Frailty and rate of fractures in patients initiating antihypertensive medications: a cohort study in primary care.

Marc F Österdahl (1) (2)*, Sarah-Jo Sinnott (2), Ian Douglas (2), Andrew Clegg (3), Laurie Tomlinson (2) Angel Wong (2),

1 – Department of Twin Research and Genetic Epidemiology, King's College London, London, UK

2 – Department of Non-Communicable Diseases Research, London School of Hygiene & Tropical Medicine, Keppel St, London, UK

3 – Academic Unit for Ageing and Stroke Research, University of Leeds, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK

*Corresponding Author: marc.osterdahl@kcl.ac.uk ORCID: 0000-0001-7363-5574

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Availability of Data and material

The datasets supporting this work are not publicly available due to CPRD licencing restrictions. Codelists for variables for fractures are however available through LSHTM data repository.

Code availability

Codelists for variables for fractures are however available through LSHTM data repository, and more detailed code available upon request from authors.

Ethics Approval

Ethical approval was granted for this project by the London School of Hygiene and Tropical Medicine Research Ethics committee (Ref: 16450) and by the Independent Scientific Advisory Committee (ISAC) of CPRD as a subset of a larger project (ISAC Protocol Number: 18_312R).

Consent

Consent to Participate: All participants in the Clinical Practice Research Datalink have given consent for the use of their health records for medical research.

Consent to Publication: All participants in the Clinical Practice Research Datalink have given consent for the publication of medical research based on their health records.

Author's Contributions

MFÖ, LT and AW, conceived the study in conjunction with SJS, ID and AC. AC developed the electronic frailty index. MFÖ conducted the analysis and wrote the first draft of this manuscript. All authors reviewed the manuscript, contributed to the interpretation of results and to its final form.

Abstract

Background

Treatment for hypertension improves cardiovascular outcomes. Frailty may be present in older people treated for hypertension, but associates with adverse drug effects, potentially including falls resulting in fractures. We aimed to determine the association between baseline frailty and fractures in patients initiated on antihypertensive treatment.

Methods

We conducted a retrospective cohort study using United Kingdom primary care data, including new-users of first-line antihypertensives aged 65 years or over. We reported degree of frailty (fit, mild, moderate, severe) at antihypertensive initiation using the Electronic Frailty Index. We examined the association of frailty with fractures using multivariable Poisson regression, and assessed for interaction between antihypertensive class and frailty.

Results

Of 113,779 patients aged 65 years or over who initiated on first-line antihypertensives, 49,634 (43%) patients were mildly or more frail. Over 4.1 years mean follow-up, 6567 (5.8%) experienced a fracture, with 3832 (58%) of these fractures occurring in frail people. Among those with severe frailty, doubling of fracture risk was observed after antihypertensive initiation, compared with fit people [adjusted rate ratio 2.26 (95% CI 1.93-2.65)]. Secondary analyses indicate this pattern was replicated for hip and arm fractures, and strongest for spine fractures, and the association between different types of antihypertensives and fractures varied by frailty (P=0.004), being lower in moderately frail users of renin-angiotensin blockers compared with calcium-channel blockers [Rate Ratio (RR) 0.81 95% CI 0.71-0.94]

Conclusions

Frailty is common among older patients initiating first-line antihypertensive treatment, and was associated with an increased fracture rate. Awareness of this is important to encourage clinicians to consider risk of falls and fractures when treating hypertension.

Key Points

- Older people initiating antihypertensives are a population with substantial frailty, which was associated with an increased risk of hip, arm, and particularly spinal fractures.
- Routine frailty assessment in this group is important to identify those with greatest risk of fracture
- Clinicians should include fracture risk when considering risks and benefits of treatment when treating with antihypertensives in frail patients

Introduction

Hypertension is the 4th most common risk factor driving mortality and morbidity in the UK [1] and is more common with increasing age [2]. Recent evidence from randomised controlled trials shows benefit from drug treatment in older adults, and possibly older people with frailty [3–5]. However, there are concerns about adverse effects of antihypertensive medications, including syncope and possibly falls [6,7] leading to fractures especially amongst elderly and frail patients. Such fractures can occur with minimal trauma, such as a fall from standing height, and are labelled 'fragility fractures' [8]. These place a substantial burden on countries' health systems, both due to immediate care costs and consequent long-term disability. Hip fractures are associated with particularly high mortality and morbidity [9], representing 54% of the €37 billion cost of all fractures in the European Union by 2010 [10].

