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Variation in Eicosanoid Genes, Non-fatal Myocardial Infarction and Ischemic Stroke

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Abstract

Objectives—Eicosanoids are lipid mediators that may play a role in atherosclerosis. We investigated the association of common genetic variation in prostaglandin H synthase 1 (*PTGS1*), prostaglandin H synthase 2 (*PTGS2*), thromboxane A2 synthase (*TBXAS1*), prostacyclin synthase (*PTGIS*), prostaglandin E synthase (*PTGES*), 5-lipoxygenase activating protein (*ALOX5AP*), 12-lipoxygenase (*ALOX12*) and 15-lipoxygenase (*ALOX15*) with the risks of myocardial infarction (MI) and ischemic stroke. A secondary aim was to replicate the interaction of *PTGS2* rs20417 (-765G to C) with aspirin use on coronary heart disease risk observed in the Atherosclerosis Risk in Communities Study.

Methods—We conducted a case-control study in a large Health Maintenance Organization. Cases were men and women, aged 30 to 79 years with incident non fatal myocardial infarction (n=1063) or ischemic stroke (n=469) between January 1995 and December 2004. Controls (n=3462) were randomly selected and frequency matched to cases on age, sex, hypertension and calendar year.

Results—Common variation in *TBXAS1* and *PTGIS* was associated with MI risk (p-value for global Chi-square test, 0.01 and 0.03 respectively). Common variation in *ALOX5AP*, *ALOX12*, *ALOX15*, *PTGS1*, *PTGS2* and *PTGES* was not associated with risks of MI and ischemic stroke. We replicated the observation of the Atherosclerosis Risk in Communities Study and observed an interaction of rs20417 with aspirin use on myocardial infarction risk (p for interaction=0.03).

Conclusions—Study results suggest that variation in *TBXAS1* and *PTGIS* may influence MI risk, and carriers of rs20417 C allele might derive greater benefits from aspirin use in primary prevention.

Keywords

epidemiology; myocardial infarction; ischemic stroke; genetic polymorphism; eicosanoic acids

INTRODUCTION

Eicosanoids are lipid mediators derived from 20-carbon polyunsaturated fatty acids with multiple biological functions. The main eicosanoids include prostaglandins, prostacyclins, thromboxanes and leukotrienes. Thromboxane 2 and prostacyclin have opposite effects on blood flow and platelet activity and may play a key role in acute coronary syndromes and atherosclerosis. (1) Prostaglandin E also affects platelet activity.(2) The leukotrienes are involved in inflammatory processes in many different tissues. (3)

The first step in prostaglandin synthesis is the formation of prostaglandin H from arachidonic acid released from the membrane in response to a variety of stimuli by one of two isoforms of prostaglandin H synthase (also known as cyclooxygenase). A non-synonymous single nucleotide polymorphism (SNP) in the prostaglandin H synthase 2 gene (*PTGS2*) has been associated with cardiovascular disease in some studies (4-6) but not others. (7,8) Prostaglandin H is in turn metabolized to thromboxane by thromboxane synthase in platelets, to prostacyclin by prostacyclin synthase in endothelial cells, and to prostaglandin E by prostaglandin E synthase in many different tissues.(9) Possible role of genetic variation in these synthases in relation to cardiovascular disease has received limited attention.

In leucocytes, 5-lipoxygenase together with 5-lipoxygenase-activating protein initializes leukotriene biosynthesis from arachidonic acid. Variation in the 5-lipoxygenase activating protein gene has been found associated with the risks of MI and stroke in some studies (10-12) but not others. (13-15) Two other lipoxygenases, 12-lipoxygenase and 15-lipoxygenase, metabolize arachidonic acid to hydroxyeicosatetraenoic acids (HETE), which may play a role in vessel wall inflammation. (16) The possible role of common genetic variation in 12-and 15-lipoxygenases in cardiovascular disease has received limited attention.

