Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(7) 1–13

DOI: 10.1177/0300060520920428
journals.sagepub.com/home/imr
SAGE

Factors associated with long-term survival in patients with stroke after coronary artery bypass grafting

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Abstract

Objective: Occurrence of a stroke within 30 days following coronary artery bypass grafting (CABG) is an uncommon, but often devastating, complication. This study aimed to identify factors associated with long-term survival (beyond 30 days) in patients with stroke after CABG.

Methods: De-identified patients' records from the Veterans Affairs Surgical Quality Improvement Program database were used to identify risk factors and perioperative complications associated with survival for up to 20 years in patients with post-CABG stroke. The multivariable Cox proportional hazards model was used for analyzing survival.

Results: The median survival time for patients with stroke (n = 1422) was 6.7 years. The mortality rate for these patients was highest in the first year post-CABG and was significantly elevated compared with non-stroke patients. Survival rates at 1, 5, and 10 years for stroke versus non-stroke patients were 79% vs. 96%, 58% vs. 83%, and 36% vs. 63%, respectively. High preoperative serum creatinine levels, postoperative occurrence of renal failure, prolonged ventilation, coma, and reoperation for bleeding were important predictors of 1-year mortality of patients with post-CABG stroke.

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Conclusions: Veterans with post-CABG stroke have a considerably higher risk for mortality during the first year compared with patients without stroke.

Keywords

Stroke, coronary artery bypass grafting, long-term survival, mortality, risk adjustment, renal failure, coma, veteran

Date received: 25 January 2020; accepted: 30 March 2020

Introduction

Stroke is the third leading cause of death in the United States.[1] Stroke may dramatically alter a person's capacity to perform activities of daily living, ability to communicate, and even behavior. For patients who have had cardiac surgery, the risk of postoperative stroke is a common concern. Reported rates of stroke within 30 days after isolated coronary artery bypass grafting (CABG) vary from 1.1% to 3.8%.[2-9] Moreover, patients who suffer post-CABG stroke often have higher rates of other in-hospital co-morbidities and/or 30-day operative mortality.[2,6,8,9] This increased mortality risk of patients with stroke after CABG surgery persists, with reduced rates of long-term survival beyond the initial hospitalization. For patients with post-CABG stroke, the greatest risk of death occurs within the first postoperative year.[6]

Many studies have previously investigated factors associated with post-CABG stroke.[1-12] The rates of postoperative occurrence of stroke and post-CABG mortality are low. Therefore, these studies were limited in their ability to detect which risk factors contributed to reduced long-term survival rates observed for patients with post-CABG stroke. A few recent studies examined the effect of postoperative stroke on long-term survival beyond the initial hospitalization.[6,8] However, no studies have investigated risk factors for long-term survival, specifically in the post-CABG stroke subgroup.

Therefore, in this study, patients' risk factors were evaluated for long-term survival of patients with post-CABG stroke. Additionally, we determined whether these risk factors differ in magnitude from those of patients without stroke post-CABG (i.e., post-CABG patients who do not have a stroke either in-hospital or within the 30-day perioperative period).

Patients and methods

Patient population

The Department of Veterans Affairs (VA) Surgical Quality Improvement Program (VASQIP) prospectively collects patient-level risk, procedural, and outcome data on all patients undergoing cardiac surgery at the national level across VA surgical centers. De-identified records for 103,686 veterans who underwent isolated CABG procedures from 44 centers between 1 October 1991 and 30 September 2011 were extracted. Therefore, there was at least 2 years follow-up of all records, with up to 22 years follow-up for some records, available. Twelve records were excluded because of missing perioperative stroke outcome variables. Of these 103,674 records remaining, 1699 (1.6%) patients experienced a postoperative stroke within 30 days of surgery and 277 (16.3%) died within 30 days. All patients who did not survive discharge to at least 30 days were also excluded for the primary analyses. However, these patients were included in the determination of overall stroke rates.

