Risk factors associated with contrast-associated acute kidney injury in ST-segment elevation myocardial infarction patients: a systematic review and meta-analysis

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ABSTRACT

Objective The objective of this systematic review and meta-analysis was to evaluate the risk factors for contrast-associated acute kidney injury (CA-AKI) in ST-elevation myocardial infarction patients treated with primary percutaneous coronary intervention.

Design Systematic review and meta-analysis.

Data sources We searched the databases of PubMed, Embase and Ovid, up to February 2022, for observational studies that investigated the association between risk factors and CA-AKI.

Results A total of 21 studies were included in the meta-analysis. Of the total 22 015 participants, 2728 developed CA-AKI. Pooled incidence was 11.91% (95% CI 9.69%, 14.14%). Patients with CA-AKI were more likely to be older, female, also had comorbidities (hypertension, diabetes, previous heart failure). Smoking (OR: 0.60; 95% CI 0.52, 0.69) and family history of CAD (coronary artery disease) (OR: 0.76; 95% CI 0.60, 0.95) were associated with lower risk of CA-AKI. Left anterior descending (LAD) artery occlusion (OR: 1.39; 95% CI 1.21, 1.59), left main disease (OR: 4.62; 95% CI 2.24, 9.53) and multivessel coronary disease (OR: 1.33; 95% CI 1.11, 1.60) were risk factors for CA-AKI. Contrast volume (weighted mean difference: 20.40; 95% CI 11.02, 29.79) was associated with increased risk in patients receiving iso-osmolar or low-osmolar non-ionic contrast.

Conclusions In addition to the known risk factors, LAD artery infarction, left main disease and multivessel disease are risk factors for CA-AKI. The unexpected favourable association between smoking, as well as family history of CAD, and CA-AKI requires further investigation.

INTRODUCTION

Contrast-associated acute kidney injury (CA-AKI) is a common iatrogenic condition, which is reported to occur in 3%–19% of patients undergoing coronary angiographic procedures.1 According to the European Society of Urogenital Radiology, contrast-induced nephropathy (CIN) after intravenous administration of iodinated contrast material is diagnosed when serum creatinine (Scr) increases by >25% or by 44 µmol/L within 3 days of exposure to contrast material, in the absence of an alternative aetiology.2 In 2012, the Kidney Disease Improving Global Outcomes working group proposed the term contrast-induced acute kidney injury (CI-AKI) to describe deterioration of renal function following contrast administration. The diagnostic criteria were: (1) increase in Scr by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours of contrast administration, (2) increase in Scr to ≥1.5 times the level within the previous 7 days or (3) urine volume ≤0.5 mL/kg/hour for 6 hours. Although the terms CIN and CI-AKI are widely used for the condition, factors such as decreased renal perfusion, hypoxaemia and hypovolaemia also contribute to the development of renal dysfunction; thus, CA-AKI may be a more appropriate term.4

In the majority of CA-AKI patients, the increase in Scr is temporary, with complete or near-complete recovery of renal function.
occuring within 3 months. However, about 20% of patients experience persistent and clinically relevant reduction of renal function. In 2014, after analysis of the 3-year prospective data of HORIZONS-AMI (ClinicalTrials.gov number, NCT00433966), Narula et al reported that CA-AKI is associated with unfavourable short-term and long-term cardiovascular and bleeding outcomes.

At present, prevention and early intervention are the strategies used to mitigate the risk of CA-AKI. Hydration, treatment with statin or acetylcysteine, use of sodium bicarbonate, renal replacement therapies and ischaemic preconditioning are beneficial, but a specific treatment for CA-AKI remains elusive. There are a variety of risk prediction models available for risk assessment prior to angiographic procedures. The Mehran risk score, for example, is commonly used for identifying patients at risk for AKI after ST-elevation myocardial infarction (STEMI). This model incorporates both patient and procedural risk factors (ie, age >75 years, hypotension, congestive heart failure, chronic kidney disease, diabetes, anaemia, use of intra-aortic balloon pump and contrast media volume).

