Journal of the American Heart Association

ORIGINAL ARTICLE

Risk and Subtypes of Stroke Following New-Onset Postoperative Atrial Fibrillation in Coronary Bypass Surgery: A Population-Based Cohort Study

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BACKGROUND: New-onset postoperative atrial fibrillation (POAF) develops in approximately one-third of patients undergoing cardiac surgery and is associated with a higher incidence of ischemic stroke and increased mortality. However, it remains unknown to what extent ischemic stroke events in patients with POAF are cardioembolic and whether anticoagulant therapy is indicated. We investigated the long-term risk and pathogenesis of postoperative stroke in patients undergoing coronary artery bypass grafting experiencing POAF.

METHODS AND RESULTS: This was a register-based cohort study. Data from the WDHR (Western Denmark Heart Registry) were linked with the DNPR (Danish National Patient Register), the Danish National Prescription Register, and the Cause of Death Register. All stroke diagnoses were verified, and ischemic stroke cases were subclassified according to pathogenesis. Furthermore, investigations of all-cause mortality and the use of anticoagulation medicine for the individual patient were performed. A total of 7813 patients without a preoperative history of atrial fibrillation underwent isolated coronary artery bypass grafting between January 1, 2010, and December 31, 2018, in Western Denmark. POAF was registered in 2049 (26.2%) patients, and a postoperative ischemic stroke was registered in 195 (2.5%) of the patients. After adjustment, there was no difference in the risk of ischemic stroke (hazard ratio [HR], 1.08 [95% CI, 0.74–1.56]) or all-cause mortality (HR, 1.09 [95% CI, 0.98–1.23]) between patients who developed POAF and non-POAF patients. Although not statistically significant, patients with POAF had a higher incidence rate (IR; per 1000 patient-years) of cardioembolic stroke (IR, 1 [95% CI, 0.6–1.6] versus IR, 0.5 [95% CI, 0.3–0.8]), whereas non-POAF patients had a higher incidence rate of large-artery occlusion stroke (IR, 1.1 [95% CI, 0.8–1.5] versus IR, 0.7 [95% CI, 0.4–1.4]). Early initiation of anticoagulation medicine was not associated with a lower risk of ischemic stroke. However, patients with POAF were more likely to die of cardiovascular causes than non-POAF patients (P<0.001).

CONCLUSIONS: We found no difference in the adjusted risk of postoperative stroke or all-cause mortality in POAF versus non-POAF patients. Patients with POAF after coronary artery bypass grafting presented with a higher, although not significant, proportion of ischemic strokes of the cardioembolic type.

Key Words: CABG ■ coronary artery bypass grafting ■ pathogenesis ■ postoperative atrial fibrillation ■ stroke

Ischemic stroke is a potentially devastating complication after cardiac surgery. Despite significant surgical and anesthetic advances, the risk of stroke remains unchanged.[1,2] A wide range of vascular diseases can lead to an ischemic stroke, and investigating the most likely mechanism is

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027010

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Earlier studies have reported a higher incidence of stroke in patients experiencing postoperative atrial fibrillation after coronary artery bypass grafting compared with patients who do not.
- This is the first study examining the types of ischemic stroke that patients undergoing coronary artery bypass grafting suffer from.

What Are the Clinical Implications?

- We found no significant difference in the distribution of cardioembolic and arteriosclerotic postoperative ischemic strokes between patients who had experienced postoperative atrial fibrillation after coronary artery bypass grafting and patients who did not.
- Early initiation of oral anticoagulants was not associated with a lower risk of ischemic stroke.

Nonstandard Abbreviations and Acronyms

DNPR	Danish National Patient Register
OAC	oral anticoagulant
POAF	new-onset postoperative atrial fibrillation
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
WDHR	Western Denmark Heart Register

important in preventing this adverse outcome and treating patients at risk.

It has been reported that patients suffering from new-onset postoperative atrial fibrillation (POAF) have an increased risk of stroke compared with patients not experiencing this complication.[3–5] Whether this is caused by thromboembolism from the left atrium or by another mechanism is poorly investigated. Furthermore, the recommended medical treatment of POAF after discharge varies in guidelines and differs greatly among cardiac surgical centers.[6–8]

The pathophysiology of peri- and early postoperative stroke after coronary artery bypass grafting (CABG) is believed to have 2 primary mechanisms: hypoperfusion during surgery and cerebral embolism caused by atheromatous debris arising mainly from surgical manipulation of the ascending aorta.[9] Stroke occurring in the late postoperative phase is usually related to POAF or cerebral vascular disease.[10] However, the available evidence does not support a clear-cut indication for commencing oral anticoagulation (OAC) treatment in all patients experiencing POAF.[11] Existing literature regarding CABG and postoperative ischemic stroke and the role of POAF does not differentiate between various stroke subtypes. This study aimed to investigate the association between POAF after CABG and the occurrence of postoperative stroke in a population-based study with long-term follow-up and further characterize strokes according to pathogenesis. We hypothesized that patients who develop new-onset POAF after CABG are at higher risk of suffering from a cardioembolic stroke than non-POAF patients and that OAC treatment in patients with POAF is associated with a lower incidence of ischemic stroke than in nontreated patients. Furthermore, our secondary hypotheses were that patients with POAF have a higher rate of mortality and are more likely to die of a cardiovascular cause.

METHODS

Data Availability

According to Danish law, it is not possible to share the data sets. Access is only granted to researchers responsible for conducting the specific study.

Data Sources and Setting

The study population was identified through the WDHR (Western Denmark Heart Registry).[12] The registry contains detailed peri- and postoperative data on all patients undergoing cardiac surgery at 3 university hospitals and 1 private hospital since 1999. The hospitals in Western Denmark perform 55% of all cardiac surgeries in Denmark. Because the registration of incident POAF in WDHR started in 2010, the investigation is limited hereto. Patient characteristics, including comorbidity variables and EuroSCORE,[13] that is, predicted 30-day mortality, as well as operative data and data on outcomes from the hospital stay, are prospectively registered in the WDHR. The surgeons treating the patients at the time of surgery were responsible for data regarding baseline characteristics, clinical and surgical information, and outcomes in the database.

