

# Benefit of an Early Invasive Management Strategy in Women With Acute Coronary Syndromes

Ruchira Glaser, MD

Howard C. Herrmann, MD

Sabina A. Murphy, MPH

Laura A. Demopoulos, MD

Peter M. DiBattiste, MD

Christopher P. Cannon, MD

Eugene Braunwald, MD

**S**TUDIES OF ACUTE CORONARY SYNDROMES (ACSs) have suggested that the sex of patients influences both patient outcomes and the response to recent advances in medical and invasive therapies for ACS.<sup>1-8</sup> In particular, no benefit of platelet glycoprotein IIb/IIIa (Gp IIb/IIIa) inhibition in women with ACS was seen in a meta-analysis, while invasive management of ACS led to worsened outcomes for women in the FRISC II (Fragmin and Revascularization during Instability in Coronary artery disease II) and RITA 3 (Randomized Intervention Trial of unstable Angina 3) randomized controlled trials<sup>6,9,10</sup> but to improved outcomes in a prospective observational study.<sup>11</sup> These conflicting data have led to controversy about the role that the sex of patients should play in determining risk and in selecting optimal management strategies.

The TACTICS-TIMI 18 (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myo-

**Context** Women who present with acute coronary syndromes (ACSs) have different characteristics than men. Reports have conflicted about whether different outcomes exist for women with use of a routine invasive management strategy. However, these studies were performed prior to the widespread use of platelet glycoprotein IIb/IIIa inhibitors and intracoronary stents.

**Objective** To determine sex differences in baseline characteristics and outcomes in ACS and whether women benefit from a contemporary early invasive management strategy.

**Design and Setting** Prospective analysis of women and men enrolled in the TACTICS-TIMI 18 randomized trial, conducted December 1997 to December 1999 in 169 centers in 9 countries in North America and Europe, with follow-up at 1 and 6 months.

**Participants** A total of 2220 patients (757 women and 1463 men) with ACS.

**Interventions** All patients received aspirin, 325 mg/d; intravenous unfractionated heparin; and tirofiban for 48 hours or until revascularization, with tirofiban administered for at least 12 hours after percutaneous coronary revascularization. Patients assigned to the early invasive strategy (n=1114) underwent coronary angiography 4 to 48 hours after randomization and revascularization when appropriate. Patients assigned to the early conservative strategy (n=1106) were treated medically and underwent coronary angiography and appropriate revascularization only if they met specified criteria.

**Main Outcome Measures** Baseline characteristics and the primary composite end point of death, myocardial infarction, or rehospitalization for ACS at 6 months in women and men assigned to early invasive vs conservative management.

**Results** Women were older and more frequently had hypertension ( $P<.001$  for both). Women less frequently had previous myocardial infarction, coronary artery bypass grafting, and elevations in cardiac markers ( $P<.001$  for all), but there was no difference in distribution of TIMI risk scores ( $P=.76$ ). Angiography and intervention rates were similar, but women had less severe coronary artery disease, including no critical lesions in 17% of women vs 9% of men ( $P<.001$ ). Women had a 28% odds reduction in the primary end point with an early invasive strategy (adjusted odds ratio [OR], 0.72; 95% confidence interval [CI], 0.47-1.11), similar to the benefit in men (adjusted OR, 0.64; 95% CI, 0.47-0.88;  $P=.60$  for sex interaction). When adjusted for baseline characteristics, the benefit of invasive therapy in women with elevated troponin T levels was further enhanced (adjusted OR, 0.47; 95% CI, 0.26-0.83).

**Conclusions** Despite differences between women and men in baseline characteristics, the benefit of an early invasive strategy incorporating tirofiban and intracoronary stents was similar in women and men and was enhanced in women presenting with markers of increased risk.

JAMA. 2002;288:3124-3129

www.jama.com

See also p 3161 and Patient Page.

**Author Affiliations and Financial Disclosures** are listed at the end of this article.

**Corresponding Author and Reprints:** Howard C.

Herrmann, MD, 9 Founders Pavilion, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104 (e-mail: howard.herrmann@uphs.upenn.edu).

cardial Infarction 18) trial demonstrated a 22% odds reduction at 6 months in the combined end point of death, myocardial infarction (MI), and rehospitalization in patients with ACS treated with a Gp IIb/IIIa inhibitor and randomized to an early invasive strategy, compared with those patients treated more conservatively.<sup>12</sup> We prospectively assessed the clinical characteristics and outcomes in women enrolled in this trial. Our primary goal was to determine whether, in the setting of a contemporary strategy, treatment should be influenced by patients' sex, or by objective measures of risk such as the TIMI risk score, ST-segment changes, and levels of troponin T.

