing), BMI (16·6% missing), and alcohol groups (17·8% missing). Missing data were assumed to be missing at random based on results from previous sensitivity analyses in this cohort exploring handling of missing data.[5] All variables were imputed categorically and ten datasets were generated with ten iterations. A multinomial logistic regression modelling technique was used to impute ethnicity, and ordinal logistic regression was used for the other ordinal variables. All variables, including the outcomes, were used to impute missing data. All analyses were performed in each imputed dataset separately; the estimates and their SEs were then combined according to Rubin's rules.[23]

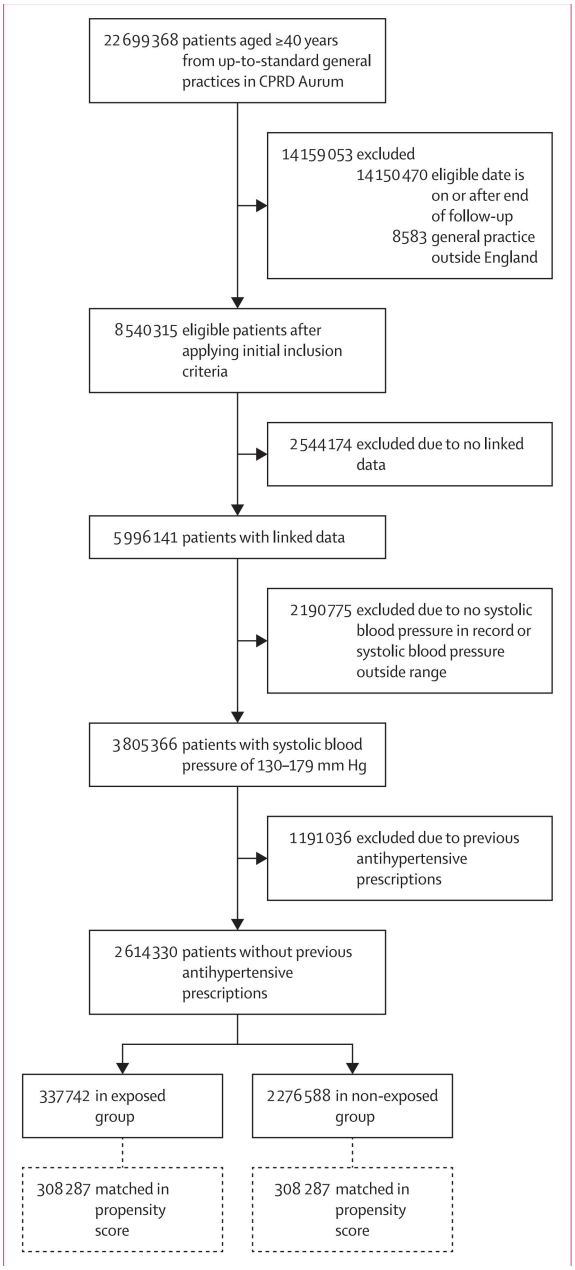

Figure 1: **Flow diagram of patient selection**
CRPD=Clinical Practice Research Datalink.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In CPRD Aurum, 3 805 366 potentially eligible patients with systolic blood pressure of 130–179 mm Hg were identified. After removing patients with previous antihypertensive prescriptions (before cohort entry), 2 614 330 patients were included in the analyses (figure 1). In total, 337 742 (12·9%) patients were exposed to antihypertensive treatment in the 12 months after cohort entry and were included in the exposed group. All other patients (n=2 276 588) were included in the non-exposed group. Baseline characteristics are presented in the table. The baseline distribution of original CPRD ethnicity categories before categorisation into four groups (Black, South Asian, mixed/other and White) is shown in the appendix (p 9). Patients in the exposed group were generally older than those in the non-exposed group (median 61 years [IQR 51–71] *vs* 53 years [46–53]). In the exposed group, 166 639 (49·3%) were female, and 171 103 (50·7%) were male. The median follow-up time for the whole population was 7·0 years (IQR 2·9–10·0). The median follow-up times by subgroup are shown in the appendix (p 10).

The main outcome of hospitalisation or death from falls was observed in 110 874 patients (4·2% of the total population), including 23 925 (7·1%) in the exposed population and 86 949 (3·8%) in the non-exposed population.

The propensity score model included 32 covariates (appendix pp 11–12). Discrimination (c-statistic 0·82) and calibration (appendix p 13) were sufficiently good. The density plot of propensities for exposed and non-exposed individuals is shown in the appendix (p 14). A total of 308 287 patients in the exposed group and 308 287 in the non-exposed group were subsequently compared in matched analysis, and all baseline variables were distributed equally (standardised mean differences <0·1; appendix pp 15–16).

