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Associations between Aspirin and other non-steroidal anti-inflammatory drugs and aortic valve or coronary artery calcification: The Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study

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Abstract

Background—The association between non-steroidal anti-inflammatory drugs (NSAIDs) and the incidence of valvular and arterial calcification is not well established despite known associations between these drugs and cardiovascular events.

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None. No authors have any relevant financial, personal or professional relationships.

Objective—To compare the association between the baseline use of aspirin with other NSAID class medications with the incidence and prevalence of aortic valve calcification (AVC) and coronary artery calcium (CAC).

Methods—The relationship of NSAID use to AVC and CAC detected by computed tomography was assessed in 6,814 participants within the Multi-Ethnic Study of Atherosclerosis (MESA) using regression modeling. Results were adjusted for age, sex, ethnicity, study site, anti-hypertensive medication use, education, income, health insurance status, diabetes, smoking, exercise, body mass index, blood pressure, serum lipids, inflammatory markers, fasting glucose, statin medication use, and a simple diet score. Medication use was assessed by medication inventory at baseline which includes the use of non-prescription NSAIDs. MESA collects information on both incident and prevalent calcification. The 4,814 participants of the Heinz Nixdorf Recall (HNR) Study, a German prospective cohort study with similar measures of calcification, were included in this analysis to enable replication.

Results—Mean age of the MESA participants was 62 years (51% female). After adjustment for possible confounding factors, a possible association between aspirin use and incident AVC (Relative Risk(RR): 1.60; 95%Confidence Interval (CI): 1.19–2.15) did not replicate in the HNR cohort (RR: 1.06; 95%CI: 0.87–1.28). There was no significant association between aspirin use and incident CAC in the MESA cohort (RR 1.08; 95%CI: 0.91–1.29) or in the HNR cohort (RR 1.24; 95%CI: 0.87–1.77). Non-aspirin NSAID use was not associated with either AVC or CAC in either cohort. There were no associations between regular cardiac dose aspirin and incident calcification in either cohort.

Conclusion—Baseline NSAID use, as assessed by medication inventory, appears to have no protective effect regarding the onset of calcification in either coronary arteries or aortic valves.

Keywords

Non-steroidal anti-inflammatory drugs; aspirin; aortic valve calcification; coronary artery calcification; Multi-Ethnic Study of Atherosclerosis; Heinz Nixdorf Recall Study

INTRODUCTION

Aspirin treatment is an effective and low cost therapeutic option for reducing cardiovascular events [1]; there is some evidence that this benefit may not extend to those with diabetes [2,3,4]. The presumed benefit of aspirin has been attributed to its antiplatelet effects, rather than its anti-inflammatory effects, as non-steroidal anti-inflammatory drugs (NSAIDs) appear to have harmful effects on cardiovascular risk [5,6] and use of NSAIDS in patients with known cardiovascular disease is discouraged by the American Heart Association[7].

One clinical study has reported that the macrophage density of carotid atherosclerotic plaques are reduced in aspirin users, suggesting an aspirin-mediated suppression of vascular inflammatory processes [6]. This could result in an association between NSAIDs and the amount of coronary artery or valvular calcification. There has also been recent study reporting increased aortic calcification among kidney transplant patients (from a Belgium cohort) who were using aspirin, although statistical significance was borderline (p=0.03) and the study specifically noted an inability to assess these associations among diabetics [8]. These previous findings suggested that a careful investigation of a potential association between NSAIDs and calcification was warranted in a larger cohort.

The goal of this study was to determine whether baseline use of NSAIDs (including aspirin) is associated with the incidence of either coronary artery calcification (CAC) or aortic valve calcification (AVC). Because of the potential that diabetes might confound this association and the specific limitation of previous reports, the results were planned to be stratified by

diabetes status. We looked at two separate but high quality cohorts, in order to replicate any associations between medications and calcification. Furthermore, we looked at both American and German participants, in case medication use was acting as a marker for some other characteristic, as levels of medication use tend to vary between these two geographic areas.

METHODS

MESA cohort

The MESA study includes 6,814 participants between the ages of 45 and 84 years from four different race/ethnic groups (28% African-American, 12% Asian, 38% Caucasian, and 22% Hispanic). MESA participants were recruited from six different field centers across the United States: Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; New York, NY and St. Paul, MN. The design of the MESA study and the recruitment of participants have been described in detail elsewhere [9]. All participants, in the MESA were given a written informed consent form with which to provide consent for participation. To date, there have been four exams in the MESA study: a baseline exam and 3 follow-up exams. The baseline exam occurred from July 2000 to April 2002. All participants were free of prevalent cardiovascular disease at baseline, all participants had information on AVC and CAC, and only a few were excluded for missing medication information (n=3). We excluded participants with any missing data on the other covariates of interest (a complete case analysis), removing another 292 participants to give 6,519 MESA participants included in the analytic cohort for prevalent disease. Only 4,932 were available for analysis of progression due to missing follow-up visits and/or scans.

