Systolic and Pulse Pressure Associate with Incident Knee Osteoarthritis: Data from the Osteoarthritis Initiative

Grace H. Lo, MD, MSc[1,2], **Timothy E. McAlindon, MD, MPH**[3], **Jeffrey N. Katz, MD, MSc**[4], **Jeffrey B. Driban, PhD**[3], **Lori Lyn Price, MAS**[5,6], **Charles B. Eaton, MD, MS**[7,8], **Nancy J. Petersen, PhD**[1], **Christie M. Ballantyne, MD**[9], and **Maria E. Suarez-Almazor, MD, PhD**[10]

[1]Department of Medicine, Baylor College of Medicine, Houston, TX, US

[2]Michael E. DeBakey Veterans Affairs Medical Center, Medical Care Line and Research Care Line; VA HSR&D Center for Innovations in Quality, Effectiveness and Safety, Houston, TX, US

[3]Division of Rheumatology, Tufts Medical Center, Boston, MA, US

[4]Orthopedics and Arthritis Center for Outcomes Research, Brigham and Women's Hospital, Boston, MA, US

[5]The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, US

[6]Tufts Clinical and Translational Science Institute, Tufts University, Boston, MA, US

[7]Department of Family Medicine, Memorial Hospital of Rhode Island, Pawtucket, RI, US

[8]Department of Epidemiology, School of Public Health, Brown University, Providence, RI, US

[9]Department of Medicine, Baylor College of Medicine and Houston Methodist DeBakey Heart and Vascular Center, Houston, US

[10]Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, US

Abstract

Address correspondence and reprint requests to Grace Hsiao-Wei Lo, MD MSc, Baylor College of Medicine, Houston, TX, 1 Baylor Plaza, BCM-285, Houston, TX 77030; ghlo@bcm.edu; Phone number: 713-798-7313; Fax number: 713-798-5780.

Objectives—We evaluated the relationship of systolic blood pressure, diastolic blood pressure, pulse pressure, and treatment with antihypertensives with knee osteoarthritis incidence in a United States cohort.

Methods—We performed a longitudinal study (2004 – 2010) nested within the Osteoarthritis Initiative Study including only individuals without knee osteoarthritis at baseline. Systolic blood pressure, diastolic blood pressure and pulse pressure were assessed at baseline, 12-, 24-, and 36-month visits. Knee radiographs at baseline, 12-, 24-, 36- and 48 month visits defined radiographic osteoarthritis, Kellgren and Lawrence grade ≥ 2. We performed logistic regression, adjusting for age, sex, body mass index, NSAID use, number of antihypertensive medications, diabetic medications, and cholesterol medications.

Results—1930 people (6040 observations) were included. Annual incidence rates of radiographic osteoarthritis by systolic blood pressure quartiles (lowest to highest) were 2.1%, 3.4%, 3.7%, and 3.7%. Fully adjusted odds ratios of incident radiographic OA for the 2nd–4th quartiles were 1.6, 1.7, and 1.6 relative to the lowest quartile (p for trend = 0.03). Pulse pressure results were similar. There was no association with diastolic blood pressure. Compared to those not taking any antihypertensive medications, those taking ≥ 3 had decreased odds (0.4, 0.1–1.0) of developing incident OA.

Conclusions—In a United States cohort, higher systolic blood pressure and pulse pressure are associated with increased incidence of radiographic knee osteoarthritis while treatment with ≥ 3 antihypertensive medications was associated with reduced incidence. These findings suggest a new and promising avenue for research on disease modification in knee osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, and a major public health problem, with at least 30 million adults in the US with clinical OA.[1] Health care expenditures are estimated at $189 billion annually in the US.[2] Further, OA is the most frequent cause of dependency in lower limb tasks, especially in the elderly,[3] and accounts for 68 million work loss days per year in the US and more than 5% of the annual retirement rate.[4] It is also the most frequent reason for arthroplasty, of which more than 700,000 are performed annually in the US,[5] equivalent to 2.2 per 1000 persons,[6] approximately triple the rates seen in Scandinavian countries where the rates are 0.7 per 1000 persons,[7–9] still a very common procedure.

The burden of knee OA is particularly heavy because only a limited number of effective treatments have been identified, including physical therapy,[10] weight loss,[11] nonsteroidal anti-inflammatory drugs (NSAIDs),[12] and arthroplasty.[13] Because the natural history of knee OA is long, much of the emphasis of randomized controlled trials has been on those with established disease and persistent symptoms. However, the opportunity to intervene may occur early in disease, supporting attempts to identify risk factors for incident OA.

