

Statin and β -Blocker Therapy and the Initial Presentation of Coronary Heart Disease

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Background: Coronary atherosclerosis develops slowly over decades but is frequently characterized clinically by sudden unstable episodes. Patients who present with unstable coronary disease, such as acute myocardial infarction, may systematically differ from patients who present with relatively stable coronary disease, such as exertional angina.

Objective: To examine whether medication use or patient characteristics influence the mode of initial clinical presentation of coronary disease.

Design: Case-control study.

Setting: Large integrated health care delivery system in northern California.

Patients: Adults whose first clinical presentation of coronary disease was either acute myocardial infarction ($n = 916$) or stable exertional angina ($n = 468$).

Measurements: Use of cardiac medications before the event from pharmacy databases and demographic, lifestyle, and clinical characteristics from self-report and clinical and administrative databases.

Results: Compared with patients with incident stable exertional angina, patients with incident acute myocardial infarction were

more likely to be men, smokers, physically inactive, and hypertensive but were less likely to have a parental history of coronary disease. Patients presenting with myocardial infarction were much less likely to have received statins (19.3% vs. 40.4%; $P < 0.001$) and β -blockers (19.0% vs. 47.7%; $P < 0.001$) than patients presenting with exertional angina. After adjustment for potential confounders, recent use of statins (adjusted odds ratio, 0.45 [95% CI, 0.32 to 0.62]) and β -blockers (adjusted odds ratio, 0.26 [CI, 0.19 to 0.35]) was associated with lower likelihoods of presenting with an acute myocardial infarction than with stable angina.

Limitations: This observational study did not have information on all possible confounding factors, including use of aspirin therapy.

Conclusion: Statin and β -blocker use was associated with lower odds of presenting with an acute myocardial infarction than with stable angina. Additional studies are needed to confirm that these therapies protect against unstable, higher-risk clinical presentations of coronary disease.

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Acute myocardial infarction is believed to result from the acute rupture of a lipid-laden coronary atherosclerotic plaque, which in turn leads to acute thrombosis, cardiac ischemia, and subsequent myocardial necrosis (1). While many epidemiologic risk factors have been established to predict the development of any clinical manifestation of coronary heart disease (that is, acute myocardial infarction, unstable angina, or angina pectoris), most studies have not attempted to differentiate between unstable presentations, such as acute coronary syndromes, and more stable presentations of coronary disease, such as exertional angina. Thus, predictors of the development of plaque rupture and acute coronary events have not been well delineated. Previous studies have identified relatively few risk factors for acute myocardial infarction in patients with underlying coronary atherosclerosis. Among patients hospitalized with an acute coronary syndrome, those with acute myocardial infarction were less likely to have been taking aspirin before admission than those with unstable angina (2). Other clinical predictors of having an acute myocardial infarction compared with unstable angina included current smoking and absence of a previous diagnosis of hypertension (3).

In several randomized, placebo-controlled trials, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

(statins) have substantially reduced the incidence of clinical coronary disease in both primary and secondary prevention populations (4, 5). In addition to their beneficial effects on cholesterol levels, statins may have important non-lipid-related effects, including reduction in inflammation (6, 7), alteration of plaque composition and stabilization of atherosclerotic plaques (8), and improvement in endothelial dysfunction (9, 10). β -Adrenergic receptor antagonists (β -blockers) have also been shown to reduce incident and recurrent major cardiovascular events compared with placebo (11–13). The favorable effects of β -blockers may be due to reduced myocardial oxygen demand as a result of lower systemic blood pressure and heart rate (14, 15), im-

See also:

Print

Editors' Notes	230
Editorial comment	296
Summary for Patients	I-22

Web-Only

CME quiz	
Conversion of figure and tables into slides	

Context

We know little about factors that are associated with initial clinical presentations of coronary disease.

Contribution

This large case-control study compared characteristics of patients whose first clinical presentation of coronary disease was either acute myocardial infarction or stable exertional angina. Patients presenting with myocardial infarction rather than stable angina had received statins and β -blockers less often; were more often men, smokers, and physically inactive; and more often had hypertension and diabetes.

Cautions

The study was observational and could not prove cause and effect.

Implications

Several factors, including statin and β -blocker therapy, might protect against higher-risk presentations of coronary disease.

