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Improving Coronary Artery Bypass Grafting in Women: Difficulties and Outcomes

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Abstract

There continues to be a clear distinction between women and men after coronary surgery. Many argue that higher mortality, complication rate, and worse outcomes among women have been attributed to smaller artery size, higher technical complexity, and more comorbidities at the time of presentation. However, evidence of only a physiologic or anatomical reason for poor outcomes is severely lacking. In this paper, we review the sex differences in coronary artery bypass grafting, the influence of race and sex, and the choice of conduit on outcomes in women. Additionally, we elucidate strategies to improve outcomes, such as including female animals in basic science, enforcing the use of guideline-directed treatments, expanding women's representation in clinical trials, increasing the number of women researchers, and developing Centers of Excellence. This review not only highlights the outcomes and challenges of women undergoing coronary surgery but also proposes avenues for potential solutions to this ongoing issue.

Keywords: Cardiovascular surgery, coronary artery bypass grafting, coronary artery disease, gender, heart, multiple arterial grafting

Sex Differences in Coronary Artery Bypass Grafting Outcomes

Heart disease is the number one killer of women, and its incidence is increasing. More women than men died in the United States between 1984 and 2013 due to cardiovascular disease (Figure 1)^(1,2). Although deaths from cardiovascular disease decreased from 1980 to 2010 largely due to reductions in major risk factors and the



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usage of evidence-based medical therapies, the death rate since 2010 has been rising⁽²⁻⁴⁾. Ford and colleagues noted that the largest contribution to the reduction in death rate was attributed to secondary prevention and that coronary revascularization [with coronary artery bypass grafting (CABG) or percutaneous intervention (PCI)] for stable or unstable coronary artery disease (CAD) accounted for 7% of the decline in death rate⁽⁴⁾. Notably, since 2010, there has been a steady increase in heart disease and mortality, secondary to increasing rates of obesity, diabetes, and hypertension⁽⁵⁾. While CABG use has declined due to increasing utilization of PCI, CABG is the preferred method in multi-vessel disease, left main disease, patients with diabetes who are appropriate CABG candidates, refractory angina, and patients unable to tolerate dual antiplatelet therapy^(6,7). More importantly, there has been a decrease in post-CABG mortality⁽⁸⁾. However, that effect has not been extended to women. Many studies have shown significant sex differences in CABG outcomes^(7,9-19). Women and non-white patients are less likely to receive guideline-directed medical and surgical



Figure 1. Yearly cardiovascular deaths in the United States in men and women

Mortality from cardiovascular disease in men and women in the United States from 1999 to 2016. The number of deaths were higher in women (orange line) compared to men (green line) from 1999 to 2016. Author made figure with data from Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality: Compressed Mortality File 1999-2016 on CDC WONDER Online Database, released June 2017 therapies despite a comparable benefit^(7,9-11,20-22). Women undergoing CABG tend to present with more risk factors and comorbidities, including hypertension, diabetes, and obesity, compared to men. In addition to being on average, ten years older, women present more frequently with a more severe angina class. Despite less extensive coronary disease (and more small vessel disease), women have greater disabling symptoms^(13,23). Notably, women are more likely to have a silent heart attack and to die within one year after their myocardial infarction (MI). These factors lead to higher postoperative morbidity and mortality rates in women. A meta analysis of 903,346 patients in randomized controlled trials (RCTs) found that women experienced an increase in operative mortality, late mortality, major adverse cardiovascular events, MI, stroke, and repeat revascularization after CABG, compared to men. However, there was no difference in operative or late mortality with the use of the off-pump technique or multiple arterial grafts (MAG)^(16,21). It should be noted that these studies do not clarify the definition of operative mortality as including intraoperative and perioperative deaths; however, our interpretation is that operative mortality includes any death, regardless of cause, occurring within 30 days after surgery.

