Atrial fibrillation (AF) is the most common cardiac arrhythmia and an independent risk factor for stroke and death. Oral anticoagulation (OAC) can reduce the risk of stroke by 64% and the risk of mortality by 26%. In some cases, AF is newly detected during a hospitalization for surgery. It is unclear whether AF encountered in this setting is associated with an increased long-term risk of stroke. Thus, uncertainty exists as to whether perioperative AF associated with noncardiac surgery poses a long-term risk of stroke and whether this risk can be reduced by long-term OAC therapy. The paucity of recommendations regarding the management of perioperative AF after noncardiac surgery in clinical practice guidelines reflects the lack of definitive data in this area.

Estimates of the incidence of postoperative AF in patients undergoing noncardiac surgery have ranged from 0.4% to 35%, depending on the type of surgery, patient population, and the method of detection. Perioperative AF has been associated with longer hospital stays, increased in-hospital mortality, and a short-term increase in the risk of stroke. However, the long-term implications of this arrhythmia are less well defined. Recent studies have shown that a large proportion of patients with postoperative AF may have recurrent AF episodes detected in the months and years after their index hospitalization, and an ongoing
perioperative AF and the risk of stroke and death occurring beyond 30 days after noncardiac surgery. Reference screening, study selection, data extraction, and quality assessment were performed in duplicate. Data were pooled using inverse variance-weighted random-effects models and presented as risk ratios (RRs).

Results: From 7344 citations, we included 31 studies (3,529,493 patients). The weighted mean incidence of perioperative AF was 0.7%. During a mean follow-up of 28.1 ± 9.4 months, perioperative AF was associated with an increased risk of stroke (1.5 vs 0.9 strokes per 100 patient-years; RR: 2.9, 95% confidence interval [CI]: 2.1-3.9, $I^2 = 78\%$). Perioperative AF was also associated with a significantly higher risk of all-cause mortality (21.0 vs 7.6 deaths per 100 patient-years; RR: 1.8, 95% CI: 1.5-2.2, $I^2 = 94\%$). The pooled adjusted hazard ratios for stroke and all-cause mortality were 1.9 (95% CI: 1.6-2.2, $I^2 = 31\%$) and 1.5 (95% CI: 1.3-1.7, $I^2 = 20\%$), respectively.

Conclusions: Patients who had perioperative AF after noncardiac surgery had a higher long-term risk of stroke and mortality compared with patients who did not. Whether this risk is modifiable with oral anticoagulation therapy should be investigated.

Methodology: Des recherches ont été effectuées dans MEDLINE et EMBASE depuis leur création jusqu’à mars 2020 pour y relever les études signalant l’association entre la FA périopératoire et le risque d’accident vasculaire cérébral et de décès survenant au-delà de 30 jours à la suite d’une chirurgie non cardiaque. Le tri des références, la sélection des études, l’extraction des données et l’évaluation de la qualité ont été effectués en double. Les données ont été regroupées à l’aide de modèles à effets aléatoires pondérés par l’inverse de la variance et présentées sous forme de rapports de risques relatifs (RR).

Résultats: Parmi 7,344 références, nous avons inclus 31 études (3,529,493 patients). L’incidence moyenne pondérée de FA périopératoire était de 0.7 %. Dans le cadre d’un suivi moyen de 28.1 ± 9.4 mois, la FA périopératoire était associée à un risque accru d’accident vasculaire cérébral (1.5 vs 0.9 accident vasculaire cérébral par 100 années-patients; RR de 2.9; intervalle de confiance [IC] à 95 %; de 2.1 à 3.9; $I^2 = 78 \%$). La FA périopératoire était également associée à un risque considérablement plus élevé de décès toutes causes confondues (21.0 vs 7.6 décès par 100 années-patients; RR de 1.8; IC à 95 %; de 1.5 à 2.2; $I^2 = 94 \%$). Les rapports de risques instantanés ajustés regroupés d’accident vasculaire cérébral et de décès toutes causes confondues étaient de 1.9 (IC à 95 %; de 1.6 à 2.2; $I^2 = 31 \%$) et de 1.5 (IC à 95 %; de 1.3 à 1.7; $I^2 = 20 \%$), respectivement.

