

New-Onset Atrial Fibrillation After Coronary Artery Bypass Graft and Long-Term Risk of Stroke: A Meta-Analysis

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Background—New-onset atrial fibrillation (NOAF) after coronary artery bypass graft is related to an increased short-term risk of stroke and mortality. We investigated whether the long-term risk of stroke is increased.

Methods and Results—We performed a systematic review and meta-analysis of studies that included patients who had coronary artery bypass graft and who afterwards developed NOAF during their index admission; these patients did not have previous atrial fibrillation. The primary outcome was risk of stroke at 6 months or more in patients who developed NOAF compared with those who did not. Odds ratios, relative risk, and hazard ratios were considered equivalent; outcomes were pooled on the log-ratio scale using a random-effects model and reported as exponentiated effect-sizes. We included 16 studies, comprising 108 711 participants with a median follow-up period of 2.05 years. Average participant age was 66.8 years, with studies including an average of 74.8% males. There was an increased long-term risk of stroke in the presence of NOAF (unadjusted studies effect-sizes=1.36, 95% confidence interval, 1.12–1.65, $P=0.001$, adjusted studies effect-sizes=1.25, 95% confidence interval, 1.09–1.42, $P=0.001$). There was evidence of moderate effect variation because of heterogeneity in studies reporting unadjusted ($P=0.021$, $I^2=49.8%$) and adjusted data ($P=0.081$, $I^2=49.1%$), and publication bias in the latter group (Egger's test, $P=0.031$). Sensitivity analysis on unadjusted data by study quality, design, and surgery did not alter the effect direction.

Conclusions—Presence of NOAF in patients post-coronary artery bypass graft is associated with increased long-term risk of stroke compared with patients without NOAF. Further studies may show whether the increased risk is mediated by atrial fibrillation and whether anticoagulation reduces risk. (*J Am Heart Assoc.* 2017;6:e007558. DOI: 10.1161/JAHA.117.007558.)

Key Words: atrial fibrillation • coronary artery bypass surgery • coronary artery graft surgery • meta-analysis • stroke • systematic review

Stroke is one of the most calamitous complications associated with cardiac surgery. In the specific context of coronary artery bypass graft (CABG), new-onset atrial fibrillation (NOAF)—where patients develop a usually transient episode of atrial fibrillation (AF) during the index hospital stay—has been strongly associated over the short term with increased stroke and mortality risk.^{1,2} Even when treated, AF is known to

recur to some degree over the long term, and NOAF has been linked with increased long-term mortality.^{3–6} More recently, some studies have associated NOAF with increased stroke risk over a longer postoperative period, although some have been more circumspect or inconclusive in their findings.^{3,4,7}

We hypothesized that there was an increased long-term stroke risk associated with development of NOAF in the post-CABG population. The aim of our investigation was to undertake a systematic review and meta-analysis of existing prospective and retrospective studies in order to investigate the change in this risk at a 6-month or greater time period postoperatively, in patients post-CABG without a history of AF who developed NOAF in the hospital compared with those who did not develop NOAF.

Methods

The data, analytic methods, and study materials have been made available to other researchers for purposes of reproducing the results or replicating the procedure.⁸ This review was registered with the PROSPERO (International Prospective Register of Systematic Reviews) (CRD42017059482) and

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Accompanying Tables S1, S2 and Figures S1, S2 are available at <http://jaha.ahajournals.org/content/6/12/e007558/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- The development of new-onset atrial fibrillation in patients post-coronary artery bypass graft is associated with a higher risk of stroke during long-term follow-up (median follow-up ≈2 years) compared with those without atrial fibrillation.

What Are the Clinical Implications?

- Longer-term monitoring may be required in patients with new-onset atrial fibrillation post-coronary artery bypass graft, and further studies should be undertaken to determine whether anticoagulation decreases stroke risk in this population.

follows the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines for meta-analysis reporting.⁹ Articles for review were retrieved by searching the databases MEDLINE (1946 to February 2017), EMBASE (1947 to February 2017), and CENTRAL (January 2012 to January 2017) on the date February 13, 2017 using the key terms “stroke” AND “cardiac surgery” AND “atrial fibrillation” with associated MeSH and Emtree headings (Table S1). From this selection duplicates were removed, leaving 3786 citations. All published studies that evaluated the incidence of stroke after 6 months or more in patients with NOAF after CABG with or without valve surgery were identified.

Citations were screened at title and abstract by 1 investigator (M.M.) and 3763 were excluded as inappropriate. Three further articles were identified from the bibliographies and reference lists of these results. Twenty-six articles were assessed by 2 reviewers (M.M. and V.T.) for applicability at full text using the Rayyan tool.¹⁰ Conflicts were resolved by consensus. Relevant articles included patients who were undergoing cardiac surgery and who did not have a previous history of AF; these articles collected data on the presence or absence of postoperative NOAF. We excluded articles in languages other than English, uncontrolled studies, and studies of special populations such as within-disease-group comparisons. We did not exclude conference abstracts. Studies of patients that did not explicitly exclude patients with preoperative AF were removed to determine only the risk of NOAF; we contacted investigators where this criterion was uncertain.⁴

Data were extracted by 1 investigator (M.M.). We collected information on principal author, year of publication, study design, and number of patients enrolled. We noted whether studies were on patient populations undergoing isolated CABG, or were on mixed populations: those undergoing CABG with a concomitant procedure such as valve surgery. For both long-term stroke and mortality, we collected event counts

and/or effect size data with associated confidence intervals where available. Where effect sizes were reported as an adjusted metric, we extracted the variables used in this adjustment.

