

## Original Investigation

# Perioperative Atrial Fibrillation and the Long-term Risk of Ischemic Stroke

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**IMPORTANCE** Clinically apparent atrial fibrillation increases the risk of ischemic stroke. In contrast, perioperative atrial fibrillation may be viewed as a transient response to physiological stress, and the long-term risk of stroke after perioperative atrial fibrillation is unclear.

**OBJECTIVE** To examine the association between perioperative atrial fibrillation and the long-term risk of stroke.

**DESIGN, SETTING, AND PARTICIPANTS** Retrospective cohort study using administrative claims data on patients hospitalized for surgery (as defined by surgical diagnosis related group codes), and discharged alive and free of documented cerebrovascular disease or preexisting atrial fibrillation from nonfederal California acute care hospitals between 2007 and 2011. Patients undergoing cardiac vs other types of surgery were analyzed separately.

**MAIN OUTCOMES AND MEASURES** Previously validated diagnosis codes were used to identify ischemic strokes after discharge from the index hospitalization for surgery. The primary predictor variable was atrial fibrillation newly diagnosed during the index hospitalization, as defined by previously validated present-on-admission codes. Patients were censored at postdischarge emergency department encounters or hospitalizations with a recorded diagnosis of atrial fibrillation.

**RESULTS** Of 1 729 360 eligible patients, 24 711 (1.43%; 95% CI, 1.41%-1.45%) had new-onset perioperative atrial fibrillation during the index hospitalization and 13 952 (0.81%; 95% CI, 0.79%-0.82%) experienced a stroke after discharge. In a Cox proportional hazards analysis accounting for potential confounders, perioperative atrial fibrillation was associated with subsequent stroke both after noncardiac and cardiac surgery.

Type of Surgery	Cumulative Rate of Stroke 1 Year After Hospitalization, % (95% CI)		Hazard Ratio (95% CI)
	Perioperative Atrial Fibrillation	No Perioperative Atrial Fibrillation	
Noncardiac	1.47 (1.24-1.75)	0.36 (0.35-0.37)	2.0 (1.7-2.3)
Cardiac	0.99 (0.81-1.20)	0.83 (0.76-0.91)	1.3 (1.1-1.6)

The association with stroke was significantly stronger for perioperative atrial fibrillation after noncardiac vs cardiac surgery ( $P < .001$  for interaction).

**CONCLUSIONS AND RELEVANCE** Among patients hospitalized for surgery, perioperative atrial fibrillation was associated with an increased long-term risk of ischemic stroke, especially following noncardiac surgery.

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**+** Author Video Interview at [jama.com](http://jama.com)

**+** Supplemental content at [jama.com](http://jama.com)

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**A**trial fibrillation (AF) and flutter affect more than 33 million people worldwide.<sup>1</sup> The presence of chronic AF confers a 3-fold increased risk of stroke, and stroke in patients with AF is associated with a longer hospital stay, greater disability, and increased mortality compared with other types of ischemic stroke.<sup>2</sup>

New-onset perioperative AF is the most common perioperative arrhythmia.<sup>3</sup> Its reported incidence ranges widely from 1% to 40% because published studies have included different patient populations in terms of the type of surgery performed and patient characteristics.<sup>4,5</sup> It is important to fully elucidate the clinical burden of perioperative AF because approximately 200 million operations are performed worldwide every year. Numerous studies have shown a strong association between the occurrence of perioperative AF and length of hospital stay, hospital costs, and mortality.<sup>6</sup> Furthermore, perioperative AF has been repeatedly associated with a higher short-term risk of perioperative stroke in the setting of cardiac surgery.<sup>7-9</sup>

Perioperative AF is often considered a self-limited entity.<sup>10</sup> However, little is known about the long-term risk of ischemic stroke in patients with perioperative AF. A few single- or dual-center studies have reported an increased long-term risk of stroke in patients with perioperative AF after cardiac surgery,<sup>11-13</sup> whereas other single-center analyses have found no such association in this population.<sup>14,15</sup> Moreover, data are scarce in regard to the long-term risk of stroke from perioperative AF in patients undergoing other types of surgery. Therefore, we sought to determine the long-term risk of ischemic stroke after perioperative AF in a large, population-based sample of patients undergoing surgery.