The MESA study collected a broad range of baseline data on study participants. MESA participants were asked to come to a morning clinic examination after an overnight fast for each exam. Participants were given standard questionnaires to assess a variety of risk factors which included demographic information, smoking, and medical history of either hypertension or diabetes. Participants were asked to bring their medications to each visit and medication use was assessed using a medication inventory approach [10,11]. Anthropometric measures were also obtained. Physical activity was defined as both intentional exercise and leisure activities (including activities such as reading and television watching) [12]. Diet was assessed by use of a food frequency questionnaire administered at participants at baseline and summarized using the simple diet score of Nettleton *et al.*[13].

Replication Cohort

The Heinz Nixdorf Recall Study (HNR; Risk factors, Evaluation of Coronary Calcium and Lifestyle Factors) is a population-based cohort study in the Ruhr area, Germany. Details of the study cohort have been described elsewhere [14,15]. Participants were randomly selected from mandatory inhabitant lists. Between 2000 and 2003, 4,814 participants aged 45–75 years were enrolled. All participants gave written informed consent. The study was approved by the ethics committee at the University Duisburg-Essen, Germany. A more complete description of the baseline recruitment procedures have been described elsewhere [16]. Participants were a random sample derived from mandatory citizen registries, provided to the study center with a response rate of 55.8%. The HNR cohort has a similar protocol for CT scanning as that used in MESA and has been previously compared with the MESA cohort study [17]. The follow-up CT scans were performed on HNR participants after 5 years, enabling assessment of incidence of calcification. Thus, as the HNR study also collected information on incidence and prevalence of AVC and CAC, this was an ideal replication cohort to confirm any unexpected finding. The CT scanning and data collection protocols for these two studies have been compared in detail elsewhere[17]. NSAID use in the

HNR study could not be split by Cox-2 selectively due to a lower number of exposed participants in the HNR cohort. After exclusions for prevalent coronary artery disease (n=327), prior heart surgery including valve replacement or reconstruction (n=11), missing CAC and AVC (n=420), missing medication information (n=259), or other missing covariates (n=331) there were 3,466 participants in the analytic cohort for prevalent disease. This was further reduced to 3,279 participants with information on CAC or AVC at follow-up.

Primary Endpoint

Cardiovascular calcification was assessed by electron-beam CT at 3 centers and multi-detector row helical CT at 3 centers. All studies were interpreted at a central reading center (Harbour-UCLA Research and Education Institute, Los Angeles, CA). Subjects underwent two consecutive scans at the same visit and results were averaged to enhance the accuracy of calcium assessments. These two scans were used to calculate prevalence of aortic valve calcification (AVC) and coronary artery calcification (CAC) at baseline. Two follow-up CT scans were performed on MESA participants after an average of approximately 900 days (Table 1) at either visit 2 or visit 3, allowing for assessment of incident AVC and CAC. The assignment of a participant to be scanned at either visit 2 or visit 3 was random.

AVC and CAC were quantified by the Agatston scoring method [18]. Detectable calcium was defined as a score >0 Agatston units (AU); a minimum focus of calcification was based on at least 4 contiguous voxels, resulting in identification of calcium of 1.15 mm3 with the multi-detector CT scanners (0.68 × 0.68 × 2.50 mm) and 1.38 mm3 with the electron-beam CT scanners (0.68 × 0.68 × 3.00 mm). Details of the image acquisition and interpretation protocols, quality control measures and inter-observer reliability characteristics have been reported [19,20].

NSAID exposure

NSAID exposure, for the purposes of this study, was grouped into three categories: aspirin use, Cox-2 selective NSAID use (celecoxib, valdecoxib and rofecoxib) and other non-selective NSAID use. As reported previously, most of the aspirin taken by participants in the MESA study is of low cardiac dosages (less than 100 mg/day) [21]. MESA also asked for a self-report of aspirin use frequency with the question “ASPIRIN: CURRENTLY USING REGULARLY” as well as the days per week of use among regular users. Similar questions were not available for the other forms of NSAID in MESA.

Definition of Diabetes

Diabetes was assessed by a combination of patient self report and reported diabetes medications. The decision to use this definition of diabetes, instead of the 2003 ADA fasting criterion was made to enable it to be comparable between the MESA cohort and the Heinz Nixdorf Recall Study. Prevalence of baseline diabetes was slightly lower in MESA using this definition (11.3%) versus the 2003 ADA fasting criterion (14.3%).

