

## Reviews

# A Systematic Review of Gender Differences in Mortality after Coronary Artery Bypass Graft Surgery and Percutaneous Coronary Interventions

CATHERINE KIM, M.D., M.P.H., RITA F. REDBERG, M.D., M.SC., TIANA PAVLIC, M.D., KIM A. EAGLE, M.D.

Division of General Internal Medicine, Departments of Medicine and Obstetrics & Gynecology, University of Michigan, Ann Arbor, Michigan, USA

### Summary

Gender differences exist in outcomes, particularly early mortality, for percutaneous interventions (PCI) and coronary artery bypass graft surgery (CABG). Better understanding of this issue may target areas for improvement for all patients undergoing revascularization. Therefore, we summarized the evidence on gender differences in PCI and CABG outcomes, particularly early mortality, and mediators of this difference. Using the key terms “women” or “gender,” “revascularization,” “coronary artery bypass,” “angioplasty,” “stent,” and “coronary intervention,” we searched MEDLINE from 1985 to 2005 for all randomized controlled trials (RCTs) and registries reporting outcomes by gender. Bibliographies and the Web sites of cardiology conferences were also reviewed. The literature was examined to identify gender differences in outcomes and mediators of these differences. We identified 23 studies reporting outcomes by gender for CABG and 48 studies reporting outcomes by gender for PCI. The majority of studies noted greater in-hospital mortality in women than in men, with mortality differences resolving with longer follow-up. Early mortality differences were reduced but not consistently eliminated after adjustment for comorbidities, procedural characteristics, and body habitus. Power to detect gender

differences after multivariate adjustment was limited by declining mortality rates and small sample size. Gender was an independent risk factor for complications after both CABG and PCI. Women experience greater complications and early mortality after revascularization. Future exploration is needed of gender differences in quality of care and benefit from combinations of stenting and antiplatelet, and anticoagulant medications in order to optimize treatment.

**Key words:** women, coronary artery bypass graft, percutaneous coronary intervention, outcomes, gender, review

Clin. Cardiol. 2007; 30: 491–495.  
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### Introduction

In the United States in 2002, 373,000 men and 142,000 women underwent CABG and 802,000 men and 402,000 women underwent a PCI, and these numbers are increasing.<sup>1</sup> Women may experience poorer outcomes, particularly greater early mortality, than men. This may be related to women’s less favorable risk profile. However, it is unclear whether additional factors contribute to the difference. Further understanding of these associations may identify opportunities to improve coronary care.

In this review, we summarize the status of gender differences in morbidity and mortality after CABG and PCI. We also summarize potential mediators of these differences. Finally, we present evidence on gender differences in specific aspects of periprocedural care that may affect outcomes, such as use of stents and adjunctive medications.

### Methods

To identify randomized trials, we reviewed MEDLINE references published between January 1, 1985, and March 31, 2005, in the subset of randomized controlled trials and human subjects with these search terms: (women OR gender) AND coronary disease AND (revascularization OR coronary artery bypass OR stent) OR angioplasty OR coronary intervention) which yielded 1,725 articles. To identify registries, we re-

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This work was supported by a grant from the Walter and Esther Hewlett Fund for Cardiovascular Research in Women (KA), the American Diabetes Association (CK), the Robert Wood Johnson Foundation (RR), and the Flight Attendant Medical Research Institute (RR).

Address for reprints:

Catherine Kim, M.D., M.P.H.  
Division of General Internal Medicine  
Departments of Medicine and Obstetrics Gynecology  
University of Michigan  
Ann Arbor, MI 48109, USA  
e-mail: cathkim@umich.edu

Received: April 18, 2006

Accepted: May 24, 2006

Published online in Wiley InterScience

(www.interscience.wiley.com).

DOI: 10.1002/clc.20000

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viewed MEDLINE references in the same period in the subset of human subjects with the addition of "registry," which yielded 441 articles. We also reviewed reference lists and web pages of cardiology conferences for articles not yet published. Finally, we reviewed summaries published by the American Heart Association, the European Heart Society, and the Cochrane Collaboration. We excluded studies that did not report outcomes separately by gender or did not report on outcomes by procedure. We excluded studies that only reported outcomes by acute coronary syndrome (ACS) type, such as non-ST-elevation myocardial infarction (NSTEMI) or STEMI, and those that did not report on mortality or on a composite endpoint including mortality. Due to the small numbers of women enrolled, lack of reporting by gender, and the relatively small number of studies, we excluded studies examining only excimer laser angioplasty, directional atherectomy, cutting balloon angioplasty, extraction atherectomy, vascular brachytherapy, and saphenous vein graft interventions.

We identified 23 studies reporting outcomes by gender for CABG and 48 studies reporting outcomes by gender for PCI; in several instances, more than one report came from the same database, and in these instances the largest dataset was reported upon.

