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

A Propensity Analysis

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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.

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ASPIRIN HAS BEEN SHOWN TO be associated with decreased cardiovascular morbidity in multiple clinical trials[1,2] but the association between aspirin use and all-cause mortality has been less well defined except in the setting of acute myocardial infarction.[3] Although a few observational analyses have suggested a longer-term survival benefit,[4-6] 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.[7]

For editorial comment see p 1228.

METHODS

Patients

The study sample was derived from 9954 consecutive adult patients undergoing stress echocardiography at the Cleveland Clinic Foundation between 1990

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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.[8] 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.[9]

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.[10] 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.[11]

Stress Testing

Symptom-limited exercise testing was performed according to Bruce, modified Bruce, or Cornell protocols as previously described.[12] 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.[13] 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.[14] Heart rate recovery was defined as the difference between heart rate at peak exercise and 1 minute thereafter.[15]

Stress Echocardiography

Details of the echocardiographic techniques used in our laboratory have been described in detail elsewhere.[8] 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 akinesis or dyskinesis 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.[16] We used the Social Security Death Index, which has been shown to be highly specific (>99.5%) and unbiased.[17,18] We have reported elsewhere on the high sensitivity (approximately 97%) of this index among Cleveland Clinic stress laboratory patients.[9] Follow-up was for a median of 3.1 years.

Statistical Analyses

Differences between aspirin users and nonusers were compared using χ^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[19] with consideration of clinically plausible interactions. The proportional hazards assumption was con-

firmed by inspection of log (–log [survival]) curves and by examination of time-dependent covariates. Survival curves were constructed using Kaplan-Meier estimates[20] with comparisons between curves based on the log-rank χ^2 statistic.

Because aspirin use was not randomly assigned in this patient population, potential confounding and selection biases were accounted for by developing a propensity score for aspirin use. The rationale and methods underlying the use of a propensity score for a proposed causal exposure variable have been previously described.[7] The propensity for aspirin use was determined without regard to outcome, using multivariable logistic regression analysis.[21] A full nonparsimonious model was developed that included 34 covariates, some of which are listed in TABLE 1. This model yielded a *c* statistic 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 propensity 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 exceeded, 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 characteristics predicted maximum absolute benefit from aspirin, we derived multivariable nonproportional hazard equations for each individual patient's predicted 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 potential benefits of bilateral mammary artery grafting.[23] The logarithm of the difference in predicted survivals with and without aspirin was then treated as the dependent variable for a linear regression analysis that sought to identify those patient characteristics most strongly associated with a large beneficial difference in predicted mortality. Appropriate regression diagnostics, including examination of residuals and testing for outliers, excessively influential observations, and multicollinearity, were performed to confirm the validity of these analyses.

