**Trends of repeat revascularization choice in patients with prior coronary artery bypass surgery**

**Short title:** Revascularization choice in prior CABG patients

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**Abstract**

**Objective:** To examine rates and predictors repeat revascularization strategies (percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)) in patients with prior CABG.

**Methods:** Using the National Inpatient Sample, patients with a history of CABG hospitalized for revascularization by PCI or CABG from January 2004 through September 2015 were included. Regression analyses were performed to examine predictors of receipt of either revascularization strategy as well as in-hospital outcomes.

**Results**: The rate of redo-CABG doubled between 2004 (5.3%) and 2015 (10.3%). Patients who underwent redo-CABG were more comorbid and experienced significantly worse major adverse cardiovascular and cerebrovascular events (MACCE; odds ratio (OR): 5.36 95% CI 5.11-5.61), mortality (OR 2.84 95% CI 2.60,-3.11), bleeding (OR 5.97 95% CI 5.44-6.55) and stroke (OR 2.15 95% CI 1.92-2.41), but there was no difference in cardiac complications between groups. Thoracic complications were high in patients undergoing redo-CABG (8%), especially in females. Factors favoring receipt of redo-CABG compared to PCI included male sex, age<80 years, and absence of diabetes and renal failure.

**Conclusion:** Reoperation in patients with prior CABG has doubled in the United States over a twelve-year period. Patients undergoing redo-CABG are more complex and associated with worse clinical outcomes than those receiving PCI.

**Key Words:** redo CABG, reoperation, percutaneous coronary intervention, outcomes, revascularization

**Abbreviations**

ACS Acute coronary syndrome

AHRQ Agency for Healthcare Research and Quality

CABG Coronary Artery Bypass Graft(ing)

CVA Cerebrovascular Accident

MACCE Major Adverse Cardiovascular and Cerebrovascular Event

NSTEACS Non-ST-Elevation Acute Coronary Syndrome;

OR Odds Ratio

PCI Percutaneous Coronary Intervention

STEMI ST-elevation myocardial infarction

**Introduction**

 Percutaneous coronary intervention (PCI) is the most commonly utilized modality of coronary revascularization worldwide, even in patients with prior coronary artery bypass grafting (CABG).(1,2) While previous studies have demonstrated worse PCI-related acute and long-term outcomes in patients with prior CABG, redo-CABG also carries a significantly higher rate of mortality compared to first-time CABG. (3-6) There is limited evidence on the rates of utilization of both revascularization strategies in recent years, as well as comparative data on outcomes of either strategy. Furthermore, little is known about how these trends have changed over the years with advances in PCI techniques, and what factors favor either strategy in contemporary practice.

 A single center study by Brener et al. compared PCI and redo CABG in 2191 patients between 1995 and 2000 and reported no difference in 30-day mortality between either revascularization strategy but lower 5 year survival in PCI than redo CABG patients in their cohort.(7) However, this study was based on a limited number of patients from a single center that represented 5-7% of all US hospitalizations. Furthermore, the study cohort was derived from over 20 years ago making it less generalizable to contemporary practice. Another study by Locker et al. reported long-term outcomes of redo CABG vs. PCI in 1612 patients with prior CABG and demonstrated higher mortality in the redo CABG compared to PCI but improved long-term survival in the CABG group thereafter. (8) While this study provides us with insights in to the long-term outcomes of redo-CABG compared to PCI, it doesn’t inform us of the trends of receipt of either strategy or any predictors that favor one over the other.

 The present study compared the rates and outcomes of PCI and redo-CABG in patients with prior CABG, and examined predictors of receipt of either procedure, in a national cohort of United States (US) hospitalizations.

# Methods

***Data Source***

The National Inpatient Sample (NIS) is the largest publicly available all-payer database of hospitalized patients in the US and is sponsored by the Agency for Healthcare Research and Quality as a part of the Healthcare Cost and Utilization Project (HCUP).(9) NIS includes anonymized data on discharge diagnoses and procedures from more than 7 million hospitalizations annually. The NIS dataset constitutes a 20% stratified sample of US community hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. The estimates of hospital characteristics, numbers of discharges, length of stay, and in-hospital mortality from the HCUP NIS for 2007 were highly comparable to three related data sources: the American Hospital Association (AHA) Annual Survey Database; the National Hospital Discharge Survey (NHDS) from the National Center for Health Statistics; and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (CMS).(3,10)

***Study Design and Population***

All hospitalization records for patients with a history of prior CABG between January 2004 through September 2015 were included, as identified using the International Classification of Diseases, ninth revision (ICD-9) codes given in Table S1 (Supplemental Material). Records with missing data on the following variables were excluded: age, sex, elective admission, primary expected payer, length of stay and median household income as illustrated in Figure S1 (Supplemental Material).