## Results

### Gender Differences in Early Mortality

Unadjusted in-hospital mortality rates from PCI registries, PCI trials, and CABG studies were higher in women than men. The majority of studies demonstrated similar late mortality between men and women. Several explanations have been offered for the increased early mortality in women: greater number of comorbidities and degree and type of vessel involvement, smaller coronary vessel size and body habitus, delayed intervention, less frequent use of arterial grafts, and racial and socioeconomic differences. Adjustment for these factors eliminated the gender difference in some studies, but not in others.

*Comorbidities, anatomy, and early mortality:* Women undergoing PCI and CABG were on average older than men and more often had diabetes, hypertension, congestive heart failure, and severe noncardiac disease. These factors, particularly age, account for much of the gender difference in early mortality in studies of both PCI<sup>2</sup> and CABG.<sup>3</sup> Paradoxically, studies have suggested that gender differences are greater in younger than in older patients.<sup>4,5</sup> Diabetes may also have a greater adverse impact on women than on men.<sup>6,7</sup> Lesion type and total number of lesions may not be independently associated with outcome after adjustment for other risk factors,<sup>8</sup> but acknowledgment of degree of vessel involvement (anatomy) as well as clinical risk factors may be required to account for gender differences.<sup>9</sup> Of note, several PCI<sup>4,8,10,11</sup> and CABG<sup>12,13</sup> series still demonstrated gender differences in early mortality after adjustment for clinical and anatomical factors.

*Smaller coronary arteries and body habitus:* Since women tend to have smaller coronary arteries than men, investigators

have explored vessel size as a mediator of women's higher mortality after CABG and PCI. Presumably, smaller vessel size would be related to lower angiographic success and/or greater periprocedural complications due to technical difficulties. However, the relationship between vessel size and outcomes is inconsistent, with some studies showing differences<sup>3,14</sup> and others showing no differences.<sup>7,15,16</sup>

When information on vessel size is not available, markers for body habitus have sometimes been used as surrogates. In one CABG registry, the correlation between body surface area (BSA) and coronary artery size was 0.9,<sup>17</sup> although other studies have found correlations as low as 0.1.<sup>18,19</sup> As with studies adjusting for reference vessel size, studies examining markers of body habitus and mortality are inconsistent. Several CABG<sup>5,20-22</sup> and PCI<sup>23-25</sup> studies have demonstrated associations between gender and mortality after adjustment for body habitus, while other CABG<sup>3,17,26</sup> and PCI<sup>11,19,27-31</sup> studies have not.

One explanation for the conflicting results may be that gender differences in mortality are more pronounced with larger BSA, and different studies may enroll patients with different ranges of body habitus.<sup>22,32,33</sup> In addition, Trabattoni *et al.* found that restenosis rates after PCI were higher in women, despite adjustment for BMI and risk factor differences. Of interest is the fact that when they also considered final balloon size, the magnitude of the gender difference was decreased.<sup>34</sup> Final balloon size, not BMI, was predictive of restenosis regardless of gender.

*Early intervention and referral:* Some studies have shown that women have longer times to PCI in the setting of ischemia,<sup>27,35-37</sup> although the effect on gender mortality differences was minimal. When disease is not as severe or more diffuse, or morbidity is higher from related procedures after early intervention such as unplanned CABG, men may benefit more than women from early intervention.

Timing of referral for CABG may affect CABG outcomes. Studies have suggested that women may be referred for CABG less often than men, and possibly later in the course of disease.<sup>37-41</sup> It is difficult to determine if referral bias before catheterization leads to increased clinical risk in women who do undergo CABG, but the contribution to mortality appears to be relatively small.

Women may be referred less for elective CABG than men but may undergo emergent CABG more often, either as the result of PCI complications or ACS.<sup>42</sup> In turn, emergent CABG is associated with greater mortality than nonemergent CABG. Stents may be more likely to close in small vessels; Watanabe *et al.* found that women were more likely to undergo same-admission CABG after stent placement, presumably because of complications or unsatisfactory angiographic results.<sup>43</sup> However, more recent reports suggest that emergent CABG may not be as important a factor in gender differences in mortality.<sup>11,16</sup>

*Graft type and off-pump technology:* Since arterial grafts have higher patency rates, widespread use of arterial grafts instead of saphenous vein grafts should reduce CABG mortality. Women have lower rates of arterial, specifically internal tho-

racic or mammary artery (IMA) use than men,<sup>15, 22, 33, 44</sup> even after adjustment for other factors such as age, nonelective surgery, and extent of disease.<sup>15, 45</sup> Thus, lower use of IMAs could be a potential mediator of gender differences in outcomes. However, the independent relationship with early mortality is inconsistent, with some CABG series demonstrating an association<sup>15, 26, 33</sup> and others finding none.<sup>22, 45–47</sup> Similarly, the use of off-pump revascularization may improve CABG outcomes, particularly periprocedural neurological events,<sup>48</sup> but it is unclear whether this effect is due to avoidance of cardiopulmonary bypass and/or other aspects of healthcare delivery, such as surgical skill.

