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Postoperative Atrial Fibrillation and Long-Term Risk of Stroke After Isolated Coronary Artery Bypass Graft Surgery

BACKGROUND: Postoperative atrial fibrillation (pAF) after coronary artery bypass grafting is a common complication. Whether pAF is associated with an increased risk of cerebrovascular accident (CVA) remains uncertain. We investigated the association between pAF and long-term risk of CVA by performing a post hoc analysis of 10-year outcomes of the ART (Arterial Revascularization Trial).

METHODS: For the present analysis, among patients enrolled in the ART (n=3102), we excluded those who did not undergo surgery (n=25), had a history of atrial fibrillation (n=45), or had no information on the incidence of pAF (n=9). The final population consisted of 3023 patients, of whom 734 (24.3%) developed pAF with the remaining 2289 maintaining sinus rhythm. Competing risk and Cox regression analyses were used to investigate the association between pAF and the risk of CVA.

RESULTS: At 10 years, the cumulative incidence of CVA was 6.3% (4.6%–8.1%) versus 3.7% (2.9%–4.5%) in patients with pAF and sinus rhythm, respectively. pAF was an independent predictor of CVA at 10 years (hazard ratio, 1.53 [95% CI, 1.06–2.23]; *P*=0.025) even when CVAs that occurred during the index admission were excluded from the analysis (hazard ratio, 1.47 [95% 1.02–2.11]; *P*=0.04).

CONCLUSIONS: Patients with pAF after coronary artery bypass grafting are at higher risk of CVA. These findings challenge the notion that pAF is a benign complication.

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Clinical Perspective

What Is New?

- Postoperative atrial fibrillation (pAF) after coronary artery bypass grafting is independently associated with a higher risk of cerebrovascular accidents at 10 years.
- The association between pAF and risk of cerebrovascular accident persists when cerebrovascular accidents that occurred before discharge are excluded.
- pAF is also independently associated with a higher risk of cardiovascular and all-cause mortality.

What Are the Clinical Implications?

- Our findings highlight the need to revisit the notion that pAF is a transient, benign condition.
- Patients with pAF after coronary artery bypass grafting should be considered for stricter surveillance with continuous heart rhythm monitoring and anticoagulation therapy in those at very high risk (ie, CHA_2DS_2-VASc score ≥4).

The incidence of postoperative atrial fibrillation (pAF) after coronary artery bypass grafting (CABG) surgery ranges between 20% and 40%. pAF typically develops within the first week after surgery, at a median time of 2 days after the operation. It generally resolves, with or without medication, within 24 to 48 hours, and most patients are discharged in sinus rhythm (SR).[1] Although pAF has traditionally been considered a transient and benign complication of CABG,[2] more recent studies have reported an association between pAF and increased early mortality and morbidity, including stroke, renal and respiratory failure, and a prolonged intensive care unit duration.[3] Although pAF may not be directly responsible for these poor outcomes, it is likely contributory and is at least a surrogate for increased morbidity and mortality after cardiac surgery.[4,5]

What remains unclear is whether patients who develop transient pAF are at higher risk of stroke after discharge because conflicting findings have been reported on the association between pAF and an increased risk of late stroke.[6–8] Consequently, current guidelines do not support long-term anticoagulation in patients with pAF after CABG.[9]

The ART (Arterial Revascularization Trial) is one of the largest randomized trials of surgical coronary revascularization and was designed to compare 10-year outcomes after bilateral versus single internal thoracic artery grafts.[10] In this post hoc analysis, we investigated the association between pAF and risk of stroke during a 10-year follow-up in patients undergoing CABG.

METHODS

The authors declare that all data are available to other researchers on reasonable request.

A post hoc analysis of the ART trial was conducted. For the present analysis, among patients enrolled in the ART (n=3102) from 2004 to 2007, we excluded those who did not undergo surgery (n=25), had a history of atrial fibrillation (AF)/flutter before surgery (n=45), and had no information on the incidence of pAF (n=9), as shown in Figure I in the Data Supplement.

The remaining 3023 patients were classified on the basis of the occurrence of pAF during their index admission. pAF was defined as the occurrence of any episode of AF or flutter (collectively called pAF for this analysis) after the index procedure through the time of discharge that lasted at least 30 seconds and was captured on a standard 12-lead ECG or cardiac telemetry.[11] After discharge, all patients underwent 12-lead ECG within 6 weeks.

Trial Design

The ART was approved by the institutional review boards of all participating centers, and informed consent was obtained from each participant. The protocol of ART has been published.[12] ART was a 2-arm, randomized, multicenter trial conducted in 28 hospitals in 7 countries, with patients being randomized equally to single or bilateral internal thoracic artery grafts. Eligible patients were those with multivessel coronary artery disease undergoing CABG, including urgent patients. Only emergency patients (refractory myocardial ischemia/cardiogenic shock) and those requiring single grafts, redo CABG, and concomitant procedures were excluded.