## METHODS

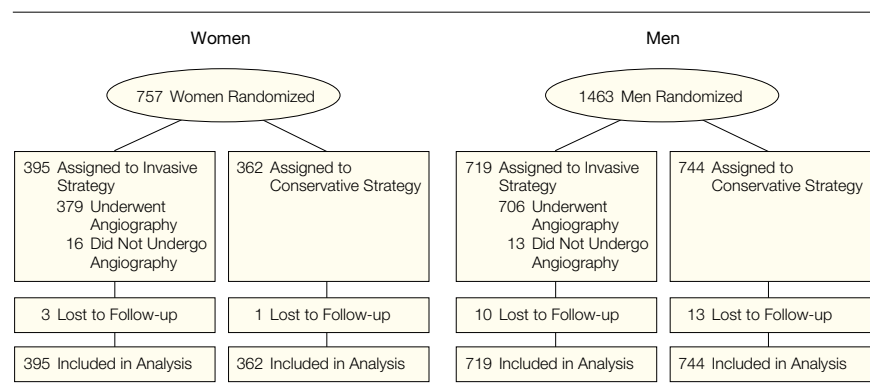
### Study Population

The study design and details of the TACTICS-TIMI 18 trial have been described previously.<sup>12,13</sup> Briefly, between December 18, 1997, and December 22, 1999, 2220 patients in 169 centers in 9 countries in North America and Europe underwent randomization to an early invasive or conservative strategy, with follow-up at 1 and 6 months (FIGURE 1). The study enrolled women and men who had experienced an episode of unstable angina within the preceding 24 hours, were candidates for coronary revascularization, and had at least 1 of the following: (1) ST-segment depression, transient ST-segment elevation, or T-wave inversion in at least 2 leads; (2) elevated levels of cardiac biomarkers; or (3) previously documented coronary disease.

### Management

All patients received 325 mg of aspirin daily (unless contraindicated), intravenous unfractionated heparin, and tirofiban (Aggrastat, Merck, West Point, Pa)<sup>14</sup> for 48 hours or until revascularization, with tirofiban administered for at least 12 hours after percutaneous coronary revascularization procedures. Patients assigned to the early invasive strategy were to undergo coronary angiography between 4 and 48

**Figure 1.** Flow of Patients Through the Trial



All patients randomized were included in the analysis by intention-to-treat principle.

hours after randomization, and revascularization when appropriate. Patients assigned to the early conservative strategy were treated medically and underwent coronary angiography and appropriate revascularization only if they met specified criteria, including prolonged angina at rest associated with electrocardiographic evidence of ischemia or changes in cardiac biomarker levels, hemodynamic instability, significant ischemia during stress testing, unstable angina requiring hospitalization, Canadian Cardiovascular Society class III or IV angina with an abnormal exercise tolerance test, or a new MI.<sup>12,13</sup>

### Statistical Analysis

All patients randomized were included in the analyses by the intention-to-treat principle. Multivariable logistic regression was performed to evaluate the effect of the sex of patients as an independent prognostic factor relating to the primary combined end point (death, MI, and rehospitalization for ACS at 6 months). Myocardial infarction was defined as new Q waves in 2 contiguous electrocardiogram leads or a creatine kinase-MB (CK-MB) fraction higher than the upper limit of normal. Within 48 hours following percutaneous coronary intervention (PCI), a new MI was defined as new Q waves or a CK-MB level elevated greater than 3 times the upper limit of normal. After coronary artery bypass graft (CABG) surgery,

only new Q waves were used to define MI. All primary end points were adjudicated by members of an independent clinical end points committee who were unaware of patients' treatment assignments. Age, hypertension, smoking status, prior CABG surgery, prior MI, an index event of non-ST-segment elevation MI, troponin T level elevation, PCI or CABG surgery during hospitalization, and an interaction variable for patients' sex were included in the multivariable model. Separate analyses were performed with the additional inclusion of the presence of significant coronary artery disease (CAD) or primary aspirin use in the model. Statistical significance was defined as  $P \leq .05$ . Survival curves using the Kaplan-Meier method were constructed to evaluate invasive vs conservative therapy in women and in men. All analyses were performed using STATA v7.0 (Stata Corp, College Station, Tex).