The risk of the main outcome of hospitalisation or death from a fall was slightly increased in patients prescribed antihypertensive treatment versus those not prescribed antihypertensives, but in subgroup analyses by sex, the confidence intervals largely overlapped between male and female patients (adjusted hazard ratio [aHR] 1·09 [95% CI 1·06–1·12] for male patients and 1·10 [1·07–1·12] for female patients; figure 2). Increased risks were also observed for the outcomes of hospitalisation or death from hypotension, syncope, and acute kidney injury but not for fractures, with overlapping confidence intervals in male and female patients for all outcomes. Absolute risk differences were overall low, with 5·5 additional fall cases (95% CI 3·4–7·7) in the male population and 9·9 additional fall cases (7·2–12·5) in the female population per 10 000 treated patients per year. The numbers needed to harm for outcome falls were high: 199 (95% CI 76–296) for male patients and 110 (76–140) for female patients (appendix p 20). All subgroup post-hoc interaction analyses were significant (p<0·0001).

In the analysis by ethnicity group, the relative association (aHR) between antihypertensive treatment and death or hospitalisation from falls was 1·32 (95% CI 1·13–1·53) in

	Non-exposed group (n=2 276 588)	Exposed group (n=337 742)
Age, years	53 (46–63)	61 (51–71)
Sex		
Female	1 141 885 (50·2%)	166 639 (49·3%)
Male	1 134 703 (49·8%)	171 103 (50·7%)
Ethnicity		
Black	64 377 (2·8%)	13 668 (4·0%)
South Asian	53 338 (2·3%)	10 948 (3·2%)
White	1 120 659 (49·2%)	196 432 (58·2%)
Mixed or other	561 427 (24·7%)	66 460 (19·7%)
Missing	476 787 (20·9%)	50 234 (14·9%)
IMD quintile		
1 (least deprived)	496 339 (21·8%)	63 054 (18·7%)
2	446 697 (19·6%)	61 791 (18·3%)
3	408 773 (18·0%)	59 908 (17·7%)
4	367 134 (16·1%)	59 474 (17·6%)
5 (most deprived)	336 890 (14·8%)	59 969 (17·8)
Missing	220 755 (9·7%)	33 546 (9·9%)
Smoking status		
Non-smoker	913 857 (40·1%)	130 781 (38·7%)
Current smoker	533 799 (23·4%)	70 633 (20·9%)
Ex-smoker	689 010 (30·3%)	118 041 (35·0%)
Missing	139 922 (6·1%)	18 287 (5·4%)
Alcohol consumption		
Non-drinker	460 864 (20·2%)	85 971 (25·5%)
Trivial (<1 unit per day)	612 400 (26·9%)	82 630 (24·5%)
Light (1–2 units per day)	450 580 (19·8%)	57 972 (17·2%)
Moderate (3–6 units per day)	154 612 (6·8%)	23 235 (6·9%)
Heavy (≥7 units per day)	44 833 (2·0%)	6953 (2·4%)
Drinker (unknown units)	139 186 (6·1%)	28 827 (8·5%)
Missing	414 113 (18·2%)	52 154 (15·4%)
BMI		
Median (IQR)	26·3 (23·6–29·7)	27·7 (24·7–31·4)
Low weight (<18·5 kg/m^2)	24 847 (1·1%)	3043 (0·9%)
Normal (≥18·5 kg/m^2 to <25 kg/m^2)	677 203 (29·7%)	76 618 (22·7%)
Overweight (≥25 kg/m^2 to <30 kg/m^2)	739 792 (32·5%)	114 219 (33·8%)
Obese (≥30 kg/m^2 to <35 kg/m^2)	305 850 (13·4%)	63 272 (18·7%)
Very obese (≥35 kg/m^2)	139 917 (6·1%)	34 943 (10·3%)
Missing	388 979 (17·1%)	45 647 (13·5%)
Systolic blood pressure, mm Hg	140 (132–148)	150 (140–160)
Diastolic blood pressure, mm Hg	82 (79–90)	89 (80–97)
Electronic frailty index score		
Median (IQR)	0·03 (0·00–0·06)	0·06 (0·03–0·11)
Fit (≤0·12)	2 130 782 (93·6%)	269 025 (79·7%)
Mild frailty (>0·12 to ≤0·24)	126 018 (5·5%)	58 636 (17·4%)
Moderate frailty (>0·24 to ≤0·36)	17 189 (0·8%)	8846 (2·6%)
Severe frailty (>0·36)	2599 (0·1%)	1235 (0·4%)
Comorbidities		
Stroke	29 222 (1·3%)	14 023 (4·2%)
Transient ischaemic attack	13 826 (0·6%)	6532 (1·9%)
Myocardial infarction	12 943 (0·6%)	17 914 (5·3%)
Heart failure	8527 (0·4%)	10 063 (3·0%)
Peripheral vascular disease	14 657 (0·6%)	7383 (2·2%)
Coronary artery bypass graft	2356 (0·1%)	4588 (1·4%)

(Table continues on next page)

