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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

# Baseline and postoperative levels of C-reactive protein and interleukins as inflammatory predictors of atrial fibrillation following cardiac surgery: a systematic review and meta-analysis

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## Abstract

**Background:** Postoperative atrial fibrillation (POAF) is a leading arrhythmia with high incidence and serious clinical implications after cardiac surgery. Cardiac surgery is associated with systemic inflammatory response including increase in cytokines and activation of endothelial and leukocyte responses.

**Aim** This systematic review and meta-analysis aimed to determine the strength of evidence for evaluating the association of inflammatory markers, such as C-reactive protein (CRP) and interleukins (IL), with POAF following isolated coronary artery bypass grafting (CABG), isolated valvular surgery, or a combination of these procedures.

**Methods:** We conducted a meta-analysis of studies evaluating measured baseline (from one week before surgical procedures) and postoperative levels (until one week after surgical procedures) of inflammatory markers in patients with POAF. A comprehensive search was performed in electronic medical databases (Medline/PubMed, Web of Science, Embase, Science Direct, and Google Scholar) from their inception through May 2017 to identify relevant studies. A comprehensive subgroup analysis was performed to explore potential sources of heterogeneity.

**Results:** A literature search of all major databases retrieved 1014 studies. After screening, 42 studies were analysed including a total of 8398 patients. Pooled analysis showed baseline levels of CRP (standard mean difference [SMD] 0.457 mg/L, $p < 0.001$), baseline levels of IL-6 (SMD 0.398 pg/mL, $p < 0.001$), postoperative levels of CRP (SMD 0.576 mg/L, $p < 0.001$), postoperative levels of IL-6 (SMD 1.66 pg/mL, $p < 0.001$), postoperative levels of IL-8 (SMD 0.839 pg/mL, $p < 0.001$), and postoperative levels of IL-10 (SMD 0.590 pg/mL, $p < 0.001$) to be relevant inflammatory parameters significantly associated with POAF.

**Conclusions:** Perioperative inflammation is proposed to be involved in the pathogenesis of POAF. Therefore, perioperative assessment of CRP, IL-6, IL-8, and IL-10 can help clinicians in terms of predicting and monitoring for POAF.


**Key words:** atrial fibrillation, inflammation, C-reactive protein, cytokines, interleukins, review, meta-analysis

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## INTRODUCTION

Postoperative atrial fibrillation (POAF) is a leading arrhythmia with serious clinical implications after cardiac surgery, precipitating a wide spectrum of complications and morbidities, such as haemodynamic instability, thromboembolism, transient ischaemic attack, stroke, end organ failure, prolonged hospitalisation, and associated increase in health care costs and mortality [1, 2]. Atrial fibrillation (AF) is diagnosed in up to 50% of patients after coronary artery bypass grafting (CABG) and in over 60% of patients after combined CABG and valve surgery with incidence peaks occurring the first three days after surgery [2, 3]. AF is based on highly complex and multifactorial pathophysiological mechanisms, such as oxidative stress, inflammation, prothrombotic state, and sympathetic/parasympathetic activation [3, 4]. An appropriate modality for diagnosis and monitoring of AF should, on the one hand, facilitate preventive and therapeutic measures by timely diagnosis, and, on the other hand, not burden patients with excessive healthcare costs, while being applicable in a majority of health centres worldwide [4]. Administration of antiarrhythmic and antioxidant therapeutics for prevention or treatment of AF can reduce its incidence and recurrence rate. Simple surgical method such as posterior pericardiotomy may reduce the risk of POAF [3, 4].

As is widely known, cardiac surgery and the use cardiopulmonary bypass (CPB) are associated with systemic inflammatory response including activation of clotting factors, platelets and fibrinolysis, increase in inflammatory cytokines, and activation of endothelial and leukocyte responses [5, 6]. AF is also associated with infiltration of immune cells and proteins mediating inflammatory response in cardiac tissue and circulatory processes [5, 6].

Various studies have been recently published focusing on the relationship between inflammation and the occurrence of POAF. However, so far, the data from the studies have been largely inconclusive. This comprehensive meta-analysis sought to determine the strength of evidence for evaluating the association of baseline and postoperative levels of high-sensitivity C-reactive protein (CRP) and interleukins (IL), such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, and IL-17 with the occurrence of POAF.

## METHODS

### *Literature search*

A comprehensive search was performed by four co-authors independently in electronic medical databases (Medline/PubMed, Web of Science, Embase, Science Direct, and Google Scholar) from their inception through 10th May 2017 to identify relevant studies on the association of measured baseline (from one week before surgery) and postoperative levels (until one week after surgery) of inflammatory markers, such as CRP and interleukins 1–17, with the occurrence of AF after isolated CABG, valvular surgery, or combined procedures. Predefined keywords for searching were: "C-reactive protein", "CRP",

"acute phase reactant", "interleukin", "interleukin-1", "IL-1", "interleukin-2", "IL-2", "interleukin-3", "IL-3", "interleukin-4", "IL-4", "interleukin-5", "IL-5", "interleukin-6", "IL-6", "interleukin-7", "IL-7", "interleukin-8", "IL-8", "interleukin-9", "IL-9", "interleukin-10", "IL-10", "interleukin-11", "IL-11", "interleukin-12", "IL-12", "interleukin-13", "IL-13", "interleukin-15", "IL-15", "interleukin-17", "IL-17", and "atrial fibrillation", "supraventricular arrhythmia", "cardiac surgery", "open heart surgery", "cardiovascular surgery", "coronary artery bypass surgery", "CABG", "valvular surgery", and "surgery". There were no limitations for the sample size of the studies, time, and language of publications. Abstracts without peer-review or those only published as congress presentations were not enrolled in the meta-analysis. Two investigators checked to find additional studies not indexed in medical databases by searching in retrieved references of the enrolled studies, recent published review articles, and meta-analyses.