Conclusions: Les patients qui souffraient de FA périopératoire à la suite d’une chirurgie non cardiaque présentaient un risque accru à long terme d’accident vasculaire cérébral et de décès par rapport aux patients qui n’en souffraient pas. Il serait approprié d’examiner la possibilité de modifier ce risque par une anticoagulothérapie orale.

Eligibility criteria

We included studies that reported on the association between perioperative AF detected after noncardiac surgery and the risk of stroke and/or death, occurring either after the index hospitalization or more than 30 days after the date of surgery. Perioperative AF was defined as AF that occurred during a hospitalization for noncardiac surgery. We excluded studies with ≤ 10 patients.

Outcomes

The primary outcome was stroke and the secondary outcome was all-cause mortality. We included haemorrhagic, ischemic, and unspecified strokes—as defined by study authors.

Data collection and analysis

Pairs of reviewers independently screened study titles and abstracts for eligibility; if either reviewer thought that the abstract was potentially eligible, it was selected for full-text review. Full papers of potentially eligible studies were retrieved. Pairs of reviewers then independently screened full texts in duplicate and recorded the main reason for exclusion. Disagreements were resolved through discussion or third-party arbitration. The studies were then assessed independently and in duplicate for risk of bias using the CLARITY tool.

Data extraction and management

Independently, 2 reviewers abstracted data on study outcomes. They also recorded study and patient characteristics including age, sex, cardiovascular comorbidities and risk factors,
operation type, and use of OAC. Results were then compared and disagreements were resolved by discussion or a third reviewer if needed. Authors were contacted to clarify ambiguities and to request data on additional data from primary reports. Data in studies published in foreign languages were extracted by reviewers who could understand the language.

**Data synthesis**

We used Review Manager 5.3 (Cochrane Collaboration) to perform the meta-analysis. We calculated risk ratios (RRs) from the dichotomous data using the inverse variance method. We assessed all data pertaining to the identified outcomes for clinical and statistical heterogeneity. We also assessed statistical heterogeneity using $I^2$. We considered an $I^2$ greater than 50% as showing substantial heterogeneity. We then analyzed data quantitatively using a random-effects model and presented them as RRs with 95% confidence intervals (CI). We pooled hazard ratios (HRs) using the generic inverse variance method with data from studies that reported adjusted HRs. The data were then analyzed using a random-effects model and presented with 95% CI.

**Subgroup analyses**

We performed prespecified subgroup analyses, assessing the risks of stroke and death according to type of surgery (ie, based on the major body system under operation). We could not perform prespecified subgroup analyses according to use of OAC therapy and age (<65 vs ≥65 years) as these data were not available.

**Assessment of the quality of the evidence**

We evaluated the quality of evidence using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach. In this framework, observational studies begin as low-quality evidence. GRADE appraises the confidence in estimates of effect by considering within-study risk of bias, directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. We inspected the funnel plots of standard errors vs effect estimates for publication bias and small-study effects.

**Results**

**Search results and study selection**

We identified a total of 7356 unique citations, from which 193 full texts were screened (Supplemental Fig. S1). Thirty-one cohort studies met inclusion criteria and were included in the meta-analysis (Supplemental Table S1): 25 retrospective and 6 prospective. Six cohort studies included all major noncardiac surgeries, whereas the others focused on 1 subtype of surgery: thoracic, orthopaedic, gastrointestinal, and vascular. Data on the occurrence of outcomes of interest were available for 3,529,727 patients over a mean follow-up of 28.1 ± 9.4 months. Previously unpublished data were obtained from 3 studies. The weighted mean incidence of perioperative AF was 0.7%; rates in individual studies ranged from 0.3% to 46%. Baseline Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack (CHADS2) scores of included patients were available in 6 studies.