We examined the association of common genetic variation in prostaglandin H synthase 1 (*PTGS1*), prostaglandin H synthase 2 (*PTGS2*), thromboxane A2 synthase (*TBXAS1*), prostacyclin synthase (*PTGIS*), prostaglandin E synthase (*PTGES*), 5-lipoxygenase activating protein (*ALOX5AP*), 12-lipoxygenase (*ALOX12*) and 15-lipoxygenase (*ALOX15*) with the risks of incident non-fatal myocardial infarction and ischemic stroke in a population-based case-control study. In addition, we investigated whether the interaction of *PTGS2* rs20417 (-765G to C) with aspirin use on coronary heart disease risk reported by the Atherosclerosis Risk in Communities Study (ARIC) (8) could be replicated.

METHODS

Setting

The setting for this study was Group Health (GH), a large health-maintenance organization in western Washington State. The methods have been described previously.(17,18) The study was approved by the GH Human Subjects Review Committee.

Identification of cases and controls

Cases were GH enrollees, 30 to 79 years of age, who survived an incident MI or ischemic stroke between January 1995 and December 2004, and who were alive at the time of study recruitment. Cases were identified from hospital discharge diagnosis codes and were validated by medical record review as previously described. (17) Diagnosis of ischemic stroke was

confirmed by computed tomography or magnetic resonance imaging. Control subjects were frequency matched on age (within decade), sex, and calendar year of identification to MI cases, the largest case group. Controls were a stratified random sample of GH enrollees sampled from the GH enrollment files on the basis of person-time, a procedure that ensures that the odds ratio (OR) approximates the relative risk.(19) Controls met the same eligibility criteria as cases but had not had an MI or stroke. All participants provided written informed consent.

Index date and eligibility

Each participant was assigned an index date. For cases, the index date was the admission date for the first MI or ischemic stroke. For the controls, the index date was a random date within the year for which they were sampled. We excluded patients with fewer than four visits before their index dates to increase the likelihood that information would be available in the medical record on important clinical characteristics. Cases whose MI or stroke was a complication of a procedure or surgery were not eligible for the study. In addition, we excluded patients who had a previous MI or stroke and whose blood specimens did not yield genotype information.

Data collection

Data collection included a review of the GH medical record, a telephone interview, and collection of a blood sample. Based on the medical record, research assistants determined eligibility and collected information on clinical characteristics and cardiovascular risk factors prior to the index date. Aspirin use was assessed during the telephone interview and defined as any use in the month prior to the index date. Research assistants were not blinded to case-control status, but they were not aware of the research hypothesis.

Genetic Variation

Single nucleotide polymorphisms (SNPs) were identified by genomic resequencing by the Seattle Program for Genomic Applications (for *PTGS1*, *PTGS2*, *PTGES*, *ALOX5AP*, *ALOX12* and *ALOX15*), Perlegen (for *PGIS*), or the HapMap (for *TBXAS1*). Among variants with a minor allele frequency of 5% or greater in the Program for Genomic Applications panel, ldSelect version 1.0 (University of Washington, Seattle; <http://pga.gs.washington.edu/>) was used to select maximally informative sets of SNPs to describe genetic variation in European Americans and African Americans using linkage disequilibrium and an r^2 of 0.64.(20)

Blood Collection and Genotyping

A blood specimen was collected from all consenting participants into tubes containing EDTA, and DNA was extracted from white blood cells using standard phenol extraction procedures. Genotyping was performed with a GoldenGate custom panel using BeadArray® technology. Genotyping for cases and controls with index dates through 2002 was performed by Illumina® (Illumina Inc, San Diego California); genotyping for later index dates was performed by the Genomics Research laboratory (Fred Hutchinson Cancer Research Center, Seattle Washington). Of the 137 SNPs successfully genotyped, 99.9% of nucleotide pairs were successfully called. SNPs were excluded if the minor allele frequency was less than 2% in the study sample. Because we had genotyped more than one SNP per bin in some instances to reduce the chance of genotyping failure, we also excluded SNP if the pairwise r^2 with another SNP was greater than 0.8. 103 SNPs were used in the analyses. All laboratory personnel were blinded to case-control status.

