

Catheter-Based Revascularization Strategies for Acute Coronary Syndromes in Women

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Women with acute coronary syndromes who present for percutaneous revascularization have clinical characteristics that place them at higher risk for adverse events. These women are older with an increased incidence of hypertension, diabetes, and congestive heart failure. At angiography, women with epicardial coronary disease tend to have smaller diameter vessels, which predict an increase in procedural complications. Recent observations suggest that in the new device era, women with unstable angina/non-Q myocardial infarction may have clinical outcomes similar to their male counterparts; however, women who present with acute ST-elevation myocardial infarction and undergo catheter-based revascularization procedures remain at increased risk for adverse events. Although adjunctive glycoprotein IIb/IIIa antagonists may improve procedural outcomes, women undergoing catheter-based revascularization procedures are at increased risk for hemorrhagic complications. Despite these high-risk features, catheter-based reperfusion therapies remain an effective treatment strategy in women with acute coronary syndromes. [Rev Cardiovasc Med. 2001;2(4):181–189]

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Women with acute coronary syndromes are increasingly being referred for catheter-based percutaneous revascularization procedures earlier in the course of their symptoms. Despite this increased awareness of women with coronary artery disease, women often have clinical characteristics at presentation, which are associated with an increased risk for adverse events. This review will highlight issues that are relevant to percutaneous revascularization strategies for women with acute coronary syndromes. These include specific clinical, angiographic, and procedural characteristics and outcomes, and the results of percutaneous coronary interventions in women with specific clinical syndromes.

Clinical, Angiographic, and Procedural Characteristics

Women who undergo percutaneous coronary intervention often do so at an increased risk for adverse events, and, in fact, have more clinical characteristics that are associated with poor outcome when compared to men. These women tend to be older and have a higher prevalence of diabetes mellitus, hypertension, and hypercholesterolemia than men.¹⁻⁶ Although fewer women who present with acute coronary syndromes have had a previous myocardial infarction or evidence of left ventricular dysfunction, they are more likely to have an episode of congestive heart failure than men, a phenomenon that has been attributed to the increased prevalence of diastolic dysfunction in women.⁷ Finally, women often have significant comorbid disease and are less likely to be considered optimal candidates for surgical revascularization as compared to men.

At angiography, women tend to have smaller diameter coronary arteries with more calcified and ostial lesions than men despite a similar total lesion number and distribution.^{3,5,8} Interestingly, it has recently been shown that patients with small diameter reference vessels (<2.5 mm) are more often women, older, and have a type-C lesion. Compared to patients with larger vessels (>2.5 mm), these patients were more likely to be treated with balloon angioplasty (73% vs 50%) and rotational atherectomy (16.1% vs 8.3%) than stents (18.5% vs 41.9%) and directional atherectomy (3.7% vs 13.5%). This difference in device utilization significantly influenced major adverse cardiac events that occurred with increased frequency in patients with small diameter vessels.⁸

It has also been suggested that plaque morphology in women may differ from men, such that there is an

increased risk for dissection during percutaneous revascularization procedures. In a recent report, women who underwent balloon angioplasty did so with a similar rate of success as men, yet had a significant increase in plaque dissection requiring stent placement (70.4% vs 52.2%, $P < .05$). Despite an adequate final result with stent placement, plaque dissection was associated with an increase in procedural complications.⁹

