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CLINICAL RESEARCH
Atrial fibrillation

C-reactive protein after coronary artery bypass graft surgery and its relationship with postoperative atrial fibrillation

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Aims Postoperative atrial fibrillation (POAF), a common complication following coronary artery bypass graft (CABG) surgery, is associated with increased morbidity and mortality. Inflammation may be an important factor for the pathogenesis of POAF, and increased preoperative levels of C-reactive protein (CRP) are associated with the development of POAF. However, the relationship between postoperative CRP and POAF is less well established.

Methods and results Patients undergoing first-time isolated CABG surgery (1 January 2000–31 December 2016) were identified using the Eastern Danish Heart Surgery Database and nationwide administrative registries. Patients with no history of atrial fibrillation and with available CRP measurements from postoperative day (POD) 4 were included. The study population was divided into quartiles based on CRP. The association between CRP levels and the odds of developing POAF was investigated using multivariable logistic regression analysis. We included 6711 patients. The CRP intervals on POD 4 for the CRP groups (lowest to highest) were ≤90, >90 to ≤127, >127 to ≤175, and >175 mg/L, respectively. Patients in the highest CRP group were older and more often men compared with patients in the lowest CRP group [median age 67 years (P25–P75: 61–73) and 84.7% men vs. median age 64 years (P25–P75: 56–70) and 77.9% men]. In the lowest and highest CRP groups, 25% and 35% developed POAF, respectively. In adjusted analysis, the highest CRP group, compared with the lowest CRP group, was associated with greater odds of developing POAF (odds ratio 1.31; 95% confidence interval 1.12–1.54).

Conclusion Increased postoperative CRP levels after CABG surgery was associated with the development of POAF.

Keywords Postoperative atrial fibrillation • Coronary artery bypass graft • C-reactive protein

Introduction

Postoperative atrial fibrillation (POAF) is a common complication to coronary artery bypass graft (CABG) surgery, occurring in ∼20–40% of patients.[1–3] Several studies have found that POAF is associated with an increased morbidity and mortality after CABG surgery.[4,5] The exact aetiology of POAF remains unknown, though the postoperative inflammatory response has been hypothesized to be an important contributor in the development of POAF.[6,7] Thus, C-reactive protein (CRP), which is widely used clinically as a serum inflammatory marker, may be of interest as a possible predictor of POAF development.

C-reactive protein levels increase significantly after surgery before reaching a peak, generally on the third postoperative day (POD).[8,9]

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What's new?

- The proportion of patients who develop postoperative atrial fibrillation (POAF) after coronary artery bypass graft surgery increase with increasing C-reactive protein (CRP) levels measured on postoperative day 4. Approximately a quarter of the patients in the lowest CRP group developed POAF, compared with over one-third of the patients in the highest CRP group. This dose–response relationship was also seen in adjusted models.
- Patients with POAF had a higher absolute risk of readmission with atrial fibrillation (AF) and a higher absolute 1-year mortality compared to patients without POAF.
- This study adds new and important information regarding inflammatory markers in the postoperative setting and risk of AF. Future studies and interventions may target inflammation in the prevention of this prevalent arrhythmia.

After peaking, CRP levels steadily decline, though they may still not have returned to preoperative levels by the end of the first postoperative week.[8,9] The magnitude of the peak postoperative CRP level seems to depend on the extent of the surgical trauma. A previous study found that CRP levels after CABG peaked on the second or third day, with most patients peaking at a CRP level in the range of 180–270 mg/L.[10]

Elevated preoperative CRP levels are associated with POAF in CABG patients.[11–13] However, data on the association between postoperative CRP levels and POAF are inconclusive and the majority of these studies include small patient cohorts (usually fewer than 150 patients). Furthermore, some of these studies contradict one another.[11,14–17] Studies with larger patient cohorts are required for further clarification.

This study investigates the association between POAF and postoperative CRP levels in patients undergoing CABG surgery.

