

Supplementary Online Content

Puttnam R, Davis BR, Pressel SL, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Collaborative Research Group. Association of 3 different antihypertensive medications with hip and pelvic fracture risk in older adults: secondary analysis of a randomized clinical trial. *JAMA Intern Med*. Published online November 21, 2016. doi:10.1001/jamainternmed.2016.6821

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline Characteristics for the In-Trial Cohort

N	Chlorthalidone 10174	Amlodipine/Lisinopril 12006	Total 22180
Age – mean (sd) years	70.4 (6.7)	70.4 (6.8)	70.4 (6.7)
55-64 – n (%)	1531 (15.1)	1798 (15.0)	3329 (15.0)
65+ - n (%)	8643 (85.0)	10208 (85.0)	18851 (85.0)
Female – n (%)	4413 (43.4)	5118 (42.6)	9531 (43.0)
Ethnicity			
White non-Hispanic – n (%)	5072 (49.9)	5996 (49.9)	11068 (49.9)
Black non-Hispanic – n (%)	3169 (31.2)	3742 (31.2)	6911 (31.2)
White Hispanic – n (%)	1204 (11.8)	1432 (11.9)	2636 (11.9)
Black Hispanic – n (%)	311 (3.1)	371 (3.1)	682 (3.1)
Other n (%)	418 (4.1)	465 (3.9)	883 (4.0)
Education, mean (sd) years	10.7 (4.1)	10.7 (4.1)	10.7 (4.1)
Receiving antihypertensive treatment – n (%)	9264 (91.1)	10969 (91.4)	20233 (91.2)
Blood pressure – mean (sd) mm Hg			
SBP	146.6 (15.8)	146.6 (15.6)	146.6 (15.7)
DBP	82.8 (10.1)	82.7 (10.1)	82.8 (10.1)
Treated at baseline			
SBP	145.6 (15.8)	145.6 (15.6)	145.6 (15.7)
DBP	82.3 (10.1)	82.3 (10.0)	82.3 (10.0)
Untreated at baseline			
SBP	156.6 (11.6)	157.1 (11.7)	156.9 (11.7)
DBP	87.8 (9.0)	87.6 (9.5)	87.7 (9.3)
Eligibility risk factors—n (%):			
Current smoking	1915 (18.8)	2229 (18.6)	4144 (18.7)
Atherosclerotic CVD	5756 (56.6)	6673 (55.6)	12429 (56.0)
History of MI or stroke	2744 (27.0)	3125 (26.0)	5869 (26.5)
History of coronary revascularization	1510 (14.8)	1746 (14.5)	3256 (14.7)
Other ASCVD	2611 (25.7)	3083 (25.7)	5694 (25.7)
Major ST depression or T-wave inversion	1064 (10.6)	1247 (10.5)	2311 (10.5)
Diabetes †	4011 (42.5)	4785 (42.9)	8796 (42.7)
HDL-C < 35 mg/dL	1232 (12.1)	1462 (12.2)	2694 (12.2)
LVH by electrocardiogram	1702 (16.7)	2027 (16.9)	3729 (16.8)
LVH by echocardiogram	500 (5.0)	587 (5.0)	1087 (5.0)
History of CHD at baseline	2959 (29.3)	3305 (27.8)*	6264 (28.5)
Body mass index – mean (sd)	29.1 (5.8)	29.1 (5.8)	29.1 (5.8)
Medication use at baseline – n (%)			
Aspirin	3904 (38.4)	4704 (39.2)	8608 (38.8)
Estrogen supplementation– FEMALES ONLY	614 (13.9)	684 (13.4)	1298 (13.6)
Atenolol use at 1 month	398 (3.9)	452 (3.8)	850 (3.8)
Cholesterol– mean (sd, N)			
Total	214.6 (43.2, 9700)	214.3 (42.7, 11392)	214.4 (42.9, 21092)
HDL	46.7 (14.7, 9699)	46.8 (14.7, 11386)	46.7 (14.7, 21085)

