**Incidence and Predictors of Postoperative Ischemic Stroke after Coronary Artery Bypass Grafting**

**Short title:** Postoperative stroke after CABG

Mohamed O. Mohamed, MRCP(UK)1,2, Sameer Hirji, MD, MPH3, Walid Mohamed4, MRCS, Edward Percy MD3, Peter Braidley, MD5, Joshua Chung, MD6, Sary Aranki, MD3, Mamas A. Mamas, DPhil1,2

1. Keele Cardiovascular Research Group, Centre for Prognosis Research, Institutes of Applied Clinical Science and Primary Care and Health Sciences, Keele University, UK
2. Department of Cardiology, Royal Stoke University Hospital, Stoke-on-Trent, UK
3. Division of Cardiac Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.
4. University Hospitals of Leicester NHS Foundation Trust, Leicester, UK
5. Sheffield teaching Hospitals NHS trust, Sheffield, UK
6. Department of Cardiac Surgery, Loma Linda University Medical Center, Loma Linda, California

**Corresponding Author:**

Mamas A. Mamas

Professor of Cardiology

Keele Cardiovascular Research Group,

Centre for Prognosis Research,

Institute for Primary Care and Health Sciences,

Keele University, UK

mamasmamas1@yahoo.co.uk

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**Abstract**

**Background:** Data on the incidence and outcomes of ischemic stroke in patients undergoing coronary artery bypass grafting (CABG) in the current era is limited. The goal of this study was to examine contemporary trends, predictors, and outcomes of ischemic stroke following CABG in a large nationally representative database over a 12-year-period.

**Methods:** The National Inpatient Sample was used to identify all adult (≥18 years) patients who underwent CABG between 2004-2015. The incidence and predictors of post-CABG ischemic stroke were assessed and in-hospital outcomes of patients with and without post-CABG stroke were compared.

**Results:** Out of 2,569,597 CABG operations, ischemic stroke occurred in 47,279 (1.8%) patients, with a rising incidence from 2004 (1.2%) to 2015 (2.3%) (P<0.001). Patient risk profiles increased over time in both cohorts, with higher Charlson comorbidity scores observed among stroke patients. Stroke was independently associated with higher rates of in-hospital mortality (3-fold), longer lengths of hospital stay (~6 more days) and higher total hospitalization cost (~$80,000 more). Age≥60 years and female sex (OR 1.33, 95% CI 1.31-1.36) were the strongest predictors of stroke (both P<0.001). Further, on-pump CABG was not an independent predictor of stroke (P=0.784).

**Conclusion:** In this nationally representative study we have shown that the rates of postoperative stroke complications following CABG have increased over time to commensurate with a parallel increase in overall baseline patient risks. Given the adverse impact of stroke on in-hospital morbidity and mortality after CABG, further studies are warranted to systematically delineate factors contributing to this striking trend.

**What’s already known about this topic?**

* Limited data exist on the incidence, predictors and outcomes of ischemic stroke in patients undergoing CABG in the current era.

**What does this article add?**

* Largest study to examine rates of postoperative stroke following CABG in a nationwide cohort over a 12-year period.
* Stroke rates have risen over a 12-year period in parallel with an increase in overall patient risk profile.
* Female sex, advanced age, AF, CKD, concomitant valvular surgery and PVD were all predictive of stroke after CABG.
* Stroke was independently associated with worse in-hospital mortality.

**Introduction**

Although coronary artery bypass grafting (CABG) has been shown to be safe and effective in appropriately selected patients1,2, ischemic stroke is a potentially devastating complication that is associated with increased risk of both short- and long-term morbidity and mortality.3,4 The most common mechanism of stroke following CABG is related to emboli originating from the ascending aorta during cross-clamping, cannulation and creation of proximal anastomoses, however, intracardiac thrombi, hypoperfusion and air emboli have all been implicated as possible causes.5 Thus, in light of this complex and multifactorial pathophysiology, several risk factors including advanced age, aortic calcification, renal failure and diabetes have all been identified to account for the early and delayed incidence of postoperative stroke.6-8

