

Supplementary Material

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

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Appendix 1: Components of the Electronic Frailty Index

Deficit	Prevalence
Anaemia and haematinic deficiency	10.6%
Arthritis	20.6%
Atrial Fibrillation	1.7%
Cerebrovascular Disease	4.2%
Chronic Kidney Disease	9.1%
Diabetes	9.7%
Dizziness	18.2%
Dyspnoea	12.1%
Falls	8.4%
Foot Problems	2.6%
Fragility Fracture	6.2%
Hearing Impairment	11.8%
Heart Failure	0.6%
Heart Valve Disease	0.6%
Housebound	12.0%
Hypertension	21.6%
Hypotension/Syncope	6.8%
Ischaemic Heart Disease	21.2%
Limitation in Physical Activity	0.6%
Memory and cognitive problems	2.3%
Mobility and transfer problems	1.3%
Osteoporosis	4.8%
Parkinsonism and tremor	0.7%
Peptic Ulcer	3.9%
Peripheral Vascular Disease	1.3%
Polypharmacy	37.4%
Requirement for Care	0.6%
Respiratory Disease	23.2%
Skin Ulcer	7.7%
Sleep disturbance	9.5%
Social Vulnerability	2.1%
*Terminal Disease	0.3%
Thyroid Disease	9.2%
Urinary Incontinence	4.6%
Urinary System disease	26.0%
Visual Impairment	11.3%
Weight loss and anorexia	3.4%

*Terminal disease was not included in the original eFI in 2016

Appendix 2: Supplementary Tables + Figures

	ACEI/ARB		CCB		Thiazide		Total
Total	36,454	(32.0%)	54,573	(48.0%)	22,752	(20.0%)	113,779
Sex							
Male	18,565	(37.0%)	24,034	(47.9%)	7,620	(15.2%)	50,219
Female	17,889	(28.1%)	30,539	(48.0%)	15,132	(23.8%)	63,560
Age							
65-69	13,329	(34.7%)	19,064	(49.6%)	6,045	(15.7%)	38,438
70-74	9,722	(32.0%)	14,852	(48.9%)	5,787	(19.1%)	30,361
75-79	6,667	(30.6%)	10,367	(47.5%)	4,778	(21.9%)	21,812
80-84	4,104	(29.8%)	6,231	(45.3%)	3,428	(24.9%)	13,763
85+	2,632	(28.0%)	4,059	(43.2%)	2,714	(28.9%)	9,405
Mean Age (standard deviation)	73.2 (6.65)		73.4 (6.66)		75.1 (7.19)		73.7 (6.81)
BMI							
underweight <18.5	599	(27.5%)	1,069	(49.1%)	507	(23.3%)	2,175
healthy weight 18.5-24.9	10,697	(29.7%)	17,696	(49.1%)	7,655	(21.2%)	36,048
overweight 25-29.9	14,579	(32.7%)	21,573	(48.5%)	8,373	(18.8%)	44,525
obesity >=30	9,107	(35.2%)	11,688	(45.2%)	5,082	(19.6%)	25,877
Missing	1,472	(28.6%)	2,547	(49.4%)	1,135	(22.0%)	5,154
Smoking							
Current smoker	5,237	(32.5%)	7,742	(48.1%)	3,122	(19.4%)	16,101
Ex-smoker	19,316	(33.2%)	27,815	(47.8%)	11,096	(19.1%)	58,227
Non-smoker	11,859	(30.2%)	18,894	(48.2%)	8,474	(21.6%)	39,227
Missing	42	(18.8%)	122	(54.5%)	60	(26.8%)	224
Alcohol							
Current drinker	26,289	(32.1%)	39,809	(48.5%)	15,926	(19.4%)	82,024
Ex-drinker	4,058	(33.2%)	5,794	(47.4%)	2,372	(19.4%)	12,224
Non-drinker	4,274	(31.2%)	6,178	(45.2%)	3,228	(23.6%)	13,680
Missing	1,833	(31.3%)	2,792	(47.7%)	1,226	(21.0%)	5,851
Osteoporosis							
Yes	5055	(28.0%)	8888	(49.1%)	4142	(22.9%)	18,085
Ethnicity							
white	16376	(32.4%)	24659	(48.7%)	8548	(16.9%)	50,583
South Asian	431	(40.2%)	510	(47.5%)	132	(12.3%)	1,073
Black	123	(23.5%)	334	(63.9%)	66	(12.6%)	523
other/mixed	157	(30.5%)	273	(53.1%)	84	(16.3%)	514
Missing	19367	(31.7%)	28797	(47.1%)	22752	(37.2%)	61,086
Deprivation (IMD Quintile)							
Least Deprived - 1	5,411	(33.1%)	7,961	(48.8%)	2,957	(18.1%)	16,329
2	5,642	(33.2%)	8,136	(47.8%)	3,227	(19.0%)	17,005
3	4,553	(33.6%)	6,391	(47.2%)	2,603	(19.2%)	13,547
4	3,717	(32.8%)	5,376	(47.4%)	2,237	(19.7%)	11,330