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

Table 1. Baseline and Exercise Characteristics According to Aspirin Use*

Variable	Aspirin (n = 2310)	No Aspirin (n = 3864)	*P* Value
Demographics			
Age, mean (SD), y	62 (11)	56 (12)	<.001
Men, No. (%)	1779 (77)	2167 (56)	<.001
Clinical history			
Diabetes, No. (%)	388 (17)	432 (11)	<.001
Hypertension, No. (%)	1224 (53)	1569 (41)	<.001
Tobacco use, No. (%)	234 (10)	500 (13)	.001
Prior coronary artery disease, No. (%)	1609 (70)	778 (20)	<.001
Prior coronary artery bypass graft, No. (%)	689 (30)	240 (6)	<.001
Prior percutaneous coronary intervention, No. (%)	667 (29)	148 (4)	<.001
Prior Q-wave MI, No. (%)	369 (16)	285 (7)	<.001
Atrial fibrillation, No. (%)	27 (1)	55 (1)	.04
Congestive heart failure, No. (%)	127 (6)	178 (5)	.12
Medication use			
Digoxin use, No. (%)	171 (7)	216 (6)	.004
β-Blocker use, No. (%)	811 (35)	550 (14)	<.001
Diltiazem/verapamil use, No. (%)	452 (20)	405 (10)	<.001
Nifedipine use, No. (%)	261 (11)	283 (7)	<.001
Lipid-lowering therapy, No. (%)	775 (34)	380 (10)	<.001
ACE inhibitor use, No. (%)	349 (15)	441 (11)	<.001
Cardiovascular assessment and exercise capacity			
Body mass index, mean (SD), kg/m^2	29 (5)	30 (7)	<.001
Ejection fraction, mean (SD), %	50 (9)	53 (7)	<.001
Resting heart rate, mean (SD), beats/min	74 (13)	79 (14)	<.001
Resting blood pressure, mean (SD), mm Hg			
Systolic	141 (21)	138 (20)	<.001
Diastolic	85 (11)	86 (11)	.04
Purpose of test to evaluate chest pain, No. (%)	300 (13)	468 (12)	.31
Mayo Risk Index ≥1, No. (%)†	2021 (87)	2517 (65)	<.001
Peak exercise capacity, mean (SD), METs			
Men	8.6 (2.4)	9.1 (2.6)	<.001
Women	6.6 (2.0)	7.3 (2.1)	<.001
Heart rate recovery, mean (SD), beats/min	28 (11)	30 (12)	<.001
Ischemic ECG changes with stress, No. (%)	430 (24)	457 (14)	<.001
Echocardiographic left ventricular ejection fraction ≤40%, No. (%)	321 (14)	226 (6)	<.001
Stress-induced ischemia on echocardiography, No. (%)	495 (21)	436 (11)	<.001
Fair or poor physical fitness for age and sex,[13] No. (%)	714 (31)	1248 (38)	.26

*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.

Table 2. Cox Proportional Hazards Analyses of Time to Death Among Patients Using Aspirin (N = 6174)*

Model	Hazard Ratio (95% CI)	*P* Value
Unadjusted	1.08 (0.85-1.39)	.50
Adjusted for age and sex	0.75 (0.58-0.96)	.02
Adjusted for age, sex, and history of CAD	0.57 (0.44-0.74)	<.001
Multivariable adjusted†	0.67 (0.51-0.87)	.002
Adjusted for age and sex among prespecified strata		
Normal LV function	0.75 (0.56-1.01)	.06
Abnormal LV function	0.54 (0.34-0.84)	.006
No history of prior CABG surgery	0.74 (0.54-1.08)	.06
History of prior CABG surgery	0.56 (0.35-0.89)	.01

*CI indicates confidence interval; CAD, coronary artery disease; LV, left ventricular; and CABG, coronary artery bypass graft.

†Adjusted for age, sex, body mass index, resting heart rate, resting systolic blood pressure, use of antihypertensive medications, digoxin, β-blockers, lipid-lowering therapy, nitrates, angiotensin-converting enzyme inhibitors, dihydropyridine and nondihydropyridine calcium channel blockers, congestive heart failure, smoking, atrial fibrillation, left and right bundle-branch block, pathologic Q waves, prior CABG surgery, prior percutaneous coronary intervention, chronic lung disease, peripheral vascular disease, exercise capacity, chronotropic response, heart rate recovery, left ventricular ejection fraction, echocardiographic evidence of myocardial ischemia, and failure of the left ventricle to decrease in size with exercise.

performed using PROC HAZARD and PROC HAZPRED (available at: http://www.clevelandclinic.org/heartcenter/hazard).

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 bivariable 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 bivariable 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.[24] 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

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

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

*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.