Because of using VASQIP de-identified data, this research project was determined to not be human subject research and waiver of informed consent was approved. This project was approved by the Colorado Multiple Institutional Review Board, the Northport VA Institutional Review Board, and the VA Surgical Quality Data Use Group.

Variables

The VASQIP database has been previously described.[13] Preoperative risk variables that were eligible for multivariable model entry within this post-CABG stroke analysis were identified (Table 1). Occurrence of stroke was defined by the VASQIP as any new objective neurological deficit lasting more than 72 hours, with immediate postoperative onset or onset within 30 days after surgery. The exact type of stroke (e.g., hemorrhagic stroke) and timing of the stroke were not available in the VASQIP database.

Survival information was obtained using the VA Beneficiary Records Locator System,[14] which is a national death registry for all veterans. The survival endpoint was assessed for all deaths, regardless of cause. In addition to the postoperative occurrence of stroke, other postoperative complications occurring within 30 days were evaluated (Table 2).

Statistical analysis

Descriptive statistics were calculated using means and standard deviations for continuous variables and percentages for categorical variables. Missing predictor variables ($<1\%$ missing) were imputed using the median for continuous variables and the most frequent value for categorical variables. Means and proportions were compared using the two-sample t-test and the chi-square test, respectively. The Kaplan–Meier product-limit estimator was used to approximate unadjusted survival, with hazard functions for comparing the stroke and non-stroke groups. Multivariate Cox proportional hazards models were used to separately investigate which factors were predictive of long-term (>1 year) and short-term survival (≤ 1 year) post-CABG. Models included an interaction term of post-CABG stroke occurrence with predictor variables to obtain and compare separate risk estimates for the stroke and non-stroke groups within the same model. The Wald test was used to test the equality of the regression coefficients for each risk factor between the stroke and non-stroke groups. A robust sandwich estimator was included to fit a marginal model accounting for clustering within a hospital. All analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Stroke and mortality rates

A total of 100,940 records and 1422 (1.4%) surviving patients with post-CABG stroke were included in the analysis. Follow-up was completed for 926,046 person-years for 100,940 patients, with an average of 9.2 years of follow-up (range: 2.3–22 years). The post-CABG 30-day stroke rate was 1.4% ($n = 1422$), and the 1-year mortality rate for patients with stroke was 20.7% ($n = 294$) compared with 3.8% ($n = 3{,}762$) for non-stroke patients ($p < 0.001$). The 30-day stroke rate decreased from 2.2% in 1991 to 1.1% in 2000, and remained close to 1.1% through to 2011. The 1-year mortality rate also decreased from approximately 25% in the 1990s to approximately 12% after 2005 following post-CABG stroke (Figure 1).

Table 1. Preoperative risk characteristics and procedural details for patients with stroke who survived >1 year vs. ≤1 year.

	Stroke		
	Survived >1 year n = 1128	Survived ≤1 year n = 294	p value
Age in years, median (IQR)	67 (61–72)	72 (66–75)	<0.01
Male sex (%)	98.9	99.0	0.95
BSA (m^2), median (IQR)	2.0 (1.9–2.1)	1.9 (1.8–2.1)	0.04
Current smoker (%)	27.9	27.9	0.99
Digoxin use (%)	7.4	15.0	<0.01
Diuretic use (%)	30.9	44.6	<0.01
Functional status (%)			
Independent	85.5	74.5	<0.01
Partially dependent	11.7	19.0	<0.01
Totally dependent	2.7	6.5	<0.01
Intravenous nitroglycerin < 48 hours before surgery (%)	14.8	22.1	<0.01
Emergent surgical priority (%)	14.8	17.0	0.35
Diabetes (%)			
None	61.3	55.8	0.09
Requiring oral therapy	19.2	22.8	0.17
Requiring insulin	19.5	21.4	0.46
Renal insufficiency (%)			
CR levels < 132.6 μmol/L	76.9	57.8	<0.01
CR levels ≥132.6 μmol/L and ≤265.2 μmol/L	22.2	36.4	<0.01
CR levels >265.2 μmol/L	1.1	5.8	<0.01
Cardiomegaly (%)	18.4	29.3	<0.01
COPD (%)	27.9	36.1	0.01
CVD (%)	38.4	46.6	0.01
PVD (%)	33.0	44.6	<0.01
Prior MI (%)			
None	43.0	35.0	0.01
>7 days before surgery	47.4	53.4	0.07
≤7 days before surgery	9.6	11.6	0.31
CCS class IV angina (%)	37.9	44.2	0.05
NYHA class IV heart failure (%)	7.5	9.5	0.26
Prior heart surgery (%)	6.6	10.9	0.01
Pulmonary rales (%)	8.2	16.7	<0.01
Number of CABG anastomoses, median (IQR)	3 (3–4)	3 (3–4)	0.35
Number of CABG anastomoses with IMA, median (IQR)	1 (1–1)	1 (0–1)	<0.01
Total CPB time (minutes), median (IQR)†	107 (81–135)	110 (81–140)	0.55

