Journal of the American College of Cardiology
© 2002 by the American College of Cardiology Foundation
Published by Elsevier Science Inc.

Vol. 40, No. 6, 2002
ISSN 0735-1097/02/$22.00
PII S0735-1097(02)02120-4

Gender Issue and CAD

Is Glycoprotein IIb/IIIa Antagonism as Effective in Women as in Men Following Percutaneous Coronary Intervention?

Lessons From the ESPRIT Study

Laura S. Fernandes, MD,* James E. Tcheng, MD, FACC,† J. Conor O'Shea, MD,† Bonnie Weiner, MD, FACC,‡ Todd J. Lorenz, MD,§ Cindy Pacchiana, MS,† Lisa G. Berdan, PA-C,† Kelly J. Maresh, RN,* Diane Joseph, BS,† Mina Madan, MD,‖ Tift Mann, MD, FACC,¶ Rakhi Kilaru, MS,† Judith S. Hochman, MD, FACC,** Neal S. Kleiman, MD, FACC,* for the ESPRIT Investigators

Houston, Texas; Durham and Raleigh, North Carolina; Worcester, Massachusetts; South San Francisco, California; Toronto, Ontario, Canada; and New York, New York

OBJECTIVES The study was done to determine whether eptifibatide, a platelet glycoprotein (GP) IIb/IIIa antagonist, prevents ischemic complications following percutaneous coronary interventions (PCIs) in women as well as in men.

BACKGROUND Eptifibatide reduces ischemic complications after nonurgent coronary stent interventions.

METHODS We compared outcomes in women (n = 562) and men (n = 1,502) enrolled in the Enhanced Suppression of the Platelet GP IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial of double-bolus eptifibatide during PCI.

RESULTS Women in the ESPRIT trial were older, and more frequently had hypertension, diabetes mellitus, or acute coronary syndromes, but were less likely to have prior PCI or coronary artery bypass graft surgery. The primary end point, a composite at 48 h of death, myocardial infarction (MI), urgent target vessel revascularization (TVR), and unplanned GP IIb/IIIa use, occurred in 10.5% of women and 7.9% of men (p = 0.082). The composite of death, MI, or TVR after one year occurred in 24.5% of women compared with 18% of men (p = 0.0008). At 48 h, eptifibatide reduced the composite of death, MI, and TVR from 14.5% to 6.0% in women versus 9.0% to 6.8% in men. At one year, these differences persisted: 28.9% versus 20.0% for women and 19.5% versus 16.6% for men. No statistical interaction existed between treatment and gender at either 48 h (p = 0.063) or one year (p = 0.2). Bleeding occurred more commonly in women (5.5% vs. 2.6%, p = 0.002), and was more common in eptifibatide-treated women. After adjustment for age, weight, and hypertension, no interaction between treatment and gender was present.

CONCLUSIONS Eptifibatide is effective to prevent ischemic complications of PCI in women and may eliminate gender-related differences in PCI outcomes. (J Am Coll Cardiol 2002;40: 1085–91) © 2002 by the American College of Cardiology Foundation

Because both the presence and the impact of coronary artery disease are increasingly recognized in women, the number of percutaneous coronary interventions (PCIs) performed in women is likely to increase as well (1). Moreover, recent studies have reported significant differences in prognostic factors and adverse clinical outcomes in women who undergo PCIs and coronary stenting as compared with men (2,3). Although numerous studies have demonstrated that antagonists of platelet glycoprotein (GP) IIb/IIIa prevent myocardial infarction (MI) and other ischemic events when used during PCI (4–7) the efficacy of GP IIb/IIIa antagonists in women has remained controversial. A recent meta-analysis of three clinical trials using abciximab observed that the effect of abciximab was not different for men versus women undergoing PCI (2). However, at the same time, retrospective analysis of data from the large Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy, (PURSUIT) study of patients with acute coronary syndromes suggested that treatment with the cyclic heptapeptide GP IIb/IIIa antagonist eptifibatide may have been more effective in men than in women (8). Whether these observations represent true biologic differences in platelet aggregation mechanisms, or in the biology of the arterial wall, between men and women (9), or whether they are due to anthropometric differences or to heterogeneous patterns of clinical care in men and women is

From the *Baylor College of Medicine and the Methodist DeBakey Heart Center, Houston Texas; †Duke Clinical Research Institute, Durham, North Carolina; ‡University of Massachusetts, Worcester, Massachusetts; §COR Therapeutics, South San Francisco, California; ‖Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada; ¶Wake Heart Associates, Raleigh, North Carolina; and **Columbia University and St. Luke's Roosevelt Hospital, New York, New York. Supported by a grant from COR Therapeutics and Key Pharmaceuticals.