## Methods

### Design

We performed a retrospective cohort study using administrative claims data on all discharges from emergency departments and acute care hospitals at nonfederal health care facilities in California. The California Office of Statewide Health Planning and Development collects these data and provides them in a deidentified format to the Agency for Healthcare Quality and Research for its Healthcare Cost and Utilization Project.<sup>16,17</sup> A unique linkage number allows each patient to be followed up over multiple years across emergency department encounters and hospitalizations, although data on outpatient visits are lacking.<sup>18</sup> Up to 25 discharge diagnoses are coded at each encounter using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*, with each diagnosis labeled as having been present before hospital admission or having newly developed during the hospitalization.<sup>19</sup> Because this publicly available database included only deidentified data, the Weill Cornell Medical College institutional review board certified our analysis as exempt from review.

### Patients

Our cohort consisted of adult patients who underwent inpatient surgery between January 1, 2007, and December 31,

2010. These dates were chosen because present-on-admission codes first became available in this data set in 2007, and the latest available data were for 2011, thereby allowing at least 1 year of follow-up for all patients. Patients who did not undergo any inpatient surgery were excluded from our cohort.

We defined surgery as any hospitalization associated with a surgical diagnosis related group (DRG) code. In a sensitivity analysis, we limited our cohort to patients undergoing major surgery, defined as a DRG code with a mean length of stay of longer than 3 days, in accordance with the methods of prior studies in this field.<sup>5</sup> Due to changes in DRG classifications over the years covered by our study, we used DRG version 24 for all years to ensure consistency.<sup>20</sup> We used major diagnostic categories for eligible surgeries, and used DRG codes to further subcategorize operations related to the circulatory system into cardiac procedures, percutaneous cardiac procedures, and vascular procedures (eTable in the Supplement). In our primary analysis, we excluded percutaneous cardiac procedures and surgeries related to pregnancy because these are not typically included in studies of perioperative vascular outcomes<sup>21</sup>; however, we performed sensitivity analyses that both separately and together added patients undergoing these procedures to our primary cohort. Given the potentially unique mechanisms of perioperative AF in the setting of cardiac surgery,<sup>22</sup> all analyses considered patients undergoing cardiac surgery separately from patients undergoing other surgery.

Because we were interested in new-onset perioperative AF, we excluded patients with any AF diagnoses recorded during encounters prior to the index hospitalization for surgery, or with AF labeled as present on admission during the index hospitalization for surgery. Atrial fibrillation was defined as ICD-9-CM codes 427.3x listed in any discharge diagnosis position. Present-on-admission codes in these California administrative claims databases have been validated to have a sensitivity of 88% and a specificity of 86%,<sup>23</sup> and the specific present-on-admission codes for AF have been validated to have a 90% concordance with either the presence of AF or any history of AF as ascertained by medical record review.<sup>24</sup>

We excluded patients with documented cerebrovascular disease (ICD-9-CM codes 430-438) before or during the index hospitalization for surgery because we were interested in the long-term risk of incident stroke after perioperative AF and because it can be difficult to determine whether a perioperative stroke was caused by AF or other perioperative factors.<sup>25</sup> For similar reasons, we excluded patients who died during the index hospitalization for surgery. Our final cohort comprised patients who were hospitalized for surgery and were discharged alive and free of any documented cerebrovascular disease or documented preexisting AF.