BSA, body surface area; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CR, creatinine; CVD, cerebrovascular disease; IMA, internal mammary artery; MI, myocardial infarction; NYHA, New York Heart Association; PVD, peripheral vascular disease; IQR, interquartile range. †Collection of CPB time was initiated in 1997.

Characteristics of patients with stroke by occurrence of 1-year survival

Univariate associations for patients' factors with 1-year survival are shown in Table 1. Patients with stroke who did not survive for at least 1 year post-CABG discharge had higher preoperative risk profiles, including older age ($p < 0.01$), more functional dependence ($p < 0.01$), a higher rate of renal

Table 2. Postoperative morbidity outcomes for patients with stroke who survived >1 year vs. ≤1 year.

	Stroke		
Outcome variable	Survived >1 year n = 1128	Survived ≤1 year n = 294	p value
Renal failure (%)	1.8	11.2	<0.01
Mediastinitis (%)	3.2	6.8	<0.01
Reoperation for bleeding (%)	3.3	8.8	<0.01
Ventilator support ≥48 hours (%)	31.9	69.7	<0.01
Repeat cardiopulmonary bypass (%)	0.4	1.4	0.08
Coma lasting ≥24 hours (%)	3.9	20.7	<0.01
Cardiac arrest requiring CPR (%)	3.3	12.2	<0.01
New mechanical circulatory support (%)	3.2	7.7	<0.01

CPR, cardiopulmonary resuscitation.

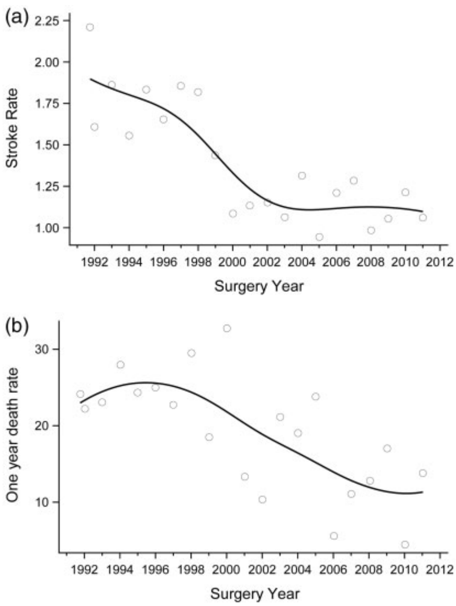

Figure 1. Proportion of patients who experienced a stroke within 30 days post-CABG surgery (a) and the proportion of those who died within 1 year post-CABG (b) for all patients who had CABG by surgery year. CABG, coronary artery bypass grafting.

insufficiency or failure ($p < 0.01$), a higher incidence of chronic obstructive pulmonary disease (COPD) ($p = 0.01$), and more severe atherosclerotic disease burden (i.e., increased rates of cerebrovascular disease [CVD] and/or peripheral vascular disease) (both $p < 0.05$) compared with those who survived for >1 year. Additionally, patients with stroke who did not survive for at least 1 year post-CABG had exacerbated progression of cardiac disease towards the end stage, as shown by a significantly greater incidence of cardiomegaly ($p < 0.01$) and higher use of diuretics ($p < 0.01$) compared with those who survived for >1 year. Patients with stroke who survived < 1 year also had a significantly higher rate of co-existing postoperative complications (all types, $p < 0.01$, except for repeat cardiopulmonary bypass) compared with those who survived for >1 year (Table 2).