—The Editors

proved endothelial function (16), and effects on atherosclerotic burden (17, 18). On the other hand, results have been somewhat mixed for the efficacy of angiotensin-converting enzyme (ACE) inhibitors (19–21), angiotensin-II-receptor blockers (22–24), calcium-channel blockers (25, 26), and diuretics (21), depending on the study sample and the comparison treatment or placebo group. However, whether use of any of these pharmacologic agents is associated with the mode of clinical presentation of coronary disease (that is, acute coronary syndrome vs. stable coronary disease) is not known. If possible, shifting the mode of initial presentations of coronary disease from acute myocardial infarction to stable angina may reduce overall patient risk and permit intervention before irreversible complications occur.

To address this question, we examined whether recent use of selected cardiovascular medications or patient characteristics were associated with the mode of initial clinical presentation in patients who developed initial symptoms of coronary disease in a large community sample of patients. We compared patients who developed an initial acute myocardial infarction with patients who developed stable exertional angina, since these syndromes are clinically distinct on the spectrum of unstable to stable symptoms of coronary atherosclerosis. We hypothesized that the recent use of statins, β -blockers, and ACE inhibitors would be associated with a lower likelihood of presenting with an acute myocardial infarction as the first sign of clinical coronary disease.

METHODS**Study Sample**

The study sample included adults who were enrolled in Kaiser Permanente of Northern California, a large integrated health care delivery system providing comprehensive care to more than 35% of insured adults in the greater San Francisco Bay area. The Kaiser Permanente membership is representative of the local surrounding and statewide insured adult population, with the exception of slightly lower proportions of persons at the extremes of age and income distribution (27). We identified all Kaiser Permanente members who first presented with symptoms of coronary disease between 28 October 2001 and 31 December 2003. Institutional review boards of the collaborating institutions approved the study.

Cases of Incident Acute Myocardial Infarction

We included men between 45 and 75 years of age and women between 55 and 75 years of age who presented with an acute myocardial infarction and who had no history of coronary disease. We searched automated laboratory and hospital discharge databases weekly to identify hospitalized patients with a serum troponin I level of 4.0 $\mu\text{g/L}$ or greater or a combination of an elevated creatine kinase-MB level of 5.6 $\mu\text{g/L}$ or greater and creatine kinase-MB index of 0.033 or greater, as well as a primary discharge diagnosis of myocardial infarction (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 410). We excluded patients who met any of the following criteria: evidence of previously diagnosed coronary disease in hospital discharge or ambulatory visit databases, previous prescriptions for nitroglycerin in the pharmacy database, previous hospitalizations with elevated serum troponin I levels, receipt of maintenance dialysis, previous organ or bone marrow transplantation, lack of a primary care provider, death before study contact, or serious cognitive impairment or uncontrolled psychiatric condition as assessed by the patient's primary provider. Primary physicians of potential participants confirmed the occurrence of an acute myocardial infarction and approved patient contact. We then screened patients by a telephone interview to confirm the absence of previously diagnosed coronary disease, coronary revascularization, or ischemic symptoms more than 14 days before admission for acute myocardial infarction, as well as any exclusion criteria that health plan databases did not identify. We also searched for previous silent myocardial infarction in the 52% of patients who had available previous electrocardiograms and excluded 2 patients with evidence of a pathologic Q wave (28). The index date for enrolled participants was the date of admission for the index hospitalization.

Cases of Incident Stable Exertional Angina

We identified men and women between 18 and 75 years of age without a history of coronary disease who presented with stable exertional angina between 28 Octo-

ber 2001 and 31 December 2003. We performed weekly searches of automated ambulatory visit databases for new diagnoses of angina pectoris (ICD-9-CM code 413.x) and applied the same exclusion criteria as described previously, except that we also excluded patients who received a prescription for nitroglycerin more than 6 months before the index date. Primary physicians of potential participants confirmed the occurrence of exertional angina and approved patient contact. We then screened patients by a telephone interview to confirm the absence of previously diagnosed coronary disease, coronary revascularization, and any exclusion criteria that the health plan database did not identify. In addition, patients had to report a history of stable chest pain or chest pressure that 1) was reproduced by the same level of physical exertion, 2) lasted more than 1 minute and less than 15 minutes, and 3) responded to rest or nitroglycerin (29). Patients could have had qualifying symptoms for no more than 6 months before the outpatient angina diagnosis and could not have reported these symptoms to a health care provider before their index date. We also searched for evidence of previous silent myocardial infarction in the 81.3% of patients with angina with available electrocardiograms and excluded 5 patients with pathologic Q waves (28). We considered the index date to be the date of the first outpatient clinic visit for angina pectoris in confirmed cases.

