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C-reactive Protein among Community-Dwelling Hypertensives on Single-agent Antihypertensive Treatment

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Abstract

Background—C-reactive protein is a predictor of adverse cardiovascular outcomes. The effect of antihypertensive therapy on C-reactive protein levels is largely unknown.

Method—We undertook a cross-sectional study of CRP levels among participants with primary hypertension on single-agent anti-hypertensive therapy in the community-based biracial Genetic Epidemiology Network of Arteriopathy cohort. Linear regression models were used to assess the association of anti-hypertensive medication class with log-transformed C-reactive protein after adjustment for age, gender, ethnicity, body mass index, smoking, diabetes, HMG-Co-A reductase inhibitor use, achieved blood pressure control (<140/90 mmHg), serum creatinine and urine albumin-to-creatinine ratios.

Results—There were 662 participants in the cohort taking single-agent therapy for hypertension. Median C-reactive protein levels differed across participants: 0.40 mg/dL for those on diuretics, 0.34 mg/dL on calcium channel blockers, 0.25 mg/dL on beta blockers and 0.27 mg/dL on renin-angiotensin-aldosterone system inhibitors ($p < 0.001$). With multivariable adjustment, the group on renin-angiotensin-aldosterone system inhibitors had a 20% lower mean CRP on average than the group on diuretics ($p = 0.044$), differences between other medication classes were not apparent. Heart rate had a strong association with C-reactive protein ($p < 0.001$).

Conclusions—Antihypertensive medication class may influence inflammation, particularly in patients on RAAS inhibitors.

Keywords

antihypertensive therapy; C-reactive protein; diuretics; inflammation; RAAS inhibitors; sibships

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Introduction

Increasing evidence supports a relationship between C-reactive protein (CRP) levels and cardiovascular disease and mortality[1–3], sudden cardiac death[2] and stroke[4]. CRP is an acute phase protein that conveniently serves as an *in vivo* bioassay to gauge the overall degree of inflammation. Elevated CRP has also emerged as a non-traditional risk factor for adverse cardiovascular outcomes, though its contribution to predicting cardiovascular disease outcomes is less impressive after traditional risk factors have been considered[5,6]. Hypertension is associated with elevated CRP[7], and among normotensive subjects, elevated CRP predicts future risk of hypertension[8]. CRP is correlating more with systolic and pulse pressure, rather than with diastolic blood pressure, even in treatment naive patients. This relationship may reflect underlying atherosclerosis[9] as elevated CRP also correlates with measures of arterial wave reflection and stiffness[10]. Low CRP values, along with normal BNP levels, predict the absence of left ventricular hypertrophy (LVH) among hypertensive individuals[11]. Nevertheless, the effect of anti-hypertensive agents from different classes on low-grade inflammation measured by CRP has received relatively little attention so far.

The available data on the effect of antihypertensives from different classes on CRP is limited to mostly small trials. Some[12,13] but not all[14,15] studies report lower CRP values with either angiotensin converting enzyme inhibitors or angiotensin receptor blockers. To date, there is only one large, community-based study reporting on the relationship between antihypertensive medication class and CRP. Recently, Palmas et al reported an association of beta-blocker use with lower CRP values, based on the baseline cohort exam from the Multi-Ethnic Study of Atherosclerosis (MESA)[16]. This relationship was observed in both monotherapy ($p<0.001$) and combination therapy groups ($p=0.021$).

The Genetic Epidemiology Network of Arteriopathy (GENOA) is a National Heart Lung and Blood Institute (NHLBI) supported bi-racial cohort study of hypertensive sibships in the community. The primary goal of our study was to determine if there is an association between anti-hypertensive medication class and CRP among community-dwelling hypertensives on single-agent therapy.