### Study selection

Studies that met the following inclusion criteria were enrolled in the analysis: 1) human subjects; 2) case-control or cohort studies; 3) patients undergoing either CABG or heart valve surgery, or a combination of both; 4) comparing patients with POAF and postoperative sinus rhythm (POSR) in terms of inflammatory markers.

### Data extraction and outcome measures

Six investigators (SA-H-S, AS, M-RL, SY, M-PS, and SJM) independently extracted the data, whereas two of them integrated and compared all of the filled checklists. A consensus standardised abstraction checklist was applied for recording data in each enrolled study in order to resolve the discrepancies. The following items were examined through subgroup analyses of disparities in the patients' characteristics for exploration of heterogeneity among the studies: 1) year of publication (before 2000 vs. after 2000); 2) geographical area (Africa, Asia, Europe, North-America, Oceania, South-America); 3) type of study (case-control vs. cohort); 4) number of patients (≤ 200 vs. > 200); 5) average age (≤ 60 vs. > 60 years); 6) percentage of male patients (≤ 70% vs. > 70%); 7) history of diabetes mellitus (≤ 30% vs. > 30%); 8) history of arterial hypertension (≤ 70% vs. > 70%); 9) history of cigarette smoking (≤ 30% vs. > 30%); 10) history of myocardial infarction (≤ 20% vs. > 20%); 11) baseline left ventricular ejection fraction (≤ 50% vs. > 50%); 12) preoperative use of medications, such as diuretics, beta-blockers, statins, angiotensin converting enzyme inhibitors or angiotensin receptor blockers (for each: ≤ 70% vs. > 70%); 13) type of surgical procedure (isolated CABG, isolated valvular surgery, combined procedures); 14) utilisation of CPB (on-pump vs. off-pump); 15) status of surgery (elective, non-elective); 16) duration of cross clamping (≤ 60 min vs. > 60 min); and 17) duration of CPB (≤ 100 min vs. > 100 min).

### Homogenisation of extracted data

Continuous data were expressed as mean ± standard deviation (SD). In cases when interquartile ranges were reported, the mean was calculated as [minimum + maximum + 2 (median)]/4 and SD as (maximum – minimum)/4 for groups with sample sizes of n ≤ 70, and (maximum – minimum)/6 for n > 70 [7].

### Quality assessment and statistical analysis

Two investigators (LM and MG) evaluated the Newcastle-Ottawa scale and design of the studies to assess the quality of the studies [8]. Total scores ranged between 0 (worst) and 9 (best quality) for case-control or cohort studies. For non-categorical data, pooled effect size was presented as standard mean difference (SMD) with 95% confidence interval (CI). Significant heterogeneity was found among the studies considering p value < 0.1 for Q test or $I^2$ > 50%. Heterogeneity among the trials was tested by applying a random effect model when indicated. Begg's test, which examines the presence of association between effect estimates and their variances, was used to evaluate publication bias. P values < 0.05 were considered statistically significant. Data analysis was carried out by STATA (version 11.0, Stata Corporation, College Station, Texas) using METAN and METABIAS commands.

## RESULTS

### Literature search strategy and included studies

A total of 1014 studies were extracted from the literature search and screened databases, of which 972 were excluded after detailed evaluation through the first review for unnecessary information (n = 870), insufficient report of endpoints of interest (n = 95), or reports on non-matched data (n = 7). Finally, 42 studies with a total of 8398 patients were included in the present meta-analysis [9–50] (Details about excluded and included studies are shown in **Supplemental Table 1 — see journal website**).

### Association of baseline levels of inflammatory markers with the occurrence of POAF

**CRP.** A total of 7671 patients were enrolled from 36 studies, of which 2240 were assigned to the POAF and 5431 to the POSR group (Table 1). The sample size of included studies ranged from 20 to 1138 cases (Table 1). Mean baseline level of CRP was 13.16 mg/L in the POAF group and 10.46 mg/L in the POSR group (Table 2). Pooled analysis showed that the mean baseline level of CRP was significantly higher in patients with POAF (positive predictor) than POSR cases, with SMD 0.457 mg/L (95% CI 0.405 to 0.509; p < 0.001) using the random effect model (Fig. 1), with considerable heterogeneity among the studies ($I^2$ = 95.5%; heterogeneity p < 0.001).

**Interleukins.** A total of 649 cases were selected from six studies on IL-6, of whom 237 were allocated to the POAF group and 412 to the POSR group (Table 1). Mean baseline level of IL-6 was 15.1 pg/mL in the POAF and 10.6 pg/mL

Table 1. Characteristics of studies included to meta-analysis evaluating association of pre- and postoperative inflammatory markers with postoperative atrial fibrillation