	Non-exposed group (n=2 276 588)	Exposed group (n=337 742)
(Continued from previous page)		
Angina	16 949 (0·7%)	21 151 (6·3%)
Atrial fibrillation	23 285 (1·0%)	16 877 (5·0%)
Diabetes	105 995 (4·7%)	50 214 (14·9%)
Chronic kidney disease	20 654 (0·9%)	15 340 (4·5%)
Cancer	79 321 (3·5%)	16 940 (5·0%)
Antihypertensive treatment prescriptions		
ACE inhibitors	0	127 757 (37·8%)
Angiotensin II receptor blockers	0	33 505 (9·9%)
Calcium channel blockers	0	97 719 (28·9%)
Thiazides and thiazide-like diuretics	0	101 587 (30·1%)
β blockers	0	109 911 (32·5%)
α blockers	0	13 330 (3·9%)
Other antihypertensives*	0	5259 (1·6%)
Number of antihypertensive prescriptions		
One	0	21 8917 (64·8%)
Two	0	91 369 (27·1%)
Three or more	0	27 456 (8·1%)
Other treatment prescriptions		
Statins	147 507 (6·5%)	105 063 (31·1%)
Antiplatelets or anticoagulants	154 521 (6·8%)	100 869 (29·9%)
Anticholinergics	192 857 (8·5%)	26 953 (8·0%)
Antidepressants	408 592 (17·9%)	61 199 (18·1%)
Benzodiazepines	389 519 (17·1%)	53 839 (15·9%)
Opioids	641 891 (28·2%)	99 138 (29·4%)

Data are median (IQR) or n (%). IMD=Index of Multiple Deprivation. ACE=angiotensin-converting enzyme. *Other antihypertensives are centrally acting antihypertensives, direct renin inhibitors, and vasodilators.

Table: **Baseline characteristics in participants grouped by non-exposure or exposure to antihypertensive treatment in the 12 months after cohort entry (total population n=2 614 330)**

Black patients, 1·22 (1·05–1·41) in south Asian patients, 1·47 (1·29–1·66) in patients of mixed or other ethnicities, and 1·05 (1·03–1·07) in White patients (figure 3). The additional events per 10 000 patients per year were low over all subgroups. For example, for the main outcome of death or hospitalisation from falls, the absolute risk difference ranged from 2·8 events (95% CI 1·9–17·5) per 10 000 patients per year (in the mixed or other ethnicity group) to 11·9 events (4·8–18·3) per 10 000 patients per year (in the Black ethnicity group). The numbers needed to harm were high for all outcomes (range from 97 [95% CI –12 to 188] to 402 [166 to 567] for falls; appendix p 20). All subgroup post-hoc interaction analyses were significant (p<0·0001).

In the analysis by social deprivation subgroup, the relative association (aHR) of antihypertensive treatment and adverse events was generally lower for the more deprived populations than the least deprived populations, although confidence intervals largely overlapped between the subgroups (aHR 1·02 [95% CI 0·99–1·06] for IMD 5 *vs* 1·16 [1·12–1·21] for IMD 1 for the falls outcome; figure 4). A similar trend was observed in the absolute risk differences for the outcomes of falls and fractures; however, for the outcomes of hypotension, syncope, and acute kidney injury, there was overlap across all subgroups. The numbers needed to harm for all IMD quintiles were high with wide confidence intervals (range from 91 [95% CI 57 to 121] to 383 [–46 384 to 53 447] for falls; appendix p 20). All subgroup post-hoc interaction analyses were significant (p<0·0001).

The aHRs, absolute risk differences, and numbers needed to harm for subgroups of patients aged 80 years or older are presented in the appendix (pp 17–19, 21; post-hoc analysis). The relative associations (aHRs) of antihypertensive treatment and outcomes were similar to the results from the main analyses. The absolute risks were higher in patients aged 80 years or older compared with other subgroups due to the higher baseline risk in this older population (appendix pp 17–19).

Discussion

In this large cohort of more than 2·6 million patients, antihypertensive treatment initiation was generally associated with an increased risk of hospitalisation or death due to falls, hypotension, syncope, and acute kidney injury, with no difference seen in the occurrence of death or hospitalisation due to fracture. The highest hazards (aHRs) were generally observed in the Black, south Asian, and mixed or other ethnicity groups (compared with the White ethnicity group), and in the least deprived populations. However, the absolute risk of these adverse events was very low. Post-hoc interaction analyses between subgroups were all significant; however, this is likely to be attributable to our large sample size. The low absolute risks and small differences in hazards between subgroups are not likely to be relevant in primary care clinical practice. Although the burden of hypertension disproportionately affects those from underserved communities,[10,11] these data should reassure physicians that the potential harms of antihypertensive therapy are low, and safety concerns should not preclude treatment in any patient group, including those typically under-represented in trials and underserved in care in the communities that were studied in this analysis.

