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
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, emergency myocardial infarction (MI), and emergency coronary bypass surgery, 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, although not consistently observed (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. 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. 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).

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 angioplasty and stenting, 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.

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. 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. Adjuvante use of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors during PCI does not confer an independent added risk of major vascular complications in women, 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.

**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. 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. Although no specific sex-based comparisons were performed or at least published in the earlier randomized clinical trials comparing stent implantation with balloon angioplasty, 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. 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. 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 or higher in women after stenting because of confounding risk factors rather than female sex.

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) trial and the paclitaxel-eluting TAXUS stent (Boston Scientific) on the basis of the
TAXUS IV (Treatment of De Novo Coronary Disease With a Single Paclitaxel-Eluting Stent trial) \(^\text{60}\) 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.\(^\text{43,61}\) Early data suggest favorable long-term results for drug-eluting stenting of small vessels (≤2.75 mm) in both men and women.\(^\text{62}\)

### 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.\(^\text{25,63,64}\) 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.\(^\text{65}\) No sex-specific data exist on the use of rotational atherectomy, cutting balloon angioplasty, or...
In general, however, these devices have not proven to reduce periprocedural events, 30-day events, or long-term restenosis rates in overall study groups; 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. 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. Women enrolled in the SAFER trial experienced a reduction in 30-day major adverse cardiovascular events (MACE), largely driven by a reduction in MI, as compared with controls. 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 the randomized placebo-controlled START (90Sr Treatment of Angiographic Restenosis) trial.

### 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. 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], RITA-3 [Randomized Intervention Treatment of Angina-3], TACTICS-TIMI 18 [Treat Angina With Aggrastat and Determine Cost of Therapy With Invasive or Conservative Strategy-Thrombolysis in Myocardial Infarction 18]), but the results in women are conflicting (Table 2).

In the TACTICS-TIMI 18 trial, 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. 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%...
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 systemic 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).73 In summary, women with UA/NSTEMI and high-risk features benefit from an invasive strategy with early intervention (within 48 hours) and adjunction of 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)
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 early revascularization for cardiogenic shock due 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 with high cTnT, OR 0.47 (0.26–0.85) for death, MI, and rehospitalization

**Thienopyridines: Ticlopidine and Clopidogrel**

The antiplatelet thienopyridine agents clopidogrel92,93 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

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**Table 3. Invasive vs Conservative Strategy for UA/NSTEMI**

<table>
<thead>
<tr>
<th>Study</th>
<th>Timing</th>
<th>End Point</th>
<th>Overall Result</th>
<th>Results in Men</th>
<th>Results in Women</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACTICS-TIMI-18,17,2002, n = 2220, 34% women</td>
<td>Angiography 4–48 h</td>
<td>Death, MI</td>
<td>30 d: Inv 4.7%, Cons 7.0%, P = 0.02; 6 mo: Inv 7.3%, Cons 9.5%, OR 0.74 (0.54–1.00)</td>
<td>6 mo: Inv 7.6%, Cons 9.4%, OR 0.68 (0.43–1.05)</td>
<td>6 mo: Inv 6.9%, Cons 9.7%, OR 0.48 (0.24–0.88)</td>
<td>Benefit greater in women with high cTnT, OR 0.47 (0.26–0.85) for death, MI, and rehospitalization</td>
</tr>
<tr>
<td>RITA-3,71 2002, n = 1810, 38% women</td>
<td>Angiography within 48 h</td>
<td>Death, MI, refractory angina at 4 mo, Death, MI at 1 y</td>
<td>4 mo: Inv 9.6%, Cons 14.5%, P = 0.001; 1 y: Inv 7.6%, Cons 8.3%, P = 0.6</td>
<td>4 mo: Inv 8.8%, Cons 17.3%; 1 y: Inv 7.0%, Cons 10.1</td>
<td>4 mo: Inv 10.9%, Cons 9.6%, P = NS; 1 y: Inv 8.6%, Cons 5.1%</td>
<td>Angina reduced with invasive strategy</td>
</tr>
<tr>
<td>FRISC II, 76, 138, 140 1999, n = 2457, 30% women</td>
<td>Revascularization within 7 d</td>
<td>Death, MI</td>
<td>6 mo: Inv 9.4%, Cons 12.1%, P &lt; 0.001; 1 y: Inv 10.4%, Cons 14.1%, P = 0.005</td>
<td>6 mo: Inv 9.6%, Cons 15.8%, P &lt; 0.001</td>
<td>6 mo: Inv 10.5%, Cons 8.3%, RR = 1.26 (0.80–1.97); 1 y: Inv 12.4%, Cons 10.5%, P = NS</td>
<td>Mortality benefit at 1 y (2.2% vs 3.9%, P = 0.02) not seen in women (4% vs 3.3%)</td>
</tr>
<tr>
<td>TIMI-88, 141, 142 1997, n = 1423, 34% women</td>
<td>Angiography 18–48 h</td>
<td>Death, MI</td>
<td>1 y: Inv 10.8%, Cons 12.2%, P = 0.4</td>
<td>Death at 6 wk: Inv 2.6%, Cons 1.4%; MI at 6 wk: Inv 5.5%, Cons 6.0%</td>
<td>Death at 6 wk: Inv 2%, Cons 4.4%; MI at 6 wk: Inv 4.4%, Cons 5.2%</td>
<td>Invasive patients less angina and rehospitalization for ischemia</td>
</tr>
</tbody>
</table>