Age alone is increasingly recognised as less useful than frailty for predicting many outcomes experienced by older patients, including mortality and fractures [11,12]. Frailty is a condition characterised by loss of biological reserves across multiple organ systems and vulnerability to physiological decompensation after a stressor event [13]. It is distinct from both co-morbidity and disability, although incorporates elements of both, and may be partly reversible [14,15]. Frailty can be quantified using the electronic frailty index (eFI) [13], created using data from routine General Practice consultations in the UK and based on the well-established cumulative deficit model of frailty [16]. It is now used both for research and recommended by National Institute for Clinical Excellence (NICE) for use in clinical practice, experiencing good uptake [17,18]. However, it was originally validated looking at mortality, hospitalisation and care-home admission, and further data is needed to establish how well eFI associates with other frailty-related outcomes.

The evidence regarding the impact of antihypertensive treatment on fracture risk is mixed. There is observational evidence of an increase in risk for the first 45 days [19]. The recent HYpertension in the Very Elderly Trial (HYVET) showed possible reductions in fracture risk for active treatment

compared to placebo, but in a secondary analysis, with a shorter follow-up time than originally planned [20,21] HYVET did not report the effects of different types of anti-hypertensive initiated on fracture risk [21]. However, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), suggested a lower fracture risk for treatment with thiazide-type diuretics compared to angiotensin converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARBs), but not calcium-channel blockers (CCBs) [22].

Awareness of an association between baseline eFI score and adverse outcomes, such as fractures, would help inform clinicians on the risks and benefits when initiating antihypertensive treatment in people with different levels of frailty. We therefore sought to examine the association between frailty, identified using the eFI, and the rate of fractures in people initiating antihypertensive therapy in contemporary UK primary care, and whether this varied by type of antihypertensive initiated.

Methods

Study Design

Data Source

This study was a population-based cohort extracted from the Clinical Practice Research Datalink-Gold (CPRD) database for a previous study [23]. This database contains anonymised primary care data for approximately 7% of the UK population, submitted by enrolled General Practitioners (GPs). It is considered representative of the UK population in terms of age, sex and ethnicity [24]. It includes coded information on demographics, diagnoses, symptoms & signs, as well as prescribing data and test results [25].

Participants

Adults enrolled in CPRD-Gold between 1 Jan 2007 and 31 December 2017, who started a NICE recommended first-line antihypertensive medication were included in the study (Figure 1). As eFI

was validated for people aged 65 years or over, people aged less than 65 years were excluded from the study [13]. First-line antihypertensive medication could be either an ACE inhibitor, or an ARB, a CCB, or a thiazide/thiazide-like diuretic [2,26]. Beta-blockers, alpha-blockers and loop diuretics were not recommended first line so were not included. Participants were enrolled on the first record of antihypertensive prescription during the study period. To ensure that the medication was started for hypertension rather than another indication, a blood pressure reading of over 140/90mmHg were required at starting date or within 1 year prior to study entry.

Exclusion criteria included a record of any prescription for an antihypertensive medication in the 1 year prior to study entry patients commencing more than one drug simultaneously and a record of a new prescription after discontinuing the first prescription. To maximise the number of eligible participants we did not use linkage to secondary care data since our outcome, fracture, is already well-recorded in primary care [26,27] Participants were followed from the date of the initiation of antihypertensives until the earliest of: occurrence of their first fracture, death, or deregistration from a CPRD practice.

