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Percutaneous Coronary Intervention and Adjunctive Pharmacotherapy in Women

A Statement for Healthcare Professionals From the American Heart Association

Alexandra J. Lansky, MD, Chair; Judith S. Hochman, MD; Patricia A. Ward, MA; Gary S. Mintz, MD; Rosalind Fabunmi, PhD; Peter B. Berger, MD; Gishel New, MD; Cindy L. Grines, MD; Cody G. Pietras; Morton J. Kern, MD; Margaret Ferrell, MD; Martin B. Leon, MD; Roxana Mehran, MD; Christopher White, MD; Jennifer H. Mieres, MD; Jeffrey W. Moses, MD; Gregg W. Stone, MD; Alice K. Jacobs, MD

Endorsed by the American College of Cardiology Foundation

Abstract—More than 1.2 million percutaneous coronary interventions are performed annually in the United States, with only an estimated 33% performed in women, despite the established benefits of percutaneous coronary intervention and adjunctive pharmacotherapy in reducing fatal and nonfatal ischemic complications in acute myocardial infarction and high-risk acute coronary syndromes. This statement reviews sex-specific data on the safety and efficacy of contemporary interventional therapies in women. (*Circulation*. 2005;111:940-953.)

Key Words: AHA Scientific Statements ■ women ■ coronary disease ■ pharmacology ■ catheterization ■ angioplasty

More than 1.2 million percutaneous coronary interventions (PCIs) are performed annually in the United States.¹ Despite the fact that more women than men die from cardiovascular disease in the United States, and despite the established benefits of PCI in reducing fatal and nonfatal ischemic complications in patients with acute myocardial infarction and high-risk acute coronary syndromes, only an estimated 33% of annual PCIs are performed in women.¹⁻⁴ In addition, women experience greater delays⁵ to intervention and are referred for diagnostic catheterization less frequently than are men.⁶⁻⁸ Although suggested reasons for referral differences have included women's older age at presentation, greater risk profile, and increased risk for an adverse procedural outcome, as well as differences in symptoms and pain perception between men and women and lower predictive accuracy of noninvasive testing in women, some evidence suggests a potential sex and race bias.⁹ In contrast, once women are referred for cardiac catheterization, revascularization rates and practices are similar to those in men.¹⁰⁻¹²

Recent advances in angioplasty equipment and technique have improved options for patients with smaller coronary and

peripheral (access) arteries. In addition, the increased use of stents and adjunctive pharmacotherapy has improved outcomes in both women and men. Nevertheless, women continue to represent 15% to 38% of the population in studies of PCI, and still relatively few sex- or race-specific data exist.

The purpose of this statement is to review what is known and not known about PCI in women and to put published data in context with contemporary coronary intervention. It is not the intention of the writing group to give specific treatment recommendations but rather to compile and collate the available sex-specific data on the safety and efficacy of interventional therapies in women. Tables 1 and 3 provide summaries of the findings in women drawn from this literature review, as well as recommendations from previously published American College of Cardiology/American Heart Association (ACC/AHA) guidelines.

Methods

The information in this statement was compiled by systematic literature review. By searching MEDLINE from January

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1988 through January 2005, the writing group identified 2156 relevant publications. Of these publications, 142 were selected on the basis of the following criteria: sex-specific trials in interventional cardiology and pharmacotherapy, randomized clinical trials or large-scale registries of at least 250 consecutive patients, and review articles. These publications were then reviewed and summarized by dedicated medical writers (P.A.W., C.G.P.). The summary was used as the basis of a draft manuscript, which was written by the writing group chair. The manuscript was subsequently submitted for review to the entire writing group, and each member was assigned a specific section. Each section was reviewed by at least 2 group members, and the final document was fact-checked by the medical writers. The data presented are sex specific and consistent with relevant current ACC/AHA guidelines. Practice recommendations or trial results without supporting sex-specific data are specified. We contacted the investigators of eligible studies that did not report findings separately by sex to obtain these data; these citations are marked with the symbol §.

Sex Differences in Outcomes of PCI

The adverse outcomes of women undergoing PCI, including the rates of short- and long-term mortality,^{13,14} nonfatal myocardial infarction (MI),² and emergency coronary bypass surgery,^{13,15} have decreased significantly over time with contemporary interventional therapies. Nevertheless, women consistently tend to have worse clinical outcomes than those of men; most of these worse outcomes are explained by the higher risk profile of women.

The increased in-hospital mortality of women undergoing elective and primary PCI as compared with men,^{16–24} although not consistently observed^{13,15,25–34} (Figures 1 and 2), appears at least in some studies to represent a complex interplay of clinical factors such as delayed onset of disease, older age, smaller body surface area, and comorbidities at the time of presentation.³⁵ In contemporary emergency, urgent, or elective stent and drug-eluting stent (DES) clinical trials and registries, adjustments for these factors largely eradicate any sex differences, dispelling the notion of a sex-specific mortality risk.^{28,32,36,37} In the majority of studies, adjusted long-term mortality rates after PCI (1 year and beyond) are similar for men and women (Figures 1 and 2).^{23,28,38–40}

Historically, restenosis and revascularization rates have not been well defined for women, partly because of the small sample of women in prospective trials with systematic angiographic follow-up, as well as the paucity of published sex-subset analyses. Interestingly, it has been reported that women have similar or lower target vessel revascularization rates as compared with men after balloon angioplasty⁴¹ and stenting,^{30,38,42} despite women's smaller vessel sizes and higher prevalence of diabetes mellitus, factors typically associated with higher restenosis and revascularization rates after PCI. In the absence of systematic angiographic and clinical follow-up, the significance of this paradoxical finding can be misleading, possibly reflecting a true reduction in the need for repeat revascularization in women, a preference for medical management based on increased age and risk, or a potential referral bias. In contemporary prospective and independently adjudicated stent and DES trials with system-

atic angiographic follow-up, restenosis and revascularization rates have been shown to be similar or higher in women as compared with men and result from confounding risk factors such as diabetes, smaller body surface area, and smaller vessel size rather than from a sex-specific risk.^{43,44}