While traditional risk factors for heart disease, such as diabetes, smoking, obesity, physical inactivity, hypertension, and dyslipidemia, are well known, unique risk factors in women, such as preterm delivery, hypertensive disorders of pregnancy, gestational diabetes, autoimmune disease, breast cancer treatment, and depression are important, nontraditional risk factors that must be recognized⁽¹⁵⁾ (Figure 2).

Many studies (retrospective, unadjusted) confirm higher operative mortality in women (up to 3 times that of men)^(8,19,24-30). However, studies with risk factor adjustment demonstrate contradictory findings. Several propensitymatched comparisons demonstrate no difference in operative mortality ^(14,17,19,31-34). In a study of 1743 patients from the STS database, women required more non-elective interventions, underwent less extensive revascularization,



Figure 2. Traditional and emerging non-traditional risk factors for cardiovascular disease in women An illustration of the increasing traditional risk factors among women, such as diabetes, smoking, obesity, physical inactivity hypertension. Additionally, there are emerging non-traditional ASCVD risk factors such as, preterm delivery, pregnancy complications like hypertensive disorders and gestational diabetes, autoimmune diseases, treatment for breast cancer and depression. Reproduced for Garcia et al.⁽¹⁵⁾. ASCVD: Atherosclerotic cardiovascular disease

and were less frequently recipients of internal mammary artery grafting, suggesting that female sex itself influenced the extent of coronary artery revascularization and the use of internal thoracic artery grafting⁽¹²⁾. In a nationwide inpatient sample of 3.6 million propensity-matched patients between 2003 and 2016 undergoing intervention after acute MI, women (33% of the cohort) had higher morbidity, mortality, and longer length of stay, compared to men⁽¹⁸⁾. This difference persisted over 14 years across PCI and CABG. What is more concerning is that studies have highlighted that women receive fewer arterial grafts than men, potentially affecting long-term outcomes⁽⁹⁾.

Influence of Race and Sex on Outcomes

Research suggests that outcomes vary not only by sex but also by race, with disparities in access to care and postoperative outcomes. In a study of over 200,000 women hospitalized for ST-elevation myocardial infarction, non-caucasian women had higher in-hospital mortality and lower odds of PCI compared to other women⁽³⁵⁾. Additionally, the study found African-Americans were less likely to receive CABG or mechanical circulatory support⁽³⁵⁾. Another study from 1999 to 2014 documented that while overall CABG utilization decreased over the study period, and there was a general decline in postCABG mortality for all groups, women and black patients consistently exhibited higher mortality rates compared to their male and white counterparts⁽⁸⁾. A study of over a million patients from the Society of Thoracic Surgeons database similarly confirmed that black and female patients had higher odds of mortality and black patients had higher postoperative complications after CABG when compared to other groups⁽³⁶⁾. This research underscores the persistent need for tailored interventions to address these disparities and improve outcomes for all patients, especially those in historically marginalized groups.

The Role of Anatomic Differences in Women's CABG Outcomes

Sex differences in CABG outcomes are multifaceted, encompassing anatomic variations, such as smaller coronary arteries in women, which may complicate surgical procedures and affect the choice of conduit, potentially influencing long-term patency rates. The selection of conduit (arterial vs. venous) plays a crucial role, as women may benefit more from arterial grafts, which have shown better long-term outcomes but are underutilized in female patients. Several technical considerations have been proposed for the treatment of women with CAD (Figure 3).



The argument that smaller coronary arteries in women largely underlies the increase in operative mortality is not supported by multiple observations. Firstly, small coronary size is often considered a contraindication to off pump CABG, yet women fare better with off-pump CABG compared to men. In addition, the disparity in operative mortality in women lessens with age, and coronary size does not change with older age⁽¹⁹⁾. The time to construct a distal anastomosis has been demonstrated to be similar between women and men, suggesting that the technical challenge for smaller arteries does not take more time⁽¹²⁾. Factors contributing to the higher operative mortality in women are thus likely multifactorial and include comorbidities, older age compared to men at the time of CAD diagnosis, and potential bias in treatment.

