Perioperative/Postoperative Atrial Fibrillation and Risk of Subsequent Stroke and/or Mortality: A Meta-Analysis

Meng-Hsin Lin, MD; Hooman Kamel, MD; Daniel E. Singer, MD; Yi-Ling Wu, DrPH; Meng Lee, MD; Bruce Ovbiagele, MD, MS

Background and Purpose—Although believed to be transient and self-limiting, new-onset perioperative/postoperative atrial fibrillation (POAF) might be a risk factor for stroke and mortality. We conducted a systematic review and meta-analysis to quantitatively and qualitatively evaluate the relationship of POAF with early and late risks of mortality and stroke.

Methods—We searched Pubmed, EMBASE, and Cochrane Library (1966 through March 2018) to identify cohort studies that reported stroke and mortality associated with POAF. We computed a random-effects estimate based on the Mantel-Haenszel method. Odds ratios with 95% CI were used as a measure of the association between POAF and early (in-hospital or within 30 days of surgery) stroke and mortality, while hazard ratios (HR) were used for long-term outcomes.

Results—Our analysis included 35 studies with 2,458,010 patients. Pooling the results from the random-effects model showed that POAF was associated with increased risks of early stroke (odds ratio, 1.62; 95% CI, 1.47–1.80), early mortality (odds ratios, 1.44; 95% CI, 1.11–1.88), long-term stroke (HR, 1.37; 95% CI, 1.07–1.77), and long-term mortality (HR, 1.37; 95% CI, 1.27–1.49). Analyses focusing on high-quality studies obtained similar results. In subgroup analyses, POAF was more strongly associated with stroke in patients undergoing noncardiac surgery (HR, 2.00; 95% CI, 1.70–2.35) than in patients undergoing cardiac surgery (HR, 1.20; 95% CI, 1.07–1.34).

Conclusions—New-onset POAF is associated with an increased risk of stroke and mortality, both in the short-term and long-term. The best strategy to reduce stroke risk among these patients needs to be determined. (Stroke. 2019;50:1364-1371. DOI: 10.1161/STROKEAHA.118.023921.)

Key Words: atrial fibrillation ■ atrial flutter ■ coronary artery bypass ■ hypertension ■ mortality ■ stroke

Atrial fibrillation is the most common serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality in the general population. Individuals with established chronic atrial fibrillation are at an increased risk of stroke, and stroke patients with atrial fibrillation have longer hospital stays, higher risk of mortality, and poorer functional outcomes compared with those without atrial fibrillation.

Atrial fibrillation occurs in 15% to 42% of patients after cardiac surgery and roughly 10% in noncardiac surgery. Although postoperative/perioperative atrial fibrillation (POAF) is believed to be self-limiting and most patients with new-onset POAF revert to sinus rhythm before hospital discharge, several studies have shown a strong association between POAF and higher risk of perioperative stroke and mortality. Although some studies suggested new-onset atrial fibrillation after coronary artery bypass grafting appeared to increase short-term and long-term mortality, other studies indicated that POAF may not have a significant effect on long-term mortality. Furthermore, stroke is a major adverse outcome in atrial fibrillation, but whether POAF is associated with early and late stroke has not been systematically explored. We, therefore, performed a systematic review and meta-analysis of cohort studies to quantitatively and qualitatively evaluate the relationships between POAF versus early and late risks of mortality and stroke.

Methods

The authors declare that all supporting data are available within the article and its online-only Data Supplement. The study was conducted according to the recommendations of the Meta-analysis of Observational Studies in Epidemiology. We searched PubMed, EMBASE, and Cochrane Library (1966 to March 2018) using the search strategy “perioperative” OR “postoperative” AND “atrial fibrillation” AND “stroke” OR “cerebrovascular disease” OR “cerebrovascular attack” OR “cerebral ischemia” OR “brain ischemia” OR...
“death” OR “mortality” OR “survival.” We restricted the search to studies in humans. No language restrictions were applied. We only included studies reported in full articles. We did not contact authors for further information. Further information was obtained through a manual search of references from recent reviews and relevant published original studies.