Statistical Analysis

We used relative risk regression [22] to estimate the association between our three groups of NSAIDs with changes in either arterial or valvular calcification. All models were stratified by diabetic status to test for effect measure modification due to the hypothesized different associations between aspirin and cardiovascular disease in these populations. We adjusted our models for potential confounders as shown in Table 1: specifically, age, sex, race, study site, body mass index, education, income, health insurance (yes/no), smoking (current, previous, and never), intentional exercise, sedentary activities (principally television

watching), systolic and diastolic blood pressure, anti-hypertensive medication user, HDL-cholesterol, LDL-cholesterol, triglycerides, inflammatory and coagulation markers (Interleukin-6, Fibrinogen antigen, c-reactive protein, Homocysteine), lipid lowering medication use, and the simple diet score.

The HNR analysis had fewer covariates available (age, sex, use of antihypertensive medication, education, income, smoking, BMI, systolic and diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, Triglycerides, Fibrinogen, c-reactive protein, lipid-lowering medication) but estimates in MESA with the level of adjustment were comparable to the fully adjusted estimates. We used robust confidence intervals due to the use of relative risk regression [22]. For the longitudinal analysis, all exposures and covariates were defined at baseline to eliminate the possibility of reverse causality (the drug being given to treat symptoms of calcification or due to post-baseline knowledge of CAC scans).

As a sensitivity analysis, we also looked at the longitudinal association to see if the results with the cross sectional model could be replicated with this approach. Furthermore, we looked a specific subset of models that adjusted for kidney function (creatinine and glomerular filtration rate) in the MESA participants. Additionally, we looked for participants with very high baseline levels of CAC or AVC (Agatston scores > 400) to see if these medications were predictive of very high levels of calcification.

We also considered whether cardiac dose aspirin, high dose aspirin not taken regularly or high dose aspirin taken regularly would be a useful stratification for the models adjusted for eGFR and creatinine. To do this in MESA we defined three categories of aspirin use: cardiac aspirin use, regular high dose use and occasional high dose use. For the HNR participants, we split Aspirin use into “full” and “occasional” use due to different measures of use being reported in that cohort. We defined full use as a cardiac dose ≤ 300 mg, taken regularly and for ≥ 3 months (at baseline). Occasional use was all other doses or low doses taken for less time, especially participants who reported taking 500 mg aspirin. The 390 Aspirin users in the full HNR cohort split into 300 full and 90 occasional aspirin users.

For models of incident AVC or CAC in MESA, we also adjusted our models for the time between CT scans (including a sensitivity test for a nonlinear term for time between scan). All analysis was conducted in SAS 9.1.3.

RESULTS

Overall, 6,516 subjects from the MESA study (mean age 62 years, 53% females) were included in this analysis. Among these participants, 930 (11%) had diabetes based on the study criteria. Aspirin-use was recorded in the medication inventory for n=1,336 (23%) of participants without diabetes and n=259 (35%) of participants with diabetes. As can be seen in Table 1, aspirin users tended to be older than participants who used no NSAIDS or participants taking non-selective NSAIDS, although not users of Cox-2 selective NSAIDs. Aspirin users showed an increased level of health seeking behavior including better diet, less current smoking and slightly more intentional exercise.

We considered the cross sectional association between aspirin use and baseline prevalence of AVC or CAC (Table 2). There was a hypothesis generating borderline significant association between aspirin and prevalence of AVC in the MESA cohort (adjusted Relative Risk (aRR) 1.2; 95% Confidence Interval (CI): 1.0 to 1.4) but not between Cox-2 selective NSAIDS and prevalent AVC (aRR 1.0; 95%CI: 0.8 to 1.3) nor other nonselective NSAIDs and prevalent AVC (aRR 0.9; 95%CI: 0.7 to 1.1). There were no associations between aspirin and prevalence of CAC (aRR 1.0; 95%CI: 0.9 to 1.1), between Cox-2 selective NSAIDS and prevalent CAC (aRR 1.1; 95%CI: 1.0 to 1.2) nor other nonselective NSAIDs

and prevalent CAC aRR 0.9; 95%CI: 0.7 to 1.1). These associations do not persist when the cohort is stratified by diabetic status (Table 2).