Methods

Study Population

The Genetic Epidemiology Network of Arteriopathy (GENOA) is part of the Family Blood Pressure Program, which recruited non-Hispanic white and black sibships with the aim of investigating the genetics of hypertension and its target organ complications[17]. Subject recruitment was community-based and black probands were identified from the Atherosclerosis Risk in Communities (ARIC) cohort in Jackson, Mississippi[18] while the Rochester Epidemiology Project in Rochester, Minnesota was used to identify white probands[19]. During the first clinic visit (between 1996 and 1999), GENOA recruited sibships containing at least two individuals with clinically diagnosed essential hypertension before age 60. Participants were diagnosed with hypertension if they had a previous clinical diagnosis of hypertension by a physician with current anti-hypertensive treatment, or had systolic blood pressure (SBP) ≥ 140 or diastolic blood pressure (DBP) ≥ 90 at the clinic visit. Exclusion criteria included secondary hypertension, alcoholism or drug abuse, pregnancy, insulin-dependent diabetes mellitus, or active malignancy. Between 2000 and 2004, 2721 (or approximately 80%) of the initial GENOA participants returned for a 2nd clinic visit. Clinic visits involved collecting blood pressure readings, a questionnaire regarding family history and cardiovascular disease (CVD) risk factors, and phlebotomy for genotyping and laboratory tests. Study visits were conducted in the morning after an overnight fast of at least eight hours. This study was limited to participants in the second GENOA clinic visit when CRP was measured.

Measurements

Height was measured by stadiometer and weight by electronic balance. Body mass index (BMI) was calculated using body weight and height and calculated as body weight in kilograms divided by height in meters squared. Blood pressure was measured with random zero sphygmomanometers and cuffs appropriate for arm size. Three readings were taken in the right arm after the participant rested in the sitting position for at least five minutes; the last two readings were averaged for the analyses. Smoking was categorized as never smoking, smoking ever and current smoker. 'Ever' smoking was defined as having smoked more than 100 cigarettes. Diabetes was defined by subjects being treated with insulin or oral agents or who had a fasting glucose level of at least 126 mg/dL. Information about the use of HMG-CoA reductase inhibitor ("statin") medications, estrogen, and aspirin was extracted from a questionnaire administered to the participants. Plasma CRP was measured by highly sensitive immunoturbidimetric assay[20]. Family history of coronary heart disease was defined by any parent or sibling of the participant with a history of myocardial infarction or documented coronary artery disease. All antihypertensives medications were obtained from the questionnaire and grouped into the following classes: diuretics, beta blockers, calcium channels blockers (CCBs), renin-angiotensin-aldosterone system (RAAS) inhibitors and "other antihypertensive agents" (OAAAs).

Statistical Methods

Analyses were limited to patients on single-agent antihypertensive therapy, partly to exclude more difficult to control hypertensive subjects with likely larger confounding co-morbid disease burden. Continuous variables were described with their median values and the respective 1st and 3rd quartiles (Q1, Q3). Categorical variables were described as count (percent). Controlled hypertension was defined by a blood pressure less than 140/90 mmHg. Differences in median CRP levels across the drug classes were assessed with a Kruskal-Wallis test. Serum creatinine, spot urine albumin/creatinine ratios (UACR) and CRP showed a skewed distribution and were log-transformed prior to analyses. An initial multiple linear regression model, referred to as the "base" model, examined the relationship of CRP among the different monotherapy drug classes after controlling for age, gender, race, blood pressure control, serum creatinine and UACR. Since all models adjusted for age, gender and race, we did not convert serum creatinine to estimated glomerular filtration rate with the Modification of Diet in Renal Diseases (MDRD) equation. The full or "complex" multiple linear regression model controlled for the variables in the initial model as well as BMI, past and current smoking status, diabetes status, and HMG-CoA reductase inhibitor therapy. Individual participants were included in the models, whenever all relevant parameters were available. Diuretic therapy was used as the reference antihypertensive drug class. Because of the non-independence of sibships, we explored additional models in which generalized estimating equations (GEE) were utilized to allow for the possible impact of familial correlations on the relationships between predictor and outcome variables. All statistical analyses have been performed with SAS 9.1.3. software.