### Measurements

Our primary predictor variable was perioperative AF, defined as ICD-9-CM codes 427.3x listed in any discharge diagnosis position and labeled as not present on admission during the index hospitalization for surgery (ie, AF newly arising during the hospitalization). To further ensure that perioperative AF di-

**Table 1. Baseline Characteristics of Patients Undergoing Surgery, Stratified by the Occurrence of Perioperative Atrial Fibrillation<sup>a</sup>**

	Perioperative Atrial Fibrillation	
	Yes (n = 24 711)	No (n = 1 704 649)
Age, mean (SD), y	71.5 (11.8)	56.2 (17.2)
Female sex	10 121 (41.0)	1 014 442 (59.5)
Race/ethnicity <sup>b</sup>		
White	17 965 (74.9)	1 036 554 (64.7)
Black	779 (3.3)	103 311 (6.5)
Hispanic	2680 (11.2)	333 785 (20.8)
Asian	2033 (8.5)	98 960 (6.2)
Other	525 (2.2)	29 996 (1.9)
Payment source <sup>c</sup>		
Medicare	16 780 (67.9)	582 448 (34.2)
Medicaid	1247 (5.1)	160 910 (9.4)
Private	5889 (23.8)	788 227 (46.2)
Self-pay	234 (1.0)	53 670 (3.2)
Other	559 (2.3)	119 205 (7.0)
Vascular risk factors		
Hypertension	17 761 (71.9)	740 464 (43.4)
Diabetes	8246 (33.4)	323 327 (19.0)
Coronary heart disease	12 431 (50.3)	177 169 (10.4)
Congestive heart failure	6599 (26.7)	59 174 (3.5)
Chronic kidney disease	3901 (15.8)	94 204 (5.5)
Chronic obstructive pulmonary disease	4342 (17.6)	93 344 (5.5)
Peripheral vascular disease	3546 (14.4)	68 036 (4.0)
Cardiac surgery	11 837 (47.9)	61 706 (3.6)
Noncardiac surgery	12 874 (52.1)	1 642 943 (96.4)
Nervous system	268 (1.1)	35 915 (2.1)
Respiratory system	1337 (5.4)	35 992 (2.1)
Digestive system	945 (3.8)	179 619 (10.5)
Hepatobiliary system and pancreas	929 (3.8)	132 059 (7.8)
Musculoskeletal system and connective tissue	4388 (17.8)	580 555 (34.1)
Kidney and urinary tract	547 (2.2)	60 980 (3.6)
Female reproductive system	400 (1.6)	234 854 (13.8)
Vascular surgery	420 (1.7)	38 774 (2.3)
Miscellaneous	3640 (14.7)	344 195 (20.2)

<sup>a</sup> Data are presented as number (%) unless otherwise indicated.

<sup>b</sup> Self-reported by patients or their surrogates. Numbers do not sum to group totals because of missing data in 5.9% of patients.

<sup>c</sup> Numbers do not sum to group totals because of missing data in 0.01% of patients.

agnoses represented truly new diagnoses of AF, we excluded patients with perioperative AF diagnoses if they had any AF diagnoses recorded during encounters prior to the index hospitalization for surgery. To further increase our ability to capture preexisting AF diagnoses, we performed a sensitivity analysis restricted to patients who had at least 1 encounter during the year prior to surgery and were free of any AF diagnoses during those encounters.

Our main outcome variable was ischemic stroke defined as ICD-9-CM codes 433.x1, 434.x1, or 436 in any hospital discharge diagnosis position without a primary discharge code for

rehabilitation (ICD-9-CM code V57) or any accompanying diagnoses of subarachnoid hemorrhage (ICD-9-CM code 430), intracerebral hemorrhage (ICD-9-CM code 431), or trauma (ICD-9-CM codes 800-804 and 850-854). This algorithm has been validated as 86% sensitive and 95% specific for ischemic stroke, and identifies cases that are 88% probable for incident stroke.<sup>26</sup>

To control for potential confounders in the relationship between perioperative AF and stroke, we adjusted for age, sex, race, insurance status, and the following cardiovascular comorbidities previously reported as risk factors for stroke or perioperative AF: hypertension, diabetes mellitus, coronary heart disease, congestive heart failure, peripheral vascular disease, chronic kidney disease, and chronic obstructive pulmonary disease.<sup>5,6,11</sup>