Manuscript received October 24, 2001; revised manuscript received June 5, 2002, accepted June 12, 2002.

Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
CI	= confidence interval
ESPRIT	= Enhanced Suppression of the Platelet GP IIb/IIIa Receptor with Integrilin Therapy
GP	= glycoprotein
HR	= hazards ratio
MI	= myocardial infarction
OR	= odds ratio
PCI	= percutaneous coronary intervention
PTCA	= percutaneous transluminal coronary angioplasty
PURSUIT	= Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
TIMI	= Thrombolysis In Myocardial Infarction trial
TVR	= target vessel revascularization

not clear. To pursue this question further, we analyzed data from a large trial of double-bolus doses of eptifibatide in patients undergoing elective stent placement.

METHODS

Study population. The methods and results of the Enhanced Suppression of the Platelet GP IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial have been previously published (7). Patients undergoing elective PCI were eligible if there were no contraindications to treatment with a platelet GP IIb/IIIa antagonist and the operating physician was uncertain whether a platelet GP IIb/IIIa antagonist was indicated. Patients were treated with aspirin 325 mg, and a thienopyridine. Heparin was given as 60 U/kg, not to exceed 6,000 U. Patients received either a placebo or eptifibatide given as two 180-μg/kg bolus doses separated by 10 min, and a 2-μg/kg/min infusion continued until hospital discharge or up to 18 to 24 h. The target activated clotting time was 200 to 300 s. The primary study end point was the composite at 48 h of death, MI, urgent target vessel revascularization (TVR), or "bail-out" use of eptifibatide. Patients were also followed for the composite of death, MI, or TVR at one year. Myocardial infarction was present when two or more values of creatine kinase-muscle brain isoenzyme within the first 24 h after PCI were at least three times the upper limit of normal. Complications related to therapy were evaluated by the rates of bleeding, blood transfusion, and stroke for 48 h or hospital discharge. Hemorrhages were classified as major or minor according to the criteria of the Thrombolysis In Myocardial Infarction (TIMI) study group (10).

Statistical analyses. Patient data were collected as part of the overall ESPRIT trial. Continuous baseline characteristics and clinical outcomes were reported as medians with 25th and 75th percentiles. Categorical variables were analyzed using Likelihood Ratio Chi-Square and Fisher exact tests. Continuous variables were analyzed using the Mann-Whitney *U* test. The cumulative event rate over time was estimated using the Kaplan-Meier method with the time to the first event of death, MI, or TVR used as the outcome variable. The Likelihood Chi-Square statistic was used to test the interaction between gender and treatment with eptifibatide following an adjustment for baseline characteristics, at 48 h and 30 days. Baseline characteristics included age, history of diabetes, acute ST-elevation, MI $\leq$7 days, prior percutaneous transluminal coronary angioplasty (PTCA), target pre-thrombus, target pre-TIMI flow, and stable angina. Unadjusted Cox proportional hazards survival models were used to compute hazard ratios for the 48-h composite end point for men versus women on eptifibatide or placebo. Adjusted Cox proportional hazards survival models were created to adjust for the differences in the baseline characteristics and treatment for the one-year primary end point. Baseline characteristics for the one-year primary end point included age, heparin pre-PCI, target pre-thrombus, treatment, and interaction of treatment and age. Adjustments were also made for body weight. Logistic regression models for bleeding were created to adjust for covariates that included age, weight, gender, treatment, and prior hypertension, which were derived from a previously developed model (11). A two-tailed p value <0.05 was considered statistically significant.