Assessment of study quality and bias was undertaken using the SIGN tools.¹¹ Retrospective cohort studies were taken as having lower methodological quality than prospective cohort studies. Publication bias was assessed graphically through the creation of funnel plots of study point estimates against precision, and explored further for small study effects using Egger’s test.¹² Egger’s test is a regression-based test of the null hypothesis that a funnel plot is symmetrical about the line $x=0$. Greater magnitude of the regression line x -intercept determined with Egger’s test indicates a higher degree of plot asymmetry, commonly taken as significant at the 5% level.

Statistical analysis was performed using the STATA/IC 14.2 statistical package. We initially studied the relationship between NOAF and long-term stroke, treating stroke at 6 months or greater after CABG as a single end point. Because CABG-associated stroke is a rare event, the assumption was made that when comparing NOAF and no-NOAF groups, hazard ratio, relative risk, and odds ratio would converge with negligible difference, enabling data pooling across studies. These outcomes were pooled on the log-scale using DerSimonian-Laird random-effects model with the inverse-variance calculation method, with the pooled effect exponentiated and resulting effect size (ES) reported on the original scale as a ratio, where ratio >1 indicates increased risk. Random-effect analysis was prespecified in preference to a fixed-effects model as it was assumed the located studies would sample different populations and hence in reality estimate different mean ESs. The random-effects model assumes that different studies estimate a distribution of ESs and hence is more appropriate for meta-analysis including varied populations. In studies that required relative risk or odds ratio calculation from binary data but included arms with zero events, 0.5 was added to all cells. A secondary analysis utilizing a fixed-effects model was conducted to complement the random-effects approach.

Heterogeneity was assessed using the I^2 statistic, which describes the percentage of variation across studies that is caused by heterogeneity rather than sampling and is known to be insensitive to small numbers of included studies.¹³ In order to explore possible sources of heterogeneity where present, we planned to undertake subgroup sensitivity analyses based on prespecified characteristics that could explain these differences between studies: study design, study quality, and type of surgery. Interaction between strata in the sensitivity analysis was assessed on the log scale using z -test logic. We also planned to perform random-effects meta-regression of the data based on common study variables such as age, sex, diabetes mellitus status, and hypertension status.

Results

Excluded Studies

Of the 26 reports located through the literature search that were assessed at full-text, 4 studies were excluded because of reporting on inappropriate outcomes such as only in-hospital stroke or combined end points.^{5,14–16} Two did not stratify stroke outcomes by NOAF presence.^{17,18} Two did not exclude preoperative AF.^{19,20} One article reported only on a stroke-related mortality end point.²¹ One was a conference abstract initially published under 1 author that was subsequently published under a different first author.²² The studied population was unclear for 1 article; after correspondence with the author, this was deemed an appropriate study for inclusion.⁴

Included Studies

We included 16 studies in this meta-analysis (Figure 1) comprising 108 711 participants with a median follow-up period of 2.05 years. Three studies reported on ischemic stroke incidence^{3,23,24} and 13 on an outcome encompassing both ischemic and hemorrhagic stroke.^{4,7,25–35} Full characteristics of each study were detailed further (Table S2).

Bias Analysis

Two citations included in this review were unpublished conference abstracts. The risk of bias in these studies was unclear from the information available. One study shared an

aim and design similar to a later full article by the same group but on a different population.^{32,33} In the meta-analysis phase of this review, exclusion of these abstracts formed part of a subgroup sensitivity analysis.

Reporting on measures affecting attrition bias was incomplete in 1 study. The Konstantino group excluded 14/161 patients from their analysis who were lost to follow-up, with no comparison between characteristics of this group and those that remained in the study cohort.²⁶

Detection bias was an issue affecting some studies. Multiple groups did not clearly define the stroke outcome, opting for definitions such as “stroke” or “neurological event.”^{3,26,27,31–35} This may have been because of the study design in some cases, such as those requiring self-reporting, another potential source of bias.³

Overall, cohort studies performed well in minimizing the risk of selection bias—drawing consecutive patients from the same population—and all studies assessed major known confounding variables.

The single randomized clinical trial from 1987 located in the literature search had the same detection bias problem common to the cohort studies: a lack of standardized outcome measurement.³⁴ Blinding and concealment methods were unclear for this study.

Graphic representations of the respective individual judgments per study item and summary domains were created (Figures S1 and S2). One study not included in these figures because of differing design is that by the Rubin group.³⁴ This was a small study with unclear selection, randomization, and blinding methods; it was judged to be of low-quality evidence.

