**Trends in Sex-based Differences in Outcomes following Coronary Artery Bypass Grafting in the United States between 2004 and 2015**

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**Highlights**

* The largest analysis examining trends of sex differences in a range of postoperative outcomes after CABG in a nationally representative cohort from the US
* Worse CABG in-hospital outcomes in females (death, stroke, thoracic complications) have persisted over a 12-year period
* Although females were at lower risk of postoperative bleeding after CABG, disparity has resolved in recent years

**Abstract**

**Background:** The present study sought to examine the trends of sex-based differences in clinical outcomes after coronary artery bypass grafting (CABG), an area in which the current evidence remains limited.

**Methods:** All US adults hospitalized for first-time isolated CABG in the National Inpatient Sample database between 2004 and 2015 were included, stratified by sex. Multivariable regression analysis examined the adjusted odds ratios (OR) of postoperative in-hospital complications in females versus males. Trend analyses of sex-based differences in in-hospital post-operative complications over the study period were performed.

**Results:** Overall,2,537,767 CABG procedures were analyzed, including 27.9% (n=708,459) females. Female sex was associated with an increase in adjusted odds of all-cause mortality (OR 1.43 95% CI 1.40, 1.45), stroke (OR 1.34 95% CI 1.32, 1.37) and thoracic complications (OR 1.28 95% CI 1.27, 1.29) and lower odds of all-cause bleeding (OR 0.87 95% CI 0.86, 0.89) compared to males. Trend analysis revealed these sex differences to be persistent for mortality, stroke and thoracic complications (*p*trend=non-significant) but eliminated for bleeding over the study period (*p*trend<0.001).

**Conclusion:** Despite technical advances over the 12-year period, worse post-operative outcomes including death, stroke, and thoracic complications have persisted in female patients after CABG. These findings are concerning and underscore the need for risk reduction strategies to address this disparity gap.

**Introduction**

The utility of coronary artery bypass grafting (CABG) as a revascularization strategy over percutaneous coronary intervention (PCI) in specific patient groups such as those with extensive coronary artery disease (CAD) and diabetes has been well established.[1, 2] Recent advancements in CABG operative techniques[3], particularly in the context of minimally invasive direct coronary artery bypass grafting (MIDCAB), off-Pump CABG, multiple arterial grafting, and the “no-touch” technique for vein graft harvesting, may have contributed to the overall improvement in CABG outcomes.[4] Despite these improvements, sex-based differences in clinical outcomes exist in patients undergoing CABG, with female sex being independently associated with higher morbidity and mortality.[5-10] These differences have been posited to be attributable to several anatomical and biological differences including the smaller size of coronary arteries[11] and the underutilization of the internal mammary artery (IMA) in females[10], as well as the role of estrogen in atherosclerosis.[12] Females have been also shown to present with more advanced CAD than males,[10] for which they are less likely to undergo invasive testing and treatment.[13, 14]

While female sex has been shown to be associated with worse CABG outcomes, the current evidence[5-10] is limited to small or single-center studies with limited geographical representation or the analysis of isolated outcomes (e.g. mortality only). As such, a comprehensive, national assessment of sex-based disparities in outcomes following surgical revascularization is lacking. Furthermore, it remains unclear whether the impact of recent advancements in surgical and perioperative practices, including the involvement of heart teams, have had an equivalent impact on both sexes. Thus, a thorough and systematic assessment of recent trends in postoperative outcome disparities will be key in the context of ongoing quality improvement efforts. The present nationally representative study explores and dissects existing trends in sex-based differences in postoperative outcomes in patients undergoing CABG in the United States (US) between 2004 and 2015.

# Materials and Methods

*Data Source*

Data was extracted from the National Inpatient Sample (NIS), the largest publicly available all-payer database of hospitalized patients in the US, which is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).[15] Further information about NIS is available in Appendix A (Supplementary Material).

*Study Design and Population*

All adult (≥18 years) hospitalizations for CABG between January 2004 through September 2015 were included, as identified using the International Classification of Diseases, ninth revision (ICD-9) codes provided in Table S1 (Supplementary Material). Records with missing data (4.4% of original cohort, n=25,286) were excluded as were patients who underwent PCI or received thrombolysis during the same admission or had a prior CABG (i.e. reoperation). Study flow chart is presented in Figure S1 (Supplementary Material). Patient characteristics, comorbidities, and clinical outcomes were extracted using the ICD-9 procedure and diagnosis codes provided in Table S1.