Information on postoperative strokes was obtained through the DNPR (Danish National Patient Register) by linking the patient's unique social security number assigned to all Danish citizens.[14] The health care system in Denmark is tax funded with free access to public hospitals. Patients with symptoms of acute stroke are exclusively admitted to public hospitals, and all hospitalized patients are registered in the DNPR. The Cause of Death Register holds information on the cause of death, date, place, and postmortem examinations on all citizens who die in Denmark.[15]

All hospital admissions and outpatient visits classified according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes I61 to I64 were identified, and diagnoses were validated at each local hospital, where the patients were treated. Patient records and descriptions of magnetic resonance imaging (MRI) and computerized tomography (CT) were used to verify a diagnosis of stroke. Where access to computerized images was possible, the actual CT and MRI scans were evaluated.

The patients were followed up until a stroke diagnosis, emigration, death, or until the end of the study period (December 31, 2020), whichever occurred first.

From the Danish National Prescription Registry,[16] which contains information on Anatomical Therapeutic Chemical classification codes and the date of purchase and package size for every prescription claimed since 1994, information on antithrombotic medicine (in the follow-up period) was retrieved. We collected information on treatment with OACs (defined as either direct-acting OACs or vitamin K antagonists) for all patients in the study population. To investigate the relationship between POAF and initiation of treatment with antithrombotic medicine, we focused on patients initiating OAC until 90 days after the day of surgery and therefore censored individuals with the need for anticoagulation treatment for reasons other than POAF/atrial fibrillation (AF).

See Supplementary Tables S1–S3 for codes.

Study Population

All patients aged ≥18 years undergoing isolated CABG surgery from January 1, 2010, through December 31, 2018, were included. Patients were excluded if they had a history of supraventricular arrythmia (including paroxysmal AF) or an ongoing preoperative AF on the day of admission before surgery. Moreover, patients were excluded if they had concomitant valve surgery or other concurrent cardiac surgical procedures.

Exposure

The exposure POAF was defined as new-onset AF occurring postoperatively during primary hospitalization in the cardiothoracic surgery ward, regardless of the duration and whether the patient received treatment for POAF. Patients were continuously monitored on telemetry the first 3 days postoperatively and longer if arrhythmic events occurred. The diagnosis of POAF and possible treatment(s) were entered in the WDHR at the responsible surgeon's discretion. Prophylactic therapy for POAF is not given as a routine in Denmark and therefore not registered in the WDHR. The WDHR does not record POAF in patients who develop the condition after transfer to other hospitals.

Outcome Measures

From this study population, we identified all patients with a primary diagnosis of either hemorrhagic, ischemic, or undetermined stroke. The patients' medical records were reviewed when possible. Only the first postoperative stroke was validated and categorized. First, all medical records were reviewed by a physician (L.F.R.) and 2 specialists in neurology (J.K.M. and G.A.) and divided into 4 categories: cerebral hemorrhage, cerebral infarction, unknown type of stroke, and no stroke/wrong diagnosis. Stroke was defined in agreement with current guidelines as a disease with a rapid onset of focal or global neurological deficit with no apparent cause other than a vascular origin and persisting beyond 24 hours.[17] Second, all patient records with a cerebral infarct diagnosis were independently reviewed by J.K.M. and G.A., and the stroke diagnosis was validated and categorized into 5 subtypes according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification of ischemic strokes[18]: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined cause, and stroke of undetermined cause. The TOAST classification focuses on establishing the most likely cause of ischemic stroke and divides the cerebral infarcts into the aforementioned 5 groups based on a combination of the patient's clinical signs and radiological findings as well as supplementary analyses, such as color duplex of extracranial arteries, ECG, echocardiography, and blood samples. The neurologists were blinded to the POAF exposure during the in-depth review of patient records. Exceptions were very early postoperative strokes, where information on postoperative supraventricular arrhythmia was visible in the medical records. Uncertainty of a stroke classification was discussed in the group (L.F.R., J.K.M., and G.A.) until agreement was made.

Because of the potential overlap between diagnoses in the registries and our research question with POAF as the exposure, the following distinctions were made: (1) a perioperative stroke was defined as stroke registered in WDHR by the surgeon treating the patient, occurring from wakeup from anesthesia to discharge either to another department or home; (2) early postoperative stroke, from discharge to 30 days postoperatively; and (3) late postoperative stroke, from 1 month onward.

The primary outcome variable was an identified ischemic stroke occurring from ≥30 days postoperatively until the end of the study period and classified into 1 of 5 categories according to the TOAST classification. The secondary outcomes were all-cause mortality and treatment with early initiation of anticoagulation.

Statistical Analysis

The characteristics of the baseline population were described using proportions for categorical variables and means and SDs for continuous data, where appropriate. We analyzed differences in proportions between groups with the Fisher exact or χ^2 test for categorical variables and differences in means with the Student *t* test for continuous variables. The *t* tests were repeated with bootstrap (1000 repetitions) to accommodate for potential nonnormality and variance inhomogeneity. The positive predictive value of a stroke diagnosis was calculated as the number of confirmed cases of stroke divided by the number of possible cases of stroke from DNPR.