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

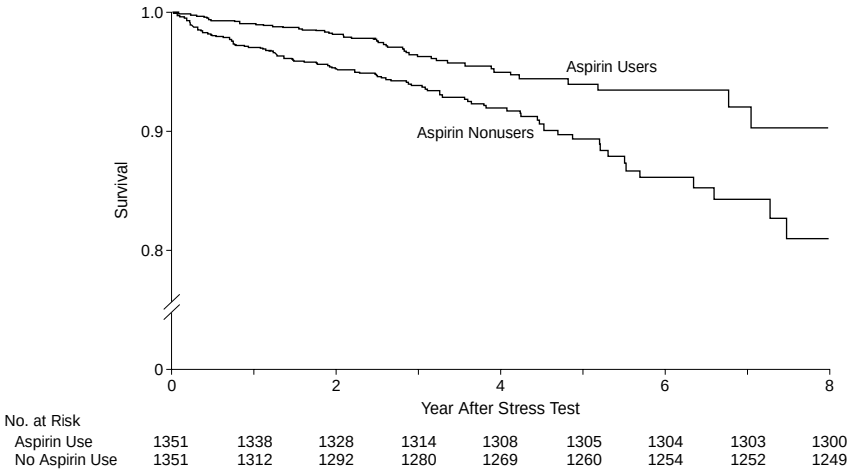


Table 4. Cox Proportional Hazards Analyses of Aspirin Use and Mortality Among Propensity-Matched Patients (n = 2702)*

Model	Hazard Ratio (95% CI)	*P* Value
Unadjusted	0.53 (0.38-0.74)	.002
Adjusted for propensity	0.53 (0.38-0.74)	<.001
Adjusted for propensity and selected variables†	0.59 (0.42-0.83)	.002
Adjusted for propensity and all covariates‡	0.56 (0.40-0.78)	<.001

*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 (†).

history,[1,25-27] patients with chronic stable angina,[28,29] patients presenting with AMI,[3,6] and patients with unstable angina.[30-33] Randomized trial evidence demonstrates that aspirin reduces all-cause mortality among patients with AMI.[3] It is less clear if aspirin use reduces long-term all-cause mortality in stable patient populations. Two recent observational analyses of patients enrolled in the Bezafibrate Infarction Prevention Trial demonstrated reduced mortality rates among patients taking aspirin, irrespective of the presence or absence of diabetes or therapy with ACE inhibitors.[4,5] Furthermore, the Collaborative Group of the Primary Prevention Project recently demonstrated in a randomized trial a similar, although not statistically significant, reduction in relative risk for all-cause mortality (0.81; 95% CI, 0.58-1.13).[34] These findings are similar to ours but did not reach statistical significance, most likely due to a small number of events.

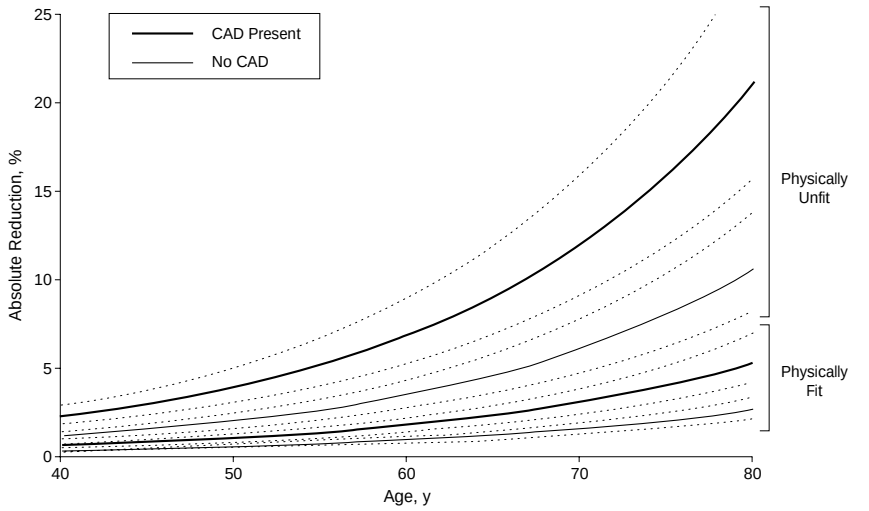
The current study extends these previous findings in several important respects. First, we demonstrated that aspirin use is associated with a reduction in long-term all-cause mortality, which is a clinically relevant, objective, and wholly unbiased end point.[16] Second, because we focused on patients 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,[4,5,26] we used propensity analysis, which has been argued to be a powerful means of accounting for baseline confounding and selection biases.[7]