| First author [reference] | Year | Country | Design | AF (number) | SR (number) | Age-AF | Age-SR | Male-AF | Male-SR | Type of surgery | CPB pump: on or off | ES or NES | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Xu [9] | 2017 | China | Case-control | 108 | 400 | 63.51 | 61.9 | 74.07 | 75 | Alone CABG | Off | ND | 7 |
| Saskin [10] | 2017 | Turkey | Cohort | 153 | 509 | 62 | 61 | 77.8 | 82.9 | Alone CABG | On | Elective | 7 |
| Saskin [11] | 2016 | Turkey | Cohort | 294 | 844 | 60.5 | 60 | 25.1 | 74.9 | Alone CABG | On | Elective | 7 |
| Cerit [12] | 2016 | Turkey | Cohort | 36 | 70 | 67.3 | 63.2 | 83.3 | 92.9 | Alone CABG | On | Elective | 7 |
| Anatolevna [13] | 2016 | Russia | Case-control | 22 | 59 | 67.7 | 65.8 | 90.9 | 74.6 | Alone CABG | Combined | ND | 7 |
| Gecmen [14] | 2016 | Turkey | Cohort | 31 | 63 | 66 | 59 | 87 | 71 | Alone CABG | On | Elective | 8 |
| Korantzopoulos [15] | 2015 | Greece | Cohort | 44 | 65 | 65.4 | 67.7 | 70 | 74 | CABG and/or valve | Combined | Elective | 8 |
| Erdem [16] | 2014 | Turkey | Cohort | 43 | 92 | 67.2 | 61.3 | 69.7 | 72.8 | Alone CABG | On | Elective | 8 |
| Narducci [17] | 2014 | Italy | Case-control | 14 | 24 | 71 | 69 | 64 | 75 | Alone CABG | On | Elective | 8 |
| Limite [18] | 2014 | Italy | Cohort | 173 | 271 | 66.2 | 56.4 | 74 | 73.4 | CABG and/or valve | On | ND | 9 |
| Erdem [19] | 2014 | Turkey | Cohort | 38 | 127 | 67 | 64.9 | 81.57 | 77.16 | Alone CABG | On | Elective | 8 |
| Pilatis [20] | 2013 | Greece | Cohort | 44 | 81 | 68 | 63 | 98 | 93 | Alone CABG | Combined | Elective | 9 |
| Cao [21] | 2013 | Norway | Case-control | 61 | 93 | 50.7 | 45.2 | 54.09 | 46.23 | Valve alone | On | ND | 8 |
| Bjorgvinsdottir [22] | 2013 | Denmark | Case-control | 62 | 63 | 69 | 66 | 79 | 84.1 | Alone CABG | Combined | Elective | 6 |
| Sabol [23] | 2012 | Slovakia | Case-control | 30 | 15 | 62.5 | 61.9 | 76.7 | 66.7 | Alone CABG | ND | ND | 7 |
| Garcia [24] | 2012 | Chile | Cohort | 38 | 142 | 73.5 | 62.4 | 76.3 | 81 | Alone CABG | On | Elective | 8 |
| Skuladottir [25] | 2011 | Iceland | Case-control | 62 | 63 | 69 | 66 | 79 | 84.1 | Alone CABG | Combined | Elective and semi-emergency | 6 |
| Gabrielli [26] | 2011 | Chile | Cohort | 18 | 52 | 70 | 62 | 66 | 73 | Alone CABG | On | Elective | 9 |
| Kaireviciute [27] | 2010 | Lithuania | Cohort | 30 | 70 | 67 | 63.2 | 93.3 | 82.9 | Alone CABG | On | Elective | 8 |
| Gasparovic [28] | 2010 | Croatia | Cohort | 55 | 160 | 66 | 60 | 67 | 73 | Alone CABG | On | Elective | 8 |
| Gibson [29] | 2010 | UK | Cohort | 107 | 168 | 68 | 63 | 87.9 | 81 | Alone CABG | Combined | Elective | 9 |
| Ji [30] | 2009 | China | Case-control | 33 | 107 | 68.8 | 64.5 | ND | ND | Alone CABG | Off | Elective | 7 |
| Girerd [31] | 2009 | Canada | Case-control | 147 | 147 | 55.7 | 58.4 | 100 | 100 | Alone CABG | Combined | Elective | 8 |
| Choi [32] | 2009 | South Korea | Cohort | 66 | 249 | 67.1 | 64.6 | 74.24 | 70.68 | Alone CABG | Off | Elective | 7 |
| Antoniades [33] | 2009 | UK | Cohort | 43 | 101 | 66.7 | 65.2 | 79.06 | 86.13 | Alone CABG | Off | Elective | 9 |
| Sezai [34] | 2009 | Japan | Case-control | 73 | 161 | 72.1 | 66.05 | 69.8 | 80.12 | Alone CABG | On | ND | 8 |
| Fontes [35] | 2009 | USA | Cohort | 17 | 43 | 71.8 | 70.3 | 94.1 | 74.4 | Alone CABG | On | Elective | 8 |
| Ziabakhsh-Tabari [36] | 2008 | Iran | Cohort | 11 | 43 | 51.4 | 57.28 | ND | ND | Alone CABG | On | Elective | 7 |
| Mehmet [37] | 2008 | Turkey | Case-control | 10 | 10 | 62.1 | 61.9 | 60 | 80 | Alone CABG | On | Elective | 7 |

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Table 1 (cont). Characteristics of studies included to meta-analysis evaluating association of pre- and postoperative inflammatory markers with postoperative atrial fibrillation

| First author [reference] | Year | Country | Design | AF (number) | SR (number) | Age-AF | Age-SR | Male-AF | Male-SR | Type of surgery | CPB pump: on or off | ES or NES | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Canbaz [38] | 2008 | Turkey | Case-control | 13 | 58 | 56 | 57 | 84.6 | 79.3 | Alone CABG | On | Elective | 7 |
| Qian [39] | 2008 | China | Case-control | 24 | 23 | ND | ND | ND | ND | Valve alone | On | Elective | 8 |
| Pretorius [40] | 2007 | USA | Cohort | 67 | 186 | 66.1 | 56.9 | 71.6 | 63.4 | CABG and/or valve | On | Elective | 7 |
| Ucar [41] | 2007 | Turkey | Cohort | 14 | 35 | 64.3 | 58.8 | 14.28 | 14.28 | Alone CABG | On | Elective | 7 |
| Ahlsson [42] | 2007 | Sweden | Cohort | 182 | 342 | 70.6 | 65.4 | 75 | 72 | CABG and/or valve | On | ND | 8 |
| Houge [43] | 2006 | USA | Case-control | 46 | 84 | 72 | 70 | 0 | 0 | CABG and/or valve | On | Elective | 6 |
| Ishida [44] | 2006 | Japan | Cohort | 11 | 28 | 70 | 60 | 64 | 75 | Alone CABG | Off | Elective | 8 |
| Lo [45] | 2005 | Netherland | Case-control | 34 | 122 | 67 | 60 | 68 | 71 | Alone CABG | Combined | Elective | 7 |
| Cosgrave [46] | 2005 | Ireland | Cohort | 55 | 94 | 65.2 | 60.9 | ND | ND | Alone CABG | On | Elective | 8 |
| Mandal [47] | 2005 | UK | Case-control | 15 | 15 | 65 | 65 | 80 | 80 | Alone CABG | Combined | Elective | 7 |
| Fontes [48] | 2005 | USA | Cohort | 26 | 46 | 71 | 63 | 81 | 80 | CABG and/or valve | On | Elective | 8 |
| Wang [49] | 2005 | China | Case-control | 93 | 301 | ND | ND | ND | ND | Alone CABG | On | Elective | 7 |
| Mandal [50] | 2004 | UK | Cohort | 62 | 267 | 65 | 64 | 79 | 83 | Alone CABG | Combined | Elective | 9 |

