1. Title:
The Association of Aspirin and Dipyridamole with Lower Extremity Arterial Disease

2. Writing Group:
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3. Timeline:
April-June, 1994: Initiation and completion of statistical analyses
June-July, 1994: Preparation of draft manuscript

4. Rationale:
There is evidence that prophylactic antiplatelet therapy is effective in improving the prognosis and local progression of lower extremity arterial disease, and that the proportional risk reduction in serious vascular events is similar to that in cardiovascular and cerebrovascular disease. Two drugs, aspirin and dipyridamole, have been shown to be effective antiplatelet agents in intervention studies on peripheral vascular disease; aspirin, by blocking the action of platelet cyclooxygenase, and consequently, reducing the synthesis of thromboxane A$_2$ (1,2), and dipyridamole, a phosphodiesterase inhibitor, by potentiating endogenous prostacyclin (3).

Many of the studies on prophylactic antiplatelet therapy relating to peripheral arterial disease have focused on efficacy in preventing re-occlusive disease in patients with saphenous vein and bio-prosthetic arterial grafts. Three studies demonstrated that aspirin in combination with dipyridamole confer a significant advantage over placebo in maintaining the patency of the arterial bypass (4,5,6), while a fourth trial found no difference between active drug and placebo (7).

In populations of patients with obstructive arterial disease not receiving reconstructive surgery, daily consumption of aspirin versus placebo resulted in a statistically significantly lower occlusion rate in femoral artery stenosis in one study (8), and in slower progression in leg arteries using a scoring of serial angiograms in another study (9).

Finally, in the Physicians Health Study, the relative risk of undergoing peripheral arterial surgery during the five year follow-up period was 0.54 (95% confidence interval of 0.30-0.95) in the group receiving low-dose aspirin every other day compared to the placebo group (10).

5. Main Hypotheses:
(a) The prevalence odds of reported use of aspirin and/or dipyridamole (within the two week period prior to visit 1) is lower among those with low ankle-brachial index (ABI), a marker of lower extremity arterial disease, in the population sample examined by the ARIC study.

(b) There is a graded, inverse relationship between reported use of aspirin and/or dipyridamole (within the two week period prior to visit 1) and the ABI in this population.

6. Data:
a) Exposure Variable: Visit 1 Medication Survey Questions 4AB through 4QB with responses of 102055
(aspirin), 102092
(buffered aspirin), 102107 (another buffered aspirin), or 107599 (dipyridamole or Persantin).

b) Outcome Variable: Visit 1 ratio of ankle-brachial systolic blood pressure (ABI).

c) Covariables as possible confounders or effect modifiers, also at Visit 1: Gender, race, age, center, prevalent CHD, history of TIA or stroke, Rose Questionnaire intermittent claudication, Rose Questionnaire angina, smoking, hypertension, cholesterol, triglyceride, diabetes, body mass index, fibrinogen, year of visit.

7. Analysis Strategy:
Regular users of aspirin or dipyridamole, not episodic takers, are the persons most likely to obtain therapeutic effect, yet knowledge of regular use as well as knowledge of indication for use are missing from the Visit 1 data. Ancillary aspirin data obtained at visit 3 ("How many days during the last two weeks was aspirin or aspirin-containing medication taken", "Was it taken to avoid a heart attack or stroke") will be examined in this analysis to potentially validate the Visit 1 exposure measure.

To help resolve the problem of determining the antecedent-consequence relationship between aspirin consumption and low ABI, stratification by presence of CHD and/or other manifestations of clinical cardiovascular disease will be performed.

REFERENCES