Methods

Data sources and covariates

All Danish citizens receive a permanent and personal identification number at birth or immigration enabling full linkage of national registries, as previously described.[18] Information about CABG surgeries and POAF development was drawn from the Eastern Danish Heart Surgery Database. Information about serum CRP measurements was gathered from an electronic registry of hospital laboratory databases. Patients' discharge diagnoses since 1994 were drawn from the Danish National Patient Registry to identify comorbidities at baseline. Patients' vital status was gathered from the Danish Civil Registration System. Information on all prescription medicine dispensed from pharmacies since 1995 is available from the Danish National Prescription Registry. International Classification of Diseases, 10th revision (ICD-10) and Anatomical Therapeutic Chemical codes that were used in this study can be found under Supplementary material online, *Table S1*.

Study population

The index date was defined as the date of the patient's CABG surgery. Patients who had undergone first-time isolated CABG surgery in the period 1 January 2000–31 December 2016 were included.

Patients with a diagnosis of atrial fibrillation (AF)/atrial flutter prior to the index date or patients who had redeemed a prescription of vitamin K antagonists or non-vitamin K oral anticoagulants within the last 6 months before the index date were excluded. Patients who died before POD 4 were also excluded. Finally, patients with missing data regarding whether they developed POAF or not during their CABG-related hospitalization were also excluded (*Figure 1*). No postoperative atrial pacing was used to influence the occurrence of AF.

Patients with available serum CRP measurements from POD 4 were included. The reason for this is because blood samples are systematically collected on the fourth POD, thus yielding the largest possible study population size. If a patient had more than one CRP measurement from POD 4, the highest value was used. Based on the POD 4 CRP levels, the study population was divided into quartiles (*Figure 1*), with CRP Group 1 having the lowest CRP levels and CRP Group 4 having the highest CRP levels.

Information about concomitant pharmacotherapy for each patient was assessed by redeemed prescriptions 180 days before the index date. Comorbidities were obtained through previous in-hospital ICD-10 diagnosis codes, available since 1994. Pneumonia or urinary tract infection (UTI) during the CABG-related hospitalization was assessed using ICD-10 diagnosis codes.

Outcomes

Patients were followed for the development of POAF as the primary outcome and AF recurrence and death within 1 year as the secondary outcome.

A patient was considered as having developed POAF if any kind of treatment-requiring AF had occurred during the patient's CABG-related hospitalization at the cardiothoracic ward, as registered in the East Danish cardiac surgery registry. Treatment was either pharmacological therapy or electrical cardioversion, though it was not possible to distinguish between the treatment types in the registry. Patients diagnosed with AF after being discharged from their CABG-related hospitalization were not considered as having developed POAF. Patients who died in-hospital after POD 4 with an AF diagnosis, while still admitted for post-CABG recovery at the cardiothoracic ward, were considered as having developed POAF.

The secondary outcomes were readmission with AF and death within 1 year after discharge from their CABG-related hospitalization.

Statistical analysis

Baseline characteristics are shown with percentages for categorical data and the median value with quartiles for continuous data. Testing for differences between groups were performed using a χ^2 test for categorical data. The distribution of mean CRP levels from the first through the seventh day after the CABG procedure was displayed graphically by constructing a box plot. A Cochran–Armitage trend test was used to examine the trend of increased levels of CRP and the associated risk of POAF.

Whether high CRP levels were associated with developing POAF was analysed in a multivariable logistic regression model adjusted for age, sex, comorbidities (diabetes, liver disease, peripheral vascular disease, chronic obstructive pulmonary disease, congestive heart failure, ischaemic heart disease, renal disease, and hypertension), hospital-acquired infections (pneumonia or UTI during the CABG-related hospitalization), length of hospital stay, and the procedure year. Sex and age were tested as effect modifiers of the association between CRP levels and POAF development.

A possible interaction between CRP levels and hospital-acquired infections was investigated by creating a new variable called infection (pneumonia or UTI) and testing it as an effect modifier of the association between high CRP levels and POAF development. A box plot was also constructed to display the differences in CRP levels between patients with or without hospital-acquired infections.