RESULTS

A total of 2,064 patients, 562 women and 1,502 men, were enrolled in the ESPRIT trial between June 3, 1999, and February 4, 2000. Women were more likely to be older, lighter in weight, have hypertension, or diabetes and were less likely to have had a prior MI or coronary artery bypass graft surgery (CABG). No difference existed between genders in the proportion of vessels narrowed >70% (p = 0.076). Percutaneous coronary interventions were performed in more than 98% of enrolled patients, with stents being used at a rate of 96% in both genders. No differences existed in procedural variables between women and men, with the exception that dilation of the right coronary artery was slightly more common in men (Table 1). Angiographic complications were uncommon and also occurred with similar frequencies among women and men (Table 2). No evidence was seen of statistical interaction between treatment and gender for any of the angiographic complications.

Various elements of the composite end point tended to occur more frequently in women within the first 48 h (Fig. 1). The difference in the event rates at 48 h was not different between the two genders (women vs. men: 10.5% vs. 7.9%, p = 0.082). However, the event rate for death, MI, and TVR was higher in women at one year (24.5% vs. 18%; hazards ratio [HR] = 1.42, 95% confidence interval [CI] 1.16, 1.75, p = 0.0008). Correction for body weight altered these rates by 0.4% or less. After adjustment for other baseline differences between men and women, the HR for the composite of ischemic events was still higher in women

Table 1. Patients' Baseline Characteristics

	Women (n = 562)	Men (n = 1,502)	p Value
Demographics			
Age (yrs)	65 (57,74)	61 (53,79)	< 0.001*
Weight (kg)	75 (64,85)	88 (78,99)	< 0.001*
Previous MI	143, 25%	509, 34%	< 0.001*
Stable angina	190, 40%	604, 34%	< 0.008*
Hypertension	381, 68%	832, 56%	< 0.001*
Diabetes	157, 28%	262, 17%	< 0.001*
Previous CABG	33, 6%	178, 12%	< 0.001*
Nonsmoker	234, 42%	362, 24%	< 0.001*
High cholesterol	331, 59%	868, 58%	< 0.66
Previous PCI	126, 22%	357, 24%	< 0.52
Single-vessel disease	452, 80%	1,205, 80.2%	0.92
Angiographic characteristics			
Infusion duration (h)	18.4 (18.0, 20.3)	18.4 (18.0, 20.1)	0.58
PCI performed, n, %	555, 98.8	1,485, 98.9	0.83
Stent placed, n, %	541, 96.3	1,442, 96.0	0.78
Thienopyridine, n, %	551, 98.2	1,464, 97.5	0.31
Maximal ACT (s)	284 (127,835)	278 (21,788)	0.90
Vessel dilated			
LAD	231, 41.1%	666, 44.3%	0.187
RCA	239, 37.3%	560, 42.5%	0.29
CFX/Ramus	159, 28.3%	492, 32.7%	0.052

Continuous variables are reported as median (25th, 75th percentiles).

ACT = activated clotting time; CABG = coronary artery bypass graft surgery; CFX = circumflex; LAD = left anterior descending; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery.

both at 48 h (HR for women vs. men 1.39 [1.0, 1.93]) and one year (HR for women vs. men 1.36 [1.09, 1.69]).

Treatment with eptifibatide resulted in a reduction in the composite end point in women and men (Fig. 2). After eptifibatide treatment, the event rates at 48 h were very similar in women and men (6.1% and 6.8%, respectively). The one-year composite rate of death, MI, or TVR was higher in women receiving placebo versus eptifibatide (28.9% vs. 20%). The directionality of treatment effect was the same in women and men (20% vs. 16.6%), although the relative reduction in risk was greater in women (30% vs. 15%). No statistical interaction existed between treatment and gender at 48 h (p = 0.063) or at one year (p = 0.2).