*Income and race:* Women have lower income than men, although the effect of income as a mediator of gender differences in revascularization outcomes has not been widely studied. In a Canadian registry, adjustment for women's lower income reduced but did not eliminate the 1-year gender differences in mortality after CABG.<sup>26</sup> In an analysis of patients undergoing PCI or CABG at the Cleveland Clinic, lower median family income was associated with higher odds of receiving PCI instead of CABG, but income was not associated with mortality after either procedure.<sup>49</sup>

The interaction of race, gender, and outcomes has not been widely studied. Of note, although racial and gender differences have been documented for revascularization, these have not been associated with similar differences in mortality.<sup>50</sup> Hartz *et al.* noted a significant interaction between race and gender in the performance of CABG, but not in CABG mortality.<sup>32</sup> In another registry, black women were at lower risk for a composite endpoint of death, MI, and revascularization at 1 year than black men, with no gender difference among white patients.<sup>16</sup>

*Adjunctive periprocedural therapies: Glycoprotein inhibitors:* Without exception, randomized trials of periprocedural therapies are at least partially funded by the companies that profit from these technologies. With this in mind, randomized trials of glycoprotein IIb/IIIa inhibitors in conjunction with PCI have generally found benefit in both men and women, usually by a composite endpoint.<sup>51, 53</sup> Gender differences may vary with the specific glycoprotein inhibitor, although the differences are small and the data are not consistent.<sup>54, 56</sup> In contrast, the effect of IIb/IIIa inhibitors may differ for CABG, with minimal benefit on mortality.<sup>57</sup>

*Adjunctive periprocedural therapies: Stents:* Studies of outcomes after coronary stenting in new device trials or registries suggest improved outcomes in both men and women when compared with past studies. As with glycoprotein inhibitors, firmer conclusions regarding the benefits of new technologies are limited by power, lack of reporting by gender, or both. Consequently, recent reductions in periprocedural mortality have made gender differences more difficult to detect, but it is unclear how much of this is attributable to the new technologies versus other improvements in care or patient selection.<sup>58</sup> Despite overall reductions in periprocedural mortality,<sup>59</sup> some studies suggest that women may not benefit as much as men from revascularization with drug-eluting stents.<sup>8, 60</sup>

## Conclusions

Gender differences in outcomes are greatest for in-hospital mortality. These differences are diminished after adjustment for risk factors such as age and diabetes. Correction for body habitus further diminishes the gender difference, although it is unclear how body habitus influences mortality. It is unclear how lower referral rates for women are related to their higher risk profile and increased adverse outcomes. Finally, it is unknown whether the uneven benefit of newer therapies, particularly drug-eluting stents and glycoprotein inhibitors, is attributable to gender differences in comorbidity patterns or other factors.

The American Heart Association's 2005 Scientific Statement notes that women have increased in-hospital mortality after both elective and primary PCI compared with men in the majority of reports, but that such differences are smaller after adjustment for women's greater age, smaller BSA, and comorbidities at the time of presentation.<sup>59</sup> Whether such differences are still significant after adjustment is unclear, since approximately half of the studies demonstrated persistently elevated adjusted odds ratios with the lower bounds of the confidence interval exceeding 1.<sup>59</sup>

The American Heart Association and the American College of Cardiology, in collaboration with the American Association for Thoracic Surgery and the Society of Thoracic Surgeons, note that in-hospital CABG mortality is on average greater in women than in men, and sometimes, but not always, this disparity was reduced after adjustment for use of IMA grafts, age, and BSA. However, the joint statement noted that CABG compared with medical therapy still appeared to benefit women in appropriately selected patients.<sup>47</sup> The European Society of Cardiology guidelines do not make specific recommendations or statements regarding gender. No Cochrane Collaboration meta-analyses or statements on PCI or CABG have examined gender-specific outcomes.

Knowledge of the reasons for gender differences in outcomes after coronary revascularization can optimize therapy for all patients. The relative importance of factors in mediating these gender differences, particularly early mortality, requires studies that are adequately powered to conduct multivariate risk adjustment, study of the interactions between therapy and overall risk factor patterns, and closer inspection of processes of care, particularly medication use, surrounding revascularization. It is essential that clinical trials and registries report gender-specific outcomes, as it is likely that predictors of risk, including gender, will continue to evolve as procedure type and patient risk profiles change. It is also important to make a careful assessment of the influence of funding sources, as studies of newer technologies are heavily reliant upon the companies benefiting from these technologies.

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