LDL	135.2 (36.7, 9157)	135.0 (36.4, 10791)	135.1 (36.5, 19948)
Serum creatinine – mean (sd, N)	1.1 (0.3, 9751)	1.0 (0.3, 11446)	1.1 (0.3, 21197)
eGFR--- mean (sd, N)			
Baseline --MDRD	74.9 (19.5, 9751)	75.3 (19.4, 11446)	75.1 (19.4, 21197)
Baseline – CKD-Epi	70.7 (17.6, 9751)	71.0 (17.5, 11446)	70.8 (17.6, 21197)
Lipid trial participants – n (%)	2423 (23.8)	2783 (23.2)	5206 (23.5)

Abbreviations: ASCVD, arteriosclerotic cardiovascular disease; CCVD, combined cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction

* p < 0.05

†History of diabetes OR fasting glucose 126+ OR non-fasting glucose 200+

eTable 2. Baseline Characteristics for the In-Trial Plus Posttrial Cohort

N	Chlorthalidone 7631	Amlodipine/Lisinopril 8991	Total 16622
Age – mean (sd) years	71.3 (6.6)	71.4 (6.6)	71.4 (6.6)
55-64 – n (%)	656 (8.6)	782 (8.7)	1438 (8.7)
65+ - n (%)	6975 (91.4)	8209 (91.3)	15184 (91.4)
Female – n (%)	4362 (57.2)	5053 (56.2)	9415 (56.6)
Ethnicity			
White non-Hispanic – n (%)	3483 (45.6)	4069 (45.3)	7552 (45.4)
Black non-Hispanic – n (%)	2401 (31.5)	2837 (31.6)	5238 (31.5)
White Hispanic – n (%)	1108 (14.5)	1340 (14.9)	2448 (14.7)
Black Hispanic – n (%)	285 (3.7)	331 (3.7)	616 (3.7)
Other n (%)	354 (4.6)	414 (4.6)	768 (4.6)
Education, mean (sd) years	10.4 (4.2)	10.4 (4.3)	10.4 (4.2)
Receiving antihypertensive treatment – n (%)	6903 (90.5)	8194 (91.1)	15097 (90.8)
Blood pressure – mean (sd) mm Hg			
SBP	147.4 (15.6)	147.4 (15.5)	147.4 (15.5)
DBP	83.2 (10.1)	83.0 (10.1)	83.1 (10.1)
Treated at baseline			
SBP	146.4 (15.6)	146.4 (15.5)	146.4 (15.5)
DBP	82.7 (10.0)	82.5 (10.0)	82.6 (10.0)
Untreated at baseline			
SBP	157.0 (12.0)	157.6 (11.7)	157.3 (11.9)
DBP	88.1 (8.9)	88.0 (9.3)	88.1 (9.1)
Eligibility risk factors– n (%)			
Current smoking	1282 (16.8)	1493 (16.6)	2775 (16.7)
Atherosclerotic CVD	4339 (56.9)	5010 (55.7)	9349 (56.2)
History of MI or stroke	1923 (25.2)	2196 (24.4)	4119 (24.8)
History of coronary revascularization	1082 (14.2)	1230 (13.7)	2312 (13.9)
Other ASCVD	2086 (27.3)	2456 (27.3)	4542 (27.3)
Major ST depression or T-wave inversion	807 (10.7)	934 (10.5)	1741 (10.6)
Diabetes†	3031 (43.1)	3604 (43.5)	6635 (43.3)
HDL-C < 35 mg/dL	776 (10.2)	954 (10.6)	1730 (10.4)
LVH by electrocardiogram	1254 (16.4)	1458 (16.2)	2712 (16.3)
LVH by echocardiogram	414 (5.5)	499 (5.6)	913 (5.5)
History of CHD at baseline	2099 (27.7)	2383 (26.7)	4482 (27.1)
Body mass index – mean (sd)	29.1 (6.0)	29.2 (6.1)	29.2 (6.1)
Medication use at baseline – n (%)			
Aspirin	2683 (35.2)	3208 (35.7)	5891 (35.4)
Estrogen supplementation– FEMALES ONLY	597 (13.7)	661 (13.1)	1258 (13.4)
Atenolol use at 1 month	280 (3.7)	300 (3.3)	580 (3.5)
Cholesterol– mean (sd, N)			
Total	217.5 (44.1, 7239)	216.6 (43.6, 8480)	217.0 (43.9, 15719)
HDL	48.2 (15.0, 7238)	48.2 (14.9, 8476)	48.2 (14.9, 15714)