Patient characteristics, comorbidities, and clinical outcomes were extracted using the ICD-9 procedure and diagnosis codes provided in Table S1 (Supplemental Material); bleeding, cardiac complications (composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis), thoracic complications (composite of hemothorax, pneumothorax, thoracic vascular injury and chest drain insertion)and acute stroke or transient ischemic attack (TIA). Bleeding was defined as any post-procedural hemorrhage using ICD-9 diagnosis codes. (Table S1)

***Outcomes***

The main outcomes were to compare 1) predictors of receiving redo-CABG versus PCI and 2) differences in in-hospital adverse events between patients undergoing PCI and redo-CABG. In-hospital adverse events included major acute cardiovascular and cerebrovascular events (MACCE), all-cause mortality, bleeding, cardiac complications and stroke. In-hospital MACCE was defined as a composite of all-cause mortality, stroke and cardiac complications in both PCI and redo CABG groups, in addition to thoracic complications in the redo CABG group.

***Statistical Analysis***

For exploratory analysis, the cohort was stratified by type of revascularization into 2 groups: PCI and redo CABG. Continuous variables are summarized using medians and interquartile range (IQR) and were compared using the Kruskal-Wallis test. Categorical variables are summarized as percentages and were analyzed using the chi squared (X2) test.

Several multivariable logistic regression models were constructed to examine 1) the predictors of the type of revascularization (redo CABG vs. PCI) and 2) all the procedure-related adverse events that we considered between PCI and redo CABG groups. All multi-level regression models were adjusted for baseline differences that may directly influence in-hospital outcomes, over two levels: patient and hospital-level covariates (all variables listed in Appendix A in Supplementary Material). Institution type and hospital region were considered to be fixed effects. All associations were summarized from the multi-level logistic regression models using odds ratios (ORs) and associated 95% confidence intervals (CIs).

All statistical analyses were performed using SPSS version 24 (IBM Corp, Armonk, NY). Additionally, all analyses used the sampling weights provided by the AHRQ, which are required because the design of the study means that different observations may have different probabilities of selection. The sampling weights for each individual discharge were hence incorporated into the relevant SPSS commands for each analysis.

A sensitivity analysis examining rates, outcomes and predictors of revascularization strategies was performed on patients with no prior history of PCI. A further sensitivity analysis of predictors

# Results

 A weighted total of 570,120 patients (unweighted n=119,122) with prior CABG hospitalized for coronary revascularization (PCI or redo CABG) were recorded between January 2004 and September 2015, of which 40,708 (7.1%, unweighted: n=8,504) underwent redo CABG and 529,142 (92.9%, unweighted: n=110,618) received PCI.

 The overall rate of redo CABG was 7.1% having risen over the study years (2004: 5.3% to 2015: 10.3%; 94% relative increase, p<.001 for trend), and was persistently higher in patients without prior PCI and lower in patients who did not undergo concomitant open-heart valvular heart intervention (repair or replacement) (Figure 1A, absolute numbers in Supplementary Table S2). The rate of redo CABG was also persistently higher in males and non-diabetics over the study period (Figures 1B and 1C).

*Patient and procedural characteristics*

Several baseline differences were observed between the revascularization groups. Patients undergoing redo CABG were younger and more likely to be males, white, admitted electively, with stable coronary disease (vs. acute coronary syndrome (ACS)) and privately insured. (Table 1) Furthermore, patients undergoing redo CABG had a higher prevalence of conditions such as arrhythmias (VT, VF and AF), dyslipidemia, bleeding disorders (thrombocytopenia and coagulopathy), anemia and PVD, and a lower prevalence of renal failure and diabetes. The overall burden of comorbidities was higher in the CABG group with a higher median Charlson Comorbidity Index (CCI; 2(1,3) vs. 1(1,2)). The trends of differences in patient characteristics were persistent or more pronounced over the study years, except age, ventricular arrhythmias and PVD whose differences became less significant between revascularization groups. (Table S3).