Next, we repeated our test of the unexpected prevalent association between aspirin use and AVC using the HNR study as a replication cohort. From the HNR study, data for incidence and prevalence of AVC and CAC as well as for all potential confounders were eligible in 3,797 subjects without known CAD at baseline (mean age 60 years, 53% females). Among these participants, 287 (8%) had diabetes. Aspirin use was documented for 390 (10%) of participants without diabetes and 59 (21%) of participants with diabetes; 275 (7%) of these had aspirin doses of 100 mg/day or less. On cross sectional analysis of prevalent AVC, the HNR cohort showed no association between aspirin use and AVC for either participants with diabetes (aRR 1.0; 95%CI: 0.5 to 1.8) nor among participants without diabetes (aRR 1.0; 95%CI: 0.7 to 1.3) (Table 3). Furthermore, as in MESA, neither aspirin use nor other nonselective NSAIDs were associated with prevalent CAC (Tables 2 and 3).

In the longitudinal analysis of the MESA cohort (our second replication approach), we restricted the cohort to participants without baseline calcification and with a follow-up CT scan. Of the 2,892 participants with no baseline CAC, 370 were excluded for missing outcome or covariate data. Of the 4,920 participants with no baseline AVC, 600 were excluded for missing covariate or outcome data. In this population, aspirin use showed a possible association with incident AVC (aRR 1.6; 95%CI: 1.2 to 2.2) but not incident CAC (aRR 1.1; 95%CI: 0.9 to 1.3) in the general population of all eligible MESA study participants (Table 4). No other form of NSAID was associated with a statistically significant difference in the risk of incident calcification.

Finally, we replicated these results with a longitudinal analysis using the HNR cohort. Of the 3,513 participants with information at both baseline and after 5 years of follow-up, we had 2,522 participants with no baseline AVC and all covariates measures. For CAC, the higher prevalence of baseline CAC left only 1,053 participants in the full model. In the HNR cohort, aspirin use was neither associated with incident AVC (aRR 1.1; 95%CI: 0.9 to 1.3) nor with incident CAC (aRR 1.2; 95%CI: 0.9 to 1.8) (Table 5), suggesting that this original finding was not confirmed under replication with a pre-specified hypothesis.

As a sensitivity analysis we added measures of kidney function as possible confounders for incident measures of CAC and AVC in the MESA cohort. The estimates for associations with incident AVC were similar for aspirin (aRR 1.6; 95%CI: 1.2 to 2.2), Cox 2 selective NSAIDs (aRR 0.9; 95%CI: 0.5 to 1.6) and other NSAIDS (aRR 1.3; 95%CI: 0.9 to 1.9). Similarly the estimates for associations with incident CAC were also similar for aspirin (aRR 1.1; 95%CI: 0.9 to 1.3), Cox 2 selective NSAIDs (aRR 0.8; 95%CI: 0.5 to 1.4) and other NSAIDS (aRR 1.1; 95%CI: 0.9 to 1.4). There we too few participants with Agatston scores for AVC > 400 to test this as a sensitivity analysis. When comparing very high prevalent CAC scores (Agatson score > 400) to participants with no CAC or lower levels of CAC, we found a borderline association with aspirin use (aRR 1.3; 95%CI: 1.1 to 1.5). There was no association with a high baseline Agatson score and either Cox 2 selective NSAIDs (aRR 1.1; 95%CI: 0.8 to 1.4) or NSAIDS (aRR 1.0; 95%CI: 0.8 to 1.3).

We also tested whether intensity of aspirin use modified associations for incident CAC or AVC in MESA. In MESA, regular users of cardiac and high dose aspirin both reported a mean of 6.2 days per week of exposure. For incident AVC, there was no risk with Cardiac Aspirin (aRR 1.2; 95%CI: 0.7 to 2.1) or Occasional High Dose Aspirin (aRR 1.3; 95%CI: 0.6 to 2.8) but a possible association with Regular High Dose Aspirin (aRR: 1.6; 95%CI: 1.1 to 2.3), although this was not defined as an *a priori* risk category. For incident CAC, there was no risk with Cardiac Aspirin (aRR 1.1; 95%CI: 0.9 to 1.5), Occasional High Dose