Previously, we found that the risk of adverse events 10 years after starting new antihypertensive treatment is low overall.[5] However, it was observed that in frail and older adults, this risk was notably increased, and numbers needed to harm were reaching numbers needed to treat. These findings showed that the harms and benefits of antihypertensive treatment are more finely balanced with increasing age (80 years to ≥90 years) and in frail patients.[5] Similarly, the current study aimed to explore the association between antihypertensive treatment and serious adverse events in other relevant and under-reported subgroups to help uncover health inequities and specific individual needs in managing hypertension. In our sensitivity analysis of patients aged 80 years or older, we observed increased absolute risks, but the differences (or lack of differences) between subgroups were broadly similar to the results of our main analyses. Furthermore, only 1% of our

	Sex	Total	Exposed group	Exposed events	Non-exposed group	Non-exposed events	Adjusted hazard ratio (95% CI)	Absolute risk difference* (95% CI)
Falls (main outcome)								
	Male	1305806	171103	8928	1134703	31724	1·09 (1·06 to 1·12)	5·5 (3·4 to 7·7)
	Female	1308524	166639	14997	1141885	55225	1·10 (1·07 to 1·12)	9·9 (7·2 to 12·5)
	Overall	2614330	337742	23925	2276588	86949	1·08 (1·06 to 1·10)	6·7 (5·6 to 8·3)
Hypotension								
	Male	1305806	171103	4242	1134703	11619	1·32 (1·27 to 1·38)	8·4 (7·1 to 9·6)
	Female	1308524	166639	3987	1141885	11500	1·39 (1·33 to 1·45)	9·5 (8·3 to 10·7)
	Overall	2614330	337742	8229	2276588	23119	1·35 (1·31 to 1·40)	8·9 (7·9 to 9·8)
Syncope								
	Male	1305806	171103	5301	1134703	17922	1·23 (1·18 to 1·27)	7·9 (6·7 to 9·4)
	Female	1308524	166639	4769	1141885	16633	1·20 (1·16 to 1·25)	6·7 (5·1 to 8·3)
	Overall	2614330	337742	1007	2276588	34555	1·21 (1·18 to 1·25)	7·2 (6·1 to 8·2)
Fracture								
	Male	1305806	171103	5228	1134703	28079	0·99 (0·95 to 1·02)	−0·5 (−2·1 to 1·2)
	Female	1308524	166639	10186	1141885	46044	1·03 (1·01 to 1·06)	2·8 (0·8 to 4·9)
	Overall	2614330	337742	15414	2276588	74123	1·01 (0·99 to 1·03)	0·4 (−0·8 to 1·7)
Acute kidney injury								
	Male	1305806	171103	9898	1134703	23969	1·38 (1·34 to 1·42)	20·0 (18·3 to 22·0)
	Female	1308524	166639	7997	1141885	18226	1·48 (1·43 to 1·53)	19·9 (18·0 to 21·7)
	Overall	2614330	337742	17895	2276588	42195	1·42 (1·39 to 1·46)	20·0 (18·5 to 21·3)

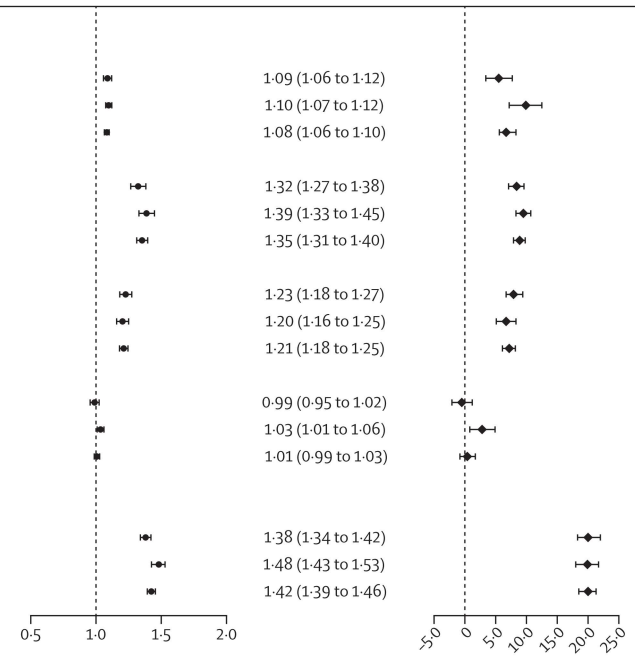

Figure 2: **Associations between antihypertensive treatment and hospitalisation or death due to falls, hypotension, syncope, fracture, and acute kidney injury by sex**
Associations are shown in terms of propensity score-adjusted hazard ratios and absolute risk differences. All subgroup post-hoc interaction analyses were significant (p<0·0001). Unadjusted analyses are provided in the appendix (p 22). *Additional events per 10 000 patients per year.

study population (29 869 individuals) were categorised as moderately or severely frail.