**Study Selection and Data Abstraction**

We included studies that prospectively or retrospectively collected data within cohort studies; patients received operation and assessed POAF at baseline, assessed incident stroke and mortality, and reported quantitative estimates of the multiple adjusted odds ratio (OR) or hazard ratio (HR) and 95% CI for stroke and mortality associated with perioperative or postoperative atrial fibrillation. Early and late outcomes were recorded separately. Early outcomes were defined as stroke or mortality occurring within 30 days of operation. Late outcomes were defined as stroke or mortality occurring after 30 days. We excluded studies with a cross-sectional or case-control design, that had preexisting atrial fibrillation before operation, and that did not report a 95% CI. Studies reported patients with perioperative or postoperative atrial flutter but not atrial fibrillation were also excluded. Two investigators (M.-H. Lin and M. Lee) independently conducted the literature search, screening of abstracts, selection of included studies, and abstraction of data. Any discrepant judgments were resolved through joint discussion to reach consensus.

**Study Quality**

We assessed the quality of eligible studies. Assessment was based on guidelines developed by the US Preventive Task Force as well as the modified checklist used in previous studies.\(^{17,18}\) We assessed 4 characteristics: prospective study design, maintenance of comparable groups, adjustment of potential confounders (ie, age, sex, hypertension, and diabetes mellitus), and documented loss of follow-up rate. Studies were graded as good quality if they met at least 3 of the 4 criteria and poor if they met fewer than 3.

**Statistical Analysis**

For data analysis, we used multiple adjusted outcome data (expressed as OR or HR and 95% CI). For the statistical analysis, we combined data using the inverse variance approach. We used a random-effects model and explored for sources of inconsistency ($I^2$) and heterogeneity. We separately pooled HR and OR, respectively, for our analysis. Reported $P$ values were 2-sided, with significance set at $<0.05$. Heterogeneity was assessed by $P$ value of $\chi^2$ and $I^2$ statistics, which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than to chance. Based on the suggestion of the Cochrane Collaboration, we regarded heterogeneity as possibly unimportant when the $I^2$ value was <40% and considerable when >75%. The Trim-and-Fill method to identify and correct for funnel plot asymmetry arising from publication bias was used with Stata 15. RevMan 5.3 was used for the meta-analysis of observational studies.

The outcomes of interest were risks of stroke and mortality in early (within 30 days or in-hospital) and long-term stages among patients with new-onset POAF. The reference group was patients without POAF at baseline. We further separated patients into cardiac and noncardiac type of surgery and compared HRs of strokes and mortality for long-term outcomes.

**Results**

We identified 101 full articles for detailed assessment, of which 24 were excluded for not having required end point, 5 for not involving any surgery, and 37 for not having appropriate data on HRs/ORs or CIs. The final analysis included 2458010 participants from 35 studies (Figure I in the online-only Data Supplement).\(^{4,5,8–10,12–15,19,19–44}\) Twelve studies reported early outcomes\(^{4,5,8,10,13,19–22,30,32,36}\) and 28 studies reported late outcomes.\(^{4,5,8–10,12–15,19–23,29,31,33–35,37–44}\) One study included patients who received both noncardiac and cardiac surgery,\(^{9}\) 6 studies included patients who received noncardiac surgery,\(^{12,13,19,40,44}\) and 28 studies included patients who received cardiac surgery,\(^{4,5,8,10,13,15,19,20,22–33,33–38,41–44}\) mostly isolated coronary artery bypass graft. Characteristics of the included studies are presented in the Table, and quality of included studies is presented in Table I in the online-only Data Supplement. Definition of stroke outcome and whether diagnosis of stroke confirmed by computed tomography or magnetic resonance imaging in each studies are presented in Table II in the online-only Data Supplement.