STEMI patients are at especially high risk for CA-AKI, but prevention is challenging. Before performing primary percutaneous coronary intervention (pPCI), the clinician needs to quickly weigh the risks of angiography and revascularisation against the risks of CA-AKI. To our knowledge, only one meta-analysis has reported the risk factors for CA-AKI in STEMI patients treated with pPCI. Of the twelve studies included in that meta-analysis, only two were published in recent 5 years. In addition, the meta-analysis only investigated associations between CA-AKI and previously identified risk factors. Throughout the past few decades, a number of studies have identified potential associations between other factors (such as hypertensive status, prognostic nutritional index, the degree of atherosclerotic lesions and the number of coronary vessels affected) and the occurrence of CA-AKI. Nonetheless, the results of these studies are inconsistent, and several of them were limited by their single-centre designs and small sample sizes. Therefore, we aimed to conduct this systematic review and meta-analysis to synthesise the most recent evidences and potentially shed new light on the prevention of CA-AKI in STEMI patients undergoing pPCI.

METHODS

We reported the systematic reviews and meta-analyses according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental table 1).

Search strategy
We searched the databases of PubMed, Embase and Ovid, up to February 2022, for observational studies that investigated the association between risk factors and CA-AKI (online supplemental table 2). The keywords used were “ST-segment elevation myocardial infarction”, “STEMI”, “acute kidney injury”, “AKI”, “contrast-associated acute kidney injury”, “CA-AKI”, “contrast-induced acute kidney injury”, “CI-AKI”, “contrast-induced nephropathy”, “CIN”, “risk” and “risk factors”.

Study selection
Studies were eligible for inclusion in the reviews of effectiveness if they (1) were investigations of humans and were published in English; (2) were prospective or retrospective observational studies; (3) reported potential risk factors of CA-AKI and (4) were studies of populations that included persons aged >18 years and had STEMI treated with pPCI. We excluded studies that (1) were not on CA-AKI; (2) did not provide detailed data on relevant risk factors; (3) evaluated specific treatments; (4) were involved with animals and children and (5) were based solely on reviews, case report, meta-analyses, commentaries, editorials, meeting abstracts or letters to the editor. When analysis of the same population was reported more than once, we included the study with the larger sample size.

Two authors (JY and CL) independently reviewed the titles and abstracts of all articles and eliminated obviously ineligible studies. The same two authors then screened the full text of the remaining studies to check whether the study met all eligibility criteria. Disagreements between the two authors in the screening process were settled by discussion and, if necessary, by consultation with a third author (SZ).

Data extraction
The following data were extracted from each study: title, first author’s name, year of publication, design, number of patients, definition of CA-AKI, equation used to calculate estimated glomerular filtration rate (eGFR), type of contrast media used, incidence of AKI, potential risk factors and so on. All the information was recorded in especially standardised forms. Where different units or reference categories were reported for the same factor, those reported in the majority of studies were used.

Quality assessment
The quality of all the included studies was assessed independently by two authors (JY and CL) in duplicate using the Newcastle-Ottawa scale (online supplemental table 3). As before, disagreements between the authors were settled by discussion (or consultation with the third author).

Statistical analysis
The pooled incidence of CA-AKI was calculated by random-effect meta-analysis and presented as number (%), along with the 95% CI. Potential risk factors for CA-AKI were included in the meta-analysis only if they were reported in at least two studies. If there was significant heterogeneity existing among studies, the random-effects model was applied. The Mantel-Haenszel OR was calculated for dichotomous data and the weighted mean difference (WMD) for continuous data. If a study only...
reported median values (with first and third quartiles), the sample mean was estimated using the method proposed by Luo et al. and the SD was estimated by the method proposed by Wan et al. The association between CA-AKI and potential risk factors was evaluated by comparing the ORs/WMDs between patients with and without CA-AKI. P<0.05 indicated statistical significance.