We found that the risk of assessed serious adverse events from antihypertensives for male and female patients was overall similar to previous results at the population level.[5] Both groups' relative and absolute risks of serious adverse events were very low. This finding is contrary to previous reports suggesting a higher risk of adverse events in female patients; although in these reports wider definitions of adverse events were chosen, the risk might differ between antihypertensive drug classes, which was not explored in our analysis.[14,24] Furthermore, antihypertensive treatment has been shown to be equally beneficial in male and female patients.[12] Thus, combined with the outcomes of the current study, the risks and benefits of antihypertensive treatment seem equal for male and female patients, and the risk of serious adverse events should not be a barrier to treatment.

We found that the risks of assessed serious adverse events among patients of White ethnicity were similar to those of the male and female subgroups. For the main outcome of hospitalisation or death due to falls, higher hazards (aHRs) were observed in Black, south Asian, and mixed or other ethnicity groups compared with those of White ethnicity, with overlap in 95% CIs between the White and south Asian subgroup. The differences were not as pronounced when looking at the absolute risks for all outcomes and, overall, risks were low for all ethnicity groups. Arguably, absolute risk differences are a more important consideration when prescribing. It was generally difficult to compare our results on adverse events across ethnicity subgroups with previous literature and trials, because information on these subgroup differences is often lacking, underscoring the need to report on ethnicity in hypertension research. The mixed or other ethnicity group formed a large proportion of the total study population (24%) and probably larger than that in UK population demographics.[25,26] Overall, our results do not imply clinically meaningful differences between ethnicity groups and serious adverse events associated with new antihypertensive therapy.

Social deprivation status was assessed by classifying patients into IMD quintiles. It has been shown that the CPRD Aurum population broadly matches the IMD in the UK population.[15] The results differed only slightly between IMD groups but were generally more favourable for the most deprived quintiles, with this group exhibiting a generally lower hazard of adverse events. This is indeed contrary to what we expected, because more deprived populations are known to be more likely to have hypertension, subsequent cardiovascular complications, comorbidities, and worse health status.[11,27] Our results might be explained by a difference in health-seeking behaviour and health literacy; the least deprived patients are more likely to find timely access to health care.[28] Put differently, the

	Ethnicity	Total	Exposed group	Exposed events	Non-exposed group	Non-exposed events	Adjusted hazard ratio (95% CI)	Absolute risk difference* (95% CI)
Falls (main outcome)								
	Black	78045	13668	383	64377	736	1·32 (1·13 to 1·53)	11·9 (4·8 to 18·3)
	South Asian	64286	10948	411	53338	869	1·22 (1·05 to 1·41)	10·3 (1·9 to 17·5)
	Mixed or other	627887	66460	497	561427	1518	1·47 (1·29 to 1·66)	2·8 (1·9 to 3·4)
	White	1317091	196432	22317	1120659	81891	1·05 (1·03 to 1·07)	6·7 (4·1 to 8·9)
	Overall	2614330	337742	23925	2276588	86949	1·08 (1·06 to 1·10)	6·7 (5·6 to 8·3)
Hypotension								
	Black	78045	13668	163	64377	285	1·29 (1·01 to 1·63)	5·0 (−0·3 to 10·6)
	South Asian	64286	10948	243	53338	404	1·53 (1·26 to 1·86)	12·6 (6·1 to 19·8)
	Mixed or other	627887	66460	175	561427	468	1·55 (1·25 to 1·93)	1·1 (0·5 to 1·6)
	White	1317091	196432	7564	1120659	21599	1·31 (1·27 to 1·35)	12·8 (11·3 to 14·3)
	Overall	2614330	337742	8229	2276588	23119	1·35 (1·31 to 1·40)	8·9 (7·9 to 9·8)
Syncope								
	Black	78045	13668	261	64377	570	1·33 (1·12 to 1·59)	8·4 (3·5 to 14·1)
	South Asian	64286	10948	234	53338	564	1·33 (1·11 to 1·60)	8·6 (2·8 to 14·8)
	Mixed or other	627887	66460	244	561427	786	1·49 (1·25 to 1·78)	1·4 (0·8 to 2·1)
	White	1317091	196432	9206	1120659	32046	1·16 (1·13 to 1·20)	9·1 (7·1 to 10·9)
	Overall	2614330	337742	1007	2276588	34555	1·21 (1·18 to 1·25)	7·2 (6·1 to 8·2)
Fracture								
	Black	78045	13668	162	64377	614	1·00 (0·82 to 1·23)	0·1 (−4·7 to 4·4)
	South Asian	64286	10948	256	53338	807	1·03 (0·87 to 1·22)	1·1 (−4·9 to 6·1)
	Mixed or other	627887	66460	321	561427	1484	1·25 (1·08 to 1·44)	1·2 (0·4 to 2·3)
	White	1317091	196432	14461	1120659	69567	0·98 (0·96 to 1·00)	−2·4 (−4·8 to −0·4)
	Overall	2614330	337742	15414	2276588	74123	1·01 (0·99 to 1·03)	0·4 (−0·8 to 1·7)
Acute kidney injury								
	Black	78045	13668	595	64377	862	1·53 (1·34 to 1·74)	25·7 (16·7 to 35·0)
	South Asian	64286	10948	538	53338	775	1·58 (1·38 to 1·81)	27·0 (19·1 to 34·8)
	Mixed or other	627887	66460	494	561427	978	1·86 (1·62 to 2·14)	3·8 (2·9 to 4·8)
	White	1317091	196432	15950	1120659	38384	1·38 (1·34 to 1·41)	28·3 (26·3 to 30·5)
	Overall	2614330	337742	17895	2276588	42195	1·42 (1·39 to 1·46)	20·0 (18·5 to 21·3)