**Early Outcomes**

For early outcomes, 7 studies reported estimates of POAF for stroke\(^{4,5,8,10,13,19,20,22,30}\) and 8 studies reported for death.\(^{4,5,8,13,19,22,31,36}\) Overall, 160 stroke events were found in 8588 patients with POAF (1.9%), whereas 240 stroke events were found in 24731 patients without POAF (1.0%). Also, 1269 deaths were found in 30361 patients with POAF (4.2%), whereas 7942 deaths were found in 428823 patients without POAF (1.9%). Pooling in the random-effects model showed that POAF was associated with increased risks of early stroke (OR, 1.62; 95% CI, 1.47–1.80; $P<0.00001$) and early mortality (OR, 1.44; 95% CI, 1.11–1.88; $P=0.007$; Figure 1). Heterogeneity was not found for stroke ($P=0.73$, $I^2=0$%) but found for mortality ($P<0.001$, $I^2=87$%). When we restricted analysis to studies with good quality for mortality outcome, heterogeneity became insignificant ($P=0.10$, $I^2=50$%). One study was distinct because a timely and aggressive therapeutic strategy was applied once POAF was found and reported early outcome using a HR, suggesting that patients with POAF had lesser hazard of early stroke (HR, 0.57; 95% CI, 0.33–0.98; $P=0.04$; Figure II in the online-only Data Supplement).\(^{30}\)

**Long-Term Outcomes**

For long-term outcomes, 3 studies with 4 independent estimates reported HRs of POAF for stroke\(^{4,10,31,37}\) and 23 studies reported for death.\(^{4,5,12,14,15,24–29,33–35,37,38,40–44}\) Overall, 643 stroke events were found in 26925 patients with POAF (2.4%), whereas 7008 stroke events were found in 1710493 patients without POAF (0.4%). Also, 5912 deaths were found in 18080 patients with POAF (32.7%), whereas 15720 deaths were found in 70217 patients without POAF (22.4%). Pooling in the random-effects model showed that POAF was associated with increased risks of long-term stroke (HR, 1.37; 95% CI, 1.07–1.77; $P=0.01$) and long-term mortality (HR, 1.37; 95% CI, 1.27–1.49; $P<0.0001$; Figure 2). Heterogeneity was found both for stroke ($P<0.00001$, $I^2=92$%) and for mortality ($P<0.00001$, $I^2=76$%). When we restricted analysis to studies with good quality for the mortality outcome, heterogeneity became insignificant ($P=0.05$, $I^2=43$%). Also, 5 studies reported OR of POAF for death.\(^{3,5,12,13,31,39}\) Overall, 1437 deaths were found in 8693 patients with POAF (16.5%), whereas 2672 deaths were found in 26438 patients without POAF (10.1%). Pooling data of ORs also showed increased risk of POAF for long-term mortality (OR, 1.43; 95% CI, 1.21–1.70; $P<0.0001$; Figure III in the online-only Data Supplement).