Vascular complications (such as access-site hematomas, bleeding complications requiring transfusion, and retroperitoneal bleeds) have improved over time in women with the development of less aggressive anticoagulation regimens, increasing use of weight-adjusted heparin dosing, and introduction of smaller sheath sizes and early sheath removal.^{45–47} Nevertheless, women still have a 1.5- to 4-times higher risk of vascular complications as compared with men (Figure 3), and female sex is an important contributing factor.^{28,32} Adjunctive use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors during PCI does not confer an independent added risk of major vascular complications in women,^{28,48,49} and the use of the direct thrombin inhibitor bivalirudin during elective PCI in lieu of unfractionated heparin appears to reduce that risk in women as it does in men.⁵⁰

Outcomes in Women by Device, Lesion Type, and Clinical Syndrome

The overall use of coronary stents, according to year 2000 data, is estimated to have reached 77% of interventional procedures in the United States, with no signs of a sex difference in stent application.^{13,32,51} These estimates are rapidly being supplanted by the increasing use of DES. Table 1 summarizes the outcomes in women after PCI by device, lesion type, and clinical syndrome.

Bare Metal Stents and DES

The wide acceptance of stents is based on the improved short-term procedural success, improved in-hospital outcomes, and reduced long-term restenosis and revascularization rates as compared with balloon angioplasty and other nonstent devices.^{52–54} Although no specific sex-based comparisons were performed or at least published in the earlier randomized clinical trials comparing stent implantation with balloon angioplasty,^{53,55} the superiority of stenting was demonstrated at all ranges of vessel sizes, including vessels <3.0 mm in diameter (specifically relevant to women). The benefits therefore have been presumed to be generalizable to women.⁵⁶ In the context of controlled clinical trials of elective stenting, the use of 3.0- to 4.0-mm stents has resulted in similar low unadjusted in-hospital mortality rates in women and men and similar rates of target vessel revascularization.⁵⁷ The long-term outcomes of small-vessel bare-metal stenting have not been evaluated in women. In a broader range of patient and lesion subsets, mortality rates are similar^{26,30,58} or higher^{18–20,23} in women after stenting because of confounding risk factors rather than female sex (Figures 1 and 2).¹³

With the recent approval of the sirolimus-eluting CYPHER stent (Cordis, Johnson & Johnson) on the basis of the SIRIUS (Sirolimus-Coated Bx VELOCITY Balloon-Expandable Stent in the treatment of patients with de novo coronary artery lesions) trial⁵⁹ and the paclitaxel-eluting TAXUS stent (Boston Scientific) on the basis of the

Study	N	Unadjusted Mortality Rate			P-Value
		% Women	Women vs. Men (%)		
Watanabe ²⁰	82783	35	1.1	0.5	<0.0001
Alfonso ¹⁹	981	16	6.0	2.0	0.01
WHC ¹⁸	7372	28	1.39	0.66	<0.002
Malenka ²⁴	12232	NA	1.64	0.7	<0.001
Bell ³⁴	3557	27	4.2	2.7	0.005
NHLBI ²²	2136	26	2.6	0.3	<0.001
NCN ^{*21}	150918	33	1.8	1.0	—
Mehillij ^{**23,42}	4264	24	3.1	1.9	0.02
Welty ³³	5989	35	1.2	0.52	0.017
Malenka ¹⁵	33666	33	1.2	1.1	0.1
NHLBI ¹³	2524	35	2.2	1.3	—
NCN ³²	109708	33	1.8	1.0	<0.001
Arnold ³¹	5000	25	1.1	0.3	0.001
NACI ³⁰	2855	34	1.4	1.1	NS
Weintraub ²⁹	10785	26	0.7	0.1	<0.001

* Adjusted OR is for women <50 years.

** In-hospital figures are for Death/MI.

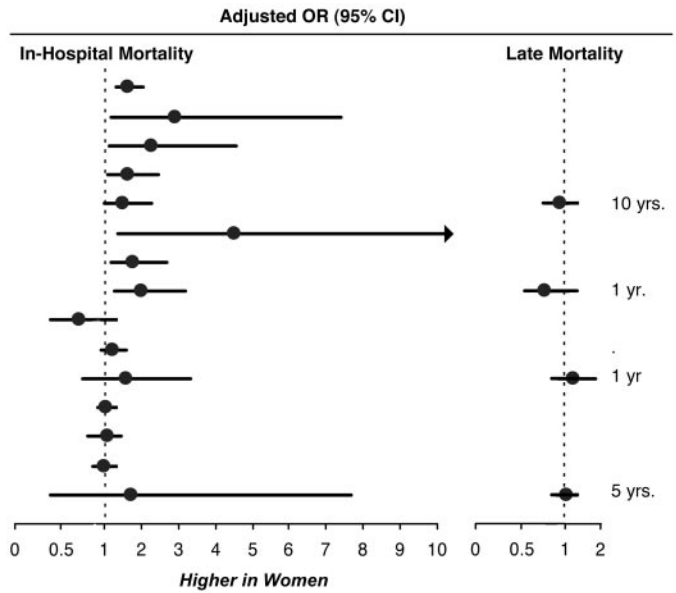


Figure 1. In-hospital and late mortality rates in women versus men after mostly elective PCI. WHC indicates Washington Hospital Center; NHLBI, National Heart, Lung, and Blood Institute; NCN, National Cardiovascular Network; and NACI, New Approaches to Coronary Intervention trial.