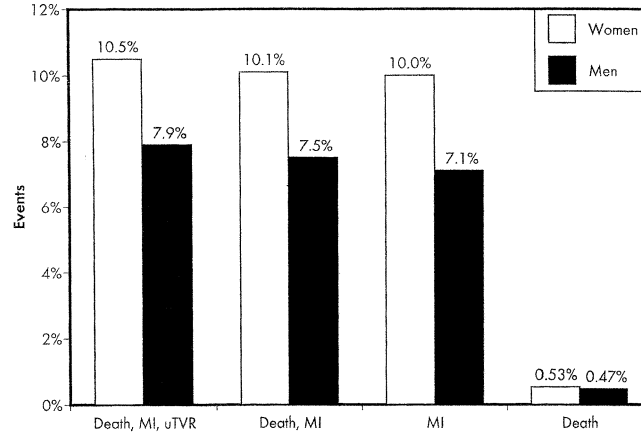

Figure 1. Individual selected elements of the composite end point at 48 h for men and women. MI = myocardial infarction; uTVR = urgent target vessel revascularization.

Survival free of death or MI was also greater in eptifibatide-treated women as compared to placebo-treated women (Fig. 3). As for the primary composite end point, no evidence was seen of statistical interaction between gender and treatment at 48 h (p = 0.32) and one year (p = 0.21). The interactions at one year also remained nonsignificant after adjustment for weight.

Major bleeding occurred more frequently in women than in men 8/506 (1.6%) and 9/1,364 (0.66%), respectively (odds ratio [OR] 2.46, 95% CI 0.94, 6.43). For major or minor bleeding, the frequencies were 28/506 (5.5%) versus 36/1,364 (2.6%) (OR 2.19, 95% CI 1.32, 3.63; p = 0.002). Among women, major or minor bleeding was more common in patients treated with eptifibatide, whereas in men the event rates were similar regardless of treatment (Table 2). After adjustment for weight, age, and hypertension according to the GUSTO model, these differences in major or minor bleeding between men and women were nonsignificant (OR 1.6, 95% CI 0.9, 2.84; p = 0.11). In the adjusted model, no interaction existed between gender and major/minor bleeding. In the unadjusted model, no statis-

Table 2. Patients' Complications

	Women (n = 562)	Men (n = 1,502)	p Value
Angiographic			
Major dissection	27 (5%)	50 (3%)	0.12
Abrupt closure	6 (1%)	15 (<1%)	0.89
No reflow	6 (1%)	21 (1%)	0.56
Thrombosis	7 (1%)	18 (1%)	0.93
Distal embolization	2 (<1%)	13 (<1%)	0.78
Side branch closure	22 (4%)	63 (4%)	0.22

	Women (n = 506)		Men (n = 1,364)		
	Eptifibatide	Placebo	Eptifibatide	Placebo	
Bleeding					
Major	6 (2.36%)	2 (0.79%)	7 (0.99%)	2 (0.30%)	0.062
Minor	14 (5.51%)	6 (2.38%)	15 (2.1%)	12 (1.82%)	0.015

The p values refer to differences between women and men.