LDL	136.6 (37.5, 6865)	135.9 (36.9, 8051)	136.2 (37.2, 14916)
Serum creatinine – mean (sd, N)	1.0 (0.3, 7275)	1.0 (0.3, 8519)	1.0 (0.3, 15794)
eGFR– mean (sd, N)			
Baseline– MDRD	73.9 (19.8, 7275)	74.1 (19.5, 8519)	74.0 (19.6, 15794)
Baseline – CKD-Epi	69.7 (17.8, 7275)	69.8 (17.7, 8519)	69.8 (17.7, 15794)
Lipid trial participants – n (%)	1847 (24.2)	2092 (23.3)	3939 (23.7)

Abbreviations: ASCVD, arteriosclerotic cardiovascular disease; CCVD, combined cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; HDL high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction

† History of diabetes OR fasting glucose 126+ OR non-fasting glucose 200+

eTable 3. Hip or Pelvis Fracture Rates per 100 and Hazard Ratios From Baseline Onward During the In-Trial Period for Chlorthalidone Only With or Without Atenolol Use at 1 Month

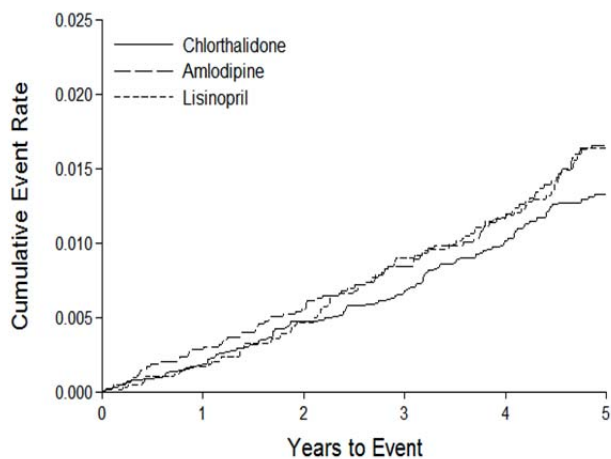
	Total	Not on Atenolol at 1 month	On Atenolol at 1 month
N (denominator)	10174	9776	398
Hip or pelvic fractures			
Events	135	128	7
1-y rate	0.19 (0.04)	0.20 (0.05)	0.00 (-)
2-y rate	0.47 (0.07)	0.45 (0.07)	1.04 (0.52)
3-y rate	0.68 (0.08)	0.66 (0.08)	1.04 (0.52)
4-y rate	1.02 (0.10)	0.98 (0.10)	1.91 (0.72)
5-y rate	1.33 (0.12)	1.30 (0.12)	1.91 (0.72)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.43 (0.67-3.07)		
Age-Adjusted			
1-y rate	0.12 (0.03)	0.12 (0.03)	0.00 (-)
2-y rate	0.30 (0.04)	0.28 (0.04)	0.90 (0.45)
3-y rate	0.44 (0.05)	0.42 (0.05)	0.90 (0.45)
4-y rate	0.67 (0.07)	0.64 (0.07)	1.66 (0.63)
5-y rate	0.89 (0.08)	0.86 (0.08)	1.66 (0.63)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.67 (0.78-3.58)		
Age and sex-adjusted			
1-y rate	0.12 (0.03)	0.12 (0.03)	0.00 (-)
2-y rate	0.30 (0.04)	0.28 (0.04)	0.89 (0.44)
3-y rate	0.43 (0.05)	0.41 (0.05)	0.89 (0.44)
4-y rate	0.66 (0.07)	0.63 (0.07)	1.65 (0.62)
5-y rate	0.88 (0.08)	0.85 (0.08)	1.65 (0.62)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.66 (0.77-3.55)		