## RESULTS

### Baseline Characteristics

One third of patients enrolled in the trial were women (Figure 1 and TABLE 1). Compared with men, women were older and more frequently had hypertension. Women less often had prior cardiac disease and a presentation with elevated levels of troponin T. The distribution of TIMI risk scores and ST-segment changes of women was not different compared with that of men.

### Angiographic Characteristics

The rates of angiography were similar in women and men randomized to either the invasive or conservative strategy (TABLE 2). In both the invasive and conservative groups, women who underwent angiography had no significant CAD more often (17% vs 9%,  $P < .001$ ), and had disease of the left main coronary artery less often (7% vs 10%,  $P = .049$ ). Similar differences between women and men in the extent of CAD were present in patients randomized to invasive or conservative therapy.

### Treatment Received

Pharmacological therapy was similar in women and men, except that women received calcium channel blockers more frequently. This difference persisted after adjustment for angiographic presence of CAD (Table 1).

Fewer women than men underwent CABG surgery in both the invasive and conservative groups (13% vs 18%,  $P = .001$ ). This difference persisted when adjusted for the presence of 3-vessel CAD or disease of the left main coronary artery (for CABG surgery in women vs men: adjusted odds ratio [OR], 0.60; 95% confidence interval [CI], 0.41-0.86;  $P = .007$ ). Rates of PCI and stent use were similar in women and men in both strategies (32% of women underwent PCI vs 33% of men; 84% of women and men underwent PCI with stent placement).

### Outcomes by Management Strategy and Sex of Patients

In women, the rate of the primary end point of death, MI, or rehospitalization for ACS at 6 months was 17% with the early invasive strategy and 19.6% with the conservative strategy. Adjustment for

differences in baseline characteristics enhanced the benefit of invasive management (women: adjusted OR, 0.72; 95% CI, 0.47-1.11; men: adjusted OR, 0.64; 95% CI, 0.47-0.88). In multivariable analysis, the sex of patients was not an independent risk factor for outcome by strategy ( $P = .60$  for interaction) (TABLE 3). The likelihood of death or nonfatal MI in women was also lower with use of the early invasive strategy, particularly when adjusted for baseline characteristics (6.6% in the early invasive strategy vs 9.7% in the conservative strategy, adjusted OR, 0.45; 95% CI, 0.24-0.88;  $P = .02$ ). In addition, female sex was not an independent risk factor for outcome even after adjustment for the presence or absence of significant stenosis at angiography.

Those women who underwent PCI had similar rates of death and MI at 6 months, compared with men (10.7% in women undergoing PCI vs 10.9% in men undergoing PCI,  $P > .99$ ). Furthermore, CABG surgery mortality at 6 months was not increased in women compared with men (5.3% vs 4.5%, respectively;  $P = .78$ ).

### Procedural Complications

Rates of major bleeding were higher in women undergoing PCI compared with men (8.3% vs 2.9%; adjusted OR, 3.6; 95% CI, 1.6-8.3;  $P = .001$ ), and this difference persisted after adjustment for baseline characteristics and a higher mean activated clotting time measured in women. Rates of bleeding (12.6% vs 15%) and stroke (2.1% vs 1.5% at 30 days) were similar in women and men undergoing CABG surgery.

### Risk Stratification

While there was a trend toward improved outcomes in those women with intermediate (3-4) and high (5-7) TIMI risk scores who received the invasive when compared with the conservative strategy, this was not statistically significant ( $P = .20$  for trend) (TABLE 4). Women with ST-segment changes had a similar trend toward improvement in death, MI, and rehospitalization for ACS with invasive management (OR, 0.66;

**Table 1.** Baseline Characteristics of Study Patients\*

Characteristic	No. (%)		P Value
	Women (n = 757)	Men (n = 1463)	
Age, mean (SD), y	64.3 (11.5)	60.5 (11.5)	<.001
Age $\geq$ 65 y	390 (52)	571 (39)	<.001
Diabetes	228 (30)	385 (26)	.06
Hypertension requiring medication or hospital treatment	553 (73)	914 (62)	<.001
Current smoker	184 (24)	427 (29)	.02
Hypercholesterolemia requiring medication or hospital treatment	471 (62)	875 (60)	.27
LDL cholesterol level $>$ 100 mg/dL	350 (68)	650 (67)	.48
Index event of NQWMI	220 (29)	606 (41)	<.001
Cardiovascular history			
Myocardial infarction	256 (34)	610 (42)	<.001
CABG surgery	126 (17)	358 (24)	<.001
Congestive heart failure	66 (9)	95 (6)	.06
Angina	87 (11)	200 (14)	.15
Aspirin use	491 (65)	986 (67)	.23
TIMI risk score			
0-2	181 (24)	371 (25)	.76
3-4	461 (61)	867 (59)	
5-7	112 (15)	225 (15)	
ST-segment deviation $\geq$ 0.5 mm	299 (40)	553 (38)	.44
Troponin T level $>$ 0.01 $\mu$ g/L	294 (47)	692 (57)	<.001
Medication use at index hospital discharge			
Aspirin	746 (98)	1438 (98)	.97
Statin	338 (45)	658 (45)	.88
$\beta$ -Blocker	462 (61)	913 (62)	.52
ACE inhibitor	138 (18)	232 (16)	.16
Calcium channel blocker	210 (28)	318 (22)	.002