*Outcomes*

The main outcomes of interest were trends in sex-based differences over the study period and odds of post-CABG in-hospital adverse events in female versus male patients. The secondary outcomes of interest were in-hospital mortality and complications after CABG. In-hospital complications included all-cause mortality, all-cause bleeding, acute stroke and cardiac (composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis) and thoracic complications (composite of hemothorax, pneumothorax, thoracic vascular injury and chest drain insertion). All-cause bleeding was defined as any postoperative hemorrhage using ICD-9 diagnosis codes.

*Statistical Analysis*

For exploratory analyses, the CABG cohort was stratified according to sex. Continuous variables are summarized using medians and interquartile range (IQR) for non-parametric data and were compared using the Kruskal-Wallis test. Categorical variables are summarized as percentages and were analyzed using the chi squared (X2) test. Trend analysis was performed using logistic regression modelling, with the inclusion of time (years) as a covariate for assessing sex-based differences in outcomes over the study period.

Several multivariable logistic regression models were constructed to examine the increased risk of procedure-related adverse outcomes in females versus males. Covariate selection was a-priori based and included those based on clinical significance and those that may directly influence in-hospital outcomes, as determined using univariate analysis. All multivariable models were adjusted for differences in socioeconomic and hospital-level factors (Appendix B in Supplementary Material). The results are reported as odds ratios (OR) with 95% confidence interval (CI).

All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY). Additionally, all analyses utilized sampling weights as required and provided by the AHRQ, to account for temporal and geographic differences in observations resulting from the sampling design. The sampling weights for each individual discharge were incorporated into the relevant SPSS commands for each analysis.

# Results

***Patient Characteristics and Demographics***

A total of 2,537,767 hospitalization records for first-time CABG procedures were recorded. Females represented 27.9% of the total cohort (n=708,459) which decreased through the study period (2004 vs. 2015: 29.4% vs. 26.2%). Isolated CABG cases (without concomitant open-heart valve surgery) accounted for 2,144,714 procedures and were comprised of 26.8% females. The utilization of internal mammary artery (IMA) graft was persistently lower in females compared to males over the study period (Figure 1). On-pump CABG was the default modality in the majority of cases in both sexes (females: 98.7%, males: 99.1%), however, its use decreased over the study period (Table S2).

The patient and operative characteristics for the total cohort, stratified by sex, are presented in Table 1a, and further stratified by grouped years in Table S2. Females were older, were less likely to be admitted electively but more likely to be insured through Medicare or Medicaid (Table 1a). There was a lower prevalence of several cardiovascular risk factors in females such as dyslipidemia, smoking, atrial fibrillation, previous ischemic heart disease or PCI, and arrhythmias as ventricular tachycardia and fibrillation. However, other comorbidities were more prevalent in females, including hypertension, hypothyroidism, valvular heart disease, anemia, peripheral vascular disease, obesity and previous CVA. Overall, females had a higher burden of comorbidity as measured by Charlson Comorbidity Index (median CCI (IQR); females vs. males: 2 (1,3) vs. 1 (0,2)). Females generally received a fewer number of grafts, with 8.9% of females requiring 4 grafts compared to 13.9% in males and were more likely to undergo concomitant valve surgery (18.9% vs. 14.2%). The pattern of sex differences in patient characteristics and surgical management was consistent across the study years (Table S2).

***In-hospital Clinical Outcomes***

A comparison of in-hospital clinical outcomes between female and male groups is shown in Table 1b and Figure 2. The outcomes are shown for the total CABG cohort and for patients who underwent isolated CABG excluding concomitant valve surgery. The crude rates for all postoperative adverse outcomes were higher in females compared to males in the total CABG cohort (all-cause mortality: 3.8% vs. 2.1%; acute stroke 2.4% vs. 1.5%; thoracic complications: 8.0% vs. 5.7%) (*p*<0.001 for all). No difference in all-cause bleeding was noted (males vs. females; 4.8% vs. 4.7%) (*p*=0.785). A similar pattern was observed in the isolated CABG cohort with a higher rate for all adverse outcomes in females (all-cause mortality: 2.7% vs. 1.6%; acute stroke: 2.1% vs. 1.3%; thoracic complications: 7.0% vs. 5.1%) except all-cause bleeding rates which were lower in females (females vs. males: 3.9% vs. 4.1%) (*p*<0.001 for all). Females had a longer hospital stay than males (median (IQR): 9 (6, 13) vs. 7 (5, 11) days) and higher total charge for their stay (median (IQR): 110783 (74637, 173366) vs. 103127 (70168, 159999) US Dollars) in the total CABG cohort with similar results in the isolated CABG cohort (Table 1b).

In multivariable analysis of adverse outcomes, female sex was associated with increased odds of all-cause mortality (OR 1.43 95% CI 1.40, 1.45), acute stroke (OR 1.34 95% CI 1.32, 1.37) and thoracic complications (OR 1.28 95% CI 1.27, 1.29), but not all-cause bleeding (OR 0.87 95% CI 0.86, 0.89) when compared to males (*p*<0.001 for all) (Figure 3a).