We obtained genotyping results on all study subjects (1063 MI cases, 469 ischemic strokes and 3462 controls) for six genes (*PTGS1*, *PTGS2*, *PTGIS*, *ALOX5AP*, *ALOX12* and *ALOX15*) and on a subset of the study subjects (186 MI cases, 66 ischemic strokes and 718 controls) for the other two genes (*TBXAS1* and *PTGES*).

Haplotype Construction

Phased haplotypes were estimated for each gene using PHASE 2.0 software (University of Washington, Seattle; <http://www.stat.washington.edu/stephens/software.html>), which computes probabilities for each haplotype pair consistent with the observed data. When ambiguous haplotypes were encountered, multiple, probability-weighted haplotypes were created. We combined haplotypes that had a frequency of less than 2% in the study population into a single “other” haplotype category.

Statistical Analysis

We used logistic regression to investigate the association of haplotypes and SNPs with risks of MI and ischemic stroke. In all analyses we used linear additive models and estimated risk for each additional copy of the variant allele. To estimate haplotype associations, we used the probabilities produced by PHASE as weights. The most common haplotype served as reference group. For these analyses, robust, 'sandwich' standard errors were used clustered on individual. For the simplest case where haplotype phase was unambiguous, the two haplotypes for an individual were treated as clustered observations; and posterior probabilities were included as weights to allow for alternative haplotype phase assignments. (21) For each gene and outcome, except *TBXAS1*, a single Wald test was used to examine the 'global' null hypothesis of no association of outcome with any of the haplotypes. These global tests formed the primary analyses. Secondly, SNP-specific associations were tested individually in separate logistic regression models.

To investigate if the interaction of *PTGS2* rs20417 with aspirin use reported by the ARIC Study (8) could be replicated, we tested the association of a cross-product of aspirin use (yes/no) by presence of the SNP variant in a model including terms for aspirin and the variant. A dominant model was used for this analysis in order to be consistent with analysis reported by the ARIC Study.

No common haplotypes were observed for the *TBXAS1* gene and thus the Wald global hypothesis test was not possible. To evaluate significant findings from *TBXAS1* in a gene-wide context, the observed test statistic for a model with all SNPs was compared to a distribution of test statistics obtained through a parametric bootstrap test ($n = 1000$ iterations).

The analyses were adjusted for race, and for the matching variables age, sex, hypertension and index year. We did not further adjust for acquired risk factors since these factors cannot confound genetic associations except through selection bias. Sensitivity analyses were conducted that restricted subjects to those of European ancestry. All statistical analyses were conducted using Intercooled STATA (version 8.2).

RESULTS

Characteristics of the 1063 MI cases, 469 ischemic stroke cases, and 3462 controls in the study are shown in Table 1. Cases and controls differed in expected ways. For example, smoking, diabetes, and high systolic blood pressure were more prevalent in cases than controls.

Prostaglandin and thromboxane genes

We genotyped 10 informative SNPs in *PTGS1*, 7 in *PTGS2*, 7 in *PTGIS*, 5 in *PTGES* and 40 in *TBXAS1*. These SNPs were in Hardy Weinberg equilibrium in white control subjects. Variation in two genes, *PTGIS* and *TBXAS1* was associated with MI risk (Tables 2 and 3). Overall, common variation in the *PTGIS* gene was associated with the risk of incident MI ($p=0.03$, 8 degrees of freedom [df]; Table 2). One haplotype in particular, Haplotype G, was associated with higher risk of MI (OR 1.54, 95% CI 1.19-2.00). While there was no global

association with ischemic stroke ($p=0.15$), the point estimate for the association of Haplotype G with higher stroke risk was similar (OR 1.57, 95% CI 1.09-2.26). In SNP analyses, one SNP, rs5602, was associated with lower risks of MI and stroke (Table 2).

Overall, common variation in *TBXAS1* was associated with risk of incident MI ($p=0.01$, 40 df, Table 3). Three SNPs, rs4725563, rs17181314 and rs3801150, were associated with higher risk and two SNPs, rs2267682 and rs8192859, with lower risk of MI (Table 3). There was no global association with the outcome of ischemic stroke ($p=0.36$), however, the point estimates for rs2267682, rs3801150 and rs8192859 were similar for the outcomes of MI and stroke.