Follow-Up

Questionnaires were sent to study participants by post every year after surgery. No clinic visits were planned apart from the routine clinical 6-week postoperative visit. Participants were sent stamped addressed envelopes to improve the return rates of postal questionnaires. Study coordinators contacted participants by telephone to alert them to the arrival of the questionnaire and to ask them about medications, adverse events, and health services resource use.

Study End Points

The primary end point was the incidence of cerebrovascular accidents (CVAs) that occurred after discharge during the 10-year follow-up. Secondary end points were 10-year cardiovascular and all-cause mortality.

End Point Definition

CVA was defined as a new neurological deficit evidenced by clinical signs of paresis, plegia, or new cognitive dysfunction, including any mental status alteration >24 hours or evidence on computed tomography or magnetic resonance imaging scan of recent brain infarct (<6 months). The modified Rankin Scale[13] was used to evaluate the degree of disability in patients with a CVA. The scale ranges from 0 to 6, from "perfect health without symptoms" to "death": 0=no symptoms;

1=no significant disability (able to carry out all usual activities despite some symptoms); 2=slight disability (able to look after own affairs without assistance but unable to carry out all previous activities); 3=moderate disability (requires some help but is able to walk unassisted); 4=moderately severe disability (unable to attend to own bodily needs without assistance and unable to walk unassisted); 5=severe disability (requires constant nursing care and attention, bedridden, incontinent); and 6=deceased.

Death was classified as cardiovascular and noncardiovascular from autopsy reports and death certificates. Cardiovascular deaths were defined as deaths with cardiac causes (ie, congestive heart failure, arrhythmias, myocardial infarction) and vascular causes (ie, CVA, dissection, pulmonary embolism).

Major bleeding was defined according to the Bleeding Academic Research Consortium definition as any hemorrhage requiring blood transfusion (type 3a), compromising patient hemodynamically (3b), requiring surgical reintervention (type 4), or resulting in patient death (type 5).[14]

Statistical Analysis

A set of baseline characteristics was selected to adjust the association between pAF and the risk of CVA: age, female sex, New York Heart Association class, left ventricular ejection fraction, diabetes mellitus, smoking status, chronic obstructive pulmonary disease, arterial hypertension (medically treated), prior myocardial infarction, body mass index, creatinine, previous CVA, peripheral vascular disease, unstable angina, previous percutaneous coronary intervention, off-pump surgery, and total number of grafts. The rate of missing data for these variables was low (Figure II in the Data Supplement), and missing data were handled with multiple imputation (ie, 10 imputed data sets) with multivariate imputation by chained equations. Individual coefficients from each imputed data set were combined according to the Rubin rules for pooling.[15] For the comparison of baseline characteristics between patients with stable SR (SR group) and those with pAF (pAF group), categorical variables were compared between the 2 groups with the χ^2 test or Fisher exact test for categorial variables and the Student *t* test or Wilcoxon rank-sum test for nonnormally distributed continuous variables. The 10-year cumulative incidence of CVA and cardiovascular mortality in the 2 groups was calculated from competing risk analysis for CVA and cardiovascular mortality, accounting for the competing risk of death, as proposed by Fine and Gray.[16] The cumulative incidence for all-cause mortality was calculated with 1–Kaplan-Meier estimates. The association between pAF and primary and secondary end points was estimated as a subdistribution hazard ratio (HR) and its 95% CI derived from univariable and bidirectional stepwise multivariable Cox models. Variables included in the final multivariable model were selected on the basis of Akaike information criterion. Proportional hazard assumption was assessed with Schoenfeld residuals, and global *P* values were reported. The SR group was used as the reference group in all analyses. Adjusted *P* values for multiple comparisons (primary and secondary end points) were calculated with Bonferroni-Holm correction.

For sensitivity analysis, the association between pAF and the primary outcomes was recalculated, restricting the analysis only to CVAs that occurred after discharge or excluding patients with evidence of pAF within 6 weeks after discharge. Finally, we calculated the CHA_2DS_2-VASc score for each patient, which is a widely adopted tool to stratify patients according to their predicted risk of CVA.[17] To investigate whether pAF was associated with an additional risk across CHA_2DS_2-VASc score categories, the interaction between CHA_2DS_2-VASc score and pAF on the risk of CVA was explored by forcing their interaction term in a Cox regression model. Relative hazard was calculated and plotted for each CHA_2DS_2-VASc score category in the pAF and SR groups. We then defined high-risk patients as those with CHA_2DS_2-VASc score ≥4, which corresponds to the 75th percentile of its distribution. The cumulative incidence of CVA is reported in 4 groups stratified by rhythm status (pAF versus SR) and baseline CHA_2DS_2-VASc score (<4 versus ≥4). The relative risk of CVA was calculated across the groups as HR and 95% CI, with univariable Cox regression and with patients with SR and CHA_2DS_2-VASc score <4 for reference. Because only a small number of patients in the pAF group received vitamin K antagonists (ie, warfarin), we reported the cumulative incidence of major bleeding and CVA stratified for anticoagulation therapy received for descriptive purposes only. Values of $P<0.05$ were considered significant. Statistical analyses were performed with R Statistical Software (version 3.2.3; R Foundation for Statistical Computing, Vienna, Austria) and the following packages: mice for multiple imputation, survival for survival analysis, finalfit for univariate and multivariate regression tables generation, and ggplot2 for figures.