Aspirin (aRR 1.2; 95%CI: 0.8 to 1.7) or Regular High Dose Aspirin (aRR: 1.1; 95%CI: 0.9 to 1.4). In HNR, there was no association with incident AVC for either "full" (aRR 1.0; 95%CI 0.9 to 1.3) or "occasional" (aRR 1.1; 95%CI: 0.7 to 1.8) aspirin users. Similarly, there were no associations with incident CAC for "full" (aRR 1.3; 95%CI: 0.9 to 2.0) or "occasional" (aRR 1.0; 95%CI: 0.5 to 2.1) aspirin users. For prevalent CAC and AVC none of the categories of aspirin use were associated with either prevalent AVC (p=0.55 for occasional, p=0.13 for regular, and p=0.49 for cardiac use) or CAC (p=0.50 for occasional, p=0.80 for regular, and p=0.46 for cardiac use), and this lack of association persisted when we stratified results by participant sex (data not shown). In HNR, there was no association with prevalent AVC for "full" aspirin users: (aRR 0.9 95%CI: 0.7 to 1.2) or "occasional" aspirin users (aRR 1.4; 95%CI: 0.9 to 2.3) or with prevalent CAC for "full" aspirin users (aRR 1.0; 95%CI: 0.97–1.1) or "occasional" aspirin users (aRR 1.1; 95%CI: 0.95 to 1.2). Unexpectedly, in HNR there were association with "full" use of aspirin and prevalent CAC in women (aRR 1.1; 95%CI: 1.0 to 1.3) and "occasional" use of aspirin and prevalent CAC in men (aRR: 1.2; 95%CI: 1.1 to 1.3). But there were no associations between "occasional" use in women (aRR 1.0; 95%CI: 0.8 to 1.3) or "full" use in men (aRR 1.0; 95%CI: 0.95 to 1.1) and prevalent CAC, nor where there any sex stratified associations between intensity of aspirin use and prevalent AVC (data not shown). Nor did stratification by sex reveal any associations between any intensity of aspirin use and incident CAC or AVC in the HNR cohort (data not shown).

As a final sensitivity analysis, we tested for any association between the time between scans and the study exposures, conditional on age, sex and race to test for bias due to length of follow-up in the longitudinal analysis among the MESA participants (who had a wide range of follow-up times). No association was found with the length of follow-up for aspirin (p=0.2670), Cox 2 selective NSAIDs (p=0.1025), or other NSAIDS (p=0.0808).

DISCUSSION

The results of this study suggest that neither aspirin nor NSAIDs are associated with risks for either prevalent or incident CAC or AVC. As aspirin is known to prevent cardiovascular events, it seems likely that they have a transient effect on cardiovascular risk, likely via their well-known effects on platelet activation. The unexpected association between incident AVC and aspirin use that was observed in the MESA cohort did not replicate in the HNR cohort (which is of equivalent quality as a prospective cohort study) and this means any results need to be interpreted with a high degree of caution. Even if the MESA association was to turn out to be replicable, it was only among regular users of high dose aspirin (which is not a common clinical use).

The statistical significance of the association between aspirin and increased AVC is borderline in the prevalent MESA cohort (with a p-value of only 0.036) and would be restricted to high intensity aspirin use based on sub-group analysis. The associations with baseline occasional aspirin use and prevalent CAC in the HNR cohort are more difficult to interpret, given that the association does not follow a clear dose response curve. Also, since a previous report has found these associations among kidney transplant patients [8], it is possible that this may be attributable to possible aspirin toxicity in patients with impaired renal function [23], which would suggest that high doses taken frequently would be the highest risk sub-group. It is also unclear if there may be additional (time-dependent) exposures that we were not able to capture that may play a confounding role in these estimates. Finally, with so many sub-groups, there should be some caution about the number of association considered in the analysis of these associations.

Taken as a whole, this suggests that the cardiovascular benefits associated with aspirin use [1], as compared to the cardiovascular risks associated with NSAIDs [7,24] may be due to the antiplatelet effects of the drug, rather than an influence on the progression of atherosclerosis. The ideal approach to aspirin treatment is still not known [25] and issues remain including differential effects by diabetes status [2] or gender [24], and determining the ideal dose for cardio protection. However, the results of this study do not detract the evidence from randomized, controlled trials showing a clear benefit of aspirin on serious cardiovascular events[2]. Instead these results provide further evidence for the hypothesis that the primary mechanism of benefit of aspirin on cardiovascular disease is mediated by its effect on platelets [26]. However, we cannot exclude the possibility that any beneficial effect of aspirin on CV risk might be due to other mechanisms that are not captured by using CAC as a measure of subclinical atherosclerosis.

This study has a number of key strengths. The data on exposure was collected before measurement of the outcome (incident calcification). In addition, the cohort studies used the well validated medication inventory approach. This means that we established that exposure occurred before the outcome and not as a consequence of it, although the medication approach used in MESA does not make day to day tracking of medication exposure possible [27]. In addition, because both multiple exposures (different NSAIDs) and multiple outcomes (AVC, CAC) were studied, it is less likely that the lack of associations with endpoints were due solely to confounding by indication [28]. The potential role of confounding by indication may be especially plausible in associations seem with prevalent CAC or AVC as there the outcome may have preceded the exposure.