TAXUS IV (Treatment of De Novo Coronary Disease With a Single Paclitaxel-Eluting Stent trial,⁶⁰ crude estimates of market penetration approach 60% to 70% and are expected to continue to rise. Both the SIRIUS trial and the TAXUS IV trial have demonstrated that the reductions in restenosis, target vessel revascularization, and major adverse cardiac events at 1-year follow-up are of similar magnitude in men and women.^{43,61} Early data suggest favorable long-term results for drug-eluting stenting of small vessels (≤ 2.75 mm) in both men and women.⁶²

Other Devices and Lesion Types

Few sex-specific data exist on the efficacy of ablative devices. Although rarely used today, directional atherectomy is associated with lower procedural success and more bleeding complications in women than in men.^{25,63,64} Excimer laser angioplasty, also rarely performed in the current PCI era, is associated with more coronary perforations in women, primarily attributed to women's smaller vessel sizes.⁶⁵ No sex-specific data exist on the use of rotational atherectomy, cutting balloon angioplasty, or

Study	N	Unadjusted Mortality Rate			P-Value
		% Women	Women vs. Men		
In-Hospital					
ACC-NCDR ¹⁷	59792	32	5.4	3.1	—
Watanabe ²⁰	36765	36	4.0	2.0	<0.0001
CARS ¹⁶	1044	30	7.9	2.3	<0.05
CADILLAC ²⁸	2082	27	3.4	1.0	0.003
Late					
Mehillij ³⁹	1937	26	13.8	12.9	—
CADILLAC ²⁸	2082	27	7.8	3.0	<0.001
Antoniucci ³⁸	1019	23	12.0	7.0	0.03

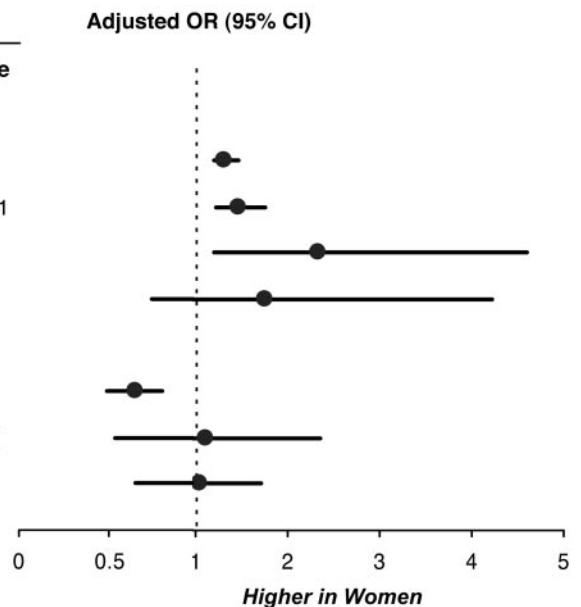


Figure 2. In-hospital and late mortality rates in women versus men after primary PCI for acute MI. ACC-NCDR indicates American College of Cardiology National Cardiovascular Data Registry; CARS, Coumadin Aspirin Reinfarction Study; all other abbreviations as in text.