Does Choice of Conduit Influence Outcomes

It has been evident since 1999 that there has been an underutilization of arterial grafts in women when compared to men⁽⁹⁾. Women have been shown to derive the same benefits from arterial and MAG compared to men^(10,20,37). However, women are less likely to receive left internal mammary artery (LIMA), right internal mammary artery, and radial artery grafts, when compared to men (Figure 4), and the female sex specifically has been associated with non-use of LIMA^(10,12,33,38-41). Compared with male patients, female patients are also less likely to have complete revascularization⁽⁹⁾. Several contemporary studies have confirmed these observations. In the Radial Artery Patency Study, the use of the radial artery to the right coronary or left circumflex artery territory was protective in women, and the patency was better than that of the vein⁽²²⁾. The use of the radial artery was associated with improved five-year survival in propensity-matched women^(37,39,42). Additionally, a study of 63,402 patients undergoing CABG found that MAG was associated with better outcomes among low-risk, but not high-risk, patients. Specifically, mortality was lower among men undergoing MAG, but not women, at seven years⁽³⁷⁾.



Figure 3. Technical considerations for coronary artery disease treatment in women

Multiple technical considerations have been suggested for the treatment of women with CAD. Reproduced from Gaudino et al.⁽¹¹⁾ with permission from Elsevier. CABG: Coronary artery bypass graft, CAD: Coronary artery disease, GDMT: Guideline-directed medical therapy, LV: Left ventricular, MI: Myocardial infarction



Strategies to Improve CABG Outcomes in Women

Improving outcomes for women undergoing CABG requires multifaceted strategies that address the unique challenges and disparities they face⁽⁴¹⁾ (Table 1). Delayed diagnosis, treatment conservatism, referral bias, and inaccurate patient and physician perception of risk, all contribute to mortality differences between male and female patients. The lack of angiographically significant CAD, lower utilization of guideline-directed surgical treatment (arterial grafts, of complete revascularization), lower utilization of guideline-directed medical treatment, and lack of involvement of women in clinical trials are also factors that lead to higher mortality in women after CABG^(7,37,41). Efforts to include more women in clinical trials and tailored approaches considering anatomic and physiologic differences are essential for improving outcomes for women in CABG.

Female Animals in Basic Science

The inclusion of female animals in basic science research is a crucial aspect of understanding gender differences in health and disease. While the National



Figure 4. Rates of internal mammary and radial artery utilization Use of arterial grafts in men and women between 2011 and 2019. The illustration shows 1,212,487 patients, women (red lines) and men (blue lines), undergoing CABG from the Society of Thoracic Surgeons (STS) database. The use of bilateral internal mammary artery (BIMA) as solid lines, radial artery graft is depicted as dashed lines, and left internal mammary artery (LIMA) as dotted lines. Women were less likely (significant for all conduits) to receive any arterial graft compared to men. Reproduced from Zwischenberger et al.(41)



Institute of Health (NIH) attempted to increase the enrollment of women in clinical trials in the 1990s, there has only recently been advocacy in the basic sciences^(43,44). The 2015 NIH Initiative on Rigor and Reproducibility dictates that a strong justification must be provided for applications proposing to study only one sex. The predominance of male animals in basic science animal models leads to a gap in knowledge regarding how biological sex influences disease processes and treatment outcomes. There has been a growing emphasis on the importance of including female animals in research to ensure findings are applicable to both sexes.

Guideline-Directed Medical and Surgical Treatment

Female patients with cardiovascular disease are more likely to receive guideline-recommended care when treated by a female physician⁽⁴⁵⁾. The 2021 ACC/AHA/ SCAI Guideline for Coronary Artery Revascularization published a class I recommendation for treatment decisions to be based on clinical indication and not on sex, race, or ethnicity⁽⁷⁾. In large part because of the overwhelming evidence, even after controlling for health care access, that once women and non-white patients enter into the health care system, they are less likely to receive reperfusion therapy, an invasive strategy, or revascularization compared with their white male counterparts⁽⁷⁾, it is clear there are disparities in treatment. More research is

 Table 1. Strategies to reduce mortality in women after coronary artery bypass grafting