Cases of Incident Fatal Coronary Heart Disease

In our sensitivity analysis, we also used electronic databases to identify patients who had either fatal myocardial infarction or sudden cardiac death as their initial presentation of coronary disease. We ascertained potential fatal myocardial infarction events by using 1) primary discharge diagnoses of acute myocardial infarction (ICD-9-CM codes 410.x) and a discharge status of death found in health plan hospitalization and billing claims databases or 2) outpatient deaths found in state death registry files that were assigned a group cause of 165 (ICD-10 codes I21 and I22). We identified potential sudden death events from 1) inpatient deaths with a primary discharge diagnosis of cardiac arrest (ICD-9-CM code 427.5) found in health plan hospitalization and billing claims databases or 2) outpatient deaths found in state death registry files that were assigned a group cause of 177. After excluding nonmembers, patients with previously diagnosed coronary disease, and those having less than 5 months of pharmacy benefit before the fatal event, we identified 2758 patients with possible incident fatal coronary disease.

Medication Exposure

To examine the association between previous recent medication use and mode of clinical presentation of coronary disease, we used automated health plan pharmacy databases to identify receipt of selected cardiac medications during the 160 days before the index date. We chose this time period to identify medications prescribed for chronic conditions, which are generally given as a 90- to 100-day

supply. The medications of interest included statins, niacin or nicotinic acid derivatives, fibrates, bile acid-binding resins, β -blockers, calcium-channel blockers, α -blockers, ACE inhibitors, angiotensin-II-receptor blockers, diuretics, and hormone replacement therapy (estrogen with or without progestins).

Covariates

All enrolled patients completed a baseline questionnaire, underwent a brief physical examination, and had blood drawn for research studies. We based age at index date on self-report and confirmed it in health plan databases. We obtained data on sex, race or ethnicity, and marital status by self-report. We also obtained data on parental and sibling history of coronary heart disease, smoking status at the index date (current, former, or never), and alcohol consumption and leisure-time activity during the 12 months before the study visit date by self-report. We ascertained personal medical history of previous ischemic stroke, peripheral arterial disease, and other relevant comorbid conditions (that is, hypertension, diabetes mellitus, chronic lung disease, cirrhosis, dementia, depression, and systemic malignant condition) by self-report and from health plan hospital discharge, billing claims, and ambulatory visit databases using relevant ICD-9-CM codes (30), a health plan longitudinal diabetes registry (31), and a regional cancer registry (32). We defined previous chronic heart failure as a previous hospitalization with a primary discharge diagnosis of heart failure using ICD-9-CM codes (33). We obtained the most recent categories of outpatient systolic blood pressure (≤ 120 mm Hg, 121 to 129 mm Hg, 130 to 139 mm Hg, 140 to 159 mm Hg, 160 to 179 mm Hg, and ≥ 180 mm Hg) and diastolic blood pressure (≤ 80 mm Hg, 81 to 84 mm Hg, 85 to 89 mm Hg, 90 to 99 mm Hg, 100 to 109 mm Hg, and ≥ 110 mm Hg) before the index date from ambulatory visit databases; these variables have been shown to reliably reflect chronic blood pressure levels (34). We also determined the number of days between the last previous blood pressure measurement and the index date. To account for potential differences in intensity of overall clinical care, we also ascertained the number of medical outpatient visits during the 12 and 24 months before the index date from administrative databases and the number of filled medication prescriptions in the outpatient pharmacy database during the 160 days before the index date. We measured body mass index at the study visit by using standard procedures and categorized it as less than 25 kg/m², 25 to 29 kg/m², and 30 kg/m² or more.

Laboratory Measurements

We searched health plan laboratory databases for evidence of testing for total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels before the index date. Kaiser Permanente laboratories routinely calculated low-density lipoprotein cholesterol values by using the Friedewald equation (35).

We obtained the value for each lipoprotein component that most recently preceded the index event date.