### Statistical Analysis

Descriptive statistics with exact confidence intervals were used to report crude rates. We used Kaplan-Meier survival statistics to calculate cumulative rates of stroke after surgery. Patients entered observation upon discharge from their first recorded hospitalization for surgery, and were censored at the time of stroke or death, or on December 31, 2011. Because clinically apparent AF is a recognized risk factor for stroke, we also censored patients at the time of postdischarge encounters with any recorded diagnosis of AF. Additionally, we censored patients at the time of a second surgery to avoid including perioperative strokes among incident strokes during follow-up. To allow comparisons with other cohorts, we calculated cumulative rates of stroke stratified by the CHA<sub>2</sub>DS<sub>2</sub>VASc score, a widely used instrument with moderate predictive value for thromboembolism in AF.<sup>27</sup>

Cox proportional hazards analysis was used to examine the association between perioperative AF and subsequent stroke while controlling for the potential confounders listed above. The model was separately applied to patients undergoing cardiac surgery vs those undergoing noncardiac surgery; a combined model was used to check the interaction between cardiac vs noncardiac surgery and perioperative AF in relation to stroke risk. We verified the proportional hazards assumption by checking the interaction between perioperative AF and time from surgery. Because our goal was to isolate the relationship between perioperative AF and stroke rather than to create a parsimonious prediction model, we left all covariates in the model regardless of their statistical significance; our findings were unchanged in sensitivity analyses with backward stepwise elimination of covariates not associated with the outcome at a significance level of  $P < .20$ .

To address the possibility of residual confounding, we performed sensitivity analyses that included the Elixhauser comorbid conditions as additional covariates.<sup>28</sup> Lastly, to explore the mechanistic plausibility of heightened stroke risk from perioperative AF, which would be expected to result specifically in cardioembolic stroke, we examined the association between perioperative AF and ICD-9-CM code 434.11, which has a specificity of 73% for embolic stroke subtypes.<sup>29</sup> Post hoc analyses examined the association between perioperative AF and stroke in subgroups defined by age (<65 years vs ≥65 years), sex, race (white vs nonwhite), CHA<sub>2</sub>DS<sub>2</sub>VASc score

(0 vs  $\geq 1$ ), and whether cardioversion was performed during the index hospitalization.

All significance testing was 2-sided, and the threshold of statistical significance was set at a level of .05. All statistical analyses were performed using Stata version 13 (StataCorp).

## Results

We included 1 729 360 eligible patients with a mean follow-up time of 2.1 years (SD, 1.3 years). Among these patients, perioperative AF was documented in 24 711 cases (1.43%; 95% CI, 1.41%-1.45%). Perioperative AF occurred much more commonly in the setting of cardiac surgery (16.10%) than in other types of surgery (0.78%;  $P < .001$ ). Patients with perioperative AF carried a greater baseline burden of vascular comorbidities (Table 1). After noncardiac surgery, cumulative 1-year rates of postdischarge encounters with a recorded diagnosis of AF were 37.28% (95% CI, 36.43%-38.15%) in those with perioperative AF and 1.51% (95% CI, 1.49%-1.52%) in those without AF; rates after cardiac surgery were 22.22% (95% CI, 21.47%-22.99%) in those with perioperative AF and 4.65% (95% CI, 4.48%-4.82%) in those without AF.

After discharge from the index hospitalization for surgery, 13 952 patients (crude rate, 0.81%; 95% CI, 0.79%-0.82%) went on to experience an ischemic stroke. Compared with patients who remained free of stroke, those with stroke were older and had a greater number of vascular comorbidities at baseline (Table 2). The risk of stroke varied in proportion to baseline CHA<sub>2</sub>DS<sub>2</sub>VASc scores (Table 3). At 1 year after hospitalization for noncardiac surgery, cumulative rates of stroke were 1.47% (95% CI, 1.24%-1.75%) in those with perioperative AF and 0.36% (95% CI, 0.35%-0.37%) in those without AF (Figure 1; eFigure 1 in the Supplement). At 1 year after cardiac surgery, cumulative rates of stroke were 0.99% (95% CI, 0.81%-1.20%) in those with perioperative AF and 0.83% (95% CI, 0.76%-0.91%) in those without AF (Figure 2; eFigure 2 in the Supplement).