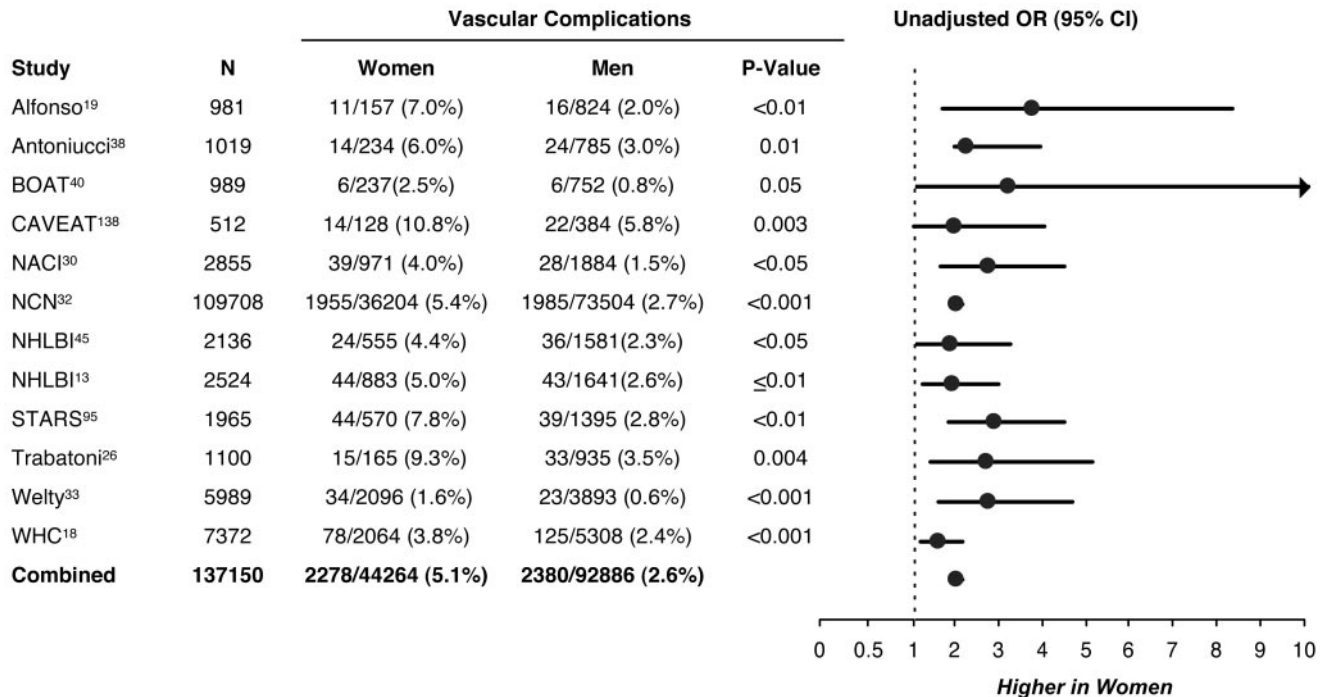


Figure 3. Meta-analysis of vascular complications in women versus men undergoing PCI. BOAT indicates Balloon vs Optimal Atherectomy trial; CAVEAT, Coronary Angioplasty Versus Excisional Atherectomy Trial; and STARS, Stent Antithrombotic Regimen Study; all other abbreviations as in Figure 1 and text.

extraction atherectomy. In general, however, these devices have not proven to reduce periprocedural events, 30-day events, or long-term restenosis rates in overall study groups⁵⁴; hence, an expected sex difference is unlikely.

Few sex-specific data exist on saphenous vein graft (SVG) interventions. Results parallel those for native vessel interventions, with women experiencing increased short-term mortality and complications but similar long-term outcome in comparison with men.⁶⁶ The only proven adjunctive devices that have demonstrated benefit in SVG interventions are embolic protection devices. In the SAFER (Saphenous Vein Graft Angioplasty Free of Emboli Randomized) trial, SVG interventions with distal protection using the PercuSurge GuardWire (Medtronic) device were shown to reduce 30-day major adverse cardiovascular events (MACE), largely driven by a reduction in MI, as compared with controls.⁶⁷ Women enrolled in the SAFER trial experienced a reduction in 30-day MACE of similar magnitude as that seen in the overall population (relative risk [RR] reduction=0.47; 95% CI 0.20 to 1.07).§ As with the overall cohort, the benefit was mainly the result of reduced rates of non-ST-elevation MI (NSTEMI). Sex-specific data are not available for the treatment of thrombus-containing SVG lesions with thrombectomy via the approved AngioJet (Possis Medical) device.

Vascular brachytherapy has been approved for the treatment of in-stent restenosis. The Beta-Cath (Novoste) ⁹⁰Sr β-radiation-emitting catheter, the only device on the market for this indication, demonstrated similar restenosis and revascularization benefits in women and in men in the randomized placebo-controlled START (⁹⁰Sr Treatment of Angiographic Restenosis) trial.⁶⁸§

Treatment of Acute Coronary Syndromes in Women

Table 2 summarizes the major randomized trials that compared an invasive versus a conservative strategy for treating acute coronary syndromes (ACS) and reported findings for women. For patients with ACS, which is defined as unstable angina (UA) or NSTEMI, evidence favors an early invasive strategy with GP IIb/IIIa inhibitor use, early catheterization within 48 hours, and revascularization (coronary intervention with stenting when suitable) for those at increased risk of death and MI.⁶⁹ Clinical trials in the modern era consistently have demonstrated benefit for men (FRISC-II [Fragmin and Fast Revascularization During Instability in Coronary Artery Disease-II],⁷⁰ RITA-3 [Randomized Intervention Treatment of Angina-3],⁷¹ TACTICS-TIMI 18 [Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18]⁴), but the results in women are conflicting (Table 2).

In the TACTICS-TIMI 18 trial,⁴ in which all subjects were treated with an early GP IIb/IIIa antagonist (tirofiban) (n=2220, 34% women), a significant reduction in death or MI (OR 0.45, 95% CI 0.24 to 0.88) occurred in invasively treated women. For the primary end point of death, MI, or rehospitalization, a significant benefit was seen in women at high risk (OR 0.47, 95% CI 0.26 to 0.83). High risk is denoted by TIMI risk score or the presence of any one of a number of serum markers of risk: creatine-kinase myocardial band, troponin, high-sensitivity C-reactive protein, and brain natriuretic peptide.^{72,73} The benefits of an early (within 24 hours) invasive strategy that primarily involves stenting are supported by a registry of 1450 UA/NSTEMI patients (29%

TABLE 1. Outcomes in Women by Device, Lesion Type, and Clinical Syndrome

Elective coronary interventions	
PCI	Indications for PCI in women are same as for men.
Bare metal stent	Stent implantation improves acute angiographic success in women. Long-term benefits of stenting (compared with balloon angioplasty) in reducing restenosis are presumed generalizable to women. No sex-based data on small-vessel stenting are available.
Drug-eluting stent	Compared with bare metal stents, CYPHER and TAXUS stents reduce restenosis and MACE at 1 y in women.
Atherectomy	Optimal directional atherectomy* is associated with modest improvements in restenosis; women have lower procedural success and more vascular complications than men. Women treated with excimer laser coronary angioplasty experience more coronary perforations than men. No sex-specific data on rotational atherectomy, transluminal extraction atherectomy, or thrombectomy (AngioJet) devices are available.
Saphenous vein graft	
Stenting	Short-term mortality and complications are increased in women.
Distal protection	Distal protection with PercuSurge GuardWire during SVG intervention reduces rate of MI at 30 d in women.
Thrombectomy	No data are available in women.
In-stent restenosis	
Vascular brachytherapy	Vascular brachytherapy with BetaCath system reduces restenosis after treatment of in-stent restenosis in women and men.
Acute coronary syndromes	
UA/NSTEMI	
PCI	Women with high-risk features appear to benefit from early invasive strategy (intervention within 48 h) with stenting, if appropriate, and adjunctive GP IIb/IIIa inhibition.
STEMI	
Balloon angioplasty	Timely primary angioplasty by a skilled team results in improved outcomes as compared with fibrinolysis in women.
Stent	Primary stenting reduces target vessel revascularization and MACE as compared with primary balloon angioplasty in women.
Drug-eluting stent	No data are available in women.
Shock	Women benefit from early revascularization for cardiogenic shock due to pump failure.