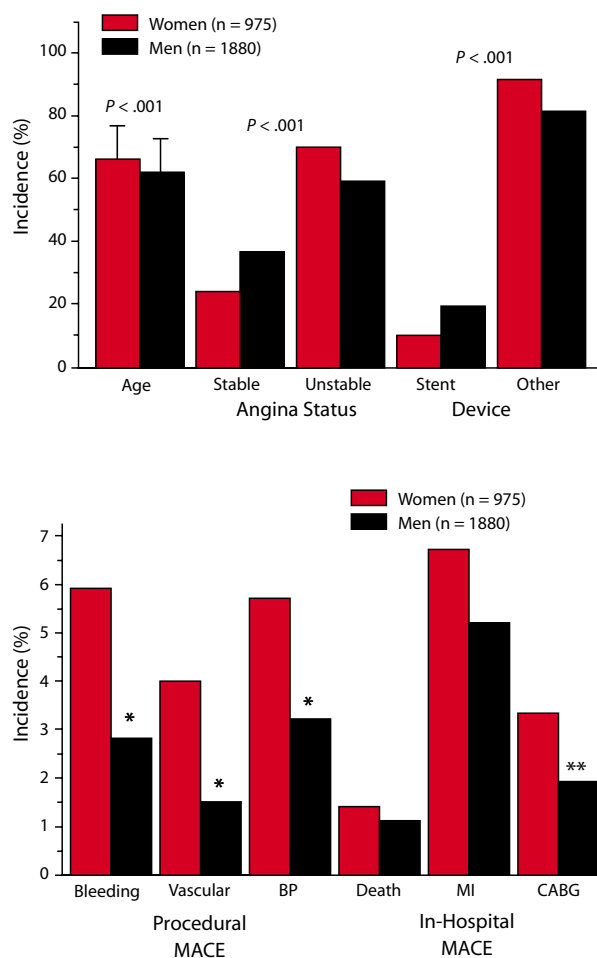
Due to differences in autonomic and hemodynamic responses in women compared to men, women may be less likely to tolerate periods of transient ischemia during percu-

taneous coronary revascularization procedures.¹⁰ For example, in a series of 140 men and 65 women undergoing single vessel coronary revascularization, total occlusion of the coronary vessel was associated with more chest pain and ST-segment changes in women. This was accompanied by a greater incidence of significant bradycardia (31% vs 13%), increase in heart rate variability (25% vs 11%), and a decrease in systolic blood pressure.¹¹

Outcomes

Historically, women undergoing percutaneous coronary intervention

Figure 1. Clinical status and device utilization (top) and procedural and in-hospital outcomes (bottom) in women undergoing percutaneous revascularization in the New Approaches to Coronary Intervention (NACI) Registry.¹² * $P < .01$, ** $P < .05$; BP, hypotension; MACE, major adverse cardiac events; MI, myocardial infarction.



had a lower procedural success rate and an increased mortality compared to men^{1,3,5}; however, in the new device era these outcomes have significantly improved. In the New Approaches to Coronary Intervention (NACI) Registry, (Figure 1) women had more adverse clinical characteristics than men including advanced age and more recent onset of symptoms that were severe and unstable. Although women were less likely to receive a stent, procedural success rates between men and women were similar. However, women experienced more procedural complications including coronary artery dissection, hypotension, vascular access repair, and need for transfusion. Despite these adverse procedural events, there was no significant gender-based difference in the rate of in-hospital death or myocardial infarction, although women were more likely to require surgical revascularization. At 1-year follow-up, more

women reported a reduction in their anginal symptoms (70% vs 62%) and required fewer repeat revascularization procedures (32% vs 36%) than men.¹² In the Bypass Angioplasty Revascularization Investigation (BARI) trial, at an average of 5.4 years follow-up, mortality rates in these high-risk women who underwent balloon angioplasty were similar to men (12.8% vs 12.0%), and after adjustment for differences in baseline characteristics, women had a significantly lower risk of death.¹³ Furthermore, in the National Heart, Lung and Blood Institute registry experience, women undergoing balloon angioplasty more recently have improved outcomes despite their high-risk status in comparison to women treated from 1985–1986.¹⁴