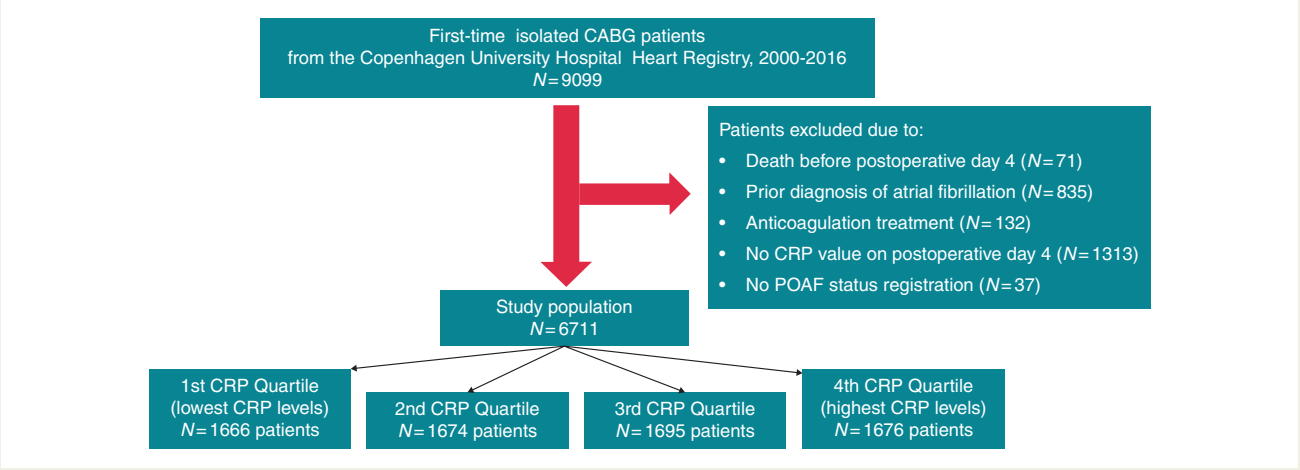

Figure 1 Selection of the study population. CABG, coronary artery bypass graft; CRP, C-reactive protein; POAF, postoperative atrial fibrillation.

Cumulative incidence of readmission with AF 1 year after discharge for CABG were calculated based on the Aalen–Johansen estimator, incorporating death as competing risk, and by the Kaplan–Meier estimator were used to calculated cumulative incidence of death 1 year after the CABG procedure. Test for difference between the cumulative incidence curves for AF readmission and death were done using Gray's test and log-rank test, respectively.

All analyses were performed using SAS software (version 9.4, 100 SAS Campus Drive, Cary, NC, USA). A *P*-value of <0.05 was considered statistically significant.

Sensitivity analysis

For purposes of sensitivity, we conducted the same analyses, but using CRP levels from POD 1 instead of POD 4.

Ethics

No ethical approval is required for anonymous registry-based studies in Denmark. The study was approved by the Danish Data Protection Agency.

Results

Characteristics of the study population

After the exclusion criteria were applied, the study population comprised 6711 patients. Patients with higher CRP levels were older and more often men compared with patients with lower CRP levels. In general, patients with higher CRP levels had more comorbidities than those with lower levels of CRP. As with the comorbidity burden, the proportion of patients receiving concomitant pharmacotherapy also generally increased with higher CRP levels.

Compared with the lowest CRP group, patients in the highest CRP group more often had a discharge diagnosis code of pneumonia or UTI, as well as had a longer length of stay, during their CABG-related hospitalization (*Table 1*).

Postoperative C-reactive protein measurements

The CRP level intervals on POD 4 for the four CRP groups (from the lowest to the highest CRP group) were ≤90, >90 to ≤127, >127 to ≤175, and >175 mg/L, respectively. Postoperative day 4 mean CRP levels [standard deviation (SD)] for the low CRP group through the high CRP group were 66 (SD 17), 109 (SD 11), 150 (SD 14), and 228 (SD 45) mg/L, respectively.

C-reactive protein levels in CABG patients generally peaked on POD 3 before steadily declining. However, on POD 7 the mean CRP level had still not dropped below the POD 1 mean CRP level (Supplementary material online, *Figure S1*). Mean CRP level on POD 4 was 138.2 mg/L (SD 64.9 mg/L) with a minimum of 2.0 mg/L and a maximum of 453.5 mg/L.