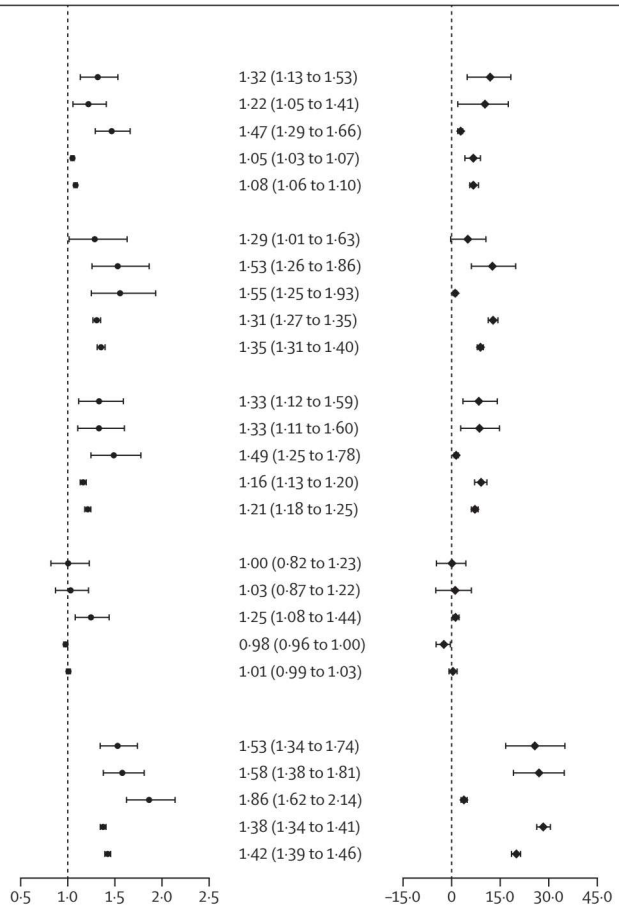

Figure 3: **Associations between antihypertensive treatment and hospitalisation or death due to falls, hypotension, syncope, fracture, and acute kidney injury by ethnicity group**
Associations are shown in terms of propensity score-adjusted hazard ratios and absolute risk differences. All subgroup post-hoc interaction analyses were significant (p<0·0001). Unadjusted analyses are provided in the appendix (p 23). *Additional events per 10 000 patients per year.

likelihood of receiving and having access to appropriate health care seems to have an inverse relationship with socioeconomic status, a phenomenon already described in the early 1970s, coined as the inverse care law.[29] Another related explanation could be worse medication adherence in the more deprived groups, which, unfortunately, could not be assessed in our dataset, and the association between adherence and social deprivation is still unclear from the literature.[30] Additionally, we checked the balance in age and sex in the IMD groups (data not shown), which did not explain the differences found. However, the differences between all IMD groups were small and, with overlapping confidence intervals, no clinically meaningful distinction can be made between IMD groups.

This was a large, nationally representative cohort of community-dwelling patients in England. This cohort allowed for analyses of small (minority) subgroups, with the smallest subgroup still comprising more than 60 000 patients. However, this study did have some limitations. For the current analyses, all types of antihypertensives were grouped together. Risks for adverse events might differ between antihypertensive drug classes for specific subgroups, such as ethnicity and sex subgroups.[7–9,12,14] Furthermore, grouping patients into four ethnicity groups might oversimplify results for some individuals, and might also not be generalisable to other countries or populations. Moreover, although we used several methods to evaluate our propensity score model and our results overall match those from randomised controlled trials, unmeasured confounding cannot be ruled out.[4] Also, time variation in exposures and confounders during follow-up was not taken into account, although, in previous analyses, individuals from the control population starting treatment at some point during follow-up had significantly lower treatment duration than individuals from the exposure group.[5] Additionally, although a 10-year follow-up time aligns with