Unstable Angina/Non-Q Myocardial Infarction

Women who present with acute coronary syndromes that undergo

percutaneous coronary interventions are also consistently older and have a higher incidence of hypertension and diabetes than men. In one report of 313 consecutive patients (210 men and 103 women) who presented to a tertiary referral center with unstable angina, women had a higher incidence of diabetes (23% vs 11%, $P = .007$) and hypertension (52% vs 32%, $P = .001$) compared to men. At angiography, the number of diseased vessels was comparable as was the proportion of women that underwent percutaneous revascularization procedures. The overall in-hospital mortality was not significantly higher in women.¹⁵ In another series of 941 women with acute coronary syndromes who underwent angioplasty, the rate of procedural success, in-hospital mortality, and emergent coronary artery bypass surgery was similar between men and women. Over a 4-year follow-up period, over-

Table 1
Revascularization in Women with Unstable Angina

	Women (n = 1160)	Men (n = 1788)	P
Mean Age (years) \pm SD	65.2 \pm 13.7	60.4 \pm 13.0	.001
Hypertension (%)	66	57	.001
Diabetes (%)	31	23	.001
Tobacco use (%)	21	28	.001
Prior MI (%)	32	39	.001
Prior CHF (%)	18	12	.001
Prior CABG (%)	16	25	.001
+ ETT* (%)	5.5	9.3	.002
Catheterization (%)	44	53	.002
PTCA (%)	12	18	.02
CABG (%)	7	10	.001

*Only 28.5% of women and 28.3% of men underwent diagnostic stress testing; CABG, coronary artery bypass surgery; CHF, congestive heart failure; ETT, exercise treadmill test; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation.

Data from Scirica et al.¹⁸

all survival was also comparable between women and men.¹⁶

In the TIMI IIIB trial and Registry, women with acute coronary syndromes were older, non-Caucasian, had a higher incidence of diabetes and hypertension, and were treated with more cardiac medications than their male counterparts. Coronary angiography demonstrated less severe obstructive epicardial coro-

ary disease (25% vs 14%, $P = .0001$). Despite these clinical and procedural differences, women and men had similar clinical outcomes.¹⁸

A recent series evaluated 101 women who presented with a non-Q myocardial infarction and underwent percutaneous revascularization prior to discharge. Women were significantly older with an increased incidence of hypertension and higher

plasty, were more likely to be older (57 vs 67 years, $P < .001$), with a higher incidence of hypertension and contraindications to thrombolytic therapy (28.5% vs 42.5%, $P = .02$) than men. Despite equivalent rates of successful reperfusion of the infarct-related artery, regardless of strategy, women had a significantly higher in-hospital mortality rate compared to men (18.7% vs 7.2%, $P = .001$).²⁰ These observations were confirmed in another series that demonstrated that women treated with thrombolytic agents achieve similar 90-minute patency rates and regional ventricular function as men; however, these benefits did not influence 30-day mortality rates, which remained higher for women (13.1% vs 4.8%, $P < .0001$).²¹

It has been suggested that women have a worse outcome following acute myocardial infarction due to differences in the utilization of diagnostic coronary angiography and subsequent percutaneous revascularization as part of the treatment plan. In the Atherosclerosis Risk in Communities (ARIC) study, women were less likely than men to undergo coronary angiography whether

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nary artery disease in women with insignificant disease reported in more women than men (25% vs 16%). Corresponding left ventricular ejection fraction was also better in women than men ($62 \pm 12\%$ vs $57 \pm 13\%$, $P < .01$). Medical management failed as often in women as in men, resulting in similar rates of percutaneous revascularization. In addition, there was no difference between men and women in the 42-day rate of death and myocardial infarction (7.4% vs 7.5%).¹⁷