A study from Japan, the Research on Osteoarthritis and Osteoporosis Against Disability (ROAD) Study, reported an association between the accumulation of metabolic syndrome factors and incident knee OA.[14] Its main focus was evaluating the relationship of metabolic syndrome as a whole, not the individual factors, as it related to incident knee OA. Hypertension was the most common factor observed occurring in 67% of the cohort. In univariate analyses, systolic but not diastolic blood pressure was higher in those who developed knee OA compared to those who did not. To validate these findings, and because results from a Japanese cohort may not be generalizable to other populations it is important to replicate the study in a different cohort, adjusting for potential confounders. Further, these findings raise the hypothesis that an increase in pulse pressure, defined as systolic blood pressure minus diastolic blood pressure, and generally regarded as an indicator of arterial stiffness[15] may be a risk factor for incident knee OA. To our knowledge, the relationship between pulse pressure and knee OA has never been evaluated. We also expected that treatment of elevated systolic pressure and pulse pressure would be associated with a reduced incidence of knee OA.

Therefore, the objectives of our study were to evaluate whether higher systolic blood pressure, diastolic blood pressure and pulse pressure and treatment with anti-hypertensives were associated with incident radiographic knee OA in a United States cohort.

MATERIALS AND METHODS

Study Design

This is a longitudinal study (2004 – 2010) nested within the Osteoarthritis Initiative (OAI), a publicly available multi-center observational study. Full details of the study design of the OAI are available online at https://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf

In this study, we included all participants of the OAI who had at least a baseline clinical visit and a 12 month follow up visit where blood pressure assessments and osteoarthritis assessments were available. Because this was a study of incident knee OA, only those who did not have OA in either knee at baseline were included in this study. This study was approved by the Institutional Review Board at Baylor College of Medicine (K23 H-30423). Each participant provided written informed consent.

Systemic Blood Pressure Measurements

Participants were asked to refrain from drinking any caffeine, eating, doing heavy physical activity, smoking or ingesting alcohol for 30 minutes prior to the blood pressure measurement. Additionally, in the clinic, they were asked to sit upright comfortably in a chair with back supported and rest for five minutes with legs and ankles uncrossed and their feet flat on the floor prior to the blood pressure assessment. A maximal inflation level was determined by adding 30mm of Hg to the palpated systolic blood pressure. Subsequently a manual systolic and diastolic blood pressure was measured using conventional mercury sphygmomanometers, stethoscopes, and the appropriate size blood pressure cuffs. Pulse pressure was defined as systolic blood pressure minus diastolic blood pressure. Blood

pressure measurements were assessed at OAI baseline, 12, 24, and 36 month visits. These data are publicly available on the OAI website (http://oai.epi-ucsf.org/datarelease/) under filenames AllClinical00_SAS (Version 0.2.2), AllClinical01_SAS (Version 1.2.1), AllClinical03_SAS (Version 3.2.1), and AllClinical05_SAS (Version 5.2.1).

Physical Activity Assessment

The Physical Activity Scale for the Elderly (PASE)[16] reflecting amount and level of physical activity over the prior 7 days was assessed at OAI baseline, 12, 24, and 36 month visits. These data were available from the same files used to obtain blood pressure data.

Medication Data

Detailed medication inventory data for prescription medicines taken during the 30 days prior to a clinic visit was obtained at OAI baseline, 12, 24, and 36 month visits. Each medication was mapped to ingredients through use of a medication-coding dictionary adapted from the Women's Health and Aging Study,[17] and these ingredients were then hierarchically-organized and numerically-coded using the Iowa Drug Information Service database of ingredients.[18] These data are publicly available on the OAI website (http://oai.epi-ucsf.org/datarelease/) under filenames MIF00_SAS (Version 0.2.2), MIF01_SAS (Version 1.2.1), MIF03_SAS (Version 3.2.1), and MIF05_SAS (Version 5.2.1).

Antihypertensive medications—GL individually reviewed medication ingredients to identify the following groups of anti-hypertensive medications: calcium channel blocker, beta blocker, angiotensin converter enzyme inhibitor, angiotensin receptor II antagonist, alpha antagonist, diuretic, or miscellaneous antihypertensive medication (i.e. hydralazine, minoxidil, and nitrates).