	IMD	Total	Exposed group	Exposed events	Non-exposed group	Non-exposed events	Adjusted hazard ratio (95% CI)	Absolute risk difference* (95% CI)
Falls (main outcome)								
	IMD 1 (least deprived)	559393	63054	4658	496339	17855	1·16 (1·12 to 1·21)	12·0 (8·2 to 15·6)
	IMD 2	508488	61791	4671	446697	17557	1·10 (1·06 to 1·15)	8·7 (4·7 to 12·6)
	IMD 3	468681	59908	4630	408773	16983	1·09 (1·05 to 1·13)	7·9 (3·7 to 12·4)
	IMD 4	426608	59474	4776	367134	16941	1·06 (1·02 to 1·10)	6·1 (1·7 to 10·6)
	IMD 5 (most deprived)	396859	59969	5171	336890	17545	1·02 (0·99 to 1·06)	2·8 (−2·2 to 7·4)
	Overall	2614330	337742	23925	2276588	86949	1·08 (1·06 to 1·10)	6·7 (5·6 to 8·3)
Hypotension								
	IMD 1 (least deprived)	559393	63054	1549	496339	4647	1·46 (1·36 to 1·56)	9·8 (7·8 to 12·1)
	IMD 2	508488	61791	1614	446697	4691	1·41 (1·31 to 1·51)	10·1 (7·6 to 12·6)
	IMD 3	468681	59908	1572	408773	4532	1·33 (1·24 to 1·42)	8·9 (6·5 to 11·5)
	IMD 4	426608	59474	1726	367134	4511	1·37 (1·28 to 1·47)	11·8 (9·2 to 14·5)
	IMD 5 (most deprived)	396859	59969	1763	336890	4730	1·24 (1·16 to 1·33)	9·0 (6·1 to 11·9)
	Overall	2614330	337742	8229	2276588	23119	1·35 (1·31 to 1·40)	8·9 (7·9 to 9·8)
Syncope								
	IMD 1 (least deprived)	559393	63054	1937	496339	7154	1·27 (1·19 to 1·35)	8·1 (5·5 to 10·6)
	IMD 2	508488	61791	1913	446697	6902	1·24 (1·16 to 1·31)	7·9 (5·1 to 10·7)
	IMD 3	468681	59908	1933	408773	6591	1·24 (1·16 to 1·31)	8·4 (5·8 to 10·8)
	IMD 4	426608	59474	2068	367134	6602	1·24 (1·17 to 1·32)	9·9 (6·7 to 13·0)
	IMD 5 (most deprived)	396859	59969	2213	336890	7290	1·11 (1·05 to 1·18)	5·7 (2·3 to 8·9)
	Overall	2614330	337742	10070	2276588	34555	1·21 (1·18 to 1·25)	7·2 (6·1 to 8·2)
Fracture								
	IMD 1 (least deprived)	559393	63054	3120	496339	16132	1·09 (1·04 to 1·14)	5·3 (2·4 to 8·2)
	IMD 2	508488	61791	3129	446697	15561	1·03 (0·99 to 1·08)	2·1 (−1·2 to 5·5)
	IMD 3	468681	59908	3041	408773	14620	1·01 (0·96 to 1·05)	0·5 (−2·6 to 3·6)
	IMD 4	426608	59474	3057	367134	13894	0·99 (0·95 to 1·04)	−0·6 (−3·9 to 2·8)
	IMD 5 (most deprived)	396859	59969	3054	336890	13842	0·94 (0·90 to 0·98)	−5·2 (−8·9 to −1·3)
	Overall	2614330	337742	15414	2276588	74123	1·01 (0·99 to 1·03)	0·4 (−0·8 to 1·7)
Acute kidney injury								
	IMD 1 (least deprived)	559393	63054	3222	496339	7884	1·57 (1·49 to 1·65)	21·2 (18·2 to 23·9)
	IMD 2	508488	61791	3360	446697	8089	1·48 (1·40 to 1·55)	21·1 (17·9 to 24·3)
	IMD 3	468681	59908	3440	408773	8396	1·40 (1·34 to 1·47)	20·6 (17·5 to 23·8)
	IMD 4	426608	59474	3790	367134	8438	1·45 (1·38 to 1·52)	26·6 (22·7 to 30·7)
	IMD 5 (most deprived)	396859	59969	4069	336890	9354	1·29 (1·23 to 1·35)	21·3 (17·4 to 25·1)
	Overall	2614330	337742	17895	2276588	42195	1·42 (1·39 to 1·46)	20·0 (18·5 to 21·3)