 The majority of patients undergoing PCI received intervention to one vessel (79.6%) compared to more than a third (37.0%) of patients who underwent redo-CABG that received a single-vessel graft. (Table 2) The majority of CABG procedures were performed on pump (79.2%) and there was a greater need for IABP or assist device support in the redo CABG group compared to the PCI group (9.5% vs. 1.5%). The pattern of differences was persistent throughout the study years (Table S4).

*In-hospital outcomes*

 The rate crudes of MACCE, all-cause mortality and in-hospital complications were significantly higher in the redo CABG group, primarily driven by a higher rate of thoracic complications (8.0%), (Table 3, Figure 2) although no differences in cardiac complications between revascularization groups were observed. Furthermore, the median length of stay and total hospitalization charges were at least two to four-fold higher in the redo CABG group compared to the PCI group (length of stay: 8 (6,11) vs. 2 (1, 3) days; total charges ($): 114147 (77104,179082) vs. 49135 (34087,73305)). A similar pattern in outcomes was observed between revascularization groups after exclusion of patients with prior PCI. (Table S5). The rates of all complications increased over the years in both PCI and redo CABG groups but the differences between them persisted. (Table S6, Figure 3)

When stratified by sex, the crude rates of MACCE and mortality were higher in females of both groups, with a greater risk in females in the CABG group. (Table S7) Thoracic complications were also higher in females undergoing CABG (8.5% vs. 7.9%). The rates of all-cause bleeding and cardiac complications were higher in females in the PCI group but no sex differences in either complication were found in the CABG group. The rate of stroke was higher in females in the PCI group (0.5% vs. 0.3%) but lower in females in the CABG group (3.1% vs. 3.8%).

 In multivariate analysis, the odds of MACCE and bleeding were five to six-fold higher in the redo CABG group (OR: 5.36 95% CI 5.11-5.61 and5.97 95% CI 5.44-6.55, respectively) while the odds of mortality and acute stroke/TIA were two to three-fold higher (OR 2.84 95% CI 2.60,-3.11 and 2.15 95% CI 1.92-2.41, respectively), compared to the PCI group (p<.001 for all). (Table 4). Female sex and concomitant open heart valve surgery (replacement or repair) were significantly associated with worse outcomes, including higher MACCE (OR 1.17 95% CI 1.13-1.22 and 1.48 95% CI 1.38-1.58, respectively), mortality (OR 1.13 95% CI 1.06-1.20 and 2.13 95% CI 1.89-2.40), stroke (OR 1.34 95% CI 1.25, 1.44 and 1.97 95% CI 1.68-2.30) and bleeding (OR 1.35 95% CI 1.25-1.45 and 1.56 95% CI 1.39-1.75). Age >60 years and STEMI were also strong predictors of MACCE, mortality and stroke. (Table S8)

*Predictors of revascularization strategy*

 Female sex was associated with reduced odds of undergoing redo CABG (OR 0.84 95% CI 0.82-0.86), as were patients older than 80 years (OR 0.58 95% CI 0.55-0.61), ACS (STEMI: OR 0.38 95% CI 0.36-0.40; NSTEACS: OR 0.69 95% CI 0.68-0.71) and those with a primary expected payer other than Medicare or Medicaid. (Table 5, Figure 4A and 4B) Several patient-related factors correlated with increased odds of receipt of redo-CABG over PCI including patients with valvular heart disease, anemia, coagulopathy, atrial fibrillation, smoking history, hypertension, lymphoma and obesity. (Figure 4A) In contrast, factors which favored of PCI over CABG included diabetes, malignancies (metastatic cancer and solid tumors), collagen disorders including rheumatoid arthritis, dementia, dyslipidemia and previous PCI. The odds of receipt of redo CABG were also higher in medium and large bed-sized hospitals and urban hospitals. (Figure 4B) In comparison to hospitals in the Northeast, patients admitted to West and South hospital regions were more likely to undergo redo CABG while those admitted to Midwest hospitals were less likely to undergo redo CABG. A similar pattern of associations persisted even after the exclusion of patients with prior PCI and those undergoing open heart valvular repair or replacement (Table 5).