This table summarizes the findings for women drawn from the literature review. It is not the intention of the writing group to provide formal treatment recommendations; rather this table should serve as a convenient point of reference. Refer to text for discussion and citations.

Optimal directional atherectomy indicates final residual stenosis <30% after intervention. All abbreviations as in text.

women) in which the death and MI rate at a mean of 20 months was lower in women than in men (7% versus 10.5% for men, HR 0.65; 95% CI 0.42 to 0.99).²

In the FRISC-II trial (n=2457, 30% women), a significant interaction between the effect of treatment with a systematic but delayed interventional approach within 7 days of symptom onset was noted, with a benefit for men but not for women and possible harm for the latter.⁷⁰ The same finding was reported for the RITA-3 trial.^{71,74} Potential explanations for the differences between TACTICS-TIMI 18 versus RITA-3 and FRISC-II include the delayed timing of intervention in the invasive arm of FRISC-II, an apparent low rate of events for women in the conservative strategy in the latter 2 studies (suggesting a lower-risk population), lack of routine use of GP IIb/IIIa antagonists, and greater use of coronary artery bypass graft surgery (CABG) with an associated high risk of death for women in FRISC-II (9.9% in women versus 1.2% in men, $P<0.001$).⁷⁵ In summary, women with UA/NSTEMI and high-risk features benefit from an invasive strategy with early intervention (within 48 hours) and adjunctive GP IIb/IIIa antagonist use.⁶⁹

Interventional Treatment of STEMI in Women

The overall superiority of primary PCI over fibrinolytic therapy has been clearly demonstrated for women. A relative

risk reduction that is similar for men and women translates to a larger absolute benefit for women because they have higher risk profiles. An estimated 56 deaths could be prevented for every 1000 women treated with primary PCI rather than fibrinolytic therapy, as compared with 42 fewer deaths per 1000 men.⁷⁶ In addition, the risk of hemorrhagic stroke is markedly reduced with primary PCI. In general, every effort should be made to expedite reperfusion therapy (medical contact to balloon time within 90 minutes). Fibrinolytic therapy should be considered for patients presenting early—within 3 hours of symptom onset—in whom access to primary PCI will be excessively delayed.^{77–79}

Primary stenting versus primary balloon angioplasty was evaluated in 2 randomized trials reporting outcomes by sex. The Stent PAMI (Primary Angioplasty for Myocardial Infarction) trial (n=900, 25% women) demonstrated a trend toward increased mortality with primary stenting using the heparin-coated stent as compared with primary balloon angioplasty, a finding that reached significance in the female cohort.⁸⁰ Since the Stent PAMI trial, the use of bare metal stents during primary PCI has been compared with primary balloon angioplasty in the large-scale randomized CADILLAC (Controlled Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-Up) trial.⁸¹ Sex-subset analyses (n=2082, 27% women)

TABLE 2. Invasive vs Conservative Strategy for UA/NSTEMI

Study	Timing	End Point	Overall Result	Results in Men	Results in Women	Comments
TACTICS-TIMI-18, ^{4,72} 2002, n=2220, 34% women	Angiography 4–48 h	Death, MI	30 d: Inv 4.7%; Cons 7.0%; <i>P</i> =0.02 6 mo: Inv 7.3%; Cons 9.5%; OR 0.74 (0.54–1.00)	6 mo: Inv 7.6%; Cons 9.4%; OR 0.68 (0.43–1.05)	6 mo: Inv 6.6%; Cons 9.7%; OR 0.45 (0.24–0.88)	Benefit greater in women with high cTnT, OR 0.47 (0.26–0.83) for death, MI, and rehospitalization
RITA-3, ⁷¹ 2002, n=1810, 38% women	Angiography within 48 h	Death, MI, refractory angina at 4 mo Death, MI at 1 y	4 mo: Inv 9.6%; Cons 14.5%; <i>P</i> =0.001 1 y: Inv 7.6%; Cons 8.3%; <i>P</i> =0.6	4 mo: Inv 8.8%; Cons 17.3% 1 y: Inv 7.0%; Cons 10.1	4 mo: Inv 10.9%; Cons 9.6%; <i>P</i> =NS 1 y: Inv 8.6%; Cons 5.1%	Angina reduced with invasive strategy
FRISC II, ^{70, 139, 140} 1999, n=2457, 30% women	Revascularization within 7 d	Death, MI	6 mo: Inv 9.4%; Cons 12.1%; <i>P</i> =0.03 1 y: Inv 10.4%; Cons 14.1%; <i>P</i> =0.005	1 y: Inv 9.6%; Cons 15.8%; <i>P</i> <0.001	6 mo: Inv 10.5%; Cons 8.3%; RR=1.26 (0.80–1.97) 1 y: Inv 12.4%; Cons 10.5%; <i>P</i> =NS	Mortality benefit at 1 y (2.2% vs 3.9%, <i>P</i> =0.02) not seen in women (4% vs 3.3%)
TIMI-IIIb, ^{141, 142} 1997, n=1423, 34% women	Angiography 18–48 h	Death, MI	1 y: Inv 10.8%; Cons 12.2%; <i>P</i> =0.4	Death at 6 wk: Inv 2.6%; Cons 1.4% MI at 6 wk: Inv 5.5%; Cons 6.0%	Death at 6 wk: Inv 2%; Cons 4.4%; <i>P</i> =NS MI at 6 wk: Inv 4.4%; Cons 5.2%	Invasive patients less angina and rehospitalization for ischemia

Inv indicates invasive; Cons, conservative; cTnT, cardiac troponin T; and NS, nonsignificant.

demonstrated the safety and efficacy at 1 year of stenting with or without abciximab in women.²⁸ Stenting significantly reduced the incidence of 1-year ischemic target revascularization by 9.6% and MACE by 9% in women as compared with balloon angioplasty with no impact on death, MI, or stroke.