***Temporal Trends in Outcomes***

In the total CABG cohort, the crude rate of all-cause mortality declined over the study period in both sexes but remained persistently higher in females (Table S3), while the rates of all-cause bleeding were initially higher in males (2004-2009) and later higher in females (2010-2015). In contrast, the rate of acute stroke and thoracic complications increased over the same period, but both remained higher in females compared to males. Similar changes were shown in the isolated CABG cohort for all-cause mortality, stroke and thoracic complications. All-cause bleeding rates in the isolated CABG cohort were higher in males between 2004-2009 and 2013-2015 and higher in females between 2010-2012.

After adjustment for potential confounders in the total CABG cohort, females remained at a persistently increased odds of mortality, stroke and thoracic complications over the study period, compared to males, and lower odds for all-cause bleeding (Figure 3b, Table S4). However, the sex difference in odds of bleeding was eliminated in later years (2014-2015). Trend analysis showed these sex differences to persist for mortality, stroke and thoracic complications (ptrend=non-significant) but not for all-cause bleeding over the study years (ptrend<0.001). Similar trends were noted in the isolated CABG cohort (Table S5).

***Predictors of Mortality***

Several factors were associated with increased odds of postoperative mortality (Table S6). The strongest patient-specific predictors included in-hospital cardiogenic shock (OR 4.17 95% CI 4.07, 4.26), advanced age (age>80 years: OR 2.76 95% CI 2.66, 2.86), coagulopathy (OR 1.68 95% CI 1.64, 1.72) and peripheral vascular disease (OR 1.58 95% CI 1.54, 1.61). Amongst operative factors, off-pump CABG was associated with increased mortality (OR 1.14 95% CI 1.08, 1.21) as was concomitant open-heart valve surgery (OR 1.80 95% CI 1.76, 1.84).

# Discussion

The present nationally representative study of more than 2.5 million CABG procedures over 12 years is the largest to report trends in sex-based differences in postoperative outcomes. This study has several important findings. First, proportionally, our analysis shows a trend towards fewer females undergoing CABG during the study period. Second, we observe that females undergoing CABG were generally older, more likely to present with acute coronary syndrome (ACS) and were more comorbid compared to males. Despite adjusting for these baseline differences, female sex was independently associated with worse outcomes after CABG, except for all-cause bleeding. On trend analysis we observe that the increased risk of postoperative outcomes (other than bleeding) in females persisted over the 12 years of the study period, even in the isolated CABG cases. Finally, we find that advanced age, off-pump CABG and concomitant open-heart valve surgery were associated with an increased risk of mortality in the overall cohort. Together these findings should raise concern that sex-based differences in outcomes have not narrowed over time and emphasize the need to further explore mechanisms for risk reduction in females undergoing CABG.

We demonstrate worse in-hospital outcomes in females after CABG, except for bleeding, which was higher in males. In addition to the increased odds of mortality (43%) and acute stroke (28%), female patients were at a 28% increased risk of thoracic complications after CABG. More importantly, we find that the increased risk of postoperative complications in females has persisted or worsened over the years, except for bleeding, which was higher in males throughout the study period. Although previous studies have demonstrated worse in-hospital outcomes in females undergoing CABG,[5-10] these were subject to several limitations as previously highlighted. In their analysis of 2 million CABG procedures between 2003 and 2012, Swaminathan et al.[8] reported increased odds of mortality (OR 1.4, 95% CI 1.36-1.43), stroke (OR 1.35, 95% CI 1.31-1.40), and other outcomes as respiratory failure, cardiogenic shock, and wound infection in females compared to males. However, their study only looked at trends of sex differences in crude mortality, without adjustment for other baseline differences between sexes, and did not examine sex-differences in other postoperative outcomes. The lack of adjustment for patient characteristics between sexes in their analysis could in part explain their conclusion of a narrowing gap of mortality between sexes, which was not evident in our study. Another recent study of 13,327 consecutive CABG procedures between 2008 and 2012 showed that females had increased odds of mortality (OR 1.35 95% CI 1.04, 1.86) compared to males after adjustment for baseline Society of Thoracic Surgeons (STS) risk factors.[7]

The sex-based differences observed in our study are comparable to those found in other types of cardiac surgery. For example, Chaker et al.[16] reported a persistently higher risk of in-hospital adverse events in females compared to males after surgical aortic valve replacement, including in-hospital mortality, vascular complications and blood transfusions. Similarly, Chung et al.[17] reported higher postoperative mortality and morbidity in females after thoracic aortic surgery.