**Figure 1** summarizes the key findings from the meta-analysis.

**Stroke**

Eight studies, including 3,497,285 patients, reported long-term incidence of stroke (Fig. 1). Over a mean follow-up of 28.2 ± 9.7 months, more patients in whom perioperative AF was detected experienced a stroke as compared with patients without perioperative AF (1.5 vs 0.9/100 patient-years; unadjusted RR: 2.9, 95% CI: 2.1-3.9, $I^2 = 78$%). The absolute risk increase for stroke in patients with perioperative AF was 0.6/100 patient-years. Pooled results from the 4 studies including 2,992,286 patients who reported adjusted HRs were adjusted HR: 1.9, 95% CI: 1.6-2.2, $I^2 = 31$% (Fig. 2; Supplemental Table S2). Data on 48,417 patients who underwent thoracic surgery were available from 4 studies with a mean follow-up of 25.3 ± 1.6 months (Table 1 and Supplemental Fig. S2). The absolute risk increase of stroke was 0.1/100 patient-years for patients with new onset-AF (0.15 vs 0.03 per 100 patient-years; RR: 1.4, 95% CI: 1.0-1.9, $I^2 = 0$%). Data on 957,317 patients who underwent orthopaedic surgery were available from 2 studies with a mean follow-up of 24.5 ± 1.8 months. The absolute risk increase of stroke was 1.0 per 100 patient-years for patients with perioperative AF (2.4 vs 1.4 per 100 patient-years; RR: 4.1, 95% CI: 1.1-15.4, $I^2 = 96$%).

**All-cause death**

Twenty-nine studies, including 1,367,009 patients, reported data on mortality beyond 30 days after surgery (Fig. 1). The mortality rate over a mean follow-up of 37.6 ± 4.9 months was higher in patients with perioperative AF compared with those without perioperative AF (21.0 vs 7.6 per 100 patient-years; unadjusted RR: 1.8, 95% CI: 1.5-2.2, $I^2 = 94$%). The absolute risk increase for mortality in patients who experienced perioperative AF was 13.4 per 100 patient-years. Pooled results from the 10 studies including 1,356,157 patients who reported adjusted HRs were similar (adjusted HR: 1.5, 95% CI: 1.3-1.7, $I^2 = 20$%) (Fig. 2).

Data on 253,218 patients who underwent oesophageal surgery were available from 7 studies with a mean follow-up of 38.4 ± 1.9 months (Supplemental Fig. S3). The absolute risk increase for mortality was 10.9 per patient 100 patient-years for patients with perioperative AF (18.3 vs 7.4 per 100 patient-years; RR: 1.7, 95% CI: 1.1-2.7, $I^2 = 89$%). Data on 3448 patients who underwent liver transplantation were available from 3 studies with a mean follow-up of 9.6 ± 3.6 months. The absolute risk increase for mortality was 17.1 per 100 patient-years for patients with perioperative AF (31.6 vs 14.5 per 100 patient-years; RR: 2.6, 95% CI: 1.9-3.7, $I^2 = 37$%). Data from 459,671 patients who underwent orthopaedic surgery were available from 4 studies with a mean follow-up of 38.1 ± 3.4 months. The absolute risk increase for mortality was 15.5 per 100 patient-years for patients with perioperative AF (24.2 vs 8.8 per 100 patient-years; RR: 2.8, 95% CI: 2.1-3.5, $I^2 = 89$%). Data from 20,889 patients who underwent thoracic surgery were available from 10 studies over a mean
A Stroke

| Study or Subgroup  | Perioperative AF Events | Total Events | Total Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|--------------------|------------------------|--------------|--------------|-------------------------------|-------------------------------|
| Butt 2018          | 516                    | 4268         | 66190        | 1313174                       | 26.7% 2.40 [2.21, 2.60]       |
| Chakriangkrai 2015 | 2                      | 73           | 1            | 220                           | 1.5% 6.03 [0.55, 65.51]       |
| Conen 2019         | 7                      | 403          | 123          | 17713                         | 10.1% 2.50 [1.17, 5.31]       |
| Gialdini 2014      | 132                    | 12874        | 5915         | 1642943                       | 25.0% 2.85 [2.40, 3.38]       |
| Higuchi 2019       | 2                      | 77           | 3            | 675                           | 2.6% 5.84 [0.99, 34.43]       |
| Imperatori 2012    | 2                      | 45           | 7            | 459                           | 3.4% 2.60 [0.56, 12.13]       |
| Khoromaei 2018     | 15                     | 3648         | 250          | 499854                        | 15.0% 8.23 [4.89, 13.84]      |
| Siontis 2018       | 34                     | 455          | 26           | 455                           | 15.7% 1.31 [0.60, 2.14]       |