AF — atrial fibrillation; CABG — coronary artery bypass graft; CPB — cardiopulmonary bypass; ES — elective surgery; ND — no data; NES — non-elective surgery; NOS — Newcastle Ottawa Scale; SR — sinus rhythm

in the POSR group (Table 2). Pooled analysis indicated that IL-6 was significantly higher in patients with POAF (positive predictor) compared to POSR with SMD of 0.398 pg/mL (95% CI 0.227 to 0.569; $p < 0.001$, $I^2 = 92.1\%$; heterogeneity $p = 0.001$; Fig. 2). Regarding pooled assessment analysis, both groups were similar regarding the baseline level of IL-8 (number of studies = 2, SMD –0.09 pg/mL, 95% CI –0.37 to 0.19; $p = 0.54$ and $I^2 = 72.6\%$; heterogeneity $p = 0.05$, **Supplemental Figure 1 — see journal website**) and IL-10 (number of studies = 3, SMD –0.241 pg/mL, 95% CI –0.50 to 0.018; $p = 0.06$ and $I^2 = 0.0\%$; heterogeneity $p = 0.39$, **Supplemental Figure 2 — see journal website**). There were no reports comparing baseline levels of other interleukins between POAF and POSR.

### *Association of postoperative levels of inflammatory markers with the occurrence of POAF*

**CRP.** A total of 5382 cases were included from 23 studies, of which 1605 were assigned to the POAF group and 3777 to the POSR group (Table 1). Mean postoperative level of CRP was 240.7 mg/L in the POAF group and 219.9 mg/L in the POSR group (Table 2). Pooled analysis showed that the mean postoperative level of CRP was significantly higher in patients with POAF (positive predictor) than POSR patients, with SMD 0.576 mg/L (95% CI 0.512 to 0.636; $p < 0.001$) utilising the random effect model (Fig. 3). There was remarkable heterogeneity among the studies ($I^2 = 96.4\%$; heterogeneity $p < 0.001$).

**Interleukins.** Regarding pooled assessment analysis, there were more patients with POAF regarding the postoperative level of IL-6 as compared to POSR (number of studies = 5, SMD 1.66 pg/mL, 95% CI 1.42 to 1.89; $p < 0.001$, and $I^2 = 93.0\%$; heterogeneity $p = 0.001$, Fig. 4), IL-8 (number of studies = 3, SMD 0.839 pg/mL, 95% CI 0.620 to 1.057; $p < 0.001$, and $I^2 = 98.1\%$; heterogeneity $p = 0.001$, **Supplemental Figure 3 — see journal website**), and IL-10 (number of studies = 4, SMD 0.590 pg/mL, 95% CI 0.395 to 0.785; $p < 0.001$, and $I^2 = 90.0\%$; heterogeneity $p = 0.001$, **Supplemental Figure 4 — see journal website**). There were no reports comparing postoperative levels of other interleukins between POAF and POSR.

### *Publication bias and subgroup analysis*

Begg's tests showed that all analyses were without publication bias except for the relationship between baseline level of CRP and the occurrence of POAF (**Supplemental Figures 5–12 — see journal website**). Classification in relation to potential heterogeneity agents and subgroup analyses are reported in detail in **Supplemental Tables 2 and 3 (see journal website)**, respectively.

## DISCUSSION

Postoperative AF is considered a serious and common postoperative complication with a peak incidence in the first