RESULTS

Study Population

The final population consisted of 3023 patients. Of these 3023, 734 (24.3%) and 2289 (75.7%) presented with pAF or stable SR, respectively, during the index hospitalization. Baseline characteristics in the 2 groups are presented in Table 1. The incidence of CVA during index admission was 14 (1.9%) and 23 (1.0%) in the pAF and SR groups, respectively. Hospital mortality was 13 (1.8%) and 16 (0.7%) in the pAF and SR groups, respectively. In 676 patients (92.1%) in the pAF group, stable SR was restored before discharge. In the SR group, 20 patients presented with new onset of AF within 6 weeks after discharge.

Medications at discharge in the 2 groups are presented in Table I in the Data Supplement. In the pAF group, Warfarin was prescribed in 61 patients (8.3%; 12 with persistent pAF, the remaining 49 with SR restoration), whereas in the SR group, warfarin was prescribed in 18 patients (0.8%). As expected, the proportion of patients discharged on amiodarone was higher in the pAF group (47.7% versus 1.7%).

Association Between pAF and 10-Year Outcomes

During the 10-year follow-up, a total of 46 CVAs (6.3%) were recorded (23 ischemic, 4 hemorrhagic and

Table 1. Baseline Characteristics in Patients With and Without Postoperative Atrial Fibrillation

Variable	Postoperative Atrial Fibrillation	Sinus Rhythm	*P* Value
Total, n	734	2289	
Age, mean (SD), y	66.41 (8.16)	62.58 (8.93)	<0.001
Ethnicity, n (%)			<0.001
White	710 (96.7)	2064 (90.2)	
East Asian	1 (0.1)	5 (0.2)	
South Asian	19 (2.6)	129 (5.6)	
Afro-Caribbean	0 (0.0)	2 (0.1)	
Black	0 (0.0)	5 (0.2)	
Hispanic	4 (0.5)	84 (3.7)	
Sex, female, n (%)	99 (13.5)	331 (14.5)	0.55
Left ventricular ejection fraction, n (%)			0.035
≥50%	527 (71.8)	1743 (76.1)	
30%–50%	186 (25.3)	503 (22.0)	
<30%	21 (2.9)	43 (1.9)	
Peripheral vascular disease, n (%)	55 (7.5)	154 (6.7)	0.53
Creatinine mean (SD), mmol/L	98.63 (23.72)	95.90 (21.07)	0.003
Body mass index, mean (SD), kg/m^2	28.29 (3.88)	28.18 (4.08)	0.51
Chronic obstructive pulmonary disease, n (%)	18 (2.5)	55 (2.4)	1.000
Smoking, n (%)			0.07
Current	90 (12.3)	346 (15.1)	
Ex-smoker	435 (59.3)	1258 (55.0)	
Never smoked	209 (28.5)	685 (29.9)	
Previous cerebrovascular accident, n (%)	48 (6.5)	129 (5.6)	0.41
New York Heart Association Class III/IV, n (%)	134 (18.3)	509 (22.2)	0.025
Diabetes mellitus, n (%)			0.17
No	546 (74.4)	1771 (77.4)	
Insulin dependent	49 (6.7)	119 (5.2)	
Not insulin dependent	139 (18.9)	399 (17.4)	
Arterial hypertension, n (%)	579 (78.9)	1766 (77.2)	0.35
Unstable angina, n (%)	53 (7.2)	182 (8.0)	0.57
Prior myocardial infarction, n (%)	326 (44.4)	938 (41.0)	0.11
Prior percutaneous coronary intervention, n (%)	124 (16.9)	354 (15.5)	0.39
Off-pump surgery, n (%)	268 (36.5)	969 (42.3)	0.006
No. of grafts, mean (SD)	3.23 (0.81)	3.17 (0.81)	0.06

