Aspirin Use and All-Cause Mortality Among Patients Being Evaluated for Known or Suspected Coronary Artery Disease: A Propensity Analysis

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Aspirin has been shown to be associated with decreased cardiovascular morbidity in multiple clinical trials, but the association between aspirin use and all-cause mortality has been less well defined except in the setting of acute myocardial infarction. Although a few observational analyses have suggested a longer-term survival benefit, it is not clear whether this benefit persists after accounting for treatment selection biases as well as established predictors of survival in patients with known or suspected coronary artery disease, in particular impaired exercise capacity, left ventricular dysfunction, and myocardial ischemia.

In this study we sought, based on an a priori hypothesis, to determine if aspirin use was associated with a reduction in all-cause mortality among stable patients referred for stress echocardiography. Because the validity of observational studies of treatment effects may be limited by selection biases and confounding factors, we performed a propensity analysis.

Context Although aspirin has been shown to reduce cardiovascular morbidity and short-term mortality following acute myocardial infarction, the association between its use and long-term all-cause mortality has not been well defined.

Objectives To determine whether aspirin is associated with a mortality benefit in stable patients with known or suspected coronary disease and to identify patient characteristics that predict the maximum absolute mortality benefit from aspirin.

Design and Setting Prospective, nonrandomized, observational cohort study conducted between 1990 and 1998 at an academic medical institution, with a median follow-up of 3.1 years.

Patients Of 6174 consecutive adults undergoing stress echocardiography for evaluation of known or suspected coronary disease, 2310 (37%) were taking aspirin. Patients with significant valvular disease or documented contraindication to aspirin use, including peptic ulcer disease, renal insufficiency, and use of nonsteroidal anti-inflammatory drugs, were excluded.

Main Outcome Measure All-cause mortality according to aspirin use.

Results During 3.1 years of follow-up, 276 patients (4.5%) died. In a simple univariable analysis, there was no association between aspirin use and mortality (4.5% vs 4.5%). However, after adjustment for age, sex, standard cardiovascular risk factors, use of other medications, coronary disease history, ejection fraction, exercise capacity, heart rate recovery, and echocardiographic ischemia, aspirin use was associated with reduced mortality (hazard ratio [HR], 0.67; 95% confidence interval [CI], 0.51-0.87; \( P = .002 \)). In further analysis using matching by propensity score, 1351 patients who were taking aspirin were at lower risk for death than 1351 patients not using aspirin (4% vs 8%, respectively; HR, 0.53; 95% CI, 0.38-0.74; \( P = .002 \)). After adjusting for the propensity for using aspirin, as well as other possible confounders and interactions, aspirin use remained associated with a lower risk for death (adjusted HR, 0.56; 95% CI, 0.40-0.78; \( P < .001 \)). The patient characteristics associated with the most aspirin-related reductions in mortality were older age, known coronary artery disease, and impaired exercise capacity.

Conclusion Aspirin use among patients undergoing stress echocardiography was independently associated with reduced long-term all-cause mortality, particularly among older patients, those with known coronary artery disease, and those with impaired exercise capacity.
ASPIRIN USE AND MORTALITY

and 1998. Patients were excluded if they had significant valvular heart disease, prior cardiac transplantation, congenital heart disease, were younger than 30 years, if they were referred for arrhythmia evaluation, for consideration of cardiac transplantation, or solely as part of a research protocol. We also excluded patients with documented contraindications to aspirin, including peptic ulcer disease, renal insufficiency, and concurrent use of nonsteroidal anti-inflammatory drugs. A total of 3780 patients were excluded. If patients had more than 1 stress echocardiogram, only the first was considered.

All patients gave informed consent before undergoing exercise testing. Approval was obtained from the Cleveland Clinic Foundation institutional review board to perform research analyses based on prospectively obtained stress laboratory databases in our institution.

Clinical Data

Data on baseline demographics, medical history, cardiovascular risk factors, and medication use (including regular use of aspirin) were collected prospectively at the time of testing. All data were entered online prior to the start of the stress test by either a physician or a trained exercise physiologist, with those entering data into the database blinded to the hypothesis of this study as well as to the results of the subsequent stress test and stress echocardiogram. Quality control has been ensured as described elsewhere. Aspirin use was confirmed by a pretest patient interview or by a physician’s note in the patient’s chart. Regular aspirin use was defined as use of aspirin daily or every other day. The timing of the last dose of all medications was prospectively recorded. Among aspirin users, 93% had taken their last dose within 24 hours while 98% had done so within 48 hours.