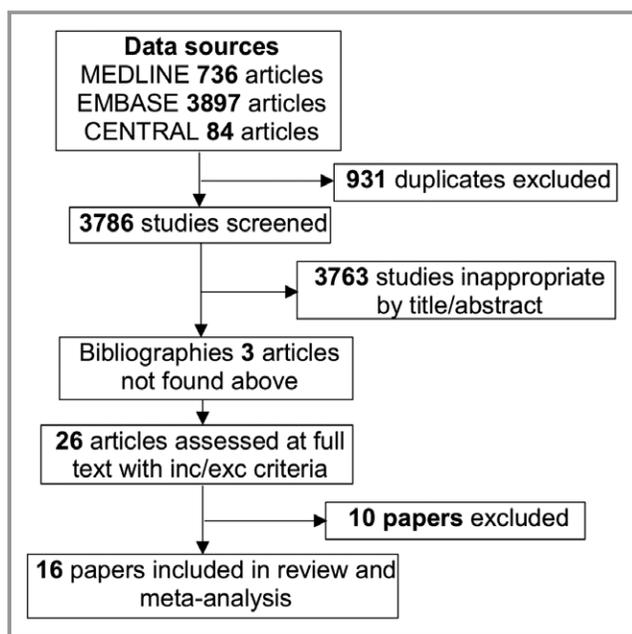


Figure 1. Study selection flowchart. inc/exc indicates inclusion/exclusion.

Combined Analysis

A pooled analysis was undertaken of unadjusted (Figure 2A) and adjusted (Figure 2B) studies reporting on long-term risk of stroke. Both study formats showed an increased long-term risk of stroke in the presence of NOAF using both random-effects (unadjusted studies ES=1.36, 95% confidence interval [CI], 1.12–1.65, $P=0.001$, adjusted studies ES=1.25, 95% CI, 1.09–1.42, $P=0.001$), and fixed-effects analyses (unadjusted studies ES=1.21, 95% CI, 1.13–1.30, $P=0.001$, adjusted studies ES=1.18, 95% CI, 1.10–1.26, $P=0.001$). There was evidence of moderate effect variation because of heterogeneity in studies reporting unadjusted data ($\chi^2=23.88$, $P=0.021$, $I^2=49.8\%$) and no statistical evidence of publication bias (intercept=0.821, $P=0.087$), although creation of a funnel plot suggested absence of small studies reporting negative correlations of postoperative AF with stroke (Figure 3A). Moderate effect variation because of heterogeneity was detected in studies reporting adjusted data ($\chi^2=9.82$, $P=0.081$, $I^2=49.1\%$), with some statistical evidence for publication bias (intercept 1.80, $P=0.031$) (Figure 3B).

