Preoperative atrial fibrillation portends poor outcomes after coronary bypass graft surgery: A systematic review and meta-analysis

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Atrial fibrillation (AF) is the most common abnormal cardiac rhythm, with an estimated prevalence of 4% in the Australian population older than the age of 30 years.¹ The incidence of AF steadily increases with age; the prevalence in those older than 80 years is up to 15%.² The loss of coordinated atrial activity by AF predisposes patients to thrombus formation and, subsequently, embolic stroke.³ Moreover, chronic AF has been associated with a 2-fold increase in the risk of premature death.³

The demographic profile of patients undergoing coronary artery bypass graft (CABG) surgery has significantly changed in the past 2 decades as the result of an increased use of coronary stents and the aging population of developed countries. Increasingly, older patients with a greater incidence of comorbidities including valvular disease, diabetes, and impaired ventricular function are undergoing CABG.⁴⁻⁶ These factors are all associated with an increased risk of AF.⁷ Hence, it is imperative to understand the clinical implications of preoperative atrial fibrillation (preAF) for patients undergoing CABG. Some cohort studies have demonstrated that preAF may be an independent risk factor for poorer perioperative outcomes and reduced long-term survival.⁸⁻¹² However, there has only been a limited evaluation of preAF in the context of CABG surgery, and the EuroSCORE has not recognized preAF as a risk modifier. Moreover, the impact of preAF on clinical outcomes according to revascularization strategy (on-pump or off-pump CABG) remains largely unexplored.

Off-pump coronary artery bypass graft (OPCAB) surgery of the inferior wall.

Central Message

Preoperative atrial fibrillation portends poorer outcomes in patients undergoing CABG, regardless of revascularization strategy.

Perspective

Atrial fibrillation (AF) is present in up to 10% of patients undergoing CABG surgery. There is uncertainty about the prognostic implications of AF in patients undergoing CABG. Our study demonstrates, through a meta-analysis, that AF portends poorer early and late outcomes after CABG.

See Editorial Commentary page 1534.

See Editorial page 1522.

The primary aim of this of this meta-analysis was to evaluate the impact of preAF on short- and long-term outcomes after CABG surgery. As a secondary outcome, the impact of preAF on clinical outcomes depending on revascularization strategy (on-pump vs off-pump) was explored. Our hypothesis is that preAF has a negative impact on early and late outcomes after CABG surgery.

METHODS

This systematic review and meta-analysis was conducted and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹³ The study was approved by the local ethics committee.

Search Strategy and Study Selection

Electronic searches were performed with Ovid Medline, Embase, and Cochrane Central Register of Controlled Trials from their dates of inception to January 2016. The search terms “coronary artery bypass”

TABLE 1. Summary of study characteristics

	Study Period	Institution	Type of CABG Surgery	Study design	Follow-up, y	Number of patients		
						AF	No AF	Total
Ad and colleagues, 2009 ¹⁷	2002-2003	Society of Thoracic Surgeons National Adult Cardiac Surgery Database	ONCABG	Retrospective OS	Perioperative	15,755	265,814	281,569
Al-Sarraf and colleagues, 2012 ⁹	2000-2008	St James's Hospital	ONCABG	Retrospective OS	Perioperative	413	3364	3777
Attaran and colleagues, 2011 ¹⁰	2000-2010	Liverpool Heart and Chest Hospital	ONCABG + OPCABG	Retrospective OS	10*	477	9984	10,461
Banach and colleagues, 2008 ¹⁸	2000-2004	Department of Cardiac Surgery, Medical University Lodz, Poland	ONCABG	Retrospective OS	3*	174	2826	3000
Boning and colleagues, 2015 ¹⁹	2008-2011	Multicenter	ONCABG + OPCABG	Retrospective OS	Perioperative	232	2071	2303
Bramer and colleagues, 2010 ²³	1998-2007	Catharina Hospital, Eindhoven	ONCABG	Retrospective OS	4.6 ± 2.9	221	8630	8851
Fukahara and colleagues, 2010 ²⁰	2000-2005	University of Toyama, Japan	OPCABG	Retrospective OS	3.3 ± 2.7	26	487	513
Ngaage and colleagues, 2007 ⁸	1993-2002	Mayo Clinic College of Medicine	ONCABG	Retrospective OS	6.7*	257	269	526
O'Neal and colleagues, 2013 ²¹	2002-2011	East Carolina Heart Institute	ONCABG	Retrospective OS	4.2 [1.85-6.55]	263	5175	5438
Quader and colleagues, 2004 ²²	1972-2000	The Cleveland Clinic Foundation	ONCABG	Retrospective OS	12.6 ± 7.3	451	46,533	46,984
Rogers and colleagues, 2006 ¹²	1996-2002	Patient Activity Tracking System Database	ONCABG	Retrospective OS	5*	125	4917	5042
Saxena and colleagues, 2015 ¹¹	2001-2009	Australasian Society of Cardiac and Thoracic Surgeons	ONCABG	Retrospective OS	3.08†	1312	20,222	21,534

Data presented as mean ± standard deviation or median [interquartile range], unless otherwise stated. CABG, Coronary artery bypass graft surgery; AF, atrial fibrillation; ONCABG, on-pump coronary artery bypass graft surgery; OS, observational study; OPCABG, off-pump coronary artery bypass graft surgery. *Median. †Mean.