Missing data on dates of surgery and discharge from the WDHR were replaced with the correct date (from the DNPR) or with an average, and unvalidated stroke diagnoses were handled with sensitivity analyses with the assumption that every stroke was ischemic varying with the presence of POAF, without POAF, or independent of POAF. Survival curves were generated using the Kaplan–Meier method, and between-group comparisons were made using the log-rank test. We calculated the risk of stroke and mortality in patients with POAF and non-POAF patients with hazard ratios (HRs) and 95% CIs and Cox proportional hazards models. The incidence of ischemic stroke in the 2 groups was calculated with competing risk analysis for mortality, as proposed by Fine and Gray.[19] Subsequently, we ran the adjusted models using inverse probability treatment weighting. To assess the long-term risk of stroke associated with POAF, we performed Cox analyses including only events after the initial hospital discharge. Weights were calculated as reciprocal probabilities obtained from a logistic regression with POAF as outcome and a selection of risk factors as predictors. These variables are listed in Table S2 and were chosen because of their association with the exposure and outcome in the literature. The balance of variables between groups was assessed using the standardized mean difference, and we considered an absolute standardized difference of ≤0.1 as sufficient, as proposed by Austin and Stuart.[20] The same variables were used for adjustment in the analyses of antithrombotic medicine as in the initial models. No formal sample size was carried out as all eligible patients in the registries were included.[21]

Statistical analyses were performed with Stata/MP version 16 (StataCorp LP, College Station, TX).

This article is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[22]

The study was approved by the Danish Patient Safety Authority (3–3013-3229/1 and 31–1522-73) and registered in the North Denmark Region research database (id-2019-115). Need for informed consent was waived. Ethical approval is not necessary for registry-based studies in Denmark.

RESULTS

The final study population comprised 7813 patients. Figure 1 shows the selection of patients. There were 21 duplicates, and 68 patients were excluded from the study because of non-Danish citizenship, thus making complete follow-up impossible. The mean length of follow-up was 6.8 years (range, 0–8 years). Baseline patient characteristics are presented in Table 1. A total of 2049 (26.2%) patients experienced POAF during hospitalization. Patients who developed POAF were older; predominantly men; and more often had chronic obstructive pulmonary disease, hypertension, and severe underlying coronary artery disease (former acute myocardial infarction). They were also more likely to have had a lower left ventricular ejection fraction, renal insufficiency (measured by serum creatinine level [>200 mmol/L]) and higher EuroSCORE at the time of surgery. Furthermore, patients with POAF were more likely to have been on extracorporeal circulation, had longer cardiopulmonary bypass times, and more often had arterial cannulation via the ascending aorta. Conversely, they were less likely to be active smokers. There was no difference in the prevalence of diabetes, prior percutaneous coronary intervention, prior stroke, or body mass index between the 2 groups. Regarding preoperative medication, only treatment with calcium antagonists was more frequent in the patients experiencing POAF. Patients who developed POAF had a longer mean hospital stay than non-POAF patients (7.6±6.9 days versus 6.4±7.6 days; P<0.001). Because of the large sample size, the normality assumption was not relevant, and this was confirmed with bootstrap calculation of standard errors, which gave the same results (data not shown).

Validation and Classification of Subtypes of Ischemic Stroke

Of the 7813 included patients from the WDHR with CABG, 514 patients were identified in the DNPR with an unvalidated stroke diagnosis either before or after cardiac surgery. A total of 327 patients suffered from a peri- or postoperative stroke, and 282 medical journals and discharge letters were retrieved (87.5%). Among these patients, 1 patient had concomitant mitral valve repair not registered in the WDHR and was therefore excluded from the study. The results are presented in Table 2. Of the 281 patients with available patient records, there were 195 with ischemic stroke, 22 with intracerebral hemorrhage, 9 with subdural hemorrhage, and 2 with an unknown type of stroke. Finally, in 51 cases, there was either no evidence for a diagnosis of stroke or the patient had a misclassified diagnosis. The positive predictive value of an ischemic stroke diagnosis in the DNPR was 86%, with a false stroke diagnosis in at least 16% of the cases.

The 158 validated postoperative infarctions were subclassified according to TOAST and, although not reaching statistical significance (P=0.201), patients with POAF had a higher incidence rate (IR) (per 1000 patient-years) of cardioembolic stroke (IR, 1 [95% CI, 0.6–1.6] versus