Include animals of both sexes in basic science research to understand physiologic differences

Use guideline-directed optimal medical care

Use guideline-directed revascularization strategies including use of arterial conduits

Enroll more women in clinical trials

Surgeon specialization in coronary surgery for women

Establish centers for specialization in the treatment of women with cardiovascular disease

Strategies that can be undertaken to reduce mortality in women after CABG. Reproduced from Zwischenberger et al.(41). CABG: Coronary artery bypass grafting



desperately needed, on eliminating biased non-guidelinedirected care from health care systems. Women fare better with off-pump CABG; this technique should be considered. Arterial grafts have shown superior patency rates compared to venous grafts, and tailoring the choice of conduit to account for the anatomic and physiologic differences in women, such as smaller coronary arteries, could enhance outcomes. Specifically, MAG is associated with better outcomes⁽³⁷⁾. Women undergoing CABG often present with a higher burden of comorbidities, and a comprehensive approach to better manage these conditions preoperatively can improve postoperative outcomes. Coordinating the focus of multidisciplinary teams could optimize patients' health through medication management, diet and exercise modifications, and closer monitoring.

Enhanced Clinical Trials Representation

Increasing the participation of women in clinical trials is critical. Historically, women have been underrepresented in cardiovascular research, leading to a gap in understanding regarding the most effective treatments for women. By ensuring more balanced gender representation, studies can provide data that is more applicable to the female population, allowing for tailored treatment strategies. Thus, the recruitment and retention of female patients should be a major goal of randomized clinical trials⁽⁴⁶⁾. However, the guidelines for women have been based on research including only men, and there is generally a lack of data on women. The first RCTs on CABG included only men; however, sixteen percent of patients undergoing CABG were female overall⁽⁴⁷⁾. Only 13 STS Database studies from 2011-2019 (1,212,487 patients) were published, and first-time isolated CABG patients were only 25% women (307,145)⁽⁴¹⁾. In an analysis of 740 clinical trials focusing on cardiovascular disease between 2010 and 2017, 38% of the participants were women⁽⁴⁸⁾. This lack of representation risks development of ineffective therapies or unintended consequences of treatments in women⁽⁴⁹⁾.

Promoting Women Researchers in Cardiac Surgery

Encouraging and supporting women researchers in the field can bring new perspectives to addressing the gender disparities in CABG outcomes. The representation of female researchers is significantly lower than that of men in cardiac surgery clinical trials⁽⁴⁶⁾. Women researchers are more likely to investigate issues affecting female patients, potentially leading to innovations in treatment and care strategies tailored to women⁽⁵⁰⁾. In a 2022 study of US clinical trials, of the 266 principal investigators (PIs) that were cardiac surgeons, 6 were women, and women PIs had only 9.5% of all studies funded by industry, and not one woman PI had a clinical trial funded by the NIH⁽⁴⁶⁾. Although resources focus heavily on recruitment strategies and support of junior female researchers, the gender disparity increases significantly at every stage of women's careers, highlighting the need for better strategies for retention throughout a woman's career⁽⁵¹⁾.

Development of Centers of Excellence

Centers of Excellence (COE) have shown improved outcomes and patient satisfaction⁽⁵²⁾. The development of COE has the potential to greatly improve outcomes for women. One of many strategies to implement would be to increase patient-physician gender concordance. Female physicians caring for female patients improve patient probability of survival compared to male physicians treating female patients^(45,53). Physician-patient congruence increases patient satisfaction (54). Additionally, patients with a female physician have been shown to be more likely to receive guideline-directed medical therapy⁽⁵⁵⁾. In a study of the outcomes of surgeries performed by female surgeons, regardless of their surgical specialty, patients had significantly lower rates of 30-day mortality. readmission, or complication within 30 days when their surgery was performed by female surgeons ⁽⁵⁶⁾.