19 unknown cause) in the pAF group. Their median modified Rankin score was 3.0 [interquartile range 1–5]. A total of 83 CVAs (3.6%) were recorded in the SR group (55 ischemic, 7 hemorrhagic, and 21 unknown). Their median modified Rankin Scale score was 2.5 (interquartile range, 1–4; Table II in the Data Supplement). The cumulative incidence of CVA at 10 years was 6.3% (4.6%–8.1%) versus 3.7% (2.9%–4.5%) in the pAF and SR groups, respectively (Table III in the Data Supplement). With univariable and multivariable Cox regression (Table 2), pAF was found to be an independent predictor of CVA at 10 years (HR, 1.53 [95% CI, 1.06–2.23]; Bonferroni-Holm–corrected *P*=0.025; global *P*=0.40; Figure 1A). Causes of death are reported in Table IV in the Data Supplement. CVA was reported as cause of death in 21 (9.7%) of 216 total deaths and in 15 (3.8%) of 394 total deaths in the pAF and SR groups, respectively. At 10 years, the cumulative incidence of cardiovascular and all-cause mortality was 11.1% (8.8%–13.4%) versus 6.4% (5.3%–7.4%) and 30.2% (26.8%–33.6%) versus 18% (16.4%–19.6%) in the pAF and SR groups, respectively. pAF was independently associated with increased risk of cardiovascular mortality (HR, 1.48 [95% CI, 1.11–1.97];

Table 2. Association Between Clinical Variables and Cerebrovascular Accidents at 10 Years

Variable	Hazard Ratios, 95% CI (Univariable)	Hazard Ratios, 95% CI (Multivariable)
Postoperative atrial fibrillation (sinus rhythm as reference)	1.79 (1.25–2.57, *P*=0.001)	1.53 (1.06–2.23, *P*=0.025)
Age	1.07 (1.05–1.10, *P*<0.001)	1.07 (1.05–1.10, *P*<0.001)
Ethnicity		
White	Reference	Reference
East Asian	0.00 (0.00–infinity, *P*=0.995)	0.00 (0.00–infinity, *P*=0.996)
South Asian	0.46 (0.15–1.45, *P*=0.186)	0.89 (0.28–2.87, *P*=0.847)
Afro-Caribbean	0.00 (0.00–infinity, *P*=0.997)	0.00 (0.00–infinity, *P*=0.998)
Black	0.00 (0.00–infinity, *P*=0.996)	0.00 (0.00–infinity, *P*=0.996)
Hispanic	2.88 (1.51–5.49, *P*=0.001)	4.95 (2.48–9.90, *P*<0.001)
Sex, female, n (%)	1.99 (1.33–2.97, *P*=0.001)	1.62 (1.07–2.46, *P*=0.024)
Left ventricular ejection fraction		
≥50%	Reference	
30%–50%	1.38 (0.94–2.03, *P*=0.101)	…
<30%	1.36 (0.43–4.29, *P*=0.603)	…
Peripheral vascular disease	1.05 (0.53–2.06, *P*=0.892)	…
Creatinine	1.01 (1.00–1.01, *P*=0.026)	…
Body mass index	0.99 (0.95–1.04, *P*=0.709)	…
Chronic obstructive pulmonary disease	1.74 (0.71–4.26, *P*=0.224)	…
Smoking		
Current	Reference	
Ex-smoker	0.77 (0.47–1.27, *P*=0.311)	0.52 (0.31–0.87, *P*=0.013)
Never smoked	1.05 (0.62–1.77, *P*=0.857)	0.60 (0.35–1.05, *P*=0.072)
Prior cerebrovascular accident	3.26 (2.02–5.25, *P*<0.001)	2.56 (1.58–4.15, *P*<0.001)
New York Heart Association Class III/IV	0.73 (0.46–1.16, *P*=0.184)	0.61 (0.37–0.98, *P*=0.043)
Diabetes mellitus		
No	Reference	
Insulin dependent	1.07 (0.50–2.30, *P*=0.869)	…
Not insulin dependent	1.12 (0.72–1.74, *P*=0.602)	…
Arterial hypertension	1.59 (0.98–2.55, *P*=0.058)	…
Unstable angina	0.79 (0.39–1.61, *P*=0.514)	…
Prior myocardial infarction	1.06 (0.75–1.50, *P*=0.740)	…
Prior percutaneous coronary intervention	1.57 (1.04–2.37, *P*=0.033)	1.85 (1.22–2.80, *P*=0.004)
Off-pump surgery	1.27 (0.90–1.80, *P*=0.173)	…
No. of grafts	1.04 (0.84–1.28, *P*=0.737)	…

Bonferroni-Holm–corrected *P*=0.01; global *P*=0.60; Table 3 and Figure 2A) and all-cause mortality (HR 1.34; 95% CI, 1.13–1.59; Bonferroni-Holm–corrected *P*=0.03; global *P*=0.10; Table V in the Data Supplement and Figure 2B). Sensitivity analysis confirmed that an independent association between pAF and risk of CVA at 10 years also existed when CVAs that occurred during the index admission were excluded (HR, 1.47 [95% CI, 1.02–2.11]; *P*=0.04; Table VI in the Data Supplement and Figure 1B) and when patients with evidence of AF within 6 weeks from discharge were excluded (HR, 1.49 [95% CI, 1.04–2.16]; *P*=0.032; Table VII in the Data Supplement). In the pAF group, the cumulative incidence of CVA and major bleeding at 10 years was 3.6% (0%–8.4%) versus 5.3% (3.5%–7.0%; Table VIII in the Data Supplement) and 3.4% (0.0%–8.1%) versus 4.1% (2.6%–5.7%; Table IX in the Data Supplement) in patients discharged with and without warfarin.