There are also limitations to any observational study that may have influenced our results. While the current study attempted to broadly account for “health seeking behaviors” such as diet, exercise, current smoking; these variables are measured with a fair degree of error, and residual confounding by lifestyle (i.e. a healthy user bias [29]) cannot entirely be ruled out. However, if the original association between aspirin use and AVC (seen in the hypothesis generating MESA findings) was purely a marker of behavioral differences leading to changers in underlying cardiovascular risk then it should also have appeared as an association between aspirin and CAC.

The weight of the evidence suggests that there is no strong association between NSAID use (including aspirin) and sub-clinical atherosclerosis (as measured by calcification of the aortic valve and coronary artery). It may be interesting to continue to test these associations as new cohorts become available, in case the association between aspirin and AVC is due to an unknown factor (as AVC is associated with increased mortality [30]).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- NSAIDs are known to be associated with cardiovascular events
- Association with calcification is less well established
- We considered two cohorts in two countries to replicate associations
- There was no consistent evidence of any associations with NSAIDs and calcification

The link between aspirin use and a reduction in cardiovascular events such as heart attacks is well known. Aspirin use is an important therapy in preventing these events. However, less well understood is whether use of aspirin may actually have beneficial effects on the development of plaque in the coronary arteries or valves of the aorta. In a combined study with a group from Germany, we looked at whether aspirin use was associated with coronary artery calcium as measured by CT scan. Our overall findings were that aspirin did not influence the development of atherosclerotic plague in the coronary arteries. This is consistent with previous scientific findings that suggest that aspirin's protective effects are due to reducing inflammation and anti-platelet effects that reduce clotting.

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Table 1

Descriptive statistics of Multi-Ethnic Study of Atherosclerosis (MESA) and Heinz Nixdorf Recall (HNR) Study stratified by baseline exposure to Non-steroidal anti-inflammatory drugs (NSAIDs)

	Multi-Ethnic Study of Atherosclerosis				Heinz Nixdorf Recall Study		
	No use of any NSAID (n=3894)	**Aspirin Use (n=1689)**	**Other Non-selective NSAID use (n=929)**	**Cox-2 Selective NSAID Use (n=299)**	**No use of any NSAID (n=3145)**	**Aspirin Use (n=390)**	**Other NSAID use (n=262)**
Age at Baseline (years)	61.3±10	65.7±10	60.0±10	64.9±10	58.9±8	63.0±8	61.2±8
Male Sex	47%	51%	33%	36%	47%	54%	32%
Asian	17%	9%	4%	8%	n.a.	n.a.	n.a.
African American	28%	23%	26%	31%	n.a.	n.a.	n.a.
European Descent	30%	48%	48%	38%	n.a.	n.a.	n.a.
Hispanic	25%	16%	22%	23%	n.a.	n.a.	n.a.
Smoker	13%	10%	15%	12%	23%	22%	22%
Ex-Smoker	33%	42%	38%	39%	34%	35%	28%
Body Mass Index (kg/m^2)	28±5	28±5	30±6	30±6	28±4	29±5	29±5
Diabetes	10%	16%	10%	15%	7%	15%	5%
Intentional Exercise (scaled by 1 standard deviation)	1.1±1.4	1.2±0.3	1.1±1.3	1.2±1.4	n.a.	n.a.	n.a.
Sedentary Activities (scaled by 1 standard deviation)	0.9±0.6	1.0±0.6	1.0±0.7	1.1±0.7	n.a.	n.a.	n.a.
Systolic Blood Pressure (mmHg)	125±21	128±21	126±22	129±22	132±21	136±22	135±20
Diastolic Blood Pressure (mmHg)	72±10	71±10	71±11	71±9	81±11	81±11	82±11
HDL Cholesterol (mg/dL)	51±15	51±15	52±16	53±15	59±17	56±17	59±16
LDL Cholesterol (mg/dl)	119±32	114±31	117±31	112±33	147±36	144±36	153± 37
Triglycerides (mg/dl)	130±90	130±78	137±89	127±71	146±100	152±85	149±87
Fasting Glucose (mg/dl)	104±32	106±31	102±28	105±27	n.a.	n.a.	n.a.
Total Homocysteine (tHcy, μmol/l)	9.18±3.3	9.67±3.5	9.24±5.5	9.55±3.5	11.9±4.5	12.2±4.0	12.1±4.1
Interleukin-6 (pg/ml)	1.49±1.2	1.60±1.2	1.64±1.3	1.80±1.7	n.a.	n.a.	n.a.
Fibrinogen antigen (mg/dl)	346±73	347±73	345±75	358±86	332±76	339±79	340±86
c-reactive protein (mg/l)	3.5±6	3.4±5	5.0±8	5.2±9	2.9±10	4.0±10	3.9±7
Less than high School Education	20%	15%	17%	22%	n.a.	n.a.	n.a.