Statistical Analysis

We performed all analyses by using SAS statistical software, version 9.0 (SAS Institute, Cary, North Carolina). We considered a 2-sided P value less than 0.05 to be statistically significant. We compared differences between patients with different modes of presentation of coronary disease by using the Student t -test or the Wilcoxon rank-sum test for continuous variables and the chi-square or Fisher exact test for categorical variables. We also examined symptom duration among treated and untreated patients with angina by using a t -test. We conducted all multivariable analyses among the subset of patients with evidence of a pharmacy drug benefit on their index date. Overall, 96.1% of patients with myocardial infarction and 96.4% of patients with exertional angina had a pharmacy drug benefit as of their index date ($P = 0.80$). We used logistic regression to identify multivariable predictors of presenting with acute myocardial infarction versus stable exertional angina. The final model included all medication classes, demographic characteristics (age, sex, and race or ethnicity), variables previously known to be associated with myocardial infarction, coexisting illnesses, number of outpatient medical visits during the previous 24 months, number of prescribed medications during the previous 160 days, and any variable that differed between groups on bivariate analyses at a P value less than 0.100. We assessed model fit by using the Hosmer–Lemeshow goodness-of-fit method (36). We also examined and found no clinically relevant interactions between medication use and sex or age, so results for only the main models are presented.

Role of the Funding Source

The Donald W. Reynolds Foundation, Las Vegas, Nevada, provided funding for our study. The authors were completely responsible for all aspects of the study design, study conduct, and reporting of results. Dr. Go had full access and control of all study data.

RESULTS

Baseline Characteristics

We prospectively enrolled 916 adults with incident acute myocardial infarction and 468 adults with incident stable exertional angina (Table 1). Mean age group or distribution of race or ethnic group did not statistically significantly differ, but fewer women presented with an acute myocardial infarction. Patients presenting with acute myocardial infarction were more likely than those with angina to be current or former cigarette smokers and to report minimal or light previous physical leisure-time activity, but they did not differ with regard to previous alcohol use. Patients with acute myocardial infarction were more likely than those with angina to have a previous diagnosis of hypertension, but other coexisting illnesses did not statis-

tically significantly differ. Patients with acute myocardial infarction were less likely than those with angina to report a parental or sibling history of coronary heart disease (Table 1). In addition, during the 12 months before the index date, the number of outpatient medical visits did not differ between patients with incident acute myocardial infarction (median, 3 visits [interquartile range, 1 visit to 5 visits]) and those with stable exertional angina (median, 3 visits [interquartile range, 2 visits to 5 visits]). During the 24 months before the index date, the number of outpatient medical visits did not differ between patients with acute myocardial infarction (median, 5 visits [interquartile range, 2 visits to 9 visits]) and those with stable exertional angina (median, 5 visits [interquartile range, 3 visits to 9 visits]).

Medication Use and Coronary Disease Presentation

Use of statin therapy before the onset of symptoms was substantially lower among patients presenting with acute myocardial infarction than among those with stable exertional angina (19.3% vs. 40.4%; $P < 0.001$). All patients receiving statins had either a self-reported or physician-assigned clinical diagnosis of dyslipidemia. Use of other lipid-lowering agents was uncommon and did not differ between groups (Table 1). Most patients who were not receiving statins on the index date were not considered eligible for lipid-lowering therapy on the basis of the National Cholesterol Education Program Adult Treatment Panel III guidelines (5): 62.1% of patients with acute myocardial infarction and 65.6% of patients with angina ($P = 0.167$). Among the 2758 patients who had a potential incident fatal myocardial infarction or sudden cardiac death that was identified from databases, only 14.0% had received statins within 160 days before the event, which was lower than the rates among enrolled patients with acute myocardial infarction ($P < 0.001$) and those with stable angina ($P < 0.001$).

Use of β -blockers before the onset of symptoms was also substantially lower among patients presenting with acute myocardial infarction than among those with stable exertional angina (19.0% vs. 47.7%; $P < 0.001$). Among patients receiving β -blockers, 90.4% had a previous diagnosis of hypertension and 2.0% had a previous diagnosis of chronic heart failure. Previous calcium-channel blocker use was slightly higher among patients with acute myocardial infarction, whereas previous use of diuretics was slightly lower (Table 1). Use of α -blockers, ACE inhibitors, or angiotensin-II-receptor blockers and, among women, hormone replacement therapy did not significantly differ between the groups. In the 2758 patients who had a potential incident fatal myocardial infarction or sudden cardiac death, previous receipt of β -blockers (21.9%) was similar to that of enrolled patients with acute myocardial infarction ($P = 0.062$) but was lower than that of those with stable angina ($P < 0.001$). However, previous calcium-channel blocker use (16.9%) was higher among patients with myocardial infarction ($P = 0.009$) and stable angina

Table 1. Baseline Characteristics of 916 Adults with Acute Myocardial Infarction and 468 Adults with Stable Exertional Angina as the First Presentation of Clinical Coronary Heart Disease from October 2001 through December 2003*