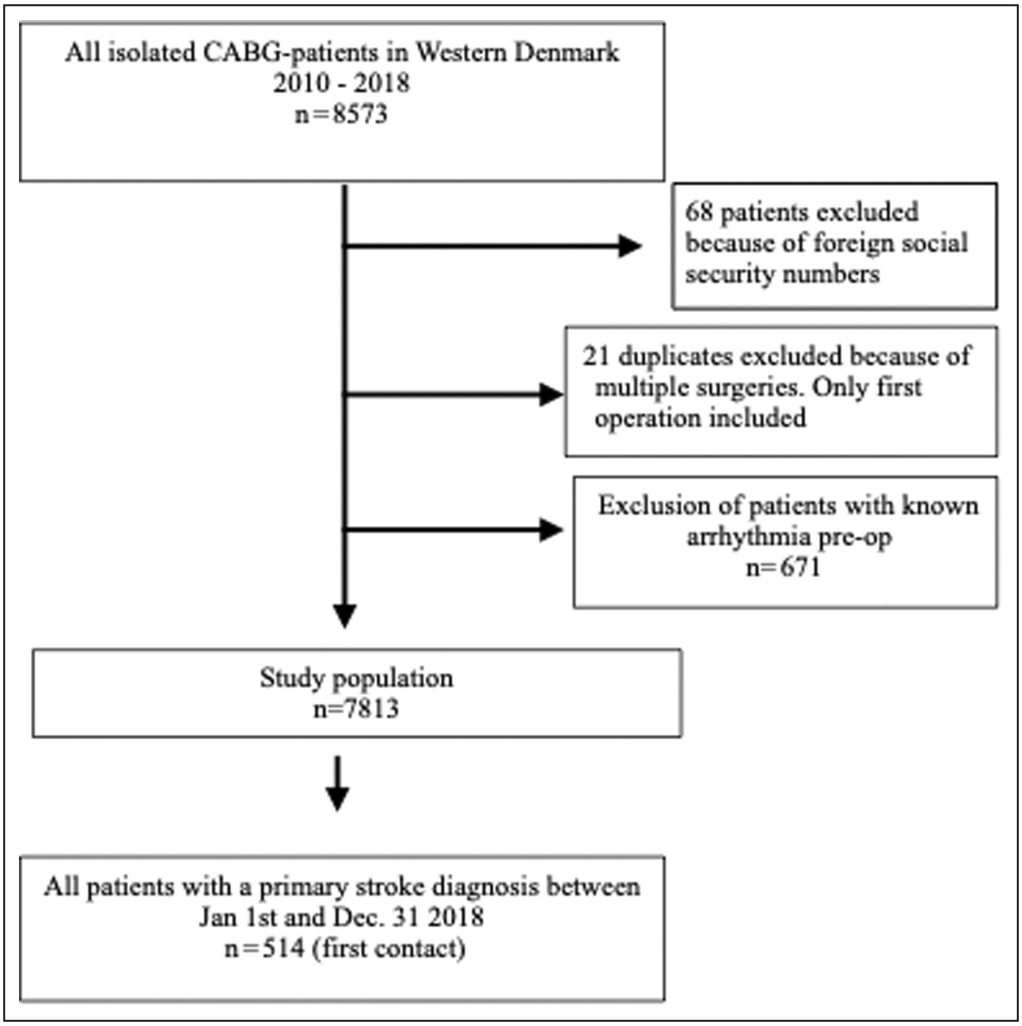

Figure 1. Flowchart of the selection of the study population.
CABG indicates coronary artery bypass grafting.

IR, 0.5 [95% CI, 0.3–0.8]), whereas non-POAF patients had a higher incidence rate of large-artery occlusion stroke (IR, 1.1 [95% CI, 0.8–1.5] versus IR, 0.7 [95% CI, 0.4–1.4]) (Table 3). Conversely, patients not experiencing POAF more frequently had a stroke of large-artery atherosclerosis origin. A total of 870 patients fulfilled the criteria of having initiated antithrombotic therapy within the first 90 days with slightly more than half of the cases having experienced POAF (n=461 [53%]). Most often, the patients were prescribed warfarin (508 [58.4%]) or rivaroxaban (155 [17.8%]), whereas apixaban, dabigatran, and edoxaban constituted a smaller share (119 [13.7%], 83 [9.5%], and 5 [0.6%], respectively).

Time-to-Event Analyses

The day of surgery was incorrectly registered in 77 (1%) patients, and the day of discharge was incorrectly registered in 677 (8.7%) patients. The dates were corrected in the combined data set with data from the other registries or replaced with “missing” when corrections were not possible.

In the competing risk analyses, the risk of ischemic stroke was not associated with POAF (HR, 1.08 [95% CI, 0.74–1.56]). In the sensitivity analyses, these results were confirmed (Figure 2). The crude and adjusted mortality curves are shown in Figure 3. POAF was not associated with an increased risk of all-cause mortality (adjusted HR, 1.09 [95% CI, 0.98–1.23]). Patients initiating antithrombotic medicine within 90 days of the day of surgery had a higher risk of ischemic stroke independent of POAF (subhazard ratio [SHR], 1.09 [95% CI, 0.52–2.25] for non-POAF patients versus SHR, 1.06 [95% CI, 0.50–2.28] for patients with POAF; Figure 4). There were no differences in the risk of cerebral hemorrhage between groups (data not shown). All the variables had an absolute standardized difference of ≤0.1.

Table 1. Preoperative Patient Characteristics and Operative Data

Total study population	No POAF, n=5764	POAF, n=2049	Total, N=7813
Male sex, total n (%)	4695 (81.5)	1712 (83.6)	6407 (82)
Age, y, mean (SD)	65.2 (9.47)	69.2 (8.02)	66.2 (9.28)
Smoking status, n (%)			
Current	1298 (22.5)	380 (18.5)	1678 (21.5)
Never	1510 (26.2)	565 (27.6)	2075 (26.6)
Former*	2725 (47.3)	1006 (49.1)	3731 (47.8)
Not given	231 (4)	98 (4.8)	329 (4.21)
Diabetes, n (%)			
No	4294 (74.5)	1548 (75.6)	5842 (74.8)
Newly discovered high BS	39 (0.7)	16 (0.8)	55 (0.7)
IDD	512 (8.9)	155 (7.6)	667 (8.5)
NIDD, medical treatment	699 (12.1)	259 (12.6)	958 (12.3)
Nonpharmacological treatment	96 (1.7)	31 (1.5)	127 (1.6)
Not given	124 (2.2)	40 (2)	164 (2.1)
COPD, n (%)	512 (8.9)	225 (10.9)	737 (9.43)
Statin use, n (%)	4318 (74.9)	1559 (76.1)	5877 (75.2)
Arterial hypertension, n (%)	3896 (67.6)	1471 (71.8)	5367 (68.7)
Former cardiac surgery, n (%)			
0	5608 (97.3)	1987 (96.9)	7595 (97.2)
1	117 (2)	51 (2.5)	168 (2.15)
≥2	20 (0.4)	2 (0.1)	22 (0.28)
Not given	19 (0.3)	9 (0.4)	28 (0.36)
Former AMI, n (%)	1390 (24.1)	558 (27.3)	1948 (24.9)
Former PCI, n (%)	1091 (18.9)	387 (18.9)	1478 (18.9)
LVEF, %, mean (SD)	53.5 (10.3)	52.7 (10.6)	53.3 (10.4)
BMI, kg/m^2, mean (SD)	27.6 (4.2)	27.7 (4.2)	27.6 (4.2)
Creatinine level, µmol/L, mean (SD)	85.9 (25.4)	89.4 (27.1)	86.8 (25.9)
Dialysis, n (%)	35 (0.6)	7 (0.3)	42 (0.54)
Previous stroke, n (%)	139 (2.4)	48 (2.3)	187 (2.4)
Selected preoperative medication, n (%)			
β-blocker	3775 (65.5)	1379 (67.3)	5154 (66)
Calcium antagonist	1613 (28)	650 (31.7)	2263 (29)
ACE inhibitor	2565 (44.5)	957 (46.7)	3522 (45.1)
Steroids, oral use	104 (1.8)	46 (2.2)	150 (1.9)
Oral anticoagulant	215 (3.7)	73 (3.56)	288 (3.7)
Platelet inhibitor	3371 (58.5)	1178 (57.5)	4549 (58.2)
EuroSCORE, mean (SD)	4.1 (5.9)	5.2 (7.4)	4.4 (6.4)
Operative components			
ECC, n (%)	4593 (79.7)	1694 (82.7)	6287 (80.5)
ECC duration, min, mean (SD)	66.6 (43.7)	70.6 (44)	67.6 (43.8)
Aortic clamp time, min, mean (SD)	37.3 (26.1)	39.8 (26.5)	37.9 (26.2)
Placement of arterial cannulas, n (%)			
Aorta	3952 (68.6)	1472 (71.8)	5424 (69.4)
Other	1812 (31.4)	577 (28.2)	2389 (30.6)

ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarct; BMI, body mass index; BS, blood sugar; COPD, chronic obstructive pulmonary disease; ECC, extracorporeal circulation; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IDD, insulin–dependent diabetes; LVEF, left ventricular ejection fraction; NIDD, non-insulin–dependent diabetes; PCI, percutaneous coronary intervention; and POAF, new-onset postoperative atrial fibrillation.

*Former smoker; stopped >1 month before the day of surgery.

Table 2. Validation of Stroke Diagnoses

Peri- and postoperative strokes (total N=327)	From DNPR, n	Validated, n (%)
Nontraumatic subarachnoid hemorrhage*	5	9 (2.8)
Nontraumatic intracerebral hemorrhage and other and unspecified nontraumatic intracranial hemorrhage†	34	22 (6.8)
Cerebral infarction‡	232	195 (59.8)
Unspecified stroke§	56	2 (0.6)
No stroke/wrong diagnoses		51 (15.6)
Not possible to access patient record/could not be validated		48 (14.4)
	PPV of cerebral infarct diagnosis: 84%	

DNPR indicates the Danish National Patient Register; and PPV, positive predictive value.
*International Classification of Diseases, Tenth Revision (ICD-10) code I60.
†ICD-10 codes I61 and I62.
‡ICD-10 code I63.
§ICD-10 code I64.

Causes of Death

Among 1594 deceased patients, there were 1134 registered causes of death in the Cause of Death Register. In-hospital deaths occurred in 66 cases, with no significant difference between patients with POAF and non-POAF patients. Of the deaths, cardiovascular diseases constituted 412 cases (36.3%), cancer 302 cases (26.6%), and respiratory diseases 80 cases (7.05%), with almost equal distribution in the remaining 11 categories (see Table S3). Patients with POAF were more likely to die of cardiovascular causes than non-POAF patients (269 [4.7%] versus 143 [7.0%]; $P<0.001$).

DISCUSSION

This study presents the results of a comprehensive analysis of the association between POAF and postoperative ischemic stroke following isolated CABG in Western Denmark between 2010 and 2018. The key findings of our study were as follows: (1) adjusted competing risk analyses showed no difference in the risk of postoperative ischemic stroke between groups; (2) patients with POAF had a higher incidence rate of cardioembolic strokes than non-POAF patients; (3) POAF was not associated with a higher mortality rate than non-POAF patients, but patients with POAF were more likely to die as a result of cardiovascular disease; and (4) early initiation of OAC (within 90 days postoperatively) did not reduce the risk of a postoperative ischemic stroke, and the risk did not vary with the presence of POAF.

Our findings and those of Conen et al,[23] Almassi et al,[24] and Jawitz et al,[25] are in contrast with larger multiple-center series that have reported an association between POAF and long-term adverse events such as stroke and death.[4,26,27] The conflicting results may partly be explained by methodological differences. For example, few studies distinguish between ischemic stroke and all-cause stroke, and the applied risk adjustment varies considerably across studies. It is remarkable that the strength of the association between POAF and the adverse outcomes was reduced in all existing studies when adjusting for multiple comorbidities and complications, demonstrating a possible additive effect of comorbidities and complications. Because the majority of patients experiencing POAF after CABG convert to sinus rhythm within a few weeks of surgery,[28,29] many surgeons refrain from initiating OACs. The question remains whether POAF after CABG has a long-term effect on the likelihood of having an ischemic stroke. Except for a few studies on the pathogenesis of perioperative strokes,[30,31] there is very little information on the subtypes of postoperative ischemic strokes that patients undergoing CABG and subsequent POAF suffer from.

To the best of our knowledge, this is the first population-based, long-term study examining the pathogenesis of postoperative strokes following CABG and the association with POAF. The findings corroborate the notion that stroke after CABG has multiple causes and that, although patients with POAF in some studies have a significant cardioembolic risk profile, the administration of OACs to this group is still debatable and not evidence based. As an increasing number of studies highlight, the present study supports that the optimal medical regimen for patients with POAF at discharge is not 1-to-1 comparable with nonsurgical, nonvalvular AF. In a large US study with 166 747 patients who underwent first-time isolated CABG, Matos et al[32] analyzed the 30-day outcome for 4 groups of

Table 3. Subtypes and Incidence Rates (per 1000 Patient-Y) of Postoperative Cerebral Infarctions in Patients With/Without POAF

Type of ischemic stroke	Incidence rate in non-POAF patients (95% CI)	Incidence rate in patients with POAF (95% CI)
Large-artery atherosclerosis	1.1 (0.8–1.5)	0.7 (0.4–1.4)
Cardioembolism	0.5 (0.3–0.8)	1 (0.6–1.6)
Small-vessel occlusion	0.7 (0.5–1)	0.8 (0.4–1.5)
Stroke of undetermined cause	0.6 (0.4–0.9)	0.7 (0.3–1.3)

POAF indicates postoperative atrial fibrillation.