\*LDL indicates low-density lipoprotein; NQWMI, non-Q-wave myocardial infarction; CABG, coronary artery bypass graft; TIMI, Thrombolysis In Myocardial Infarction; and ACE, angiotensin-converting enzyme.

95% CI, 0.38-1.15;  $P=.14$ ), and a significant reduction in death and MI (OR, 0.41; 95% CI, 0.19-0.89;  $P=.02$ ). Women with elevated levels of troponin T had marked benefit with an invasive strategy; the rate of the primary end point was 19% in the invasive group and 29% in the conservative group (OR, 0.56; 95% CI, 0.32-0.97;  $P=.02$ ). When adjusted for baseline characteristics, the benefit of invasive therapy in women with elevated troponin T levels was further enhanced (adjusted OR, 0.47; 95% CI, 0.26-0.83) (FIGURE 2).

## COMMENT

This study demonstrates important differences in the baseline clinical and angiographic characteristics between women and men presenting with unstable angina and non-ST-segment elevation MI. Importantly, these differences do not translate into significant differences in major outcomes between women and men who both benefit from a contemporary management strategy for ACS incorporating early invasive treatment and platelet Gp IIb/IIIa inhibitor use.

Previous analyses of women in trials of ACS have included those of the TIMI IIIB trial and the FRISC II trial.<sup>1,6</sup> In TIMI IIIB, outcomes for women, adjusted for comorbidity, were similar to those for men, with no difference between invasive and conservative therapy. In the present analysis of the TACTICS-TIMI 18 trial there were similar differences in baseline characteristics, but there was additionally a benefit for an invasive strategy for both women and men. The improved outcome for women receiving invasive therapy may reflect the routine use of a platelet Gp IIb/IIIa inhibitor and the high use of intracoronary stents.<sup>15-17</sup>

In a recent analysis of the FRISC II trial, women who were treated with invasive therapy had significantly worse outcomes compared with women treated with a conservative strategy (for invasive strategy, including adjustment for presence of coronary disease: OR for death or MI, 1.72; 95% CI, 1.11-2.65;  $P=.01$ ). The FRISC II inves-

tigators cite the lower prevalence in women of CAD at angiography as a potential explanation for the worse outcomes with invasive management in that trial, although the difference persisted after adjustment for CAD. In our cohort as well, there was a lower prevalence of severe CAD in women compared with men, but women still de-

rived the overall benefit of invasive management found in the trial.

Several important differences between these randomized controlled trials may explain the discordant findings. First, the women undergoing CABG surgery in the FRISC II trial had significantly higher mortality rates at 12 months (9.9%) than did the men

**Table 2.** Degree of Coronary Artery Disease at Initial Angiography

	No. (%)		P Value
	Women	Men	
Angiography performed	555 (75)	1091 (76)	.56
Invasive strategy only	379 (97)	706 (98)	.20
Conservative strategy only	176 (50)	385 (54)	.28
Diseased coronary vessels			
All patients			
None	95 (17)	99 (9)	
1	172 (31)	259 (24)	<.001
2	147 (26)	303 (28)	
3	141 (25)	430 (39)	
Left main coronary artery	40 (7)	111 (10)	.05
Invasive strategy only			
None	70 (18)	73 (10)	
1	116 (31)	162 (23)	<.001
2	93 (25)	208 (29)	
3	100 (26)	263 (37)	
Left main coronary artery	27 (7)	65 (9)	.24
Conservative strategy only			
None	25 (14)	26 (7)	
1	56 (32)	97 (25)	<.001
2	54 (31)	95 (25)	
3	41 (23)	167 (43)	
Left main coronary artery	13 (7)	46 (12)	.10