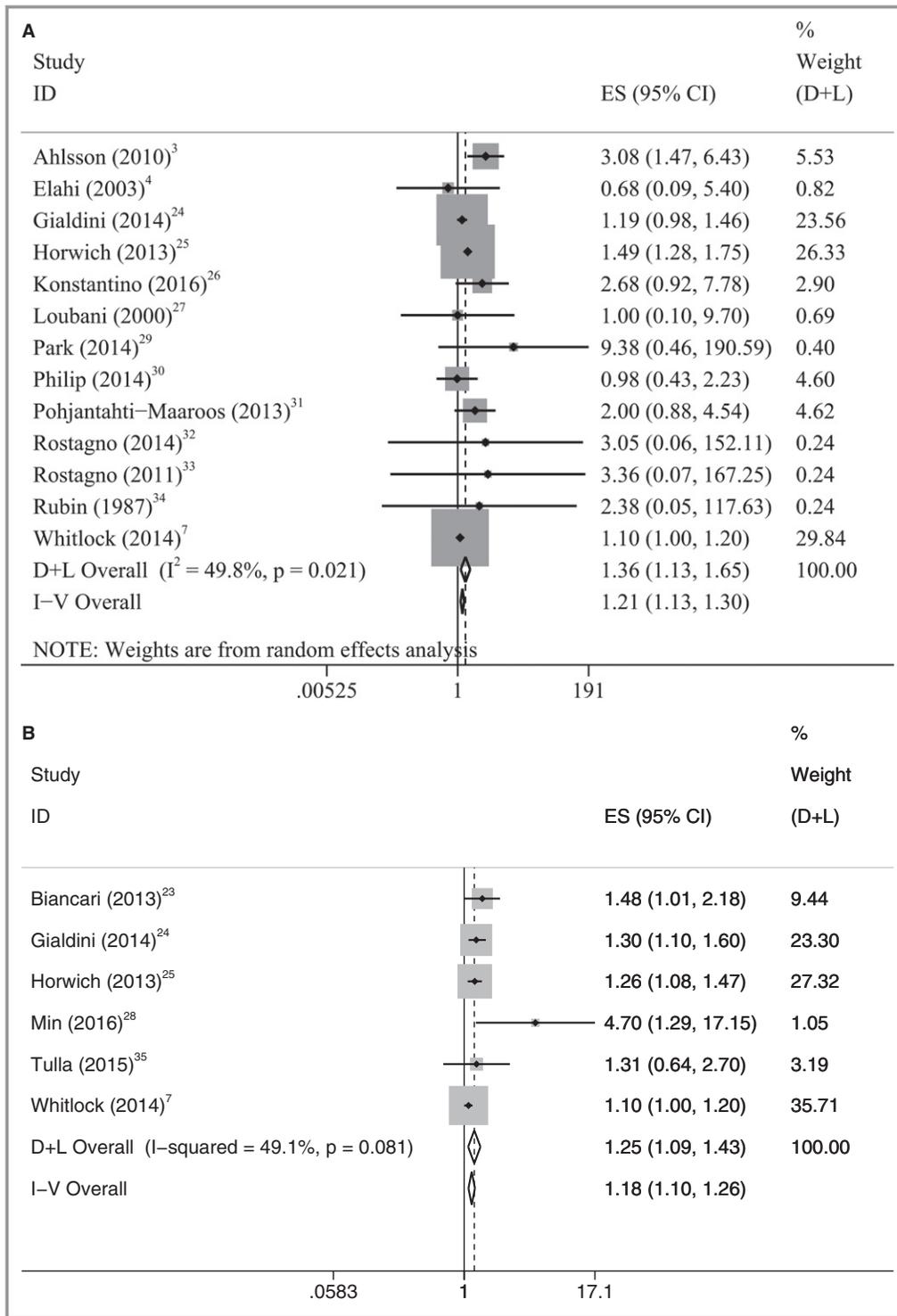


Figure 2. A and B, Forest plots (unadjusted and adjusted outcomes)—overall increased risk of stroke associated with new-onset atrial fibrillation, by both random effects (D+L) and fixed-effects (I-V) analysis. CI indicates confidence interval; ES, effect size.

A secondary pooled analysis was undertaken of unadjusted and adjusted studies reporting on long-term risk of mortality.^{3,25–28,30,31,34,35} Both study formats showed an increased long-term risk of mortality in the presence of NOAF

(unadjusted studies ES=1.88, 95% CI, 1.03–3.45, *P*=0.041, adjusted studies ES=1.58, 95% CI, 1.14–2.19, *P*=0.006). There is evidence of moderate heterogeneity in studies reporting unadjusted data ($\chi^2=18.48$, *P*=0.005, *I*²=67.5%) and

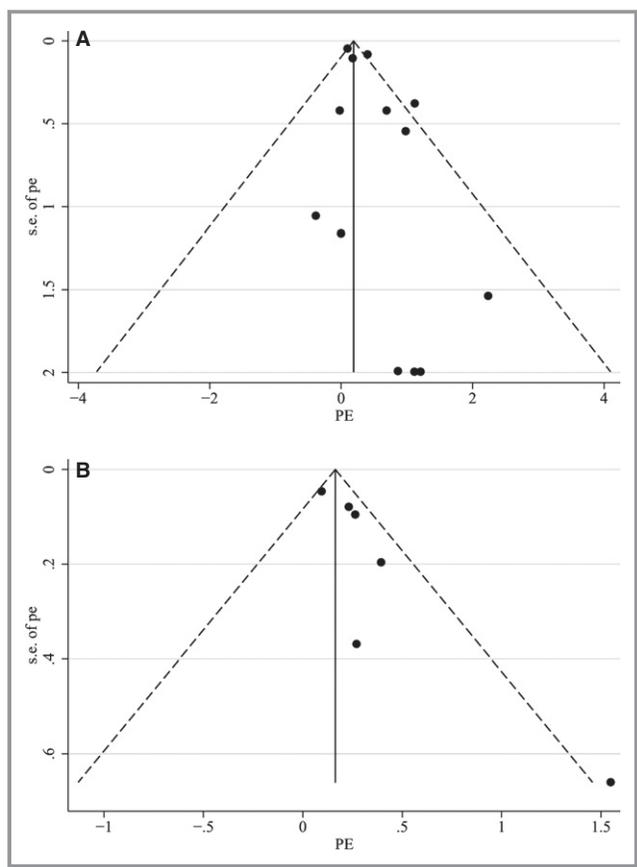


Figure 3. A and B, Funnel plots (unadjusted and adjusted outcomes). PE indicates point estimate; s.e., standard error.

moderate heterogeneity in studies reporting adjusted data ($\chi^2=14.06$, $P=0.007$, $I^2=71.6\%$). Publication bias was not assessed for this secondary outcome.

Sensitivity Analysis and Meta-Regression

A subgroup analysis was undertaken on the unadjusted data, stratified by study quality, study design, and surgical population (Figure 4). Stratification by quality and design resulted in increased heterogeneity in the respective good-quality and retrospective study arms; however, when analyzed by surgical population, there was a decrease in heterogeneity in both the CABG-only and mixed CABG/valve arms ($I^2=0.0\%$ and 18.2% , respectively). Patients with NOAF in the CABG-only stratum were determined to have an increased risk of long-term stroke when compared with those without NOAF (ES=1.54, 95% CI, 1.33–1.78, $P<0.001$). This risk, although still increased, was lower in the mixed stratum (ES=1.14, 95% CI, 1.01–1.28, $P=0.03$). The absolute difference on the log-scale for NOAF-associated stroke risk between these 2 latter strata was 0.30 ($I^2=89.8$, $P<0.01$). Similar results were obtained when comparing poor- versus

good-quality studies (difference in log-ES 0.73, $I^2=88.2$, $P<0.01$) and prospective versus retrospective studies (difference in log-ES 0.89, $I^2=88.3$, $P<0.01$).