Postoperative atrial fibrillation by C-reactive protein groups and factors associated with postoperative atrial fibrillation

The proportion of patients developing POAF gradually increased by CRP groups; 24.5%, 30.2%, 31.6%, and 35.1%, per CRP groups from lowest to highest (*Figure 2*).

In a multivariable-adjusted analysis, it was found that being in the highest CRP group, age above 70 years, hypertension, and male sex were factors associated with an increased risk of POAF (*Figure 3*). Furthermore, the odds of developing POAF increased with increasing CRP levels. Patients with CRP levels >175 mg/L had an odds ratio of 1.31 [95% confidence interval (CI) 1.12–1.54] compared to the reference (CRP levels ≤90 mg/L). Hospital-acquired infections (pneumonia and/or UTI) during the CABG-related hospitalization showed no significant interaction with CRP levels.

Admission with atrial fibrillation post-discharge, in-hospital mortality, and 1-year mortality

Patients who developed POAF have a higher cumulative incidence of readmission with AF 1 year after discharge from the CABG procedure compared to patients without POAF [12.9% 95% CI (11.5–14.5) vs. 3.7% 95% CI (3.2–4.3), respectively]. From the lowest to the highest CRP group 0.8%, 0.8%, 1.5%, and 2.0% died in-hospital, respectively. From the lowest to the highest CRP group the in-hospital

Table 1 Baseline characteristics of the study population

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Demographics				
Number (%)	1666 (24.8)	1674 (24.9)	1695 (25.3)	1676 (25.0)
Male gender, *n* (%)	1298 (77.9)	1400 (83.6)	1395 (82.3)	1420 (84.7)
Median age (years) (P25–P75)	64 (56–70)	65 (58–72)	67 (59–73)	67 (61–73)
Comorbidity, medical history prior to CABG, *n* (%)				
Acute myocardial infarction	804 (48.2)	894 (53.4)	885 (52.2)	872 (52.0)
Ischaemic heart disease	1602 (96.1)	1606 (95.9)	1624 (95.8)	1594 (95.1)
Hypertension	752 (45.1)	811 (48.4)	824 (48.6)	880 (52.5)
Heart failure	274 (16.4)	332 (19.8)	292 (17.2)	341 (20.3)
Diabetes	337 (20.2)	322 (19.3)	348 (20.5)	389 (23.2)
Peripheral vascular disease	192 (11.5)	223 (13.3)	216 (12.7)	284 (16.9)
Renal disease	44 (2.6)	64 (3.8)	84 (4.9)	155 (9.2)
Chronic obstructive lung disease	94 (5.6)	121 (7.2)	155 (9.1)	183 (10.9)
Medication 6 months prior to CABG, *n* (%)				
Acetylsalicylic acid	1033 (62.0)	1035 (61.8)	1063 (62.7)	1023 (61.0)
Clopidogrel or ticagrelor	207 (12.4)	218 (13.0)	189 (11.1)	188 (11.2)
Corticosteroids	47 (2.8)	47 (2.8)	53 (3.1)	84 (5.0)
Lipid-lowering medication	1132 (67.9)	1072 (64.0)	1068 (63.0)	1066 (63.6)
Diuretics	384 (23.0)	436 (26.0)	458 (27.0)	503 (30.0)
Antiadrenergic	24 (1.4)	37 (2.2)	28 (1.6)	29 (1.7)
Renin–angiotensin system	662 (39.7)	714 (42.6)	728 (42.9)	775 (46.2)
Calcium-channel blockers	432 (25.9)	509 (30.4)	548 (32.3)	574 (34.2)
Beta-blockers	908 (54.5)	889 (53.1)	885 (52.2)	849 (50.6)
During CABG-related hospitalization				
Median length of stay (days) (P25–P75)	10 (7–19)	12 (7–21)	13 (8–21)	15 (9–25)
Pneumonia, *n* (%)	137 (8.2)	215 (12.8)	250 (14.7)	280 (16.7)
Urinary tract infection, *n* (%)	101 (6.06)	106 (6.32)	101 (5.90)	196 (11.68)