Table 2. Information about haematological indices and their levels in each study

| First author [reference] | Markers | Levels |
|---|---|---|
| Measurement of inflammatory markers | | |
| Xu [9] | CRP | Preoperative: CRP [AF: 4.52 ± 2.88 vs. SR: 3.99 ± 3.48]<br>Postoperative: CRP [AF: 29.35 ± 19.1 vs. SR: 24.98 ± 12.68] |
| Saskin [10] | CRP | Preoperative: CRP [AF: 1.64 ± 0.76 vs. SR: 0.85 ± 0.35] |
| Saskin [11] | CRP | Preoperative: CRP [AF: 10.3 ± 8.3 vs. SR: 5.4 ± 2.9]<br>Postoperative: CRP [AF: 309 ± 34 vs. SR: 249 ± 48] |
| Cerit [12] | CRP | Preoperative: CRP [AF: 21 ± 47 vs. SR: 9 ± 14] |
| Anatolevna [13] | CRP, IL-6, IL-8, IL-10 | Preoperative:<br>CRP [AF: 1.4 ± 1.3 vs. SR: 1.2 ± 0.93]<br>IL-6 [AF: 30.1 ± 26.5 vs. SR: 25.7 ± 13.2]<br>IL-8 [AF: 2.7 ± 2.4 vs. SR: 2.2 ± 1.3]<br>IL-10 [AF: 6.3 ± 3.3 vs. SR: 7.4 ± 4.7]<br>Postoperative:<br>CRP [AF: 4.7 ± 0.7 vs. SR: 4.5 ± 0.8]<br>IL-6 [AF: 72.7 ± 60.8 vs. SR: 38 ± 34.6]<br>IL-8 [AF: 11.9 ± 6 vs. SR: 7.7 ± 5.4]<br>IL-10 [AF: 11.9 ± 6.4 vs. SR: 11.6 ± 5.7] |
| Gecmen [14] | CRP | Preoperative: CRP [AF: 33.9 ± 27.5 vs. SR: 27.5 ± 22.7] |
| Korantzopoulos [15] | CRP | Preoperative: CRP [AF: 83.25 ± 49.75 vs. SR: 43.75 ± 1.6] |
| Erdem [16] | CRP | Preoperative: CRP [AF: 10.6 ± 8.5 vs. SR: 5.6 ± 6.5] |
| Narducci [17] | CRP | Preoperative: CRP [AF: 10.4 ± 4.2 vs. SR: 5.67 ± 2.72]<br>Postoperative: CRP [AF: 41.35 ± 3.25 vs. SR: 45.95 ± 5.25] |
| Limite [18] | CRP | Preoperative: CRP [AF: 2.92 ± 0.28 vs. SR: 2.95 ± 0.3]<br>Postoperative: CRP [AF: 196.92 ± 25.65 vs. SR: 172.2 ± 20.46] |
| Erdem [19] | CRP | Preoperative: CRP [AF: 8.9 ± 19.6 vs. SR: 5.3 ± 8.7] |
| Pilatis [20] | CRP | Preoperative: CRP [AF: 4.82 ± 1.47 vs. SR: 3.95 ± 0.51]<br>Postoperative: CRP [AF: 114.78 ± 11 vs. SR: 128.25 ± 7.83] |
| Cao [21] | CRP | Preoperative: CRP [AF: 5.76 ± 1.61 vs. SR: 2.73 ± 0.94] |
| Bjorgvinsdottir [22] | CRP, IL-8, IL-10 | Preoperative:<br>IL-8 [AF: 12 ± 8 vs. SR: 14.75 ± 10.75]<br>IL-10 [AF: 30.75 ± 22.75 vs. SR: 40.75 ± 31.75]<br>Postoperative:<br>CRP [AF: 221.25 ± 95 vs. SR: 199.5 ± 84]<br>IL-8 [AF: 54.5 ± 50.5 vs. SR: 92 ± 88]<br>IL-10 [AF: 71 ± 54.25 vs. SR: 68 ± 51.5] |
| Sabol [23] | CRP | Postoperative: CRP [AF: 138.1 ± 41.1 vs. SR: 69.9 ± 25.8] |
| Garcia [24] | CRP | Preoperative: CRP [AF: 24 ± 23 vs. SR: 25 ± 27] |
| Skuladottir [25] | CRP | Postoperative: CRP [AF: 221.25 ± 95 vs. SR: 199.5 ± 84] |
| Gabrielli [26] | CRP | Preoperative: CRP [AF: 68 ± 14 vs. SR: 57 ± 12] |
| Kaireviciute [27] | CRP, IL-6 | Postoperative:<br>CRP [AF: 4.47 ± 1.57 vs. SR: 2.15 ± 0.56]<br>IL-6 [AF: 39.8 ± 20.6 vs. SR: 20.9 ± 9.3] |
| Gasparovic [28] | CRP | Preoperative: CRP [AF: 6 ± 16 vs. SR: 6 ± 13]<br>Postoperative: CRP [AF: 149 ± 82 vs. SR: 137 ± 72] |
| Gibson [29] | CRP | Preoperative: CRP [AF: 2.44 ± 0.69 vs. SR: 1.91 ± 0.5]<br>Postoperative: CRP [AF: 175.5 ± 13.66 vs. SR: 163.25 ± 8.83] |
| Ji [30] | CRP | Postoperative: CRP [AF: 165.7 ± 29.4 vs. SR: 105.3 ± 18.7] |
| Girerd [31] | CRP, IL-6 | Preoperative:<br>CRP [AF: 1.95 ± 2.67 vs. SR: 1.49 ± 2.74]<br>IL-6 [AF: 2.3 ± 1.6 vs. SR: 2.2 ± 2.1] |

→

Table 2 (cont). Information about haematological indices and their levels in each study