Over several decades, we have witnessed significant technical and technological advancements in the context of CABG. These include routine use of preoperative and intraoperative advanced imaging platforms, improvements in surgical technique, and optimization of cardiopulmonary bypass systems.9-11 The adoption of multidisciplinary heart teams to commensurate with improvements in perioperative care and temporal changes in patient demographics and risk profiles have also gained appreciable momentum.12,13 However, there is limited contemporary data examining the incidence of stroke following CABG in the setting of these patient- and system-level changes.1,4,10,14,15 Prior analyses from single centres are limited by their applicability to a wider context, while existing data from randomized controlled trials may only be applicable to carefully selected low-risk patients which may underestimate the true incidence seen in the real world. Additionally, previous national database studies have not addressed outcomes related to important subgroups of patient risk, or predictors of stroke in a contemporary context. The purpose of this study was to examine contemporary trends, predictors, and outcomes of ischemic stroke following CABG in a large nationally representative database over a 12-year period.

# 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.16 The NIS dataset constitutes a 20% stratified sample of US hospitals and provides sampling weights to calculate national estimates that represent more than 95% of the US population. Further information about the NIS is available in **Supplement Appendix A**.

*Study Design and Population*

All hospitalization records for adult patients aged ≥18 years undergoing CABG between January 2004 through September 2015 were included, as identified using the International Classification of Diseases, ninth revision (ICD-9) codes provided in **Supplement Table S1**. The cohort was restricted to September 2015 due to a transition to the ICD-10 coding system from October 2015, which has different classifications for certain procedures and comorbidity variables. Patients who underwent percutaneous coronary intervention (PCI) or received thrombolysis during the same admission or had a prior CABG (i.e. reoperation) were excluded. Records with missing data (4.4% of original cohort, n=25,286) on the following variables were also excluded: age, sex, elective admission, primary expected payer, death, hospital bed size or location, and median household income as illustrated in **Supplement Figure S1**. All patient characteristics, comorbidities, and clinical outcomes were extracted using relevant ICD-9 procedure and diagnosis codes.

*Outcomes*

The main outcomes were to examine 1) rates of stroke after CABG over the study period, stratified by procedural and patient subgroups, and 2) predictors of stroke after CABG. The secondary outcome measure was to compare the rates of in-hospital adverse events between stroke and non-stroke groups, all-cause mortality, bleeding (defined as any post-procedural haemorrhage), cardiac complications (composite of cardiac tamponade, hemopericardium, pericardial effusion and pericardiocentesis) and thoracic complications (composite of haemothorax, pneumothorax, thoracic vascular injury and chest drain insertion). In-hospital MACE was defined as a composite of all-cause mortality, cardiac complications and thoracic complications.

*Statistical Analysis*

For exploratory analysis, the CABG cohort was stratified according by the occurrence of postoperative stroke into 2 groups: Stroke and No-stroke. Continuous variables were assessed for normality of distribution using the Kolmogorov-Smirnov test, and were 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 analysed using the chi squared (X2) test. Costs were calculated using hospital charges and cost-to-charge ratios in US dollars. Multivariable logistic regression models were constructed to examine 1) predictors of postoperative stroke, and 2) adjusted odds ratios (OR) of in-hospital mortality in the Stroke group versus the No-stroke group. Survey procedures were applied to (1) generate national estimates and variances using given probability weights and (2) to account for clustering of outcomes by sampling unit (i.e. hospital) and sampling variation by region and year, as described previously.17,18 Age and sex standardised stroke rates were calculated based on the 2012 US population census (available at https://www.census.gov/data/tables/2012/demo/age-and-sex/2012-age-sex-composition.html).

All multivariable models were adjusted for differences in socioeconomic, clinical, and hospital-level covariates that may directly influence in-hospital outcomes. Further information on the analysis procedure is provided in **Supplement Appendix B**. Trend analysis was performed using linear regression modelling with the inclusion of time (years) as a covariate as well as using the Cochran-Armitage.