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.[35] 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.[1] Additionally, those patients and those evaluated in other primary prevention trials had low rates of cardiovascular risk factors.[27,34] 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.[31,33,36] 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.[37]

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 A_2,[38] which may then reduce the risk of fatal cardiovascular events.[39,40] Recently, increasing interest has focused on inflammation, as assessed by C-reactive protein levels and cardiovascular risk.[41,42] Aspirin has been shown to reduce C-reactive protein levels.[41] 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.[43]

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,[44] recent work has suggested that observational studies, when properly done, are not likely to produce misleading or bi-

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.[23] CAD indicates coronary artery disease. Physically unfit is defined as fair or poor functional capacity for age and sex.[13]

ased results.[45-47] Furthermore, we used propensity analysis to enable an even more rigorous adjustment for selection bias and confounding than would be possible with standard multivariable analysis.[7] Nonetheless, it must be acknowledged that observational studies can only partially control for factors actually measured and can adjust for these factors only as well as the instrument used to measure them is capable. In contrast, randomization allocates both known and unknown confounding variables and avoids the introduction of bias from either the participants or their physicians. Other limitations of our study included lack of information about aspirin dose, aspirin allergy, or duration of treatment, as well as lack of data regarding medication adjustments made after stress testing.

Despite these limitations, the association between aspirin use and reduced mortality meets currently accepted criteria for likely causality.[48] The association was strong, with a greater than 30% reduction in risk of death. A temporal pattern is evident in Kaplan-Meier analyses. Biological plausibility is present, considering the known importance of increased platelet activity associated with coronary artery disease, aging,[49] and impaired physical fitness.[24] Our results are consistent with other observational non–propensity-adjusted analyses[5] and with a recent randomized study,[34] and the association appears to be largely unaffected by possible bias and confounding, whether assessed by standard multivariable analyses or more rigorous propensity analyses. Thus, our findings provide additional support for recommending the routine use of aspirin in patients with, or at risk for, cardiovascular disease—not only for preventing morbid events but also for reducing all-cause mortality.

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Acquisition of data: Thamilarasan, Watanabe, Lauer.
Analysis and interpretation of data: Gum, Blackstone, Lauer.
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Critical revision of the manuscript for important intellectual content: Gum, Thamilarasan, Watanabe, Blackstone, Lauer.
Obtained funding: Lauer; Blackstone.
Statistical expertise: Blackstone, Lauer.
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How Do Observational Studies Expand the Evidence Base for Therapy?

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THE IMPRESSIVE ADVANCES IN CARDIOVASCULAR THERAPY during the last several decades owe a great deal to randomized trials.[1] The foundation for 21st-century cardiovascular care has been laid, therapy by therapy, through the disciplined application of randomized trial methodology to important scientific insights and therapeutic uncertainties. The random assignment of patients to receive one care strategy or therapy vs another has allowed investigators to separate consistent therapeutic efficacy "signals" from the "noise" of patient variability and physician bias.

Ethical design of randomized trials obligates the investigator to enroll patients with characteristics indicating a relatively high likelihood of benefit and low likelihood of harm from participation in the trial.[1] But how far can the results obtained from the special populations enrolled in trials[2] be extrapolated to others who would not have been enrolled? Given the delicate balance between risk and benefit of therapy, should patients with too high a comorbidity burden to enroll in a trial be denied possible benefit because of uncertainty? Should low-risk patients, who are not enrolled in trials because the number of patients to study would be so large that the trial would become unfeasible, be denied the opportunity to lower their risk further? Or, on the other hand, is the risk greater than the benefit for patients with clinical characteristics outside the bounds of clinical trials enrollment criteria?

To address the applicability of randomized controlled trial results to a broader population, the effectiveness of therapies should be examined in patient cohorts heretofore unstudied. More and more, "outcomes researchers" are working to plough this intellectual field, making use of randomized trials databases,[3] clinical registries,[4] quality performance measurement databases,[5] institutional clinical databases,[6] and others, as more of the information used for medical care is gathered, stored, and reported electronically.