Total (95% CI) 21642 3475443 100.0% 2.86 [2.12, 3.87]

Data from 46,928 patients who underwent vascular surgery were available from 4 studies over a mean follow-up of 29.6 ± 14.2 months. The absolute risk increase for mortality was 8.5 per 100 patient-years for patients with perioperative AF (23.8 vs 15.3 per 100 patient-years; RR: 1.7, 95% CI: 1.2-2.4, I² = 93%).

Methodological quality of individual studies

The overall methodological quality (risk of bias) of included studies was moderate (Supplemental Table S3).

B All-Cause Mortality

| Study or Subgroup  | Perioperative AF Events | Total Events | Total Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|--------------------|------------------------|--------------|--------------|-------------------------------|-------------------------------|
| Booka 2017         | 22                     | 42           | 144          | 360                           | 4.1% 1.31 [0.96, 1.79]        |
| Branch 2012        | 50                     | 108          | 89           | 211                           | 4.3% 1.10 [0.85, 1.42]        |
| Butt 2018          | 2773                   | 4268         | 316503       | 1313174                       | 4.7% 2.70 [2.64, 2.76]        |
| Cardinale 1999     | 5                      | 28           | 33           | 205                           | 2.3% 1.11 [0.47, 2.60]        |
| Chakriangkrai 2015 | 22                     | 73           | 42           | 220                           | 3.7% 1.58 [1.01, 2.46]        |
| Chin 2018          | 29                     | 63           | 176          | 520                           | 4.2% 1.36 [1.01, 1.82]        |
| Conen 2019         | 46                     | 404          | 957          | 17713                         | 4.2% 2.11 [1.59, 2.79]        |
| Day 2016           | 2                      | 31           | 5            | 83                            | 1.0% 1.07 [0.22, 5.24]        |
| Goodman 2007       | 37                     | 52           | 170          | 484                           | 4.4% 2.03 [1.64, 2.50]        |
| Higuchi 2019       | 3                      | 77           | 32           | 675                           | 1.6% 0.82 [0.26, 2.62]        |
| Imperatori 2012    | 29                     | 42           | 270          | 405                           | 4.4% 1.04 [0.84, 1.28]        |
| Isadiinso 2011     | 27                     | 62           | 9            | 75                            | 2.8% 3.63 [1.85, 7.13]        |
| Kothari 2016       | 135                    | 560          | 1415         | 14588                         | 4.5% 2.49 [2.13, 2.90]        |
| Leibowitz 2017     | 9                      | 15           | 73           | 385                           | 3.6% 3.25 [2.05, 5.15]        |
| Mason 2007         | 42                     | 68           | 162          | 265                           | 4.4% 1.01 [0.82, 1.29]        |
| McCormack 2014     | 19                     | 65           | 56           | 275                           | 3.6% 1.44 [0.92, 2.24]        |
| Moon 2018          | 6                      | 13           | 174          | 1046                          | 3.1% 2.77 [1.52, 5.07]        |
| Noranor 2009       | 2                      | 20           | 7            | 180                           | 1.1% 2.57 [0.57, 11.55]       |
| Orrego 2012        | 20                     | 93           | 43           | 273                           | 3.5% 1.37 [0.85, 2.20]        |
| Rachwan 2020       | 20                     | 94           | 55           | 908                           | 3.6% 3.51 [2.20, 5.50]        |
| Raghavan 2015      | 12                     | 46           | 12           | 85                            | 2.7% 1.85 [0.90, 3.78]        |
| Rostagno 2018      | 41                     | 104          | 607          | 2902                          | 4.3% 1.88 [1.47, 2.42]        |
| Siontis 2018       | 244                    | 455          | 193          | 455                           | 4.6% 1.26 [1.10, 1.45]        |
| Stawicki 2011      | 6                      | 32           | 0            | 124                           | 0.4% 49.24 [2.85, 851.93]     |
| Tao 2020           | 71                     | 101          | 444          | 2337                          | 4.5% 3.70 [3.18, 4.31]        |
| Uhm 2017           | 25                     | 45           | 29           | 102                           | 3.6% 1.95 [1.30, 2.93]        |
| Wells 2017         | 7                      | 27           | 11           | 61                            | 2.3% 1.44 [0.63, 3.30]        |
| Winkel 2010        | 38                     | 55           | 239          | 458                           | 4.4% 1.32 [1.08, 1.61]        |
| Xia 2015           | 24                     | 102          | 148          | 1285                          | 3.9% 2.04 [1.40, 2.99]        |