Characteristic	Patients with Acute MI (n = 916)	Patients with Stable Exertional Angina (n = 468)	P Value
Mean (SD) age, y	61.6 (8.4)	60.8 (8.5)	0.24
Women, %	23.2	33.8	<0.001
Race or ethnicity, %			0.89
White European or Middle Eastern	69.0	69.2	
African American	4.0	3.2	
Hispanic or Latino	9.5	10.7	
South Asian	2.1	1.3	
Asian or Pacific Islander	5.5	5.1	
Native American	0.2	0.0	
Multiethnic (not Hispanic)	9.4	10.3	
Marital status, %			0.55
Married or with domestic partner	72.1	75.7	
Divorced or separated	14.9	13.3	
Widowed	7.6	6.2	
Never married	5.4	4.7	
Cigarette smoking, %			0.025
Current	9.7	7.3	
Former	55.3	50.6	
Never	35.0	42.1	
Alcohol use in previous 12 mo, %	68.2	73.1	0.063
Leisure-time activity in past 12 mo, %			0.005
Minimal	32.9	30.0	
Light	21.0	13.3	
Moderate	32.6	39.7	
Heavy	13.6	17.0	
Medical history, %			
Chronic heart failure	1.5	0.4	0.070
Stroke or TIA	9.4	10.0	0.70
Peripheral arterial disease	9.8	9.0	0.61
Diabetes mellitus	26.1	23.1	0.22
Diagnosed hypertension	82.1	76.5	0.010
Chronic lung disease	24.2	27.8	0.151
Cirrhosis of the liver	0.1	0.2	1.0
Systemic malignant condition	9.7	8.1	0.33
Known dementia	0.7	0.4	0.72
Known depression	20.4	21.4	0.68
Parental history of coronary disease, %	47.2	58.6	<0.001
Sibling history of coronary disease, %	20.4	26.5	0.010
Medications received within 160 d before event, %			
Statin	19.3	40.4	<0.001
Niacin	0.8	0.6	1.0
Cholestyramine	0.3	0.6	0.41
Colestipol	0.1	0.4	0.27
Colesevelam	0.0	0.2	0.34
Gemfibrozil	1.4	2.4	0.28
Fenofibrate	0.1	0.6	0.081
β -Blockers	19.0	47.7	<0.001
Calcium-channel blocker	13.3	9.8	0.060
α -Blocker	2.0	1.3	0.51
ACE inhibitor	20.6	24.6	0.094
ARB	2.8	3.4	0.62
Diuretic	18.9	23.3	0.054
Hormone replacement therapy	33.0†	36.1‡	0.54

* ACE = angiotensin-converting enzyme; ARB = angiotensin-II-receptor blocker; MI = myocardial infarction; TIA = transient ischemic attack.

†n = 212 women.

‡n = 158 women.

Table 2. Blood Pressure, Body Mass Index, and Cholesterol Levels before the Index Event among Patients Presenting with Acute Myocardial Infarction or Stable Exertional Angina*

Characteristic	Patients with Acute MI (n = 916)	Patients with Stable Exertional Angina (n = 468)	P Value
Systolic BP, %†			
≤120 mm Hg	17.0	23.0	0.050
121–129 mm Hg	12.6	15.7	
130–139 mm Hg	28.9	24.4	
140–159 mm Hg	30.5	26.1	
160–179 mm Hg	8.7	8.9	
≥180 mm Hg	2.3	1.9	
Diastolic BP, %‡			
≤80 mm Hg	55.2	67.3	<0.001
81–84 mm Hg	17.3	10.1	
85–89 mm Hg	11.0	8.2	
90–99 mm Hg	12.4	11.2	
100–109 mm Hg	3.5	1.2	
≥110 mm Hg	0.6	2.1	
Mean (SD) BMI, kg/m²	29.2 (5.4)	29.1 (4.9)	0.71
BMI, %			
<25 kg/m ²	20.4	19.3	0.90
25–29 kg/m ²	43.0	43.8	
≥30 kg/m ²	36.7	36.9	
Mean (SD) total cholesterol level			
Patients tested, %	90.1	94.9	0.002
mmol/L	5.76 (1.03)	5.65 (1.07)	0.068
mg/dL	222.4 (39.9)	218.3 (41.4)	0.068
Mean (SD) LDL cholesterol level			
Patients tested, %	76.7	88.0	<0.001
mmol/L	3.57 (0.90)	3.42 (0.91)	0.010
mg/dL	137.8 (34.8)	132.2 (35.2)	0.010
Mean (SD) HDL cholesterol level			
Patients tested, %	85.8	93.4	<0.001
mmol/L	1.17 (0.32)	1.23 (0.34)	0.004
mg/dL	45.1 (12.5)	47.3 (13.2)	0.004
Mean (SD) triglyceride level			
Patients tested, %	77.3	88.7	<0.001
mmol/L	2.20 (1.29)	2.26 (1.49)	0.49
mg/dL	194.6 (114.6)	199.7 (132.1)	0.49

* BMI = body mass index; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction.