# Results

*Patient and Operative Characteristics*

In total, 2,569,597 CABG operations were included. The mean age in the overall cohort was 67 years (IQR 59,74) and 28% were female (**Table 1a**). Ischemic stroke occurred in 47,279 (1.8%) patients overall (Stroke cohort). Compared to the No-stroke cohort, the Stroke cohort was significantly older (71 vs 67 years) and more likely female (37.4% vs. 27.8%), and of African American ethnicity (9.3% vs 6.4%; all P<0.001). The Stroke cohort also tended to have a higher comorbidity burden of congestive heart failure, atrial fibrillation and chronic renal failure but a lower prevalence of diabetes, hypertension and obesity (all P<0.001). Not surprisingly, patients in the Stroke cohort who also had atrial fibrillation had significantly higher CHADVASC scores compared to the No-stroke cohort (Score 2+: 91.3% vs 87.6%; P<0.001).

In terms of operative characteristics, there was a higher rate of multi-vessel coronary revascularization in the Stroke cohort (3-vessel: 28.5% vs 27.8%; 4-vessel: 13% vs 12.5%) and more concomitant heart valve procedures (26.2% vs 15.3%), predominantly aortic and mitral valve replacements followed by mitral valve repair. (**Table 1b**) There was also a higher rate of intraoperative assist device or balloon pump in the Stroke group (13.7% vs 8.4%; all P<0.001).

*In-hospital Outcomes*

All-cause mortality was 12.5% in the Stroke cohort versus 2.4% in the No-stroke cohort (P<0.001; **Table 1b)**. After adjustment for potential confounders, mortality remained significantly higher in the Stroke cohort (OR 3.03 [2.93, 3.13], P<0.001). All other adverse events were higher in the Stroke cohort compared to the No-stroke cohort (all-cause bleeding: 5.9% vs. 3.6%; thoracic complications: 11.1% vs. 6.25; cardiac complications: 1.0% vs. 0.2%, P<0.001 for all). Stroke cohort patients had significantly longer lengths of hospital stay (14 days vs 8 days) and total hospitalization cost ($180,526 vs $104,553; both P<0.001).

*Analysis of Temporal Trends*

Between 2004 and 2015, the overall incidence of ischemic stroke events increased from 1.2% to 2.3% (Ptrend<0.001; **Figure 1)**. A similar pattern was observed with the age-sex standardised stroke rate, which increased from 2004 (1,643 [1,005; 2,282] per 100,000 population) to 2015 (2,691 [1,884; 3,497] per 100,000 population). When further stratifying the patient cohort by baseline cardiac rhythm (**Figure 1**), age, sex, we observed significant increases in stroke incidences over time (**Figure 2**) (Ptrend<0.001 for all). Similar findings were observed when examining trends by procedure status (elective vs non-elective) and procedure type (**Figure 2**) (Ptrend<0.001 for both). Furthermore, during the study period, we also observed a concomitant increase in patient risk profiles over time (as measured by the mean Charlson Comorbidity scores) in both cohorts, although much higher scores were observed in the Stroke cohort (**Figure 3a**) (Ptrend<0.001 for both).

*Predictors of Postoperative Stroke*

On multivariable logistic regression analysis, several baseline and operative factors were predictive of postoperative stroke in patients undergoing CABG (**Figure 3b; Table S2**). Increased age above 60 years as well as female sex (OR 1.33, 95% CI 1.31-1.36) were the strongest baseline predictors (both P<0.001). Other factors included clinical presentation with both ST-segment and non-ST-segment elevation myocardial infarction, the presence of preoperative cardiac arrest, atrial fibrillation, peripheral vascular disease, and chronic renal failure. While concomitant valvular procedures and increasing numbers of vessels grafted were predictive of stroke with increasing odds ratio (both P<0.001), on-pump CABG was not a significant predictor of stroke (P=0.784).

# Discussion

This longitudinal, nationally representative study of 2.5 million CABG operations has several important findings: First, we demonstrate that the rates of postoperative stroke complications following CABG have increased over time during the 12-year study period. This temporal increase has been accompanied by a parallel increase in overall baseline patient risk. Second, we found that there exists significant age and sex-based temporal differences in stroke incidences, which was worse among females and octogenarians, respectively. Third, we observed a significant association between the incidence of stroke and higher rates of in-hospital morbidity and mortality. And finally, we also found that female sex, advanced age, atrial fibrillation, chronic renal failure, concomitant procedures and peripheral vascular disease were all predictive of stroke after CABG.