Age, sex, and race-adjusted

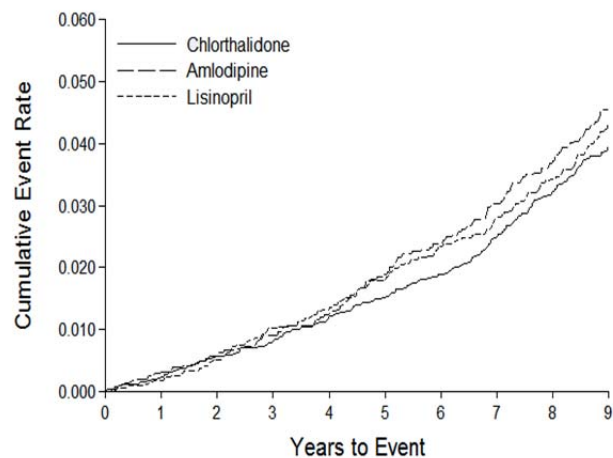
1-y rate	0.11 (0.03)	0.11 (0.03)	0.00 (-)
2-y rate	0.28 (0.04)	0.26 (0.04)	0.88 (0.44)
3-y rate	0.40 (0.05)	0.39 (0.05)	0.88 (0.44)
4-y rate	0.62 (0.06)	0.59 (0.06)	1.61 (0.61)
5-y rate	0.82 (0.08)	0.80 (0.08)	1.61 (0.61)
HR on atenolol vs not on atenolol at 1 month (95% CI)	1.50 (0.70-3.22)		

eFigure 1. Kaplan-Meier Curves for Hip and Pelvic Fractures by the Three Primary Antihypertensive Medications Used in ALLHAT. Curves A and B are from the time of randomization during the in-trial and during the in-trial and posttrial periods. Curves C and D are from one year after randomization for the in-trial and the in-trial and posttrial periods.

A. In-trial cohort



B. In-trial plus post-trial cohort



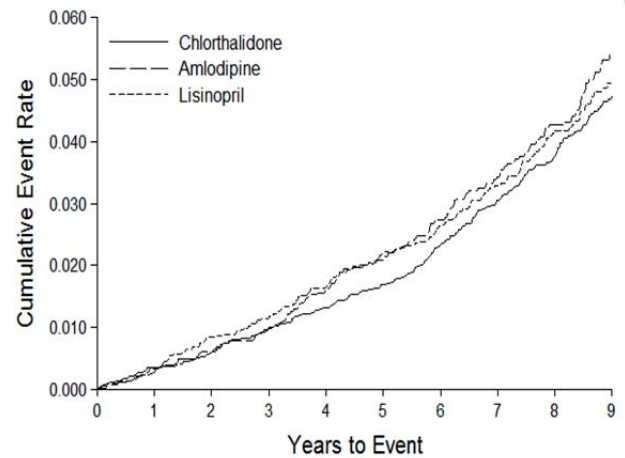
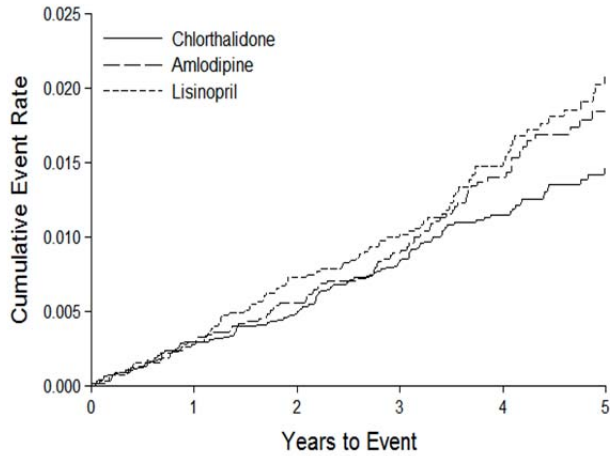
	Hazard Ratio (95% CI), <i>P</i>	Hazard Ratio (95% CI), <i>P</i>
Unadjusted	A/C = 1.27 (0.98 – 1.64), <i>P</i> = 0.071 L/C = 1.28 (0.99 – 1.66), <i>P</i> = 0.058	A/C = 1.18 (0.98 – 1.42), <i>P</i> = 0.078 L/C = 1.11 (0.92 – 1.34), <i>P</i> = 0.279
Adjusted*	A/C = 1.22 (0.93 – 1.59), <i>P</i> = 0.148 L/C = 1.33 (1.02 – 1.73), <i>P</i> = 0.036	A/C = 1.15 (0.95 – 1.40), <i>P</i> = 0.161 L/C = 1.15 (0.94 – 1.40), <i>P</i> = 0.171

Abbreviations: A, amlodipine; C, chlorthalidone; L, lisinopril

* Adjusted for age, race, gender, diabetes, prevalent cardiovascular disease (CVD), baseline glomerular filtration rate (eGFR), body mass index (BMI) and smoking.