In Cox proportional hazards analyses accounting for potentially confounding factors, perioperative AF remained associated with stroke both after noncardiac surgery (hazard ratio [HR], 2.0; 95% CI, 1.7-2.3) and cardiac surgery (HR, 1.3; 95% CI, 1.1-1.6). The association was significantly stronger for perioperative AF after noncardiac surgery than after cardiac surgery ( $P < .001$  for interaction). Limiting the outcome to the embolic stroke diagnosis code further strengthened the association between perioperative AF and stroke both in the setting of noncardiac surgery (HR, 4.9; 95% CI, 3.5-6.7) and cardiac surgery (HR, 2.1; 95% CI, 1.4-3.1).

Our findings were not substantially changed in sensitivity analyses that accounted for the Elixhauser comorbidity index; included percutaneous cardiac procedures, obstetrical procedures, or both; or were limited to operations with an average length of stay longer than 3 days or to patients with at least 1 encounter in the year prior to surgery. We found no significant evidence of variation in the association between perioperative AF and stroke across subgroups defined by age, sex, race, baseline stroke risk, or whether cardioversion was performed during the index hospitalization.

**Table 2. Baseline Characteristics of Patients Undergoing Surgery, Stratified by the Occurrence of Ischemic Stroke After Discharge<sup>a</sup>**

	Ischemic Stroke After Discharge	
	Yes (n = 13 952)	No (n = 1 715 408)
Age, mean (SD), y	69.9 (14.0)	56.4 (17.2)
Female	7644 (54.8)	1 016 919 (59.3)
Race/ethnicity <sup>b</sup>		
White	8684 (64.6)	1 045 835 (64.8)
Black	1219 (9.1)	102 871 (6.4)
Hispanic	2458 (18.3)	334 007 (20.7)
Asian	856 (6.4)	100 137 (6.2)
Other	223 (1.7)	30 298 (1.9)
Payment source <sup>c</sup>		
Medicare	9184 (65.8)	590 044 (34.4)
Medicaid	1193 (8.6)	160 964 (9.4)
Private	2861 (20.5)	791 255 (46.1)
Self-pay	239 (1.7)	53 665 (3.1)
Other	473 (3.4)	119 291 (7.0)
Vascular risk factors		
Hypertension	9916 (71.1)	748 309 (43.6)
Diabetes	5016 (36.0)	326 557 (19.0)
Coronary heart disease	3648 (26.2)	185 952 (10.8)
Congestive heart failure	1559 (11.2)	64 214 (3.7)
Chronic kidney disease	2108 (15.1)	95 997 (5.6)
Chronic obstructive pulmonary disease	1578 (11.3)	96 108 (5.6)
Peripheral vascular disease	1481 (10.6)	70 101 (4.1)
CHA <sub>2</sub> DS <sub>2</sub> VASc score, median (IQR) <sup>d</sup>	3 (2-4)	1 (1-3)

Abbreviation: IQR, interquartile range.

<sup>a</sup> Data are presented as number (%) unless otherwise indicated.  $P < .001$  for all comparisons.

<sup>b</sup> Self-reported by patients or their surrogates. Numbers do not sum to group totals because of missing data in 5.9% of patients.

<sup>c</sup> Numbers do not sum to group totals because of missing data in 0.01% of patients.

<sup>d</sup> Assigns 2 points each for age of 75 years or older, prior stroke, or transient ischemic attack; and 1 point each for hypertension, diabetes, peripheral vascular disease, age of 65 to 74 years, or female sex. This score has been shown to have moderate predictive value for thromboembolism in atrial fibrillation.<sup>27</sup>

## Discussion

In a large cohort of patients undergoing inpatient surgery, we found a significant association between perioperative AF and the long-term risk of ischemic stroke, even after controlling for potential confounders and censoring patients at the time of postdischarge AF diagnoses. The strength of this association was significantly greater for perioperative AF that occurred in the setting of noncardiac surgery rather than cardiac surgery.