# Discussion

 The present study is the first to examine trends and predictors of choice of repeat revascularization in a nationwide cohort of more than 500,000 patients with prior CABG. We show that the rate of redo-CABG has doubled between 2004 and 2015. We examined trends of in-hospital outcomes of patients with prior CABG depending on the type of revascularization strategy and report a higher risk of mortality and complications such as acute stroke and all-cause bleeding in those undergoing redo CABG, primarily driven by their higher risk profile and treatment of more complex disease, and demonstrate persistence of this risk over the years. Finally, we report different patient, institutional and sociodemographic factors favoring either PCI or a re-do CABG revascularization strategy.

Repeat revascularization in patients with prior CABG is complicated and there is limited evidence to support the choice of revascularization strategy in this high risk group, although PCI remains the most commonly used modality.(2,7) PCI in patients with prior CABG are associated with an increased risk of complications such as restenosis and stent thrombosis whereas redo CABG is associated with significantly higher mortality compared to first-time CABG.(4,5,11-13) There are currently no data on the rates of PCI and redo CABG in patients with prior CABG, and how these rates have changed over time from a national perspective. Although our analysis shows that PCI is the most common revascularization strategy in this risk group, we report doubling of the rate of redo CABG procedures between 2004 and 2015. We also observe persistently lower rates of redo CABG in women and diabetics possibly due to operators’ concerns about the higher risk of postoperative complications in these groups as demonstrated in previous studies.(14,15)

Findings from the few studies comparing efficacy of either revascularization strategy in this cohort have been inconsistent and were largely limited by small sample size as well as the analyses of highly selected cohorts derived from randomized trials or registries.(7,16-18) In the AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) randomized trial and registry experience, an analysis of approximately 500 patients with prior CABG undergoing PCI or redo-CABG between 1995 and 2000 demonstrated a long term survival advantage with PCI at 36 months across all subgroups (randomized cohort, patient-choice registry and physician directed registry).(16) Although the study reflects practice from over 2 decades and was based on a modest sample size, it provided important insights into the short- and long-term survival associated with either revascularization strategy. No other procedure-related outcomes were assessed in the AWESOME study. In contrast, in a study by Harskamp et al. no difference in long term outcomes (composite of death, myocardial infarction and repeat revascularization) between redo CABG and PCI outcomes was demonstrated. (18)However, their analysis was based on a very small number of patients (PCI=243, redo CABG=44) and may have been underpowered to detect any meaningful clinical differences between the groups. Furthermore, it did not consider the risk of thoracic complications that would mainly arise in the CABG group.

Our findings demonstrate that mortality, bleeding and stroke complications were two to five-fold higher in patients undergoing redo-CABG compared to PCI. Furthermore, complication rates in both groups were higher than published rates for either intervention in patients without prior CABG. Although the risks of complications increased in both groups over the years, they remain significantly higher in the redo CABG group throughout the study period. The rise in complications is likely due to the increasing complexity of patients undergoing either intervention as demonstrated by their higher CCI index in our analysis. We also observe significant rates of thoracic complications in the redo CABG group, which could explain their higher mortality compared to those undergoing PCI, and no difference in cardiac complications between revascularization strategies. These complications may be in part due to the complexity of patients undergoing redo CABG, who undergo more extensive revascularization with more complex lesion characteristics compared to those who receive PCI. Furthermore, we find that women experienced higher rates of mortality in both revascularization groups (13-34% increased odds), especially in the CABG group, and higher rates of thoracic complications following CABG. The latter could be attributed to anatomical differences between sexes such as smaller chest cavities and thinner and smaller vessels in females, increasing their susceptibility to mechanical complications.(14,19,20) These findings may also explain the low rates of redo CABG in females compared to males as physicians may be reluctant to refer these patients for reoperation or surgeons may be refusing to operate on them due to their inherently high risk of complications.

