Atrial Fibrillation After Cardiac Surgery – A Systematic Review and Meta-Analysis

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Abbreviations

AF: atrial fibrillation
CABG: coronary artery bypass grafting
COPD: chronic obstructive pulmonary disease
ECG: electrocardiogram
ICU: intensive care unit
IRR: incidence rate ratio
NSR: normal sinus rhythm
OR: odds ratio
POAF: new-onset post-operative atrial fibrillation
SMD: standardized mean difference
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1. Summary

1.1. English

Background
New-onset post-operative atrial fibrillation (POAF) after cardiac surgery is common, with rates up to 60%. POAF has been associated with early and late stroke, but its association with other cardiovascular outcomes is less known. The objective of this study was to perform a systematic review and a meta-analysis of the studies reporting the association of POAF with peri-operative and long-term outcomes in cardiac surgery.

Methods
We performed a systematic review and a meta-analysis of studies presenting outcomes for cardiac surgery based on the presence or absence of POAF. Three libraries were assessed (MEDLINE, EMBASE and Cochrane Library) and 57 studies (total of 246,340 patients) were selected. Peri-operative mortality was the primary outcome. Inverse variance method and random model were performed. Leave-one-out analysis, sub-group analyses and meta-regression were conducted.

Results
POAF was associated with peri-operative mortality (odds ratio [OR]= 1.92, 95% confidence interval [CI] 1.58; 2.33), peri-operative stroke (OR= 2.17, 95% CI 1.90; 2.49), peri-operative myocardial infarction (OR= 1.28, 95% CI 1.06; 1.54), peri-operative acute renal failure (OR= 2.74, 95% CI 2.42; 3.11), hospital length of stay (standardized mean difference [SMD]= 0.80, 95% CI 0.53; 1.07), ICU stay (SMD= 0.55, 95% CI 0.24; 0.86), long-term mortality (incidence rate ratio [IRR]= 1.54, 95% CI 1.40; 1.69), long-term stroke (IRR= 1.33, 95% CI 1.21;1.46) and long-standing persistent atrial fibrillation (IRR= 4.73, 95% CI 3.36; 6.66).

Conclusion
The results suggest that POAF in cardiac surgery is associated with an increased occurrence of most short and long-term cardiovascular adverse events. However, the direct causality of this association remains to be established.
1.2. German

Hintergrund und Ziele der Studie
Neu auftretendes postoperatives Vorhofflimmern (POAF) nach einer Herzoperation ist mit Raten von bis zu 60% häufig. POAF wurde bereits mit frühem und spätem Schlaganfall in Verbindung gebracht, ob aber ein Zusammenhang mit anderen kardiovaskulären Ereignissen besteht ist noch weitgehend unbekannt. Das Ziel dieser Studie war die Erstellung einer systematischen Datenübersicht, sowie die Durchführung einer Metaanalyse anhand von Studien, die den Zusammenhang von POAF mit perioperativen und langfristigen Ergebnissen in der Herzchirurgie untersucht haben.

Methodik

Ergebnisse
POAF war mit perioperativer Sterblichkeit (Odds Ratio [OR] = 1,92, 95% Konfidenzintervall [CI] 1,58; 2,33), perioperativem Schlaganfall (OR = 2,17, 95% CI 1,90; 2,49), perioperativem Myokardinfarkt (OR = 1,28, 95% CI 1,06; 1,54), perioperativem akuten Nierenversagen (OR = 2,74, 95% CI 2,42; 3,11), der Aufenthaltsdauer im Krankenhaus (standardisierte mittlere Differenz [SMD] = 0,80, 95% CI 0,53; 1,07) und auf der Intensivstation (SMD = 0,55, 95% CI 0,24; 0,86), Langzeitsterblichkeit (Inzidenzratenverhältnis [IRR] = 1,54, 95% CI 1,40; 1,69), langfristig auftretendem Schlaganfall (IRR = 1,33) 95% CI 1,21; 1,46) und lang anhaltendem Vorhofflimmern (IRR = 4,73, 95% CI 3,36; 6,66) assoziiert.
Schlussfolgerungen
2. Introduction

2.1. Definition

New-onset postoperative atrial fibrillation (POAF) is defined as the new development of atrial fibrillation after surgery in patients with previous sinus rhythm (NSR) and no history of atrial fibrillation (AF) (Lubitz et al. 2015). It is the most important type of secondary AF (AF resulting from identifiable, primary, acute conditions) (Lubitz et al. 2015). The POAF episodes are often brief, paroxysmal and asymptomatic (Funk et al. 2003), with a peak incidence between days 2 and 4 after surgery (Funk et al. 2003, Mathew et al. 2004). Recurrences are frequent, especially during the first postoperative week (Lee et al. 2000).

2.2. Epidemiology

POAF is a common complication of surgery, with an incidence varying from 10–63% (Villareal et al. 2004, Echahidi et al. 2008) for cardiac surgeries (38–63% for valve surgery and 10–33% for coronary artery bypass graft surgery) (Turagam et al. 2016) and from 0.3–30% for non-cardiac surgeries (Christians et al. 2001, Echahidi et al. 2008). The incidence of POAF has increased continuously over the past decades, and the reason is probably related with the aging process of the population undergoing heart surgery. Nowadays, POAF represents approximately one-third of cases of secondary atrial fibrillation (Greenberg et al. 2017), and AF recurrence rate in patients who develop POAF after cardiothoracic surgery (46%) is lower than that in patients with POAF after non-thoracic surgery (64%) (Lubitz et al. 2015), supporting a greater role of transient factors than of a pre-existing substrate.

2.3. Pathophysiology

Underlying mechanisms are not completely defined but they include intraoperative and postoperative phenomena combined with the presence of pre-existing factors. This combination results in a totally vulnerable scenario for atrial fibrillation induction and maintenance (Nattel 2002, Andrade et al. 2014, Heijman et al. 2018, Dobrev et al. 2019).
Dobrev and colleagues (Dobrev et al. 2019) described in a structured model that POAF is mainly promoted by factors inducing atrial arrhythmogenic remodeling before surgery, as well as factors increasing the substrate vulnerability or the type/number of triggers postoperatively. Activation of the autonomic nervous system (Hogue et al. 1998, Echahidi et al. 2008) and local inflammation—related to surgical lesions (Gaudino et al. 2003, Ishii et al. 2005, Echahidi et al. 2008) and postoperative pericarditis (Ishii et al. 2005)—are the principal transient factors associated.

The literature showed that drugs that increase sympathetic tone increase the incidence of POAF (Feneck et al. 2001, Argalious et al. 2005) and perioperative β-blocker use reduces the incidence of POAF (White et al. 1984, Lamb et al. 1988). The incidence of POAF is lower after cardiac transplantation than after other forms of cardiac surgery (Argalious et al. 2005) and pharmacological denervation with botulinum toxin prevents POAF (Pokushalov et al. 2015). Factors that reinforce the idea from a combined sympathovagal triggering of POAF (Amar et al. 2003).

In addition, elevated preoperative plasma levels of IL-2 and IL-6 (important cytokines that mediate inflammatory responses) are also reported in some studies (Gaudino et al. 2003, Ucar et al. 2007, Pretorius et al. 2007, Hak et al. 2009). Postoperative activation of C-reactive protein has been also associated with POAF occurrence (Kaireviciute et al. 2010), and corticosteroids can reduce the incidence of POAF by inhibiting cytokine release (Ho und Tan 2009).

In summary, POAF appears to be promoted by addition of transient postoperative factors on a pre-existing and surgery-induced substrate, resulting in a re-entry structural and electrical remodeling.