Resting heart rate was based on a 30-second recording of pulse, while blood pressure was measured to the nearest 1 mm Hg using indirect mercury column sphygmomanometry. Height and weight were directly measured and body mass index was calculated as weight in kilograms divided by the square of height in meters. Diabetes was considered present if insulin or oral hypoglycemic medications were being used or if the patient had been prescribed a diabetic diet. Hypertension was defined as a resting systolic blood pressure of 140 mm Hg or greater, a resting diastolic pressure of 90 mm Hg or greater, or use of medications to reduce blood pressure. Prior coronary artery disease was defined as prior myocardial infarction, coronary artery revascularization, or the presence of at least 1 coronary stenosis (50% or greater diameter) on a prior coronary angiogram. Congestive heart failure was coded if a diagnosis was noted in the patient’s record. For a global description of risk, the Mayo Risk Index was used; this index has a score from 0 to 5 with 1 point each for male sex, prior myocardial infarction, diabetes, insulin use, and typical angina pectoris. This score has been shown to correlate well with left main or 3-vessel coronary artery disease.

Stress Testing

Symptom-limited exercise testing was performed according to Bruce, modified Bruce, or Cornell protocols as previously described. Exercise capacity was estimated in metabolic equivalent tasks (METs) (1 MET = oxygen consumption of 3.5 mL/kg per minute) and classified as being impaired if measured as fair or poor for age and sex, according to a validated classification scheme. An abnormal ST-segment response was considered present if, in the absence of an abnormal resting electrocardiogram or digitalis use, there was at least 1 mm of horizontal or downsloping ST-segment depression 80 milliseconds after the J-point. Chronotropic response was assessed by proportion of heart rate reserve used.

Heart rate recovery was defined as the difference between heart rate at peak exercise and 1 minute thereafter.

Stress Echocardiography

Details of the echocardiographic techniques used in our laboratory have been described in detail elsewhere. Briefly, images were obtained with the patient in the left lateral decubitus position. Parasternal long and short as well as apical 2- and 4-chamber images were obtained at baseline and immediately after exercise. Images were recorded on videotape diskette after online digitization. Images were reviewed and interpreted by 2 physician echocardiographers on the same day of examination regardless of image quality and in a blinded fashion with respect to clinical data, exercise data, and the hypothesis of this study. Ischemia and scarring were graded by a standard 16-segment model of the left ventricle. Myocardial ischemia was considered present if a new or progressive wall-motion abnormality was present on the postexercise images. Myocardial scarring was diagnosed by resting wall-motion akinesia or dyskinesia that was unchanged with stress.

End Points

The primary end point was all-cause mortality. As we have discussed elsewhere, the use of “cardiac” or “cardiovascular” mortality as an end point has a number of inherent limitations, including incorrect or biased documentation by treating physicians and inaccurate clinical assessments in an environment characterized by low autopsy rates. We used the Social Security Death Index, which has been shown to be highly specific (>99.5%) and unbiased. We have reported elsewhere on the high sensitivity (approximately 97%) of this index among Cleveland Clinic stress laboratory patients. Follow-up was for a median of 3.1 years.

Statistical Analyses

Differences between aspirin users and nonusers were compared using $\chi^2$ statistics for categorical variables and $t$ or Wilcoxon rank sum tests, as appropriate, for continuous variables. Aspirin use was related to all-cause mortality using univariable and multivariable Cox proportional hazard regression analyses with consideration of clinically plausible interactions. The proportional hazards assumption was con-
firmed by inspection of log (−log [sur-
ival]) curves and by examination of
time-dependent covariates. Survival
curves were constructed using Kaplan-
Meier estimates20 with comparisons be-
tween curves based on the log-rank χ²
 statistic.