These findings were confirmed in the Global Unstable Angina Registry and Treatment Evaluation (GUARANTEE) Registry (Table 1), which evaluated 2948 patients (39% women) with unstable angina admitted to 35 hospitals in the United States. Women presented with more adverse clinical characteristics than men, yet were less likely to undergo cardiac catheterization (44% vs 53%, $P = .002$) or coronary angioplasty (12% vs 18%, $P = .02$). Of those women that did proceed to angiography, they had less severe coronary artery disease than men, and, in fact, were more likely to have insignificant epicardial coronary

ejection fraction ($50 \pm 10\%$ vs $47 \pm 1\%$, $P < .001$) than men. Percutaneous revascularization rates were similar between women and men, although fewer lesions were dilated per patient in females (1.38 vs 1.51, $P < .04$). Interestingly, there was a trend towards an increase in in-hospital death rates in women (4% vs 1%, $P = .058$); however, at 1-year follow-up, women had a significantly lower survival rate than men (89% vs 95%, $P < .04$). Repeat percutaneous revas-

The prognosis for women following acute myocardial infarction in the thrombolytic era remains controversial.

cularization rates were similar between women and men but men were more likely to undergo coronary artery bypass surgery during this time.¹⁹

Myocardial Infarction

The prognosis for women following acute myocardial infarction in the thrombolytic era remains controversial. Women admitted during the first 6 hours of an acute myocardial infarction, treated with thrombolytic agents or primary or rescue angio-

treated at a community or teaching hospital.²² In contrast to these observations, a recent single center experience demonstrated that age-adjusted rates of coronary angiography were similar between women and men as was the rate of coronary angioplasty.²³

Primary Angioplasty

Since women are at higher risk for early and late mortality following acute myocardial infarction and are more likely to have a contraindica-

tion to thrombolysis than men, mechanical reperfusion has been advocated as a therapeutic strategy. Catheter-based revascularization strategies to restore coronary patency during acute myocardial infarction in the absence of prior or concomitant thrombolytic therapy, or primary angioplasty, result in a higher infarct-related artery patency rate,²⁴ smaller enzymatic infarct size, preservation of left ventricular function and improved clinical outcome compared to thrombolytic therapy.²⁵⁻²⁷

Women who present with acute ST-elevation myocardial infarction comprise a higher risk patient population than their male counterparts. This was demonstrated in the Primary Angioplasty in Myocardial Infarction (PAMI) trial, which compared primary angioplasty with tissue-type plasminogen activator, and revealed that women were older (65.7 vs 57.7 years, $P < .0001$), with a higher incidence of systemic hypertension (54% vs 39%, $P < .005$),

diabetes mellitus (19% vs 10%, $P < .03$) and congestive heart failure (5% vs 0%, $P = .002$) compared to men. Women were also more likely to present later following the onset of symptoms (229 vs 174 minutes, $P = .0004$). These observations were believed to contribute to the 3.3-fold increase in in-hospital mortality observed in women compared to men (9.3% vs 2.8%, $P = .0005$).^{25,28} In fact, in the subgroup of women who were assigned to undergo coronary angiography, women were more likely to have either insignificant coronary artery disease that did not require percutaneous revascularization or surgical disease. In women that did undergo percutaneous revascularization, the in-hospital mortality rate was not significantly different compared to men (4.0% vs 2.1%). Interestingly, younger age as well as percutaneous revascularization were independent predictors of in-hospital survival in women. Of note, cerebrovascular hemorrhage

occurred in 5.3% of women assigned to thrombolytic therapy as compared with 0.7% of men ($P = .037$). There was no gender-specific significant increase in bleeding events with primary angioplasty. These observations suggest that primary angioplasty improves survival in women and reduces the risk of intracranial hemorrhage associated with thrombolytic agents.^{28,29}

Contemporary percutaneous revascularization strategies for the treatment of acute myocardial infarction increasingly involve stent implantation. The Stent-PAMI trial compared coronary stent implantation utilizing a heparin-coated stent with balloon angioplasty. At 6-month follow-up, fewer patients in the stent group had angina (11.3% vs 16.9%, $P = .02$) or required target vessel revascularization due to recurrent ischemia (7.7% vs 17%, $P < .001$) than in the angioplasty group. In addition, the combined endpoint of death, reinfarction, disabling stroke, or target-