We found no association of common variation in *PTGSI*, *PTGS2* and *PGES* with risks of MI and ischemic stroke (Supplemental Tables 1, 2 and 3)

Replication of interaction of *PTGS2* rs20417 with aspirin use

The suggested interaction of rs20417 (-765G to C) with aspirin use on the risk of coronary heart disease observed in the ARIC Study (8) was replicated in this dataset. Table 4 shows the odds ratios of myocardial infarction and ischemic stroke associated with rs20417 among subjects with and without aspirin directly compared to the ARIC findings. To address the question of effectiveness of aspirin we also computed the odds ratios associated with aspirin among subjects with and without the variant (another way to present the same data). The odds ratio of myocardial infarction associated with aspirin use was 0.83 (95% CI 0.70-1.00) among homozygous carriers of the common allele, and 0.59 (95% CI 0.45-0.77) among carriers of the variant (p for interaction 0.03). There was no interaction of rs20417 with aspirin use on the risk of ischemic stroke ($p=0.39$).

Lipoxygenase genes

We genotyped 18 informative common SNPs in *ALOX5AP*, 8 in *ALOX12* and 8 in *ALOX15*. These SNPs were in Hardy Weinberg equilibrium in white control subjects. We found no global association of common variation in these three genes with the risks of MI and ischemic stroke (Supplemental Tables 4, 5 and 6).

Similar results were obtained in all the analyses when restricted to white study subjects (not shown).

DISCUSSION

In this population-based case-control study, we found an association of common variation in *TBXAS1* and *PTGIS* genes with the risk of incident non-fatal MI, but not with the risk of ischemic stroke. We found no association of common gene variation in *PTGSI*, *PTGS2*, *PTGES*, *ALOX5AP*, *ALOX12* and *ALOX15* with MI and ischemic stroke risks. We also found an interaction of *PTGS2* rs20417 (-765G to C) with aspirin use on the risk of MI, thereby replicating the ARIC Study findings. (8)

Thromboxane and prostacyclin have opposite effects on platelets, and may affect the risk of thrombosis. (1) Thromboxane A_2 produced by aggregating platelets is a potent platelet activator and vasoconstrictor. The lower risk of MI and death among patients taking low dose aspirin is believed to be mediated by suppression of thromboxane and its metabolites. (22) Prostacyclin, produced by endothelial cells, is a vasodilator that inhibits platelet activation and specifically limits the platelet response to thromboxane A_2 . Suppression of prostacyclin production may be responsible for the increased risk of coronary events with Cox-2 inhibitors. (23) An association of common variation in *TBXAS1* and *PTGIS* with MI risk is suggestive of a possible role of thromboxane synthase and prostacyclin synthase in MI. However, whether

the observed variation in the synthase genes has an effect on the production of thromboxane and prostacyclin is not known. In addition, our study findings need to be replicated.

An association of *TBXAS1* variation with cardiovascular disease has not been reported. Associations of *PTGIS* variants with cardiovascular disease outcomes were reported in a Japanese population: rs5629, a synonymous SNP in exon 8, was associated with MI, (24) and the number of tandem repeats in the promoter region was associated with cerebral infarction. (25) In our study, rs729824 which is in linkage disequilibrium with rs5626 ($r^2 > 0.8$ in the HapMAP-CEU unrelated population) was not associated with MI (OR=1.07).