OR “CABG” were combined with “atrial fibrillation” AND (“baseline OR “pre-operative”) as key words and Medical Subject Headings terms. This was supplemented searching the reference lists by hand of key reviews and all potentially relevant studies.

Two reviewers (A.S., S.A.V.) independently screened the title and abstract of records identified in the search. Full-text publications were subsequently reviewed separately if either reviewer considered the manuscript as being potentially eligible. Disagreements regarding final study inclusion were resolved by discussion and consensus.

Eligibility Criteria

Eligible studies were those reporting on clinical outcomes of isolated CABG according to the presence or absence of baseline AF. Both

randomized controlled trials and observational studies were eligible for inclusion. Noncomparative studies lacking a control group of patients without preAF were excluded. Studies presenting mixed data for different cardiac surgeries were only included if clinical outcomes for the isolated CABG cohort were separately reported. Studies reporting outcomes of patients undergoing concomitant AF surgery were excluded.

All publications were limited to those involving human subjects and written in English. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded. Studies with fewer than 100 patients in either arm were also excluded. Review articles were omitted because of potential publication bias and duplication of results. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment.

TABLE 2. Baseline patient characteristics in studies examining impact of preoperative atrial fibrillation on outcomes after isolated coronary artery bypass grafting

Study	Age		Male		Diabetes		Previous MI	
	AF	No AF	AF	No AF	AF	No AF	AF	No AF
Ad and colleagues, 2009 ¹⁷	NR	NR	72	72	38*	36*	53*	45*
Al-Sarraf and colleagues, 2012 ⁹	NR	NR	NR	NR	NR	NR	NR	NR
ONCABG	70.1 [64.8-74.9]	70.4 [65.5-75.0]	89	89	26	25	NR	NR
OPCABG	70.7 [65.5-75.3]	71.3 [65.5-75.6]	88	88	32	30	NR	NR
Banach and colleagues, 2008 ¹⁸	64.4 ± 7.9*	59.7 ± 9.5*	58*	70*	18*	15*	NR	NR
ONCABG	78.8	78.4	70	67	18	14	39	38
OPCABG	78.8	78.6	80	67	22	14	37	36
Bramer and colleagues, 2010 ²³	69.8 ± 7.8	70.2 ± 7.7	76	74	24	19	NR	NR
Fukahara and colleagues, 2010 ²⁰	69.9 ± 10.1	67.0 ± 9.8	85	78	8	14	35	40
Ngaage and colleagues, 2007 ⁸	71 ± 8	70 ± 8	79	79	35	26	55	52
O'Neal and colleagues 2013 ²¹	NR	NR	NR	NR	NR	NR	NR	NR
Quader and colleagues, 2004 ²²	66.2 ± 9.0	66.6 ± 9.0	81	80	22	20	54	55
Rogers and colleagues, 2006 ¹²	68 [64-73]*	64 [57-70]*	85	81	24*	16*	53*	43*
Saxena and colleagues, 2015 ¹¹	71.1 ± 8.6*	65.2 ± 10.5*	77	78	36	33	33*	25*

Data presented as mean ± SD, median [IQR], or % of patients. *MI*, Myocardial infarction; *PVD*, peripheral vascular disease; *CVD*, cerebrovascular disease; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *HTN*, hypertension; *AF*, atrial fibrillation; *NR*, not reported; *ONCABG*, on-pump coronary artery bypass graft surgery; *OPCABG*, off-pump coronary artery bypass graft surgery. **P* < .05.

Data Extraction and Quality Assessment

All data were independently extracted from text, tables, and figures by 2 investigators (S.A.V. and S.B.). The final results were reviewed by the senior reviewer (A.S.). For each study, the following information was extracted: study period, institution, study design, patient characteristics and risk factors, procedural details, and clinical outcomes.

The predetermined primary endpoint was perioperative all-cause mortality, defined as death occurring within 30 days of surgery or during the same hospitalization. Secondary endpoints included perioperative morbidity (stroke, acute renal failure, myocardial infarction, wound infection, prolonged ventilation, reoperation for any cause, reoperation for bleeding, need for transfusion) and midterm survival. The definition of wound infection was inconsistent between studies; some studies reported on sternal wound infection, whereas others reported any surgical-site infection (eg, sternal and/or graft).

