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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.
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 calcification (CAC).
Methods: The relationship of NSAID use to AVC and CAC detected by computed tomography was assessed in 6814 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 4814 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

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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.

1. 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 [2–4]. 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 is 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.

2. Methods

2.1. MESA cohort

The MESA study includes 6814 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 6519 MESA participants included in the analytic cohort for prevalent disease. Only 4932 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].

2.2. 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, 4814 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 3466 participants in the analytic cohort for prevalent disease. This was further reduced to 3279 participants with information on CAC or AVC at follow-up.

2.3. 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