Non-steroidal anti-inflammatory drugs (NSAIDs)—Participants were asked whether they took either over-the-counter or prescription NSAIDs on most days of the month in the last month. GL also individually reviewed medication ingredients to identify traditional NSAIDs and Cox-2 inhibitors. If participants reported an NSAID (including diclofenac, etodolac, ibuprofen, indomethacin, ketorolac, ketoprofen, meloxicam, nabumetome, naproxen, piroxicam, rofecoxib, or celecoxib) in their medication inventory or answered affirmative to the dichotomous questions about NSAIDs, they were categorized as being exposed to an NSAID.

Diabetic medications—GL individually reviewed medication ingredients to identify all of the following diabetic medications: glipizide, glyburide, glimepiride, glibonuride, repaglinide, nateglinide, metformin, rosiglitazone, pioglitazone, and insulin. If participants were on any of these medications, they were categorized as taking a diabetic medication. Because serum glucose levels were not available for these participants, this was the best alternative method available for assessing diabetes status at the baseline, 12, 24 and 36 month follow up visits.

Cholesterol medications—Using the medication inventory, GL identified the following medications as lipid lowering medications: atorvastatin, fluvastatin, lovastatin, rosuvastatin,

simvastatin, niacin, colesevelam, colestipol, cholestyramine, fenofibrate, and gemfibrozil. If participants were on any of these medications, they were categorized as taking cholesterol medications. Classification of hyperlipidemia status based on medication administration was our best effort to appropriately classify people's hyperlipidemia status since we did not have information on fasting lipid panels at any study visit.

Knee Radiographs

Weight-bearing, fixed-flexion, posterior-anterior radiographs of bilateral knees were obtained at the OAI baseline, 12, 24, 36, and 48 month visits. Central readers [19] scored these for overall radiographic severity using Kellgren-Lawrence grades (0 – 4) using the Osteoarthritis Research Society International Atlas.[20] These data are publicly available on the OAI website (http://oai.epi-ucsf.org/datarelease/), filename kXR_SQ_BU06_SAS (Version 6.3)). The reliability for these readings (read-reread) was substantial[21] (weighted kappa [intra-rater reliability] = 0.71 [95%CI 0.55 – 0.87]).[22] Those knees with a Kellgren and Lawrence grade 2 were defined as having radiographic OA (ROA). If a knee had a total joint replacement, it was assigned as having ROA.

Outcome Definition

<u>Incident ROA</u> was a person-based definition reflecting the development of ROA in either knee 12 months after the exposure assessment.

Covariates

Sex was based on self-report from the OAI baseline visit. Date of birth from OAI baseline visit was used to calculate participant age at each OAI visit. Body mass index (BMI) at each visit was calculated as weight (measured at each visit) divided by most recently measured height squared (kg/m^2) (measured at every other OAI visit).

Statistical Analysis

We evaluated the influence of systolic blood pressure, diastolic blood pressure, and pulse pressure quartiles including time points at baseline, months 12, 24, and 36, on the development of incident ROA in at least one knee 12 months after blood pressure assessments, meaning months 12, 24, 36 and 48. Each time point was treated as a separate observation. (E.g. we evaluated whether a participant's quartile of systolic blood pressure at baseline was predictive of incident OA at the 12 month visit. Then if the participant did not develop OA, we evaluated whether his/her quartile of systolic blood pressure at 12 months was predictive of incident OA at the 24 month visit, etc.) We performed repeated measures longitudinal analyses using generalized estimating equations to adjust for correlations across visits within the same person over time.[23] Once participants developed incident ROA, they were censored from the analyses. Each participant could contribute up to 4 observation periods. The Cochran-Armitage trend test was used to assess for statistically significant trends.[24, 25] We performed the analyses unadjusted and then adjusted for potential confounders including age, sex, body mass index, PASE, NSAIDs use, number of antihypertensive medications (0, 1, 2 or 3), diabetic medication use, and cholesterol medication use at the baseline, 12, 24, and 36 month visits. Participants missing either

radiographic readings or blood pressure readings were excluded from the analyses at that particular visit.

Because systolic blood pressure and pulse pressure quartiles 2–4 did not exhibit a typical dose response relationship, we performed post hoc logistic regression analyses collapsing those quartiles into one group.

All analyses were performed using SAS version 9.4. P-values <0.05 were considered statistically significant.

RESULTS

In total 1930 participants contributed 6040 observations. A flow diagram for the cohort is included in figure 1. Mean age was 59.2 (9.1) years, mean body mass index was 27.2 (4.5) kg/m^2 and 42% of the group were male.

Number of antihypertensive medications, diabetic medication use, and cholesterol medication use were all associated with increased systolic blood pressure and pulse pressure (Table 1).