Shock

Female sex is an independent risk factor for the development of cardiogenic shock complicating acute MI.⁸² Age is an additional risk factor for the development of these complications, such that older women are at substantial risk of cardiogenic shock. Once shock develops, however, female sex is not independently related to outcome.⁸³ Women benefit from early revascularization for cardiogenic shock due to pump failure. According to the ACC/AHA guidelines for the treatment of STEMI, PCI or CABG is recommended for patients <75 years old who are suitable for revascularization, and revascularization is reasonable for selected patients ≥75 years old.⁷⁸ These guidelines are not sex specific.

Adjunctive Pharmacotherapy in Women Undergoing PCI

Table 3 summarizes important clinical findings and recommendations for pharmacological therapy for women derived from published studies (discussed below) and previous ACC/AHA practice guidelines.

Antiplatelet Agents

Aspirin

Numerous clinical trials have demonstrated a benefit for the use of aspirin in ACS, after coronary artery revascularization (PCI and CABG), and for the secondary prevention of ischemic heart disease.^{84,85} Despite the strong evidence for clinical benefit, aspirin is underused in the secondary prevention of coronary artery disease in high-risk women.^{86–89}

According to the ACC/AHA guidelines, aspirin (162 to 325 mg) should be administered in the initial management of all patients (men and women) with UA/NSTEMI,⁸⁴ acute

MI,^{78,90} or suspected acute MI, and results in an estimated 23% to 30% reduction in mortality.⁸⁵ Soluble aspirin (80 to 325 mg) administration is mandatory in all nonallergic patients at least 2 hours before PCI⁹¹ and should be continued indefinitely at a lower dose (75 to 162 mg) for secondary prevention.

Thienopyridines: Ticlopidine and Clopidogrel

The antiplatelet thienopyridine agents clopidogrel^{92,93} and ticlopidine⁸⁵ are adenosine diphosphate receptor antagonists that have been shown to reduce ischemic events in ACS patients. When given in addition to aspirin, these agents reduce the rates of subacute stent thrombosis after stent implantation.^{94,95} Previous guidelines recommended that the thienopyridines (preferably clopidogrel) be substituted for aspirin only in aspirin-allergic patients (men or women) for secondary prevention.^{78,96} Given their comparable efficacy but increased rates of neutropenia, thrombotic thrombocytopenia, and aplastic anemia with ticlopidine,^{92,97–99} clopidogrel is used in most cases.

In UA/NSTEMI patients treated with PCI,¹⁰⁰ combination therapy with aspirin and clopidogrel for up to 12 months was shown to be superior to aspirin alone, with a similar risk reduction in women (RR 0.77, 95% CI 0.52 to 1.15) and men (RR 0.65, 95% CI 0.48 to 0.87). In the CREDO (Clopidogrel for the Reduction of Events During Observation) trial (n=2116, 29% women),¹⁰¹ long-term treatment with clopidogrel for up to 1 year after elective PCI was associated with a 27% relative risk reduction in the combined risk of death, MI, or stroke and a 32% nonsignificant relative risk reduction in the combined end point in women (RR reduction 95% CI 58.9% to –12.1%). Dual antiplatelet therapy is associated with increased bleeding risk as the dose of aspirin increases, and reducing the aspirin dose (75 to 100 mg/day) 1 month after PCI should be considered for patients who have not received a DES.¹⁰² The safety of low-dose (<325 mg) aspirin 1 month after PCI with DES has not been determined.

The optimal timing and loading dose of clopidogrel before PCI has been controversial. Much of the variation in outcomes appears largely attributable to the loading dose and

TABLE 3. Pharmacotherapy in Women

Antiplatelets	
Aspirin	Women undergoing elective PCI or PCI for ACS should receive aspirin 80–325 mg at least 2 h before procedure. Aspirin should be continued indefinitely on a daily basis for secondary prevention, but exact dose after treatment with DES has not been determined.
Thienopyridines	
Clopidogrel	Women undergoing elective PCI or PCI for ACS should receive clopidogrel 300–600-mg load; clopidogrel, 75 mg, should be continued for at least 2–4 wk after bare metal stent implantation and for several months after drug-eluting stent implantation (3 mo for sirolimus, 6 mo for paclitaxel). Optimal loading dose and pretreatment time for clopidogrel remain unclear. Clopidogrel should be withdrawn for 5–7 d before planned CABG to minimize bleeding complications.
Ticlopidine	Ticlopidine (500-mg load, 250 mg twice daily) can substitute for clopidogrel in clopidogrel-intolerant patients.
GP IIb/IIIa inhibitors	
	GP IIb/IIIa inhibition reduces ischemic complications in high-risk (troponin-positive, diabetic, older adult) patients including women undergoing elective PCI or PCI for ACS with balloon angioplasty or stenting. GP IIb/IIIa inhibition with abciximab in women with STEMI (without shock) undergoing primary balloon angioplasty or stenting may reduce ischemic complications without increasing risk of major bleeding.
Antithrombin agents	
UFH	During STEMI, UFH treatment benefit is established in women. Observational data support use of empiric UFH during PCI in women to achieve an ACT of 250–300 s. Current guidelines advise weight-adjusted UFH (60- to 70-U/kg IV bolus; 12- to 15-U·kg ⁻¹ ·h ⁻¹ infusion) with target activated clotting time 250–300 s for HemoTec and 300–350 s for HemoChron. Lower doses may be considered in women and older adult patients and when UFH is combined with GP IIb/IIIa inhibitors during PCI; maximum bolus and infusion when UFH is used as adjunct to fibrinolytic therapy is 4000-U bolus and 1000-U/h infusion. No established benefit of long-term UFH after PCI exists.
Low-molecular-weight heparin	Women with UA/NSTEMI treated with LMWH experience more bleeding complications than do men. Combined LMWH and GPIIb/IIIa inhibition appears effective in women with UA/NSTEMI undergoing PCI; however, it is associated with increased bleeding.
Direct thrombin inhibitors	Bivalirudin and provisional GPIIb/IIIa results in similar outcomes compared with UFH with planned GPIIb/IIIa inhibitors during PCI and up to 6 mo after PCI, and fewer bleeding complications in women.