Prognostic Implication of CHA_2DS_2-VASc Score in Patients With pAF

The distribution of baseline CHA_2DS_2-VASc score in the pAF and SR groups is reported in Table X in the Data Supplement. Mean CHA_2DS_2-VASc score was 3.46±1.31 and 3.17±1.29 in the pAF and SR groups,

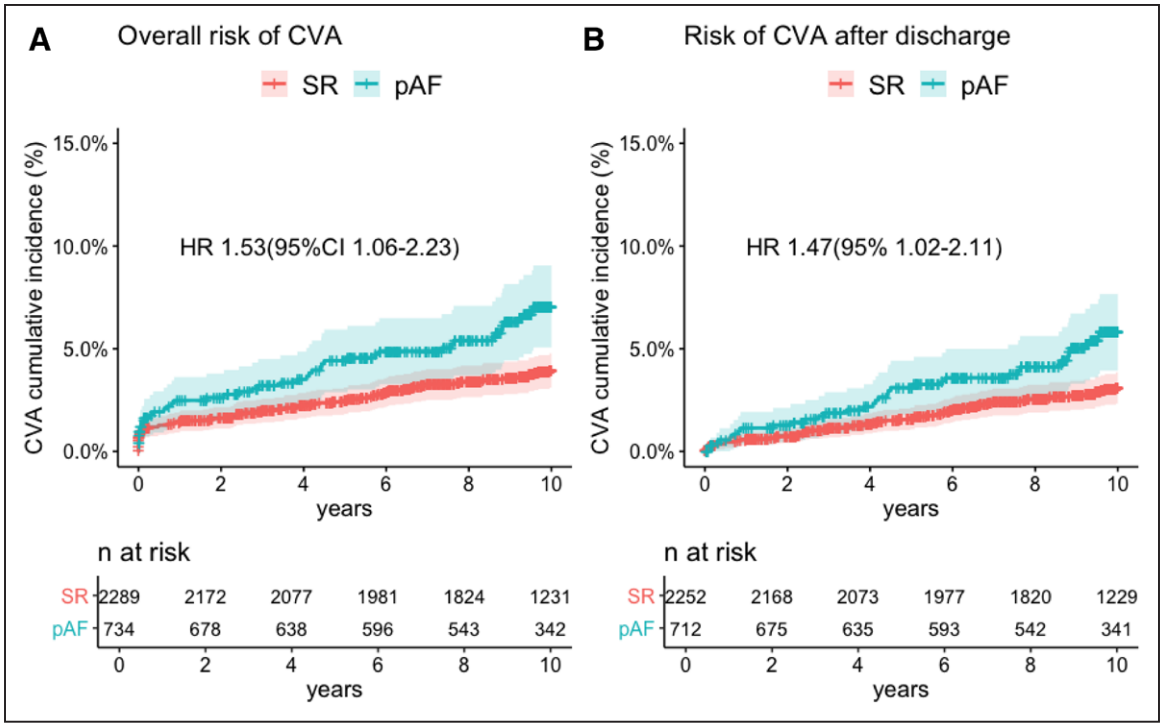

Figure 1. Cumulative incidence of cerebrovascular accident.
A, Cumulative incidence of cerebrovascular accident (CVA) in patients with postoperative atrial fibrillation (pAF) and stable sinus rhythm (SR) in the overall sample. **B**, Cumulative incidence of CVA in patients with pAF and stable SR after discharge (ie, CVA that occurred during index hospitalization were excluded). HR indicates hazard ratio.

respectively (P<0.001). We found a significant interaction between CHA_2DS_2-VASc score and pAF on the risk of CVA (P=0.01; Figure III in the Data Supplement). The cumulative incidence of CVA in the pAF and SR groups stratified by CHA_2DS_2-VASc score is reported in Table XI in the Data Supplement. The risk of CVA was comparable between the pAF and SR groups for a CHA_2DS_2-VASc score <4 but was significantly higher in patients with pAF for a CHA_2DS_2-VASc score ≥4. Compared with patients with a CHA_2DS_2-VASc score <4 in the SR group, a CHA_2DS_2-VASc score ≥4 in patients with SR was associated with 2-fold relative risk increase of CVA (HR, 2.13 [95% CI, 1.38–3.27]), whereas a CHA_2DS_2-VASc score ≥4 in those with pAF was associated with a 4-fold relative risk increase of CVA (HR, 4.05 [95% CI, 2.54–6.46]; Figure 3).

Results for the prognostic implication of the $CHADS_2$ score,[18] an earlier, simplified form of the CHA_2DS_2-VASc score, are presented in Tables XII and XIII and Figure IV in the Data Supplement.