Quartile: the study population was divided into four groups based on CRP levels on the fourth postoperative day. Quartile 1 includes the lowest CRP levels, while Quartile 4 includes the highest.
CABG, coronary artery bypass graft; CRP, C-reactive protein.

mortality was 2.7%, 1.4%, 3.5%, and 3.4% accordingly for POAF patients and for patients without POAF it was 0.2%, 0.5%, 0.6%, and 1.2%, respectively. Postoperative AF patients additionally had a higher absolute risk of mortality after 1 year compared to patients without POAF [5.4% 95% CI (4.5–6.4) vs. 2.7% 95% CI (2.2–3.2), respectively] (Supplementary material online, *Figures S2 and S3*).

Infection and C-reactive protein

Patients who developed a hospital-acquired infection generally had a higher CRP level (~21 mg/L) than patients without infection (Supplementary material online, *Figure S4*). Both among patients with and without infection, the proportion of patients with POAF increased from the lowest to the highest quartile (Supplementary material online, *Figure S5*).

Sensitivity analysis

A sensitivity analysis using patients with CRP measurements from POD 1 still found a statistically significant association between the highest CRP group and POAF development.

Discussion

We investigated the association between postoperative CRP and POAF after CABG surgery. Our study yielded three main findings. First, patients with higher CRP levels were more likely to be older males and with a higher comorbidity burden compared with patients with lower CRP levels. Second, the proportion of patients developing POAF increased from the lowest to the highest CRP group—approximately a quarter of the patients in the lowest CRP group developed POAF, compared with over one-third of the patients in the highest CRP group. This relationship held true in adjusted analyses. Third, patients developing POAF have higher absolute risk of readmission for AF and higher risk of in-hospital mortality as well as 1-year mortality compared to patients who did not develop POAF.

Patients with higher CRP levels were more likely to be older men, as well as having a higher comorbidity burden and use of concomitant pharmacotherapy compared with patients with lower CRP levels. However, the proportion of patients on lipid-lowering medication and beta-blockers increased gradually from the high CRP group to the low CRP group. Patients in the highest CRP group were more often registered with pneumonia or UTI during their CABG-related