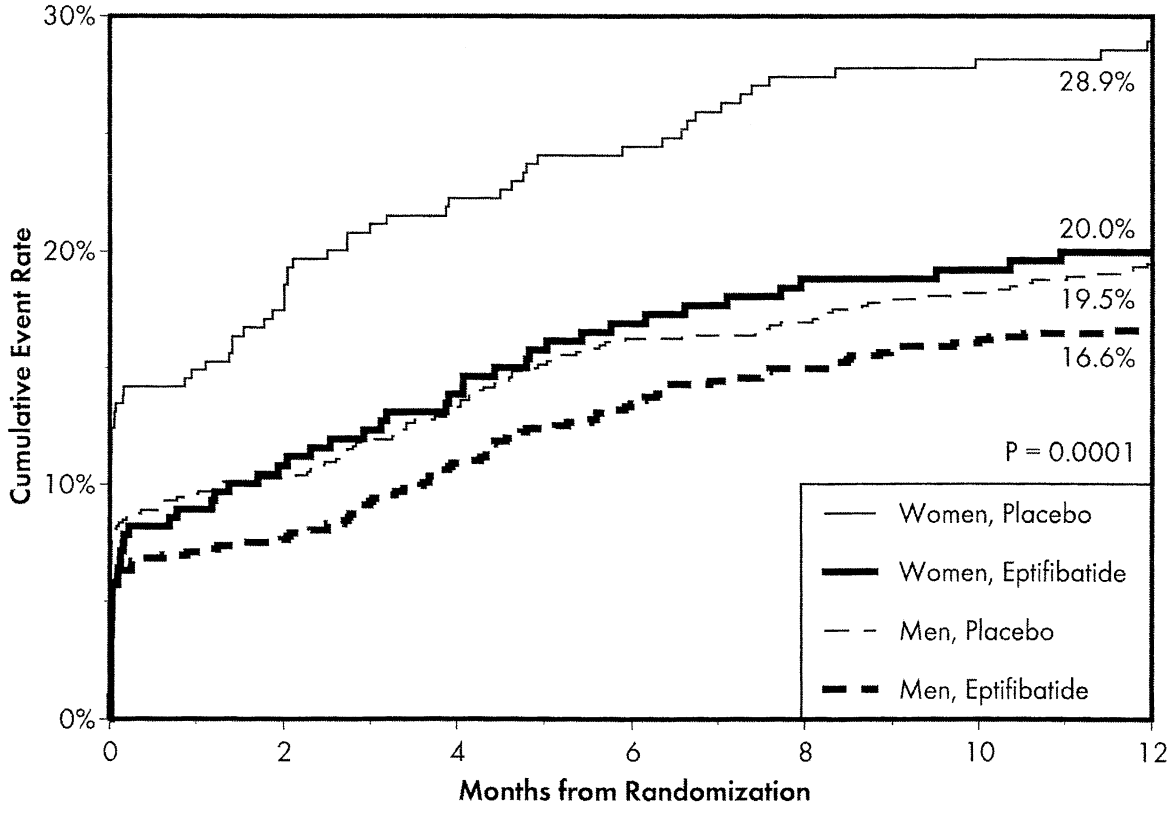

Figure 2. Kaplan-Meier estimates of the composite of death, myocardial infarction, or target vessel revascularization during the first year, according to gender and treatment with eptifibatide.

tical interaction existed between gender and treatment for major bleeding ($p = 0.94$), minor bleeding ($p = 0.26$), or major or minor bleeding ($p = 0.26$). The most common site for major or minor non–CABG-related bleeding was at the femoral access site (36% in men and 64% in women).

DISCUSSION

We found that treatment with a double-bolus regimen of the platelet GP IIb/IIIa antagonist eptifibatide offered similar protection against serious ischemic events among women and men. Event-free survival was better in women receiving eptifibatide compared with placebo treatment. At the end of 48 h there was a trend toward greater benefit in women than in men, perhaps reflecting the higher overall risk in women. At this point, eptifibatide reduced the frequency of events in women to rates comparable to those observed in men. However, over the course of the ensuing year, the rates of the composite end point diverged, and the evidence of interaction between treatment and gender became less, suggesting that the need for further revascularization and perhaps the overall risk of coronary heart disease in women remained higher than in men.

Importance of gender differences in PCI. Coronary heart disease is the leading cause of mortality and morbidity in the U.S. in both women and in men. After accounting for the increasing proportion of women in the aging population, each year more women die of cardiovascular disease than men (12). Comparison of reports from a decade ago with those of the past several years would suggest that coronary artery disease is increasingly recognized in women (13,14). Consequently, the proportion of female patients undergoing PCI has increased over the past two decades (1,15). Most investigations have reported differences in clinical characteristics between women and men undergoing PCI. As in the current study, women undergoing PCIs are more likely to be older, and more likely to have hypertension, diabetes mellitus, and lower rates of prior MI and CABG (2,3,16–20).

Whether there are in fact differences in clinical outcomes following PCI is less clear. In the early experience, female gender was reported to be an independent predictor of both abrupt vessel closure (21) and of mortality in the event of a procedural complication (22). Long-term follow-up in the second National Heart, Lung, and Blood Institute PTCA Registry revealed worse outcomes four years after an index procedure in women. However, this finding was partially explained by the presence of more risk factors for mortality (23). Bell et al. (16) observed that, in the years preceding the frequent use of GP IIb/IIIa antagonists, procedural success rates were similar in women and men, but that female gender was a weak but independent predictor of in-hospital mortality. Correction for body surface area further weakened this association. Jacobs et al. (3) observed that within the Bypass Angioplasty Revascularization Investigation