DISCUSSION

In the cohort of patients undergoing CABG surgery in the ART trial, we found a significant association between pAF and the risk of CVA at 10 years, and this association continued after controlling for potential confounders. Half of the patients developing CVA presented with the least moderate disability (ie, median Rankin Scale score of 3). In patients with pAF, CVA was more frequently reported as the cause of death compared with patients who remained in SR. Overall, pAF was associated with an increased risk of cardiovascular and all-cause mortality.

pAF has long been considered a benign, self-limiting condition that converts to SR before hospital discharge in most cases.[2] However, recent evidence suggests that the occurrence of pAF is associated with patients with a larger burden of comorbidities, so causality between pAF and long-term mortality remains unclear.[4,5]

Limited and conflicting data are available on the association between pAF and CVA. To the best of our knowledge, no previous study has demonstrated the association between pAF and long-term (>10 years) risk of CVA. By using linked administrative data in the province of Ontario between 1996 and 2006, Whitlock et al[6] reported that pAF was associated with an increased incidence of stroke and death up to 2 years after CABG. A post hoc analysis of the EXCEL trial (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) reported an increased risk of stroke at 3 years after CABG in patients with pAF.[7] In both studies, the association between pAF and the risk of stroke was driven mainly by events occurring before discharge, In contrast, a recent analysis from the Danish nationwide registries showed no significant increase in the risk of thromboembolism in patients with pAF after

Table 3. Association Between Clinical Variables and Cardiovascular Mortality at 10 Years

Variable	Hazard Ratios, 95% CI (Univariable)	Hazard Ratios, 95% CI (Multivariable)
Postoperative atrial fibrillation (sinus rhythm as reference)	1.86 (1.42–2.45, *P*<0.001)	1.48 (1.11–1.97, *P*=0.007)
Age	1.08 (1.06–1.10, *P*<0.001)	1.08 (1.06–1.10, *P*<0.001)
Ethnicity		
White	Reference	
East Asian	2.19 (0.31–15.65, *P*=0.433)	7.77 (1.07–56.53, *P*=0.043)
South Asian	0.53 (0.23–1.19, *P*=0.123)	1.11 (0.49–2.56, *P*=0.798)
Afro-Caribbean	0.00 (0.00–infinity, *P*=0.991)	0.00 (0.00–infinity, *P*=0.994)
Black	3.49 (0.49–24.90, *P*=0.212)	4.48 (0.59–34.16, *P*=0.148)
Hispanic	1.88 (1.05–3.37, *P*=0.033)	2.99 (1.61–5.57, *P*=0.001)
Sex, female, n (%)	2.18 (1.61–2.95, *P*<0.001)	2.13 (1.54–2.94, *P*<0.001)
Left ventricular ejection fraction		
≥50%	Reference	
30%–50%	2.38 (1.80–3.15, *P*<0.001)	2.18 (1.63–2.92, *P*<0.001)
<30%	5.35 (3.13–9.15, *P*<0.001)	3.96 (2.27–6.90, *P*<0.001)
Peripheral vascular disease	1.91 (1.27–2.87, *P*=0.002)	…
Creatinine	1.01 (1.01–1.02, *P*<0.001)	1.01 (1.00–1.01, *P*<0.001)
Body mass index	1.01 (0.98–1.05, *P*=0.378)	…
Chronic obstructive pulmonary disease	1.88 (0.97–3.67, *P*=0.063)	…
Smoking		
Current	Reference	
Ex-smoker	0.70 (0.49–1.00, *P*=0.051)	0.43 (0.30–0.63, *P*<0.001)
Never smoked	0.65 (0.44–0.97, *P*=0.034)	0.35 (0.23–0.53, *P*<0.001)
Prior cerebrovascular accident	2.35 (1.56–3.54, *P*<0.001)	1.70 (1.12–2.59, *P*=0.012)
New York Heart Association Class III/IV	1.48 (1.10–1.99, *P*=0.009)	…
Diabetes mellitus		
No	Reference	
Insulin dependent	2.70 (1.79–4.07, *P*<0.001)	1.86 (1.22–2.85, *P*=0.004)
Not insulin dependent	1.21 (0.86–1.71, *P*=0.265)	1.11 (0.78–1.57, *P*=0.567)
Arterial hypertension	1.49 (1.04–2.13, *P*=0.028)	…
Unstable angina	1.39 (0.90–2.14, *P*=0.137)	…
Prior myocardial infarction	1.76 (1.35–2.30, *P*<0.001)	1.47 (1.11–1.94, *P*=0.007)
Prior percutaneous coronary intervention	1.05 (0.73–1.50, *P*=0.792)	…
Off-pump surgery	1.38 (1.06–1.79, *P*=0.017)	…
No. of grafts	0.95 (0.81–1.12, *P*=0.561)	…