With respect to the unadjusted study data, univariable random-effects meta-regression by mean participant age and reported stroke risk factors such as diabetes mellitus and smoking history did not detect an association with an increase in NOAF-related stroke risk, with confidence intervals overlapping the null-effect line. Meta-regression by proportion of male participants (0.013, 95% CI, 0.0002–0.027, $P=0.046$) suggested that studies that included more males detected more stroke events (Table).

One study with adjusted analysis that only included patients with NOAF persisting at discharge was included in the meta-analysis.³⁵ As this population was slightly different from that of other studies (where NOAF was absent by time of discharge), an additional analysis excluding this study was performed to determine the result of this study on the main outcome, with minimal effect detected (ES=1.25, 95% CI, 1.08–1.45, $P=0.003$).

Discussion

The results of this meta-analysis describe an association between NOAF occurring after isolated cardiac bypass surgery or combined bypass surgery and valve replacement and an increased long-term risk of stroke. The heterogeneity in study results was moderate in both studies that did not adjust for prognostic covariates and studies that did. The heterogeneity was partially explained by differences in study quality and the characteristics of the studied populations. Studies that included a higher proportion of males generally reported a higher risk of NOAF-associated stroke, although this was a weakly significant interaction with a small effect. A recent study on the short-term risk of NOAF-related stroke determined that there was no significant association between sex and risk over this briefer time period.³⁶

The adverse effects of NOAFs are in line with the results of NOAF occurring in the context of other cardiac surgeries. Two studies found that patients undergoing isolated bioprosthetic aortic valve replacement were at higher risk of NOAF-associated long-term stroke.^{37,38} One meta-analysis of patients who had undergone CABG detected a similarly increased NOAF-associated long-term mortality risk (odds ratio 2.19, 95% CI, 2.14–3.08) at 1-year follow-up.⁶

Interestingly, our analysis showed that studies of isolated CABG reported a higher risk of long-term stroke than studies that did not differentiate between patients undergoing isolated CABG or who additionally underwent valve surgery. Considering that those studies included up to 80% isolated CABG patients, this difference was an unexpected finding.

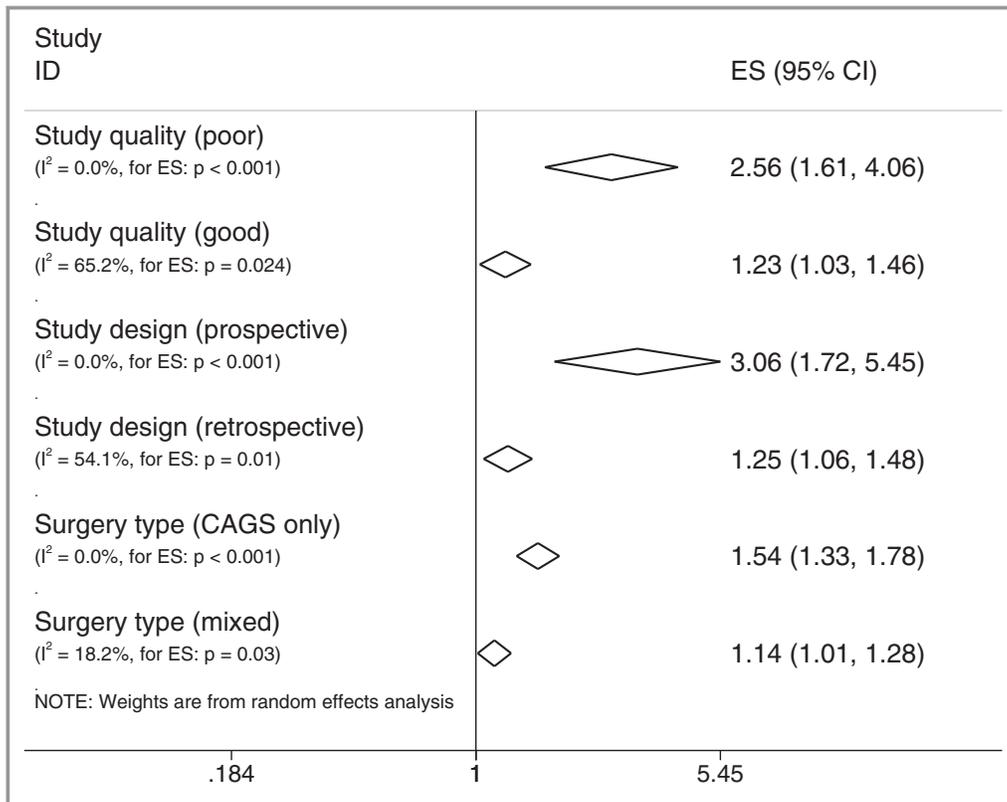


Figure 4. Sensitivity analysis (unadjusted outcomes). ES indicates effect size; CI, confidence interval.