† At most recent outpatient visit before index date for 781 patients with acute MI and 426 patients with stable exertional angina.

‡ At most recent outpatient visit before index date for 782 patients with acute MI and 428 patients with stable exertional angina.

($P < 0.001$). Previous ACE inhibitor use (25.8%) was higher in enrolled patients with acute myocardial infarction ($P = 0.004$) but was similar to those with stable angina, while previous receipt of diuretics was higher (33.4%) than that in both enrolled groups ($P < 0.001$ for both). The other selected medications had no other material differences.

Duration of symptoms did not significantly differ between patients with angina who were treated and those who were not treated with statins ($P = 0.97$) or β -blockers ($P = 0.171$). Furthermore, among treated patients, duration of treatment with statins ($P = 0.33$) or β -blockers ($P = 0.91$) did not significantly differ between patients with myocardial infarction and patients with angina.

Overall, the median number of prescribed unique

medications was lower in patients who presented with acute myocardial infarction than in those who presented with stable exertional angina (3 medications vs. 5 medications; $P < 0.001$).

Clinical Predictors of Coronary Disease Presentation

Patients who presented with acute myocardial infarction were more likely to have had higher levels of diastolic blood pressure at previous outpatient visits than patients presenting with stable exertional angina (Table 2). Patients with acute myocardial infarction were also more likely to have a longer time since their last blood pressure measurement (median, 96 days [interquartile range, 29 days to 221 days]) than patients presenting with angina (median, 37 days [interquartile range, 14 days to 118.5 days]; $P <$

0.001). Mean body mass index was elevated to a similar degree in both groups (Table 2), and the number of clinical cardiovascular risk factors was similar in both groups ($P = 0.20$).

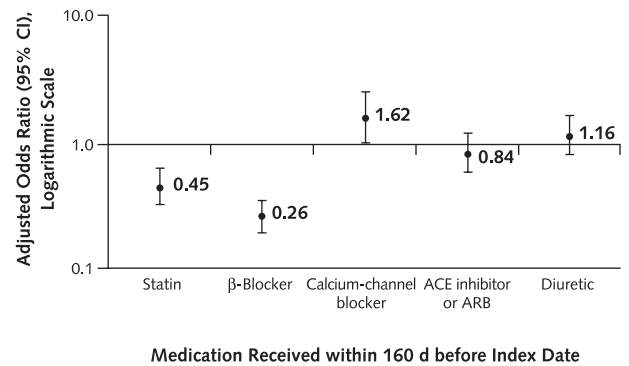
Testing for lipoprotein levels before the index date was slightly more common among patients presenting with stable exertional angina (Table 2). Among tested patients, mean low-density lipoprotein cholesterol level was 0.14 mmol/L (5.3 mg/dL) lower and mean high-density lipoprotein cholesterol level was 0.05 mmol/L (2.1 mg/dL) higher in patients with stable angina than in patients with acute myocardial infarction, whereas mean total cholesterol or triglyceride levels did not differ statistically. Among patients who were not receiving lipid-lowering therapy at the index date but who had available previous lipoprotein data, mean high-density lipoprotein cholesterol level was 0.10 mmol/L (4.0 mg/dL) higher in patients with stable exertional angina than in those with acute myocardial infarction, but total cholesterol, low-density lipoprotein cholesterol, or triglyceride levels did not statistically significantly differ between groups (data not shown).