Because aspirin use was not ran-
domly assigned in this patient popu-
lation, potential confounding and selec-
tion biases were accounted for by
developing a propensity score for as-
pirin use. The rationale and methods
underlying the use of a propensity score
for a proposed causal exposure vari-
dable have been previously described.7
The propensity for aspirin use was de-
termined without regard to outcome,
using multivariable logistic regres-
sion.21 A full nonparsimonious
model was developed that included 34
covariates, some of which are listed in
 TABLE 1. This model yielded a c sta-
tistic of 0.83, indicating a strong ability
to differentiate between aspirin users
and nonusers. A propensity score for
aspirin use was then calculated from the
logistic equation for each patient. This
score ranged from 0.03 to 0.98 and, in
effect, represented the probability that
a patient would be using aspirin.

Using a macro (available at: http://
www2.sas.com/proceedings/sugi26
/p214-26.pdf), we used the propen-
sity scores to match aspirin users to
unique control patients. Specifically, we
sought to match each aspirin user to a
non–aspirin-using patient who had a
propensity score that was identical to
5 digits. If this could not be done, we
then proceeded to a 4-, 3-, 2-, or 1-digit
match. Once this threshold was ex-
ceeded, that aspirin-using patient was
excluded. We were able to match 1351
aspirin-using patients to 1351 unique
non–aspirin-using patients.

To determine which patient charac-
teristics predicted maximum absolute
benefit from aspirin, we derived multi-
variable nonproportional hazard equa-
tions for each individual patient’s pre-
dicted survival using a wholly parametric
method.22 For the propensity-matched
patients, each patient-specific equation
was solved twice, once as if the patient
had been taking aspirin and once as if
he/she had not been taking aspirin; this
approach is similar to another analysis
we have described analyzing the poten-
tial benefits of bilateral mammary ar-
tery grafting.23 The logarithm of the dif-
ference in predicted survivals with and
without aspirin was then treated as the
dependent variable for a linear regres-
sion analysis that sought to identify those
patient characteristics most strongly as-
associated with a large beneficial differ-
ence in predicted mortality. Appropriate
regression diagnostics, including ex-
amination of residuals and testing for
outliers, exceptionally influential obser-
vations, and multicollinearity, were per-
duced to confirm the validity of these
analyses.

All analyses were performed using
SAS version 8.1 (SAS Institute, Cary,
NC). Parametric survival analyses were

RESULTS
Patient Characteristics
Among 6174 adult patients eligible for analysis, 2310 (37%) were taking aspirin at the time of stress echocardiography. Baseline and exercise characteristics according to aspirin use are summarized in Table 1. Aspirin users were older and more likely to be men; they were also more likely to have hypertension, diabetes, and prior histories of coronary artery disease, coronary artery bypass grafting, and percutaneous coronary intervention. Patients taking aspirin were also more likely to be taking β-blockers, lipid-lowering drugs, and angiotensin-converting enzyme (ACE) inhibitors. They were more likely to have ischemic ST-segment changes during stress and echocardiographic evidence of stress-induced ischemia. The patients not using aspirin had higher left ventricular ejection fraction and were more likely to be smokers.

Aspirin Use and Mortality
During 3.1 years of follow-up, 276 patients (4.5%) died. Table 2 summarizes mortality outcomes based on aspirin use. In a crude analysis, there was no association between aspirin use and mortality (4.5% vs 4.5%). After adjusting only for age and sex, an association between aspirin use and reduced mortality became evident, with an even stronger association noted after further adjusting for a history of known coronary artery disease. This association was not materially affected by adjusting for other confounders (Table 2).

Prespecified stratified bivaraible analyses were performed according to age, sex, diabetes, smoking, prior myocardial revascularization procedures, use of β-blockers or ACE inhibitors, left ventricular systolic function, and echocardiographic evidence of ischemia. The only possible noted interactions with aspirin in bivaraible analyses were a left ventricular ejection fraction of 40% or less and a prior history of coronary artery bypass grafting. However, these interaction terms were not significant after multivariable adjustment. Stratified multivariable analyses showed reduced mortality associated with aspirin use irrespective of left ventricular function or history of prior coronary artery bypass grafting (Table 2).

Aspirin Use and Mortality in Propensity-Matched Patients
Based on systematically collected data for 34 variables including baseline demographics, medical risk factors, and the interactions between them, a logistic regression model was used to generate a propensity score for aspirin use. Major independent correlates of aspirin use included prior percutaneous or surgical myocardial revascularization, male sex, lipid-lowering therapy, nitrate use, and history of coronary artery disease.