The inconsistency index (I^2) was used to assess heterogeneity across studies and classified as low (I^2<25%), moderate (25%≤I^2<50%) or high (I^2≥50%). Publication bias was assessed using funnel plots and Egger’s tests. Because the impact of different study designs on baseline characteristic of included patients is expected, preplanned subgroup analyses were performed to assess the impact on heterogeneity for all individual risk factors by study design. Because the impact of different contrast agent types on risk factors associated with contrast agent use is expected, subgroup analyses were performed to examine the influence of contrast agent on the pooled outcomes. Sensitivity analysis was performed using the leave-one-out method, that is, by iteratively removing a study from the meta-analysis and observing the change in overall effect. If substantial heterogeneity was present, meta-regression analysis was performed based on age, proportion of women, sample size, study design and country of study. And all available influencing factors (eg, baseline Scr and contrast volume) reported in studies were included as covariates. Statistical analysis was performed using Cochrane Collaboration’s RevMan V.5.3 and Stata SE V.14.0 (Stata Corp).

Patient and public involvement
Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS
Study selection
Among the 658 publications that were initially identified, 484 records were excluded after screening the Titles and Abstracts. After reading the full text of the remaining articles, 153 other studies were discarded. Finally, 21 studies (13 retrospective, 8 prospective) that met all eligibility criteria were included in this meta-analysis (figure 1). The characteristics of the included studies are outlined in table 1.

A total of 179 potential risk factors were reported in these 21 studies, but 105 were not evaluated in this meta-analysis because they were not mentioned in more than two studies. There were a total of 22,015 participants (mean age, 60.7 years; 18,383 males and 3,632 females) in the 21 studies. Two thousand seven hundred and twenty-eight of these patients were diagnosed with CA-AKI and the incidence of CA-AKI varied from 5% to 19% among studies. The pooled incidence of CA-AKI was 11.91% (95% CI 9.69, 14.14; online supplemental figure 1) with significant heterogeneity (I^2=93%; p<0.001). The differences of eGFR estimation and diagnostic criteria may affect the incidence of CA-AKI. Thus, these two factors were included as covariates in meta-regression. And the result showed that none of the variables tested were responsible for the heterogeneity including age, sex, sample size, study design, country of study, eGFR estimation and diagnostic criteria.

Patient characteristics
Patient characteristics that were associated with an increased likelihood of CA-AKI (online supplemental table 4) included age (WMD: 7.74; 95% CI 5.81, 9.68), female gender (OR: 1.39; 95% CI 1.18, 1.63), lower weight (WMD: −2.84; 95% CI −4.11, −1.57), lower body mass index (WMD: −0.38; 95% CI −0.74, −0.01), lower diastolic blood pressure (WMD: −3.43; 95% CI −5.18, −1.68) and heart rate (WMD: 3.03; 95% CI 0.30, 5.77). Height and systolic blood pressure were not associated with CA-AKI. Hypertension (OR: 1.83; 95% CI 1.51, 2.23), diabetes (OR: 1.56; 95% CI 1.29, 1.89), heart failure (OR: 2.10; 95% CI 1.62, 2.73), chronic kidney disease (OR: 4.57; 95% CI 2.77, 7.52), history of myocardial infarction (OR: 1.34; 95% CI 1.07, 1.67) and previous coronary artery bypass graft (OR: 1.72; 95% CI 1.25, 2.37) were significantly associated with increased risk of CA-AKI. But no association was found between CA-AKI and other medical conditions including hyperlipidemia, coronary artery disease (CAD) history, previous PCI, cerebrovascular disease, stroke history and peripheral artery disease.

Use of ACE inhibitors/angiotensin receptor blockers (OR: 3.41; 95% CI 2.52, 4.62) and aspirin (OR: 2.32; 95% CI 1.11, 4.86) before admission were significantly associated with occurrence of CA-AKI, while beta-blocker and statin were not.