Results

Of the 2721 GENOA participants who participated in the 2nd clinic visit, 584 (21.5%) were normotensive without blood pressure lowering medications, 225 (8.3%) were hypertensive without receiving anti-hypertensive therapy, and 56 (2.1%) were receiving blood pressure lowering medication without the diagnosis of hypertension. The remaining 1856 (68.2%) were hypertensive and taking anti-hypertensive therapy: 1186 (63.9%) were taking more than one anti-hypertensive agent and 670 (36.1%) were taking exclusively single-agent therapy for high blood pressure. Median blood pressure was 122/74 for all normotensives, 149/84 for hypertensives not taking anti-hypertensive therapy, and 136/77 for treated hypertensives. Median CRP (Q1, Q3) was 0.30 mg/dL (0.14, 0.62) in the entire GENOA cohort, 0.21 mg/dL

(0.10, 0.46) in normotensives, 0.27 mg/dL (0.16, 0.55) in untreated hypertensives, and 0.33 mg/dL (0.16, 0.69) in treated hypertensives and 0.30 mg/dL (0.15–0.60) in hypertensives on monotherapy.

Of the participants on single-agent therapy, 8 were excluded due to missing CRP data. Thus, the final analyzed cohort had 662 participants, of which 227 (34.3%) were men and 330 (49.9%) were black. In our sample, 138 (20.9%) participants were treated with beta-blockers, 117 (17.7%) with calcium-channel blockers (CCBs), 175 (26.4%) with diuretics, 202 (30.5%) with RAAS inhibitors and 30 (4.5%) with “other antihypertensive agents” (OAAs).

Table 1 describes the cohort according to drug class. Median CRP was different across the anti-hypertensive drug classes ($p<0.001$) with diuretic treated subjects having the highest median CRP (0.40 mg/dL), followed by CCBs (0.34 mg/dL), RAAS inhibitors (0.27 mg/dL), beta-blockers and OAAs (0.25 mg/dl for both). After adjustment for base variables (age, gender, race, blood pressure control, serum creatinine and UACR), both beta-blocker therapy ($p=0.043$) and RAAS inhibitor therapy ($p=0.024$) were associated with a 24% lower mean CRP compared to diuretic therapy (Table 2, Model 1). However, the overall test for drug class differences in this model was not significant ($p=0.11$). In a model including the covariates of our “base” model plus BMI, smoking, diabetes, and statins we were able to explain 24.6% of the variation of CRP (Table 2, Model 2). In this “complex” model, increasing age ($p=0.027$), BMI ($p<0.001$), and current smoker vs. nonsmoker status ($p<0.001$) were associated with higher CRP values while male gender was associated with lower CRP values ($p<0.001$). There was no overall differences in anti-hypertensive class ($p=0.240$) in this model, but in pairwise analysis, RAAS inhibitors class had a 20% lower mean CRP than the diuretics class ($p=0.044$). Adjustment for sibship using generalized estimating equations (GEEs) did not meaningfully influence these associations with RAAS inhibitor class still having lower CRP values than the diuretics class ($p=0.019$). Optional inclusion of peripheral artery disease did not modify the results.

We repeated our analyses using a multivariable model similar to the one reported from the MESA cohort[16]. This did not meaningfully change our findings. The overall effect of antihypertensive agent class was not significant ($p=0.263$), but on pairwise contrast with the reference group of diuretics (Table 2, Model 3), the RAAS inhibitor class had a 21% lower mean CRP ($p=0.033$). Estrogen use ($p<0.001$) and thiazolidinedione class antidiabetic agents use ($p=0.002$) showed very significant associations with CRP in this model in addition to strong relationships with gender, BMI, and current smoking status that we had previously seen in our complex model.

In an attempt to explain our discordant findings with MESA cohort, we explored variation of heart rate control confounding results. When we incorporated heart rate into our models (per beats/minute), it exerted a strong influence on CRP (base model: $p<0.001$; complex model: $p<0.001$)(Table not shown). An increase of heart rate by 10 beats/minute resulted in a 15% increase of mean CRP in the base model and 13% increase of mean CRP in the complex model. In the base model the association of beta-blocker with CRP disappeared ($p=0.344$). Beta-blocker and CRP were not associated in either the complex model without heart rate or the model with heart rate included ($p=0.752$). In both the base and complex models with heart rate added, the association of RAAS inhibitors with lower CRP persisted: 25% lower mean CRP values compared to the diuretic group in the base model ($p=0.017$) and 20% lower mean CRP values in the complex model ($p=0.037$)

Both beta blockade and RAAS inhibitors suppresses the renin-angiotensin system. Therefore, we performed analyses combining the beta blocker and RAAS inhibitors drug classes and excluding OAA class due to the small number of OAA participants. Mean CRP was not

different between CCBs and diuretics in pairwise comparison, whereas the combined beta blocker + ACE inhibitor class was associated with 18% lower mean CRP than in the diuretics group both, in our complex model ($p=0.044$) and in the model similar to Palmas et al. from MESA ($p=0.036$) (Table not shown). Major determinants of CRP (i.e., gender, BMI, current smoking) remained statistically significant ($p<0.001$).