Study quality was assessed with the Newcastle-Ottawa Scale for cohort studies, which has established validity and is recommended by the Cochrane Collaboration. A maximum total of 9 points is possible over the areas of sample selection (0-4 points), comparability of cohorts (0-2 points), and outcome assessment (0-3 points), with a score greater than 5 indicating reasonable study quality.

Statistical Analysis

The odds ratio (OR) or hazards ratio (HR) were used as summary statistics, and reported with 95% confidence intervals (CIs). When available, multivariable adjusted or propensity-matched ratios were extracted from individual studies. Otherwise, unadjusted ratios were computed from the exposure distribution given in the papers.

Meta-analyses were performed with random-effects models (inverse-variance technique) to take into account the anticipated clinical and methodologic diversity between studies. The *I*² statistic was used to estimate the percentage of total variation across studies due to heterogeneity rather than chance, with values exceeding 50% indicative of considerable heterogeneity. Subgroup analysis was conducted to specifically examine the impact of preAF on outcomes after conventional

and off-pump CABG. Sensitivity analysis by study quality was conducted, excluding studies that did not report propensity-matched or multivariable adjusted ratios. In all manuscripts that were analyzed, the groups of stratified based on the presence or absence of preAF.

Publication bias was assessed by the use of funnel plots comparing log ORs with their standard error. Egger's linear regression method¹⁴ and Begg's rank correlation test¹⁵ were used to detect funnel plot asymmetry, and the Trim-and-Fill method was used to explore the impact of studies potentially missing due to publication bias.¹⁶ Statistical analysis was conducted with Review Manager Version 5.1.2 (Cochrane Collaboration, Software Update, Oxford, United Kingdom) and Comprehensive Meta-Analysis v2.2 (Biostat Inc, Englewood, NJ). All *P* values were 2 sided, and values < .05 were considered statistically significant.

RESULTS

Study Characteristics

A total of 1105 unique records were identified through the database and bibliographic searches. After considerable filtering, 1024 were excluded on the basis of title and abstract content. After the full text of the remaining 81 articles was screened, 12 studies met the inclusion criteria.^{8-12,17-23}

All included studies were retrospective observational reports (Table 1). These included data on a total of 389,998 patients who underwent CABG; 370,292 patients did not have preAF and 19,706 had preAF. The median study sample size was 5240 (range, 513-281,569). In 3 studies, outcome reporting was limited to the perioperative period.^{9,17,19} In the remaining studies, the mean or median follow-up time ranged from 3 to 12.6 years. All included studies had a Newcastle-Ottawa Scale score of at least 5, indicating good quality. Quality assessment scores for

TABLE 2. Continued

PVD		CVD		LVEF %		NYHA III/IV		HTN	
AF	No AF	AF	No AF	AF	No AF	AF	No AF	AF	No AF
23*	16*	21*	13*	NR	NR	66*	58*	81*	76*
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
17	18	NR	NR	15 (<30%)	14 (<30%)	NR	NR	69	68
18	16	NR	NR	18 (<30%)	18 (<30%)	NR	NR	75	75
NR	NR	NR	NR	39.4 ± 6.7*	43.7 ± 9.6*	NR	NR	NR	NR
35	33	9	8	3 (<30%)*	7 (<30%)*	55	42	NR	NR
35	32	11	10	5 (<30%)*	2 (<30%)*	60	44	NR	NR
15	15	8	11	33.5 (<50%)	30.8 (<50%)	NR	NR	48	41
8	6	27	20	50.0 ± 14.6*	56.1 ± 12.2*	NR	NR	58	56
NR	NR	11	10	53.0 ± 14	56.0 ± 16	92	87	74	71
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
27	28	NR	NR	NR	NR	39	38	73	74
17*	9*	19*	8*	45 (<50%)*	27 (<50%)*	50*	34*	67*	58*
18*	12*	17*	11*	8 (<30%)*	4 (<30%)*	32*	21*	82*	77*

individual studies are displayed in Table E1. Baseline demographic characteristics and risk-factor profiles of study participants are summarized in Table 2.

Clinical Outcomes

Entire cohort. The impact of preAF on perioperative and late outcomes after isolated CABG is summarized in Table 3. There was a statistically significant association between preAF and perioperative mortality (OR, 1.64; 95% CI, 1.29-2.09; $P < .001$; $I^2 = 54\%$). PreAF was also associated with stroke (OR, 1.50; 95% CI, 1.06-2.11; $P = .02$; $I^2 = 63\%$), acute renal failure (OR, 1.50; 95% CI, 1.23-1.83; $P < .001$; $I^2 = 48\%$), prolonged ventilation (OR, 1.40;

95% CI, 1.16-1.68; $P < .001$; $I^2 = 53\%$), and reoperation for bleeding (OR, 1.22; 95% CI, 1.07-1.40; $P = .003$, $I^2 = 19\%$). PreAF was not associated with an increased incidence of infective complications, re-exploration for bleeding, myocardial infarction, or perioperative blood transfusion.