Table 2
Outcomes in Women Undergoing Primary Angioplasty for Acute Myocardial Infarction

	Women (n=227)	Men (n=673)	P
Mean Age (years) \pm SD	66 \pm 12	58 \pm 12	.0001
Hypertension (%)	53.3	38.3	.0001
Diabetes (%)	21.9	12.7	.0009
Hypercholesterolemia (%)	48.2	39.9	.045
Procedural Characteristics			
Infarct vessel size (mm)	2.96	3.12	.0001
TIMI grade 3 flow (%)	94	90	.07
Six-month outcome			
Mortality (%)	7.9	2.0	.0002
Reinfarction (%)	6.4	2.7	.01
Stroke (%)	2.0	0.3	.01
TVR (%)	13.8	10.5	NS

SD, standard deviation; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization.
Data from Stone et al.³¹

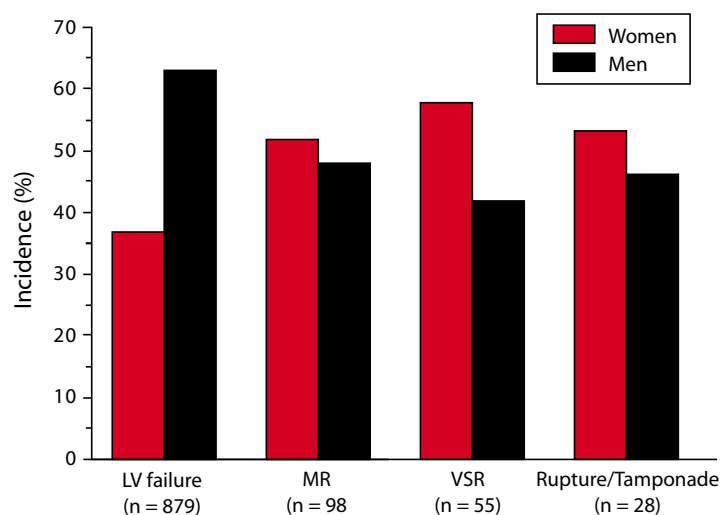


Figure 2. The etiologies of cardiogenic shock in women.³²⁻³⁶ LV, left ventricular; MR, mitral regurgitation; VSR, ventricular septal rupture.

vessel revascularization occurred in fewer patients in the stent group than in the angioplasty group (12.6% vs 20.1%, $P < .01$).³⁰

Women enrolled in this trial had more clinical characteristics that portend a worse outcome than their male counterparts (Table 2). Women were older (66 vs 58 years, $P < .0001$), and had a higher incidence of hypertension, diabetes, and hypercholesterolemia compared to men. At angiography, women had a smaller diameter infarct-related artery; however, Thrombolysis in Myocardial Infarction (TIMI) grade-3 flow was restored more frequently in women than men (94% vs 90%, $P = .07$). Interestingly, despite this improved procedural success, women had increased 6-month rates of mortality (7.9% vs 2.0%, $P = .0002$), reinfarction (6.4% vs 2.7%, $P = .01$), and cerebrovascular accident (2.0% vs 0.3%, $P = .01$). These observations again demonstrate that women who undergo contemporary catheter-based reperfusion therapies remain at increased risk for adverse outcomes.³¹

Cardiogenic Shock

Cardiogenic shock, defined as sys-

temic hypotension accompanied by end-organ hypoperfusion and elevated cardiac filling pressures, complicates acute myocardial infarction in 5% to 15% of patients.³² Patients who present with or develop shock are more likely to be women.³² To determine if catheter-based revascularization therapies improve outcome in cardiogenic shock, the Should We Emergently Revascularize Occluded Coronary Arteries for Cardiogenic Shock (SHOCK) trial was conducted and reported no significant difference in 30-day mortality between patients assigned to medical therapy or percutaneous or surgical revascularization; however, by 6 months there was a survival benefit for patients who underwent revascularization procedures. Notably, patients 75 years of age or older did significantly worse if they underwent coronary artery bypass surgery or angioplasty.³³ As women who present with acute ST-elevation myocardial infarction are often older, these observations suggest a worse outcome in this group of female patients. In the SHOCK registry (Figure 2), women accounted for