<table>
<thead>
<tr>
<th>Study, Country</th>
<th>Population Characteristics</th>
<th>Sample Size (Women, %)</th>
<th>Age, y POAF/No. POAF</th>
<th>Percentage of Cardiac Surgery</th>
<th>Study Duration, y</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hogue et al., United States</td>
<td>CABG and valve surgery</td>
<td>2972 (36)</td>
<td>NA/NA</td>
<td>100</td>
<td>6</td>
<td>In-hospital stroke</td>
</tr>
<tr>
<td>Stamou et al., United States</td>
<td>Isolated CABG</td>
<td>16528 (27)</td>
<td>NA/NA</td>
<td>100</td>
<td>10</td>
<td>In-hospital stroke</td>
</tr>
<tr>
<td>Villareal et al., United States</td>
<td>Isolated CABG</td>
<td>6477 (25)</td>
<td>67.9±9.6/62.2±10.7</td>
<td>100</td>
<td>4</td>
<td>In-hospital end points: death, stroke; long-term mortality</td>
</tr>
<tr>
<td>Nielsen et al., United States</td>
<td>Lung transplantation</td>
<td>198 (NA)</td>
<td>52.8/47.5</td>
<td>0</td>
<td>3</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Kalavrouziotis et al., Canada</td>
<td>Isolated CABG or concomitant CABG and valve surgery</td>
<td>7347 (26)</td>
<td>NA/NA</td>
<td>100</td>
<td>8.5</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Mariscalco and Engström, Sweden</td>
<td>Cardiothoracic surgery</td>
<td>8434 (27)</td>
<td>69.9±8.0/65.0±9.6</td>
<td>100</td>
<td>1</td>
<td>One-year all-cause mortality</td>
</tr>
<tr>
<td>Mariscalco et al., Italy</td>
<td>Isolated CABG</td>
<td>1832 (21)</td>
<td>68.4±7.9/63.7±9.1</td>
<td>100</td>
<td>4.3</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Ahlsson et al., Sweden</td>
<td>First isolated CABG</td>
<td>1419 (25)</td>
<td>69.2±8.1/64.9±9.5</td>
<td>100</td>
<td>8</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Filardo et al., United States</td>
<td>First isolated CABG</td>
<td>6899 (28)</td>
<td>69.1±62.2</td>
<td>100</td>
<td>10</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Bramer et al., the Netherlands</td>
<td>First isolated CABG</td>
<td>5098 (22)</td>
<td>68.5±8.1/64±9.7</td>
<td>100</td>
<td>2.5</td>
<td>Early (&lt;30 d) and long-term mortality</td>
</tr>
<tr>
<td>Filardo et al., United States</td>
<td>Aortic valve replacement with/without CABG</td>
<td>1039 (36)</td>
<td>74.2/65.7</td>
<td>100</td>
<td>4.4</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>El-Chami et al., United States</td>
<td>Isolated CABG</td>
<td>16196 (28)</td>
<td>67.5±9.5/61.3±10.9</td>
<td>100</td>
<td>6</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Ahlsson et al., Sweden</td>
<td>First isolated CABG</td>
<td>571 (22)</td>
<td>69.2±7.6/64.6±9.4</td>
<td>100</td>
<td>6.9</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Bramer et al., the Netherlands</td>
<td>Mitral valve repair/replacement with/without CABG or tricuspid valve surgery</td>
<td>856 (40)</td>
<td>67±9.5/62±11</td>
<td>100</td>
<td>3.1</td>
<td>Early (&lt;30 d) and long-term mortality</td>
</tr>
<tr>
<td>Tarakji et al., United States</td>
<td>Primary isolated or reoperative CABG</td>
<td>45432 (21)</td>
<td>Stroke/no stroke: 67/63</td>
<td>100</td>
<td>11</td>
<td>Early stroke</td>
</tr>
<tr>
<td>Bhave et al., United States</td>
<td>Major noncardiac surgery</td>
<td>370447 (57)</td>
<td>74.6±10.6/62.4±16.2</td>
<td>0</td>
<td>1</td>
<td>In-hospital mortality</td>
</tr>
<tr>
<td>Amlmassi et al., United States</td>
<td>Isolated CABG</td>
<td>2103 (NA)</td>
<td>65.3±8.5/61.6±8.2</td>
<td>100</td>
<td>1</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Saxena et al., Australia</td>
<td>Isolated CABG</td>
<td>19497 (NA)</td>
<td>69.0±9.0/64.0±10.7</td>
<td>100</td>
<td>3.7</td>
<td>Early stroke and mortality; long-term mortality</td>
</tr>
<tr>
<td>Imperatori et al., Italy</td>
<td>Elective pulmonary lobectomy</td>
<td>454 (19)</td>
<td>68.6±6.8/65.0±8.9</td>
<td>0</td>
<td>3</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Horwich et al., Canada</td>
<td>First isolated CABG</td>
<td>8058 (25)</td>
<td>NA/NA</td>
<td>100</td>
<td>5.7</td>
<td>Long-term stroke or mortality</td>
</tr>
<tr>
<td>O’Neal et al., United States</td>
<td>First isolated CABG</td>
<td>13165 (30)</td>
<td>66±9.3 (Black POAF)/68±9.0 (White POAF)/62±10 (No POAF)</td>
<td>100</td>
<td>8.2</td>
<td>Long-term mortality</td>
</tr>
<tr>
<td>Lapar et al., United States</td>
<td>First isolated CABG</td>
<td>49264 (29)</td>
<td>69±10/63±11</td>
<td>100</td>
<td>12</td>
<td>Early mortality</td>
</tr>
<tr>
<td>Whitlock et al., Canada</td>
<td>CABG, isolated valvular surgery, or combined surgery</td>
<td>108711 (26)</td>
<td>Percentage of age &gt;65: 68%/48%</td>
<td>100</td>
<td>2</td>
<td>Early and long-term stroke</td>
</tr>
<tr>
<td>Gialdini et al., United States</td>
<td>Inpatient major surgery</td>
<td>1729360 (59)</td>
<td>71.5±56.2</td>
<td>4.2</td>
<td>2.1</td>
<td>Long-term ischemic stroke</td>
</tr>
<tr>
<td>Thoren et al., Sweden</td>
<td>First isolated CABG</td>
<td>7428 (21)</td>
<td>69.0±7.7/65.2±9.1</td>
<td>100</td>
<td>9.8</td>
<td>Long-term mortality</td>
</tr>
</tbody>
</table>