2.4. Risk Factors

Atrial remodeling is an important predisposing factor for POAF, therefore elements that interfere in this situation play a significant role in this pathology. Registries have been showed the independent association between some specific factors and POAF in cardiac surgery, such as: elevated age, male sex, congestive heart failure, arterial hypertension, obesity, white ethnicity, chronic obstructive pulmonary disease (COPD), mitral valve surgery, use of intra-aortic balloon pump, long cross-clamp time and bicalval cannulation (Aranki et al. 1996,

2.5. Possible Deleterious Effect

POAF as a post-operative complication has major adverse consequences for patients and the health care system, including increased risks of post-operative stroke, peri-operative acute kidney injury (El-Chami et al. 2010, Thorén et al. 2020), increased length of hospital stay (Echahidi et al. 2008, Almassi et al. 2019) and mortality (El-Chami et al. 2010, Thorén et al. 2020). Notably is also the fact that the high AF recurrence rates in patients with POAF make this condition a clear marker of subsequent risk of long-standing persistent AF.

2.6. Underestimated Risk

Despite the high incidence, POAF has generally not been considered harmful, because of its perceived reversibility. Evidence from prospective randomized trial suggests that the vast majority of patients after CABG surgery return to normal sinus rhythm within 60 days, irrespective of the therapeutic strategy (rhythm control or rate control) (Gillinov et al. 2016).

At the same time, several studies demonstrate the hazardous potential of POAF in several clinical endpoints such as mortality, stroke, heart failure and chronic AF (Almassi et al. 2019, Thorén et al. 2020, Filardo et al. 2020).

Thus, it appears unclear whether POAF is harmless or harmful and the current perception of POAF may be influenced by individual publications.
3. Hypothesis and Aim of the Study

Based on the perceived controversy from the recent randomized trial evidence (Gillinov et al. 2016) and the associations presented from propensity matched studies (Schwann et al. 2018, Filardo et al. 2020), we set out to systematically review the entire literature and thoroughly address the impact of POAF on clinical outcomes, focusing on all classic cardiovascular adverse events during the peri-operative period and long-term follow-up.
4. Original Publication

4.1. Manuscript

Atrial Fibrillation after Cardiac Surgery –
A Systematic Review and Meta-Analysis

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GLOSSARY OF ABBREVIATIONS

AF: atrial fibrillation
CABG: coronary artery bypass grafting
ECG: electrocardiogram
IRR: incidence rate radio
NSR: normal sinus rhythm
OR: odds ratio
POAF: new-onset post-operative atrial fibrillation
SMD: standardized mean difference
Central Message: POAF is associated with peri-operative mortality, stroke, myocardial infarction, acute renal failure and long-term mortality, stroke, long-standing persistent AF, hospital and ICU length of stay.
Perspective Statement: While a directly causal relationship between POAF and these adverse cardiovascular events cannot be totally established, the information represents an important milestone for future hypotheses about its etiology and for designing randomized trials addressing its prevention/treatment.
ABSTRACT

Objective: New-onset post-operative atrial fibrillation (POAF) after cardiac surgery is common, with rates up to 60%. POAF has been associated with early and late stroke, but its association with other cardiovascular outcomes is less known. The objective was to perform a meta-analysis of the studies reporting the association of POAF with peri-operative and long-term outcomes in cardiac surgery.

Methods: We performed a systematic review and a meta-analysis of studies presenting outcomes for cardiac surgery based on the presence or absence of POAF. MEDLINE, EMBASE and Cochrane Library were assessed, 57 studies (246,340 patients) were selected. Peri-operative mortality was the primary outcome. Inverse variance method and random model were performed. Leave-one-out analysis, sub-group analyses and meta-regression were conducted.

Results: POAF was associated with peri-operative mortality (odds ratio [OR]= 1.92, 95% confidence interval [CI] 1.58; 2.33), peri-operative stroke (OR= 2.17, 95% CI 1.90; 2.49), peri-operative myocardial infarction (OR= 1.28, 95% CI 1.06; 1.54), peri-operative acute renal failure (OR= 2.74, 95% CI 2.42; 3.11), hospital (standardized mean difference [SMD]= 0.80, 95% CI 0.53; 1.07) and ICU stay (SMD= 0.55, 95% CI 0.24; 0.86), long-term mortality (incidence rate ratio [IRR]= 1.54, 95% CI 1.40; 1.69), long-term stroke (IRR= 1.33, 95% CI 1.21; 1.46) and long-standing persistent atrial fibrillation (IRR= 4.73, 95% CI 3.36; 6.66).

Conclusion: The results suggest that POAF in cardiac surgery is associated with an increased occurrence of most short and long-term cardiovascular adverse events. However, the causality of this association remains to be established.

KEYWORDS

post-operative atrial fibrillation, atrial fibrillation, heart surgery, arrhythmia
INTRODUCTION

New-onset postoperative atrial fibrillation (POAF) is defined as the new development of atrial fibrillation after surgery in patients with previous sinus rhythm (NSR) and no history of atrial fibrillation (AF). It is the most important type of secondary AF (AF resulting from identifiable, primary, acute conditions).

POAF is a common complication of surgery, with an incidence varying from 10–63% for cardiac surgeries (38–63% for valve and 10–33% for coronary artery bypass graft surgery). Despite the high incidence, POAF has generally not been considered harmful, because of its perceived reversibility. Evidence from prospective randomized trials suggests that the vast majority of patients after CABG surgery return to normal sinus rhythm within 60 days.

In contrast, other non-randomized evidence suggests that POAF may be associated with increased risks of post-operative stroke, peri-operative acute kidney injury, increased length of hospital stay and mortality. Even meta-analyses have addressed this topic, but limited their assessment to stroke and peri-operative mortality, mixed cardiac and non-cardiac surgery patients or are already outdated because many important studies appeared only recently.

Based on the perceived controversy from the recent randomized trial evidence and the associations presented from propensity matched studies and meta-analyses, we set out to systematically review the entire literature and thoroughly address the impact of POAF on clinical outcome, focusing on all classic cardiovascular adverse events during the peri-operative period and long-term follow-up.

METHODS

This analysis was prospectively registered on the International Prospective Register of Systematic Reviews in Health and Social Care (PROSPERO, ID number CRD42020181049).
Ethical and IRB approval was not required for this analysis as no human or animal subjects were involved.

**Search strategy**

A medical librarian (MD) performed a comprehensive literature search to identify contemporary studies comparing outcomes in patients with POAF with those in NSR after cardiac surgery. Searches were run on April 22, 2020 in the following databases: Ovid MEDLINE® (ALL; 2008 to present); Ovid EMBASE (1974 to present); and The Cochrane Library (Wiley). The full search strategy for Ovid MEDLINE is available in **Supplementary Table 1**.

**Study selection and eligibility criteria**

The study selection was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) strategy. After de-duplication, records were screened by two independent reviewers (TC and HK). Any discrepancies and disagreements were resolved by a third author (TD). All titles and abstracts were reviewed against pre-defined inclusion and exclusion criteria. Studies were considered for inclusion if they were written in English and reported direct comparison between POAF patients and NSR patients following cardiac surgery and had at least 1 outcome of interest reported. Studies evaluating non-cardiac surgeries, conference abstracts and proceedings and case reports were excluded. Included studies indicated clearly that the patients were evaluated on admission and that they had also no previous history of alleged atrial fibrillation.

Following the first round of screening, full text was pulled for selected studies for a second round of eligibility screening. Reference lists for articles in these selected studies were also searched for any relevant articles not captured by the original search strategy.

**Data abstraction and quality assessment**
The data extraction and the quality assessment were performed independently by two different investigators (TC and HK) and verified by a third investigator (TD) for accuracy. The following variables were extracted: age, sex, left ventricular ejection fraction, hypertension, diabetes, chronic obstructive pulmonary disease, prior cerebrovascular accident, prior myocardial infarction, prior use of beta-blockers, previous heart surgery, chronic renal failure, serum creatinine level.