C. In-trial cohort

D. In-trial plus post-trial cohort

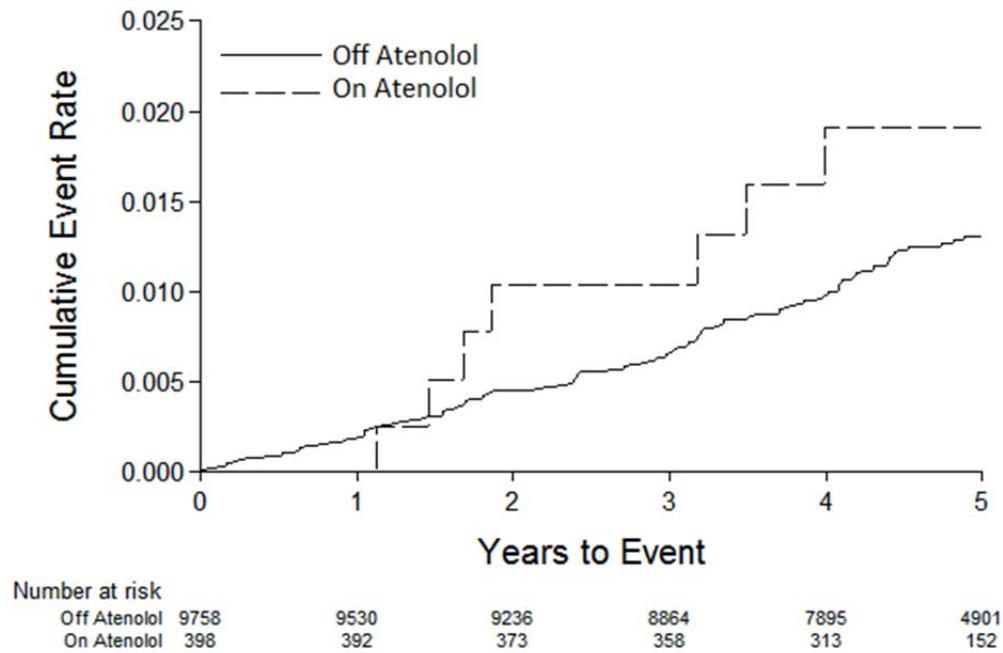


	Hazard ratio (95% CI), <i>P</i>	Hazard ratio (95% CI), <i>P</i>
Unadjusted	A/C = 1.23 (0.93 - 1.63), <i>P</i> = 0.14 L/C = 1.34 (1.02 - 1.76), <i>P</i> = 0.04	A/C = 1.16 (0.96 - 1.41), <i>P</i> = 0.12 L/C = 1.12 (0.92 - 1.36), <i>P</i> = 0.25
Adjusted*	A/C = 1.21 (0.91 - 1.62), <i>P</i> = 0.19 L/C = 1.39 (1.05 - 1.84), <i>P</i> = 0.02	A/C = 1.15 (0.94 - 1.40), <i>P</i> = 0.18 L/C = 1.16 (0.95 - 1.43), <i>P</i> = 0.15

Abbreviations: A, Amlodipine; C, chlorthalidone; L, Lisinopril

* Adjusted for age, race, gender, diabetes, baseline or at year 1 estimated glomerular filtration ratio (eGFR), incident at year 1 and prevalent cardiovascular disease, body mass index, and smoking.