Our study findings are in accordance with prior work from other single-centre and large database experiences, and those reported in landmark trials such as the SYNTAX and FREEDOM trials.1,4,10,14,15,19. However, this study is the first national analysis in the literature to examine trends in a large cohort over a longitudinal 12-year period. According to the STS Adult Cardiac Surgery Database, the incidence of postoperative stroke after CABG was 1.3%, which decreased from 1.6% in 2000 to 1.2% in 2009.10 In comparison, the overall stroke rate in our study was 1.8%, but which increased from 1.2% to 2.3% in 2015. The reported differences may relate to differences in the years analysed. Our study examined a longer time period ending in a more recent cohort, during which time we saw a clear increase in patient risk profile. There may also be differences in patient populations related to study exclusion criteria or to sampling and reporting differences between clinical databases such as the STS and the NIS, which is an all-payer administrative database comprised of a weighted national sample 20 Other factors contributing to the upward trend of postoperative stroke over the years could include the increased recognition and detection of this complication as well as the wider availability of imaging modalities such as MRI to ascertain the diagnosis.

Our results are also consistent with prior reports that have examined the adverse impact of postoperative stroke on short-term outcomes. For perioperative mortality, studies have reported rates ranging from 16 to 20% in CABG patients with a postoperative stroke.4,15 The observed rate of all-cause mortality in the Stroke cohort was relatively lower, at 12.5%, but still almost 5-fold higher than that in the No-stroke cohort. We also found a strong association between the incidence of stroke and rates of in-hospital all-cause mortality and MACE, which also included cardiac complications and thoracic complications. Likewise, we found that stroke was associated with higher hospital resource utilization in terms of longer lengths of hospital stay (~6 more days) and higher total hospitalization cost (~$80,000 more).

Existing literature examining risk factors for stroke after CABG is extensive.21-23 The most important risk factors for stroke are age, dialysis dependency, chronic lung disease, atrial fibrillation and atherosclerotic burden of the aorta and coronary vessels.21-23 Our study highlighted some of these factors including atrial fibrillation, age, heart failure, chronic renal failure and previous stroke. Interestingly, female sex was one of the strongest predictors of stroke and was associated with 33% higher odds of stroke after CABG. These sex-based differences were also evident when we examined stroke trends over time, where we observed persistently elevated stroke rates in females (mean 2.5%) compared to males (1.6%). These differences in stroke risk may be attributable to differences in biology, use of hormone replacement therapy and differential burden of atherosclerotic disease.24 Females may also represent a high-risk cohort with more advanced disease at the time of symptom onset and disease recognition. Likewise, the study also highlighted some novel predictors of stroke including the presence of metastatic cancer which haven’t been described before in randomized controlled trials due to the fact that they exclude high risk patients. The pathophysiology of stroke may be secondary to the hypercoagulable state observed in cancer patients.

Interestingly, this study highlighted the prevalence of significant differences in stroke complications over time by age. While stroke rates increased for all ages across the study interval but appeared to plateau after 2008, the rates remained persistently elevated and more than 2-fold higher among the septuagenarians and octogenarians compared to patients aged 60 years or less. This finding was also evident in the multivariable logistic model where increasing age above 60 years was associated with increased odds of stroke complications. The higher stroke rates among patients with advanced age makes intuitive sense as this likely represented a cohort with increasing burden of coronary artery disease and other comorbidities.

Historically, most CABG procedures have been performed while on cardiopulmonary bypass. It was not until the late 1990s when interest in on-pump CABG surgery emerged and subsequently peaked. However, the efficacy between on-pump and conventional CABG in terms of CABG is still debated given mixed results in terms of perioperative mortality, stroke, renal failure, stroke and transfusion requirements.25-27 In a recent pooled analysis of 59 randomized studies (n=8,961 patients), there was a 30% reduction in occurrence of postoperative stroke with on-pump CABG surgery but no significant differences in mortality or myocardial infarction.26 In contrast, in the German Off-Pump Coronary Artery Bypass Grafting in Elderly patients trial, which included 2,394 elderly patients aged 75 years or older, stroke rates were not statistically significant between the conventional versus on-pump CABG group at 30-days (OR 0.83, 95% CI: 0.5-1.38).27 We observed a similar finding such that on-pump CABG was not an independent predictor of stroke.