Total (95% CI) 7145 1359864 100.0% 1.80 [1.51, 2.15]

Figure 1. Risk of stroke and all-cause mortality in patients with and without perioperative atrial fibrillation after noncardiac surgery. AF, atrial fibrillation; CI, confidence interval.
The incidence of perioperative AF was significantly higher in prospective studies compared with retrospective studies (2.9% vs 0.7%, \( P < 0.001 \)); however, the RR for stroke and all-cause mortality did not differ significantly between study designs (Supplemental Table S4). There were 13 studies that either included pre-existing AF or did not mention whether patients with pre-existing AF were excluded. However, event rates between studies did not differ significantly (Supplemental Table S5). Seven studies reported on treatment with OAC. One study excluded patients on OAC and 2 adjusted for use of OAC in their analyses.

Quality of evidence

Visual inspection of funnel plots did not lead to concerns about publication bias (Supplemental Fig. S3).

### Table 1. Summary of meta-analysis findings of perioperative atrial fibrillation vs no perioperative atrial fibrillation after noncardiac surgery

| Outcome                     | Surgery subtype       | Number of studies | Total number of patients | Events | No events | Absolute risk (%) | Mean follow-up (mo) ± SD | RR (95% CI) | \( I^2 \) (%) |
|-----------------------------|-----------------------|-------------------|--------------------------|--------|----------|-------------------|---------------------------|-------------|-------------|
| **Stroke**                  | Any noncardiac        | 8                 | 3,497,285                | 710    | 72,515   | 1.2               | 28.2 ± 9.7                | 2.9 (2.1-3.9) | 78          |
|                             | Thoracic surgery      | 4                 | 48,417                   | 45     | 996      | 0.9               | 25.3 ± 1.6                | 1.4 (1.0-1.9) | 0           |
|                             | Orthopaedic surgery   | 2                 | 957,317                  | 201    | 26,942   | 1.1               | 24.5 ± 18.6               | 4.1 (1.1-15.4) | 96          |
| **All-cause mortality**     | Any noncardiac        | 29                | 1,367,009                | 3766   | 322,098  | 29.0              | 37.6 ± 4.9                | 1.8 (1.5-2.2) | 94          |
|                             | Esophageal surgery    | 7                 | 253,218                  | 84     | 59,484   | 35.4              | 38.4 ± 1.9                | 1.7 (1.1-2.7) | 89          |
|                             | Liver transplantation | 3                 | 3,448                    | 50     | 377      | 12.3              | 9.6 ± 3.6                 | 2.6 (1.9-3.7) | 37          |
|                             | Orthopaedic surgery   | 4                 | 459,671                  | 1203   | 127,717  | 42.8              | 38.1 ± 3.4                | 2.8 (2.1-3.5) | 89          |
|                             | Thoracic surgery      | 10                | 20,889                   | 536    | 7659     | 8.4               | 37.7 ± 7.7                | 1.3 (1.1-1.6) | 68          |
|                             | Vascular surgery      | 4                 | 46,928                   | 429    | 17,498   | 5.7               | 29.6 ± 14.2               | 1.7 (1.2-2.4) | 93          |

AF, atrial fibrillation; CI, confidence interval; RR, risk ratio; SD, standard deviation.
stroke and all-cause mortality, we judged that the quality of evidence according to the GRADE framework was low (Table 2). We made this judgement because the evidence consisted exclusively of observational studies and we did not detect any other major issues.

**Discussion**

In this systematic review and meta-analysis of 31 studies including 3,529,727 individuals, perioperative AF after noncardiac surgery was associated with significant increases in the long-term risks of stroke and death beyond 30 days after surgery. These observations were consistent across all surgical subtypes. These results support the need for trials to definitely assess the risks and benefits of OAC treatment in this population.