Inv indicates invasive; Cons, conservative; cTnT, cardiac troponin T; and NS, nonsignificant.
TABLE 3. Pharmacotherapy in Women

<table>
<thead>
<tr>
<th>Antithrombin agents</th>
<th>Thienopyridines</th>
<th>Antiplatelets</th>
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<tr>
<td>UFH</td>
<td>Ticlopidine</td>
<td>Aspirin</td>
<td>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.</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>Ticlopidine (500-mg load, 250 mg twice daily) can substitute for clopidogrel in clopidogrel-intolerant patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>Ticlopidine</td>
<td>Ticlopidine 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.</td>
<td></td>
</tr>
</tbody>
</table>

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. Pretreatment timing; a 300-mg loading dose requires up to 6 hours for maximal antiplatelet effect and optimal outcomes, 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. No sex-specific data are available with associated with a low rate of MACE among low-risk patients undergoing PCI. 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. 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.

Clopideogrel administered before CABG has been associated with a significant increase in perioperative bleeding 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. Although the risk of minor bleeding complications is increased in women. 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). 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.

A pooled analysis of the EPIC (Evaluation of c7E3 for Prevention of Ischemic Complications), EPilogue (Evaluation of PTCA to Improve Long-Term Outcome by c7E3 GP IIb/IIIa Receptor Blockade), and EPISTENT (Evaluation of IIb/IIIa Platelet Inhibitors for Stenting) trials (n = 6595, 27% women) showed that abciximab treatment during PCI was equally beneficial in men and women. 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...
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this context, it is reasonable to start treatment with abciximab in women and men.\textsuperscript{114} Therefore, these agents should be levels in whom GP IIb/IIIa inhibitors were equally effective the exception of a subset of patients with elevated troponin shown little benefit and possible harm among women, with

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\textsuperscript{-1} are recommended when used as an adjunct to fibrinolytic therapy.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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)\textsuperscript{134} (n=3987 patients; 29% women) and SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors)\textsuperscript{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, \(P<0.001\))\textsuperscript{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.\textsuperscript{50} Protection from periprocedural ischemic complications was similar in both treatment groups, and bivalirudin was

**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.\textsuperscript{69,78,131} Because of the risks of bleeding, weight-adjusted dosing (60- to 70-U/kg IV bolus; 12- to 15-U · kg\textsuperscript{-1} · h\textsuperscript{-1} infusion, ACT of 250 to 300 seconds for the HemoTec [HemoTec] device and 300 to 350 for the Hemochron [International Technidyne]
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...
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.

References


Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. The EPIC Investigation. 


Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPIDOG Investigators.


Percutaneous Coronary Intervention and Adjunctive Pharmacotherapy in Women: A Statement for Healthcare Professionals From the American Heart Association

Endorsed by the American College of Cardiology Foundation

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