| First author [reference] | Markers | Levels |
|---|---|---|
| Choi [32] | CRP | Preoperative: CRP [AF: 6.6 ± 12.7 vs. SR: 4.7 ± 11.4] |
| | | Postoperative: CRP [AF: 177.1 ± 99.2 vs. SR: 150.3 ± 55.7] |
| Antoniades [33] | CRP | Preoperative: CRP [AF: 1.4 ± 0.55 vs. SR: 1.52 ± 0.42] |
| Sezai [34] | CRP | Preoperative: CRP [AF: 6.9 ± 17.4 vs. SR: 11.9 ± 27.9] |
| | | Postoperative: CRP [AF: 45.6 ± 29.2 vs. SR: 47.1 ± 29] |
| Fontes [35] | CRP | Preoperative: CRP [AF: 12 ± 22 vs. SR: 13 ± 18] |
| | | Postoperative: CRP [AF: 189 ± 74 vs. SR: 179 ± 54] |
| Ziabakhsh-Tabari [36] | CRP, IL-6 | Preoperative:<br>CRP [AF: 10.42 ± 9.58 vs. SR: 8.4 ± 4.9]<br>IL-6 [AF: 3.95 ± 1.02 vs. SR: 1.24 ± 0.8] |
| | | Postoperative: CRP [AF: 175.3 ± 60.1 vs. SR: 175.4 ± 64.4] |
| Mehmet OC [[37] | CRP | Preoperative: CRP [AF: 5.4 ± 3.1 vs. SR: 6.5 ± 4.4] |
| | | Postoperative: CRP [AF: 4.6 ± 1.7 vs. SR: 5 ± 1.4] |
| Canbaz [38] | CRP, IL-6, IL-10 | Preoperative:<br>CRP [AF: 23 ± 17 vs. SR: 17 ± 14]<br>IL-6 [AF: 11 ± 19 vs. SR: 9 ± 11]<br>IL-10 [AF: 60 ± 80 vs. SR: 50 ± 80] |
| | | Postoperative:<br>CRP [AF: 53 ± 17 vs. SR: 45 ± 17]<br>IL-6 [AF: 38 ± 36 vs. SR: 27 ± 37]<br>IL-10 [AF: 190 ± 130 vs. SR: 120 ± 150] |
| Qian [39] | CRP | Preoperative: CRP [AF: 2.73 ± 1.73 vs. SR: 2.34 ± 1.54] |
| Pretorius [40] | CRP, IL-6, IL-8, IL-10 | Postoperative:<br>CRP [AF: 13.1 ± 3.6 vs. SR: 14.1 ± 2.6]<br>IL-6 [AF: 380.6 ± 151.1 vs. SR: 174.8 ± 16.9]<br>IL-8 [AF: 85.2 ± 63.1 vs. SR: 18.6 ± 2.3]<br>IL-10 [AF: 2712.5 ± 298.6 vs. SR: 2463.6 ± 162] |
| Ucar [41] | CRP, IL-6 | Preoperative:<br>CRP [AF: 0.6 ± 0.2 vs. SR: 0.3 ± 0.2]<br>IL-6 [AF: 7.4 ± 3.6 vs. SR: 6.2 ± 2.9] |
| | | Postoperative:<br>CRP [AF: 22.4 ± 4.1 vs. SR: 16.9 ± 1.9]<br>IL-6 [AF: 100.7 ± 65.8 vs. SR: 36.9 ± 15.9] |
| Ahlsson [42] | CRP | Preoperative:<br>CRP [AF: 5.6 ± 9.1 vs. SR: 5 ± 6.4] |
| | | Postoperative: CRP [AF: 175.3 ± 60.1 vs. SR: 175.4 ± 64.4] |
| Houge JR [43] | CRP | Preoperative: CRP [AF: 13.3 ± 2.5 vs. SR: 11.7 ± 1.4] |
| Ishida [44] | IL-6 | Postoperative: IL-6 [AF: 435 ± 175 vs. SR: 247 ± 102] |
| Lo [45] | CRP | Preoperative: CRP [AF: 4.07 ± 1.57 vs. SR: 1.7 ± 0.45] |
| Cosgrave [46] | CRP | Preoperative: CRP [AF: 26.05 ± 7.25 vs. SR: 36.07 ± 8.05] |
| | | Postoperative: CRP [AF: 2372.5 ± 297.5 vs. SR: 2532.5 ± 201.6] |
| Mandal [47] | CRP | Preoperative: CRP [AF: 2.4 ± 1.2 vs. SR: 1.95 ± 1] |
| Fontes [48] | CRP | Preoperative: CRP [AF: 2.2 ± 3.2 vs. SR: 1.8 ± 2.1] |
| Wang [49] | CRP | Preoperative: CRP [AF: 43 ± 38 vs. SR: 39 ± 36] |
| | | Postoperative: CRP [AF: 542 ± 279 vs. SR: 219 ± 164] |
| Mandal [50] | CRP | Preoperative: CRP [AF: 1.92 ± 0.97 vs. SR: 2.56 ± 0.8] |

AF — atrial fibrillation; CRP — C-reactive protein [mg/L]; IL — interleukin [pg/mL]; SR — sinus rhythm

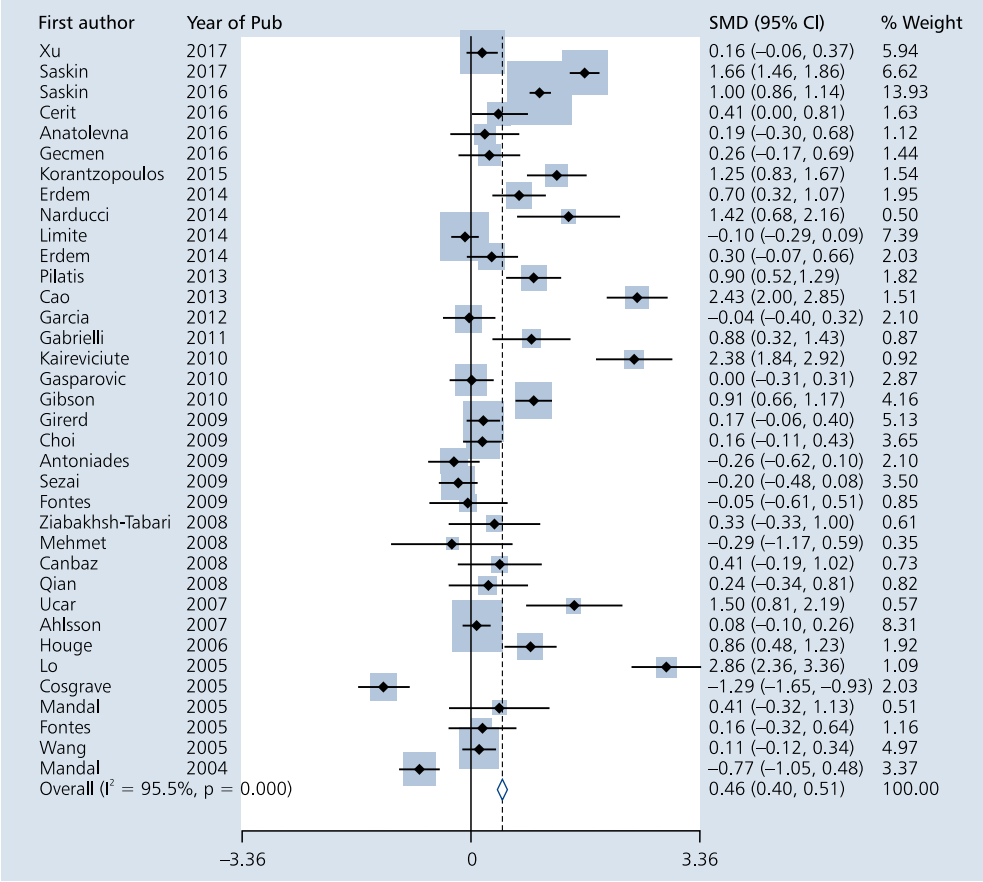


Figure 1. Forest plot of standard mean difference (SMD) for association between baseline level of C-reactive protein and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