Most studies of perioperative AF and stroke have focused on the early risk of stroke after cardiac surgery,<sup>7-9,30-33</sup> whereas we focused on the long-term risk of stroke after the immediate perioperative period. Analyses of long-term stroke risk after cardiac surgery have lacked population-based samples and

Table 3. Cumulative 1-Year Rates of Ischemic Stroke in Patients With Perioperative Atrial Fibrillation

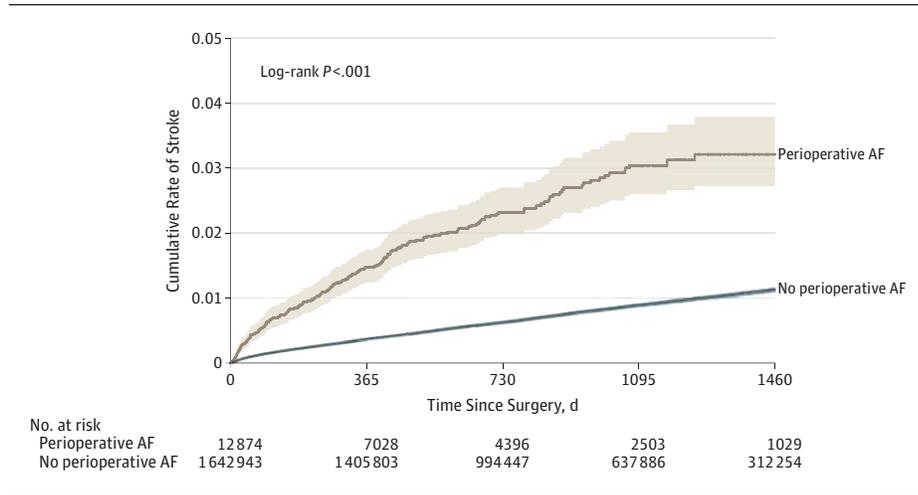
CHA <sub>2</sub> DS <sub>2</sub> VASc Score <sup>a</sup>	Perioperative Atrial Fibrillation Associated With Surgery					
	Cardiac (n = 11 837)			Noncardiac (n = 12 874)		
	No. of Patients	No. of Strokes	Cumulative 1-y Rate of Stroke (95% CI), % <sup>b</sup>	No. of Patients	No. of Strokes	Cumulative 1-y Rate of Stroke (95% CI), % <sup>b</sup>
0	352	3	1.0 (0.3-3.0)	596	2	0.5 (0.1-1.8)
1	1308	10	0.9 (0.5-1.6)	1382	7	0.7 (0.3-1.4)
2	2539	16	0.7 (0.4-1.2)	2407	16	1.0 (0.6-1.6)
3	3089	23	0.9 (0.6-1.3)	3259	36	1.6 (1.1-2.2)
4	2661	28	1.3 (0.9-1.9)	3185	44	2.0 (1.5-2.7)
5	1402	13	1.2 (0.7-2.1)	1596	19	1.9 (1.2-3.0)
6	447	6	1.9 (0.9-4.3)	404	7	2.7 (1.3-5.7)
7	39	0	NA <sup>c</sup>	45	1	2.9 (0.4-18.6)

<sup>a</sup> Assigns 2 points each for age of 75 years or older, prior stroke, or transient ischemic attack; and 1 point each for hypertension, diabetes, peripheral vascular disease, age of 65 to 74 years, or female sex. This score has been shown to have moderate predictive value for thromboembolism in atrial fibrillation.<sup>27</sup> No patient had a score of greater than 7 because patients with stroke or transient ischemic attack at baseline were excluded.

<sup>b</sup> Patients were censored at the time of postdischarge encounters with a recorded atrial fibrillation diagnosis.