Most Deprived - 5 Missing	2,444 (32.0%) 14,687 (30.6%)	3,607 (47.2%) 23,102 (48.2%)	1,597 (20.9%) 10,131 (21.1%)	7,648 47,920
Bisphosphonate Ever Prescribed	4,754 (29.3%)	7,618 (46.9%)	3,880 (23.9%)	16252
Year of Drug Initiation				
2007	6,673 (38.7%)	5,632 (32.7%)	4916 (28.5%)	17,221
2008	5,629 (36.5%)	5,473 (35.5%)	4324 (28.0%)	15,426
2009	4,947 (35.9%)	5,197 (37.7%)	3654 (26.5%)	13,798
2010	4,151 (33.6%)	5,072 (41.0%)	3141 (25.4%)	12,364
2011	3,396 (31.7%)	5,073 (47.4%)	2236 (20.9%)	10,705
2012	2,953 (28.6%)	6,027 (58.4%)	1342 (13.0%)	10,322
2013	2,684 (27.9%)	5,839 (60.7%)	1100 (11.4%)	9,623
2014	2,124 (26.6%)	5,067 (63.5%)	794 (9.9%)	7,985
2015	1,730 (25.4%)	4,515 (66.3%)	563 (8.3%)	6,808
2016	1,185 (22.7%)	3,622 (69.5%)	407 (7.8%)	5,214
2017	982 (22.8%)	3,056 (70.9%)	275 (6.4%)	4,313

Supplementary Table 1: Baseline Characteristics by Antihypertensive Drug
Data presented with row percentages
ACEI/ARB = Angiotensin Converting Enzyme Inhibitor or Angiotensin-receptor blocker, CCB= Calcium Channel Blocker
BMI= Body Mass Index, IMD= Index of Multiple Deprivation

	Total number	(Col%)	Person-Years	(Col%)	Fractures	Rate (/1000years)	Crude Rate Ratio	(95% CI)
Total Cohort	113779		466923		6576	14.06		
Sex								
Male	50,219	(44%)	209557	(45%)	1295	6.18	1.00	(baseline)
Female	63,560	(56%)	257367	(55%)	5272	20.48	3.31	(3.12-3.52)
Age								
65-69	38,438	(77%)	166091	(79%)	1326	7.98	1.00	(baseline)
70-74	30,361	(60%)	130060	(62%)	1500	11.53	1.44	(1.34-1.56)
75-79	21,812	(43%)	90494	(43%)	1530	16.91	2.12	(1.97-2.28)
80-84	13,763	(27%)	51830	(25%)	1228	23.69	2.97	(2.75-3.21)
85+	9,405	(19%)	28446	(14%)	983	34.56	4.33	(3.99-4.70)