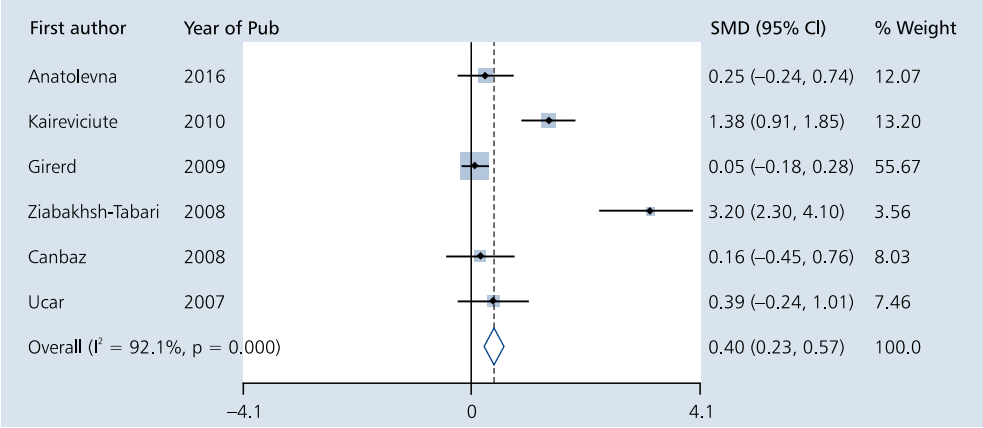


Figure 2. Forest plot of standard mean difference (SMD) for association between baseline level of interleukin-6 and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

three days after cardiac surgery [51]. POAF is of high clinical importance for its negative effects on short-, average-, and long-term clinical outcomes. Despite good response to therapy and a number of treatment modalities for this common arrhythmia, preliminary diagnosis of POAF as well as prophylactic therapy could prevent potential complications and morbidities, lower health care costs, mortality rates, and reduce length of stay in intensive care unit and in hospital.

On the other hand, it is well-known that coronary artery disease is considered one of the most important and common

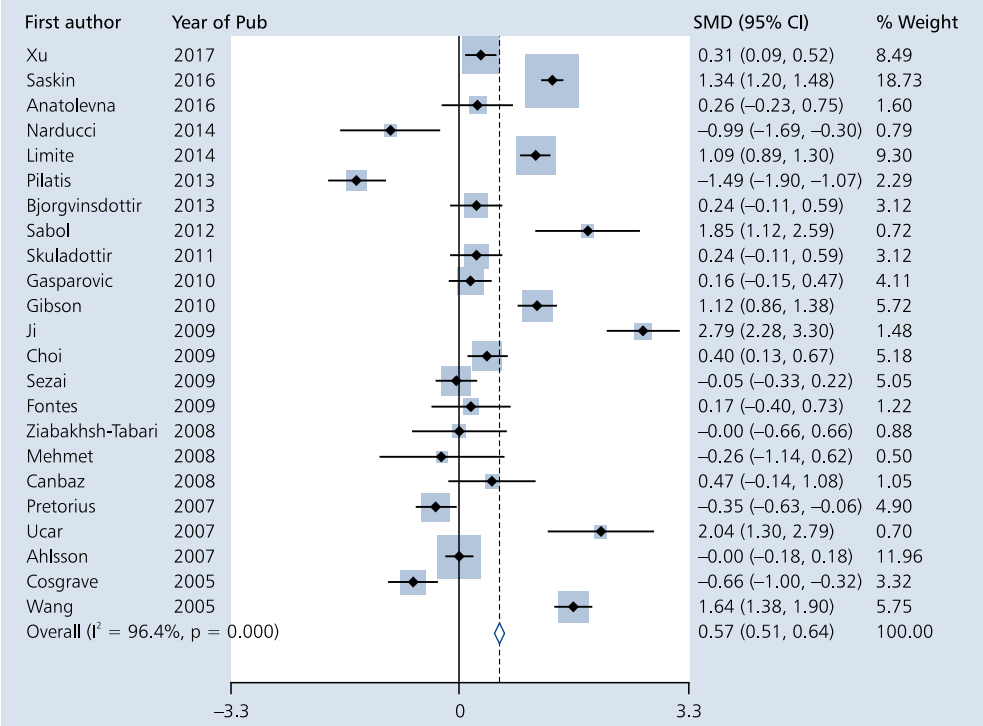


Figure 3. Forest plot of standard mean difference (SMD) for association between postoperative level of C-reactive protein and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