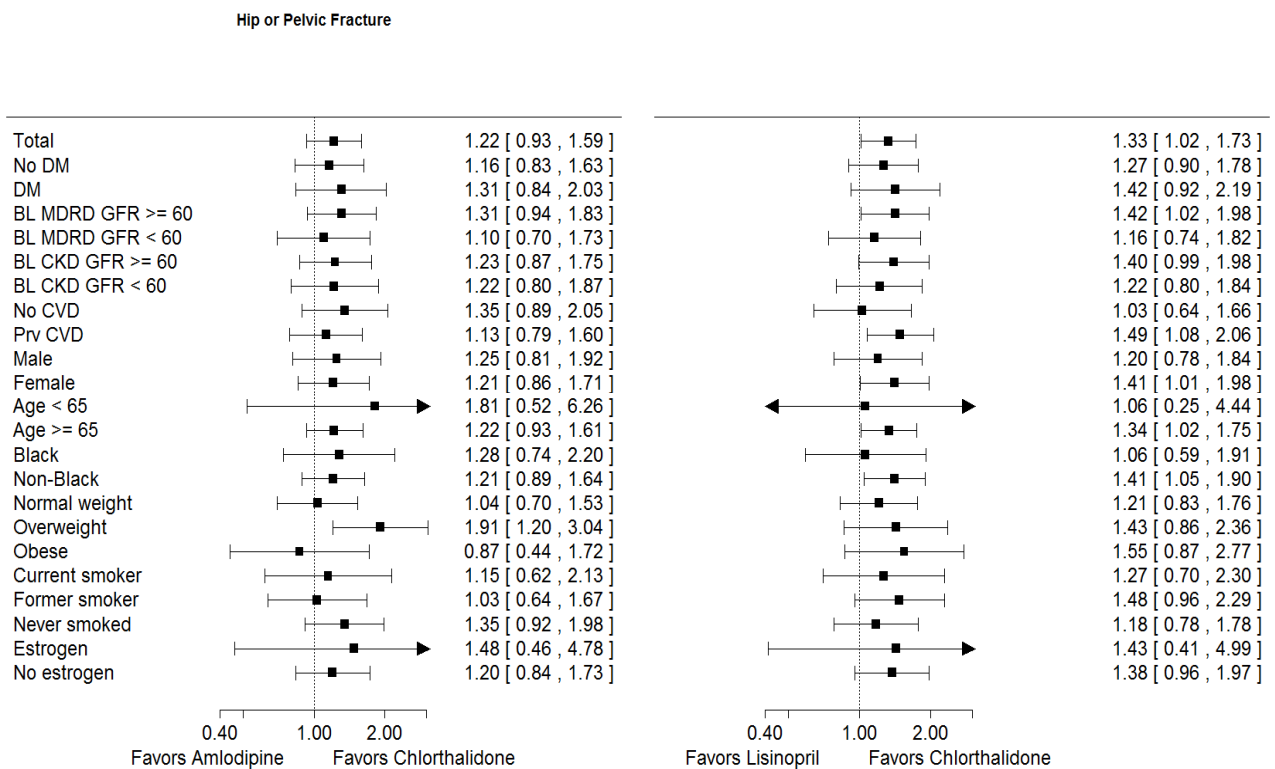
eFigure 2. Kaplan-Meier Curves for Hip and Pelvic Fractures for the In-Trial Cohort in the Chlorthalidone Group by Atenolol Use at 1 Month



	Hazard ratio (95% CI), <i>P</i>
Unadjusted	1.43 (0.67 – 3.07), <i>P</i> = 0.352
Adjusted*	1.29 (0.56 – 2.95), <i>P</i> = 0.548

*Adjusted for age, race, gender, diabetes, baseline estimated glomerular filtration ratio (eGFR), prevalent cardiovascular disease, body mass index, and smoking.

eFigure 3. Adjusted In-Trial Hazard Ratios for Hip or Pelvic Fracture in Those Randomized to Chlorthalidone Compared With Amlodipine or Chlorthalidone Compared With Lisinopril, by Various Demographic and Health Characteristics^{*†}



Abbreviations: BL, baseline; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; Prv, prevalent; Yr, year.

* Adjusted for age, race, gender, diabetes, baseline estimated glomerular filtration rate (eGFR), prevalent cardiovascular disease, body mass index (BMI) and smoking.

† For estrogen, women only.