Multivariable Association of Recent Medication Use and Coronary Disease Presentation

We evaluated the association between receipt of targeted therapies and the likelihood of presenting with acute myocardial infarction compared with stable exertional angina by using multivariable logistic regression. Statin or β -blocker use was associated with substantially lower odds of presenting with acute myocardial infarction versus stable exertional angina even after adjustment for sociodemographic characteristics, lifestyle habits, cardiovascular risk factor status, family history of coronary disease, coexisting illnesses, body mass index, number of outpatient medical visits in the previous 12 months, number of prescription medications within the 160 days before the index date, and other medication use (Figure). After adjustment for potential confounders, recent use of calcium-channel blockers was associated with a higher likelihood of incident acute myocardial infarction (adjusted odds ratio, 1.62 [95% CI, 1.01 to 2.59]). The associations between recent use of ACE inhibitors, angiotensin-II-receptor blockers, or diuretics and the mode of coronary disease presentation were not statistically significant (Figure).

Clinical predictors in the multivariable model that were associated with a higher likelihood of presenting with acute myocardial infarction were previous diagnosed hypertension (adjusted odds ratio, 1.92 [CI, 1.35 to 2.73]), previous diabetes mellitus (odds ratio, 1.69 [CI, 1.15 to 2.49]), current cigarette smoking (odds ratio, 1.72 [CI, 0.99 to 2.97]) or former cigarette smoking (odds ratio, 1.35 [CI, 1.01 to 1.79]), and male sex (odds ratio, 1.89 [CI, 1.37 to 2.56]). No evidence suggested poor fit of the final model ($P = 0.100$ for the Hosmer–Lemeshow test).

Figure. Multivariable associations between recent medication use and odds of presenting with acute myocardial infarction compared with stable exertional angina among patients with clinical coronary disease.



Variables in the final model included all listed medication classes, age, sex, race or ethnicity, parental history of coronary heart disease, smoking status, previous alcohol use, physical activity, previous stroke, previous peripheral arterial disease, previous hospitalization for heart failure, diabetes mellitus, previous hypertension, systemic malignant condition, diagnosed dementia, diagnosed depression, cirrhosis, chronic lung disease, body mass index, number of outpatient medical visits in the previous 12 months, and number of prescription medications within the 160 days before the index date. Error bars represent 95% CIs. ACE = angiotensin-converting enzyme; ARB = angiotensin-II-receptor blocker.

DISCUSSION

The natural history of coronary atherosclerosis is characterized by long periods of clinical stability punctuated by episodes of unstable, acute ischemic symptoms that are associated with atherosclerotic plaque rupture and thrombosis. Much of the risk for coronary disease is the consequence of these episodes of clinical instability, particularly at the point when the first symptoms of the disease develop. Systematic differences among patients may affect patients' vulnerability to acute ischemic episodes and may allow identification of higher-risk patients who may benefit from more aggressive primary prevention measures. Treatments that reduce the risk for unstable episodes of acute ischemia in patients with underlying coronary atherosclerosis might prevent the most serious complications of the disease.

We conducted our study to identify predictors of developing an acute myocardial infarction as the initial clinical presentation of coronary disease. We chose patients who presented with stable exertional angina as a comparison group to isolate risk factors for clinical instability rather than risk factors for underlying coronary atherosclerosis itself. Our results suggest that systematic differences do exist between patients who develop unstable, higher-risk symptoms and patients who develop stable, lower-risk symptoms of coronary disease. The most striking differences between these groups were the markedly lower previous use of statins and β -blockers in the patients who presented with an acute myocardial infarction as their ini-

tial presentation of coronary disease. These results suggest that statins and β -blockers may act to stabilize the underlying coronary plaque and reduce patient vulnerability to acute ischemic events.

The association between use of statins and β -blockers and the mode of initial presentation of coronary disease that we observed cannot be readily explained by measured confounding factors. All patients had access to comprehensive medical care and had a drug benefit, with prescription medications received through health plan pharmacies. In addition, frequency of ambulatory care during the 24 months before the incident coronary diagnosis was similar in both groups. Other cardiovascular medications were used fairly commonly in all patients, but use of these other medications was similar in both groups (Table 1). Statins and β -blockers were prescribed well before self-reported symptom onset, as verified by comprehensive pharmacy records, demonstrating that the onset of symptoms did not initiate use of these therapies.