There was a statistically significant increased incidence of ROA with increased systolic blood pressure and pulse pressure quartiles (Table 2 and 3), but not with diastolic blood pressure (Table 4). The associations between both systolic blood pressure and pulse pressure and incident knee ROA persisted after adjusting for age, sex, body mass index, PASE, NSAID use, number of antihypertensive medications, diabetic medications, and cholesterol medications (Tables 2 and 3). Post-hoc analyses comparing systolic blood pressure quartiles 2–4 (ROA incidence of 3.6%) against quartile 1 (2.1%) resulted in unadjusted and adjusted odds ratios (ORs) of 1.7 (95% confidence interval [CI] 1.2 – 2.5) and 1.6 (95%CI 1.1 – 2.4) respectively. Comparing pulse pressure quartiles 2–4 (ROA incidence 3.6%) against quartile 1 (2.2%), unadjusted and adjusted ORs were 1.7 (95%CI 1.2 – 2.4) and 1.6 (95%CI 1.1 – 2.4).

In the fully adjusted models, greater number of anti-hypertensive medications was associated with a lower risk of incident ROA. Participants taking ≥3 anti-hypertensive medications had decreased odds (0.4, 0.1–1.0) of developing incident ROA compared to those not taking any antihypertensive medications. However, adding anti-hypertensive medications into the model did not substantively change the point estimates for the risk of ROA related to systolic blood pressure and pulse pressure. Diabetic medication use and cholesterol medication use were not statistically significant variables in the adjusted models and also did not substantively change the point estimates for the risk of ROA related to systolic blood pressure and pulse pressure, although each individually is related to systolic blood pressure and pulse pressure (Table 1).

DISCUSSION

We have demonstrated that higher systolic blood pressure and pulse pressure, but not diastolic blood pressure, were associated with increased incidence of ROA in a US based

cohort, the OAI. Further, use of three or more antihypertensive agents was associated with a lower incidence of ROA. Prior uncontrolled studies have described that hypertension is common among people with OA.[26, 27] The Japanese ROAD study[14] presented univariate unadjusted analysis identifying an association between incident ROA and systolic but not diastolic blood pressure. After adjusting for potential confounders including physical activity and NSAID use, with a known side effect of hypertension [28, 29], as well as diabetes and cholesterol medications, our study has replicated this relationship, and we are the first to show an association of pulse pressure with incident ROA.

Systolic and diastolic blood pressures are the maximal and minimal pressures in the aorta during the cardiac cycle. Pulse pressure is the difference between the two. We found elevated systolic blood pressure and pulse pressure but not diastolic blood pressure to associate with incident knee ROA. A pulse pressure of greater than 38 conferred a 70% increased odds for incident ROA. Similarly, a systolic blood pressure of greater than 111 conferred a 70% increased odds for incident ROA. Many people on the largest number of medications had substantially elevated systolic blood pressure and pulse pressures, consistent with real world management of hypertension.[30] Interestingly, those taking 3 anti-hypertensive medications had decreased odds (0.4, 0.1–1.0) of developing incident OA compared to those not taking any antihypertensive medications, suggesting that treatment of hypertension may reduce the incidence of knee OA.

The pattern of having an elevated systolic blood pressure and pulse pressure without an elevated diastolic blood pressure is consistent with isolated systolic hypertension, though the specific definition is a systolic blood pressure > 160 when the diastolic blood pressure < 95. [31] This is a phenomenon attributed to arterial stiffness,[32] aortic stiffness and endothelial dysfunction.[15] Isolated systolic hypertension confers an increased risk for cardiovascular death.[33] Although there is controversy surrounding whether OA is associated with increased cardiovascular death[34, 35], some studies do suggest this,[36, 37] perhaps because OA is a marker of arterial stiffness which would be in keeping with a growing concept that there might be a vascular pathology to OA.[38] Hussain et al found that those who received incident knee arthroplasties for knee OA had smaller caliber retinal arterioles compared to those who did not receive arthroplasties.[39] Though caliber of retinal arterioles is not a direct measure of vascular pathology at the site of the joint, it is a measure of small arteries and bearing in mind that using arthroplasty as a marker of OA is suboptimal,[40] this study supports the idea of a vascular pathology to OA. It will be of great interest to better understand differences that exist within specific joint structures, including bone marrow lesions, menisci, synovitis, ligament damage, and attrition in those with and without elevated systolic blood pressure and pulse pressure prior to the development of knee OA. While the OAI has a wealth of data, MRIs which can ascertain these lesions, at present have only been read on a fraction of the available images. Basic science research on the effect of increased systolic blood pressure and pulse pressure on key joint structures may also be illuminating.