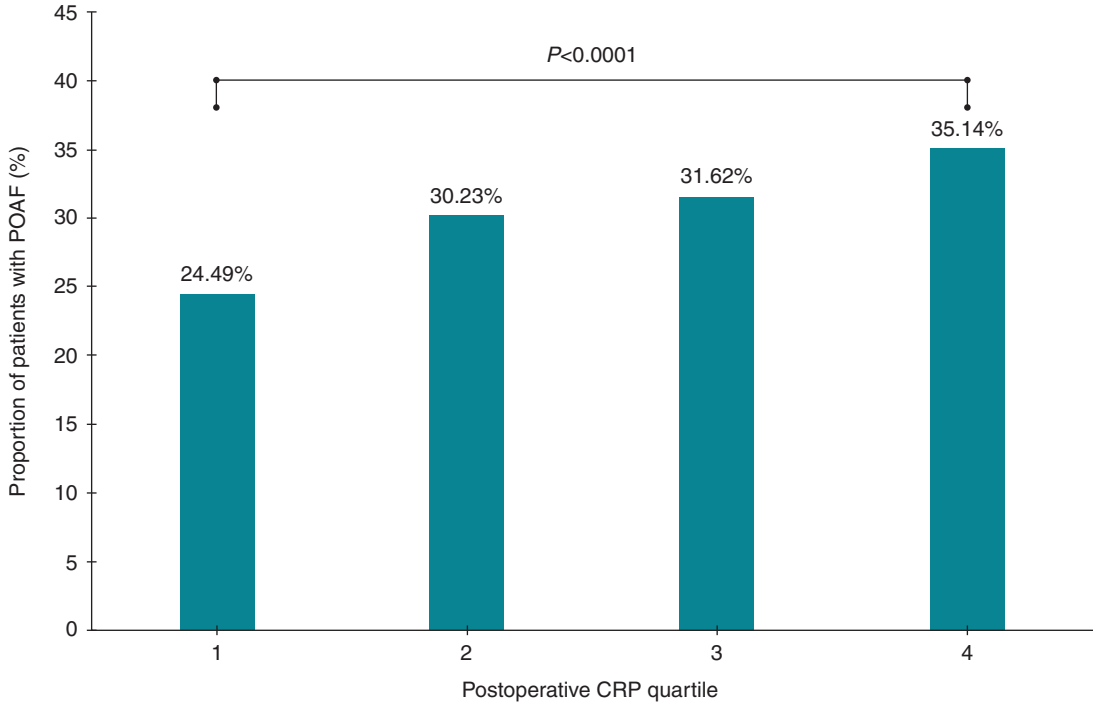

Figure 2 Proportion of patients who develop POAF for each of the postoperative CRP quartiles. CRP, C-reactive protein; POAF, postoperative atrial fibrillation.

hospitalization, as well as had a longer length of stay, than patients in the lowest CRP group. It is well established that increasing age is a significant risk factor associated with POAF development,[11,15] which this study also supports. One study found that patients with POAF were ~10 years older than those without.[11]

Prior studies have identified that POAF occurs in ~20–40% of CABG patients.[1,2] Our study found a similar proportion. However, up until now it has been sparsely studied whether the proportion of patients who develop POAF differ by postoperative CRP levels. Our findings showed that the proportion of patients developing POAF increased from the lowest to the highest CRP group, as an exposure–response relationship, while the odds of developing POAF gradually increased from the lowest to the highest CRP group.

While preoperative CRP levels have been shown to be associated with POAF,[11–13] the relationship between postoperative CRP levels and POAF remains unclear. A few studies[14,19] have found a statistically significant positive association between POAF and increased postoperative CRP levels, but most of the studies on the subject have not found a significant association.[15–17] Furthermore, most of these studies have included <150 patients. The strengths of our study include the much larger patient cohort, the combination of several registries and available serum CRP measurements for each included patient.

Although most studies on the subject do not support CRP as being associated with POAF, several studies have found an association between POAF and serum inflammatory markers such as interleukin (IL)-6[11,14] and IL-8,[17] as well as brain natriuretic peptide.[15,16] A previous study by Min *et al.*[10] investigated the association between postoperative CRP levels and long-term postoperative major adverse cardiovascular and cerebral events (MACCE) in CABG patients. The study found that postoperative CRP levels above 180 mg/L were associated with long-term MACCE. While the study[10] did not investigate any association with POAF, it does support the notion that inflammation is associated with more adverse outcomes. C-reactive protein in itself is not likely to be a pathogenic factor, but rather act as an inflammatory marker to reveal the extent of the inflammatory response. The inflammatory response is likely complex, involving many both pro- and anti-inflammatory factors such as ILs, as well as advanced intracellular processes, such as the activation of the inflammasome—which serves to further propagate the inflammatory process. The inflammation then probably results in pathological damage to cardiac cells and changes to the heart's electrical conductive system, thus bringing about AF.

Consequently, our study also supports the general notion in the literature that inflammation is an important pathogenic factor in the development of POAF.[10,11,14–17] While our study does not prove any causality between CRP and POAF, the finding that the sensitivity analysis showed an association between POAF and CRP levels from the first POD supports the hypothesis that inflammation likely precedes POAF and not the other way around.

The inflammation may develop as part of the postoperative stress response, as it is well documented that surgery leads to an increase in CRP levels.[8–10] The inflammation may also be caused by postoperative hospital-acquired infections, altered liver function, as well as local complications related to surgery (i.e. haematomas). This study accounted for hospital-acquired infections by including pneumonia and UTI in the multivariate analysis. The data on these hospital-acquired infections were obtained using ICD-10 diagnosis codes during the CABG-related