(Continued)
Subgroup Analyses
We conducted subgroup analyses for the impact of POAC on long-term outcomes based on surgery type (cardiac versus noncardiac), study quality (good versus poor), follow-up duration (≤3 years versus >3 years), sample size (<2000 versus >2000), and publication year (before 2010 versus 2010 and thereafter), presented in Figure 3. POAF was associated with higher risk of stroke in patients receiving noncardiac surgery than cardiac surgery (HR, 2.00; 95% CI, 1.70–2.35 versus HR, 1.20; 95% CI, 1.07–1.34; \( P \) for subgroup difference <0.0001). Also, POAF was more strongly associated with mortality in studies with good quality than in studies with poor quality (HR, 1.46; 95% CI, 1.34–1.60 versus HR, 1.24; 95% CI, 1.14–1.35; \( P \)=0.01 for subgroup difference) and sample size <2000 than >2000 (HR, 1.58; 95% CI, 1.37–1.83 versus HR, 1.27; 95% CI, 1.17–1.38; \( P \) for subgroup difference =0.01).

Publication Bias
Trim-and-Fill method showed that potential publication bias was found in early stroke (\( P=0.004; \) Figure IV in the online-only Data Supplement), and magnitude of recalculated risk was slightly decreased (OR, 1.43; 95% CI, 1.19–1.72). Trim-and-Fill

---

Table. Continued

<table>
<thead>
<tr>
<th>Study, Country</th>
<th>Population Characteristics</th>
<th>Sample Size (Women, %)</th>
<th>Age, y POAF/No. POAF Percentage of Cardiac Surgery</th>
<th>Study Duration, y</th>
<th>End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Shaar et al, United States</td>
<td>First isolated CABG</td>
<td>6305 (31)</td>
<td>67.6±6.6/62.5±10.6</td>
<td>100</td>
<td>9.7</td>
</tr>
<tr>
<td>Tulla et al, Finland</td>
<td>First isolated CABG</td>
<td>276 (25)</td>
<td>70.2±7.6/7.6±8</td>
<td>100</td>
<td>8.5</td>
</tr>
<tr>
<td>Melduni et al, United States</td>
<td>Isolated CABG, or valvular repair/ replacement, or combination</td>
<td>603 (30)</td>
<td>71.4±10.7/62.1±13.3</td>
<td>100</td>
<td>8.3</td>
</tr>
<tr>
<td>Xia et al, United States</td>
<td>Liver transplantation</td>
<td>1387 (37)</td>
<td>58.8±9.1/54±11.4</td>
<td>0</td>
<td>7.5</td>
</tr>
<tr>
<td>Kothari et al, United States</td>
<td>Abdominal aortic aneurysm repair</td>
<td>15148 (19)</td>
<td>75.6±7.7/73.7±8.5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Omer et al, United States</td>
<td>First isolated CABG</td>
<td>1248 (1)</td>
<td>64.3±6.8/62±7</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>Lee et al, Korea</td>
<td>First isolated CABG</td>
<td>1664 (29)</td>
<td>68±7/65±7</td>
<td>100</td>
<td>4.1</td>
</tr>
<tr>
<td>Swinkels et al, the Netherlands</td>
<td>Aortic valve replacement with/ without CABG</td>
<td>569 (48)</td>
<td>65.4±10.7/64.1±10.9</td>
<td>100</td>
<td>17.8</td>
</tr>
<tr>
<td>Fengsrud et al, Sweden</td>
<td>First isolated CABG</td>
<td>615 (22)</td>
<td>69.2±6.4/6±9.4</td>
<td>100</td>
<td>15</td>
</tr>
<tr>
<td>Leibowitz et al, Israel</td>
<td>Hip fracture repair</td>
<td>410 (66)</td>
<td>82.8±80</td>
<td>1</td>
<td>Long-term mortality</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; and NA, not available; POAF, perioperative/postoperative atrial fibrillation.
method also showed that potential publication bias was found in long-term mortality ($P<0.0001$; Figure V in the online-only Data Supplement), and magnitude of recalculated risk was slightly decreased (HR, 1.30; 95% CI, 1.21–1.40).