Interestingly, meta-analysis of eighteen studies showed that smoking was negatively associated with CA-AKI (OR: 0.60; 95% CI 0.52, 0.69; p<0.001), and there was moderate heterogeneity among the studies (I^2=38%; p=0.051; figure 2A). Although none of the included studies identified smoking as an independent protective factor, univariate analyses consistently demonstrated a neutral or favourable association between smoking and CA-AKI. Visual inspection of the funnel plot showed rough symmetry (figure 2B), and the quantitative Egger’s test showed no significant publication bias (p=0.077). Sensitivity analysis indicated consistency in the result (figure 2C). None of subgroup effects for the variables mentioned above were found in the subsequent meta-regression analysis.

Meta-analysis of six studies showed a favourable association between family history of CAD and CA-AKI (figure 3A). The pooled OR was 0.76, and the heterogeneity was moderate (I^2=41%, p=0.133). Sensitivity analysis revealed no significance after omitting the studies by El-Ahmadi et al or Narula et al. However, the overall trend was favourable for CA-AKI (figure 3B).

Funnel plots were presented in online supplemental figure 2. We did not draw funnel plots of some factors due to limited number of the included studies (<10).
Subgroup analyses of all individual risk factors were performed according to the study designs, and no statistical differences were observed.

Procedure-related and disease-related factors
Online supplemental table 5 provides a summary of pooled outcomes of procedure-related and disease-related factors for CA-AKI. Meta-analyses showed significant association between occurrence of CA-AKI and heart failure (Killip ≥ 2) (OR: 5.37; 95% CI 3.67, 7.85), cardiogenic shock (OR: 4.91; 95% CI 3.76, 6.41), hypotension (OR: 2.90; 95% CI 1.95, 4.33), cardiac arrest (OR: 2.13; 95% CI 1.32, 3.45), intra-aortic balloon pump use (OR: 4.80; 95% CI 2.97, 7.76), anaemia (OR: 1.91; 95% CI 1.53, 2.39), pain-to-balloon time (WMD: 29.37; 95% CI 9.37, 49.37) and multivessel PCI (OR: 2.83; 95% CI 1.62, 4.99). CA-AKI was not significantly associated with angiographic access site, stent length or tirofiban use. Contrast volume (WMD: 20.40; 95% CI 11.02, 29.79) and ratio of contrast volume to eGFR (WMD: 0.84; 95% CI 0.66, 1.03) were associated with increased risk for CA-AKI.

We divided the studies into four groups (low-osmolar non-ionic, low-osmolar ionic, iso-osmolar non-ionic and other (ie, more than one contrast agent used or type of contrast agent not mentioned)) based on contrast agent type. Meta-analysis showed that (online supplemental figure 3A) contrast volume was a risk factor for CA-AKI in the low-osmolar and iso-osmolar non-ionic subgroups. Significant heterogeneity was present in the low-osmolar non-ionic group (I² = 85%). The shape of the funnel plot was asymmetric (online supplemental figure 3B), indicating that publication bias may be related to potential studies with negative results unpublished. Meta-regression included contrast agent type as a covariate because it was considered a significant factor, and the result showed that none of the variables tested were responsible for the heterogeneity. CA-AKI risk did not differ significantly
between the low- and iso-osmolar non-ionic subgroups (p=0.10, I² = 63.1%). Funnel plots of other factors were presented in online supplemental figure 4.

Angiography-related risk factors for CA-AKI were including multivessel coronary disease (OR, 1.33; 95% CI 1.11, 1.60), left anterior descending (LAD) artery occlusion (OR, 1.39; 95% CI 1.21, 1.59), left main coronary artery (LM) disease (OR, 4.62; 95% CI 2.24, 9.53) and anterior wall myocardial infarction (OR, 1.57; 95% CI 1.20, 2.05). There was modest heterogeneity among the studies (I² = 37%; p = 0.08) that reported the predictive value of multivessel coronary disease (figure 4A). The sensitivity analysis showed consistency (figure 4B), and the quantitative Egger’s test (p = 0.794) showed no significant publication bias. Meta-regression did not identify variables mentioned above as sources of the heterogeneity. Contrast volume was not included in the meta-regression analysis as a covariate because two studies26 38 did not report the data.