Overall survival for patients with stroke

There were 966 deaths in the subset of 1422 stroke patients over the 22-year period. Kaplan–Meier estimates of survival at 1, 5, 10, and 15 years for patients with stroke compared with non-stroke patients were 79% vs. 96%, 58% vs. 83%, 36% vs. 63%, and 22% vs. 47%, respectively. The unadjusted median survival time for patients with stroke was 6.7 years (95% confidence interval [CI]: 6.2–7.3 years) compared with 14.0 years (95% CI: 13.9–14.1) in non-stroke patients.

The Kaplan–Meier unadjusted survival function for patients with stroke and non-stroke patients is shown in Figure 2a. The corresponding hazard function (interpreted as the instantaneous rate of death for a given time interval) is shown in Figure 2b. Importantly, the mortality rate for patients with stroke was highest in the first year post-CABG compared with non-stroke patients (log-rank test, $p < 0.01$). After this time, this difference in risk became relatively constant, but was still elevated compared with that of non-stroke patients. The observation that the risk for death differed in the time up to and after 1 year resulted in a second set of analyses to determine whether the same risk factors associated with survival up to 1 year are different from those that are important for survival after 1 year.

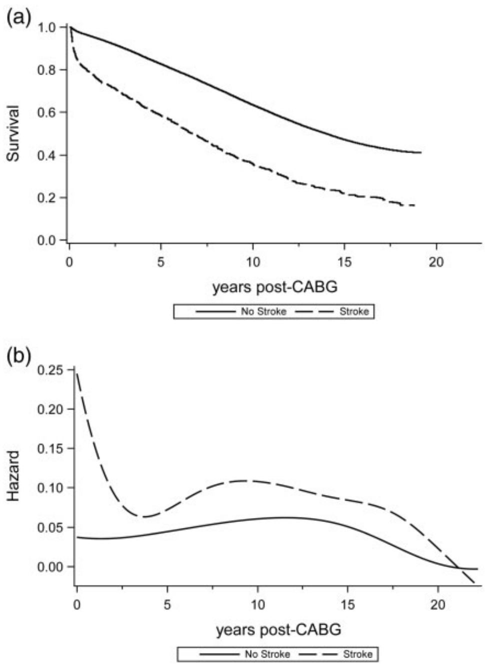

Figure 2. Kaplan–Meier survival curve for patients who had CABG by 30-day stroke occurrence shows the proportion of patients who survived in relation to the number of years post-CABG (a). The corresponding hazard functions for patients who had CABG by 30-day stroke occurrence shows the instantaneous death rate (deaths per day) (b). The hazard at the indicated number of years post-CABG is related to the death rate in a small interval around that time, provided that the event has not already occurred. In both panels, time 0 corresponds to the day of the CABG procedure. CABG, coronary artery bypass grafting.

Predictors of 1-year survival for patients with stroke compared with non-stroke patients

A multivariate Cox model based on the observation of the higher hazard rate in patients with stroke, especially within the first year post-CABG, was constructed. In this model, a time horizon set at 1 year post-CABG was used to estimate risk factors associated with death within the first 11 months after the 30-day post-surgery period. For comparing risks between patients with and without stroke, this model included stroke, risk factors, and an interaction of each risk factor with the stroke indicator to obtain risk estimates separately for each group. The resulting hazard ratios (HRs) were used to determine which factors remained useful for assessing 1-year survival for patients who experienced post-CABG stroke and survived discharge through the initial 30 days. Using the interaction terms, HR estimates with 95% CIs were compared between patients with and without stroke (Figure 3).