The association between the risk for acute myocardial infarction and lower use of statins and β -blockers that we found in our study is consistent with evidence from placebo-controlled clinical trials. In secondary prevention studies, statins and β -blockers have reduced the rate of recurrent myocardial infarction and cardiac death (4, 11, 12, 37). In primary prevention studies, statins have also reduced the risk for cardiovascular death (38–40). Very few of these trials, however, reported the effects of statins on the development of exertional angina, so whether therapy may have shifted the mode of presentation of coronary disease from acute myocardial infarction to stable angina is unclear. Fewer trials in primary prevention populations have examined whether β -blockers prevent cardiac events (13). Randomized trials in patients with hypertension have not found that β -blockers are more efficacious than other drug classes (24, 25, 41, 42). Case–control studies suggest, however, that β -blockers may reduce myocardial infarction in patients with hypertension (43, 44). We observed that calcium-channel blocker therapy was associated with higher odds of presenting with acute myocardial infarction versus stable angina, a finding that remained statistically significant after adjustment for confounders and use of other therapies. These results extend those of a previously reported case–control study, which observed a higher adjusted odds of acute myocardial infarction with use of short-acting calcium-channel blockers than with use of diuretics (43). Of note, while previous use of ACE inhibitors or angiotensin-II–receptor blockers was relatively low in the overall cohort (22.0%), it was substantially higher in those with diabetes (49.2%) or chronic heart failure (50.0%).

We also found that clinical and demographic factors affected the likelihood that the presenting symptom of coronary disease would be an acute myocardial infarction rather than exertional angina. Relatively few previous studies have examined factors predictive of the mode of presen-

tation of coronary disease, but several of our findings are similar to those of earlier studies. We found that current smoking was associated with acute myocardial infarction, as did investigators in the Women's Health Initiative (45) and the Uppsala Longitudinal Study of Adult Men (46). Smoking increases inflammation (47) and coagulability (48) and may predispose patients to occlusive coronary thrombosis on underlying atherosclerotic lesions (49). A history of hypertension and diabetes mellitus was also associated with myocardial infarction in our study (Table 1). Other studies have also reported associations of hypertension with acute myocardial infarction rather than lower-risk manifestations of coronary disease (45, 46). Elevated blood pressure increases myocardial oxygen demand, and higher vascular wall stress may contribute to coronary plaque rupture. Diabetes mellitus is known to increase the risk for cardiovascular complications (50), and our observation of a higher likelihood of presenting with myocardial infarction versus exertional angina is consistent with a previous study in older women (45).

In our study, women were less likely than men to develop acute myocardial infarction compared with angina as the initial presentation of coronary disease. In other studies, women were less likely than men to develop ST-segment elevation myocardial infarction (3) and to report chest pain symptoms in the setting of acute coronary syndromes (51). Our study confirms that symptoms of coronary disease may differ between men and women. The potential mechanisms that underlie these differences warrant further investigation.

Our study had several strengths. We studied a large, diverse sample of well-characterized patients with enzyme-positive acute myocardial infarction and stable exertional angina as the first presentation of clinical coronary disease. We also had detailed information on sociodemographic characteristics, clinical information, and prescribed medications from both patient self-report and automated clinical databases. Our study was limited by the absence of comprehensive information on whether patients previously attempted to use statin or β -blocker therapy in the distant past but discontinued it either spontaneously or because of an adverse side effect, as well as whether patients declined these medications. We also could not determine whether use of aspirin, which may be associated with statin and β -blocker use, contributed to our findings because its use was not systematically recorded in the pharmacy database. While we had information on cigarette smoking status, use of alcohol, and physical activity, we did not have information on dietary patterns, but dietary differences are unlikely to explain our observations. Despite our extensive adjustment for potential confounders, frequency of previous medical care, and overall number of prescribed medications, residual treatment selection bias and confounding by indication or contraindication for the various therapies studied may have occurred. The similar eligibility for statins and β -blockers and similar distribution of predicted

cardiovascular risk among untreated patients suggest that major confounding is unlikely. We also could not enroll patients with acute myocardial infarction or stable angina who died before attempted contact or who had sudden cardiac death, but unadjusted rates of statin and β -blocker use in identified patients with possible fatal myocardial infarction or sudden cardiac death were notably lower than those of patients presenting with incident stable angina, which is consistent with our findings. However, the inability to enroll patients with fatal myocardial infarction or sudden death precludes our ability to detect variables associated with these clinical presentations of coronary disease. Finally, we conducted our study among health plan members within an integrated health care delivery system in northern California, so our findings may not be completely generalizable to other health care settings or to uninsured persons.

In conclusion, recent use of statins and β -blockers was associated with lower odds of presenting with an acute myocardial infarction than with stable exertional angina among patients with new-onset symptoms of coronary disease. Although our findings must be confirmed by randomized studies, they suggest that use of statins and β -blockers for primary prevention may not only reduce the incidence of coronary disease but may also increase the likelihood of a more stable, lower-risk clinical presentation of coronary atherosclerosis.

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