Nine studies reported sufficient data for quantitative analysis of late mortality.^{4,8,10,12,18,20-23} Analysis of pooled data from these studies indicated that preAF was independently associated with late mortality (HR, 1.74; 95% CI, 1.42-2.13; $P < .001$; $I^2 = 76\%$).

Sensitivity analysis. Eight studies,^{9-12,17,18,22,23} involving a total of 381,218 patients, reported propensity-matched or adjusted ratios for the primary endpoint of perioperative

TABLE 3. Meta-analysis of the association of preoperative AF with outcomes after CABG (all studies)

Outcome	No. of cohorts	OR/HR*	95% CI	P value	I ² (%)
Mortality	13	1.64	1.29-2.09	<.001	54
Stroke	11	1.50	1.06-2.11	.02	63
Acute renal failure	11	1.50	1.23-1.83	<.001	48
Prolonged ventilation	9	1.40	1.16-1.68	<.001	53
Reoperation	5	1.22	1.07-1.40	.003	19
Infective complications	7	1.30	0.98-1.73	.07	0
Re-exploration for bleeding	7	1.05	0.72-1.53	.80	43
Myocardial infarction	7	0.76	0.49-1.19	.24	0
Blood transfusion	3	0.94	0.83-1.06	.31	0
Late mortality	9	1.74	1.42-2.13	<.001	76

OR, Odds ratio; HR, hazard ratio; CI, confidence intervals. *HR was the summary statistic for late mortality. For all other outcomes displayed, OR was the summary statistic.

TABLE 4. Meta-analysis of the association of preoperative AF with CABG (adjusted studies)

Outcome	No. of cohorts	OR/HR*	95% CI	P value	I ² (%)
Mortality	8	1.56	1.21-2.03	<.001	60
Stroke	6	1.18	1.07-1.31	<.001	0
Acute renal failure	6	1.43	1.13-1.82	.003	59
Prolonged ventilation	6	1.34	1.09-1.65	.005	62
Reoperation	3	1.24	1.09-1.42	.001	30
Infective complications	5	1.33	0.99-1.79	.06	0
Re-exploration for bleeding	3	1.32	0.79-2.22	.29	65
Myocardial infarction	4	0.69	0.39-1.22	.20	0
Blood transfusion	3	0.94	0.83-1.06	.31	0
Late mortality	6	1.47	1.32-1.63	<.001	0

OR, Odds ratio; HR, hazard ratio; CI, confidence intervals. *HR was the summary statistic for late mortality. For all other outcomes displayed, OR was the summary statistic.

mortality. The impact of preAF on early and late outcomes in this study cohort is provided in Table 4. A sensitivity analysis including only these studies still demonstrated a significant association between preAF and perioperative mortality (OR, 1.56; 95% CI, 1.21-2.03; $P < .001$; $I^2 = 60\%$; Figure 1). PreAF also remained significantly associated with an increased risk of stroke, acute renal failure, prolonged ventilation, and reoperation for bleeding. Sensitivity analysis confirmed that preAF was a risk factor for late mortality (HR, 1.47; 95% CI, 1.32-1.63; $P < .001$) and eliminated heterogeneity ($I^2 = 0\%$).

Subgroup analysis: On-pump CABG. Eleven studies,^{8-12,17-19,21-23} involving a total of 384,666 patients, examined patients undergoing on-pump CABG surgery. Of these, 19,402 patients presented with preAF and 365,264 did not present with preAF. A summary of the impact of preAF on early and late outcomes in this study cohort is provided in Table 5. In subgroup analysis of on-pump CABG patients, preAF was associated with an increased risk of 4 perioperative complications including mortality (OR, 1.53; 95% CI, 1.21-1.94; $P < .001$; $I^2 = 50\%$, Figure 2), acute renal failure (OR, 1.41; 95% CI, 1.17-1.69; $P < .001$; $I^2 = 39\%$), prolonged ventilation (OR, 1.34; 95% CI, 1.13-1.60; $P < .001$; $I^2 = 49\%$), and

reoperation for bleeding (OR, 1.23; 95% CI, 1.04-1.46; $P = .01$; $I^2 = 38\%$). Pre AF was associated with late mortality (OR, 1.69; 95% CI, 1.34-2.15; $P < .001$; $I^2 = 81\%$) following on-pump CABG.