Mixed surgical population studies were uniformly large-scale retrospective analyses, whereas studies on isolated CABG populations included a number of prospectively designed studies; the latter studies tended to detect a larger effect and it is perhaps the absence of prospective study types in the mixed population group that contributes to the apparent difference in detected risk. Another explanation may be that the requirement for anticoagulation in patients who undergo

valve surgery mitigates the risk of cardioembolic stroke associated with NOAF in the patients undergoing combined procedures. One study in this analysis noted the prevalence of ongoing anticoagulation, but across other studies this aspect was not reported explicitly, making it difficult to infer the effect this has on NOAF-associated stroke risk.³⁰ Both prospective studies and studies of poorer quality—2 subgroups of studies that largely overlapped—demonstrated a significantly higher NOAF-associated stroke risk compared with retrospective and higher-quality studies. This may be because poorer-quality studies tended to have a weak definition of stroke and hence were likely to capture more incidences of this outcome.

Limitations of this study include those common to all meta-analyses. Where effect variation because of heterogeneity between studies is high, it may not be appropriate to statistically combine them, and even where effect variation because of heterogeneity is statistically low, it may still be inappropriate to compare studies on populations differing in outcomes, adjustment variables, or inclusion/exclusion criteria. In the studies we identified, effect variation because of heterogeneity was moderate and somewhat explained by subgroup analysis on the surgical population studied. The proportion of male participants within each study was associated with an increase in NOAF-associated stroke risk.

Table. Random-Effects Meta-Regression Results

Variable	No. of Studies	Coefficient	Lower 95% CI	Higher 95% CI	P Value
Males, %	10	0.013	0.0002	0.027	0.046
Mean BMI	3	-0.09	-0.74	0.56	0.79
Hypertension, %	10	-0.018	-0.36	0	0.058
Hyperlipidemia, %	4	0.02	-0.021	0.062	0.35
Diabetes mellitus, %	10	-0.018	-0.055	0.19	0.35
Previous AMI, %	5	0.0088	-0.12	0.14	0.9
Smoking history, %	6	-0.017	-0.035	0	0.061

AMI indicates acute myocardial infarction; BMI, body mass index; CI, confidence interval.

With respect to this, meta-regression methods analyze an imperfect and observational association. Because it does not have the benefit of randomization to strengthen detected associations, the possibility exists that a meta-regression analysis may be assessing an actual association with an unmeasured confounder. Like many meta-analyses, we were unable to assess within-study heterogeneity as we did not have access to patient-level data.

Many studies included in this meta-analysis poorly defined the stroke outcome, which may have introduced a detection bias.^{3,26,27,31–35} Most made no differentiation between ischemic and hemorrhagic outcomes,^{4,7,25–35} and no studies classified ischemic strokes by cause or determined timing of AF recurrences and stroke, factors that could have proven useful in delineating the relationship between NOAF and ischemic stroke further. NOAF is a difficult outcome to explicitly prove; most studies did not explicitly document preoperative absence of AF through ECG—although even this may have missed AF episodes—and instead appeared to rely upon history.^{3,4,23,25–35} This may have overestimated the NOAF-associated stroke data in some studies by including patients with pre-existing AF. Two studies relied on *International Classification of Diseases* codes related to presence of AF to exclude patients where this occurred during previous admissions.^{7,24}

Conclusion

NOAF after CABG is associated with a long-term increased risk of stroke and mortality compared with populations with no NOAF. Further research is required to determine whether this increased risk is mediated by AF and whether anticoagulation decreases risk. Longer-term monitoring may be required to assess the need for anticoagulation in patients with NOAF. Future studies in the domain must unambiguously describe stroke outcomes where measured.

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Disclosures

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Supplemental Material

Table S1. Search Strategy

MEDLINE

- 1) exp atrial fibrillation/
- 2) (atrial adj4 fibrillat*).mp.
- 3) (auricular adj4 fibrillat*).mp.
- 4) (supraventricular adj4 fibrillat*).mp.
- 5) supraventricular tachycardia/ or tachycardia, ectopic atrial/
- 6) (supraventricular adj4 tachycardia).mp.
- 7) 1 or 2 or 3 or 4 or 5 or 6
- 8) exp cardiac surgical procedures/
- 9) (cardiac adj4 surg*).mp.
- 10) (heart adj4 surg*).mp.
- 11) (coronary adj4 surg*).mp.
- 12) (coronary adj4 bypass).mp.
- 13) CABG.mp.
- 14) (valve adj4 surg*).mp.
- 15) (valve adj4 replace*).mp.
- 16) 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
- 17) cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/
- 18) (isch?emi* adj6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or attack*)).mp.
- 19) CVA.mp.
- 20) ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)).mp.
- 21) 17 or 18 or 19 or 20
- 22) 7 and 16 and 21

EMBASE

- 1) exp atrial fibrillation/
- 2) (atrial adj4 fibrillat*).mp.
- 3) (auricular adj4 fibrillat*).mp.
- 4) (supraventricular adj4 fibrillat*).mp.