approximately 40% of the patients and were more likely to be in cardiogenic shock due to acute severe mitral regurgitation,³⁴ ventricular septal rupture,³⁵ or isolated right ventricular shock,³⁶ than from predominant left ventricular pump failure. Shock resulting from ventricular septal rupture was associated with a significant increase in mortality compared with shock secondary to severe left ventricular dysfunction.³⁶ Women followed in the registry were more often diabetic with multivessel disease, yet the combined percutaneous and surgical revascularization rate for these patients was lower than that for non-diabetic patients with single vessel disease.³⁷

Rescue Angioplasty

Rescue angioplasty refers to the use of catheter-based reperfusion therapies to mechanically reopen an occluded infarct-related artery following failed thrombolytic administration. Although this strategy is utilized frequently, data regarding its efficacy remains controversial. Contrary to expectation, early studies demonstrated that patients who underwent a successful rescue procedure, compared to those where TIMI grade 3 flow was not achieved, had a higher rate of in-hospital adverse events. In fact, patients who underwent percutaneous revascularization procedures had a similar incidence of adverse outcomes as patients who failed thrombolytic therapy and had no further intervention.³⁸ One possible explanation for these findings is that patients who are selected for catheter-based revascularization following thrombolytic failure represent a patient population at high-risk for poor outcome.³⁹

Interestingly, in the rescue angioplasty trial, which randomized patients who presented with an anterior myocardial infarction treated

with thrombolytic agents and had a totally occluded infarct-related artery at angiography to conservative treatment or mechanical revascularization, women who underwent catheter-based revascularization procedures had a lower mortality rate, less congestive heart failure, and improved exercise ejection fraction compared to women treated conservatively. Therefore, this suggested that women may represent one patient cohort that benefits from this procedure.⁴⁰

However, the risk of hemorrhagic complications may limit the benefits realized by rescue intervention in women. It has been suggested that patients that fail thrombolytic therapy may have an increased or recalcitrant thrombus burden that requires additional aggressive antiplatelet pharmacologic therapy. This strategy has met with some uncertainty, especially in women, who appear to be at increased risk for hemorrhagic complications. In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-III trial, which investigated the role of abciximab in a subgroup of patients undergoing rescue angioplasty, there was a trend towards increased bleeding complications in abciximab-treated patients.⁴¹ In fact, moderate to severe hemorrhagic

complications have been documented in up to 18% of patients undergoing rescue catheter-based revascularization procedures and female gender was shown to be an independent predictor of this adverse event.⁴²

Facilitated Angioplasty

Facilitated catheter-based revascularization procedures combine reduced dose thrombolytic agents with percutaneous coronary intervention in an attempt to improve early infarct-related artery patency rates. This strategy was initially believed to

restored mechanically within 1 hour, ejection fraction was improved compared to those patients whose artery remained occluded for more than 1 hour (62.5% vs 57.3%).⁴³ Although this strategy appears efficacious, due to the increased risk of bleeding complications, further investigation is warranted.