Cyclo-oxygenases 1 and 2 convert arachidonic acid into precursors of thromboxane and prostacyclin. We found no overall association of common variation in *PTGS1* and *PTGS2* with risks of MI and ischemic stroke. Several studies have investigated the association of a functional polymorphism of *PTGS2*, rs20417 (-765G to C), with the risk of cardiovascular disease. In particular, the C allele was associated with lower risks of MI (OR 0.48) and stroke (OR 0.33) in an Italian population. (4) In another study in Italy, heterozygotes appeared at lower risk of cerebrovascular ischemia, however the number of cases was small. (5) The C allele was also associated with lower carotid IMT in a subgroup of hypercholesterolemic subjects. (6) In contrast, the C allele was not associated with MI in the Physicians' Health Study. (7) In the ARIC Study, the C allele was not associated with coronary heart disease risk, however there was a suggestion of an interaction with aspirin use among European Americans. (8) Recently, the C allele was reported to be associated with higher (not lower) risk of stroke in African Americans in ARIC. (26) In our study, rs20417 C allele was not associated with risks of MI (OR 0.93) or ischemic stroke (OR 0.93, Supplemental Table 2). However, we observed an interaction of rs20417 with aspirin use on the risk of MI, similar to the one observed in the ARIC Study. (8) Aspirin reduces the risk of cardiovascular disease in primary prevention, however, its benefit is offset by a concomitant increased risk of bleeding. (27,28) Together with ARIC's report, the study results suggest that carriers of rs20417 C allele might derive greater benefits from aspirin use in primary prevention than non carriers.

In ARIC, two correlated SNPs from *PTGS1*, rs10306114 and rs10306110, were reported associated with stroke, but not with coronary heart disease risk in European Americans. (8) We did not genotype rs10306114 and rs10306110 in our study. However, rs3842787, in linkage disequilibrium with both rs10306114 and rs10306110 ($r^2 = 0.99$ with both in the Seattle PGA Panel 1 European CEPH population), was not associated with ischemic stroke (OR 0.96) or MI (OR 1.02) in the present study (Supplemental Table 1).

Prostaglandin E synthase expression is coupled to cyclo-oxygenase 2 and induced by inflammatory stimuli in several tissues (29) and there is up-regulation in symptomatic atherosclerotic plaques. (30,31) We did not find an association of variation in *PTGES* with the risk of MI and ischemic stroke.

The association of *ALOX5AP* variation with MI and stroke has been investigated in several studies with inconsistent results. (10-15) Efforts have focused on a 4-SNP haplotype named HapA found associated with higher risk of MI and stroke in an Icelandic population (11) and a Scottish cohort, (10) and another haplotype HapB associated with MI in a British cohort. (11) However, HapA and HapB were not associated with MI in the Physicians' Health Study (15) and in a large study of patients undergoing angiography in Germany, (13) and were not associated with stroke in a German study (12) and two US studies. (14,15) We did not investigate "HapA" which included a SNP outside the region of the gene. Instead, we examined tagSNPs that covered variation in the whole gene. With this approach, we found no association of common variation in the *ALOX5AP* gene with MI and ischemic stroke.

A rare non-synonymous SNP in *ALOX15*, rs34210653, was recently reported to be associated with higher risk of coronary heart disease in the Coronary Artery Risk Development in Young Adults study and in ARIC. (32) This SNP had not been identified by resequencing by Seattle Program for Genomic Applications and was not included in our study. Overall, we found no association of common variation in *ALOX15* and *ALOX12* with MI and ischemic stroke risks.

This study has a number of limitations. This genetic association study is prone to the potential confounding effects of population substructure. To address this possibility, we have adjusted for self-reported race in all analyses and performed sensitivity analyses restricted to white individuals. The population of black individuals was too small to address risk differences by race. All participants in this primary prevention study were survivors of their incident events and survived to give a blood sample. Findings may not be generalizable to men and women who do not survive their event. In addition, findings may not apply to patients with prior MI and stroke who were excluded from this study. For two of the genes examined, results were available only on a subset of study subjects limiting the power to detect associations. We performed 16 global tests with eight genes and two outcomes, and we would expect one association by chance at $\alpha=0.05$.

Strengths of the study include the population-based study design which would minimize the possibility of selection bias, and the evaluation of common genotyping variation covering the entire genes.