Just as randomized controlled trials demand rigorous and ethical study design, so do observational studies. Design considerations for observational studies include definition of the cohort with respect to appropriateness and risk of the therapy under examination, specification of an appropriate baseline time for assessment of risk and subsequent outcome, and the ability to adjust for inequalities in susceptibility to the outcome.[7] Careful investigators are mindful of the vulnerability of observational studies to bias resulting from nonrandom assignment of patients to therapy, and search for ways to express and minimize the potential for such residual confounding

In this issue of THE JOURNAL, Gum and colleagues[8] present a thoughtful analysis of a cohort of patients who underwent stress echocardiography at their institution for evaluation of known or suspected coronary artery disease, to examine the relationship between aspirin use and all-cause mortality. The authors used propensity analysis[9,10] to minimize the potential for residual confounding around aspirin use in their cohort. By interposing an analytic step akin to retrospective case-control matching, propensity analysis extends the potential for multivariate regression techniques to account for differences in baseline characteristics of patients using aspirin vs those not using aspirin. Because the assignment of aspirin vs no aspirin could not be randomized, potential therapeutic selection bias was addressed by developing a propensity score for aspirin use. Attributes important in the selection of aspirin therapy are gathered into a single composite that summarizes the likelihood for a patient with any given set of characteristics to receive aspirin. The outcomes analysis addressing the question of whether aspirin use is associated with lower mortality is then performed on a subcohort of pairs of patients, 1 patient using aspirin and 1 not, with both members of the pair having the same aspirin-use propensity score. Summarizing the likelihood of receiving aspirin in a single score results in a loss of some of the clinical texture of individual cases—patients with different characteristics may have the same score—but a gain in analytic facility.

See also p 1187.

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Use of the propensity score allows for the assessment of whether the background characteristics of the treatment and control groups overlap enough to allow a sensible estimation of treatment effect from the data set. Since effectiveness cannot be inferred by extrapolation beyond the propensity cohort, conclusions drawn from propensity analysis may not apply to the full cohort, and thus propensity-based studies may not be as useful as other risk adjustment techniques for extending the results of randomized controlled trials to certain understudied groups. Particularly for individuals at very high risk for toxicity or adverse outcome, there may not exist appropriate "propensity matched" pairs of observations.

Although propensity analysis is a powerful and helpful technique for observational studies, it is not the only way to address concerns about residual confounding. Other investigators have used the instrumental variables approach, relying on the existence of characteristics that are associated with substantial variation in treatment but that have no direct effect on the outcome of interest.[11] Cohort selection also can serve to minimize residual confounding in observational studies. In very large data sets it may be possible to select a smaller analysis cohort with the specific study hypothesis in mind, focusing the analysis on patients with characteristics that differ little, except in the characteristic under examination.[12,13] When clinician as well as patient characteristics are under consideration for their modulating effect on care and outcomes, adjustment for care for groups of patients by several clinicians using cluster analysis[14] or hierarchical linear modeling[15] can be considered. Gum et al studied patients selected to undergo stress echocardiography for known or suspected coronary artery disease at a single referral institution and the choice of propensity analysis to address confounding was appropriate for their cohort.

Can propensity analysis or other risk-adjustment techniques account for all residual confounding? Although the similarity of the subcohorts examined in the propensity analysis by Gum et al may imply this (as in Table 3 of their article), it is not possible short of true randomization to account fully for variability in characteristics of patients and physicians. Even propensity analysis cannot adjust for subtle differences among patients in the severity of various characteristics or combinations of characteristics and patient preferences that weigh in physician decisionmaking and affect patient outcome.