Adjunctive Glycoprotein IIb/IIIa Antagonists

Thrombus formation is associated with acute coronary syndromes and has been shown to complicate per-

Women who present with acute coronary syndromes that undergo percutaneous coronary interventions are also consistently older and have a higher incidence of hypertension and diabetes than men.

be deleterious; however, in the Plasminogen-Activator Angioplasty Compatibility (PACT) trial, which randomized patients to a bolus of a short acting thrombolytic agent or placebo and immediate angioplasty, women who received the thrombolytic bolus had a significant increase in vessel patency. Notably, it was found that the time to restoration of coronary flow determined left ventricular function. If the infarct-related artery was patent on initial angiography or flow was

cutaneous revascularization procedures.⁴⁴ It has been suggested that there is a gender-based difference in platelet function and this may account for some of the differences in outcomes in women compared to men. As women are believed to have hyperreactive platelets, it follows that they would benefit significantly from the addition of these platelet antagonists.⁴⁵

In women treated with abciximab in the EPIC, EPILOG, and EPISTENT trials, analysis of the pooled data

Main Points

- Women undergoing percutaneous interventions have more clinical characteristics associated with poor outcomes than men, including older age, and higher prevalence of diabetes, hypertension, and hypercholesterolemia.
- Women have smaller diameter arteries than men, making them more likely to be treated by angioplasty and rotational atherectomy than stents and directional atherectomy.
- Though women experienced a higher procedural complication rate (dissection, hypotension, vascular access repair and need for transfusion) there was no difference in the rate of in-hospital mortality or myocardial infarction.
- Regardless of strategy used to treat women with acute myocardial infarction, they had a significantly higher in-hospital mortality rate compared to men.
- Primary coronary angioplasty seems to result in improved survival and reduces the risk of intracranial hemorrhage associated with thrombolytic agents.
- Women who undergo catheter based revascularization procedures, especially diabetic women, benefit from the use of glycoprotein IIb/IIIa receptor antagonists.

demonstrated that platelet inhibition with this agent resulted in a significant reduction in the primary endpoint of death, myocardial infarction, or urgent revascularization at 30 days (12.7% vs 6.5%, $P < .001$), and that this reduction in adverse events was evident at 6 months (16.0% vs 9.9%, $P < .001$). At 1-year follow-up, there was also a reduction in mortality from 4% to 2.5%.⁴⁶

Diabetic women, a high-risk subset of women, appeared to benefit significantly from the addition of abciximab to percutaneous revascularization procedures. While there was no early difference observed in acute outcomes, by 1 year there was a marked reduction in death, myocardial infarction, or target vessel revascularization in women who received abciximab with catheter-based reperfusion therapies. This benefit was largely driven by a decrease in target vessel revascularization rates, which were reduced, from 21.1% in the stent-placebo group to 4.5% in the stent-abciximab group ($P = .02$).⁴⁷ The administration of a glycoprotein IIb/IIIa antagonist did not increase major bleeding events; however, there was a detectable increase in minor bleeding events (4.7% vs 6.7%).⁴⁷

It has also been reported that women who received eptifibatide as an adjunct to catheter-based revascularization procedures also had a significant reduction in the rate of death, myocardial infarction, urgent revascularization, or bailout stent placement (11.6% vs 9.1%, $P < .04$), that was gender-independent with no significant increase in bleeding complications.⁴⁸ Women received a similar positive benefit with eptifibatide in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, which investigated the role of this

agent as an adjunct to stent placement. Sub-group analysis revealed that women who received eptifibatide had a 58% relative reduction in events compared with women treated with placebo.⁴⁹ In women treated with tirofiban in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS) trial, a similar 7-day composite endpoint reduction occurred in men and women.⁵⁰

These studies suggest that women who undergo catheter-based revascularization procedures, especially diabetic women, will benefit from the adjunctive administration of a glycoprotein IIb/IIIa receptor antagonist; however, the risk-benefit profile with respect to bleeding complications may influence the decision to select one of these agents.

Conclusion

Women are increasingly offered catheter-based procedures as part of a revascularization strategy in the new device era. As patients, women with acute coronary syndromes are older with an increased incidence of coronary artery disease risk factors that predict a worse outcome. In fact, this profile suggests that women undergo interventional procedures at higher risk for major adverse events; however, recent advances in device design and adjunctive pharmacologic therapies have improved outcomes and suggest that catheter-based revascularization strategies are safe and efficacious in women. ■

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