For short term binary outcomes, number of events were extracted from the included studies and expressed as odds ratio, for long term outcomes, incidence rate ratio was estimated.

Risk of bias was assessed based on Newcastle-Ottawa assessment scale (Supplementary Table 2)\textsuperscript{15}. Publication bias was also assessed for the primary outcome (Supplementary Figure 1).

**Outcomes and effect summary**

The primary outcome was peri-operative mortality.

Secondary outcomes were long-term mortality, peri-operative and long-term stroke, peri-operative myocardial infarction, acute renal failure, long-standing persistent AF, hospital length of stay and intensive care unit length of stay. The peri-operative outcomes were defined as in-hospital or 30-day events.

Subgroup analysis of recent studies (published year: up to 2010 and after 2010), a sub-group analysis based on the method used for rhythm monitoring (comparison between continuous monitoring in intensive care unit and irregular electrocardiography until discharge vs. continuous monitoring during entire hospital stay) and a subgroup analysis addressing the type of surgery (CABG, CABG and valve surgery or valve surgery) were performed to test the solidity of the main analysis.

**Data analysis**

Peri-operative binary outcomes were reported as odds ratios (OR) while long-term outcomes,
were reported as incidence rate ratio (IRR); for both estimates the generic inverse variance method was used and 95% confidence intervals (CIs) were also presented. Sub-group analyses of the primary outcome were reported as OR associated with subgroup difference P-interaction (SGD-P) with 95% CI. Continuous outcomes were expressed as standardized mean difference (SMD) with 95% CI.

Random effect meta-analysis was performed using “metafor” and “meta” package \(^{16,17}\). NSR was the reference for all pairwise comparisons. Heterogeneity was reported as low (I\(^2\)= 0%–25%), moderate (I\(^2\)= 26%–50%), or high (I\(^2\) > 50\%)\(^{18}\). Leave-one-out analysis for the primary outcome was performed to assess the robustness of the obtained estimate. Meta-regression was used to explore the effects of age, sex, left ventricle ejection fraction, comorbidities, use of beta-blockers and previous heart surgery on the OR of the primary outcome.

Statistical significance was set at the 2-tailed 0.05 level, without multiplicity adjustments. All statistical analyses were performed using R (version 3.3.3, R Project for Statistical Computing) within RStudio.

### RESULTS

**Description of included studies**

A total of 6,632 records were identified through database searching. After duplicate records were removed, a total of 4,541 citations were retrieved and their titles and abstracts were screened. A total of 57 studies were included in the final analysis, with a total of 246,340 patients. The full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining the study selection process is available in Figure 1\(^{19,20}\). A complete list of studies included in the final analysis is presented in Supplementary Table 3.
All studies were observational. Sixteen studies were multicenter; 22 originated from the United States, 3 from Canada, 3 from Netherlands, 3 from Sweden, 3 from Brazil, 2 from Finland, 2 from Turkey, 2 from Iran, 2 from Australia, 2 from Korea, 2 from the United Kingdom, 1 each from Denmark, Serbia, Austria, Japan, Taiwan, Israel, Saudi Arabia, Malaysia, and Colombia. The number of patients in each study ranged from 44 to 49,264. The mean age ranged from 54.6 to 77.4 years. The percentage of female sex in each study ranged from 0.9 to 68.0%. In terms of patient comorbidities, the prevalence of hypertension ranged from 30.4 to 97.0%, the prevalence of diabetes ranged from 3.4 to 66.7%, the prevalence of chronic obstructive pulmonary disease ranged from 0.5 to 41.8%, the prevalence of prior cerebrovascular accident ranged from 0.6 to 29.2%, the prevalence of prior myocardial infarction ranged from 2.2 to 73.0% and the prevalence of chronic renal failure ranged from 1.0 to 15.0% (Supplementary Table 4).

Outcomes

Detailed results of the meta-analysis are outlined in Figure 6 – Graphical Abstract and summarized in Table 1.

Primary outcome

Occurrence of POAF was associated with increased peri-operative mortality (OR= 1.92, 95% CI 1.58; 2.33, p<0.0001, Figure 2). This finding was consistent in sub-analyses of studies published before and after 2010 (OR= 2.06, 95% CI 1.32; 3.20, and OR= 1.87, 95% CI 1.51; 2.32, p-interaction=0.71, Figure 3), in studies that used continuous monitoring in intensive care unit and daily electrocardiography until discharge and continuous monitoring during entire hospital stay (OR= 1.95, 95% CI 1.49; 2.56, and OR= 3.25, 95% CI 1.31; 8.07, p-interaction=0.30, Figure 4) and in individual studies addressing just CABG, CABG and valve surgery and, finally, just valve surgery (OR= 2.40, 95% CI 1.86; 3.09, OR= 1.66, 95% CI 0.75; 3.68, and OR= 0.89, 95% CI 0.28; 2.81, p-
interaction = 0.19, Figure 5). Leave-one-out analysis confirmed the solidity of the pooled estimate (Supplementary Figure 2).

Secondary outcomes

POAF was associated with peri-operative stroke (OR= 2.17, 95% CI 1.90; 2.49, p<0.0001,
Supplementary Figure 3), peri-operative myocardial infarction (OR= 1.28, 95% CI 1.06; 1.54,
p=0.0094, Supplementary Figure 4) and peri-operative acute renal failure (OR= 2.74, 95% CI
2.42; 3.11, p<0.0001, Supplementary Figure 5).

POAF was also associated with hospital length of stay (SMD= 0.80, 95% CI 0.53; 1.07,
p<0.0001, Supplementary Figure 6) and stay in the intensive care unit (SMD= 0.55, 95% CI
0.24; 0.86, p<0.0001, Supplementary Figure 7).

Finally, POAF was associated with long-term mortality (IRR= 1.54, 95% CI 1.40; 1.69,
p<0.0001, Supplementary Figure 8), long-term stroke (IRR= 1.33, 95% CI 1.21; 1.46,
p<0.0001, Supplementary Figure 9) and long-standing persistent AF (IRR= 4.73, 95% CI 3.36;
6.66, p<0.0001, Supplementary Figure 10).

Meta-regression

At meta-regression, the proportion of female patients was inversely associated with the OR for
the primary outcome (beta=-0.0293, p=0.0043). The proportion of diabetes and presence of
prior myocardial infarction were associated with "higher" OR for the primary outcome (beta=
0.0144, p=0.0056 and 0.0122, p=0.0303; respectively - Supplementary Table 5).

Discussion

Our analysis suggests that POAF in cardiac surgery is associated with an increased occurrence
of most short and long-term cardiovascular adverse events. Specifically, POAF appears to be
associated with peri-operative mortality, peri-operative stroke, peri-operative myocardial
infarction, peri-operative acute renal failure and long-term mortality, long-term stroke, long-
standing persistent AF, as well as hospital length of stay and intensive care unit length of stay
(Video 1).

However, our results cannot prove causation and it is unclear if POAF was involved in the
pathogenesis of the associated outcomes, or if it was only a marker of increased cardiovascular
risk. Recent data suggest that a pre-existing arrhythmogenic substrate exists before surgery and
discriminates who is going to develop POAF. It may potentially explain the long-term
recurrence rate of AF and the occurrence of other cardiovascular events 21.

It is known that factors such as inflammation, myocardial ischemia and autonomic nervous
system activation are thought to be superimposed on susceptible atrial substrates, making the
atrium vulnerable to AF induction and maintenance 22. In addition, pre-existing atrial fibrosis
may predispose patients to developing atrial fibrillation, which may have implications for the
timing of cardiac interventions 23.