CABG. However, AF was associated with an increased risk of rehospitalization for AF.[8]

In the present analysis, we found an independent association between pAF and 10-year risk of CVA. Although a relevant number of CVAs occurred within 30 days, the incidence of CVA continued to be higher in the pAF patients at mid- and long-term follow-up, and the association between pAF and CVA persisted when CVAs that occurred during index hospitalization were excluded. The association of pAF with CVA was evident even in patients with a high CHA_2DS_2-VASc score (≥4). If this association is validated in other studies, this finding could be used to stratify patients with pAF and to identify those who may benefit from stricter surveillance with continuous heart rhythm monitoring or anticoagulation therapy. In particular, little evidence exists on the efficacy and safety of anticoagulation therapy in patients with pAF, and current recommendations are driven mainly by the therapy for nonsurgical AF modified by the potential risk of bleeding in the postoperative period.[19] Current guidelines recommend anticoagulation for patients with a prolonged duration of pAF (>48 hours)[20] for at least 4 weeks. However, it remains unclear if the benefit of long-term anticoagulation for thromboembolism prevention outweighs the bleeding risk in this population. It must also be considered that post-CABG patients usually receive 1 or 2 antiplatelet

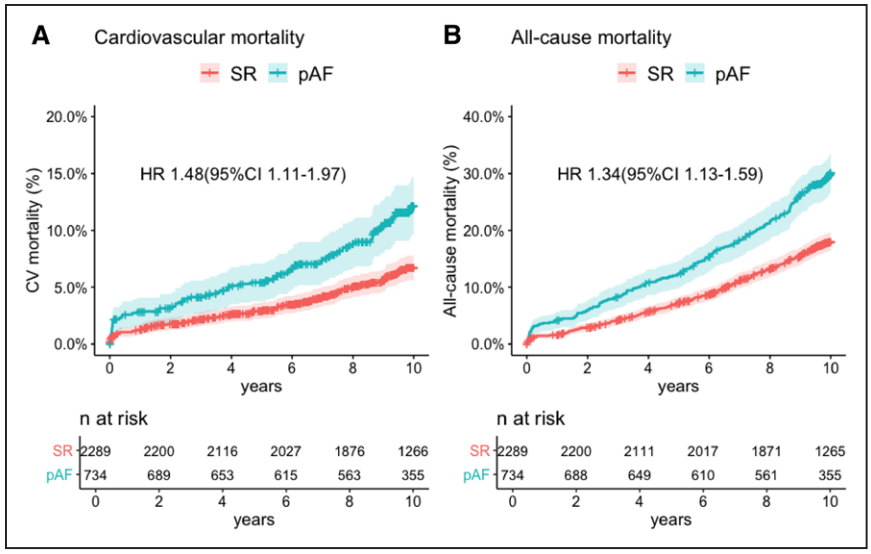

Figure 2. Cumulative incidence of cardiovascular and all-cause death.
A, Cumulative incidence of cardiovascular (CV) deaths in patients with postoperative atrial fibrillation (pAF) and stable sinus rhythm (SR). **B**, Cumulative incidence of all-cause deaths in patients with pAF and stable SR. HR indicates hazard ratio.

agents to prevent graft failure, and the combination of antiplatelet and anticoagulation therapies might significantly increase the risk of bleeding. The present post hoc analysis was largely underpowered to investigate whether the prescription of anticoagulation therapy was associated with the risk of CVA or bleeding. However, it is worth noting that in the present cohort the cumulative incidence of CVA in the pAF group was lower among patients discharged on warfarin and that patients discharged on warfarin presented a comparable risk of severe bleeding compared with patients discharged without it. Further benefit may be achieved by the use of novel oral anticoagulants, which can prevent new CVAs in high-risk patients with a reduced risk of bleeding compared with warfarin. This is related to a safer pharmacodynamic profile and fewer interactions with other drugs and food, which prevent supratherapeutic international normalized ratio, traditionally associated with warfarin. In a retrospective analysis of 960 patients undergoing isolated CABG, 29 patients with pAF were discharged on novel oral anticoagulants compared with