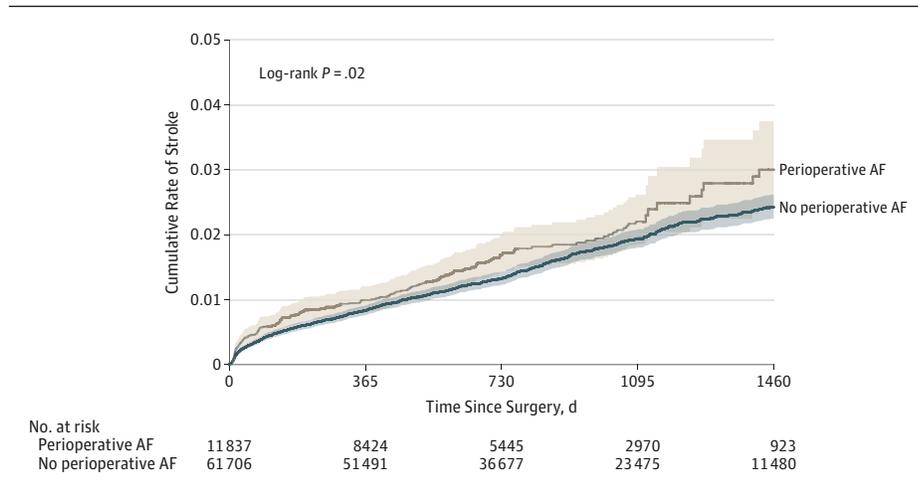
<sup>c</sup> Rate could not be calculated due to insufficient numbers of patients in this stratum.

Figure 1. Cumulative Rates of Ischemic Stroke After Hospitalization for Noncardiac Surgery



Rates of stroke differed significantly depending on the occurrence of perioperative atrial fibrillation (AF) during the index hospitalization for surgery. Patients were censored at the time of postdischarge encounters with a recorded AF diagnosis.

Figure 2. Cumulative Rates of Ischemic Stroke After Hospitalization for Cardiac Surgery



Rates of stroke differed significantly depending on the occurrence of perioperative atrial fibrillation (AF) during the index hospitalization for surgery. Patients were censored at the time of postdischarge encounters with a recorded AF diagnosis.

have reported conflicting results.<sup>11-15</sup> To our knowledge, little population-based data exist on the long-term risk of stroke in patients with perioperative AF after noncardiac surgery. Despite the paucity of prior data from surgical populations, several other studies support the validity of our findings. Cardiac operations, especially procedures involving pericardiotomy, frequently provoke an isolated form of AF that appears to be a directly induced response to surgery.<sup>34</sup> However, in the absence of this type of direct cardiac manipulation, transient AF may reflect an increased predisposition to stroke. An analysis of patients with recently implanted pacemakers or defibrillators found that a single 6-minute episode of subclinical AF was sufficient to increase the risk of subsequent stroke.<sup>35,36</sup> This may be true even when AF is provoked by physiological stress; for example, new-onset AF in patients hospitalized with severe sepsis has been associated with both the short-term and long-term risk of stroke.<sup>24</sup> These considerations are consistent with our finding of a significantly stronger association between perioperative AF and stroke in patients undergoing noncardiac surgery than in those undergoing cardiac surgery.

Our study has several limitations. First, we were unable to determine the duration of perioperative AF episodes, and the relatively low rate of perioperative AF in our study compared with prior studies of cardiac surgery<sup>4</sup> raises the possibility of underascertainment of perioperative AF. Therefore, it may be that our findings do not pertain to very brief, self-terminating episodes of perioperative AF, and that the aggregate risk might be highly concentrated among individuals with persistent AF postsurgery. On the other hand, although a lack of outpatient data prevented us from censoring patients at the time of ambulatory encounters for AF, we found an association with stroke even after censoring patients at the time of postdischarge emergency department visits or hospitalizations with a recorded AF diagnosis. This suggests that our study included many perioperative AF cases that were transient, and that clinically apparent recurrences of AF may not completely mediate our findings.