Discussion

In GENOA participants, single-agent antihypertensive therapy class was associated with significant CRP differences in unadjusted analysis, with the diuretic therapy group having distinctly higher CRP values. After adjusting for confounding variables, the overall statistical difference across antihypertensive medications classes was no longer significant. However, when diuretics were taken as a reference group, RAAS inhibitor class had a significantly lower adjusted CRP value. The initial association of beta blocker therapy with lower CRP values was attenuated in more complex models. However, when beta blockers and RAAS inhibitors were combined, the association with lower CRP values maintained significance, in comparison with reference group of diuretics. We also reaffirmed established risk factors for elevated CRP from this cohort: age, BMI, current smoking, female gender and estrogen hormone use. Achieved blood pressure control, however, did not show any association with CRP.

This study adds to a limited literature assessing the relationship between inflammation and anti-hypertensive therapy. In a small cohort study, valsartan 40–80 mg/day significantly reduced tumor necrosis factor- α and interleukin-6 levels, but no effect on CRP was demonstrated [12]. In a small, placebo-controlled, three-month trial olmesartan reduced CRP levels by about 21% [14]. A comparative trial of hydrochlorothiazide, lisinopril and candesartan in type 2 diabetics resulted in no detectable CRP changes [15]. In the REASON trial, combined therapy with perindopril-indapamide was more effective than beta-blockade to lower CRP in hypertensive subjects [13].

MESA, the only community-based study to date, reported a strong association of lower CRP values with beta-blocker use, both in the monotherapy group as well as in the group on combination therapy [16]. Being on a beta blocker was associated with lower CRP values in general, an effect which persisted after multivariate adjustment ($p=0.021$). Among 1314 MESA participants on single-agent antihypertensive therapy, the predicted CRP lowering effect of being on beta blocker (vs. reference group of diuretics) was a mean adjusted 0.75 mg/L (0.075 mg/dl) ($p<0.001$), while the predicted lowering effect of being on RAAS inhibitor was weaker at 0.47 mg/L (0.047 mg/dL) ($p<0.046$). In our cohort the association of lower CRP with beta blocker use was much weaker and not statistically significant after adjusting for confounding variables. With regard to beta blocker therapy, the reason for these discordant findings remains unclear. Our results remained remarkably similar in multiple different models, including one very similar to Palmas et. al. (Table 2, Model 3.). However, our finding and those from MESA investigators both demonstrated an association of RAAS inhibitor with lower CRP against the reference group of diuretics.

Achieved blood pressure control in general did not exert any influence on CRP. Therefore, while adjustment for hypertension control in our study was dichotomous (according achieved good control or not), rather than continuous by Palmas et al., blood pressure control was unlikely to explain the difference. In fact, one common finding emerging from both studies is the dissociation between achieved blood pressure control and CRP. Adjustment of the former authors for left ventricular hypertrophy (LVH) by EKG criteria could potentially explain part of the difference, as LVH has a strong positive association with CRP [11]. RAAS inhibitors may be more efficacious than other antihypertensive drug classes in achieving LVH regression [21], and adjustment for LVH may have weakened the effect of RAAS class. Alternatively,

efficacy of beta blockade with regard to variation of dosage and achieved heart rate control may have differed between the cohorts and influenced the result. In our study, observed heart rate had not only a strong positive association with CRP, but incorporating heart rate into the modeling immediately negated any effect of beta blocker use. This association between heart rate and CRP has been observed by other authors, as well[22,23]. The seemingly small difference predicted in our model between diuretic and RAAS class (approximately 20% difference) may be clinically meaningful. According to a joint published statement from the American Heart Association/Center of Disease Control, values between 1 – 3 mg/L vs. > 3 mg/L separates average vs. high risk general population tertiles[24]. Similar differences in CRP were associated with an approximately 50% increased risk of heart disease[3,25,26]

It is noteworthy that even the “full” multivariable model offered only a limited (approximately 25%) explanation for the variation of CRP. Heritability is likely to explain a larger portion of the variation[27], and has been recently linked to several distinct chromosomal regions[28]. The rest of the variation likely reflected a combination of measurement error, within-individual variation and unmeasured environmental factors such as diet and lifestyle that may influence CRP levels.