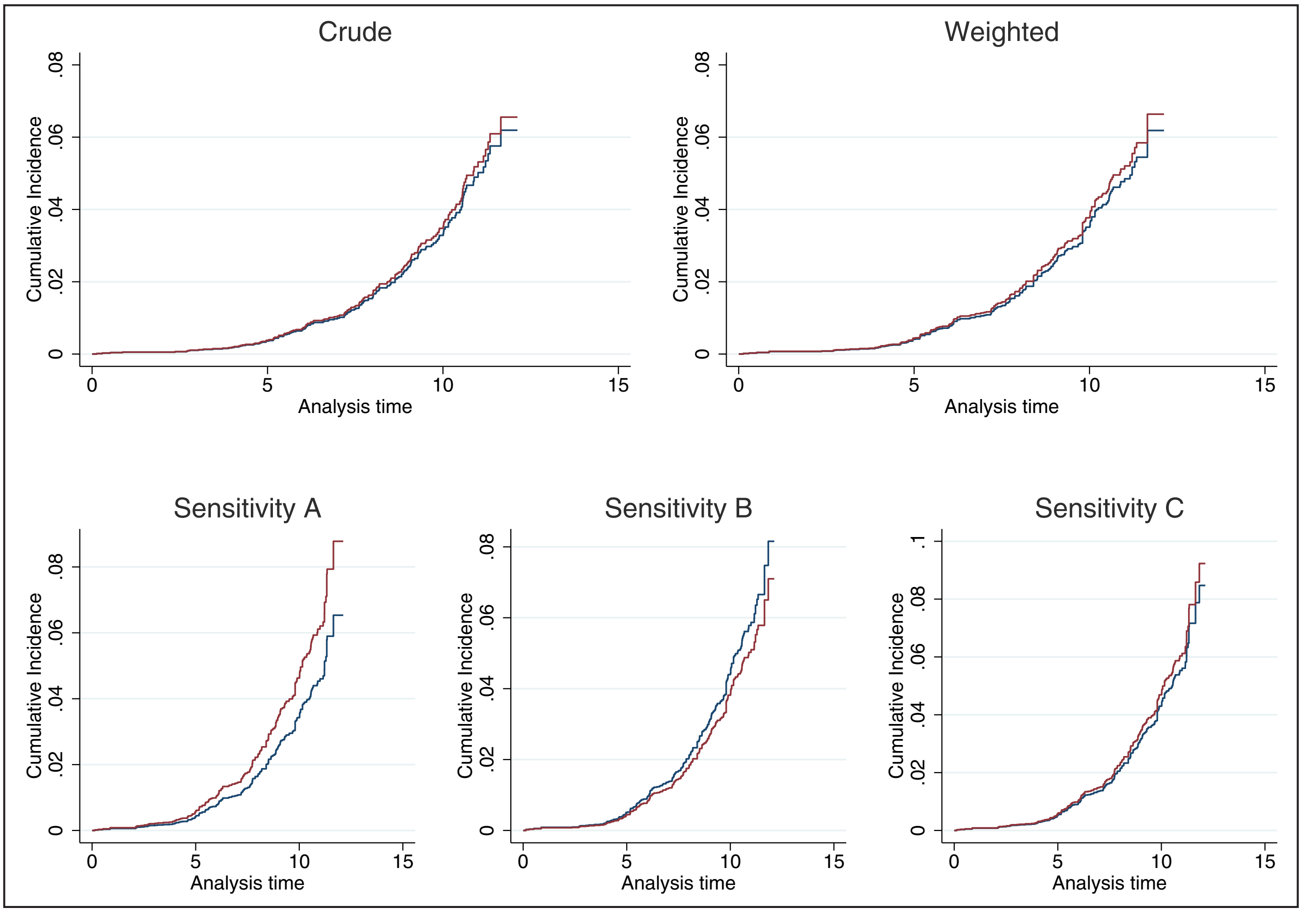

Figure 2. Competing risk analyses of ischemic stroke.
Cumulative incidence of ischemic stroke during follow-up for patients with and without POAF after CABG: red indicates POAF, and blue indicates non-POAF. (**Top**) Cumulative incidence of ischemic stroke (hazard ratio [HR], 1.07 [95% CI, 0.75–1.61]) and adjusted cumulative incidence of ischemic stroke (HR, 1.08 [95% CI, 0.74–1.56]). (**Bottom**) Sensitivity analyses. Sensitivity A assumes unvalidated strokes were ischemic in patients who had POAF, sensitivity B assumes unvalidated strokes were ischemic in patients not experiencing POAF, and sensitivity C assumes unvalidated strokes were ischemic regardless of POAF status. CABG indicates coronary artery bypass grafting; and POAF, new-onset postoperative atrial fibrillation.

patients based on discharge medications: amiodarone with or without OAC, OAC alone, or neither. The patients treated with OACs had a ≥4-fold increase in the risk of major bleeding, and among those discharged with OACs, there was no significant difference in the adjusted rate of strokes at 30 days. Similarly, Butt et al investigated the thromboembolic risk in 2108 patients with CABG with POAF compared with 8432 patients with AF with a median follow-up time of 5.1 years.[33] They found that the long-term thromboembolic risk was lower among patients with new-onset POAF compared with a nonvalvular AF cohort not associated with surgery.[33] In addition, a recent meta-analysis supports the notion that patients undergoing noncardiac surgery have a higher risk of cardioembolic events than patients undergoing cardiac surgery.[28] The study included data on 2 458 010 patients across 35 studies and found a higher risk of stroke in patients undergoing noncardiac surgery (HR, 2.00 [95% CI, 1.70–2.35]) versus those undergoing cardiac surgery (HR, 1.20 [95% CI, 1.07–1.34]; *P*>0.001). Given the significance of these neurologic complications, the risk of the recurrence of AF and potential hemorrhage associated with antithrombotic medicine must be considered when treating patients with heart disease postoperatively.