For patients with stroke, preoperative serum creatinine levels $> 265.2\,\mu mol/L$ (HR [95% CI]: 3.9 [1.8–8.7]), age (1.8 [1.5–2.2], in decades), digoxin use (1.8 [1.3–2.4]), and postoperatively, ventilator support > 48 hours (2.9 [2.2–3.8]), coma > 24 hours (2.4 [1.7–3.3]), and renal failure requiring dialysis (2.0 [1.4–2.8]) were the main factors related to mortality within 1 year. Other significant factors are shown in Figure 3. Surprisingly, the independent

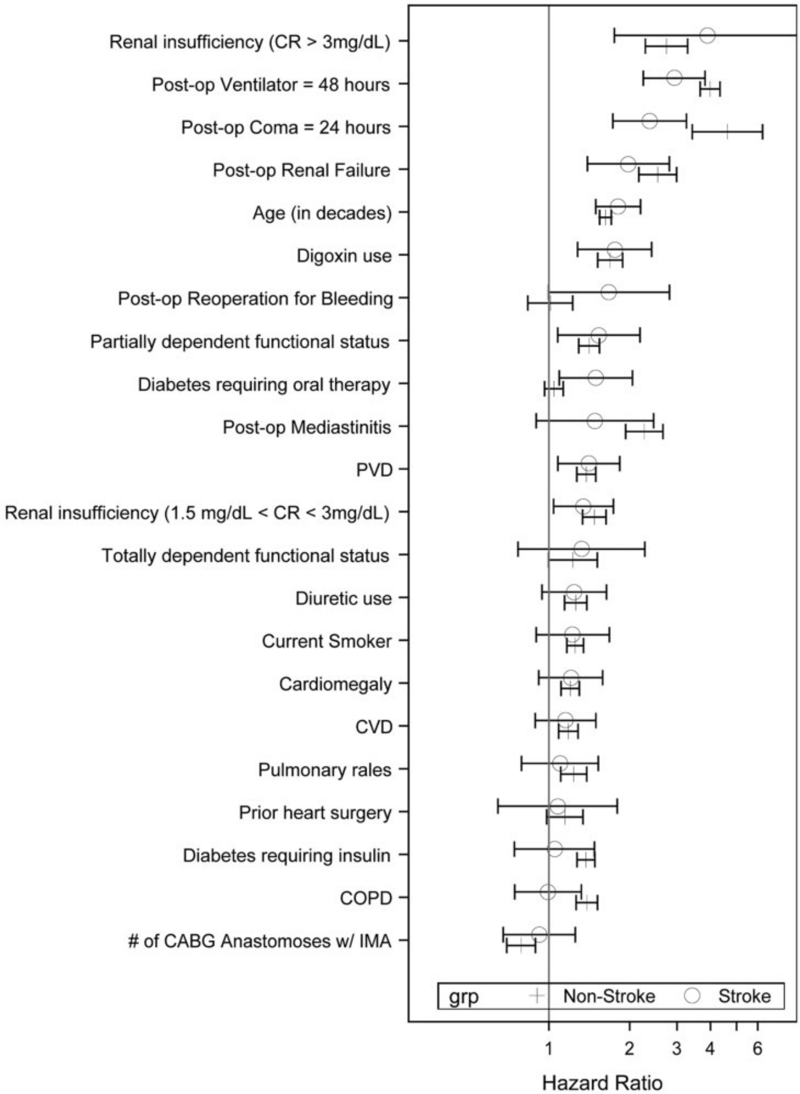

Figure 3. Hazard ratios and 95% confidence intervals (whiskers) from a multivariate survival model for each predictor for patients with stroke compared with non-stroke patients for 1-year survival. Hazard ratios correspond to the shift in the hazard function attributable to the predictor. CR, creatinine; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; IMA, internal mammary artery.

risk associated with preoperative CVD was not significant for survival in the stroke group (HR: 1.2, $p = 0.25$). The most significant risk variables from the stroke group were consistent with those for the non-stroke group. The following variables had significantly different HRs between the stroke and non-stroke groups: COPD (HR: 1.0 vs. 1.4, $p = 0.04$), ventilator support > 48 hours (HR: 2.9 vs. 4.0, $p = 0.01$), and coma (HR: 2.4 vs. 4.6, $p < 0.01$). These variables posed greater risks for non-stroke patients than for patients with stroke.