This table summarizes the findings for women drawn from the literature review. It is not the intention of the writing group to provide formal treatment recommendations; rather, this table should serve as a convenient point of reference. Refer to text for discussion and citations. When recommendations are provided, they are based on previously published ACC/AHA guidelines.

pretreatment timing; a 300-mg loading dose requires up to 6 hours for maximal antiplatelet effect and optimal outcomes,^{100,101,103} whereas a 600-mg loading dose achieves maximal antiplatelet effect within 2 hours and has been associated with a low rate of MACE among low-risk patients undergoing PCI.^{104,105} No sex-specific data are available with regard to clopidogrel dosing. In the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment) trial (n=2159, 24% women), no additional benefit for the GP IIb/IIIa inhibitor abciximab was found among low-risk PCI patients (patients with ACS, insulin-requiring diabetics, and other high-risk patients were excluded) pretreated with a 600-mg loading dose of clopidogrel.¹⁰⁶ Death, MI, and target vessel revascularization at 30 days did not differ between the abciximab and placebo groups in either the entire population (4.0% versus 4.0%, $P=0.82$) or the female subset (3.0% versus 3.0%), placing in doubt the role of adjunctive GP IIb/IIIa inhibitors in the era of optimal pretreatment with clopidogrel, at least in relatively low-risk patients.

Clopidogrel administered before CABG has been associated with a significant increase in perioperative bleeding^{107,108} and should be discontinued 5 to 7 days before elective CABG unless the urgency for revascularization outweighs the bleeding risk.

GP IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors as an adjunct to unfractionated heparin (UFH) are beneficial for women undergoing PCI and are not associated with an independent risk of major bleeding complications in this setting,^{28,48,49,109} although the risk of minor bleeding complications is increased in women.⁴⁹ An overview of 10 randomized, placebo-controlled trials of GP IIb/IIIa inhibitors as adjunctive therapy to PCI (n=13 166, 26% women) showed a significant reduction in the combined end point of death or nonfatal MI out to 6 months after PCI (OR 0.76, 95% CI 0.64 to 0.91, $P<0.001$).¹¹⁰ The benefits for GP IIb/IIIa inhibitors, particularly as an adjunct to stenting, seem to be greatest in high-risk patients, including women, especially older women and those with positive troponins, diabetes, and thrombotic lesions.^{111–114}

A pooled analysis of the EPIC (Evaluation of c7E3 for Prevention of Ischemic Complications),¹¹⁵ EPILOG (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blockade),^{116,117} and EPISTENT (Evaluation of IIb/IIIa Platelet Inhibitors for Stenting)¹¹⁸ trials (n=6595, 27% women) showed that abciximab treatment during PCI was equally beneficial in men and women.⁴⁹ The composite incidence of death, MI, or urgent revascularization was reduced from 16.0% to 9.9% ($P<0.001$) at 6 months, and at 1 year a significant reduction in mortality (4.0% versus

2.5% for abciximab, $P=0.03$) occurred in women treated with abciximab. Although women treated with abciximab experienced more major bleeding than did men (3.0% versus 1.3%), this increase was independent of abciximab. An increased risk of minor bleeding was associated with abciximab treatment in women (6.7% versus 4.7% for placebo, $P=0.02$).

Although other GP IIb/IIIa inhibitors, including eptifibatide⁴⁸ and tirofiban,¹¹⁹ have been shown to be safe and effective in women during PCI, the TARGET (Do Tirofiban and ReoPro Give Similar Efficacy) trial ($n=2398$, 27% women) showed a clear benefit of abciximab over tirofiban in preventing periprocedural and 30-day ischemic complications, a finding that was consistent regardless of age, sex, and the presence or absence of pretreatment with clopidogrel¹²⁰; however, the 6-month event rates in the 2 groups were not significantly different.¹²¹ Abciximab has never been directly compared with a double-bolus eptifibatide regimen, and thus no comparative recommendations can be made about the relative safety and efficacy of these 2 agents as adjuncts to UFH in patients undergoing PCI.