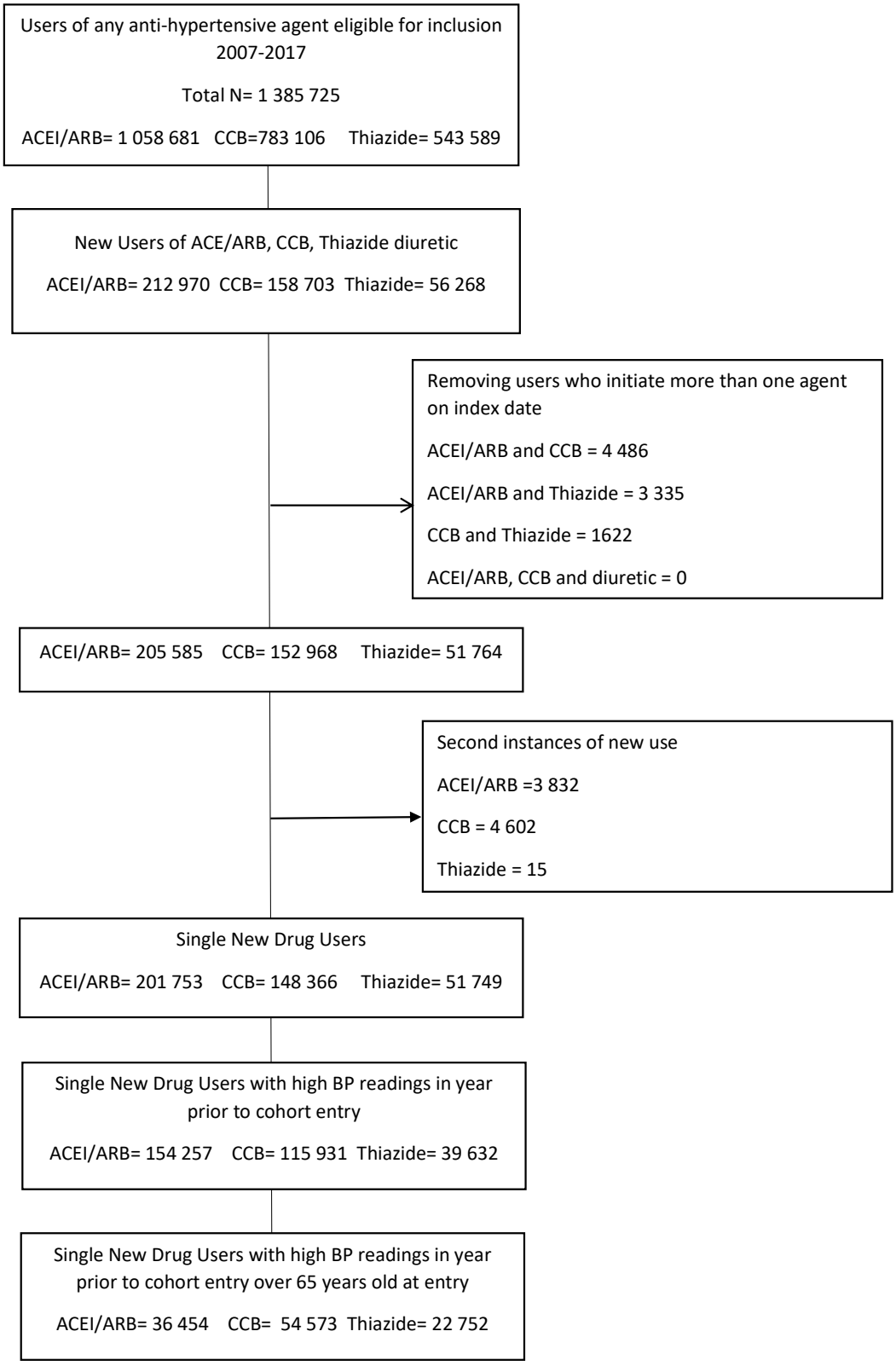

Fig. 1 Study Flowchart
ACEI/ARB= Angiotensin Converting Enzyme Inhibitor or Angiotensin II receptor blocker, CCB= Calcium Channel blocker, Thiazide= Thiazide or Thiazide-like diuretic. BP = Blood Pressure

Exposure

Frailty was defined using eFI, with the addition of terminal illness [13]. This uses a cumulative deficit model of frailty, counting 37 components associated with ageing and adverse outcomes, to generate a score. A component is present if a relevant abnormal test result, clinic measurement or Read code is associated with the patient at the time of antihypertensive drug initiation. Pre-established cut points from the original eFI development cohort were used to define four categories of frailty: "Fit" (score<=0.12), "Mild Frailty" (score >0.12 and ≤0.24), "Moderate Frailty" (score >0.24 and ≤0.36) and "Severe Frailty" (score >0.36).

Outcome

Our primary outcome was the rate of any fragility fracture and its association with frailty. This was extracted from CPRD, using pre-established Read codes lists for hip, arm, or spine fractures. Previous work has validated the recording of fractures in CPRD [26]. Sites were chosen in line with those included in NICE guidelines on osteoporosis, and previous studies using CPRD [8,28]. An additional category of fragility fractures of unspecified location was also used. Individual fracture sites and the rate of fractures by drug class were analysed as secondary outcomes.

Covariates

We defined Covariates *a priori* based on previous knowledge and review of the relevant literature [8,29,30]. We included biological covariates of age and sex, and lifestyle covariates of smoking, alcohol consumption and body-mass-index (BMI), osteoporosis (including the presence of either a Read code for osteoporosis *or* previous fragility fractures) , calendar year (to account for changing guidelines regarding treatment of [2,31] and seasonal effect of injury (winter/summer) (Figure 1). (**Supplementary Figure 1)**. The use of bisphosphonates is only available as prescriptions issued, but

as treatment compliance is known to be poor this was considered insufficient for inclusion in primary analysis [32].

Missing Data

The selected covariates are known to be acceptably recorded in CPRD, and low levels of missing data (<5%) were expected for covariates such as smoking, alcohol consumption and BMI [24,33]. We therefore used complete case analysis in our fully adjusted model. We anticipated more missing data for ethnicity, known to be poorly recorded in CPRD [34,35] so confined this to sensitivity analysis. Deprivation data is only available through linkage, which is only possible for 60% of practices [24].