Supplementary Table 2: Unadjusted rate of any fracture in cohort

	Total number	(Col%)	Person-Years	(Col%)	Fractures	Adjusted Rate Ratio	(95% CI)
Total Cohort	113779		466923		6576		
BMI							
underweight <18.5	2175	(2%)	6938	(1%)	264	1.63	(1.45-1.83)
healthy weight 18.5-24.9	36048	(32%)	145145	(31%)	2756	1.00	(baseline)
overweight 25-29.9	44525	(39%)	188991	(40%)	2234	0.77	(0.73-0.80)
obesity >=30	25877	(23%)	109766	(24%)	1049	0.64	(0.60-0.67)
Missing	5154	(5%)	16082	(3%)	264		

Smoking					
Current smoker	16101 (14%)	65525 (14%)	950	1.00 (baseline)	
Ex-smoker	58227 (51%)	236045 (51%)	3083	0.81 (0.75-0.87)	
Non-smoker	39227 (34%)	164635 (35%)	2520	0.76 (0.71-0.82)	
Missing	224 (0%)	718 (0%)	14		
Alcohol					
Current drinker	82024 (72%)	343175 (73%)	4420	1.00 (baseline)	
Ex-drinker	12224 (11%)	46349 (10%)	807	1.09 (1.01-1.18)	
Non-drinker	13680 (12%)	57887 (12%)	1017	0.99 (0.92-1.06)	
Missing	5851 (5%)	19513 (4%)	323		
Osteoporosis					
Yes	18085 (16%)	67006 (14%)	2057	1.86 (1.76-1.96)	
Ethnicity					
white	50583 (44%)	206483 (44%)	2742	1.00 (baseline)	
South Asian	1073 (1%)	3838 (1%)	25	0.54 (0.36-0.80)	
Black	523 (0%)	2088 (0%)	9	0.37 (0.19-0.72)	
other/mixed	514 (0%)	2022 (0%)	18	0.76 (0.48-1.21)	
Missing	61086 (54%)	252492 (54%)	3773		
Deprivation (IMD Category)					
Least Deprived - 1	16329 (14%)	64492 (14%)	911	1.00 (baseline)	
2	17005 (15%)	66289 (14%)	830	0.87 (0.80-0.96)	
3	13547 (12%)	52259 (11%)	745	1.00 (0.91-1.10)	
4	11330 (10%)	44548 (10%)	613	0.97 (0.87-1.07)	
Most Deprived - 5	7648 (7%)	29934 (6%)	421	1.00 (0.89-1.12)	
Missing	47920 (42%)	209401 (45%)	3047		
Bisphosphonate					
Ever Prescribed	16252 (14%)	69196 (15%)	1421	1.06 (0.99-1.13)	
Participants contributing at least once to each season					
Summer (May-Oct)		235225 (50%)	3182	1.00 (baseline)	
Winter (Nov-April)		231698 (50%)	3385	1.08 (1.03-1.13)	
Participants contributing to each year of Study					
2007		8866 (2%)	97	1.00 (baseline)	
2008		23662 (5%)	263	1.03 (0.82-1.30)	
2009		35836 (8%)	504	1.33 (1.07-1.65)	
2010		45070 (10%)	565	1.21 (0.98-1.50)	
2011		51589 (11%)	653	1.24 (1.00-1.54)	
2012		56777 (12%)	850	1.49 (1.21-1.84)	
2013		58794 (13%)	887	1.54 (1.25-1.89)	
2014		57261 (12%)	838	1.51 (1.23-1.87)	
2015		51268 (11%)	768	1.57 (1.27-1.94)	
2016		41684 (9%)	614	1.57 (1.27-1.95)	
2017		36117 (8%)	528	1.59 (1.28-1.97)	
Supplementary Table 3 : Adjusted rate of any fracture by baseline characteristics of cohort					
Adjusted for Age + Sex only					
Total number with column percentages					