Conclusions

This study conducted in a largely white population suggests that common variation in thromboxane synthase and prostacycline synthase genes, *TBXAS1* and *PTGIS*, is associated with incident MI, and carriers of *PTGS2* rs20417 C allele might derive greater benefits from aspirin use in primary prevention than non carriers. Replication in other study populations is needed to corroborate these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of cases and controls

Characteristics	MI Cases N=1063	Ischemic stroke Cases N=469	Controls N=3462
Age *, years	65.5 (9.8)	68.3 (9.1)	65.2 (9.7)
Women *, %	56.5	69.5	57.7
Treated hypertension *, %	73.1	72.7	73.3
Whites, %	91.3	90.8	91.3
Current smokers, %	20.1	14.1	10.5
Diabetes, %	23.6	25.0	11.9
Angina, %	16.1	9.6	7.7
Cardiovascular disease, %	21.7	14.7	11.2
Family history of MI, %	55.6	46.1	46.1
Body mass index, kg/m ²	30.3 (6.2)	30.4 (6.9)	29.6 (6.2)
Most recent blood pressure:			
Systolic, mm Hg	141.5 (20.0)	145.5 (21.9)	137.4 (18.6)
Diastolic, mm Hg (among treated hypertensives)	80.2 (11.6)	81.0 (11.7)	79.95 (10.7)
Cholesterol, mg/dL	228.8 (46.9)	226.2 (44.9)	218.0 (52.2)
HDL, mg/dL	49.4 (15.3)	52.4 (16.8)	53.8 (17.2)
Aspirin use, %	53.5	52.6	60.1

* Matching factors

Table 2
Common variation in PGIS and risks of myocardial infarction and ischemic stroke

Haplotype	Rs561	Rs5602	Rs729824	Rs6090996	Rs5628	Rs6091000	Rs476496	Haplotype frequency	OR of MI (95% confidence interval)*	OR of ischemic stroke (95% confidence interval)*
A	G	A	A	G	G	A	A	32.0	REF	REF
B	G	G	G	G	G	A	A	14.9	1.18 (1.03-1.35)	1.18 (0.97-1.42)
C	G	A	A	G	G	A	G	11.5	1.15 (0.99-1.32)	0.93 (0.76-1.16)
D	G	G	A	A	G	A	A	8.3	1.11 (0.94-1.32)	1.13 (0.89-1.44)
E	G	G	A	G	G	A	A	6.8	1.12 (0.93-1.36)	0.95 (0.73-1.25)
F	G	G	G	G	G	A	G	6.7	1.12 (0.92-1.35)	1.17 (0.90-1.52)
G	G	G	A	A	G	G	A	2.5	1.54 (1.19-2.00)	1.57 (1.09-2.26)
H	G	G	A	A	G	A	G	2.1	1.17 (0.88-1.54)	1.23 (0.82-1.83)
Other								15.2	1.23 (1.06-1.42)	1.00 (0.80-1.23)
MAF, %	3.1	37	22	18	6.1	5.0	21		Global p-value: 0.03	Global p-value: 0.15
OR of MI (95% confidence interval) [†]	1.28 (0.96-1.70)	0.88 (0.79-0.96)	1.07 (0.96-1.20)	1.10 (0.98-1.24)	1.11 (0.92-1.35)	1.20 (0.98-1.46)	1.03 (0.92-1.15)			
OR of ischemic stroke (95% confidence interval)	1.22 (0.81-1.84)	0.84 (0.73-0.97)	1.16 (0.99-1.35)	1.07 (0.91-1.27)	0.97 (0.73-1.29)	1.36 (1.04-1.77)	0.95 (0.81-1.12)			

Minor alleles are shown in bold.

* Results from haplotype analyses.
† Results from SNP analyses.

Table 3

Common variation in TBXAS1 and risks of myocardial infarction and ischemic stroke