	Multi-Ethnic Study of Atherosclerosis				Heinz Nixdorf Recall Study		
	No use of any NSAID (n=3894)	**Aspirin Use (n=1689)**	**Other Non-selective NSAID use (n=929)**	**Cox-2 Selective NSAID Use (n=299)**	**No use of any NSAID (n=3145)**	**Aspirin Use (n=390)**	**Other NSAID use (n=262)**
College Education	17%	17%	19%	13%	n.a.	n.a.	n.a.
Graduate School Education	16%	24%	17%	18%	n.a.	n.a.	n.a.
Income < 25,000/year	37%	31%	31%	37%	n.a.	n.a.	n.a.
Income > 50,000 and ≤ 100,000/year	25%	24%	26%	23%	n.a.	n.a.	n.a.
Income > 100,000/year	11%	17%	16%	11%	n.a.	n.a.	n.a.
No Health Insurance	12%	5%	7%	4%	n.a.	n.a.	n.a.
Anti-hypertensive Medication Use	27%	46%	36%	48%	29%	57%	38%
HMG CoA reducatace inhibitor use	11%	25%	12%	22%	n.a.	n.a.	n.a.
Diet Score	0.14±3.5	0.31±3.5	−0.51±3.3	0.34±3.1	n.a.	n.a.	n.a.
Agatson Calcium Score (AVC)	21±195	43±260	23±172	22±133	23±222	55±425	38±153
Agatson Calcium Score (CAC)	117±375	222±500	108±357	177±454	147±333	344±700	177±506
Time between Scans (days)	894±313	871±311	879±303	864±308	n.a.	n.a.	n.a.
Glomerular filtration rate	82.8±17.7	78.1±16.7	80.8±22.1	77.9±18.5	92.3±21.2	88.2±17.9	94.6±23.2
Creatinine (mg/dL)	0.94±0.28	0.99±0.33	0.93±0.21	0.95±0.23	0.93±0.21	0.95±0.16	0.93±0.35

Table 2

Crude and adjusted relative risks (RR) for the association between prevalent Aortic Valve Calcification and Coronary Artery Calcification and baseline Non-Steroidal Anti-Inflammatory Drug (NSAID) use stratified by diabetes at baseline. Data from MESA (n=6516)

	Prevalence of Aortic Valve Calcification				Prevalence of Coronary Artery Calcification			
	Crude (95%CI)	**p- value**	**Adjusted RR(95%CI)***	**p- value**	**Crude (95%CI)**	**p- value**	**Adjusted RR(95%CI)***	**p- value**
Diabetic at Baseline (n=743)								
Aspirin (n=281)	1.46 (1.13; 1.90)	0.01	1.19 (0.90; 1.58)	0.23	1.22 (1.10;1.35)	<0.01	1.05 (0.94; 1.17)	0.37
Non-selective NSAID (n=139)	1.10 (0.77;1.54)	0.61	1.33 (0.89; 1.99)	0.16	1.01 (0.87;1.16)	0.84	1.04 (0.88; 1.22)	0.64
Cox-2 selective NSAID(n=79)	1.26 (0.85;1.88)	0.24	1.29 (0.83; 2.00)	0.25	0.96 (0.79;1.15)	0.24	0.94 (0.76; 1.15)	0.54
Not Diabetic at Baseline (n=5776)								
Aspirin (n=1314)	1.61 (1.39; 1.87)	<0.01	1.06 (0.92; 1.25)	0.41	1.31 (1.23;1.38)	<0.01	0.99 (0.93; 1.04)	0.63
Non-selective NSAID (n=984)	0.83 (0.68; 1.02)	0.07	0.96 (0.77; 1.18)	0.68	0.90 (0.83;0.97)	0.01	0.99 (0.92; 1.06)	0.76
Cox-2 selective NSAID(n=367)	1.24 (0.96; 1.59)	0.10	0.88 (0.67; 1.16)	0.37	1.22 (1.12;1.34)	<0.01	1.07 (0.99; 1.17)	0.11

*Adjusted for age, sex, ethnicity, study site, anti-hypertensive medication use, education, income, health insurance status, smoking, exercise, body mass index, sedentary lifestyle, time between CT scans, blood pressure at baseline, HDL cholesterol, LDL cholesterol, Triglycerides, homocysteine, IL6, Fibrinogen, CRP, statin medication use and simple diet score.