Limitations and Strengths

There were several potential limitations to this study. This was a strictly observational and cross sectional study and thus, the results are primarily hypothesis-generating findings, rather than conclusive results. The size of the cohort available for final analysis was relatively small, especially when considering the number of variables. A longitudinal study is needed to fully assess the effect of anti-hypertensive medication class on CRP and low-degree inflammation. Other potential confounders, including unaccounted demographic variation, local variation of practice pattern (race and cohort recruitment site completely overlapped) or severity of diseases may have influenced the results. CRP levels are variable and a single measurement may not appropriately capture a subject's true baseline[29]. We also do not have baseline CRP values available from this cohort and the duration of treatment with antihypertensive agent class was unknown. The GENOA population of hypertensive sibships may have different CRP values from general population or have a different pattern of response to an individual stressor. We cannot rule out the possibility that the indication for the anti-hypertensive therapy - as opposed to the anti-hypertensive therapy itself - may have influenced CRP levels. However, the group on RAAS inhibitors had a relatively larger percentage of diabetics and beta-blocker use was more frequent in the presence of coronary heart disease (CHD). Therefore, if anything, this should have weakened any association of lower CRP values with RAAS inhibitors as diabetics and participants with CHD are more likely to have more advanced atherosclerosis and a larger co-morbid disease burden. The strengths of this study include the sample size, bi-racial composition and community recruitment of participants. We also have attempted to adjust for multiple confounding variables and our results showed consistency in all statistical models. Monitoring CRP is not currently part of practice guidelines and, therefore, unlikely that practitioners' prescribing habits serendipitously would have influenced our results.

Conclusions

Antihypertensive medication class may have an influence on low-grade inflammation, as demonstrated in our cohort by significant differences between those on diuretics and RAAS inhibitors. We have re-confirmed previously reported associations of elevated CRP sibships with age, BMI, current smoking status, female gender, exogenous estrogens and heart rate in the GENOA cohort ascertained through hypertensive sibships. Achieved blood pressure control did not influence CRP. The relative contributions of suppressing low-degree inflammation with antihypertensive therapy to improve clinical outcomes could be fully

examined appropriately only in a prospective controlled trial. More studies are needed and future controlled trials of antihypertensive agents on outcomes may include monitoring of CRP values.

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Descriptive statistics of variables according to anti-hypertensive agent class among patients receiving mono-therapy in the GENOA cohort