Establishing specialized centers focused on cardiovascular care for women can ensure that female patients receive the most advanced and tailored treatments





available^(37,58). Like centers of its kind in other specialties, these centers can serve as hubs for research and education, foster innovation in treatment approaches, and raise awareness about cardiovascular care needs of women^(52,59). Multidisciplinary teams that include cardiologists, surgeons, dietitians, rehabilitation specialists, and mental health professionals can provide focused holistic care for women undergoing CABG, but will require a concerted effort from healthcare providers, researchers, and policymakers⁽⁶⁰⁾. This approach ensures that all aspects of a patient's health are addressed, from surgical preparation to recovery and long-term health maintenance. COE allow for increased education of physicians and patients on the nuances of coronary disease and treatment in women.

Educating healthcare professionals about the sexspecific risks and outcomes associated with CABG can improve preoperative planning and postoperative care. Continuous medical education programs should include a review of the anatomic and physiologic differences between men and women, the impact of comorbidities, the nuances of patient management, and recent clinical trial evidence to ensure tailored and effective treatment strategies for women. This will empower women with better knowledge of their condition, treatment options, and the risks and benefits of CABG, which can help in shared decision-making. Optimizing outcomes by these methods involves comprehensive strategies that extend beyond surgical techniques⁽⁴⁷⁾ (Table 2).

Recently, the United States government announced a 100 million dollar investment in women's health⁽⁶¹⁾. The Advanced Research Projects Agency for Health aims to support innovation, investment, research, and patient advocacy to proactively seek solutions in women's healthcare⁽⁶²⁾. As the leading cause of death among women continues to be cardiovascular disease, investment in centers devoted to the cardiac care of women should be a priority.

Focusing The Future Research: Improving CABG Outcomes in Women

In conclusion, inequalities between male and female CABG patients have been reported in operative mortality, late mortality, and morbidity. Beyond the potential anatomic disparity, poor outcomes in this population are multifactorial with lower rates of PCI and complete

Table 2. Challenges and solutions for women undergoing coronary artery bypass grafting

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Characteristics in women compared with men with CAD	Unique challenges in women with CAD	Potential solutions to improve outcomes in women
Average several years older Multiple risk factors/comorbidities	Delayed CAD diagnosis, treatment conservatism, and referral basis	Preoperative factors Establish effective diagnostic tests in women
More likely to have silent heart attack	Lack of angiographically significant CAD	Improve time to diagnosis Reduce treatment conservatism
More likely to present with sudden death	Diagnostic test inaccuracy	Patient and physician education regarding perception of risk
More likely to die within 1 year after MI	Incorrect patient and physician perception of risk	
More often with urgent or emergent presentation More severe angina class Diabetes more powerful risk factor	Lower intraoperative utilization of guideline directed surgical treatment: arterial grafts, complete revascularization	Intraoperative factors Use of arterial grafts Complete revascularization
Greater disabling symptoms despite less extensive coronary disease (small vessel disease)	Smaller coronaries	Other factors
	Suboptimal involvement in clinical trials	Sex concordance (physician and patient)
Longer time to diagnosis Less likely to undergo ECG, undergo catheterization, receive antiplatelet and statin, and receive revascularization		Centers of specialization for women's health

A summary of the characteristics of CAD in women compared to men, the specific challenges providers face in management of CAD in women, and potential preoperative and intraoperative solutions found to improve CABG outcomes in women. Reproduced from Cho, et al.⁽⁴⁷⁾ with permission pending from Wolters Kluwer Health. CABG: Coronary artery bypass graft, CAD: Coronary artery disease, MI: myocardial infarction, ECG: Electrocardiogram





revascularization. Adopting the aforementioned approaches, increasing the number of female surgeons, enhancing heart team discussions at multidisciplinary conferences, and ensuring an adequate offering of PCI or CABG where appropriate, would begin to improve CABG outcomes in women. Healthcare systems and clinicians can significantly enhance the quality of care for women undergoing CABG and thus improve surgical outcomes and patient satisfaction.

Ethics

Footnotes

Authorship Contributions

Literature Search: Briscoe JB, Lawton JS, Writing: Briscoe JB, Lawton JS.

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