Statistical Analysis

We conducted Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (95% CI) for any fracture according to frailty category with 'Fit' as the reference group. We conducted a univariable model, an age- and sex-adjusted model, and a multivariable fully-adjusted model. Our fully-adjusted model assessing association between frailty and fracture was adjusted for age, sex, BMI, smoking, alcohol, osteoporosis, season and year of study. All data management and analyses were performed using Stata 16 (StataCorp, Texas).

In a pre-planned secondary analysis, we calculated rate of fracture for each fracture site, adjusting for the same co-variates as the primary analysis. We pre-specified analysis of an interaction between frailty and the class of antihypertensive on the risk of fracture, using a likelihood ratio test for interaction. In sensitivity analyses, due to anticipated missing data, we also adjusted separately for ethnicity and patient-level index of multiple deprivation [24,25]. In addition, we also explored the effect of bisphosphonate as a potential confounder of the model, although compliance is known to be poor compared to prescription.

Results

Study Population and baseline Characteristics

We identified 113,779 people aged 65 or over who initiated either ACEI/ARB, CCB or thiazide diuretic between 2007-2017. Mean follow-up was 4.1 years (standard deviation (SD) 2.8 years), yielding a total of 466,923 person-years of follow-up (**Figure 1**).

A total of 32% (36,454/113,779) initiated ACEI/ARB, 48% (54,573/113,779) a CCB and 20.0% (22,752/113,779) thiazide diuretics. The proportions changed with age, with 34.7% (13,329/38,438) of patients aged 65-69 years initiating ACEI/ARB, compared to 28.0% (2,632/9,405) aged over 85 years, whilst 15.7% (6,045/38,438) of those aged 65-69 years were prescribed thiazide diuretics, compared to 28.9% (2,714/9,405) aged over 85 years. The proportion of people initiating thiazide diuretics fell each year from 28.5% (4,916/17,221) in 2007 to 6.4% (275/4,313) in 2017, with CCB use progressively increasing from 32.7% (5,632/17,221) in 2007 to 70.9% (3,056/4,313) in 2017. (**Supplementary Table 1**).

Frailty

More than half of participants (56.4%) were classified as 'fit', 32.0% as 'mild frailty', 10.5% 'moderate frailty' and 1.2% 'severe frailty' (**Table 1**). Older people were more likely to be categorised as frail: participants who were 'fit' had a mean age of 71 years (SD 6) compared to 82 years (SD 8) for people categorised as 'severely frail'. People categorised as 'severely frail' were more likely to be underweight than the 'fit' (6.1% vs 1.3%), less likely to smoke and drink alcohol, more likely to have a diagnosis of osteoporosis (57.9% vs 7.8%), to have been prescribed a bisphosphonate (44.9% vs 7.8%) and to be the most deprived (10.5% vs 6.0%).

	EFI Group							
	Fit N=64,145		Mildly frail N=36,373		Moderately frail N= 11,904		Severely frail N=1,357	
Sex								
Female	32250	(50.3%)	21987	(60.4%)	8263	(69.4%)	1060	(78.1%)
Age (years)								
65-69	27,054	(42.2%)	9,627	(26.5%)	1656	(13.9%)	101	(7.4%)
70-74	18,610	(29.0%)	9,400	(25.8%)	2,205	(18.5%)	146	(10.8%)
75-79	10,892	(17.0%)	8,029	(22.1%)	2,678	(22.5%)	213	(15.7%)
80-84	5,273	(8.2%)	5,530	(15.2%)	2,628	(22.1%)	332	(24.5%)
85+	2,316	(3.6%)	3,787	(10.4%)	2,737	(23.0%)	565	(41.6%)
Mean Age (SD)	71.9	(5.8)	74.9	(0.1)	78.5	(7.5)	82.1	(7.6)
Body Mass Index (kg/m^2)								
Underweight <18.5	821	(1.3%)	815	(2.2%)	456	(3.8%)	83	(6.1%)
Healthy weight 18.5-24.9	19553	(30.5%)	11723	(32.2%)	4233	(35.6%)	539	(39.7%)
Overweight 25-29.9	25932	(40.4%)	14027	(38.6%)	4144	(34.8%)	422	(31.1%)
Obesity ≥30	14382	(22.4%)	8573	(23.6%)	2642	(22.2%)	280	(20.6%)
Missing	3457	(5.4%)	1235	(3.4%)	429	(3.6%)	33	(2.4%)
Smoking								
Current smoker	9794	(15.3%)	4738	(13.0%)	1399	(11.8%)	170	(12.5%)
Ex-smoker	30655	(47.8%)	19812	(54.5%)	6939	(58.3%)	821	(60.5%)
Non-smoker	23543	(36.7%)	11769	(32.4%)	3551	(29.8%)	364	(26.8%)
Missing	153	(0.2%)	54	(0.1%)	15	(0.1%)	2	(0.1%)
Alcohol								
Current drinker	48218	(75.2%)	25569	(70.3%)	7473	(62.8%)	764	(56.3%)
Ex-drinker	5171	(8.1%)	4575	(12.6%)	2121	(17.8%)	357	(26.3%)
Non-drinker	7006	(10.9%)	4648	(12.8%)	1827	(15.3%)	199	(14.7%)
Missing	3750	(5.8%)	1581	(4.3%)	483	(4.1%)	37	(2.7%)
Osteoporosis								
Ever coded	4991	(7.8%)	7793	(21.4%)	4515	(37.9%)	786	(57.9%)
Ethnicity								
White	28333	(44.2%)	16387	(45.1%)	5291	(44.4%)	572	(42.2%)
South Asian	489	(0.8%)	429	(1.2%)	143	(1.2%)	12	(0.9%)
Black	309	(0.5%)	159	(0.4%)	51	(0.4%)	4	(0.3%)
Other/mixed	316	(0.5%)	152	(0.4%)	43	(0.4%)	3	(0.2%)
Missing	34698	(54.1%)	19246	(52.9%)	6376	(53.6%)	766	(56.4%)