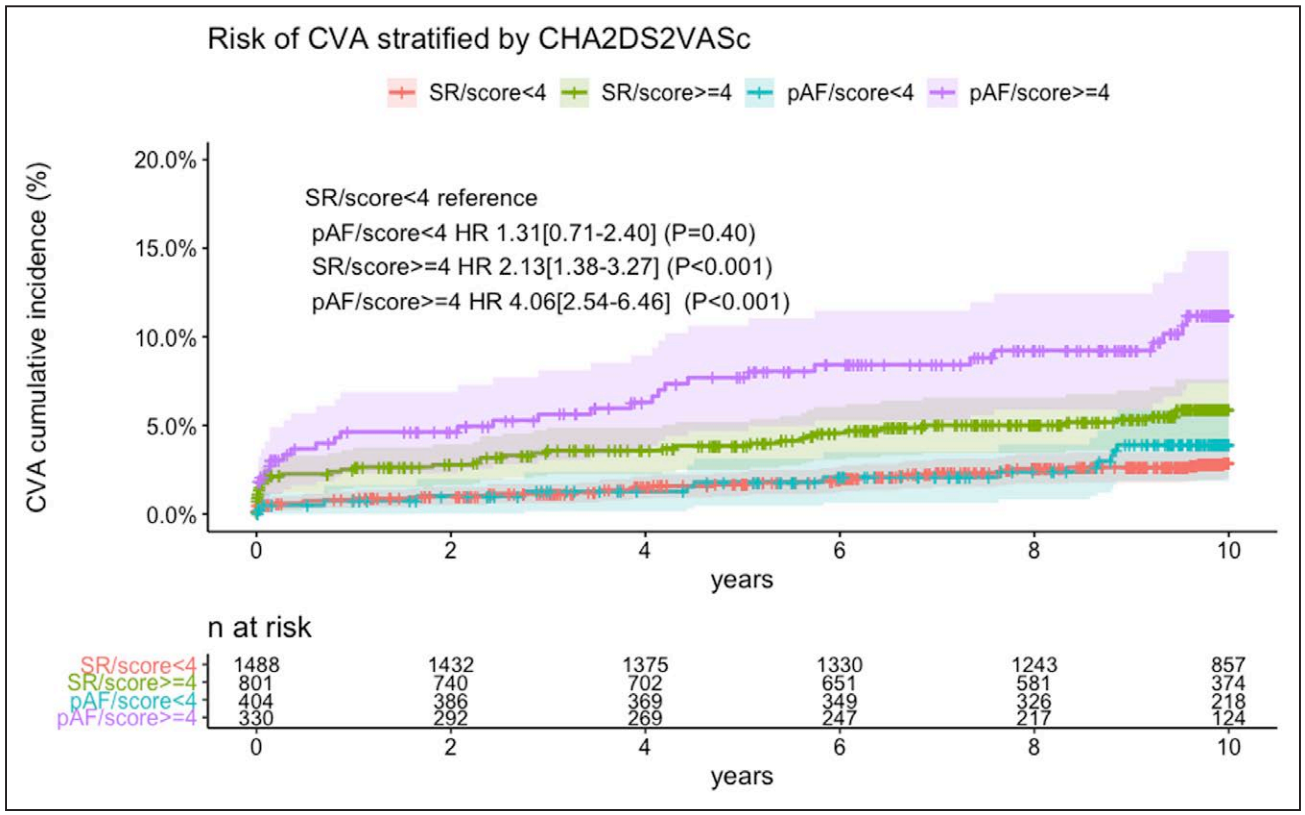

Figure 3. Cumulative incidence of cerebrovascular accident (CVA) with postoperative atrial fibrillation (pAF) and stable sinus rhythm (SR) stratified by CHA_2DS_2-VASc score <4 or ≥4.
HR indicates hazard ratio.

77 discharged on warfarin. Late postoperative outcomes showed 3 readmissions for major bleeding, all in patients discharged on warfarin, whereas no readmissions for major bleeding were recorded in patients discharged on a novel anticoagulation regimen.[21]

Moreover, attention should be given to each episode of pAF, regardless of its duration, to tailor a stricter surveillance in patients developing this complication. In fact, pAF has been shown to be associated with the late recurrence of AF, which exposes patients to the risk of CVA and late mortality.[22,23] Hence, this requires the clinician to undertake a more intense follow-up with the aim of identifying late recurrence of arrhythmias in a timely manner.

The present analysis has several limitations. We had no information on the duration of pAF in those cases with SR restoration before discharge; therefore, we were unable to correlate the duration of pAF with clinical outcomes. Moreover, the ART cohort enrolled a relatively low-risk subset of patients with CABG, and these results may not be generalizable to the real-world CABG population. The ART used questionnaires for follow-up, and it is possible that adverse events may have been underreported. However, for patients requiring hospital admission, copies of medical records were retrieved, and information on adverse events was collected. As previously highlighted, this post hoc analysis was largely underpowered to detect any difference in clinical outcomes in patients discharged on anticoagulation therapy; larger studies are needed to define the risks and benefits of such therapy in patients with pAF. Last, studies using continuous heart rhythm monitoring are needed to assess the risk of recurrence of atrial dysrhythmias in patients with pAF.

CONCLUSIONS

In the ART, the occurrence of pAF after CABG was associated with an increased 10-year risk of CVA and mortality. This association highlights the need to revisit the notion that pAF is a transient, benign condition. In particular, special consideration should be given to patients at higher baseline risk of CVA (CHA_2DS_2-VASc score ≥4) who develop pAF.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

ART Investigators
Expanded Results
Data Supplement Tables I–XIII
Data Supplement Figures I–IV

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