Table 3

Replication #1. Crude and adjusted relative risks (RR) for the association between prevalent Aortic Value Calcification and Coronary Artery Calcification and baseline Non-Steroidal Anti-Inflammatory Drug (NSAID) use, stratified by diabetes at baseline in the Heinz Nixdorf Recall Study cohort. Data from HNR (n=3797, [n=3466 in adjusted analysis])

	Prevalence of Aortic Valve Calcification				**Prevalence of Coronary Artery Calcification**			
	Crude (95%CI)	**p-value**	**Adjusted RR(95%CI)***	**p- value**	**Crude (95%CI)**	**p-value**	**Adjusted RR(95%CI)***	**p-value**
Diabetic at baseline (n=287)								
Aspirin (n=59)	1.40 (0.79; 2.46)	0.25	0.91 (0.47; 1.77)	0.78	1.12 (1.02; 1.22)	0.02	1.05 (0.95; 1.17)	0.36
NSAID (n=18)	XXX				1.11 (0.99; 1.26)	0.09	1.01 (0.86; 1.20)	0.86
Not Diabetic at baseline (n=3510)								
Aspirin (n=331)	1.68 (1.29; 2.18)	<0.001	0.99 (0.75; 1.30)	0.93	1.19 (1.12; 1.27)	<0.001	1.03 (0.96; 1.09)	0.42
NSAID (n=269)	1.43 (1.05; 1.93)	0.021	1.28 (0.95; 1.72)	0.11	1.08 (0.99; 1.16)	0.07	1.01 (0.94; 1.09)	0.76

*Adjusted for age, sex, use of antihypertensive medication, education, income, smoking, body mass index, blood pressure, HDL-cholesterol, LDL-cholesterol, Triglycerides, Fibrinogen, CRP, lipid-lowering medication.

XXX: Not defined due to zero cell.

Table 4

Replication #2. Crude and adjusted relative risks (RR) for the association between incident Aortic Valve Calcification and Coronary Artery Calcification and baseline Non-Steroidal Anti-Inflammatory Drug (NSAID) use. Reference group is non-users. Data from MESA (n=2522 for CAC analysis, n=4550 for AVC analysis)

	Crude RR (95%CI)	p-value	Adjusted RR (95%CI)*	p-value
Incidence of Aortic Valve Calcification (n=204)				
Aspirin (n=1150)	1.91 (1.44; 2.52)	<0.01	1.60 (1.19;2.15)	<0.01
Non-selective NSAID (n=874)	1.06 (0.75; 1.51)	0.73	1.35 (0.95;1.92)	0.09
Cox-2 selective NSAID (n=320)	1.20 (0.73;1.98)	0.48	0.94 (0.55;1.60)	0.82
Incidence of Coronary Artery Calcification (n=526)				
Aspirin (n=559)	1.36 (1.15; 1.61)	<0.01	1.08 (0.91;1.29)	0.39
Non-selective NSAID (n=543)	1.08 (0.90; 1.29)	0.42	1.09 (0.91;1.32)	0.36
Cox-2 selective NSAID(n=160)	1.04 (0.76; 1.42)	0.80	0.90 (0.65;1.26)	0.56

*Adjusted for age, sex, ethnicity, study site, anti-hypertensive medication use, education, income, health insurance status, diabetes, smoking, exercise, body mass index, sedentary lifestyle, time between CT scans, blood pressure at baseline, HDL cholesterol, LDL cholesterol, Triglycerides, homocysteine, IL6, Fibrinogen, CRP, fasting glucose, statin medication use and simple diet score.

Table 5

Replication #2. Crude and adjusted relative risks (RR) for the association between incident Aortic Valve Calcification and Coronary Artery Calcification and baseline Non-Steroidal Anti-Inflammatory Drug (NSAID) use in the Heinz Nixdorf Recall Study cohort. Reference group is non-users. Data from HNR [n=1043 for CAC, n=2522 for AVC (adjusted analyses)].

	Crude RR (95%CI)	p-value	Adjusted RR (95%CI)*	p-value
Incidence of Aortic Valve Calcification (n=699)				
Aspirin (n=246)	1.49 (1.24;1.78)	<0.0001	1.06 (0.87;1.28)	0.58
NSAID (n=175)	0.87 (0.65;1.16)	0.34	0.72 (0.54;0.97)	0.03
Incidence of Coronary Artery Calcification (n=298)				
Aspirin (n=73)	1.49 (1.08;2.04)	0.01	1.24 (0.87:1.77)	0.24
NSAID (n=70)	0.99 (0.66;1.49)	0.96	0.86 (0.56;1.32)	0.50

*Adjusted for age, sex, use of antihypertensive medication, education, income, smoking, body mass index, blood pressure, HDL-cholesterol, LDL-cholesterol, Triglycerides, Fibrinogen, CRP, lipid-lowering medication, time between scans.