While our findings provide a comprehensive overview of contemporary trends in stroke complications after CABG, they also raise some concern especially given the fact that stroke complications have nearly doubled from 2004 to 2015. While the reasons for the observed trends are likely multifactorial, there are 2 plausible reasons. First, the increasing comorbidity burden of the overall patient pool undergoing CABG. Following landmark studies such as the SYNTAX, STICH, and FREEDOM trials, increasingly more high-risk patients with comorbidities and complex coronary disease have been treated primarily with CABG.1,14,19 Patients with advanced age also have a significant number of comorbid conditions such as chronic renal failure and atrial fibrillation, which are known risk factors for stroke.22,23 Thus, not surprisingly, we found a concomitant temporal increase in overall baseline patient risks over time in both the Stroke and No-stroke cohorts, as also previously demonstrated.12 The second reason we suspect is the increasing case complexity. Most patients in the Stroke cohort had multi-vessel coronary disease, and 1 in 5 patients underwent concomitant heart valve surgery. Thus, the longer procedure time and increased aortic manipulation in these settings most likely contributed to the increased stroke rates.

There are a number of measures that could be implemented to reduce the neurologic risks associated with CABG. These include routine preoperative screening for aortic disease using computed tomographic angiography and use of intraoperative epiaortic scanning as part of the surgical planning process. Unfortunately, we were unable to assess trends in use or efficacy of these strategies within the present study. However, both these techniques, which aid to minimize manipulation of the ascending aorta in patients with high atheromatous aortic burden, have shown to be associated with reduced risk of stroke after CABG when used in the proper setting.11,28 The role of other technical advancements such as embolic protection devices remains to be determined. Most importantly, multidisciplinary evaluation of severe coronary artery disease is paramount to ensure evidence-based, best practices for patient selection, patient prognostication, and overall risk stratification.

*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.29,30 Furthermore, NIS only captures in-hospital outcomes and it is possible that longer-term data would demonstrate a greater incidence of postoperative stroke beyond discharge and greater survival differences between patients with and without postoperative stroke. Finally, we were unable to objectively measure, or adjust for, the preoperative surgical risk using validated scores (e.g. EUROSCORE II or STS) due to the lack of availability of all required parameters.

**Conclusion**

 In conclusion, in this large, longitudinal, nationally representative study of 2.5 million CABG operations, we have shown that the rates of postoperative stroke complications following CABG have increased over time to commensurate with a parallel increase in overall baseline patient risks. Given the adverse impact of stroke on in-hospital morbidity and mortality after CABG, further studies are warranted to systematically delineate factors contributing to this striking trend.

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**Figure Legends and captions**

**Figure 1. Trends of postoperative stroke incidence in the overall cohort and by atrial fibrillation subgroup**

**Caption: \***2015 only includes admissions from 1st January through 30th September, ptrend <0.001 for both

**Figure 2. Trends of postoperative stoke incidence according to different subgroups (A) Age (B) Sex (C) Procedure status and (D) Procedure type**

**Caption: \***2015 only includes admissions from 1st January through 30th September, ptrend <0.001 for all

**Figure 3a. Trends in patient risk profile according to Charlson Comorbidity Index between 2004 and 2015**

**Caption \***2015 only includes admissions from 1st January through 30th September; No=no stroke group; Yes=stroke group, ptrend <0.001

**Figure 3b. Forest Plot of predictors of postoperative stroke**

**Caption:** § non-significant; † p≤0.01; ‡ p<0.001; CABG: coronary artery bypass graft; CAD: coronary artery disease; CVA: cerebrovascular accident; NSTEACS: non-ST-elevation acute coronary syndrome; STEMI: ST-Elevation myocardial infarction