Socio-economic Status*									
Least Deprived	1	9361	(14.6%)	5188	(14.3%)	1610	(13.5%)	170	(12.5%)
	2	9741	(15.2%)	5353	(14.7%)	1737	(14.6%)	174	(12.8%)
	3	7627	(11.9%)	4292	(11.8%)	1449	(12.2%)	179	(13.2%)
	4	6084	(9.5%)	3785	(10.4%)	1295	(10.9%)	166	(12.2%)
Most Deprived	5	3844	(6.0%)	2594	(7.1%)	1067	(9.0%)	143	(10.5%)
Missing		27488	(42.9%)	15161	(41.7%)	4746	(39.9%)	525	(38.7%)
Drug Class									
ACEI/ARB		19,302	(30.1%)	12,478	(34.3%)	4,170	(35.0%)	504	(37.1%)
Calcium channel blockers		32,123	(50.1%)	16,667	(45.8%)	5,210	(43.8%)	573	(42.2%)
Thiazide Diuretics		12,720	(19.8%)	7,228	(19.9%)	2,524	(21.2%)	280	(20.6%)
Bisphosphonate									
Ever Prescribed		5,032	(7.8%)	6,813	(18.7%)	3,798	(31.9%)	609	(44.9%)

Table 1: Associations between eFI group and baseline characteristics of cohort
Data presented are number of participants with column percentages.
*Socio-economic status as quintile of Index of Multiple Deprivation
ACEI/ARB – Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

Fractures

Overall, 6,567 (5.8%) patients experienced a fracture during follow-up. This yielded an unadjusted fracture rate of 14.1/1000 person years at risk (PYAR). Fracture rate increased with increasing age and female sex, as well as low BMI and osteoporosis (**Supplementary Tables 2 and 3**). Hip fractures were 32% of all recorded first fractures, whilst 35% were arm fractures, 13% spinal and 20% were fragility fractures without a specified site. (**Table 2**)

Primary outcome

Of all fractures, 58% occurred in patients with some degree of frailty **(Supplementary Figure 2)**. In the fully adjusted model, people with severe frailty experienced an increased rate of any fracture compared to those in the fit category (RR 2.26, 95% CI 1.93-2.65). An increased rate was also seen for those categorised with moderate frailty (RR 1.68, 95% CI 1.56-1.82) and mild frailty (RR1.34, 95% CI 1.26-1.43), compared to the fit category.

Secondary outcomes

In secondary analyses, the increased association between frailty and fracture rate remained for all fracture sites, but was strongest for spine (RR 3.49, 95% CI 2.31-5.25) and weakest for arm (RR1.95, 95% CI 1.46-2.62) **(Figure 2, Supplementary Table 4)**