### Discussion

In this meta-analysis of 35 cohort studies, with more than 2.4 million participants, we observed that patients with new-onset POAF had 62% higher odds of early stroke or 44% higher odds of mortality compared with those without POAF; patients with new-onset POAF had 37% higher risk of long-term stroke and 37% higher risk of long-term mortality compared with those without POAF, and risk of long-term stroke was substantially higher among patients with new-onset POAF who received noncardiac surgery. All the studies included in our meta-analysis reported a multiple adjusted relative risk, which probably mitigated the possibility of known confounding influencing our results. Since studies enrolling patients with preexisting atrial fibrillation before operation were excluded, the detrimental effect was associated with new-onset POAF, rather than chronic atrial fibrillation.

We found that POAF after cardiac surgery significantly was associated with increased risks of early stroke and mortality. Most POAF occurred within 2 to 4 days after surgery, with peak incidence on postoperative day 2.35 Acute atrial fibrillation raises risk of thrombus formation in the left atrial appendage, resulting in increased risk of systemic embolization and stroke.46 It is also possible that patients with sicker hearts may be more likely to have atrial fibrillation and also more likely to die. Findings from our study are consistent with those of previously published studies, suggesting that patients who develop POAF have poorer preoperative, intraoperative risk profiles, and postoperative complications, including stroke and death.8,41

It is believed that most POAF is self-limiting and converts to sinus rhythm before hospital discharge, after the underlying precipitating factors have come under control.47 However, in our study, occurrence of POAF was still linked to significantly greater hazards of long-term stroke and mortality. El-Chami et al48 enrolled 23 patients with POAF after coronary artery bypass graft and used implantable loop recorder to detect recurrence of atrial fibrillation, and long-term monitoring showed that 60.9% of patients with POAF developed recurrent atrial fibrillation (ie, any atrial fibrillation episodes >6 minutes). POAF after cardiac surgery is an independent predictor of late atrial fibrillation, with a 4-fold to 5-fold higher risk.6,49

In the Framingham Study, about 31% patients with atrial fibrillation were diagnosed during a secondary precipitant, and both cardiothoracic surgery and noncardiothoracic surgery...
were common secondary precipitants. About 42% of participants with secondary precipitants experienced recurrent atrial fibrillation in the first 5 years after the initial episode. Of note, long-term atrial fibrillation–related stroke and mortality risks were similar between individuals with and without secondary atrial fibrillation precipitants.

In subgroup analysis of cardiac and noncardiac surgery, POAF seems to have a more harmful effect on the long-term outcome of patients receiving noncardiac surgery versus cardiac surgery, even though the incidence of POAF is higher in patients with cardiac surgery than those with noncardiac surgery. Presence of POAF doubled risk of stroke in patients who received noncardiac surgery, but only increased risk of stroke by 20% in patients who received cardiac surgery. The comparison between effects in cardiac and noncardiac surgery effects is a bit more about potential mechanisms. In cardiac surgery, direct manipulation of heart, injuries of atrium from surgical incision, and local inflammation may lead to abnormal atrial conduction, which could precipitate POAF. When the reversible precipitants are removed, atrial fibrillation will likely revert to sinus rhythm. The precise mechanism for POAF in noncardiac surgery is not well-defined at this time but is probably multifactorial and more systemic in nature.

It is plausible that patients who would develop new-onset atrial fibrillation after noncardiac surgery are likely to be sicker or have poorer baseline conditioning than those who do not have develop POAF. Unlike POAF in cardiac surgery for which trigger factors may be ameliorated after surgery, the trigger factors that cause people to develop POAF in noncardiac surgery are likely to remain (eg, systemic factors and poor conditioning) after surgery, which would make recurrent atrial fibrillation and higher long-term stroke risk, all the more likely.