Two additional sensitivity analyses were performed to 1) evaluate the time-related effect of declining stroke and mortality rates by including the year of surgery as a covariate and 2) to exclude off-pump procedures. Our results were not changed by the analysis including the year of surgery. However, the findings were slightly altered by excluding off-pump patients. For patients with stroke who received an on-pump versus an off-pump CABG procedure, the effect of preoperative serum creatinine levels > 265.2 μmol/L was slightly increased (HR: 3.9 [1.8–8.7) to 4.7 [2.1–10.8]). However, this did not change the set of risk factors or perioperative complications associated with 1-year survival.

Predictors of survival for patients with stroke compared with non-stroke patients for those surviving past the initial year

In addition to evaluation of risk factors associated with early survival, long-term outcomes were similarly of interest. Of the 96,884 patients who survived the first year post-CABG, 1128 (1.2%) experienced a postoperative stroke within 30 days of surgery. In this postoperative stroke group, the 5- and 10-year survival rates were 57% and 19% compared with 65% and 26%, respectively, in the non-stroke group. These higher survival rates were conditional based on a patient's survival to the end of the first year after surgery. However, the rates reported above were conditional only on 30-day survival. For this additional analysis, Figure 4 shows HRs and 95% CIs for each risk factor for patients with stroke and non-stroke patients. Preoperative diuretic use, CVD, COPD, and current smoking status were significant predictors of mortality beyond 1 year in the stroke group (HR [95% CI]: 1.3 [1.1–1.6], 1.3 [1.1–1.5], 1.2 [1.0–1.5], and 1.3 [1.0–1.5], $p = 0.01$, $p<0.01$, $p = 0.03$, and $p = 0.02$, respectively) (Figure 4). Other risk factors, such as age ($p < 0.01$), renal function ($p < 0.01$), peripheral vascular disease ($p < 0.01$), and coma ($p = 0.01$), which were significant predictors for 1-year mortality, were also significant for long-term mortality. The HR for totally dependent functional status was significantly different between the stroke and non-stroke groups (HR: 0.7 [0.4–1.2] vs. 1.1 [1.0–1.2], $p = 0.03$).

Discussion

This study identified predictors of 1-year and long-term survival for patients with post-CABG stroke. Preoperative serum creatinine levels and postoperative renal failure complications, along with reoperation for bleeding, were important predictors of 1-year survival of patients with post-CABG stroke. Other factors included postoperative complications of prolonged ventilation and coma, although these were less important risk factors for long-term survival after surviving for the first year. Surprisingly, CVD, which has been found to be associated with a risk of post-CABG stroke[2-4,12] was not significantly associated with 1-year survival, but was important for long-term survival, particularly if the patient survived past 1 year, and carried a similar long-term risk for non-stroke patients. Increased risk associated with reoperation for bleeding and coma complications remained higher for patients with stroke than for non-stroke patients after 1 year. Sensitivity analyses did not change this study's results.

Our finding that patients with post-CABG stroke had a much higher risk for 1-year mortality compared with non-stroke patients is in agreement with other published studies.[5,6,15-17] We observed a decline in the 30-day stroke rate over time. Tarakji et al.[6] reported a similar decline from 2.6%