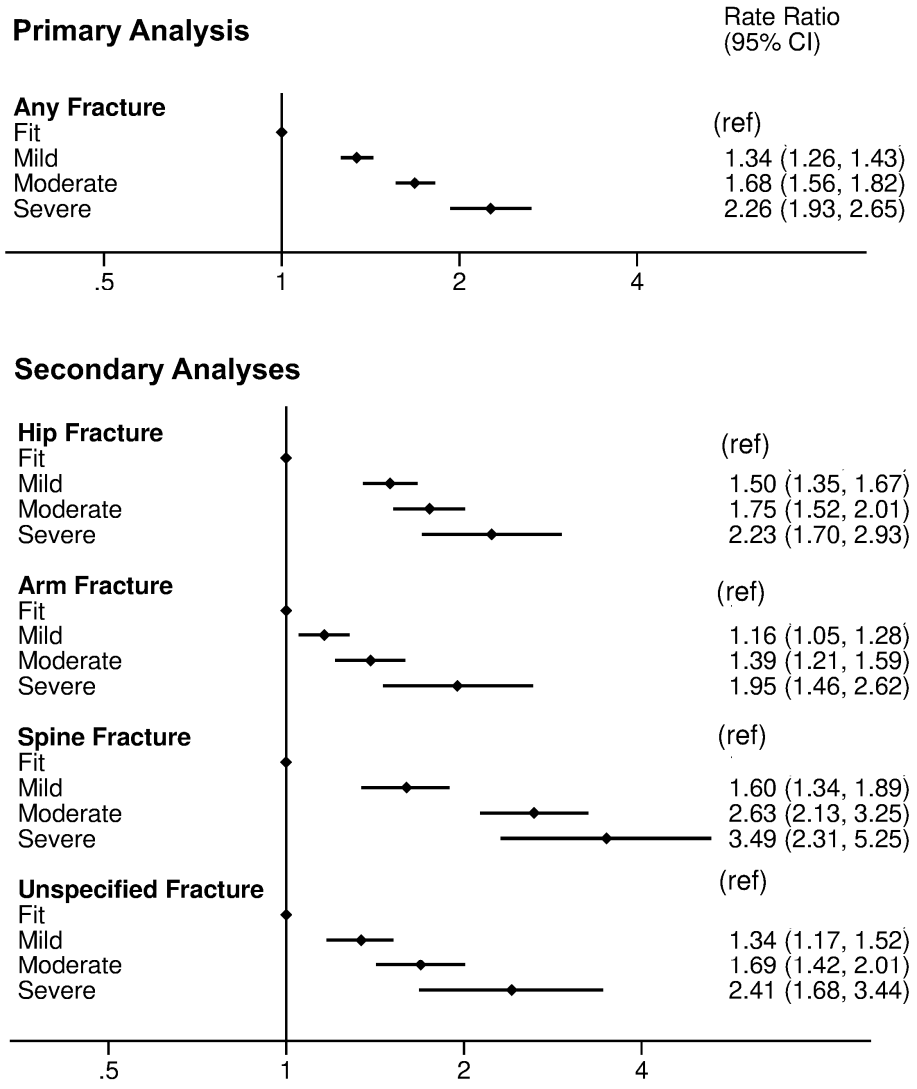

Fig. 2 Fully Adjusted Rate ratio for Any Fracture by eFI category
Secondary Analyses: Fully adjusted rate ratio for fracture at each site by eFI category
Adjusted for age, sex, BMI, smoking, alcohol, osteoporosis, season and year of study

Increasing frailty also increased the rate of fractures for all drug classes (**Table 2**). There was no evidence for a difference in fracture rate by drug class without accounting for eFI (**Supplementary Table 6**)

We found some evidence that the association between type of antihypertensives and rate of fracture varied by frailty (p=0.004). In particular, ACEI/ARB users with moderate frailty had a lower rate of fracture than moderately frail CCB users (RR 0.81 95% CI 0.71-0.94) (**Table 3**)

Drug Class	EFI Group			
	Fit	Mild	Mod	Severe
ACEI/ARB	1	1.53	1.68	2.73
	(ref)	(1.38-1.70)	(1.46-1.92)	(2.12-3.51)
CCB	1	1.37	1.91	2.58
	(ref)	(1.26-1.50)	(1.71-2.14)	(2.03-3.28)
Thiazide	1	1.20	1.62	1.76
	(ref)	(1.07-1.34)	(1.41-1.87)	(1.25-2.48)
Summary	1	1.37	1.75	2.40
	(ref)	(1.29-1.45)	(1.62-1.89)	(2.05-2.82)

Table 2: Rate ratio for any fracture for each eFI Group by drug class

Likelihood ratio test for interaction p=0.004
Adjusted for age, sex, season, year of study, BMI, smoking, alcohol consumption, osteoporosis
CCB- Calcium Channel Blocker, ACEI/ARB – Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

Table 2: Rate ratio for any fracture in each frailty category for each drug class

Drug Class	EFI Group				Summary Adjusted RR
	Fit	Mild	Mod	Severe	
CCB	1.00	1.00	1.00	1.00	1.00
	-	-	-	-	-
ACEI/ARB	0.93	1.03	0.81	0.98	0.95
	(0.84-1.02)	(0.94-1.14)	(0.71-0.94)	(0.71-1.36)	(0.89-1.01)
Thiazide	1.07	0.94	0.91	0.73	0.98
	(0.98-1.18)	(0.84-1.04)	(0.79-1.06)	(0.49-1.10)	(0.92-1.05)