Baseline characteristics comparing the propensity-matched aspirin users and aspirin nonusers are shown in Table 3. As opposed to the entire population, these propensity-matched patients were well matched; the only significant difference was that men who used aspirin had a slightly higher functional capacity than men who did not. During follow-up, 153 (6%) patients died. Aspirin use was associated with a lower risk of death (4% vs 8%, P = .002) (Figure 1 and Table 4).

Aspirin use was significantly associated with reduced mortality by univariable analysis and multivariable analysis. We found no interactions between aspirin use and older age, impaired left ventricular systolic function, diabetes, smoking, history of coronary artery disease, prior coronary intervention, and echocardiographic evidence of myocardial ischemia.

Characteristics Predictive of Maximum Absolute Mortality Benefit From Aspirin
Based on wholly parametric-derived patient-specific survival equations, a predicted absolute mortality difference from aspirin use was derived for each propensity-matched patient. The 3 strongest correlates of a large absolute mortality benefit were age, impaired exercise capacity, and a history of known coronary artery disease. A linear regression equation relating these 3 variables to the logarithm of the absolute survival difference associated with aspirin demonstrated that 74% of the variability in survival difference could be explained (Figure 2). Older patients who had either impaired exercise capacity or known coronary artery disease appeared to derive the greatest absolute benefit from aspirin use.
Use of Aspirin and Mortality Among Women

In the main cohort of 6174 patients, there were 2228 (36%) women, among them 531 (24%) regular users of aspirin. During 3.1 years of follow-up 77 women died, with no difference noted between aspirin users and nonusers (3.8% vs 3.4%). After adjusting for age, Mayo Risk Index, ejection fraction, history of prior coronary artery bypass surgery, and functional capacity, aspirin use was associated with a lower mortality rate (adjusted hazard ratio, 0.59; 95% confidence interval [CI], 0.35-1.00; \( P = .05 \)).

In the propensity-matched cohort of 2702 patients, there were 777 women; 400 (51%) regularly used aspirin. There were 36 deaths, with aspirin use associated with a lower risk (3.5% vs 5.8%). After adjustment for age, propensity score, ejection fraction, and functional capacity, aspirin use remained predictive of a lower risk of death (adjusted hazard ratio, 0.50; 95% CI, 0.25-1.00; \( P = .05 \)).

**COMMENT**

Among consecutive patients referred for stress echocardiography to evaluate known or suspected coronary artery disease, aspirin use was associated with a substantial reduction of all-cause mortality. When we assessed mortality risk using a standard Cox regression analysis among all patients, a 33% reduction in mortality was found. Subsequently, we performed a rigorous propensity analysis, limiting analyses to 2702 propensity-matched patients. The results were essentially unchanged, with aspirin associated with a substantial reduction in risk of death.

We estimated the absolute benefit of aspirin based on specific patient characteristics, thus predicting which patients might benefit most from aspirin treatment. We showed aspirin to be particularly beneficial among patients who were older, who had impaired exercise capacity, or who had a history of coronary artery disease. Sedentary patients subjected to strenuous exercise have been shown to have increased platelet activation and hyperreactivity compared with physically fit subjects. Thus, aspirin may “treat” poor physical fitness by attenuating the associated increased platelet activation. To the best of our knowledge, this is the first study suggesting aspirin to be beneficial in patients with impaired exercise capacity—one of the most powerful predictors of mortality in patients with known or suspected heart disease. We were only able to demonstrate this association because we specifically analyzed a population of patients undergoing exercise testing.

Extensive literature documents the cardiovascular benefits of aspirin therapy among adults without a cardiovascular disease. We specifically analyzed a population of patients with known or suspected heart disease. We were only able to demonstrate this association because we specifically analyzed a population of patients undergoing exercise testing.