Subgroup analysis: Off-pump CABG. Three studies,^{10,19,20} involving a total of 5322 patients, examined patients undergoing off-pump CABG surgery. Of these, 305 patients presented with preAF and 5027 did not present with preAF. A summary of the impact of preAF on early and late outcomes in this study cohort is provided in Table 6. In subgroup analysis of patients who underwent off-pump CABG, preAF was associated with an increased risk of perioperative mortality (OR, 2.75; 95% CI, 1.35-5.59; $P = .005$, $I^2 = 18\%$, Figure 3). There was a trend toward an increased incidence of acute renal failure (OR, 2.29; 95% CI, 0.98-5.35; $P = .06$; $I^2 = 63\%$). PreAF was associated with an increased risk of late mortality (HR, 1.97; 95% CI, 1.26-3.08; $P = .003$, $I^2 = 33\%$) after off-pump CABG.

Subgroup analysis: Studies excluding Society of Thoracic Surgeons. A subgroup analysis was performed of studies excluding the large Society of Thoracic Surgeons study (Table 7).¹⁷ In this analysis, preAF was associated with an increased risk of perioperative mortality (OR,

FIGURE 1. Meta-analysis of the association of preoperative AF with perioperative mortality after CABG (adjusted studies). SE, Standard error; IV, symptoms of heart failure at rest; CI, confidence interval; OPCABG, off-pump coronary artery bypass grafting; AF, atrial fibrillation.

TABLE 5. Meta-analysis of the association of preoperative AF with outcomes after on-pump CABG

Outcome	No. of cohorts	OR/HR*	95% CI	P value	I ² (%)
Mortality	10	1.53	1.21-1.94	<.001	50
Stroke	9	1.22	0.98-1.51	.08	18
Acute renal failure	9	1.41	1.17-1.69	<.001	39
Prolonged ventilation	8	1.34	1.13-1.60	<.001	49
Reoperation	4	1.23	1.04-1.46	.01	38
Infective complications	6	1.31	0.98-1.76	.07	0
Re-exploration for bleeding	5	1.13	0.75-1.72	.56	50
Myocardial infarction	5	0.66	0.38-1.15	.15	0
Blood transfusion	3	0.94	0.83-1.06	.31	0
Late mortality	7	1.69	1.34-2.15	<.001	81

OR, Odds ratio; HR, hazard ratio; CI, confidence intervals. *HR was the summary statistic for late mortality. For all other outcomes displayed, OR was the summary statistic.

1.74; 95% CI, 1.33-2.28; $P < .001$), acute renal failure (OR, 1.60; 95% CI, 1.23-2.08; $P < .001$), and prolonged ventilation (OR, 1.52; 95% CI, 1.15-2.00; $P = .003$). There was a clear association of preAF with late mortality (HR, 1.74; 95% CI, 1.42-2.13).

Subgroup analysis: Excluding studies enrolling patients before 2000. A subgroup analysis of studies that recruited patients after 2000 is presented in Table 8. Four studies were excluded.^{8,12,22,23} In this analysis, preAF was associated with an increased risk of perioperative mortality (OR, 1.83; 95% CI, 1.39-2.43; $P < .001$), stroke (OR, 1.54; 95% CI, 1.02-2.32; $P = .04$), acute renal failure (OR, 1.52; 95% CI, 1.20-1.93; $P < .001$), prolonged ventilation (OR, 1.44; 95% CI, 1.14-1.83; $P = .002$), reoperation for bleeding (OR, 1.19; 95% CI, 1.13-1.26), and infective complications (OR, 1.42; 95% CI, 1.02-1.97; $P = .04$). There was a clear association of preAF with late mortality (HR, 1.91; 95% CI, 1.43-2.55; $P < .001$).

Publication bias. Both Egger's linear regression method ($P = .13$) and Begg's rank correlation test ($P = .30$) suggested publication bias was not an influencing factor when perioperative mortality was selected as an endpoint. Accounting for potentially missing studies using the

imputed trim-and-fill method did not alter the result obtained for perioperative mortality.

DISCUSSION

The present meta-analysis demonstrated the preAF is an independent risk factor for poorer perioperative outcomes and reduced overall survival after CABG. There has been considerable debate among clinicians as to whether preAF independently predisposes patients to a poorer outcome or whether it is simply a marker of a more complex physiological milieu. Certainly, preAF is associated with age, cardiovascular comorbidities, impaired ventricular function, and critical perioperative state.^{7,11}

Nevertheless, our study demonstrated an independent association between preAF and poorer perioperative outcomes. A cumulative analysis of the 13 studies demonstrated that preAF increased the risk of perioperative mortality by 64% (OR, 1.64; 95% CI, 1.29-2.09; $P < .001$). Even when only studies that included propensity-matched or adjusted ratios were analyzed, preAF was independently associated with a 56% increase in the risk of perioperative mortality (OR, 1.56; 95% CI, 1.21-2.03; $P < .001$). This is an important clinical finding particularly, given that

FIGURE 2. Meta-analysis of the association of preoperative AF with perioperative mortality after on-pump CABG. SE, Standard error; IV, symptoms of heart failure at rest; CI, confidence interval; AF, atrial fibrillation.