Different clinical factors have also been described that may contribute to the development of
POAF. They range from pre-operative (hypertension, myocardial ischemia, valvular
abnormalities), through peri-operative (surgical trauma, local inflammation, large fluid shifts,
electrolyte disturbances) to post-operative conditions and events (inotropic drugs, atrial pacing,
pneumonia) 6,22. Thus, the combination of pre-disposing substrates for the natural development
of AF with peri-operative events would then increase the risk of POAF. This conceptual model
could explain the differences between classic surgery and TAVI for aortic valve replacement
24, 25 and the significant rate of POAF in non-cardiac surgery 26.

Although previous meta-analyses addressed this topic, they had significant limitations. For
instance, even the latest publication in the field 44 analyzed only 2 outcomes (stroke and
mortality) and did not include some of the important contemporary publications on POAF post-
cardiac surgery with more than 20,000 patients \cite{4, 7, 12, 13, 27, 30}. To the best of our knowledge, our comprehensive meta-analysis is the first to assess all important cardiovascular adverse events. We provide a broad overview of a number of important clinical outcomes and their association with POAF after cardiac surgery. Most of the analyzed publications were contemporary, with 75% of them (43 studies) published in the last 10 years. Furthermore, our sub-group analyses address some key issues when it comes to studies investigating POAF: the method used for rhythm monitoring and the type of cardiac surgical procedure. Both could potentially impact the results (i.e., the incidence of POAF can substantially vary between studies that use continuous monitoring for the entire in-hospital stay vs daily ECG after ICU discharge; and also between studies with different types of surgery procedures). We are the first to address those aspects as well as the first to compare the results of modern studies compared to the ones published before 2010. Additionally, we performed a meta-regression to measure the effect of 12 different pre-operative factors. The profound statistical evaluation of the topic provides robustness to the associations and underscores the previous publications. The outcomes of our meta-analysis are relevant as a significant number of patients after cardiac surgery develop POAF.

A recent STS-database analysis illustrates the magnitude of this problem \cite{31}. According to this study in the year 2017 in the US 64,751 of 233,022 patients undergoing CABG, aortic and mitral valve surgeries (or combinations of those) developed POAF \cite{31}. Considering all cardiac surgery procedures performed in the US per year, this finding would translate into approximately 100,000 patients that are affected from POAF per year only in the US. Aranki et al \cite{32} demonstrated that POAF can result in an extra cost of $10,000 to $11,500 to the hospital per patient developing this complication in the US. Furthermore, using the above numbers and American Heart Association (AHA) statistics assuming a POAF incidence of 30%, the extra cost due to POAF can be calculated to exceed $2 billion/year \cite{6}. 
Considering the possible negative effects of POAF, patients and physicians may be reluctant to recommend/undergo surgery. However, it is important to note that current indications for cardiac surgery are often free of alternatives (e.g., endocarditis), and the generated outcomes are often still superior to their existing interventional (i.e., TAVI) or conservative alternatives with regards to long-term perspective. It therefore appears that the positive effects of surgery outweigh the negative influence of POAF.

Given the association of POAF with worse peri-operative and long-term outcomes, the interest in this topic has recently grown. Based on the assumption that successful prevention or treatment of AF may be able to further improve outcomes of cardiac surgery, randomized trials have already been performed or recently initiated. Some of them have concentrated on preventing or reducing the incidence of POAF and others on the treatment and prevention of adverse events. The Anticoagulation for New-Onset Post-Operative Atrial Fibrillation after CABG (PACES) trial of the cardiothoracic surgical trials network (CTSN) [NCT04045665] is a good example of the latter.

In this context, our comprehensive meta-analysis provides a broad overview on POAF and its association with the most important clinical outcomes. Thus, the information we present might be useful when building future hypotheses or designing future randomized control trials on this topic.

**STUDY STRENGTH AND LIMITATIONS**

This analysis was conducted at study level rather than patient level. All studies were observational in nature. However, there are no randomized trials addressing this issue, which is not unexpected since equipoise for an adequate conservative control group does not exist. Another limitation of this study is the fact that patients with preexisting episodes of silent atrial fibrillation preoperatively might have also been included in the individual studies. However
this possibility exists for both investigated groups (NSR and POAF).

Since one of the inclusion criteria for the review was general studies concerning POAF, the aggregate study population was potentially heterogeneous. We pooled related outcomes and included the definitions of others that may be different among different studies, as acute renal failure and long-persistent AF (Supplementary Table 6).

We investigated the greatest number of contemporary studies so far and analyzed 9 different outcomes. Moreover, we performed different subgroup analyses and a meta-regression of 12 different pre-operative factors.

CONCLUSION

POAF after cardiac surgery appears to be associated with increased occurrence of a plethora of cardiovascular adverse events. However, the causality of these associations remains to be established.
Acknowledgements: We thank Mr. Benjamin May for editorial assistance.
BIBLIOGRAPHIC REFERENCES

4. Thorén E, Wernroth ML, Christersson C, Grinnemo KH, Jidéus L, Ståhle E. Compared with matched controls, patients with postoperative atrial fibrillation (POAF) have increased long-term AF after CABG, and POAF is further associated with increased ischemic stroke, heart failure and mortality even after adjustment for AF. Clin Res Cardiol. 2020.
FIGURE TITLES

Figure 1. PRISMA Flow Diagram.

Figure 2. Forest plot for peri-operative mortality.

Figure 3. Sub-group analysis of recent studies in peri-operative mortality (before and after 2010).

Figure 4. Sub-group analysis of rhythm monitoring in peri-operative mortality: comparison between continuous monitoring in intensive care unit and irregular electrocardiogram (ECG) until discharge vs. continuous monitoring during entire hospital stay.

Figure 5. Sub-group analysis of peri-operative mortality: comparison between type of surgeries (CABG; CABG and valve surgery; valve surgery).

Figure 6. Graphical Abstract.

Figure 7. Central Picture.
FIGURE LEGENDS

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Figure 2. Forest plot showing pooled rates of peri-operative mortality in patients with post-operative atrial fibrillation (POAF) versus no POAF. POAF compared with no POAF was associated with increased peri-operative mortality. Abbreviations: AVR= aortic valve replacement, CABG= coronary arterial bypass grafting, CI= confidence interval, MVR= mitral valve replacement, OR= odds ratio.

Figure 3. Forest plot for subgroup analysis of peri-operative mortality in studies published prior to the year 2010 and studies published after the year 2010. Abbreviations: AVR= aortic valve replacement, CABG= coronary arterial bypass grafting, CI= confidence interval, MVR= mitral valve replacement, OR= odds ratio.

Figure 4. Forest plot for subgroup analysis of rhythm monitoring type on peri-operative mortality (continuous monitoring in intensive care unit and irregular electrocardiogram (ECG) until discharge vs. continuous monitoring during entire hospital stay). Abbreviations: CI= confidence interval, OR= odds ratio.

Figure 5. Sub-group analysis of peri-operative mortality: comparison between type of surgeries (CABG; CABG and valve surgery; valve surgery). Abbreviations: CABG= coronary arterial bypass grafting, CI= confidence interval, OR= odds ratio.
Figure 6. Graphical Abstract. POAF after cardiac surgery appears to be associated with increased occurrence of peri-operative mortality, peri-operative stroke, peri-operative myocardial infarction, peri-operative acute renal failure, hospital length of stay, intensive care unit length of stay, long-term mortality, long-term stroke and long-standing persistent atrial fibrillation.