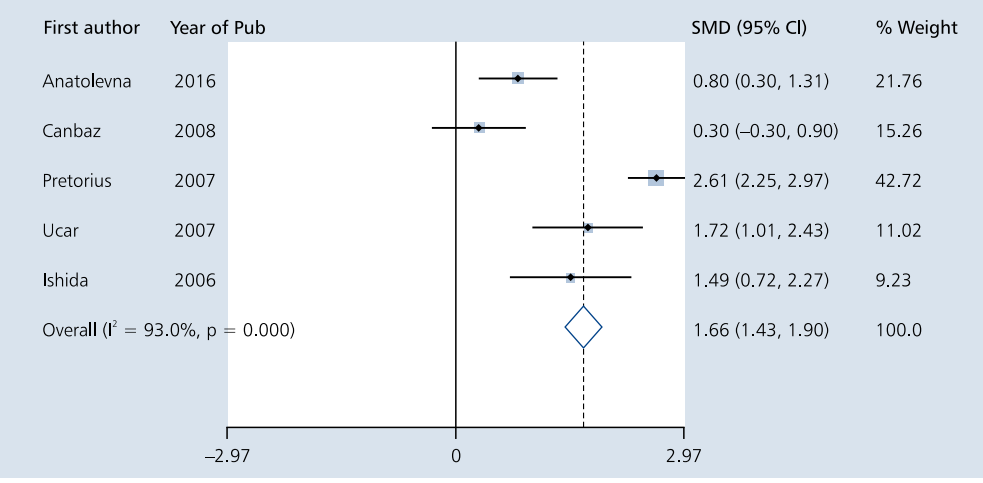


Figure 4. Forest plot of standard mean difference (SMD) for association between postoperative level of interleukin-6 and occurrence of postoperative atrial fibrillation; CI — confidence interval; Pub — publication

chronic diseases, while CABG is being extensively performed worldwide as an appropriate revascularisation procedure for this disease [51–53]. The incidence of POAF after CABG is significant accounting for ca. 50% of patients after surgery. In this respect, diagnosis, prophylaxis, treatment, and follow-up of POAF require a large number of laboratory and clinical investigations [51–53].

Today, inflammation is believed to be a critical pathological mechanism responsible for AF. Firstly, patients with coronary artery disease often present with preoperative chronic inflammatory state with physiological and cardiac haemodynamic changes or coexisting co-morbidities [54–56]. Secondly, a major inflammatory response develops during surgery and is related to a wide range of factors, such as surgical trauma, CPB, and organ reperfusion injury [55, 56]. Thirdly, myocardial ischaemia, reperfusion, and re-oxygenation activate further pro-inflammatory processes [57, 58]. Evidence increasingly supports the influence

of an acute inflammation on the pathogenesis of AF, which is largely based on association between the white blood cell counts and the incidence of AF [57–59]. Patients with higher leukocyte count are more likely to develop AF, and patients developing AF show higher monocyte activation with increased neutrophil-to-lymphocyte ratio [52].

In the present meta-analysis, the association of CRP and interleukins with the occurrence of new-onset POAF was investigated. The results of our study indicated significantly higher baseline levels of CRP in patients with POAF compared to those with POSR, thus being considered as a positive predictor. Subgroup analysis showed that the association of baseline CRP with the occurrence of POAF was not related to the type of surgery because this association was observed in isolated CABG, isolated valvular surgery, as well as combined CABG and valvular surgery. Previous research also showed an association between AF and CRP in various clinical settings. Yo et al. [60] reported that the level of CRP was directly associated with the recurrence of AF patients who underwent cardioversion, thus being a positive predictor. Rezaei et al. [61] showed that treatment with anti-inflammatory drugs not only decreased levels of CRP, but also decreased the occurrence of AF. Therefore, they affirmed a direct relationship between CRP levels as an inflammatory marker and the occurrence of AF [61].

Our findings also revealed that higher postoperative levels of CRP were associated with the occurrence of AF. In total, it can be concluded that measuring CRP levels before surgery, during postoperative intensive care unit stay, and on the ward can obviously warn of the risk of AF occurrence and help clinicians as an additional source for diagnosis and monitoring purposes.

According to the literature, interleukins are believed to be capable of modulating cardiovascular function by a variety of mechanisms, including promotion of left ventricle remodelling, induction of contractile dysfunction, and changing the response of myocardial B-adrenergic receptors [57–59]. Thus, our findings regarding involvement of various interleukins in pathophysiological mechanisms of development of POAF might be supported by this previous evidence.

On the other hand, it is noteworthy that in light of previous findings, a number of inflammatory mediators generated in response to CPB and ischaemia-reperfusion could contribute to cardiac functional depression and apoptosis [57–59]. Among other things, these changes may alter electrical activity and trigger arrhythmias [57–59]. The present study demonstrated that the baseline level of IL-6 was significantly higher in patients with POAF compared to POSR and could be used as a pre-operative positive predictor. Interestingly, the baseline levels of IL-8 and IL-10 were not significantly different in the two groups. On the other hand, measuring interleukin levels after surgery indicated that IL-6, IL-8, and IL-10 were much higher in the POAF group than in the POSR group.

Consequently, IL-6 can be introduced as an inflammatory marker sensitive to the physiological changes of cardiac tissue before surgery and prior to activation and release of other inflammatory markers during surgery [57–59]. It should be noted that after surgery an increase in other interleukins was probably observed due to perioperative trauma, CPB, and myocardial ischaemia-reperfusion. Zakkar et al. [57] pointed out that cytokines, particularly IL-6, IL-8, and IL-10, significantly increased during and following cardiac surgery and might influence the occurrence of AF as acute-inflammatory markers [57].

### *Limitations of the study*

This review is a study-level meta-analysis with a natural lack of available data on end-points assessed in studies included in the meta-analysis. Also, there are different definitions of arrhythmia and sinus rhythm between studies and there is a lack of data on different types of surgical procedures.

## CONCLUSIONS

Finally, we can conclude that inflammation is proposed as a possible mechanism in pathogenesis of POAF. Measuring the levels of inflammatory markers such as CRP, IL-6, IL-8, and IL-10 perioperatively can work as positive predictors for POAF. Therefore, these inflammatory markers should be taken into account during the hospital stay of patients referred for cardiac surgery, because they might help clinicians in terms of prediction, diagnosis, and monitoring of POAF. Another limitation that should be addressed in future studies is potential use of prophylactic treatment for POAF as a response to increased levels of inflammatory markers with the view to preventing the occurrence of this arrhythmia and its consequent complications.

***Conflict of interest:*** *none declared*

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