TABLE 6. Meta-analysis of the association of preoperative AF with outcomes after off-pump CABG

Outcome	No. of cohorts	OR/HR*	95% CI	P value	I ² (%)
Mortality	3	2.75	1.35-5.59	.005	18
Stroke	2	3.71	2.21-6.22	<.001	0
Acute renal failure	2	2.29	0.98-5.35	.06	63
Prolonged ventilation	1	—	—	—	—
Reoperation	1	—	—	—	—
Wound infection	1	—	—	—	—
Reoperation for bleeding	2	0.72	0.27-1.95	.52	36
Myocardial infarction	2	0.99	0.46-2.13	.99	0
Blood transfusion	0	—	—	—	—
Late mortality	2	1.97	1.26-3.08	.003	33

OR, Odds ratio; HR, hazard ratio; CI, confidence intervals. *HR was the summary statistic for late mortality. For all other outcomes displayed, OR was the summary statistic.

previous cohort studies may have been underpowered to detect a clinical difference.^{8,12}

After mortality, the most significant sequela of AF is the increased risk of stroke. Our analyses demonstrated that preAF increased the risk of perioperative stroke by 50% (OR, 1.50; 95% CI, 1.06-2.11; $P = .02$). Off-pump CABG has been shown to reduce the incidence of perioperative stroke.²⁴ Theoretically then, an off-pump revascularization strategy may reduce the incidence of stroke in patients with preAF. Attaran and colleagues¹⁰ performed a matched analysis which compared the outcomes of patients with and without preAF based on revascularization strategy (on-pump or off-pump). The authors demonstrated that, in patients undergoing on-pump CABG, preAF was associated with a significantly greater risk of stroke (5.4% vs 1.6%, $P < .001$). In contrast, in patients undergoing off-pump CABG, preAF was not associated with stroke (0% vs 0.5%, $P > .99$). Our analyses, however, demonstrated that preAF was associated with a greater than 3-fold increase in the risk of stroke in patients undergoing off-pump CABG (OR, 3.71; 95% CI, 2.21-6.22; $P < .001$). The optimal revascularization strategy for patients with preAF, therefore, remains unclear, and further prospective investigation is required. It must be noted that confounding factors may have influenced the observed outcomes. For example, the presence or absence

of aortic crossclamping can influence the incidence of postoperative stroke. Unfortunately, we are unable to determine on a case-by-case basis precisely what proportion of the study population had aortic crossclamping.

PreAF also was associated with an independently increased risk of acute renal failure, prolonged ventilation, and reoperation for bleeding. Several mechanisms have been proposed to explain the association between preAF and poorer early outcomes. It has been suggested that reduced ventricular filling due to AF results in hypoperfusion of end organs such as the brain and kidneys, rendering patients susceptible to stroke and renal impairment.¹² Encouragingly, however, we found no association between preAF and perioperative myocardial infarction. Moreover, our study showed no association between preAF and the rate of bleeding or blood transfusion between the 2 groups. This is an interesting observation, given that it is probable that a greater percentage of patients in preAF were on preoperative anticoagulants. The lack of a significant difference in the rate of bleeding may reflect good clinical management of preoperative anticoagulants in patients with preAF. It may also relate to good intraoperative management of coagulopathy/bleeding.

Our study demonstrated a strong association between preAF and late mortality. A cumulative analysis of the 9 studies showed that preAF increased the risk of late

FIGURE 3. Meta-analysis of the association of preoperative AF with perioperative mortality after off-pump CABG. SE, Standard error; IV, symptoms of heart failure at rest; CI, confidence interval; OPCABG, off-pump coronary artery bypass grafting; AF, atrial fibrillation.

TABLE 7. Sensitivity analysis (excluding the STS study)

Outcome	No. of cohorts	OR/HR*	95% CI	P value	I ² (%)
Mortality	12	1.74	1.33-2.28	<.001	37
Stroke	10	1.55	0.99-2.41	.05	60
Acute renal failure	10	1.60	1.23-2.08	<.001	44
Prolonged ventilation	8	1.52	1.15-2.00	.003	54
Reoperation	4	1.30	0.98-1.73	.07	9
Wound infection	7	1.30	0.98-1.73	.07	0
Reoperation for Bleeding	7	1.05	0.72-1.53	.80	43
Myocardial infarction	7	0.76	0.49-1.19	.24	0
Late mortality	9	1.74	1.42-2.13	<.001	76

OR, Odds ratio; HR, hazard ratio; CI, confidence intervals. *HR was the summary statistic for late mortality. For all other outcomes displayed, OR was the summary statistic.

mortality by up to 74% (HR, 1.74; 95% CI, 1.42-2.13; $P < .001$). Even when only propensity-matched or adjusted studies were analyzed, late mortality was increased by 47% (HR, 1.47; 95% CI, 1.32-1.63; $P < .001$) with excellent homogeneity across studies ($I^2 = 0$). Our results were consistent with several of the studies included in the meta-analysis. Banach and colleagues¹⁸ evaluated 3000 patients who underwent isolated CABG and demonstrated that 3-year survival was 20% lower in patients who had preAF (71% vs 91%, $P < .001$). Rogers and colleagues¹² similarly showed an absolute survival difference of 20% after 3 years (70% vs 90%; HR, 1.49; 95% CI, 1.06-2.08; $P = .020$).