Figure 7. Central Picture. Outcomes of POAF compared with no POAF in cardiac surgery.
Table 1: Outcomes summary.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Studies</th>
<th>Patients</th>
<th>Measured estimate</th>
<th>Effect estimate</th>
<th>Heterogeneity (I^2)</th>
<th>Higher in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peri-operative outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>34</td>
<td>171563</td>
<td>OR</td>
<td>1.92 [1.58; 2.33], P&lt; 0.0001</td>
<td>80.0%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td>Stroke</td>
<td>35</td>
<td>179158</td>
<td>OR</td>
<td>2.17 [1.90; 2.49], P&lt; 0.0001</td>
<td>52.2%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>20</td>
<td>143464</td>
<td>OR</td>
<td>1.28 [1.06; 1.54], P=0.0094</td>
<td>64.7%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>22</td>
<td>139663</td>
<td>OR</td>
<td>2.74 [2.42; 3.11], P&lt; 0.0001</td>
<td>61.8%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td>Length of hospital stay</td>
<td>34</td>
<td>222442</td>
<td>SMD</td>
<td>0.80 [0.53; 1.07], P&lt; 0.0001</td>
<td>99.6%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td>Intensive care unit stay</td>
<td>15</td>
<td>75529</td>
<td>SMD</td>
<td>0.55 [0.24; 0.86], P&lt; 0.0001</td>
<td>99.5%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td><strong>Long term outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>28</td>
<td>-----</td>
<td>IRR</td>
<td>1.54 [1.40; 1.69], P&lt; 0.0001</td>
<td>83.8%, P&lt;0.001</td>
<td>POAF</td>
</tr>
<tr>
<td>Stroke</td>
<td>5</td>
<td>-----</td>
<td>IRR</td>
<td>1.33 [1.21; 1.46], P&lt; 0.0001</td>
<td>0.0%, P=5321</td>
<td>POAF</td>
</tr>
<tr>
<td>Long-standing persistent atrial fibrillation</td>
<td>10</td>
<td>-----</td>
<td>IRR</td>
<td>4.73 [3.36; 6.66], P&lt; 0.0001</td>
<td>70.6%, P=0.0014</td>
<td>POAF</td>
</tr>
</tbody>
</table>

IRR= incidence rate ratio; OR= odds ratio; POAF= post-operative atrial fibrillation;

SMD= standard mean difference.
Figure 1. PRISMA Flow Diagram.
Figure 2. Forest plot for peri-operative mortality.
Figure 3. Sub-group analysis of recent studies in peri-operative mortality (before and after 2010).

### Peri-operative mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>POAF Events</th>
<th>No POAF Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>After year 2010</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataran 2011 – AV/ACABG</td>
<td>44</td>
<td>994</td>
<td>35</td>
<td>994</td>
<td>1.27 [0.81; 2.00]</td>
<td>3.7%</td>
</tr>
<tr>
<td>Ataran 2011 – CABG</td>
<td>125</td>
<td>3278</td>
<td>66</td>
<td>3278</td>
<td>1.93 [1.43; 2.61]</td>
<td>4.2%</td>
</tr>
<tr>
<td>Ataran 2011 – MVR/CABG</td>
<td>14</td>
<td>243</td>
<td>14</td>
<td>243</td>
<td>1.00 [0.47; 2.14]</td>
<td>2.7%</td>
</tr>
<tr>
<td>Ataran 2011 – Others</td>
<td>45</td>
<td>424</td>
<td>43</td>
<td>424</td>
<td>1.05 [0.66; 1.64]</td>
<td>3.7%</td>
</tr>
<tr>
<td>Bramer 2011</td>
<td>28</td>
<td>361</td>
<td>34</td>
<td>495</td>
<td>1.05 [0.62; 1.79]</td>
<td>3.5%</td>
</tr>
<tr>
<td>Carrier-acerb 2019</td>
<td>2</td>
<td>51</td>
<td>1</td>
<td>45</td>
<td>1.80 [0.16; 20.50]</td>
<td>0.6%</td>
</tr>
<tr>
<td>Farouk 2018</td>
<td>6</td>
<td>183</td>
<td>8</td>
<td>454</td>
<td>2.88 [1.09; 7.59]</td>
<td>2.2%</td>
</tr>
<tr>
<td>Filardo 2019</td>
<td>101</td>
<td>2896</td>
<td>39</td>
<td>4890</td>
<td>4.49 [3.10; 6.92]</td>
<td>4.0%</td>
</tr>
<tr>
<td>Gised 2012</td>
<td>43</td>
<td>1868</td>
<td>44</td>
<td>4860</td>
<td>2.58 [1.69; 3.94]</td>
<td>3.8%</td>
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<tr>
<td>Helgadottir 2012</td>
<td>15</td>
<td>326</td>
<td>3</td>
<td>418</td>
<td>6.67 [1.91; 23.25]</td>
<td>1.6%</td>
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<tr>
<td>Horwich 2013</td>
<td>63</td>
<td>2214</td>
<td>128</td>
<td>5844</td>
<td>1.31 [0.96; 1.78]</td>
<td>4.2%</td>
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<tr>
<td>Ismai 2017</td>
<td>1</td>
<td>84</td>
<td>1</td>
<td>168</td>
<td>2.01 [0.12; 32.57]</td>
<td>0.4%</td>
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<tr>
<td>Ivanovic 2014</td>
<td>3</td>
<td>103</td>
<td>1</td>
<td>537</td>
<td>10.98 [1.10; 103.79]</td>
<td>0.6%</td>
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<tr>
<td>Kosmides 2018</td>
<td>18</td>
<td>161</td>
<td>31</td>
<td>893</td>
<td>3.50 [1.91; 6.42]</td>
<td>3.2%</td>
</tr>
<tr>
<td>Laper 2014</td>
<td>370</td>
<td>6556</td>
<td>600</td>
<td>40009</td>
<td>2.41 [2.12; 2.74]</td>
<td>4.6%</td>
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<tr>
<td>Luft 2011</td>
<td>38</td>
<td>1178</td>
<td>40</td>
<td>1890</td>
<td>1.54 [0.98; 2.42]</td>
<td>3.7%</td>
</tr>
<tr>
<td>Omer 2016</td>
<td>4</td>
<td>215</td>
<td>3</td>
<td>1033</td>
<td>6.51 [1.45; 29.29]</td>
<td>1.2%</td>
</tr>
<tr>
<td>Philip 2014</td>
<td>10</td>
<td>1480</td>
<td>15</td>
<td>3645</td>
<td>1.64 [0.73; 3.65]</td>
<td>2.6%</td>
</tr>
<tr>
<td>Pivato 2014</td>
<td>5</td>
<td>114</td>
<td>20</td>
<td>234</td>
<td>0.49 [0.16; 1.34]</td>
<td>2.1%</td>
</tr>
<tr>
<td>Saxena 2012</td>
<td>95</td>
<td>5547</td>
<td>170</td>
<td>13950</td>
<td>1.41 [1.10; 1.82]</td>
<td>4.3%</td>
</tr>
<tr>
<td>Saxena 2013</td>
<td>11</td>
<td>592</td>
<td>7</td>
<td>592</td>
<td>1.58 [0.61; 4.11]</td>
<td>2.2%</td>
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<tr>
<td>Steinberg 2014</td>
<td>53</td>
<td>676</td>
<td>67</td>
<td>1714</td>
<td>2.09 [1.44; 3.03]</td>
<td>4.0%</td>
</tr>
<tr>
<td>Swededs 2017</td>
<td>3</td>
<td>241</td>
<td>9</td>
<td>328</td>
<td>0.45 [0.12; 1.67]</td>
<td>1.5%</td>
</tr>
<tr>
<td>Tsai 2015</td>
<td>21</td>
<td>128</td>
<td>3</td>
<td>140</td>
<td>9.13 [2.65; 31.44]</td>
<td>1.6%</td>
</tr>
<tr>
<td>Wedinger 2014</td>
<td>1</td>
<td>59</td>
<td>2</td>
<td>325</td>
<td>2.78 [0.25; 31.21]</td>
<td>0.6%</td>
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</tbody>
</table>