				EFI Group			
			Total	Fit	Mild	Moderate	Severe
Participants			113779	64145	36373	11904	1357
PYAR			466,923	280104	143051	40200	3568
Any Fracture	N (row %)		6,567	2735 (42)	2485 (38)	1165 (18)	182 (3)
	Unadjusted Rate (/1000 PYAR)		14.1	9.8	17.4	29.0	51.0
	Fully Adjusted	RR CI		1.00 (ref)	1.34 (1.26-1.43)	1.68 (1.56-1.82)	2.26 (1.93-2.65)
Hip Fracture	N (row %)		2,080	775 (37)	839 (40)	403 (19)	63 (3)
	Unadjusted Rate (/1000 PYAR)		4.5	2.8	5.9	10	17.7
	Fully Adjusted	RR CI		1.00 (ref)	1.50 (1.35-1.67)	1.75 (1.52-2.01)	2.23 (1.70-2.93)
Arm Fracture	N (row %)		2,325	1,108(48)	824 (35)	340(15)	53(2)
	Unadjusted Rate (/1000 PYAR)		5.0	4.0	5.8	8.5	14.9
	Fully Adjusted	RR CI		1.00 (ref)	1.16 (1.05-1.28)	1.39 (1.21-1.59)	1.95 (1.46-2.62)
Spine Fracture	N (row %)		827	297	313	188	29
	Unadjusted Rate (/1000 PYAR)		1.8	1.1	2.2	4.7	8.1
	Fully Adjusted	RR CI		1.00 (ref)	1.60 (1.34-1.89)	2.63 (2.13-3.25)	3.49 (2.31-5.25)
Unspecified Fracture	N (row %)		1,335	555	509	234	37
	Unadjusted Rate (/1000 PYAR)		2.9	2.0	3.6	5.8	10.4
	Fully Adjusted	RR CI		1.00 (ref)	1.34 (1.17-1.52)	1.69 (1.42-2.01)	2.41 (1.68-3.44)

Supplementary Table 4: Fracture rate by eFI group

Adjusted for age, sex, BMI, smoking, alcohol, osteoporosis, season and year of study

p<0.001 for all fracture sites by likelihood ratio test

PYAR= person-years at risk RR=Rate Ratio CI= 95% confidence Interval

		EFI Group				Participants	Person-Years
		Fit	Mild	Moderate	Severe		
Fully Adjusted	RR	1.00	1.34	1.68	2.26	113,779	466,923
	CI		(1.26-1.43)	(1.56-1.82)	(1.93-2.65)		
with Ethnicity	RR	1.00	1.28	1.77	2.44	49,545	203,817
	CI		(1.17-1.40)	(1.57-1.99)	(1.92-3.09)		
with IMD	RR	1.00	1.31	1.74	2.34	60,376	239,484
	CI		(1.21-1.42)	(1.57-1.94)	(1.90-2.88)		
with bisphosphonates	RR	1.00	1.37	1.75	2.38	113,779	466,923
	CI		(1.29-1.45)	(1.62-1.90)	(2.03-2.80)		

Supplementary Table 5: Sensitivity Analyses on rate of any fracture by eFI group

Additionally adjusted for age, sex, osteoporosis, season, year of study, smoking, alcohol and BMI