The cause for increased late mortality in patients with preAF is multifactorial. First, preAF may predispose patients to thromboembolic or hemorrhagic events.²⁵ Second, long-term AF may induce tachycardia-related cardiomyopathy.²⁶ Third, long-term AF exacerbates congestive heart failure.²⁷ Finally, potentially fatal anticoagulation-related complications are more common in patients with preAF due to the high use of warfarin.¹⁰

Given the implications of preAF on poorer perioperative and long-term outcomes, some investigators have advocated to role of adjunct strategies to treat AF. European guidelines suggest that all patients with symptomatic preAF

who are undergoing cardiac surgery should be offered concomitant perioperative ablation (recommendation Class IIa, Level A²⁸). They also recognize that surgical ablation should be considered in asymptomatic patients with preAF (Class IIb, Level C).²⁸ Cheng and colleagues²⁹ performed a meta-analysis of 33 studies including 10 randomized controlled trials (RCTs) that compared the outcomes of patients who underwent concomitant AF surgery with those that did not. The authors demonstrated a greater rate of sinus rhythm in RCT and non-RCT studies compared with cardiac surgery alone, and this effect remained robust over the long term (5 years). There is evidence that patients with successful sinus restoration had improved survival who were treated but remained in AF.³⁰ Concomitant left atrial occlusion has also been advocated as a treatment strategy to reduce stroke and perioperative mortality in patients with preAF, but further evidence is required to validate its clinical efficacy.³⁰

Despite this evidence, the uptake of concomitant AF surgery has been inconsistent. An analysis of data from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (2005-2010) showed that only 27.5% of patients undergoing CABG underwent ablation compared with 61.5% of patients undergoing mitral valve repair.³¹ As

TABLE 8. Subgroup analysis (excluding studies enrolling patients before 2000)

Outcome	No. of cohorts	OR/HR*	95% CI	P value	I ² (%)
Mortality	9	1.83	1.39-2.43	<.001	60
Stroke	8	1.54	1.02-2.32	.04	73
Acute renal failure	8	1.52	1.20-1.93	<.001	62
Prolonged ventilation	6	1.44	1.14-1.83	.002	69
Reoperation	4	1.19	1.13-1.26	<.001	0
Wound infection	4	1.42	1.02-1.97	.04	0
Reoperation for bleeding	5	1.14	0.67-1.92	.63	54
Myocardial infarction	5	0.76	0.45-1.30	.32	0
Late mortality	9	1.97	1.43-2.55	<.001	84

OR, Odds ratio; HR, hazard ratio; CI, confidence intervals. *HR was the summary statistic for late mortality. For all other outcomes displayed, OR was the summary statistic.

VIDEO 1. Professor Paul Bannon explaining the contribution of this study. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)32735-6/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)32735-6/fulltext).

discussed by La Meir and colleagues,³² there are several reasons why concomitant ablation has not been universally adopted. First, there is a lack of large RCTs demonstrating the prognostic benefit of restoring sinus rhythm. Second, many surgeons do not believe that the additional technical complexity of AF ablation justifies the future benefits of sinus rhythm, particularly in patients who do not require an atriotomy. Overall, given the negative implications of preAF on both short- and long-term outcomes, there is a need for further investigate the impact of concomitant ablative strategy in patients with preAF undergoing CABG.

Our study has several limitations. First, all included studies were retrospective, observational reports. Second, considerable heterogeneity was detected in the analysis of several perioperative complications including mortality, stroke, prolonged ventilation, and acute renal failure. This may reflect differences in reporting standards, data collection, endpoint definitions, or perioperative management across institutions. For example, the incidence of preAF varied between studies. Although, to some degree, this reflects real variation across centers, it is likely that there were differences in screening practices across institutions. Third, due to the nature of the included studies, we could not determine the impact of the type or duration of preAF on clinical outcomes. Fourth, our analysis of off-pump CABG was limited by the small number of studies reporting clinical endpoints. Fifth, AF is associated with primary or secondary structural and physiologic derangements that can have a direct influence on outcomes after cardiac operations that would not be possible to account for in the study design of a meta-analysis. Finally,

the analysis of early and late mortality was limited to an assessment of overall mortality rather than disease-specific or event-specific mortality. Moreover, we were unable to gather sufficient data to evaluate the impact of preAF on late stroke, which is an important clinical endpoint.