**Table 3. Selected Baseline and Exercise Characteristics According to Aspirin Use in Propensity-Matched Patients***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aspirin (n = 1351)</th>
<th>No Aspirin (n = 1351)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60 (11)</td>
<td>61 (11)</td>
<td>.16</td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>951 (70)</td>
<td>974 (72)</td>
<td>.33</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>203 (15)</td>
<td>207 (15)</td>
<td>.83</td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>679 (50)</td>
<td>698 (52)</td>
<td>.46</td>
</tr>
<tr>
<td>Tobacco use, No. (%)</td>
<td>161 (12)</td>
<td>162 (12)</td>
<td>.95</td>
</tr>
<tr>
<td>Cardiac variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior coronary artery disease, No. (%)</td>
<td>652 (48)</td>
<td>659 (49)</td>
<td>.79</td>
</tr>
<tr>
<td>Prior coronary artery bypass graft, No.</td>
<td>251 (19)</td>
<td>235 (17)</td>
<td>.42</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention, No. (%)</td>
<td>166 (12)</td>
<td>147 (11)</td>
<td>.25</td>
</tr>
<tr>
<td>Prior Q-wave MI, No. (%)</td>
<td>194 (14)</td>
<td>206 (15)</td>
<td>.52</td>
</tr>
<tr>
<td>Atrial fibrillation, No. (%)</td>
<td>21 (2)</td>
<td>24 (2)</td>
<td>.65</td>
</tr>
<tr>
<td>Congestive heart failure, No. (%)</td>
<td>79 (6)</td>
<td>89 (7)</td>
<td>.43</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digoxin use, No. (%)</td>
<td>115 (9)</td>
<td>114 (9)</td>
<td>.94</td>
</tr>
<tr>
<td>( \beta )-Blocker use, No (%)</td>
<td>352 (26)</td>
<td>358 (26)</td>
<td>.79</td>
</tr>
<tr>
<td>Diltiazem/verapamil use, No. (%)</td>
<td>223 (17)</td>
<td>223 (17)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Nifedipine use, No. (%)</td>
<td>127 (9)</td>
<td>144 (11)</td>
<td>.28</td>
</tr>
<tr>
<td>Lipid-lowering therapy, No. (%)</td>
<td>281 (21)</td>
<td>271 (20)</td>
<td>.63</td>
</tr>
<tr>
<td>ACE inhibitor use, No. (%)</td>
<td>209 (15)</td>
<td>214 (16)</td>
<td>.79</td>
</tr>
<tr>
<td>Cardiovascular assessment and exercise capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>29 (6)</td>
<td>29 (6)</td>
<td>.83</td>
</tr>
<tr>
<td>Ejection fraction, mean (SD), %</td>
<td>51 (8)</td>
<td>51 (9)</td>
<td>.65</td>
</tr>
<tr>
<td>Resting heart rate, mean (SD), beats/min</td>
<td>77 (13)</td>
<td>76 (14)</td>
<td>.13</td>
</tr>
<tr>
<td>Resting blood pressure, mean (SD), mm Hg</td>
<td>141 (21)</td>
<td>141 (21)</td>
<td>.68</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85 (11)</td>
<td>86 (11)</td>
<td>.57</td>
</tr>
<tr>
<td>Purpose of test to evaluate chest pain, No. (%)</td>
<td>153 (11)</td>
<td>159 (12)</td>
<td>.72</td>
</tr>
<tr>
<td>Mayo Risk Index ≥1, No. (%)</td>
<td>1108 (82)</td>
<td>1110 (82)</td>
<td>.92</td>
</tr>
<tr>
<td>Peak exercise capacity, mean (SD), METs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8.7 (2.5)</td>
<td>8.3 (2.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Women</td>
<td>6.5 (2.0)</td>
<td>6.7 (2.0)</td>
<td>.13</td>
</tr>
<tr>
<td>Heart rate recovery, mean (SD), beats/min</td>
<td>28 (12)</td>
<td>28 (11)</td>
<td>.82</td>
</tr>
<tr>
<td>Ischemic ECG changes with stress, No. (%)</td>
<td>231 (22)</td>
<td>223 (21)</td>
<td>.64</td>
</tr>
<tr>
<td>Echocardiographic left ventricular ejection fraction ≤40%, No. (%)</td>
<td>147 (11)</td>
<td>156 (12)</td>
<td>.50</td>
</tr>
<tr>
<td>Stress-induced ischemia on echocardiography, No. (%)</td>
<td>239 (18)</td>
<td>259 (19)</td>
<td>.32</td>
</tr>
<tr>
<td>Fair or poor physical fitness for age and sex, No. (%)</td>
<td>445 (33)</td>
<td>459 (34)</td>
<td>.57</td>
</tr>
</tbody>
</table>

*MI indicates myocardial infarction; ACE, angiotensin-converting enzyme; MET, metabolic equivalent task; and ECG, electrocardiogram.
†The Mayo Risk Index is described in the “Methods” section.