- 5) supraventricular tachycardia/ or ectopic atrial tachycardia/
- 6) (supraventricular adj4 tachycardia).mp.
- 7) 1 or 2 or 3 or 4 or 5 or 6
- 8) exp heart surgery/
- 9) (cardiac adj4 surg*).mp.
- 10) (heart adj4 surg*).mp.
- 11) (coronary adj4 surg*).mp.
- 12) (coronary adj4 bypass).mp.
- 13) CABG.mp.
- 14) (valve adj4 surg*).mp.
- 15) (valve adj4 replace*).mp.
- 16) 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
- 17) cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/
- 18) (isch?emi* adj6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or attack*)).mp.
- 19) CVA.mp.
- 20) ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation or basilar artery or vertebral artery) adj5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)).mp.
- 21) 17 or 18 or 19 or 20
- 22) 7 and 16 and 21

CENTRAL

- 1) [mh "Atrial Fibrillation"]
- 2) atrial NEAR/4 fibrillat*
- 3) auricular NEAR/4 fibrillat*
- 4) supraventricular NEAR/4 fibrillat*
- 5) [mh ^"Tachycardia, Supraventricular"] or [mh ^"Tachycardia, Ectopic Atrial"]
- 6) supraventricular NEAR/4 tachycardia
- 7) #1 OR #2 OR #3 OR #4 OR #5 OR #6
- 8) [mh "Cardiac Surgical Procedures"]
- 9) cardiac NEAR/4 surg*
- 10) heart NEAR/4 surg*
- 11) coronary NEAR/4 surg*

- 12) coronary NEAR/4 bypass
- 13) CABG
- 14) valve NEAR/4 surg*
- 15) valve NEAR/4 replace*
- 16) #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
- 17) [mh ^"cerebrovascular disease"] or [mh ^"cerebral artery disease"] or [mh ^"cerebrovascular accident"] or [mh stroke] or [mh ^"vertebrobasilar insufficiency"] or [mh ^"carotid artery disease"] or [mh "carotid artery obstruction"] or [mh "brain infarction"] or [mh "brain ischemia"] or [mh "occlusive cerebrovascular disease"] or [mh ^"stroke patient"]
- 18) (isch*mi* near/6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or attack*))
- 19) CVA
- 20) ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation or basilar artery or vertebral artery) NEAR/5 (isch*mi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*))
- 21) #17 or #18 or #19 or #20
- 22) #7 AND #16 AND #21

Table S2. Study Characteristics

Author	Study period	Institution	Country	Study type	Follow-up (years)	Sample size	# with NOAF	Inc. criteria	Exc. criteria	Exposure	Outcomes
Ahlsson (2010)¹	1999-2000	Örebro University Hospital	Sweden	Prospective cohort	6	571	165	Underwent primary CABG. Survived day 5 postop	History of AF, PPM	ECG-verified AF episode lasting 1+ minutes during the first 7 postoperative days	LOS, in-hospital stroke, 30-day mortality, late development of AF, cause of death, hospitalisations for arrhythmia related events e.g. stroke)
Biancari (2013)²	1990-2006	Oulu University Hospital	Finland	Retrospective cohort	7.2	1226	384	Undergoing primary CABG, residents of Oulu	Preoperative AF	Postoperative AF	30-day and late stroke with CHADS2 and CHA2DS2-VASc stratification. Stroke was defined as new neurologic deficit after surgery lasting > 24 hours with or without new structural changes detected after computed tomographic or magnetic resonance imaging +/-

											neurologist review
Elahi (2003)³	1999-2000	Glenfield Hospital	United Kingdom	Retrospective cohort	1	877	136	Undergoing CABG	Previous heart surgery, associated valvular disease	ECG-verified AF or documented in notes	Stroke, development or persistence of AF over follow-up, preoperative influencing variables
Gialdini (2014)⁴	2007-2010	Multicentre Californian nonfederal health care facilities	USA	Retrospective cohort	2.1	73543	11837	Adults that underwent surgery	Percutaneous cardiac procedures, pregnancy related procedures, previous AF diagnosis, cerebrovascular disease	Perioperative AF (ICD-9-CM 427.3x)	Ischaemic stroke (433.x1, 434.x1, 436) without rehab, SAH, ICH or trauma
Horwich (2013)⁵	1995-2009	Queen Elizabeth II Health Sciences Centre	Canada	Retrospective cohort	5.7	8058	2214	Undergoing first time isolated CABG, residents of Nova Scotia, eligible for health insurance coverage	Previous AF	Any episode of AF occurring after CABG that required intervention	New stroke or death by ICD-9 and ICD-10 codes
Konstantino (2016)⁶	2002-2003	Soroka Univeristy Medical Centre	Israel	Prospective cohort	8.5	136	37	Isolated CABG surgery	Prior history, lost to follow-up	Postoperative AF (ICD-9 427.3)	Predictors of long-term AF, correlation between POAF and long-term AF. Stroke, death.