There some limitations to this study. Serum glucose and cholesterol levels were not measured. Therefore we used diabetic and cholesterol medication use which were available at each visit, as surrogate assessments for these conditions. Both medication groups were

associated with systolic blood pressure and pulse pressure; however, neither was associated with incident ROA. The lack of associations of diabetic and cholesterol medication use with incident ROA may have resulted from confounding by indication. Therefore, it is still possible that hyperlipidemia[41–43] and diabetes[44] are risk factors for incident ROA. There is the potential that targeting hyperlipidemia and diabetes, other components of metabolic syndrome, might be helpful in preventing incident OA, important questions to address in future research. An additional limitation is that because this an observational study where participants were initiated on medications in a real world setting for hypertension to treat elevated blood pressure, we cannot be certain that initiation of antihypertensive agents for the purpose of reducing the risk of knee OA will actually be effective. A double blinded randomized controlled trial would be needed to address this question. However, it would be prudent to derive a greater understanding of the pathophysiology behind this relationship before embarking on such an intervention study, particularly because the threshold at which SBP seems to confer a greater risk of knee OA is lower than the treatment target for elevated SBP. It is not clear that the risk-benefit ratio is sufficient to recommend this intervention at present.

Given the high prevalence of systemic hypertension and knee OA, the current paucity of practical knee OA preventative strategies and disease modifying therapies, the potential implications of our findings are substantial. Though future epidemiologic studies are needed to confirm our findings, this study provides evidence to suggest a new and promising avenue for research on disease modification in knee OA.

Acknowledgments

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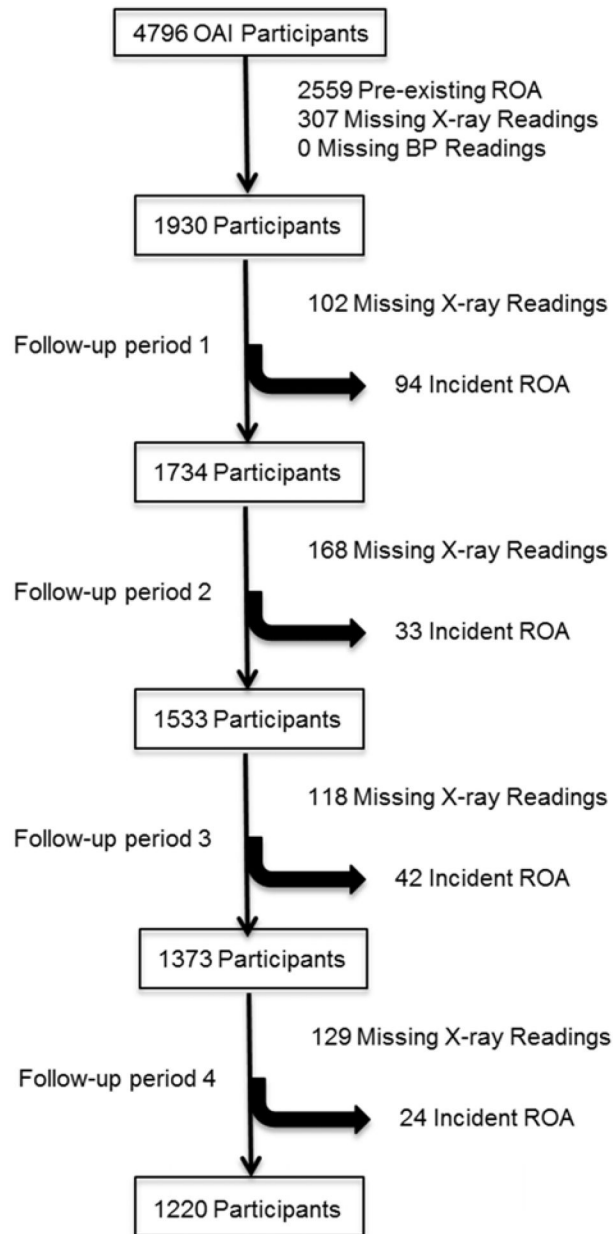
Figure 1.
Flow diagram of participants included.

Table 1

Relationship of medications with systolic blood pressure (SBP) and pulse pressure (PP).