The harmful effect of POAF in noncardiac surgery raises curiosity that whether use of certain drugs, such as β-blockers, before operation, is helpful for these patients. POISE trial (Perioperative Ischemic Evaluation) randomly assigned over 8000 patients who were undergoing noncardiac surgery to receive extended-release metoprolol or placebo, and the study treatment was started 2 to 4 hours before surgery and continued for 30 days. Although there were fewer new atrial fibrillation events in patients receiving metoprolol, total mortality and stroke significantly increased in this group. Therefore, β-blocker therapy to patients undergoing noncardiac surgery may not be a reasonable choice based on these findings from a large clinical trial.
One of the studies included in our analysis was distinct from the others due to an unanticipated finding of lower risk of postoperative stroke with new-onset POAF. To treat new-onset POAF, clinicians initially try early medical or electric conversion and, if POAF recurs or is persistent, rate control and anticoagulation. This strategy appears to lower the risk of anticipated stroke. Although these results came from single large prospective cohort, it may not be unreasonable to consider adopting a timely and aggressive therapeutic strategy once POAF is found.

This study has several limitations. First, meta-analysis may be biased when the literature search fails to identify all relevant studies or the selection criteria for including a study are applied in a subjective manner. To minimize these risks, we performed thorough searches across multiple literature databases and used explicit criteria for study selection, data extraction, and data analysis. Second, substantial heterogeneity existed in end points of early mortality, as well as late mortality and stroke. Still, when we restricted analysis in studies with good quality, magnitude of heterogeneity reduced in end points of early and late mortality. On the contrary, we found the heterogeneity of the long-term stroke end point came from patients receiving cardiac versus noncardiac surgery. Also, publication bias was found with a slight underrepresentation of small studies showing neutral or unexpected protective effects for long-term outcomes. Furthermore, unmeasured confounding factors may exist even only studies reported multiple-adjusted estimates were included. All such issues were likely to undermine the reliability of the conclusions. Third, although most POAF is likely to be transient and self-limiting, persistent atrial fibrillation might exist. The included studies did not report paroxysmal versus persistent atrial fibrillation separately, and further analysis could not be done in this meta-analysis. Furthermore, some patients with new-onset POAF might actually have unrecognized paroxysmal atrial fibrillation before operation. Therefore, the new diagnosis of atrial fibrillation in the postoperative period may be highly confounded by detection bias. Finally, the generalizability might be good because the type of surgery varied among included studies. However, only 1 study was derived from an Asian population, and further studies in such a population might be warranted.

Summary

In conclusion, new-onset POAF is not only associated with increased risk of early stroke and mortality after surgery but also associated with increased risk of long-term stroke and mortality. Risk of long-term stroke was substantially higher among patients with new-onset POAF who received noncardiac surgery than those who received cardiac surgery. Since the increased risk of stroke in patients with POAF, the best strategy to reduce stroke risk (empirical lifelong anticoagulation versus monitoring for AF recurrence) needs to be determined in future studies.

Sources of Funding

This work was supported by Ministry of Science and Technology, Taiwan, grant number: MOST105-2628-B-182-008-MY2, and Chang Gung Memorial Hospital, Taiwan, grant number: CORPG6D0101, CORPG6D0102, CORPG6D0103 (Dr Lee). The sponsors played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

Disclosures

Dr Kamel reports support from NIH/NINDS (R01NS097443, U01NS095869, and U01NS106513) (significant) and is Deputy Editor for JAMA Neurology (significant). Dr Kamel serves as a steering committee member of Medtronic’s Stroke AF trial (modest), receives in-kind study drug from BMS-Pfizer and in-kind study assays for the ARCADIA trial (modest), and has served on an advisory board for Roivant Sciences (modest). Support from Roivant Sciences, Medtronic, and BMS are relevant to the current work. Dr Singer received research support from Boehringer Ingelheim (Stroke prevention in atrial fibrillation) and Boehringer Ingelheim (Stroke prevention in atrial fibrillation). Dr Singer serves in Consulting/Advisory Boards for Boehringer Ingelheim (Treatment of venous thromboembolic disease), Bristol-Myers Squibb (Stroke prevention in atrial fibrillation), CVS Health (Stroke prevention in atrial fibrillation), Johnson and Johnson (Stroke prevention in atrial fibrillation), Merck (Stroke prevention in atrial fibrillation), Pfizer (Stroke prevention in atrial fibrillation), and Medtronic (February 2017). The other authors report no conflicts.

References