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‡For a list of covariates, see Table 2 footnote (†).

†Selected variables included prior coronary artery disease, prior coronary artery bypass grafting, prior percutaneous intervention, and ejection fraction ≤40%. ¶For a list of covariates, see Table 2 footnote (†).

Table 4. Cox Proportional Hazards Analyses of Aspirin Use and Mortality Among Propensity-Matched Patients (n = 2702)*

<table>
<thead>
<tr>
<th>Model</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.53 (0.38-0.74)</td>
<td>.002</td>
</tr>
<tr>
<td>Adjusted for propensity</td>
<td>0.53 (0.38-0.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusted for propensity and selected variables</td>
<td>0.59 (0.42-0.83)</td>
<td>.002</td>
</tr>
<tr>
<td>Adjusted for propensity and all covariates‡</td>
<td>0.56 (0.40-0.78)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†Selected variables included prior coronary artery disease, prior coronary artery bypass grafting, prior percutaneous intervention, and ejection fraction ≤40%.
‡For a list of covariates, see Table 2 footnote (†).

The current study extends these previous findings in several important respects. First, we demonstrated that aspirin use is associated with a reduction in long-term all-cause mortality, which is a clinically relevant, objective, and wholly unbiased end point. Second, because we focused on patients referred for stress echocardiography we were able to account for several critical predictors of mortality, including left ventricular systolic function, stress-induced myocardial ischemia, and impaired exercise capacity. Third, unlike prior observational studies of aspirin use and outcome, we used propensity analysis, which has been argued to be a powerful means of accounting for baseline confounding and selection biases.

Furthermore, we observed this mortality reduction in a large cohort of consecutive patients seen within a clinical practice, as opposed to a clinical trial. It has been argued that patients enrolled in clinical trials may not be representative of patients seen in practice. The patients included in our study population may represent a more representative sample of “real world” patients referred for evaluation of known or suspected cardiovascular disease than those included in many of the randomized controlled trials that have previously evaluated aspirin use for mortality reduction. Among the patients included in the Physicians’ Health Study, 84% had no history of cardiovascular disease. Additionally, those patients and those evaluated in other primary prevention trials had low rates of cardiovascular risk factors. The studies evaluating aspirin use by patients with unstable angina also enrolled comparatively few patients with multiple cardiac risk factors or positive histories of previous coronary intervention. Thus, the lower-risk population enrolled in the previous randomized trials may have contributed to their finding no mortality benefit. Furthermore, in a follow-up report of the Physicians’ Health Study evaluating posttrial self-selected aspirin use and subsequent mortality, self-selected aspirin use was associated with multiple cardiovascular risk factors and a decrease in all-cause mortality.

The mechanisms by which aspirin may reduce mortality include its platelet-blocking effects, its anti-inflammatory properties, or other as-yet unknown actions. Aspirin has been shown to be a powerful antiplatelet agent that acts by blocking the production of thromboxane A2, which may then reduce the risk of fatal cardiovascular events. Recently, increasing interest has focused on inflammation, as assessed by C-reactive protein levels and cardiovascular risk. Aspirin has been shown to reduce C-reactive protein levels. In the randomized Physicians’ Health Study the reduction in cardiovascular risk associated with aspirin was most pronounced among men with elevated baseline C-reactive protein levels.

The major limitation of this study is that aspirin use was not based on a randomized assignment. Although the use of observational studies for assessment of treatment effects is controversial, recent work has suggested that observational studies, when properly done, are not likely to produce misleading or biased results.

Figure 1. Kaplan-Meier Curve Relating Aspirin Use to Time to Death Among Propensity-Matched Patients

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Figure 2. Predicted Absolute Reduction in 5-Year Mortality by Age, Exercise Capacity, and History of CAD

Estimates are based on wholly parametric multivariable patient-specific survival equations. For each patient, equations were solved twice, once assuming aspirin use and once assuming nonuse. Dashed lines represent 95% confidence intervals. Methods used to derive these curves are explained in the “Methods” section and elsewhere.13 CAD indicates coronary artery disease. Physically unfit is defined as fair or poor functional capacity for age and sex.13

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