Table 3: Rate ratio for any fracture for each drug class by eFI Group - CCB as reference

Likelihood ratio test for interaction p=0.004
Adjusted for age, sex, season, year of study, BMI, smoking, alcohol consumption, osteoporosis
CCB- Calcium Channel Blocker, ACEI/ARB – Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker

Table 3: Rate ratio for any fracture for each drug class by eFI Group - CCB as reference

Sensitivity Analyses

We did not see any meaningful difference from our estimates for the primary analysis for any of the sensitivity analyses (**Supplementary Table 5** and **Figure 3**).

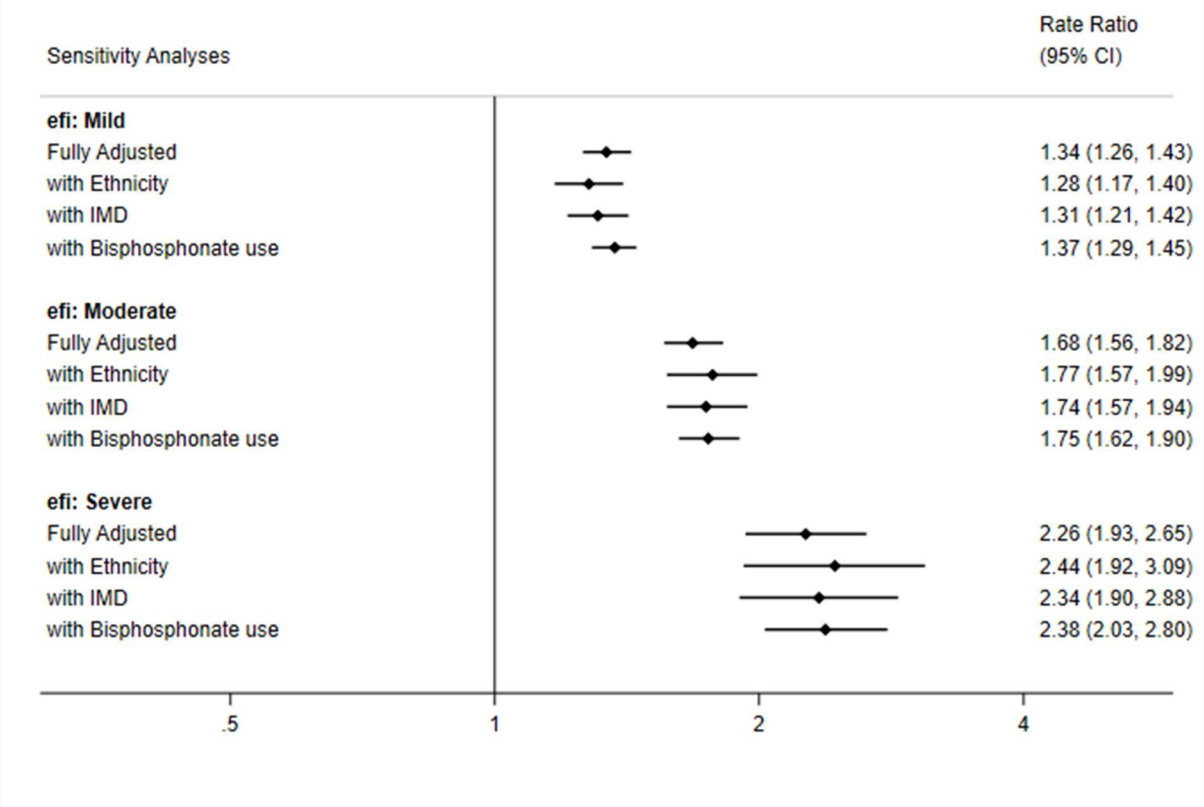

Fig.3 Sensitivity Analyses on rate of any fracture by eFI Group
Additionally adjusted for age, sex, osteoporosis season, year of study, smoking, alcohol and BMI

Discussion

In this large cohort study reflecting routine clinical care, a primary analysis with adjustment for covariates demonstrated an increased risk of fractures among people aged 65 years or over initiating antihypertensives associated with every level of increased frailty relative to fit people aged 65 years or over. We also found evidence that association between type of antihypertensives and fractures varied by frailty.