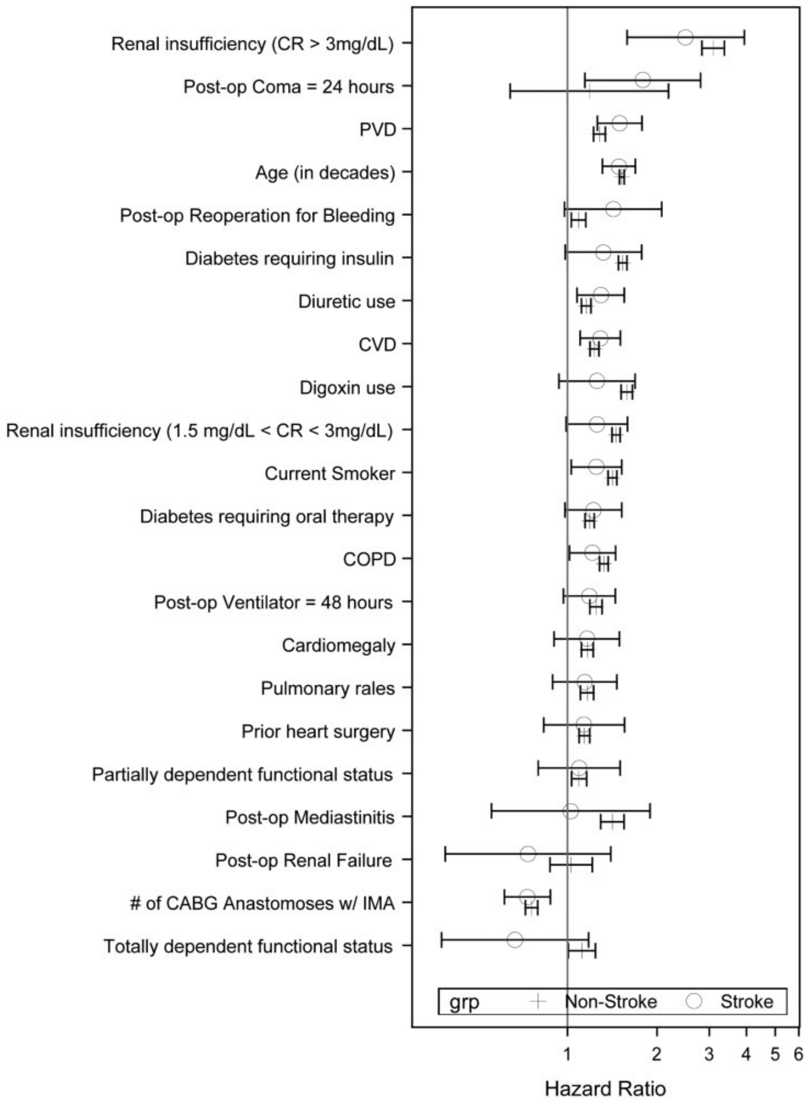

Figure 4. Hazard ratios and 95% confidence intervals (whiskers) for each predictor from stroke patients compared with non-stroke patients for survival past 1 year. Hazard ratios correspond to the shift in the hazard function attributable to the predictor. CR, creatinine; PVD, peripheral vascular disease; CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; IMA, internal mammary artery.

in 1988 to 0.91% in 2010. A history of prior stroke is known to be a predictor of subsequent stroke, including post-cardiac surgery stroke.[1-6,9]

To the best of our knowledge, this is the first study to report the risk factors for survival following a post-CABG stroke event. Interestingly, the risk factors found for stroke have also been implicated as the same post-CABG risk factors for mortality following occurrence of stroke.[18,19] Our study and previous studies show that the majority of post-CABG strokes occur in the subgroup of patients with the most advanced cardiovascular disease; where older age may represent a marker of increased atherosclerotic burden rather than independent patients' risk characteristics that may cause a stroke, per se.[20]

The significantly higher risk of 1-year mortality associated with reoperation for bleeding in the stroke group (Figure 3) may reflect hypotension and/or poor perfusion. However, there may be an association between transfusion and stroke.[2,21] Because blood product use was not collected as part of the VASQIP database, this question could not be directly investigated. The lower risk of 1-year mortality associated with ventilator dependence and coma in the stroke group is likely due to the higher incidence of death within 30 days for patients with stroke who suffered these particular complications.