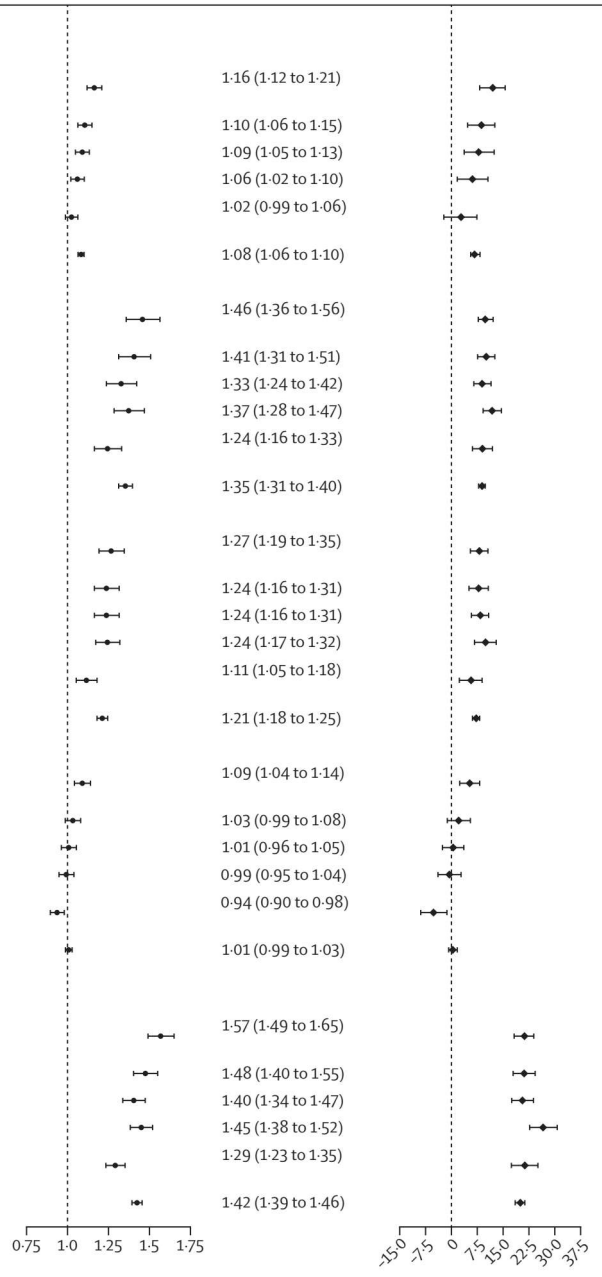

Figure 4: **Associations between antihypertensive treatment and hospitalisation or death due to falls, hypotension, syncope, fracture, and acute kidney injury by socioeconomic status categorised as IMD quintiles**

Associations are shown in terms of propensity score-adjusted hazard ratios and absolute risk differences. All subgroup post-hoc interaction analyses were significant (p<0·0001). Unadjusted analyses are provided in the appendix (p 24). IMD=Index of Multiple Deprivation. *Additional events per 10 000 patients per year.

previous literature on cardiovascular disease risk and benefits and harms of antihypertensive treatment, our research does not provide information on short-term adverse outcomes risk and development of comorbidities, such as in the first 2–5 years after starting antihypertensive treatment. We used a landmark analysis to minimise immortal time bias; our findings are conditional on individuals remaining alive and under observation at 12 months and might not capture adverse effects occurring shortly after antihypertensive treatment initiation. Furthermore, excluding patients younger than 40 years could have resulted in selection bias if ethnicity or IMD groups are differently

distributed among younger patients starting antihypertensive treatment. Additionally, data on non-steroidal anti-inflammatory drug (NSAID) prescriptions or over-the-counter use were not available, which could have negatively affected the outcome of kidney injury. It is unclear whether NSAID use would differ between exposed and non-exposed groups and what effect this would have on our results. Lastly, these analyses were conducted in patients initiating antihypertensive treatment between 1998 and 2018. Although this period reflects contemporary practice only up to the end of 2018, prescribing patterns and clinical management are unlikely to have changed substantially in more recent years. Nevertheless, more subtle developments since this period might affect the direct applicability of these findings to current practice. Furthermore, it is unknown whether these results also apply to patients already using antihypertensives long term and those with previous prescriptions.

In conclusion, in a large, nationally representative cohort of community-dwelling patients from England, the absolute risk of serious adverse events, including hospitalisation or death from falls, after starting new antihypertensive treatment was low and similar across patient subgroups based on sex, ethnicity, and socioeconomic status. These data suggest that no distinction should be made among these groups when considering the harms of antihypertensives in individual treatment decisions in primary care. Nevertheless, our findings must be interpreted with caution because unmeasured confounding cannot be completely ruled out.

STRATIFY Investigators

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Contributors

JPS initiated the project. JPS and FSvR were involved in the conceptualisation of the project. FSvR and AW performed the formal analyses. FSvR, JPS, and AW directly accessed and verified the underlying data reported in the manuscript. FSvR wrote the first draft. FSvR, JPS, AW, G-JG, CK, SS, AB, AC, RAP, BKB, FDRH, and RM were involved in writing (editing and revising) the manuscript and agreed to its final version and the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data were obtained via a CPRD institutional licence. Requests for data sharing should be made directly to the CPRD (https://cprd.com). The Hospital Episode Statistics data used in this analysis are reused with permission from NHS Digital (https://digital.nhs.uk) who retain the copyright for those data. The Office for National Statistics provided mortality data. The Office for National Statistics and NHS Digital bear no responsibility for the analysis or interpretation of the data. Complete code lists used to define variables used in this analysis can be found at https://github.com/jamessheppard48/STRATIFYBP/tree/Causal-inference-project.

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