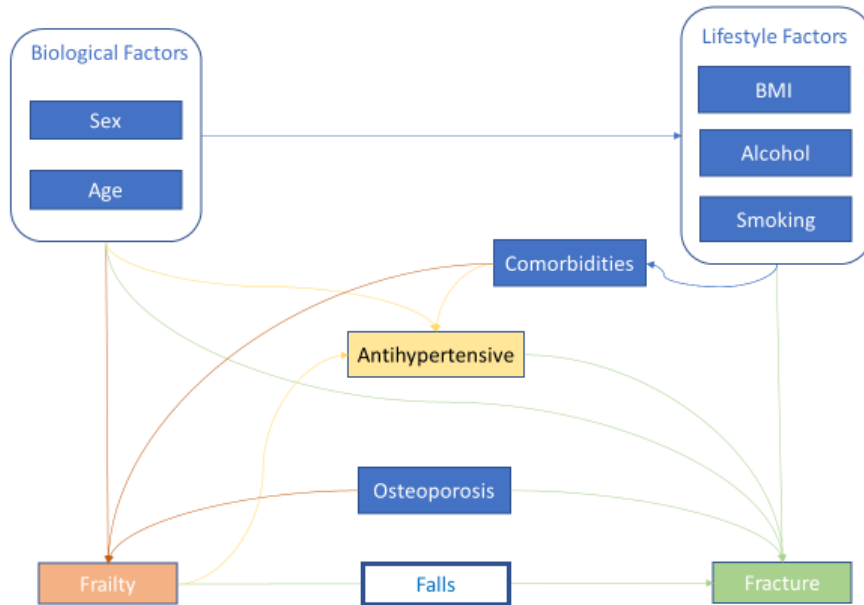
			Total	Drug Class			P-Value
				CCB	ACEI/ARB	Thiazide	
Any Fracture	Fully Adjusted	N=	6,567	2,790	2,003	1,774	p=0.78
		RR		1.00	0.99	0.97	
		CI			(0.93-1.05)	(0.91-1.04)	
Hip Fracture	Fully Adjusted	N=	2,080	848	636	596	p=0.78
		RR		1.00	1.02	0.98	
		CI			(0.92-1.14)	(0.87-1.10)	
Arm Fracture	Fully Adjusted	N=	2,325	1,019	677	629	p=0.18
		RR		1.00	0.90	0.98	
		CI			(0.82-1.01)	(0.88-1.09)	
Spine Fracture	Fully Adjusted	N=	827	355	262	210	p=0.99
		RR		1.00	1.01	1.01	
		CI			(0.85-1.19)	(0.85-1.21)	
Unspec Fracture	Fully Adjusted	N=	1,335	568	428	339	p=0.19
		RR		1.00	1.08	0.95	
		CI			(0.95-1.24)	(0.82-1.09)	

Supplementary Table 6: Rate of Fracture by Drug Class for specific fracture sites

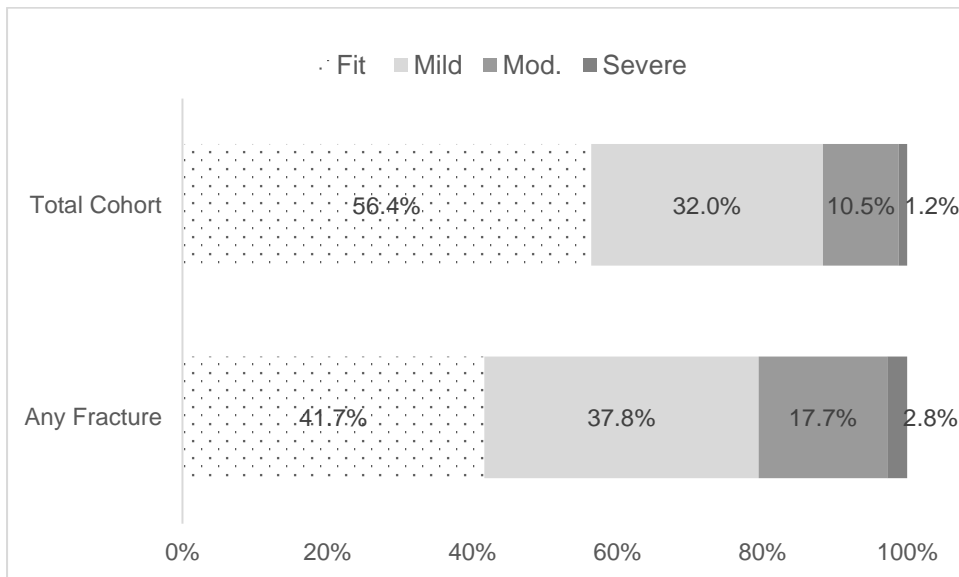
ACEI/ARB= Angiotensin Converting Enzyme Inhibitor or Angiotensin receptor blocker, CCB= Calcium channel blocker

RR: Rate Ratio, CI= 95% Confidence interval. P-values from likelihood ratio test.

Adjusted for Age, sex, season, year of study, smoking, alcohol osteoporosis and BMI



Supplementary Figure 1: Conceptual Framework



Supplementary Figure 2 Proportion of: Total cohort in each eFI group; those experiencing any fracture by eFI group;