The increased risk of mortality and postoperative complications in females could be attributed to several biological and anatomical differences, including smaller coronary artery and conduit sizes in females[11] as well as the role of estrogen in atherogenesis and thrombosis.[12] Furthermore, females are more likely to present with symptomatic coronary artery disease requiring urgent surgical intervention, at a more advanced age than men[10], and with a lower New York Heart Association (NYHA) functional classification[5]. When compared to males, they are also less likely to receive evidence-based therapies [13], cardiac catheterization and timely reperfusion [14] in the context of ACS. The observed risk of postoperative complications in females in our study may explain the decline in the proportion of females undergoing CABG over the study period, reflecting surgeons’ concerns about the increased operative risk of female patients and consequent referral for alternative revascularization strategies (e.g. PCI) or conservative medical management.

Furthermore, several technical considerations have been proposed thus far to address the inherent risk of postoperative complications in females.[18] From an operative perspective, increased rates of IMA utilization should be sought in females, as this has been associated with lower postoperative mortality after CABG.[19] Historically, females have been less likely to receive IMA grafts compared to males, due to concerns about their smaller coronary targets, and this finding was further demonstrated in our study.[5, 10] However, the difference in IMA diameter has been shown to be clinically insignificant between sexes.[20] Another approach aims to tailor perioperative management of comorbidities to accommodate differences in disease burden between sexes. Diabetes is more common in females than males undergoing CABG[10] and postoperative mortality has been shown to be independently related to the degree of perioperative hyperglycemia. Continuous insulin infusions given to postoperative diabetic patients have been shown to reduce CABG mortality by 57%[21] and their routine use could particularly benefit female patients. Similarly, previous studies have shown a higher prevalence of hypothyroidism in females undergoing CABG compared to males[22] and an inverse relationship between CABG mortality and both levothyroxine dose and free thyroxine concentration found in females, but not males.[23] Close perioperative monitoring of thyroid functions and maintenance of an euthyroid state may therefore help reduce female operative mortality.

Our study also identifies several independent predictors of mortality after CABG. While several of these findings are well recognized in established risk scores (e.g. EuroSCORE II or STS)[24, 25], our study further confirms these predictors in a large and unselected cohort. The strongest predictors included in-hospital cardiogenic shock, age>80 years, pulmonary circulation disorder and peripheral vascular disease (PVD). Our results also show that off-pump CABG technique was associated with an increased risk of mortality after CABG with a slight increase in the proportion of off-pump CABG numbers over the study period. A recent meta-analysis[26] of 54 studies reviewing 16,261 patients concluded there was no difference in 30-day mortality between the two techniques. Future high-quality trials are warranted to further inform cardiac surgeons on this subject since on-pump CABG remains the standard operative technique in the US.

**Limitations**

There are several limitations to the present study. First, the observational nature of this study provides insight into associations but does not allow us to imply causality. The NIS is an administrative dataset that may be subject to coding inaccuracies introducing a potential source of bias. However, its coverage of a nationally representative sample and a wide range of comorbidities and operative characteristics mitigates these risks. Furthermore, the use of ICD-9 codes in administrative datasets has been previously validated for the purpose of cardiovascular outcomes research.[27, 28] Second, the NIS does not contain specific operative details (anatomical patterns of disease, type of grafts used, surgeon experience or stage in training, inpatient pharmacotherapy) that may remain as unadjusted confounders in our analysis. Third, the NIS only captures in-hospital outcomes and it is possible that sex differences in outcomes may be more pronounced on long term follow up. Finally, we could not adjust for all variables used in validated operative risk prediction models (e.g. EuroSCORE II or STS) due to the absence of some score components from our dataset.[24, 25]

**Conclusion**

In our study of over 2.5 million CABG procedures over a 12-year period, we show that female sex was associated with worse postoperative outcomes, with the exception of bleeding, and that these differences persisted over the study years. These findings highlight the need for future studies to investigate the mechanisms responsible for these differences and develop methods to reduce the inherent female operative risk.

**Conflict of Interest:** none.

**Figure Legends:**

**Figure 1. Trend of IMA utilization in both sexes over the study period**

IMA: internal mammary artery; \*2015 only includes admissions from 1st January through

30th September

**Figure 2. In-hospital adverse events according to sex**

p<0.001 for all outcomes

**Figure 3a. Adjusted odds ratios (OR) and 95% confidence intervals (CI) of adverse outcomes in females\***

\*reference is male sex; p<0.001 for all outcomes

**Figure 3b. Temporal trends of adjusted odds ratios (OR) and 95% confidence intervals (CI) of adverse clinical outcomes in females (2004-2015\*)**

\*2015 only includes admissions from 1st January through 30th September; p=non-significant for all trends

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