Our study highlights important patient-related, sociodemographic and institutional predictors of the choice of revascularization strategy in patients with prior CABG in an unselected real-world population. We show that female sex, age>80 years, absence of concomitant valvular disease, previous PCI, dementia and malignancies (except lymphoma) favor receipt of PCI over redo CABG. In contrast, factors such as anemia, coagulopathy and lymphoma correlated with receipt of CABG over PCI, likely due to the increased bleeding risk in these patients who would otherwise require a longer commitment to dual antiplatelet therapy if they were to undergo PCI.(21) Although concomitant valvular disease was associated with an increase in odds of receipt of redo CABG over PCI, the rates of isolated redo CABG still increased over the study period. However, the expanding indication of transcatheter valvular interventions to intermediate and low-operative risk patients may favor PCI in these patients in the future. (22,23) Interestingly, there was a geographic variation in revascularization strategy preference where patients admitted to hospitals in the South and West regions were more likely to undergo redo CABG (19% and 22%, respectively) in comparison to hospitals in the Northeast, while those admitted to Midwest hospitals were 5% less likely to undergo redo CABG. Similarly, the odds of receipt of redo CABG were higher larger bed size and urban hospitals compared to small and rural hospitals, respectively. Furthermore, we find that admissions with primary payer other than Medicaid and Medicare correlated with higher odds of receipt of redo CABG over PCI. The present study is the first to examine such predictors from a national perspective and we believe that it provides important insights for the Heart Team, including cardiologists and cardiac surgeons, into trends of current practice and clinical outcomes of this high risk population when deciding on their optimal revascularization strategy.(24)

*Limitations*

As with most observational studies, there remains a possibility of unmeasured or unrecognized confounders that may contribute to the adverse outcomes, although capture of a wide range of comorbid conditions in the NIS may help to mitigate this bias. The NIS is an administrative dataset that may be subject to coding inaccuracies, although the use of ICD-9 codes has been previously validated for the purpose of cardiovascular outcomes research.(25,26) While the NIS database contained many variables of interest, additional data (platelet count, antithrombotic regimen, exact LV function, type of graft used, operator/surgeon experience, and lesion characteristics where applicable) are not routinely collected and may provide additional information to better stratify risk, case complexity, and procedural outcomes. Furthermore, NIS only captures in-hospital outcomes and it is possible that longer-term data would demonstrate even greater survival differences between PCI and CABG as previously shown two previous studies.(16) (8) Finally, we were unable to objectively measure the preoperative surgical risk using validated scores (e.g. EUROSCORE II or STS) for patients in the redo CABG group due to the lack of availability of all required parameters.(27,28) However, due to significantly higher comorbidities in the CABG group, it can be presumed that they would have a higher STS score.

**Conclusion**

 Despite PCI being the most common revascularization strategy in patients with prior CABG, especially females and diabetics, the rate of redo CABG in the United States has doubled over a twelve-year period. In this nationwide analysis we demonstrate that patients undergoing redo CABG are more complex and are associated with worse clinical outcomes. Our analysis highlights important predictors of the choice of revascularization, including patient comorbidities, sex, age, type of clinical syndrome and other sociodemographic factors.

# Conflicts

No authors have reported any disclosures or relationships with the industry.

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**Figure titles and legends:**

**Figure 1. Temporal trends of redo CABG over the study period in A) overall cohort and patients with no prior PCI, and stratified by B) sex and C) presence of diabetes mellitus**

**Footnote:** \*2015 (inclusive 1st January- 30th September only); CABG: coronary artery bypass grafting; p<.001 for trend; DM: diabetes mellitus

**Figure 2. In-hospital complications according to type of revascularization**

**Footnote:** \*MACCE: Major adverse cardiovascular and cerebrovascular events; CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

**Figure 3. Trends of in-hospital complications according to type of revascularization (2004-2015) \***

**Footnote:** \*MACCE: Major adverse cardiovascular and cerebrovascular events; \*\*2015 (inclusive 1st January- 30th September only); CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention

**Figure 4. A) Patient and B) Demographic predictors of receipt of CABG (vs. PCI) \***

\*Reference is receipt of percutaneous coronary intervention (PCI); AF: atrial fibrillation; AMI: acute myocardial infarction; CABG: coronary artery bypass grafting; NSTEACS: Non-ST-Elevation Acute Coronary Syndrome; STEMI: ST-Elevation Myocardial Infarction

**Supplementary Figures:**

**Supplementary Figure S1.** Flow chart of cohort selection process