Random effects model 32579

Year 2010 or before

<table>
<thead>
<tr>
<th>Study</th>
<th>POAF Events</th>
<th>No POAF Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>Weight</th>
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<tr>
<td>Allessi 2010</td>
<td>4</td>
<td>165</td>
<td>1</td>
<td>406</td>
<td>10.06 [1.12; 90.71]</td>
<td>0.7%</td>
</tr>
<tr>
<td>Almassi 1997</td>
<td>68</td>
<td>1143</td>
<td>80</td>
<td>2712</td>
<td>2.08 [1.48; 2.90]</td>
<td>4.1%</td>
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<tr>
<td>Bramer 2010</td>
<td>35</td>
<td>1122</td>
<td>64</td>
<td>3976</td>
<td>1.97 [1.30; 2.99]</td>
<td>3.8%</td>
</tr>
<tr>
<td>Hakata 2002</td>
<td>11</td>
<td>1141</td>
<td>41</td>
<td>2535</td>
<td>0.59 [0.30; 1.16]</td>
<td>3.0%</td>
</tr>
<tr>
<td>Harada 2002</td>
<td>2</td>
<td>238</td>
<td>0</td>
<td>477</td>
<td>10.10 [0.40; 211.12]</td>
<td>0.4%</td>
</tr>
<tr>
<td>Kalamazoulos 2007</td>
<td>58</td>
<td>2015</td>
<td>71</td>
<td>2015</td>
<td>0.81 [0.57; 1.15]</td>
<td>4.0%</td>
</tr>
<tr>
<td>Mariscalco 2007</td>
<td>28</td>
<td>2155</td>
<td>63</td>
<td>6279</td>
<td>1.20 [0.76; 1.91]</td>
<td>3.7%</td>
</tr>
<tr>
<td>Mariscalco 2008</td>
<td>19</td>
<td>570</td>
<td>7</td>
<td>1262</td>
<td>6.18 [2.58; 14.79]</td>
<td>2.4%</td>
</tr>
<tr>
<td>Niseogi 2007</td>
<td>2</td>
<td>91</td>
<td>11</td>
<td>335</td>
<td>0.66 [0.14; 3.04]</td>
<td>1.2%</td>
</tr>
<tr>
<td>Stansfield 2005</td>
<td>43</td>
<td>1129</td>
<td>108</td>
<td>14451</td>
<td>5.26 [3.07; 8.53]</td>
<td>4.0%</td>
</tr>
<tr>
<td>Stamus 2000</td>
<td>7</td>
<td>206</td>
<td>6</td>
<td>763</td>
<td>4.44 [1.48; 13.35]</td>
<td>1.9%</td>
</tr>
<tr>
<td>Villareal 2004</td>
<td>74</td>
<td>994</td>
<td>186</td>
<td>5481</td>
<td>2.29 [1.73; 3.02]</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Random effects model 10969

Heterogeneity: $I^2 = 79\%$, $R^2 = 0.1597$, $p < 0.01$

### Random effects model 43648

Heterogeneity: $I^2 = 80\%$, $R^2 = 0.2108$, $p < 0.01$

Test for subgroup differences: $X^2 = 0.14$, $d.f. = 1 (p = 0.71)$

No POAF POAF
Figure 4. Sub-group analysis of rhythm monitoring in peri-operative mortality: comparison between continuous monitoring in intensive care unit and irregular electrocardiogram (ECG) until discharge vs. continuous monitoring during entire hospital stay.

### Peri-operative mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Odds Ratio</th>
<th>95%–CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Continuous + ECG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ahlsson 2010</td>
<td>4 165 1 406</td>
<td>10.06</td>
<td>[1.12; 90.71]</td>
<td>1.1%</td>
</tr>
<tr>
<td>Bramer 2010</td>
<td>35 1122 64 3976</td>
<td>1.97</td>
<td>[1.30; 2.99]</td>
<td>5.4%</td>
</tr>
<tr>
<td>Bramer 2011</td>
<td>26 361 34 495</td>
<td>1.05</td>
<td>[0.62; 1.79]</td>
<td>5.0%</td>
</tr>
<tr>
<td>Filardo 2019</td>
<td>101 2896 39 4890</td>
<td>4.49</td>
<td>[3.10; 6.62]</td>
<td>5.6%</td>
</tr>
<tr>
<td>Gireld 2012</td>
<td>43 1868 44 4860</td>
<td>2.58</td>
<td>[1.68; 3.94]</td>
<td>5.4%</td>
</tr>
<tr>
<td>Hakala 2002</td>
<td>11 1141 41 2535</td>
<td>0.59</td>
<td>[0.30; 1.16]</td>
<td>4.4%</td>
</tr>
<tr>
<td>Heigedottir 2012</td>
<td>15 326 3 418  0.67</td>
<td>[1.91; 23.29]</td>
<td>2.5%</td>
<td></td>
</tr>
<tr>
<td>Ivanovic 2014</td>
<td>3 103 1 357</td>
<td>10.60</td>
<td>[1.10; 103.79]</td>
<td>1.1%</td>
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<tr>
<td>Kalavrouzotis 2007</td>
<td>58 2015 71 2015</td>
<td>0.81</td>
<td>[0.57; 1.15]</td>
<td>5.6%</td>
</tr>
<tr>
<td>Kosmidou 2018</td>
<td>18 161 31 893</td>
<td>3.60</td>
<td>[1.91; 6.42]</td>
<td>4.7%</td>
</tr>
<tr>
<td>Lapar 2014</td>
<td>370 9255 680 40009</td>
<td>2.41</td>
<td>[2.12; 2.74]</td>
<td>6.2%</td>
</tr>
<tr>
<td>Mariscalco 2007</td>
<td>26 2155 63 6279</td>
<td>1.20</td>
<td>[0.76; 1.91]</td>
<td>5.3%</td>
</tr>
<tr>
<td>Mariscalco 2008</td>
<td>19 570 7 1262</td>
<td>0.18</td>
<td>[2.08; 14.79]</td>
<td>3.6%</td>
</tr>
<tr>
<td>Nisanoglu 2007</td>
<td>2 91 11 335</td>
<td>0.66</td>
<td>[0.14; 3.04]</td>
<td>1.9%</td>
</tr>
<tr>
<td>Philip 2014</td>
<td>10 1490 15 3645</td>
<td>1.64</td>
<td>[0.73; 3.65]</td>
<td>3.9%</td>
</tr>
<tr>
<td>Pyhatto 2014</td>
<td>5 114 20 234</td>
<td>0.49</td>
<td>[0.18; 1.34]</td>
<td>3.2%</td>
</tr>
<tr>
<td>Saxena 2012</td>
<td>95 5547 170 13950</td>
<td>1.41</td>
<td>[1.10; 1.82]</td>
<td>6.0%</td>
</tr>
<tr>
<td>Saxena 2013</td>
<td>11 592 7 592</td>
<td>1.58</td>
<td>[0.61; 4.11]</td>
<td>3.4%</td>
</tr>
<tr>
<td>Tsai 2015</td>
<td>21 126 3 140</td>
<td>9.13</td>
<td>[2.65; 31.44]</td>
<td>2.6%</td>
</tr>
<tr>
<td>Villareal 2004</td>
<td>74 994 186 5481</td>
<td>2.29</td>
<td>[1.73; 3.02]</td>
<td>5.9%</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td>31692 92772</td>
<td>1.95</td>
<td>[1.49; 2.55]</td>
<td>62.7%</td>
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</tbody>
</table>