**Table 3.** Clinical Outcomes at 180 Days Associated With Invasive vs Conservative Strategy\*

Outcome	Strategy, No. (%)		OR (95% CI)	Adjusted OR (95% CI)
	Invasive	Conservative		
	<b>Women</b>			
Total No.	395	362		
Death	15 (3.8)	13 (3.6)	1.06 (0.50-2.26)	0.94 (0.37-2.44)
Death/MI	26 (6.6)	35 (9.7)	0.66 (0.39-1.12)	0.45 (0.24-0.88)
Death/MI/rehospitalization for ACS	67 (17.0)	71 (19.6)	0.84 (0.58-1.21)	0.72 (0.47-1.11)
	<b>Men</b>			
Total No.	719	744		
Death	22 (3.1)	26 (3.5)	0.87 (0.40-1.55)	0.75 (0.36-1.56)
Death/MI	55 (7.6)	70 (9.4)	0.80 (0.55-1.15)	0.68 (0.43-1.05)
Death/MI/rehospitalization for ACS	110 (15.3)	144 (19.4)	0.75 (0.57-0.99)	0.64 (0.47-0.88)

\*Covariates include treatment group, coronary artery bypass graft surgery during index hospitalization, percutaneous coronary intervention during index hospitalization, age, hypertension, current smoking, prior myocardial infarction (MI), index event MI, prior coronary artery bypass graft surgery, prior congestive heart failure, and troponin T status (for women, covariates also include use of calcium channel blockers and prior use of aspirin). OR indicates odds ratio; CI, confidence interval; and ACS, acute coronary syndrome.



(1.2%), and higher mortality rates than did women undergoing CABG surgery in our trial at 6 months (5.3%). Although it has been demonstrated that women may have increased mortality with CABG surgery when compared with men, recent studies have shown that most of this difference is related to comorbid conditions.<sup>18-20</sup> Second, the patients undergoing invasive manage-

ment in TACTICS-TIMI 18 did so within the first 48 hours of presentation, whereas patients in the FRISC II trial did so on average during the fifth day after presentation. It is possible that earlier therapy may have enhanced the benefits seen in women, as well as men.

The RITA 3 trial found that women did not retain the benefits of invasive management found in the overall trial.<sup>10</sup>

However, the women in this trial may represent a cohort at lower risk, with lower rates of death and MI at 1 year in women in both the invasive (8.6%) and conservative groups (5.1%) than those of patients enrolled in the FRISC II and TACTICS-TIMI 18 trials (12.4% vs 10.5% in FRISC II at 1 year; 6.6% vs 9.7% in TACTICS at 6 months). Additionally, these lower event rates were observed despite a more sensitive definition of MI used in the RITA 3 trial, implying a cohort at even lower risk. The finding that the benefits of invasive therapy are significantly mitigated in women at lower risk are not dissimilar from our findings, where the benefit of invasive management was primarily confined to women with markers of increased risk.

An important finding of our study was the predictive value of the serum marker, troponin T, in women with ACS. Although troponin T had greater predictive value for benefit than ST-segment changes and the TIMI risk score, the trends were similar for all 3 of these measures of risk. A test that can predict enhanced benefit with early invasive management may be especially useful in women with ACS, since the proportion of women presenting with chest pain and criteria for ACS who ultimately do not have significant CAD is higher than in men.<sup>1,21-23</sup>

There are important limitations to this analysis. The women enrolled in this study are part of a randomized trial and may not be representative of all women who present with ACS. However, the women in this trial had baseline characteristics similar to those in registry data.<sup>1,4</sup> Also, subanalyses may not be adequately powered to detect differences among women.

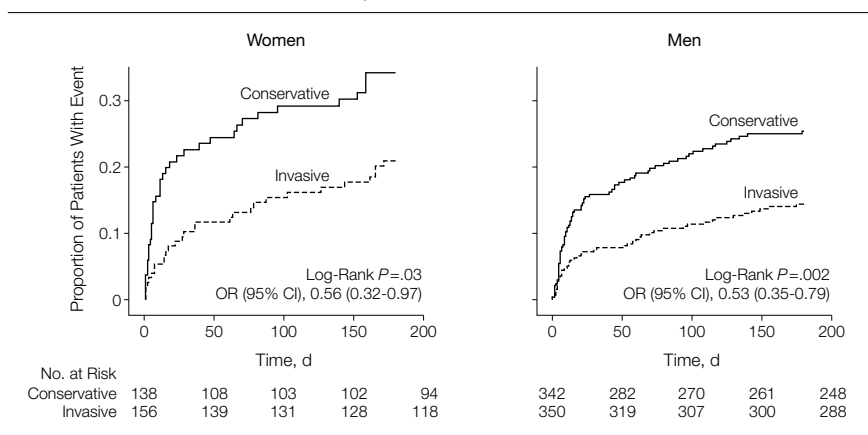
The optimal management of women with ACS has been unclear. This study shows that important differences exist in both baseline characteristics and presentation findings between women and men. The hypothesis that higher procedural complications, comorbidities, and less severe disease at angiography in women may favor conservative therapy is not supported by our data.