	% taking number of anti HTN meds				% taking DM meds	% taking chol meds
	0	1	2	3		
SBP						
Quartile 1 (76 – 111)	79% (1374/1737)	13% (225/1737)	6% (105/1737)	2% (33/1737)	3% (44/1737)	22% (378/1737)
Quartile 2 (112 – 121)	70% (1099/1571)	16% (244/1571)	11% (165/1571)	4% (63/1571)	5% (83/1571)	31% (481/1571)
Quartile 3 (122 – 130)	61% (854/1396)	21% (287/1396)	12% (173/1396)	6% (82/1396)	5% (68/1396)	32% (453/1396)
Quartile 4 (131 – 208)	49% (656/1336)	26% (342/1336)	16% (218/1336)	9% (120/1336)	8% (110/1336)	34% (458/1336)
PP						
Quartile 1 (10 – 38)	78% (1441/1849)	13% (242/1849)	7% (130/1849)	2% (36/1849)	2% (40/1849)	22% (402/1849)
Quartile 2 (39 – 44)	72% (855/1190)	18% (212/1190)	7% (83/1190)	3% (40/1190)	4% (53/1190)	28% (337/1190)
Quartile 3 (45 – 54)	64% (1011/1588)	19% (307/1588)	12% (194/1588)	5% (76/1588)	5% (78/1588)	30% (481/1588)
Quartile 4 (55 – 136)	48% (676/1413)	24% (337/1413)	18% (254/1413)	10% (146/1413)	10% (134/1413)	39% (550/1413)

Table 2

Odds Ratios (ORs) of Incident ROA across SBP Quartiles. There were 1930 participants, contributing 6040 observation periods, for a total of 192 events.

	Incidence of ROA by Systolic BP Quartile	Unadjusted OR (95% CI)	OR (95% CI) Adjusted for Age, Sex, BMI, PASE, NSAID use, number of anti-hypertensive meds, diabetes meds, cholesterol meds
SBP Quartile 1 (76 – 111)	37/1737 (2.1%)	Referent	Referent
SBP Quartile 2 (112 – 121)	54/1571 (3.4%)	1.6 (1.1 – 2.5)	1.6 (1.0 – 2.5)
SBP Quartile 3 (122 – 130)	51/1396 (3.7%)	1.7 (1.1 – 2.7)	1.7 (1.1 – 2.6)
SBP Quartile 4 (131 – 208)	50/1336 (3.7%)	1.8 (1.2 – 2.7)	1.7 (1.0 – 2.6)
		p-for trend = 0.007	p-for trend = 0.03

Table 3

Odds Ratios of Incident ROA across Pulse Pressure (PP) Quartiles. There were 1930 participants, contributing 6040 observation periods, for a total of 192 events.

	Incidence of ROA by PP Quartile	Unadjusted OR (95% CI)	OR (95% CI) Adjusted for Age, Sex, BMI, PASE, NSAID use, number of anti-hypertensive meds, diabetes meds, cholesterol meds
PP Quartile 1 (10 – 38)	40/1849 (2.2%)	Referent	Referent
PP Quartile 2 (39 – 44)	47/1190 (4.0%)	1.9 (1.2 – 2.8)	1.8 (1.2 – 2.8)
PP Quartile 3 (45 – 54)	50/1588 (3.2%)	1.5 (1.0 – 2.2)	1.4 (0.9 – 2.2)
PP Quartile 4 (55 – 136)	55/1413 (3.9%)	1.8 (1.2 – 2.8)	1.8 (1.1 – 2.8)
		p-for trend = 0.01	p-for trend = 0.03

Table 4

Odds Ratios of Incident ROA across Diastolic Pressure (DBP) Quartiles. There were 1930 participants, contributing 6040 observation periods, for a total of 192 events.

	Incidence of ROA by DBP Quartile	Unadjusted OR (95% CI)	OR (95% CI) Adjusted for Age, Sex, BMI, PASE, NSAID use, number of anti-hypertensive meds, diabetes meds, cholesterol meds
DBP Quartile 1 (36 – 68)	54/1601 (3.4%)	Referent	Referent
DBP Quartile 2 (69 – 74)	48/1544 (3.1%)	0.9 (0.6 – 1.4)	0.9 (0.6 – 1.4)
DBP Quartile 3 (75 – 80)	54/1583 (3.4%)	1.0 (0.7 – 1.5)	1.0 (0.6 – 1.4)
DBP Quartile 4 (82 – 116)	36/1276 (2.7%)	0.8 (0.5 – 1.2)	0.7 (0.5 – 1.2)
		p-for trend = 0.5	p-for trend = 0.3