Current American guidelines (American Heart Association, American College of Cardiology, and Heart Rhythm Society) for the management of POAF recommend initiation of OAC to patients when deemed clinically significant, defined by the requirement of rate or rhythm control agents or when POAF persists after discharge.[34,35] Similarly, the 2020 European Association for Cardio-Thoracic Surgery/European Society of Cardiology guideline for the treatment of POAF recommends “long-term OAC in patients at risk of stroke considering the anticipated net clinical benefit” (Class IIa recommendation; Level of Evidence B).[11] Both guidelines refrain from recommending clear

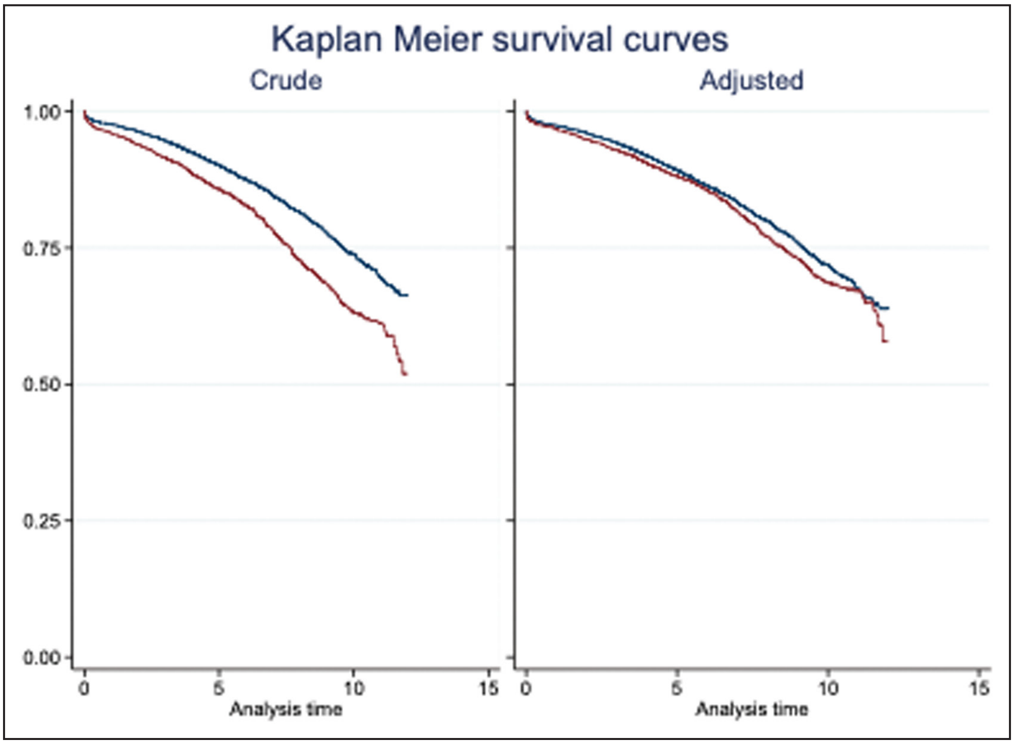

Figure 3. Kaplan–Meier survival estimates according to the occurrence of POAF, unadjusted and adjusted.
Kaplan–Meier survival curves for overall mortality by POAF: crude and adjusted analyses by inverse propensity weighted analyses. Red indicates POAF, and blue indicates non-POAF. POAF indicates new-onset postoperative atrial fibrillation.

suggestions on the indication and duration of OAC treatment. Our study showed a low absolute risk of ischemic stroke, and it is doubtful that the benefit–risk balance of treating every patient with POAF after CABG with OACs will be acceptable. Randomized clinical studies to address the role of OAC therapy for POAF are warranted.

The randomized EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial compared percutaneous coronary intervention with drug-eluting stents and CABG in patients with left-main coronary artery disease.[36] One interesting finding was an increased rate of cardiovascular death among patients with POAF versus non-POAF patients primarily as a result of stroke-related and heart failure–related causes (2.6% versus 0.6% [*P*=0.005] and 1.9 versus 0.4% [*P*=0.009], respectively). These findings correspond with the results of the present study and indicate that POAF has a detrimental effect either through arrhythmia-driven heart failure or enhanced cardioembolism.

Stroke after cardiac surgery has multiple causes. In line with the results of the present study, the pathogenesis of later ischemic strokes is less highlighted, but the available evidence suggests a combination of POAF and atherosclerosis.[9,10]

Strengths and Limitations

Our study has several strengths and limitations that should be acknowledged. According to a validation study from 2017, the predictive value of stroke discharge diagnoses in the DNPR was only 69.3%.[37] Therefore, each patient with a primary stroke diagnosis was further investigated through patient records to ensure increased validity of the outcome, and we had access to medical records or discharge letters from >87% of the patients with possible stroke identified in the DNPR. Furthermore, the majority of patients were admitted in the central region of Denmark, where we also had access to brain images to help with the correct classification of strokes. Because all patients have free access to public health care, it is unlikely that patients would have had a major cerebral event in the follow-up period not registered in the database.