**Table 4.** Death, Myocardial Infarction, or Rehospitalization for Acute Coronary Syndrome, by Measures of Risk\*

Subgroup	Strategy, No. (%)		OR (95% CI)	P Value for Interaction
	Invasive	Conservative		
<b>Women</b>				
TIMI score				
0-2	15 (17)	11 (12)	1.59 (0.69-3.67)	.09
3-4	38 (16)	46 (21)	0.72 (0.45-1.16)	
5-7	14 (21)	14 (32)	0.56 (0.23-1.32)	
ST-segment changes				
Yes	29 (18)	35 (25)	0.66 (0.38-1.15)	.27
No	38 (16)	36 (16)	1.00 (0.61-1.65)	
Elevated troponin T levels				
Yes	29 (19)	40 (29)	0.56 (0.32-0.97)	.02
No	29 (17)	19 (12)	1.46 (0.78-2.72)	
<b>Men</b>				
TIMI score				
0-2	19 (11)	23 (12)	0.88 (0.46-1.68)	.57
3-4	68 (16)	90 (20)	0.77 (0.54-1.09)	
5-7	23 (19)	31 (30)	0.53 (0.29-1.00)	
ST-segment changes				
Yes	42 (15)	75 (27)	0.49 (0.32-0.75)	.01
No	68 (15)	69 (15)	1.04 (0.72-1.49)	
Elevated troponin T levels				
Yes	46 (13)	76 (22)	0.53 (0.35-0.79)	.04
No	40 (17)	44 (16)	1.02 (0.64-1.62)	

\*OR indicates odds ratio; CI, confidence interval; and TIMI, Thrombolysis In Myocardial Infarction.

**Figure 2.** Death, Myocardial Infarction, and Rehospitalization for Acute Coronary Syndrome in Women and Men With Elevated Troponin T Levels, by Strategy



Median follow-up time, 180 days for both women and men. OR indicates odds ratio; CI, confidence interval.

In fact, our prospectively defined, randomized data show that women with unstable angina and non-ST-segment elevation MI benefit, as do men, from broader inclusion in contemporary management strategies incorporating Gp IIb/IIIa inhibitors and early invasive therapy with stents. This is especially true for women with objective evidence of ischemia including ST-segment changes and elevations in the levels of the serum marker troponin T. In this regard, the choice of an inva-

sive vs conservative strategy for ACS should be based on objective risk stratification measures, and not be influenced by the sex of patients.

**Author Affiliations:** Department of Medicine, University of Pennsylvania, Philadelphia (Drs Glaser and Herrmann); Department of Medicine, Brigham and Women's Hospital, Boston, Mass (Ms Murphy, and Drs Cannon and Braunwald); and Merck Research Laboratories, Blue Bell, Pa (Drs Demopoulos and DiBattiste).

**Financial Disclosures:** Dr Herrmann has received honoraria and research funding from Merck and Co. Drs Demopoulos and DiBattiste are employees of Merck and Co and potentially own stock and/or hold

stock options in the company. Dr Braunwald has received study support from Merck and Co.

**Author Contributions:** Study concept and design: Glaser, Herrmann, Demopoulos, Cannon.

**Acquisition of data:** Herrmann, DiBattiste, Cannon. **Analysis and interpretation of data:** Glaser, Herrmann, Murphy, DiBattiste, Cannon, Braunwald.

**Drafting of the manuscript:** Glaser, Herrmann.

**Critical revision of the manuscript for important intellectual content:** Glaser, Herrmann, Murphy, Demopoulos, DiBattiste, Cannon, Braunwald.

**Statistical expertise:** Herrmann, Murphy, Glaser.

**Obtained funding:** Demopoulos, Cannon, Braunwald.

**Administrative, technical, or material support:** DiBattiste, Braunwald.

**Study supervision:** Herrmann, DiBattiste, Cannon.

**Funding/Support:** The original TACTICS-TIMI 18 trial was funded by Merck and Co.; no additional funding was provided for this subanalysis.

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