Table 1

Descriptive statistics of variables according to anti-hypertensive agent class					
Variable	Beta-Blocker (N=138)	Calcium Channel Blocker (N=117)	Diuretic (N=175)	RAAS Inhibitor (N=202)	Other Anti- Hypertensive (N=30)
Male gender	49 (36)	33 (28)	42 (24)	87 (43)	16 (53)
African-American race	26 (19)	85 (73)	99 (57)	96 (48)	24 (80)
Age, years	60 (52, 67)	63 (57, 68)	63 (55, 67)	61 (54, 66)	67 (61, 73)
Body Mass Index, kg/m ²	30 (26, 33)	29 (27, 34)	31 (28, 36)	30 (26, 35)	30 (27, 32)
Coronary Heart Disease	15 (11)	3 (2.6)	5 (2.9)	11 (5.4)	1 (3.3)
Ever Smoker	66 (48)	51 (44)	67 (38)	88 (44)	13 (43)
Smoking, pack-years	23 (6.5, 42)	19 (6.9, 35)	17 (6.8, 29)	22 (9.9, 38)	30 (12, 38)
SBP, mmHg	135 (124, 146)	139 (131, 153)	133 (124, 144)	133 (122, 147)	138 (126, 145)
DBP, mmHg	77 (72, 81)	82 (74, 87)	77 (71, 82)	78 (73, 85)	80 (74, 87)
Pulse Pressure, mmHg	58 (50, 67)	59 (48, 70)	56 (46, 69)	56 (46, 68)	55 (50, 68)
ABI	1.12 (1.03, 1.20)	1.05 (0.99, 1.12)	1.07 (0.99, 1.14)	1.06 (1.00, 1.17)	1.05 (1.00, 1.16)
Total Cholesterol, mg/dL	192 (175, 218)	206 (183, 232)	200 (180, 228)	192 (172, 226)	189 (168, 218)
HDL Cholesterol, mg/dL	52 (42, 61)	56 (47, 64)	55 (46, 68)	51 (41, 62)	52 (43, 59)
Calculated LDL Cholesterol, mg/dL	116 (98, 138)	127 (105, 148)	118 (98, 146)	116 (97, 144)	110 (100, 137)
Diabetes	10 (7.2)	22 (19)	31 (18)	69 (34)	8 (27)
Serum Creatinine, mg/dL	0.8 (0.7, 1.0)	0.8 (0.6, 0.9)	0.85 (0.7, 1.0)	0.9 (0.7, 1.1)	0.9 (0.7, 1.1)
Urine Albumin-Creatinine Ratio, mg/g	3.1 (1.6, 6.7)	4.5 (2.2, 18)	3.9 (2.0, 7.1)	5 (2.4, 12)	4.4 (1.9, 10)
C-Reactive Protein, mg/dL	0.25 (0.13, 0.55)	0.34 (0.17, 0.60)	0.40 (0.20, 0.79)	0.27 (0.13, 0.54)	0.25 (0.11, 0.53)

Quantitative variables are presented as median (Q1, Q3) and categorical variables as count (percent). Legends: RAAS inhibitor= renin-angiotensin-aldosterone inhibitor; SBP=systolic blood pressure; DBP=diastolic blood pressure; ABI: ankle-brachial index

Table 2

Prediction of log-transformed CRP in the GENOA cohort by single drug antihypertensive therapy, with adjustment for demographics, co-morbidities, and other medications.

Variable	Model 1 Base Model		Model 2 Complex Model		Model 3 (Model similar to MESA)	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
Beta-Blockers	-0.244	0.043	-0.143	0.205	-0.132	0.232
Calcium-Channel Blockers	-0.191	0.114	-0.128	0.259	-0.120	0.278
Other Anti-Hypertensives	-0.355	0.071	-0.311	0.091	-0.248	0.169
RAAS Inhibitors	-0.235	0.024	-0.199	0.044	-0.207	0.033
Diuretics	0.000		0.000		0.000	
Intercept	-0.988	0.001	-3.283	<.001	-2.665	<.001
Age	-0.001	0.866	0.009	0.027	0.009	0.032
Gender (Male vs. Female)	-0.657	<.001	-0.587	<.001	-0.455	<.001
Race (Black vs. Non-Black)	0.066	0.469	-0.047	0.586	0.029	0.746
Achieved Blood Pressure Control	0.156	0.062	0.110	0.162		
Log Transformed Serum Creatinine	0.098	0.543	0.128	0.402		
Log Transformed Urine Albumin-Creatinine Ratio	0.089	0.004	0.050	0.099	0.063	0.041
Body Mass Index			0.055	<.001	0.054	<.001
Past Smoking			0.053	0.518	0.028	0.733
Current Smoking			0.469	<.001	0.504	<.001
Presence of Diabetes			0.114	0.249	0.147	0.300
Statins (HMG-Co-A reductase inhibitors)			-0.174	0.056	-0.114	0.231
Family History of Premature Coronary Heart Disease					-0.079	0.290
Systolic Blood Pressure					-0.006	0.012
Calculated Low-Density Lipoprotein					0.001	0.167
High Density Lipoprotein					-0.004	0.139
Aspirin Use					0.111	0.163

Variable	Model 1 Base Model		Model 2 Complex Model		Model 3 (Model similar to MESA)	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
Estrogen Replacement					0.415	<.001
Insulin Use					0.110	0.570
Thiazolidinedione Class Antidiabetic Agents					-0.850	0.002
Sulfanylurea Class Antidiabetic Agents					0.085	0.614
Biguanide Class Antidiabetic Agent					-0.009	0.955