Patients with a history of ischemic stroke within 10 years before surgery might have had other incidents even earlier. In addition, we did not investigate whether patients had carotid thrombendarteriectomy performed either pre, peri-, or postoperatively. These

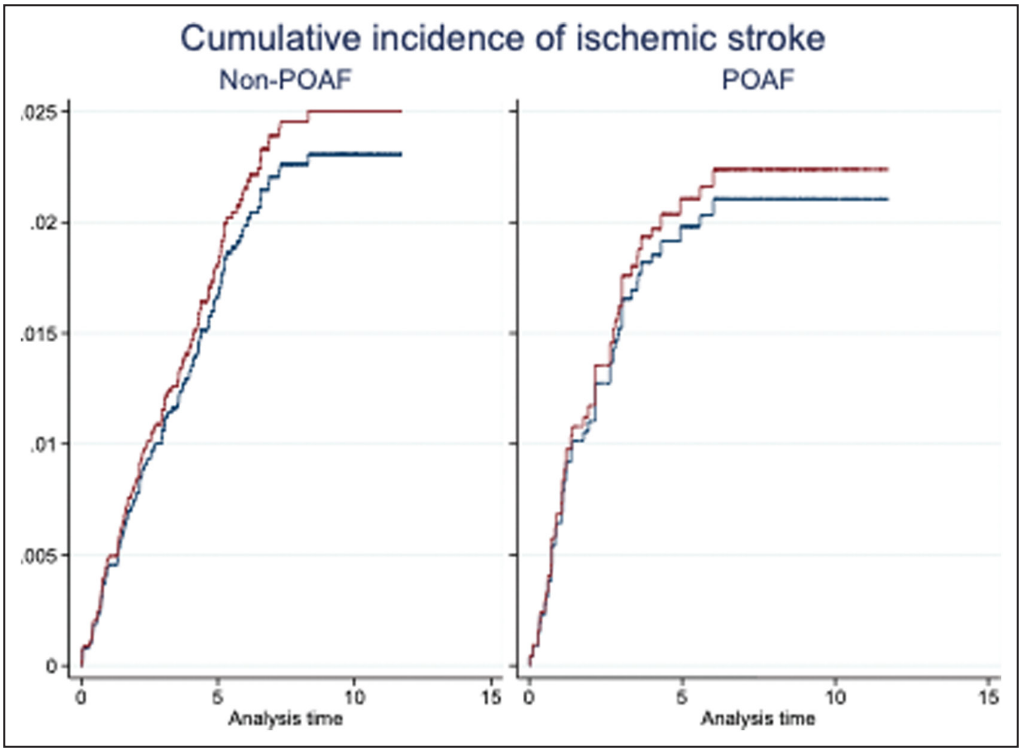

Figure 4. Treatment with oral anticoagulants and risk of ischemic stroke.
Red indicates patients treated with oral anticoagulants, and blue indicates patients not treated with oral anticoagulants. Cumulative incidence of ischemic stroke during follow-up for patients when early treatment with oral anticoagulants (within 90 days after operation), either warfarin or direct-acting oral anticoagulants, had been initiated. POAF indicates new-onset postoperative atrial fibrillation.

data were not available for this study. Either way, we suspect that this particular subgroup would be very small. Only specific stroke codes (I60–64) were obtained from registries, which might impose some selection bias in overlooking, for example, retinal occlusion and transient ischemic attack incidents before surgery. Furthermore, stroke diagnosis and treatment have improved during the past decade with the implementation of special stroke units, and the validity may have changed during the study period depending on the hospital of the given diagnosis.

The TOAST classification system has some obvious disadvantages, as the classification comes with high interrater disagreement, especially with minor strokes. Furthermore, that clinical testing is frequently stopped if 1 cause is identified, resulting in many patients being classified with a low level of confidence. However, classification has proven stronger when differentiating between atherosclerosis and cardioembolism.[38]

CONCLUSIONS

We found no evidence that the development of POAF was associated with a higher risk of postoperative ischemic stroke or all-cause mortality. Although not statistically significant, patients with POAF experienced a higher incidence rate of cardioembolic stroke than non-POAF patients, who had a higher incidence rate of stroke associated with large-artery arteriosclerosis. Peroral treatment with antithrombotic medicine was not associated with a lower risk of stroke, regardless of POAF.

ARTICLE INFORMATION

Received June 1, 2022; accepted November 2, 2022.

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Sources of Funding

This research received funding from the A.P. Moller Foundation (grant number 20-L-0258) and the Research Department of the Department of Cardiothoracic Surgery at Aalborg University Hospital.

Disclosures

None.

Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. ICD-10 codes and ATC codes used in this project

Stroke cohort		
Hemorrhagic and ischemic stroke	ICD-10	I60 I61 I62 I63 I64
Antithrombotic medicine Warfarin Apixaban Rivaroxaban Edoxaban Dabigatran	ATC	B01AA03 B01AF02 B01AF01 B01AF03 B01AE07

Table S2. Variables included in the inverse probability weighting analysis

1. Age
2. Sex
3. Body mass index
4. Extracorporeal circulation
5. Duration of extracorporeal circulation
6. Aortic cross clamp time
7. Duration of hospital stay
8. Left ventricular ejection fraction
9. History of smoking
10. History of diabetes
11. Hypertension treatment
12. Former Acute myocardial infarct
13. Dialysis
14. Chronic obstructive pulmonary disease
15. Peripheral vascular(arterial) disease
16. History of cerebrovascular disease
17. Acute status before initiation of surgery

Table S3. Death causes. Number and percentages

Causes of death	No POAF	POAF	Total
Cardio	269 (4.7)	143 (7.0)	412 (5.3)
Cerebral hemorrhage	10 (0.2)	6 (0.3)	16 (0.2)
Ischemic stroke	21 (0.4)	9 (0.4)	30 (0.4)
Vascular	28 (0.5)	9 (0.4)	37 (0.5)
Cancer	206 (3.6)	96 (4.7)	302 (3.9)
Endocrine	36 (0.6)	17 (0.83)	53 (0.7)
Infection	14 (0.2)	10 (0.5)	24 (0.3)
Psychiatric	16 (0.3)	5 (0.2)	21 (0.3)
Nervous	12 (0.2)	7 (0.3)	19 (0.2)
Respiratory	41 (0.7)	39 (1.9)	80 (1.0)
Digestive/Skin/Bone	33 (0.6)	18 (0.9)	51 (0.7)
Urinary/Reproductive	15 (0.3)	6 (0.3)	21 (0.3)
Unspecified	29 (0.5)	12 (0.6)	41 (0.5)
Other	20 (0.4)	7 (0.3)	27 (0.4)
			1134

Significance of association: $P < 0.001$.