The strong association of stroke and long-term survival with preoperative renal insufficiency and failure, as well as postoperative renal failure requiring dialysis, has been reported in multiple studies.[2-5,7,10,16,18,22] Chronic kidney disease is recognized as a major independent cardiovascular disease risk, especially for older individuals;[23] biological changes in renal failure appear to accelerate cardiovascular disease. The subgroup of patients with stroke and renal failure may have mixed dyslipidemias (particularly lower high-density lipoprotein cholesterol and higher triglyceride levels),[24,25] and may require treatment with multiple lipid-lowering drugs.[24]

Study limitations

Because of using de-identified records of the VASQIP database, our findings are limited to the variables originally gathered that were available for the entire study period. Because VASQIP database updates routinely occur, more recent VASQIP risk models may not be based exclusively upon this set of historical variables (e.g., pulmonary rales and digoxin use are no longer captured in the VASQIP database). Details for preoperative neurological assessments, atrial fibrillation, and prior stroke, as well as timing, type, and severity of post-CABG stroke, were not available in the VASQIP database, and therefore, could not be examined in this study.

The lack of more detailed VASQIP stroke-related data is an important limitation of this study. In other studies, the timing of stroke occurrence and type of stroke were found to affect long-term prognosis.[6,16,22,26] Toumpoulis et al.[17] investigated predictors and long-term outcomes related to early (within 24 hours) versus late (24 hours to discharge) post-CABG stroke. These authors found that early stroke was associated with respiratory failure and bleeding requiring reoperation, while late stroke was associated with preoperative and postoperative renal failure. Whitlock et al.[27] defined early stroke as during index hospital admission and reported an association with preoperative requirement for dialysis. Another study showed that patients with stroke and watershed infarct (usually attributed to global hypoperfusion or embolic showers) showed markedly decreased 1-year survival (38.9% vs. 71.5% for embolic stroke), and those with mixed infarct types showed the lowest 1-year survival (27.8%).[16] More watershed strokes occur after cardiac surgery than in any other population.[28] Large watershed strokes are associated with use of intraoperative circulatory arrest, prolonged cardiopulmonary bypass times (>113–120 minutes[16,28-30]), and an intraoperative decrease in mean arterial pressure of at least 10 mm Hg below baseline in patients with hypertension.[28] Cardiac arrest requiring resuscitation has also been associated with watershed infarcts and early mortality.[28] Additionally, higher rates of cardiac arrest requiring resuscitation were documented in our veteran stroke subgroup who did not survive past 1 year.

As a challenge, there are different definitions for post-CABG "permanent" versus "transient" stroke. The long-established VASQIP definition for permanent stroke was based on a 72-hour threshold. In contrast, other studies reported stroke as a neurological deficit lasting longer than 24 hours. Moreover, prior stroke rates have been generally under-reported when validated against brain imaging as the gold standard assessment.[16] Compared with other studies, veterans with post-CABG mild strokes may be under-reported using VASQIP criteria. Finally, findings from our unique veteran population (e.g., older men with a high rate of baseline comorbidities) may not be generalizable to non-veteran populations.

Summary

Veterans with post-CABG stroke are at a considerably higher risk for mortality during the first year, and at higher risk compared with those without stroke, which is in agreement with previous literature describing smaller studies.[2,6,8,9] Moreover, risk factors in post-CABG stroke for 1-year mortality differ in magnitude compared with those for long-term mortality. Development of post-CABG stroke survival risk scores may be useful to surgeons, patients, and their families in predicting their probability of long-term survival. In conclusion, further research appears warranted to identify new post-CABG stroke treatment strategies (e.g., post-discharge consultations and/or follow-up care visits) to improve long-term outcomes.

Abbreviations

BSA – body surface area
CABG – coronary artery bypass grafting
CCS – Canadian Cardiovascular Society
CI – confidence interval
COPD – chronic obstructive pulmonary disease
CPB – cardiopulmonary bypass
CR – creatinine
CVD – cerebrovascular disease
HR – hazard ratio
IMA – internal mammary artery
MI – myocardial infarction
NYHA – New York Heart Association
PVD – peripheral vascular disease
SD – standard deviation
VASQIP – Veterans Affairs Surgical Quality Improvement Program
VA – Veterans Affairs.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This study was partially supported by the VAMC Offices of Research and Development in Denver, Colorado and Northport, New York.

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