Heterogeneity: $I^2 = 84\%$, $r^2 = 0.2445$, $p < 0.01$

### Continuous Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Odds Ratio</th>
<th>95%–CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carter–storch 2019</td>
<td>2 51 1 45</td>
<td>1.80</td>
<td>[0.16; 20.50]</td>
<td>0.9%</td>
</tr>
<tr>
<td>Horwich 2013</td>
<td>63 2214 128 5844</td>
<td>1.31</td>
<td>[0.96; 1.78]</td>
<td>5.8%</td>
</tr>
<tr>
<td>Omer 2016</td>
<td>4 215 3 1033</td>
<td>6.51</td>
<td>[1.45; 29.29]</td>
<td>2.0%</td>
</tr>
<tr>
<td>Shirzad 2010</td>
<td>43 1129 108 14451</td>
<td>5.26</td>
<td>[3.67; 7.53]</td>
<td>5.6%</td>
</tr>
<tr>
<td>Stamatou 2000</td>
<td>7 206 6 763</td>
<td>4.44</td>
<td>[1.48; 13.30]</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td>3615 22139</td>
<td>3.33</td>
<td>[1.31; 8.07]</td>
<td>17.3%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 89\%$, $r^2 = 0.7617$, $p < 0.01$

### Random effects model

<table>
<thead>
<tr>
<th>Events</th>
<th>Odds Ratio</th>
<th>95%–CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>34907 114908</strong></td>
<td>2.12</td>
<td>[1.64; 2.74]</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 85\%$, $r^2 = 0.2968$, $p < 0.01$

Test for subgroup differences: $\chi^2 = 1.09$, df = 1 ($p = 0.30$)
Figure 5. Sub-group analysis of peri-operative mortality: comparison between type of surgeries (CABG; CABG and valve surgery; valve surgery).
Figure 6. Graphical Abstract.
Figure 7. Central Picture.
4.2. Letter of Acceptance

Date: Mar 12, 2021
To: "Torsten Doenst" doenst@med.uni-jena.de;benjamin.may@med.uni-jena.de
cc: rakesh arora (rakeshcarora@gmail.com), stephen.fremes@sunnybrook.ca
From: "Journal of Thoracic and Cardiovascular Surgery" jtcvs@aats.org
Subject: Acceptance of your Submission JTCVS-20-3301R2

Re: Original Manuscript JTCVS-20-3301R2
Atrial Fibrillation after Cardiac Surgery – A Systematic Review and Meta-Analysis

http://jtcvs.editorialmanager.com

Dear Dr. Doenst:

The editorial staff of The Journal of Thoracic and Cardiovascular Surgery is pleased to inform you that, after careful review, your Original Manuscript "Atrial Fibrillation after Cardiac Surgery – A Systematic Review and Meta-Analysis" has been accepted for publication.

You will receive an electronic copyright form and electronic page proofs directly from Elsevier Science Publishing. Once received, please return these proofs with all necessary corrections to Elsevier within 48 hours.

Thank you for your interest in and support of The Journal of Thoracic and Cardiovascular Surgery.

Sincerely,

Richard D. Weisel, MD, Editor
Rakesh C. Arora, MD, PhD, Associate Editor
Stephen E. Fremes, MD, MSc, Associate Statistical Editor

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5. Discussion

The meta-analysis suggests that POAF in cardiac surgery is associated with an increased occurrence of most short and long-term cardiovascular adverse events. Specifically, POAF appears to be associated with peri-operative mortality, peri-operative stroke, peri-operative myocardial infarction, peri-operative acute renal failure and long-term mortality, long-term stroke, long-standing persistent AF, as well as hospital length of stay and intensive care unit length of stay. We addressed the specific aspects of the meta-analysis, its strengths and limitations in the discussion of the original manuscript in the last section. I here discuss the general meaning of the associations found in our meta-analysis and meta-regression.

These results suggest that POAF should no longer be understood as transitory, self-sufficient and potentially clinical insignificant complication in cardiac surgery. The main concern arising from these findings shows that the cardiovascular community can benefit from better surgical outcomes if they comprehend the underlying mechanism of this condition. A key question addresses the role of POAF as an indicator of a particular combination of risk factors or as the main causative element itself.

5.1. Causality Aspects

A key question is whether POAF is a cause or merely an indicator of the described complications. It is conceivable that POAF occurs most frequently in patients with comorbidities and is therefore associated with increased mortality. It will currently be impossible to provide a definitive answer to this question because of the lack of an ideal control group of patients not having undergone surgery with otherwise the same demographic characteristics.

Anyway, cardiac surgery patients have higher incidence of POAF compared with those undergoing non-cardiac surgery (Christians et al. 2001, Villareal et al. 2004, Echahidi et al. 2008, Turagam et al. 2016). In this context, a certain degree of causality may be expected, mainly based on an exposure-response relationship: the incidence of POAF increases as the cardiac surgical approach becomes more invasive (Mihos et al. 2013, Tanawuttiwat et al. 2014). This notion is supported also in randomized trials comparing CABG and PCI where
similar patients in both groups show an increased incidence of POAF between procedures based on its level of invasiveness (i.e., CABG compared with PCI procedure –18.0% versus 0.1%) (Stone et al. 2016, Kosmidou et al. 2018). These findings reinforce the idea that reducing the degree of operative trauma may result in the reduction of POAF incidence. Thus, minimally invasive approaches may have to be investigated for their ability to reduce this adverse event. Observational evidence suggests that minimally-invasive procedures may indeed be associated with lower rates of POAF in comparison with the traditional approach (Tabata et al. 2008, Murzi et al. 2012, Glauber et al. 2013, Doenst und Lamelas 2017, Doenst et al. 2020, Faerber et al. 2020).

5.2. Race and Sex Difference

POAF also appears to be influenced by differences in the genetic background. For instance, POAF was observed to be a stronger predictor of operative mortality in Black individuals compared with White patients undergoing elective CABG (Efird et al. 2013). Black patients are less likely to develop POAF following CABG than Whites despite Black patients having an increased prevalence of POAF risk factors, such as age, hypertension, obesity and heart failure (Lahiri et al. 2011, Sun et al. 2011, Rader et al. 2011, Efird et al. 2013).

Male gender is also one of the possible risk factors described in the literature. The apparent protective effect of female sex shows not to be a mere coincidence, because male sex is frequently identified as an independent risk factor for POAF in CABG patients (Zacharias et al. 2005, Filardo et al. 2009, Alam et al. 2013, Almassi et al. 2019).

The race influence and how female sex protects against POAF are statements that require further research. Sex-specific studies have historically been missing from the evidence base but have been called for in recent years to help address continuing sex-related disparities in health care issues and key outcomes (Girardi et al. 2019, Gaudino et al. 2020a, Gaudino et al. 2020b).
5.3. **Long-standing Atrial Fibrillation as a Consequence of POAF**

An important point of our meta-analysis is the fact that it did not only show an association with short-term outcomes, but especially with long-term clinical adverse events. One of these implications that deserves specific attention is the fact that the meta-analysis demonstrates increased occurrence of long-standing AF in individuals that developed POAF (Ahlsson et al. 2010, Pillarisettil et al. 2014, Melduni et al. 2015, Tulla et al. 2015, Konstantino et al. 2016, Lee et al. 2017, Park et al. 2017, Carter-Storch et al. 2019, Thorén et al. 2020). Patients with POAF can present increased incidence of AF not only compared with patients without POAF but also compared with matched presumably healthy controls (Thorén et al. 2020). This increase in AF compared with controls persisted over time and was valid after more than 10 years of follow-up. On the other hand, the non-POAF cohort showed no increase in AF beyond the first postoperative year (Thorén et al. 2020). This finding supports the notion that a certain substrate for the development of AF is present at an increased prevalence in those patients developing POAF. Thus, surgical trauma triggers AF earlier than it would appear naturally anyway (Dobrev et al. 2019). The fact that POAF may lead to chronic AF then of course introduces all adverse events associated with chronic AF into the POAF arena. Patients with chronic AF show a dramatic increase in the incidence of pathologies such as stroke and heart failure (Chen et al. 2018, Vintila et al. 2019). Based on the economic, health and social impact from atrial fibrillation, these results are certainly alarming and accentuate the harmful potential of POAF (Chen et al. 2018, Vintila et al. 2019). Therefore, it is clear that POAF is a clinical entity that deserves attention and probably the investment of efforts to combat it through new medical therapies, new surgical approaches and new therapeutic alternatives.