In women undergoing primary angioplasty for STEMI, abciximab may reduce short-term ischemic events without significantly increasing major bleeding complications.²⁸ In this context, it is reasonable to start treatment with abciximab as early as possible before primary PCI.⁷⁸ In contrast, the use of GP IIb/IIIa inhibitors during rescue PCI after failed thrombolytic therapy has been associated with increased bleeding rates, especially in women and older adult patients.^{123–126}

GP IIb/IIIa inhibitor administration is recommended for patients with UA/NSTEMI in whom a catheterization and PCI are planned and may be administered just before PCI. Although eptifibatide and tirofiban are useful for upstream use before cardiac catheterization, it is important to note that in patients with UA/NSTEMI who are managed with a conservative strategy, eptifibatide¹²⁷ and tirofiban¹²⁸ have shown little benefit and possible harm among women, with the exception of a subset of patients with elevated troponin levels in whom GP IIb/IIIa inhibitors were equally effective in women and men.¹¹⁴ Therefore, these agents should be reserved for women who undergo PCI or who are at high risk, in particular those with elevated troponins, in whom PCI is not planned. In ACS patients scheduled to undergo PCI, abciximab is recommended during or just before the procedure⁶⁹; however, it plays no role in the medical management of ACS in either women or men.^{129,130}

Antithrombin Agents

Unfractionated Heparin

In women, UFH is used commonly in combination with aspirin in patients undergoing primary angioplasty or receiving fibrinolytic therapy for evolving MI, in the medical management of UA/NSTEMI, and during elective or urgent PCI either with or without GP IIb/IIIa inhibitors.^{69,78,131} Because of the risks of bleeding, weight-adjusted dosing (60- to 70-U/kg IV bolus; 12- to 15-U · kg⁻¹ · h⁻¹ infusion, ACT of 250 to 300 seconds for the HemoTec [HemoTec] device and 300 to 350 for the Hemochron [International Technidyne]

device) is advised in the ACC/AHA guidelines for the treatment of STEMI—the lower dosing regimen and a maximum 4000-U bolus with 1000 U · h⁻¹ are recommended when used as an adjunct to fibrinolytic therapy.⁷⁸ The guidelines also note that lower doses may be used in women and older adults, particularly when UFH is combined with GP IIb/IIIa inhibitors during PCI, and vascular sheaths removed as soon as possible to reduce bleeding rates.^{47,115} In patients likely to undergo CABG, UFH is preferred to low-molecular-weight heparin (LMWH) because of its shorter half-life and because it can be rapidly reversed with protamine.⁶⁹

Low-Molecular-Weight Heparin

Compared with UFH, LMWH has greater bioavailability, is more conveniently administered by subcutaneous injection, exhibits a more linear and predictable dose response, causes less activation of platelets, and is less likely to result in heparin-induced thrombocytopenia (HIT).¹³² Routine assays for LMWH monitoring (antifactor Xa levels) are not widely available, but the data suggest that monitoring may be helpful in high-risk patient groups including pregnant women, patients at weight extremes, and people with chronic renal impairment.^{131–133}

The efficacy and safety of enoxaparin in patients with UA/NSTEMI undergoing an invasive strategy has been studied in 2 noninferiority trials: the A-to-Z (Aggrastat to Zocor phases)¹³⁴ ($n=3987$ patients; 29% women) and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors)¹³⁵ ($n=9978$ patients; 34% women) studies. No statistically significant benefit was noted for enoxaparin over standard UFH in the setting of PCI for ACS in either women or men, and evidence was found for a slight increase in bleeding complications with enoxaparin.

Direct Antithrombins

Direct antithrombins act on both clot-bound and circulating thrombin, have linear kinetics and higher thrombin specificity than UFH, and are not associated with platelet activation or HIT. Bivalirudin, a synthetic direct antithrombin with a short half-life, has been studied extensively in PCI and has been used in patients undergoing PCI for elective and urgent (UA/NSTEMI) indications. Argatroban has been used in patients at high risk for HIT undergoing PCI.

In comparison with UFH, direct thrombin inhibitors have been shown to be of most benefit in patients undergoing PCI. In a meta-analysis of 8497 patients undergoing elective or urgent PCI for ACS, direct thrombin inhibitors were associated with a 32% relative risk reduction in death or MI as compared with UFH (4.6% versus 6.6% for UFH, RR reduction 0.68, 95% CI 0.57 to 0.83, $P<0.001$)¹³⁶ and with lower rates of bleeding complications. In the REPLACE-2 (Randomized Evaluation in Percutaneous Coronary Intervention Linking Angiomax to Reduced Clinical Events) trial, 6010 patients (26% women) undergoing elective or urgent PCI were randomized to either UFH and planned use of GP IIb/IIIa inhibitors or bivalirudin and provisional or “bailout” GP IIb/IIIa inhibitors.⁵⁰ Protection from periprocedural ischemic complications was similar in both treatment groups, and bivalirudin was

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associated with a significant reduction in major bleeding complications. These findings were confirmed in women, in whom major and minor bleeding was significantly reduced from 34.1% with UFH to 19.7% with bivalirudin ($P < 0.0001$).¹³⁷

Opportunities for Improving the Evidence Base and Outcomes for Women

In the face of a rising mortality burden in women with cardiovascular disease and the established benefits of PCI in reducing both fatal and nonfatal events for women with

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high-risk ACS and STEMI, PCI is performed less frequently and with greater delays in women. Better understanding and narrowing of this apparent treatment disparity is a priority. Areas of specific interest to the interventional population of women afflicted with CAD include (1) improving referral for early therapy; (2) optimizing therapy for patients with diabetes and small-vessel coronary disease, which is extremely prevalent in women; and (3) refining treatment pathways and strategies for women with STEMI, in whom mortality rates and bleeding risk remain higher than in men.

To further optimize clinical outcomes of women undergoing PCI, evidence-based evaluation in randomized clinical trials must emphasize increased recruitment of women, with mandates to include sex-specific, ethnic, and racial sex-based results. Specifically, to understand the potential benefit or detriment of new interventional therapies or adjunctive pharmacotherapy, outcomes of women based on randomized treatment allocation, with women as their own controls, are essential.

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