SNP	MAF, %	OR of MI (95 % CI)	OR of ischemic stroke (95 % CI)
rs10487661	4	1.35 (0.82-2.22)	1.96 (1.03-3.7)
rs10277664	32	0.86 (0.67-1.09)	1.00 (0.69-1.45)
rs17178226	11	0.82 (0.57-1.18)	1.04 (1.01-1.07)
rs12667080	12	0.90 (0.64-1.27)	0.93 (0.53-1.61)
rs1019178	35	0.94 (0.75-1.19)	0.97 (0.67-1.40)
rs2267679	33	1.25 (0.99-1.57)	1.24 (0.87-1.79)
rs2267682	37	0.70 (0.55-0.89)	0.76 (0.52-1.09)
rs41708	6	1.31 (0.85-2.03)	1.48 (0.79-2.77)
rs3779134	10	0.74 (0.49-1.12)	1.02 (0.55-1.87)
rs12532529	13	0.82 (0.59-1.16)	0.63 (0.35-1.13)
rs194149	25	1.02 (0.79-1.31)	1.49 (1.02-2.19)
rs8192813	5	0.94 (0.57-1.57)	1.47 (0.78-2.77)
rs3801153	12	0.95 (0.68-1.33)	0.67 (0.36-1.22)
rs6464435	27	0.95 (0.74-1.22)	1.02 (0.69-1.49)
rs2299891	29	1.18 (0.93-1.50)	1.17 (0.79-1.72)
rs2284205	16	1.29 (0.96-1.73)	1.20 (0.75-1.92)
rs4726473	22	1.04 (0.79-1.35)	1.14 (0.75-1.74)
rs13239058	17	0.79 (0.59-1.08)	0.96 (0.60-1.52)
rs1003816	11	1.13 (0.79-1.61)	1.52 (0.90-2.57)
rs4725563	21	1.33 (1.02-1.74)	1.16 (0.75-1.78)
rs17181314	8	1.50 (1.01-2.22)	0.88 (0.43-1.81)
rs41721	17	1.12 (0.83-1.49)	1.12 (0.71-1.77)
rs42334	12	0.92 (0.66-1.29)	1.15 (0.70-1.89)
rs6962291	28	0.97 (0.75-1.25)	1.06 (0.72-1.56)
rs2267701	13	1.24 (0.91-1.70)	0.93 (0.55-1.57)
rs740150	18	0.99 (0.74-1.34)	1.39 (0.89-2.16)
rs11772680	11	0.97 (0.67-1.41)	0.93 (0.52-1.67)
rs10487667	22	1.06 (0.81-1.38)	1.53 (1.02-2.32)
rs3801150	28	1.30 (1.02-1.65)	1.55 (1.08-2.21)
rs4726499	19	0.83 (0.62-1.11)	1.20 (0.78-1.83)
rs7806848	28	1.10 (0.86-1.40)	1.19 (0.80-1.76)
rs8192856	7	1.42 (0.96-2.12)	0.97 (0.47-2.01)
rs17161326	14	0.70 (0.50-1.00)	0.61 (0.35-1.07)
rs3801148	37	0.86 (0.69-1.09)	0.94 (0.65-1.35)
rs8192859	19	0.65 (0.48-0.90)	0.65 (0.39-1.11)
rs2267706	19	0.94 (0.71-1.24)	1.41 (0.94-2.10)
rs10242928	9	0.85 (0.56-1.28)	0.97 (0.52-1.81)
rs2072190	32	0.91 (0.72-1.16)	0.94 (0.65-1.36)
rs2269996	18	1.04 (0.78-1.38)	0.97 (0.63-1.51)

SNP	MAF, %	OR of MI (95 % CI)	OR of ischemic stroke (95 % CI)
rs3735351	10	1.09 (0.75-1.58)	1.14 (0.65-2.00)
Global p-value*		0.011	0.36

Table 4
Interaction of *PTGS2* rs20417 with aspirin and comparison with ARIC* Study report

	This study				ARIC*	
	Case MAF	Control MAF	Odds ratio of myocardial infarction [†]	p-value	Hazard ratio of coronary heart disease [†]	p-value
All subjects	14.4%	15.0 %	1.08 (0.83-1.42)	0.57	1.08 (0.83-1.42)	0.57
No aspirin	16.6%	15.0 %	1.17 (0.93-1.48)	0.18	1.36 (0.97-1.90)	0.08
Aspirin	13.0%	14.9 %	0.82 (0.66-1.03)	0.09	0.60(0.36-1.02)	0.06
Interaction			0.70 (0.51-0.97)	0.03	0.57 (0.31-1.05)	0.07

* Atherosclerosis Risk in Communities Study, from reference #8

[†] G/C+G/C versus G/G