Loubani (2000) ⁷	Unclear. Published 2000	Glenfield Hospital	United Kingdom	Retrospective cohort	0.5	375	94	Undergoing elective CABG	Emergency, concomitant surgical procedure, preoperative supraventricular arrhythmia	ECG-verified AF	Influences on development of SVA, clinical consequence and recurrence
Min (2016) ⁸	2010-2012	Samsung Medical Centre	Korea	Retrospective cohort	1	192	106	Undergoing off-pump CABG	Required conversion to cardiopulmonary bypass (subgroup analysis excluded preop AF)	New arrhythmia requiring treatment	In-hospital major adverse events and one-year major adverse cardiovascular and cerebral events. Stroke defined as new ischaemic or haemorrhagic event CVA with neurological deficit >24hr
Park (2014) ⁹	2010-2012	Samsung Medical Centre	Korea	Prospective cohort	1	113	39	Undergoing elective CABG	Emergency surgery, pre-existing AF, pacemaker, enrolled into other studies, MAZE procedure	Postoperative AF > 5 mins or requiring cardioversion	AF recurrence, stroke (new focal neurological deficit lasting > 24 hours with CT/MRI confirmation)
Philip (2014) ¹⁰	1993-2005	Cleveland Clinic	USA	Retrospective cohort	1	5205	1490	Undergoing first-time isolated CABG, > 18	Preoperative AF, bleeding diathesis, hypercoagulable state chronic anticoagulation with warfarin, combined valve or MAZE procedure, prior open heart surgery, preop echo	ECG/telemetry verified AF or flutter	Death, MI, stroke (new, acute focal neurological deficit due to ischaemia or haemorrhage and supported by neuroimaging)

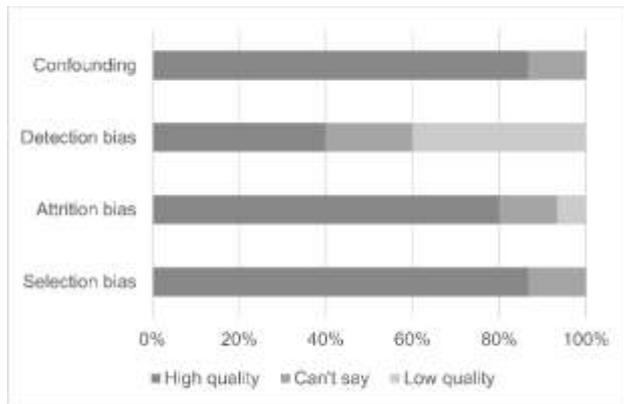
									compatible with valve disease		
Pohjantahti-Maaroos (2013)¹¹	2004-2008	Kuopio University Hospital	Finland	Retrospective cohort	5.6	519	177	Undergoing cardiac surgery	Prior AF	Postoperative AF	Death, stroke, MI, late AF
Rostagno (2014)¹²	2009	AOU Careggi Hospital	Italy	Prospective cohort	2	229	56	Undergoing isolated CABG, in sinus rhythm on admission	Atrial fibrillation, hyperthyroidism, MAZE, more than mild valvular disease, creatinine clearance < 30mL/min	Symptomatic arrhythmic episodes or asymptomatic episodes > 15mins on ECG	Recurrence of AF, stroke, mortality, role of on/off-pump CABG on POAF development
Rostagno (2011)¹³	2007	AOU Careggi Hospital	Italy	Prospective cohort	1.4	229	52	Undergoing isolated CABG, in sinus rhythm on admission	Unclear	Postoperative AF	Recurrence of AF, stroke, mortality, role of on/off-pump CABG on POAF development
Rubin (1987)¹⁴	Unclear. Published 1987	Westchester County Medical Centre	USA	RCT	2.2	123	36	Undergoing CABG	Prior AF, lung disease with bronchospasm, brittle diabetes, previous severe bradycardia, high degree AV block, known digoxin/propranolol sensitivity, EF < 0.5, intraoperative stroke/MI/death	ECG-verified AF > 30 seconds	Stroke, arrhythmia recurrence, angina (questionnaire follow-up)
Tulla (2014)¹⁵	2000-2010	Kuopio University Hospital	Finland	Retrospective cohort	8.5	138	138	Undergoing isolated CABG, in AF at time of discharge	Prior AF	ECG-verified AF > 5mins	Recurrence of AF, stroke, mortality, MI, other cardiac disorders

Whitlock (2014)¹⁶	1996-2007	Multicentre study in Ontario province	Canada	Retrospective cohort	2	108711	18046	Undergoing CABG or CABG + valve, > 18	Prior AF	Index admission coded for atrial fibrillation	Stroke (ICD-9 and ICD-10), death, combined stroke and death
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Figure S1. Bias analysis (cohort studies)

	Selection bias	Attrition bias	Detection bias	Confounding
Ahlsson 2010 ¹	+	+	-	+
Biancari 2013 ²	+	+	+	+
Elahi 2003 ³	+	+	?	+
Gialdini 2014 ⁴	+	+	+	+
Horwich 2013 ⁵	+	+	+	+
Konstantino 2016 ⁶	+	-	-	+
Loubani 2000 ⁷	+	+	-	+
Min 2016 ⁸	+	+	+	+
Park 2014 ⁹	+	+	-	+
Philip 2014 ¹⁰	+	+	+	+
Pohjantahti 2013 ¹¹	?	?	?	?
Rostagno 2014 ¹²	+	+	-	+
Rostagno 2011 ¹³	?	?	?	?
Tulla 2014 ¹⁴	+	+	-	+
Whitlock 2014 ¹⁵	+	+	+	+

Figure S2. Overall risk of bias (cohort studies).



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