Perioperative AF after noncardiac surgery was consistently associated with a significant increase in the risk of stroke. The recommendations regarding management of AF after noncardiac surgery in clinical practice guidelines reflect uncertainty in this area, but the findings from this meta-analysis contribute to our growing understanding of the risks of postoperative AF.9,60 However, our findings do not necessarily mean that patients with perioperative AF after noncardiac surgery should receive long-term OAC. We found that the absolute risk of stroke in patients with perioperative AF was 0.6 per 100 patient-years over a mean follow-up of 28.2 ± 9.7 months. In studies that reported CHADS2 scores,47,48,50 these scores ranged from 0 to 4; this corresponds to a predicted annual risk of stroke between 2.8% and 4.0%, as shown in previous population-based studies of patients with clinical AF who were not taking OAC.61 Therefore, the incidences of stroke observed in this review are lower than one might expect, even after accounting for mortality and for the potential use of OAC in some patients. Depending on the type of surgery and the presence of other risk factors, this absolute risk of stroke may be too low to justify initiation of OAC. An annual stroke risk of 1.5% is the threshold above which the Canadian Cardiovascular Society recommends initiating OAC.62 In contrast, the American College of Cardiology/American Heart Association recommend to initiate OAC for a Congestive Heart Failure, Hypertension, Age (≥ 75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female) (CHA2DS2-VASc) score ≥ 2 (equivalent to a 2.5% annual stroke risk).8 We must note that the lack of information about the use of OAC in the included studies limits our interpretation of stroke risk. As additional consideration, the risk of bleeding may be different in the postoperative population.63-65

Mortality was significantly higher in patients with perioperative AF after noncardiac surgery as a whole and in all subgroups. This is consistent with previous literature for AF in general and after noncardiac surgery specifically.4,20 The risk of mortality in this population is striking. It highlights the vulnerability of this population; AF occurring after noncardiac surgery may be a marker of frailty. It also suggests that death is an important competing risk that needs to be considered in randomized control trials in this population.

In the end, there is a pressing need to evaluate the risks and benefits of OAC in this population. The randomized Anticoagulation for Stroke Prevention in Patients with Recent Episodes of Perioperative Atrial Fibrillation after Noncardiac Surgery (ASPIRE-AF, NCT03968393) trial is ongoing.
Although awaiting the results of this trial, perioperative AF after noncardiac surgery should not be dismissed, and patients who experience this arrhythmia likely need close follow-up and shared decision-making on whether to initiate OAC.

Strengths and limitations

This systematic review and meta-analysis is, to the best of our knowledge, the largest and most comprehensive on the topic, looking at study-level data. Although the meta-analysis conducted by Lin et al. also included a large population of 2,458,010 patients, it also included those who underwent cardiac surgery. In fact, it had only included 7 papers studying patients who underwent noncardiac surgery. In addition, strict inclusion criteria for studies were applied, and the authors of included studies were contacted for missing data. The study protocol was preregistered, and we used validated tools to evaluate the methodological quality of individual studies and our confidence in the body of evidence.

The major limitation of this review is that all included studies were subject to residual confounding, with little adjustment for important covariates in most studies. We also found important methodological differences between studies in this review. Associations presented in this study were mainly estimated based on aggregated study-level rather than patient-level data, which precludes assessing the relationship between many prognostic variables and our outcome of interest. Furthermore, this may have led to ecological bias. In addition, most studies did not report the number of patients who were taking OAC, and although we collected data on stroke and death, we did not collect data on bleeding events. In addition, many studies included patients with pre-existing AF, which may increase the rates of perioperative AF and bias the association between AF and stroke.\(^{35,51,55,56}\)

Conclusions

The detection of perioperative AF after noncardiac surgery is significantly associated with increased risk of stroke and all-cause mortality persisting well beyond the immediate follow-up period. The absolute risk of strokes in these patients is relatively low. These findings highlight the need for a large, randomized clinical trial investigating the benefits of OAC therapy on long-term stroke risk in this patient population.

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**Supplementary Material**

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