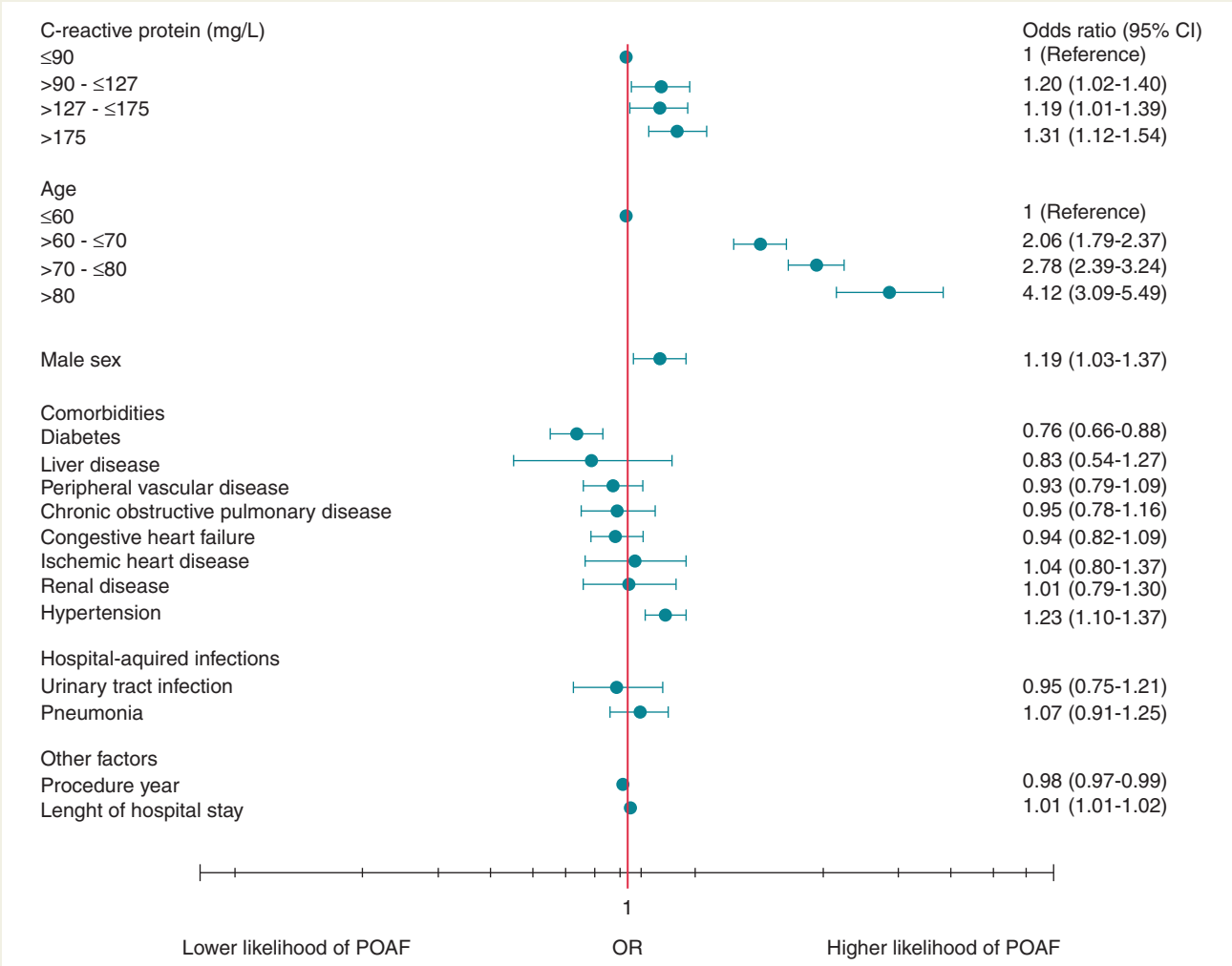

Figure 3 Factors associated with the development of POAF after coronary artery graft surgery. CI, confidence interval; OR, odds ratio; POAF, postoperative atrial fibrillation.

hospitalization. Although more patients in the highest CRP group developed pneumonia or UTI during their CABG-related hospitalization when compared with the lowest CRP group, CRP levels above 175 mg/L were still associated with developing POAF in the multivariate model adjusting for these infections. Additionally, no interaction was found between CRP levels and hospital-acquired infections (pneumonia or UTI) on the development of POAF.