What then do observational studies of therapeutic interventions add to the results of randomized controlled trials? When the effect size of the intervention is large, as it is, for example, for the hazard of smoking,[16,17] observational studies suffice to support practice recommendations (in this case, to advise stopping smoking, an intervention with little "toxicity"). But when the effect size is smaller, and especially when the intervention may have risk for harm, practice recommendations based on observational studies alone must be tempered with skepticism about nonrandom patient selection. Although observational studies of hormone replacement therapy indicated potential benefit,[18] the Heart and Estrogen/progestin Replacement Study (HERS) randomized controlled trial revealed no net efficacy for hormone replacement therapy.[19,20] Observational studies can also indicate where practices shown to be efficacious in special populations may not be widely generalizable, such as heparin administration after acute myocardial infarction[21] or thrombolytic therapy for non–ST-segment-elevation acute coronary syndromes.[22]

When the results of observational studies and randomized trials are congruent in both direction and magnitude, as is true for the findings of Gum et al,[8] the case for broader therapeutic effectiveness is strengthened. Sophisticated observational studies such as that of Gum et al provide assurance that extending the results of the randomized trials of aspirin to unstudied or understudied patient groups, in this case those with suspected coronary artery disease who have impaired exercise capacity, will provide benefit rather than harm. Insightful scrutiny of patterns and outcomes of care in population-based cohorts, informed by insights from basic science research and the results of randomized clinical trials, assures physicians about risks and benefits of therapies for patients not enrolled in trials, and helps to guarantee that as many patients as possible are considered for effective therapies.

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Sarcopenia—Understanding the Dynamics of Aging Muscle

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SARCOPENIA IS NOT A DISEASE BUT RATHER REFERS SPECIFICALLY to the universal, involuntary decline in lean body mass that occurs with age, primarily due to the loss of skeletal muscle.[1] Sarcopenia has important consequences. The loss of lean body mass reduces function, and loss of approximately 40% of lean body mass is fatal.[2-5] Sarcopenia is distinct from wasting—involuntary weight loss due to inadequate intake, which is seen in starvation, advanced cancer, or acquired immunodeficiency syndrome. Sarcopenia also differs from cachexia, a cytokine-driven loss of lean body mass that occurs despite maintenance of weight, which is seen in patients with rheumatoid arthritis, congestive heart failure, or renal failure.[6] However, sarcopenia is the backdrop against which the drama of disease is played out: a body already depleted of protein because of aging is less able to withstand the protein catabolism that comes with acute illness or inadequate protein intake.[7]

Protein stores in humans have at least 2 important functions. First, unlike fat, which is truly stored in the sense that it is in reserve for times of starvation, body proteins are in use as contractile proteins in muscle, antibodies, enzymes, etc. Thus, loss of protein means loss of function. Second, during illness, nitrogen must be mobilized from muscle to provide amino acids to the immune system, liver, and other organs. If adequate nitrogen cannot be provided, either exogenously from diet or endogenously from muscle, the body's capacity to withstand an acute insult declines, and—at about 60% of baseline nitrogen throughput—the body ceases to function.[2-5] Thus, it is likely that some of the explanation for the poorer outcomes observed with nearly all diseases in older persons relates to their lower body protein stores. Muscle is the major source of protein for functions such as antibody production, wound healing, and white blood cell production during illness. If the body's protein reserves are already depleted by sarcopenia, there is less to mobilize for illness.

The determinants of sarcopenia include genetic and environmental factors,[8] with a complex series of poorly understood interactions. Amino acids and proteins are the primary substrates for skeletal muscle mass maintenance. Therefore, knowledge of amino acid kinetics and the balance between protein synthesis and protein breakdown is pivotal to understand how sarcopenia develops. Until now, most studies have indicated that muscle protein synthesis declines with age, suggesting that sarcopenia is due to failure of muscle protein synthesis.[9-11]

In this issue of THE JOURNAL, Volpi and colleagues[12] report findings from the largest reported study to date to examine basal muscle protein synthesis, as well as the first direct measures of protein breakdown and net muscle protein balance in a group of healthy older men. The three-compartment model developed by this group of investigators uses amino acids labeled with stable isotopes to examine the rates of inward and outward transport of amino acids in muscle and to determine the rates of muscle protein synthesis and breakdown and the size of the intracellular free amino acid pool. Contrary to the notion of reduced protein synthesis with age, muscle protein synthesis was slightly higher in healthy older men compared with healthy young

See also p 1206.

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