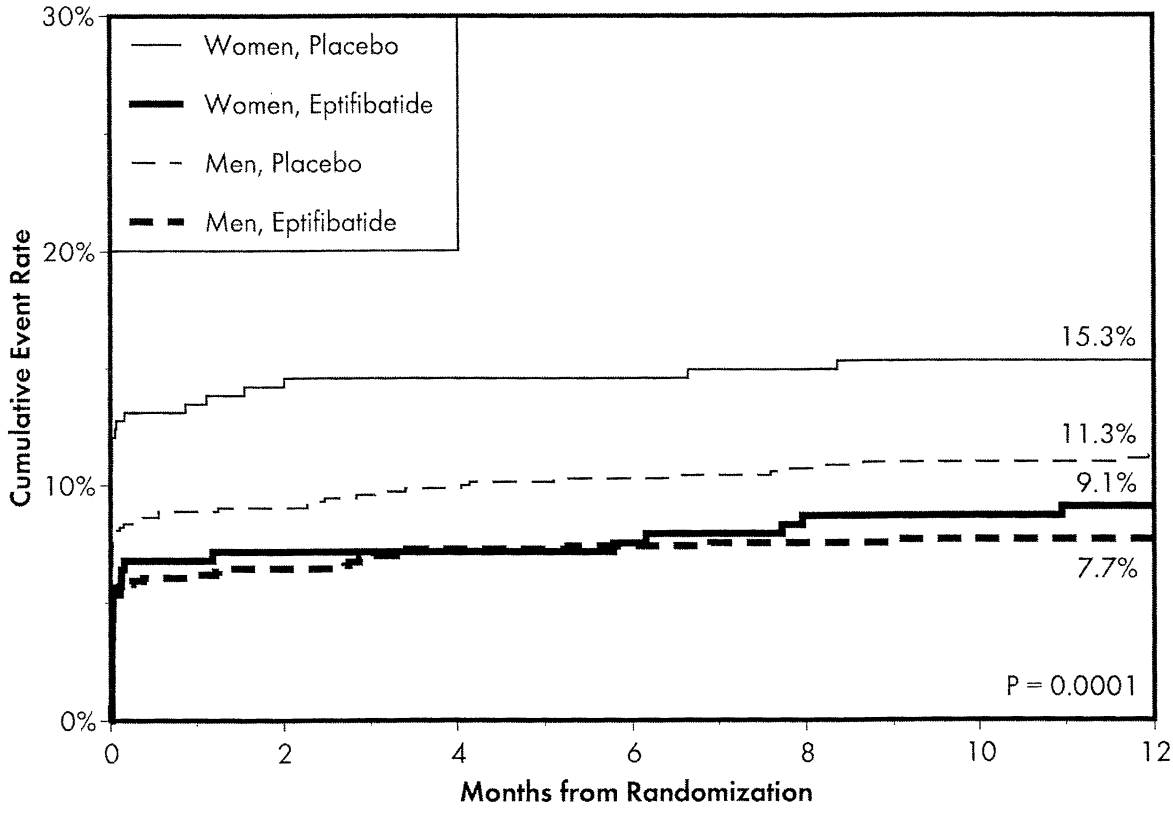

Figure 3. Kaplan-Meier estimates of death or myocardial infarction during the first year according to gender and eptifibatide treatment.

(BARI), five-year survival among women undergoing PCI was nearly identical to that of men. However, when the randomized cohort from this trial was pooled with a registry cohort, female gender proved to be an independent predictor of improved outcome. More appropriate selection of patients and the availability of intracoronary stents may have led to reductions in the observed differences between men and women (17,20). However, vascular complications and postprocedural acute renal failure remain more common in women (18,20).

Comparison with other studies. Although periprocedural morbidity and mortality following PCI are prevented by GP IIb/IIIa antagonists, few investigators have compared the protective effects of GP IIb/IIIa antagonists in men and women. In a pooled analysis from the Evaluation of Platelet Inhibition on Ischemic Complications of PTCA (EPIC), Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG), and Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trials, the primary end point, a composite of death, MI, and urgent TVR at 30 days, was reduced in patients treated with abciximab from 11.3% to 5.8% ($p < 0.001$) in men compared with a reduction from 12.7% to 6.5% ($p < 0.001$) in women. This benefit persisted to one year. However, women in this analysis were also more prone to develop major and minor bleeding complications (2).