Furthermore, while it was found that patients with hospital-acquired infections had a slightly higher CRP level (roughly 21 mg/L, Supplementary material online, *Figure S4*) than patients with no infection and that a larger proportion of patients in a given quartile were found to have a postoperative infection than in a quartile with lower CRP levels, the majority of patients in any given quartile did not have an infection. Thus, the higher CRP levels of the patients in the higher quartiles cannot be attributed to infection alone (Supplementary material online, *Figure S5*).

Patients with POAF had a higher absolute risk of readmission with AF compared to patients without POAF and also a higher absolute 1-year mortality. This suggests that POAF may lead to long-term complications, perhaps due to inflammation-mediated pathological changes in the heart, thus leading to a higher risk of AF and 1-year mortality (and the generally increased morbidity and mortality associated with POAF).[4,5,8–10]

An interesting hypothesis that may be drawn from this study concerns the value of POAF prediction and prophylaxis. While the intention of our study was not to show whether CRP has a good predictive value regarding POAF, our findings and the literature support the idea of using serum inflammatory markers to identify patients with a high risk of POAF development. Consequently, our findings provide a supportive theoretical background for further studies that might examine CRP's predictive value. This may be of value in terms of clinical treatment plans and strategies, allowing for early recognition and perhaps even preventative measures, to lessen the negative effects of POAF. Statins have shown promise as a possible prophylactic therapy, though more research is needed on the subject.[10,20] Min *et al.*[10] showed in an observational study that the rate of MACCE decreased significantly in CABG patients who received postoperative statins, compared with those who did not. A study by

Rezaei et al.[20] showed that perioperative statin treatment in patients undergoing cardiac surgery resulted in decreased POAF development, lower postoperative CRP levels, and a shorter length of stay.

We examined patients undergoing CABG and found an exposure–response relationship between higher levels of postoperative CRP and the associated risk of POAF. Inflammation may be a way to modify the risk of POAF—a highly prevalent postoperative complication that prolongs hospitalization and has been associated with adverse long-term outcomes. The overall results of our study seem to indicate that inflammation plays a significant pathogenic role in the development of POAF.

Strengths and limitations

The strengths of this study include the large cohort of CABG patients from nationwide registries linked with a large clinical database with high completeness and data quality as well as the availability of CRP values for each individual patient. All CRP measurements analysed at the regional hospital laboratories were readily available. Thus, this should not create considerable selection bias. Furthermore, all patients with POAF can be considered as having had a clinically significant occurrence of POAF, as only patients who received treatment for POAF were included as cases.

Several patients were excluded because CRP measurements from POD 4 were not available, though we have no reason to suspect that patients who had their CRP levels measured were specifically selected in any way. The study only investigates the association between POAF and CRP levels on POD 4, which limits the predictive value of the study findings, as POAF typically develops before POD 4. However, the goal of the study was not to investigate the predictive value of CRP. Even so, the sensitivity analysis found an association between high CRP levels and the development of POAF, even when using data from the first POD. This finding might support the initiation of further studies that may investigate the predictive value of CRP levels from the first or second POD.

The registry did not include potentially interesting clinical factors and laboratory values such as temperature, leucocytes, and IL-levels, which could have strengthened the study in terms of providing more information regarding inflammation and possible infections.

The study only followed patients until discharge. Thus, POAF development occurring after discharge was not registered. However, it may be discussed, whether POAF as a term should be used after the first postoperative week.

Conclusion

We examined patients undergoing CABG and found a dose–response relationship between higher levels of postoperative CRP and the associated risk of POAF. Inflammation may be a way to modify risk of POAF—a highly prevalent postoperative complication that prolongs hospitalization and has been associated with adverse long-term outcomes.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: G.H.G.: research grants from BMS, Pfizer, Bayer, and Boehringer Ingelheim. C.T.-P.: research contract with Bayer and Biotronic; speaker fees from Bayer and BMS. E.L.F.: independent research grant from Janssen Pharmaceutical and BMS. All other authors declared no conflict of interest.

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