5.4. **Management and Possible Treatments**

5.4.1. **Medication**

Nowadays, perioperative beta-blocker treatment is the main pharmacologic therapy with the objective to reduce rates of POAF (Echahidi et al. 2008, Dobrev et al. 2019). Other therapies such as amiodarone, verapamil, diltiazem, and digoxin are used less frequently and are generally less effective (Buckley et al. 2007). Due to the low efficacy of traditional drug therapy, new solutions have been proposed in order to act not only in the causative mechanism, but also in the prophylaxis of possible deleterious effects.
In this context, the use of anticoagulants proved to be a potential treatment in POAF due to its classic use in chronic atrial fibrillation. Recently, El-Chami and colleagues analyzed the connection between anticoagulation and survival in cardiac surgery patients with POAF, showing mortality reduction in patients treated with warfarin, after adjusting for age, sex, and medical comorbidities (El-Chami et al. 2010).

Generally, anticoagulation in atrial fibrillation has been aimed at reducing stroke risk and minimizing other side effects. However, anticoagulation in patients with POAF is an unexplored topic. No guidelines provide specific recommendations for initiation of anticoagulation for POAF in the post-cardiac surgery population (Macle et al. 2016, Kirchhof et al. 2016). The majority of evidence for anticoagulation in AF emerges mostly from the non-surgical community, which have a substantially different risk profile compared to surgical patients in terms of bleeding risk and, above all, as possible trigger for AF. Accordingly, as the profile of patients is different and especially the etiology of AF, it is difficult to draw conclusions about the therapeutic efficacy of these drugs. Thus, undoubtedly the role of anticoagulation in POAF is a topic that needs to be explored with an accurate study design through a randomized clinical approach.

In the long term, for the patient with long-standing persistent atrial fibrillation after cardiac surgery, the use of Novel Oral Anticoagulants (NOAC) may be plausible, as a number of studies have shown NOACs reduce bleeding risk and other severe complications in comparison with warfarin (Hicks et al. 2016, Aimo et al. 2018). However, no data has shown the effect of NOACs in the specific population of patients developing POAF.

5.4.2. Bi-atrial Pacing

Bi-atrial pacing has emerged as a promising approach to reduce the incidence of POAF. The rationale is that the electric maintenance of atrio-ventricular synchrony has shown to reduce the incidence of atrial fibrillation by suppressing premature atrial complexes and runs of supraventricular re-entry rhythm (Saksena et al. 1996, Gillis et al. 1999).
A recent work on the topic, showed in a pairwise and network meta-analysis involving 14 trials that bi-atrial pacing, compared to other pacing modalities, is associated with lower rates of POAF following CABG (Ruan et al. 2020). These findings demonstrate that an effective therapy for POAF is plausible and accessible. However, bi-atrial pacing has not yet been accepted in routine practice, possibly for its technical need for the tedious need to place two epicardial pacemaker wires. We are currently starting a trial in our Department to assess the impact of bi-atrial pacing and the possible therapeutic impact of atrial cardioversion on the incidence and clinical course of POAF (Defi-Pace trial). Other trials are currently ongoing in this field.

5.5. Current Prospective Trials on POAF

5.5.1. CABG-AF Trial

CABG-AF is a multicenter trial where study patients undergoing CABG, without previous history of atrial fibrillation or other complex rhythm disorders are receiving an event-recorder implantation at the end of surgery. Their heart rhythms are being continuously monitored for up to 3 years. Data concerning the development of atrial fibrillation, atrial fibrillation burden, atrial fibrillation density, number and length of atrial fibrillation, episodes, silent vs. symptomatic episodes, stroke and mortality will be collected and evaluated. Our center is one of the four surgical centers participating in the study within the German Heart Network.

5.5.2. PACES Trial

The Anticoagulation for New-Onset Post-Operative Atrial Fibrillation after CABG (PACES) trial [NCT04045665] is a multicenter randomized controlled trial with the aim to evaluate the effectiveness (prevention of thromboembolic events) and safety (major bleeding) of adding oral anticoagulation (OAC) to background antiplatelet therapy in patients who develop new-onset post-operative atrial fibrillation (POAF) after isolated coronary artery bypass graft (CABG) surgery. In the trial, 3200 patients are been randomized in 2 arms:

- OAC-based strategy (experimental arm): OAC with vitamin K antagonist (VKA) with international normalized ratio (INR) target 2-3 or any approved direct oral anticoagulant (apixaban, rivaroxaban, edoxaban or dabigatran) in addition to
background antiplatelet therapy with aspirin 75-325mg once-daily or a P2Y12-inhibitor (clopidogrel or ticagrelor);

- Antiplatelet-only strategy (control arm): with aspirin 75-325mg once-daily or a P2Y12-inhibitor (clopidogrel or ticagrelor).

The primary outcome of the study is a composite of death, stroke, transient ischemic attack, myocardial infarction, systemic arterial thromboembolism or venous thromboembolism.
6. Conclusions

POAF after cardiac surgery appears to be associated with increased occurrence of a plethora of cardiovascular adverse events. While a directly causal relationship between POAF and these adverse cardiovascular events cannot be totally established. The information represents an important milestone for future hypotheses about etiology from POAF and for designing randomized trials addressing its prevention/treatment.
7. Bibliography References


Thorén E, Wernroth ML, Christersson C, Grimmelmo KH, Jidéus L, Ståhle E. 2020. Compared with matched controls, patients with postoperative atrial fibrillation (POAF) have increased long-term AF after CABG, and POAF is further associated with increased ischemic stroke, heart failure and mortality even after adjustment for AF. Clin Res Cardiol.


8. Appendix

8.1. Sworn Statement
(*ehrenwörtliche Erklärung*)

I hereby declare that I am familiar with the doctoral regulations of the Medical Faculty of the Friedrich Schiller University.

I wrote the dissertation myself and all aids, personal communications and sources I used are given in my work.

The following people supported me in the selection and evaluation of the material as well as in the preparation of the manuscript: Univ. Prof. Dr. med. Torsten Doenst and Dr. med. Hristo Kirov as well as the other co-authors of the manuscript.

The help of a doctoral advisor was not used and that third parties did not receive any direct or indirect monetary benefits from me for work related to the content of the submitted dissertation.

I have not yet submitted the dissertation as an examination paper for a state or other scientific examination.

I have not submitted the same, essentially similar or a different dissertation to another university as a dissertation.

__________________________  ______________________
Place, Date                       T. Caldonazo
8.2. Acknowledgments

I would like to thank Univ. Prof. Dr. med. Torsten Doenst for guidance, trust and patience. His competent support had fundamental importance for this work, and his commitment with research and with teaching moulds admirable values that make him a great example for me not only in the clinical activities, but especially in the scientific field.

I would like also to thank all the co-authors of the publication, in special Dr. med Hristo Kirov. They supported me with technical advice and instructions, which were fundamental to perform this work.

Finally, I am totally grateful for the constant support from my parents, my brother and my friends.