Second, without outpatient data, we may have misclassified cases of previously diagnosed AF as perioperative AF, and therefore the aggregate risk might be highly concentrated among patients with a prior history of AF not detected by our data. However, present-on-admission codes appear to reliably differentiate newly diagnosed AF from AF recurrence in those with a history of AF.<sup>24</sup> Furthermore, our results were unchanged in sensitivity analyses designed to further augment our ability to ascertain preexisting AF by restricting our cohort to patients who had at least 1 encounter during the year prior to surgery and were free of any AF diagnoses during those encounters. Similarly, some cases labeled as perioperative AF may have represented previously undiagnosed AF that predated the index hospitalization, but even in this case, our find-

ings would still suggest that AF that comes to light for the first time during a hospitalization for surgery predisposes patients to subsequent stroke.

Third, some cases of subclinical AF may have been missed entirely during the hospitalization for surgery, but such non-differential misclassification of cases would be expected to bias our study toward the null.

Fourth, we lacked data on the means of ascertainment of perioperative AF diagnoses, and it is possible that relatively sicker patients underwent more intensive cardiac monitoring in the perioperative setting, resulting in ascertainment bias that may have artificially inflated the association between perioperative AF and stroke. This is unlikely to completely account for our results because a sensitivity analysis controlling for the Elixhauser comorbidity index did not materially affect the strength of the association between perioperative AF and subsequent stroke.

Fifth, given the lack of data on medication use, we were unable to account for antithrombotic treatments that could have influenced rates of stroke. However, this would be expected to bias our findings in a conservative direction because some patients with perioperative AF were presumably treated with anticoagulant drugs that would have reduced their risk of stroke.

Sixth, the association between perioperative AF and subsequent stroke would have been made more plausible by demonstrating a specific association between perioperative AF and cardioembolic stroke, but we were unable to assign definitive stroke subtypes because we did not have direct access to patient charts. However, we found an even stronger association between perioperative AF and a stroke diagnosis code that is fairly specific for embolic stroke.

Our results may have significant implications for the care of perioperative patients. The associations we found suggest that while many cases of perioperative AF after cardiac surgery may be an isolated response to the stress of surgery, perioperative AF after noncardiac surgery may be similar to other etiologies of AF in regard to future thromboembolic risk. Our results suggest the need for future studies involving long-term ambulatory cardiac monitoring to better delineate the risk associated with transient vs persistent perioperative AF, as well as randomized clinical trials to determine optimal strategies for antithrombotic therapy in patients with perioperative AF and a significant burden of other risk factors for stroke.

## Conclusions

Among patients hospitalized for surgery, perioperative AF was associated with an increased long-term risk of ischemic stroke, especially following noncardiac surgery.

### ARTICLE INFORMATION

**Author Contributions:** Dr Kamel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Gialdini, Bhavne, Iadecola, Kamel.

*Acquisition, analysis, or interpretation of data:* Gialdini, Nearing, Bhavne, Bonuccelli, Healey, Kamel.

*Drafting of the manuscript:* Gialdini, Nearing, Iadecola.

*Critical revision of the manuscript for important intellectual content:* Gialdini, Bhavne, Bonuccelli, Healey, Kamel.

**Statistical analysis:** Bhavé, Kamel.

**Obtained funding:** Iadecola, Kamel.

**Administrative, technical, or material support:** Nearing, Bhavé, Kamel.

**Study supervision:** Gialdini, Bonuccelli, Iadecola, Kamel.

**Conflict of Interest Disclosures:** The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Healey reported receiving research grants from Medtronic, St Jude Medical, Boston Scientific, Boehringer-Ingelheim, and Bristol-Myers Squibb; and serving on advisory boards for Boehringer-Ingelheim and Bayer. Dr Kamel reported serving on a medical advisory board and a speakers bureau for Genentech. No other disclosures were reported.

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**Role of the Sponsors:** The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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