Unlike the current analysis, data from the PURSUIT trial suggested an interaction between gender and eptifibatide treatment effect consistent with more bleeding as well as less protection against ischemia in women. Several factors may account for the different observations made in PURSUIT and ESPRIT. Foremost among these are the homogeneity of the population enrolled and the therapeutic approach in the ESPRIT trial compared with the heterogeneity of the population and clinical practices in PURSUIT.

As a "real world" trial, PURSUIT permitted the care provider wide latitude in patient enrollment and treatment of patients with suspected (but not necessarily confirmed) acute coronary syndromes. Whether and when to perform PCI as well as procedural details were left to individual PCI operators; 25% of patients in PURSUIT underwent coronary intervention, and approximately 12.5% underwent intervention while receiving the study drug (24). Additionally, 60% of the interventions in PURSUIT involved placement of an intracoronary stent compared with 96% in ESPRIT. Moreover, PURSUIT was performed on an international basis, and there appeared to be important interactions between gender and regional clinical practice. In North America, for example, the frequency of early (<72 h) intervention was highest in PURSUIT, and the outcomes of men and women were not different (25). ESPRIT was performed entirely in North America. By design, the strategies tested in ESPRIT represent a considerably more homogeneous treatment pattern. A recent meta-analysis of GP IIb/IIIa antagonists in patients with acute coronary syndromes confirmed these findings. A beneficial treatment

effect was observed in men, but not in women. However, when the analysis was restricted to patients with objective markers of active ischemia (i.e., troponin-T elevation), no interaction existed between gender and GP IIb/IIIa treatment (26).

It is important to emphasize that ESPRIT included a population of patients largely undergoing nonurgent procedures using modern interventional techniques. Approximately 96% of patients enrolled in ESPRIT received intracoronary stents and postprocedural treatment with a thienopyridine. The current data, then, performed in an extremely homogeneously managed population, indicate that the clinical benefit of GP IIb/IIIa antagonism with eptifibatide is likely to be similar in women and in men.

Study limitations. The current analysis has three limitations. First, by design, ESPRIT lacked adequate statistical power to analyze results for each gender independently. Second, because ESPRIT was designed to collect information rapidly in a large population, there was no angiographic core laboratory, and the amount of angiographic data is consequently limited. Detailed comparison of angiographic differences between women and men is therefore not possible within this data set. More detailed data concerning angiographic characteristics of lesions dilated and of coronary arterial diameters would have been useful to understand the one-year outcomes, particularly as postprocedural lesion diameter is a major determinant of restenosis (27). Similarly, we did not inquire about menopausal status or the use of hormone replacement therapy. Finally, the ESPRIT population was limited to patients undergoing nonurgent procedures and did not include patients undergoing primary PCI.

Clinical implications. Even in the modern era of PCI, periprocedural ischemic events are more common among women than among men. Double-bolus eptifibatide in the setting of low-dose-adjusted heparin, aspirin, and a thienopyridine prevented ischemic events similarly in both women and men immediately after PCI, with sustained results up to one year. Although bleeding after eptifibatide treatment was more common in women than in men, no difference was seen after adjustment for previously identified major covariates. These findings suggest that platelet GP IIb/IIIa antagonism with eptifibatide is an effective therapy to prevent ischemic complications in women undergoing PCIs.

Reprint requests and correspondence: Dr. Neal S. Kleiman, The Methodist Hospital, 6565 Fannin Street, F-1090, Houston, Texas 77030. E-mail: nkleiman@bcm.tmc.edu.