The overall association between increasing frailty, as defined by eFI, and increasing rates of fracture is in line with our hypothesis and current literature [12,28]. Secondary analyses demonstrated that the association between fracture site and eFI was strongest for spinal fractures, and weakest for arm. This may be because arm fractures may occur due to high impact injuries sustained by physically fit and active participants while spinal fractures in this group are often fragility fractures. This suggests that eFI is particularly helpful to clinicians, as fragility fractures are of great concern, but may be preventable through implementation of evidence-based interventions [8]. In line with NHS initiatives such as “Making Every Contact Count”, this suggests the initiation of antihypertensive medication could be an appropriate point to consider a patient’s eFI score and for the clinician to then consider fracture risk if frail [36].

We observed a lower risk of fractures associated with ACEI/ARB than CCB in moderately frail people; however, further research is required to validate this finding as a clear dose-response relationship was not demonstrated, and the risk of fracture associated with ACEI/ARB or CCB was similar in severely frail patients. It is possible that some of the association between CCB users and increased fracture rate, compared with ACEI/ARB is due to residual confounding, if there are deficits related to frailty not captured by eFI, and ACEI/ARBs were preferentially prescribed to less frail participants.

A recent secondary analysis of the ALLHAT trial has suggested that CCBs increased the risk of falls in the first year of treatment, compared to an ACEI or Thiazide [37]. This could lead to fractures, but fractures were not assessed by the trial. However, this was not sustained over the entire follow-up

period, nor did they stratify by frailty. Ideally association between fracture risk and class of antihypertensive would be compared prospectively in a trial, although as seen by HYVET, large numbers would be needed to have power to compare different treatments for hypertension [20]. For clinicians, the relationship between frailty and fractures, is an important relationship to be aware of, so that they might take further measures to assess a frail person's risk of fracture when starting an antihypertensive, although further research is needed to establish if this truly varies by drug class. This can help trigger shared decision making between clinicians and frailer patients, allowing them to benefit both from the potential reduction in cardiovascular risk, whilst mitigating their increased fracture risk, possibly through further assessments and interventions, which may need to be evaluated in this context.

We have conducted a large cohort study, with long follow-up time and a wide distribution of age which was well-powered for each level of frailty and able to assess site-specific fractures. Our results are reflective of treatment patterns and outcome rates in routine clinical care. Our outcome of fracture is clinically objective and well recorded in CPRD[27]. We were able to adjust for detailed covariates, including those involved in the eFI with little (<4%) missing data.

There are several limitations in our study, in particular that despite detailed covariate adjustment there could have been residual confounding. Although results were not affected by adjustment for ethnicity, deprivation, and bisphosphonate use in sensitivity analyses, data on steroid use, calcium supplementation, or vitamin D levels were not available. These factors could be linked to frailty and fracture rate [8,30]. Osteoporosis is likely to be underdiagnosed in this population as it is asymptomatic before the first fracture [38]. Although there is some data on falls in CPRD, used to calculate eFI, it is not validated and does not include information on frequency of falls, and likely under-reported [39]. We have attempted to ensure that our medications were initiated for hypertension as opposed to another indication (eg: Heart failure), by requiring a hypertensive blood pressure recording (over 140/90mmHg) at starting date or within 1 year prior, as well as excluding

people who initiated more than one drug simultaneously. However, we cannot exclude the possibility that some patients initiated drugs for other reasons, and some of these may increase the risk of falls and fractures. Calcium channel blockers are least likely to have alternative indications compared with other medications, therefore it might affect the findings for its comparison with other drug classes.

Although the eFI is now widely used clinically and in research, it relies on the assumption that the absence of a Read code, or abnormal result, indicates the absence of the deficit. There has been limited validation of CPRD records for some deficits, which may have underestimated the true prevalence and severity of frailty in our population, and bias our estimate towards null. Conversely, codes may remain on a patient's record, (e.g. following a period of being housebound) even if no longer relevant. Despite these limitations, eFI has been successfully validated by comparison with other internationally established measures of frailty [40]. As our primary question for the study was the association between fracture rates and frailty at the point of drug initiation, we have used eFI score and medication usage at baseline only. Whilst eFI is not validated for longitudinal assessment, we acknowledge that both frailty and medication usage may change during the study duration, and further studies are needed to explore patterns of frailty and medication use over time amongst people treated with antihypertensives.

Finally, CPRD also only provides data on prescriptions issued which may not reflect actual medication use by participants. Antihypertensive adherence can be poor and may be worse with increased frailty [41] but this would likely bias our findings to the null.

Conclusion

We demonstrate that a substantial proportion of people aged 65 years or over initiating antihypertensive treatment are frail, and that frailty is associated with subsequent rate of fractures. We have also demonstrated that the association between different classes of antihypertensive and fractures may vary by frailty. There may be an increased risk of fractures associated with CCBs

compared with ACEI/ARB in moderately frail people, but much further research is needed to recapitulate this association. Clinicians and patients should be aware of these associations to weigh the potential benefits of antihypertensive therapy against the risk of fractures in the context of frailty.

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