In conclusion, this meta-analysis demonstrates that preAF is associated with poorer perioperative outcomes and reduced long-term survival after CABG. Our study does not prove causality, but it does suggest that there is need to evaluate the role of adjunct ablative strategies (Video 1).

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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TABLE E1. Quality assessment scores for individual studies

Study	NOS quality assessment		
	Selection of cohorts	Comparability of cohorts	Outcome assessment
Ad and colleagues, 2009 ¹⁷	****	**	**
Al-Sarraf and colleagues, 2012 ⁹	***	**	**
Attaran and colleagues, 2011 ¹⁰	****	**	***
Banach and colleagues, 2008 ¹⁸	***	**	**
Boning and colleagues, 2015 ¹⁹	***	—	**
Bramer and colleagues, 2010 ²³	****	**	***
Fukahara and colleagues, 2010 ²⁰	***	*	**
Ngaage and colleagues, 2007 ⁸	**	*	**
O'Neal and colleagues 2013 ²¹	**	*	***
Quader and colleagues, 2004 ²²	****	**	***
Rogers and colleagues, 2006 ¹²	****	**	***
Saxena and colleagues, 2015 ¹¹	****	**	***

The number of asterisks represents how many individual criterion within the subsection were fulfilled (from * to ****). NOS, Newcastle-Ottawa Scale.

TABLE E2. Summary of statistical analysis

Study	Critical appraisal of statistical analysis		
	Proportional hazard assumptions verified?	Form of statistical adjustment	Variables accounted for in adjustment
Ad and colleagues, 2009 ¹⁷	NR	Multivariable regression models	Age, BMI, LVEF, eGFR, sex, race, smoking status, family history of CAD, diabetes, hypercholesterolemia, HTN, CVA, IE, chronic lung disease, immunosuppressive treatment, PVD, previous PCI/CABG, triple-vessel disease, CHF, MI, angina, NYHA IV, left main disease, cardiogenic shock
Al-Sarraf and colleagues, 2012 ⁹	NR	Multivariable regression models	Logistic EuroSCORE
Attaran and colleagues, 2011 ¹⁰	NR	Propensity matching	Age, BMI, LVEF, renal dysfunction, sex, smoking status, diabetes, hypercholesterolemia, HTN, CVA, respiratory disease, PVD, previous surgery, triple-vessel disease, recent MI, angina class IV, logistic EuroSCORE
Banach and colleagues, 2008 ¹⁸	NR	Multivariable regression models	NR
Boning and colleagues, 2015 ¹⁹	NA	Not performed	NA
Bramer and colleagues, 2010 ²³	NR	Propensity matching	Age, obesity/underweight, reduced LVEF, creatinine clearance, sex, diabetes, HTN, CVA, COPD, PVD
Fukahara and colleagues, 2010 ²⁰	NR	Multivariable regression models	Age, hemodialysis, preoperative LVEF, sex, previous CVA, PVD, new-onset postoperative AF
Ngaage and colleagues, 2007 ⁸	NR	Multivariable regression models	Postoperative dialysis, diabetes, previous CVA, COPD, MI, cardiomegaly
O'Neal and colleagues 2013 ²¹	NR	Multivariable regression models	Age, race, sex, hypertension, previous CVA, CHF, severity of CAD
Quader and colleagues, 2004 ²²	NR	Propensity matching	Age, BMI, renal insufficiency, LV dysfunction, sex, diabetes, hypercholesterolemia, hypertension, previous CVA, respiratory disease, PVD, previous surgery, NYHA class, MI, ventricular arrhythmias
Rogers and colleagues, 2006 ¹²	NR	Multivariable regression models	Age, BMI, renal dysfunction, sex, LVEF, smoking status, NYHA class, diabetes, CHF, previous MI, Parsonnet score, off-pump/on-pump CABG, severity of CAD, GI disease, graft conduits used
Saxena and colleagues, 2015 ¹¹	NR	Multivariable regression models	Age, obesity, renal failure, LVEF, sex, smoking status, diabetes, hypercholesterolemia, HTN, CVA, COPD, PVD, previous cardiac surgery, CHF, triple-vessel disease, recent MI, unstable angina, NYHA class, left main stenosis, EuroSCORE

BMI, Body mass index; *LVEF*, left ventricular ejection fraction; *eGFR*, estimated glomerular filtration rate; *CAD*, coronary artery disease; *NR*, not reported; *HTN*, hypertension; *CVA*, cerebrovascular accident; *IE*, infective endocarditis; *PVD*, peripheral vascular disease; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting; *CHF*, congestive heart failure; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *NA*, not available; *COPD*, chronic obstructive pulmonary disease; *AF*, atrial fibrillation; *LV*, left ventricular *GI*, gastrointestinal.