REFERENCES

1. Williams DO, Holubkov R, Yeh W, et al. Percutaneous coronary intervention in the current era compared with 1985–1986: the National Heart, Lung, and Blood Institute registries. Circulation 2000; 102:2945–51.
2. Cho L, Topol EJ, Balog C, et al. Clinical benefit of glycoprotein IIb/IIIa blockade with abciximab is independent of gender: pooled analysis from EPIC, EPILOG and EPISTENT trials. Evaluation of 7E3 for the Prevention of Ischemic Complications. Evaluation in Percutaneous Transluminal Coronary Angioplasty to Improve Long-Term Outcome with Abciximab GP IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stent. J Am Coll Cardiol 2000;36: 381–6.
3. Jacobs AK, Kelsey SF, Brooks MM, et al. Better outcome for women compared with men undergoing coronary revascularization: a report from the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 1998;98:1279–85.
4. The EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956–61.
5. The EPILOG investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689–96.
6. EPISTENT investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. Lancet 1998;352:87–92.
7. The ESPRIT investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037–44.
8. The PURSUIT trial investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436–43.
9. Faraday N, Goldschmidt-Clermont PJ, Bray PF. Gender differences in platelet GPIIb/IIIa activation. Thromb Haemost 1997;77:748–54.
10. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.
11. Berkowitz SD, Granger CB, Pieper KS, et al. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. The Global Utilization of Streptokinase and Tissue Plasminogen activator for Occluded coronary arteries (GUSTO) I investigators. Circulation 1997;95:2508–16.
12. American Heart Association. 2001 Heart and Stroke Statistical Update. Dallas, TX: American Heart Association, 2001.
13. Steingart RM, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease. Survival and Ventricular Enlargement investigators. N Engl J Med 1991;325:226–30.
14. Miller TD, Roger VL, Hodge DO, Hopfenspirger MR, Bailey KR, Gibbons RJ. Gender differences and temporal trends in clinical characteristics, stress test results and use of invasive procedures in patients undergoing evaluation for coronary artery disease. J Am Coll Cardiol 2001;38:690–7.
15. Detre K, Holubkov R, Kelsey S, et al. Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981. The National Heart, Lung, and Blood Institute Registry. N Engl J Med 1988;318: 265–70.
16. Bell MR, Holmes DR Jr., Berger PB, Garratt KN, Bailey KR, Gersh BJ. The changing in-hospital mortality of women undergoing percutaneous transluminal coronary angioplasty. JAMA 1993;269:2091–5.
17. Mehilli J, Kastrati A, Dirschinger J, Bollwein H, Neumann FJ, Schomig A. Differences in prognostic factors and outcomes between women and men undergoing coronary artery stenting. JAMA 2000; 284:1799–805.
18. Robertson T, Kennard ED, Mehta S, et al. Influence of gender on in-hospital clinical and angiographic outcomes and on one-year follow-up in the New Approaches to Coronary Intervention (NACI) registry. Am J Cardiol 1997;80:26K–39K.
19. Antoniucci D, Valenti R, Moschi G, et al. Sex-based differences in clinical and angiographic outcomes after primary angioplasty or stenting for acute myocardial infarction. Am J Cardiol 2001;87:289–93.
20. Ahmed JM, Dangas G, Lansky AJ, et al. Influence of gender on early and one-year clinical outcomes after saphenous vein graft stenting. Am J Cardiol 2001;87:401–5.
21. Ellis SG, Roubin GS, King SB III, et al. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. Circulation 1988;77:372–9.

22. Ellis SG, Roubin GS, King SB III, et al. In-hospital cardiac mortality after acute closure after coronary angioplasty: analysis of risk factors from 8,207 procedures. J Am Coll Cardiol 1988;11:211–6.
23. Kelsey SF, James M, Holubkov AL, Holubkov R, Cowley MJ, Detre KM. Results of percutaneous transluminal coronary angioplasty in women. 1985–1986 National Heart, Lung, and Blood Institute's Coronary Angioplasty Registry. Circulation 1993;87:720–7.
24. Kleiman NS, Lincoff AM, Flaker GC, et al. Early percutaneous coronary intervention, platelet inhibition with eptifibatide, and clinical outcomes in patients with acute coronary syndromes. PURSUIT investigators. Circulation 2000;101:751–7.
25. Lincoff AM, Harrington RA, Califf RM, et al. Management of patients with acute coronary syndromes in the United States by platelet glycoprotein IIb/IIIa inhibition. Insights from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. Circulation 2000;102:1093–100.
26. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. Lancet 2002;359:189–98.
27. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993;21:15–25.