LABORATORY AND ECHOCARDIOGRAPHIC PARAMETERS
Among the laboratory and echocardiographic parameters, the following factors were found to be associated with CA-AKI (online supplemental table 6) — lower haemoglobin (WMD: −0.60; 95% CI −0.76, −0.44), lower haematocrit (WMD: −2.22; 95% CI −3.94, −0.50), baseline SCr (WMD: 0.19; 95% CI 0.11, 0.26), creatinine peak (WMD: 0.82; 95% CI 0.55, 1.09), blood urea nitrogen (WMD: 14.61; 95% CI 4.61, 24.61), lower eGFR on admission (WMD: −16.49; 95% CI −21.41, −11.56), eGFR < 60 mL/min/1.73m² (OR, 2.54; 95% CI 1.50, 4.30), neutrophil gelatinase-associated lipocalin (NGAL) (WMD: 93.87; 95% CI 53.89, 133.86), peak creatine kinase-MB (WMD: 0.19; 95% CI 0.11, 0.26).

DISCUSSION

To the best of our knowledge, this is the first meta-analysis to systematically identify the risk factors for CA-AKI in STEMI patients treated with pPCI. This meta-analysis not only validated the established risk factors for CA-AKI (eg, age, female sex, comorbidities, haemodynamic instability and contrast volume), but also found that smoking and family history of CAD were negatively associated with the incidence of CA-AKI. Besides, multivessel coronary disease, LAD artery occlusion and LM disease may be incorporated into prediction models to estimate the likelihood of CA-AKI occurrence. Furthermore, data available for evaluating some risk factors (eg, angiographic access site and NAGL) are not inclusive enough to draw a reliable and convincing conclusion. We, therefore, recommend that more well-designed studies with large samples on this specific population are warranted.

Predictive incidence

In this meta-analysis, the pooled incidence of CA-AKI among STEMI patients receiving pPCI was 11.91%, which is consistent with most previous studies. However, we found the significant inconsistency of overall incidence (I²=93%) and none of the factors considered were significant, which might be attributed to lack of key variables (eg, baseline renal function and haemodynamic condition) in some included studies. As the criteria for diagnosing CA-AKI is still a matter of debate, another concern is that the diagnostic threshold was not consistent in all studies.

Unexpected findings

Smoking is a well-established risk factor for cardiovascular disease and is associated with adverse prognosis in patients undergoing revascularisation. Yet, the...
The current study revealed that smokers with STEMI are less likely to develop AKI following pPCI procedures than non-smokers. A similar phenomenon known as the ‘smoker’s paradox’ has been reported in CAD, especially myocardial infarction, where smokers have more favourable clinical outcomes than non-smokers. The interaction between smoking and the effectiveness of antiplatelet drugs is a plausible explanation for the paradox. Smokers show better response to antiplatelet therapies than non-smokers, and antiplatelet therapies have been shown to preserve renal function in animal and clinical studies. Nicotine’s anti-inflammatory effect may be another possible explanation. Although smoking increases long-term mortality, the possibility of improvement in short-term renal outcomes from smoking should not be ruled out. Differences in the baseline characteristics of smokers and non-smokers may have confounded the results of these studies.

More rigorous, well-designed observational studies are needed to clarify the correlation between smoking and CA-AKI.

Family history of CAD is a well-established independent risk factor for coronary heart disease events over the short term (<10 years). However, our meta-analysis found that STEMI patients with family history of CAD had lower incidence of CA-AKI events than patients without family history of CAD. Similar paradoxical survival benefits have been reported in some observational studies. A prior study analysing the data of 2123 492 patients admitted with STEMI found that patients with family history of CAD had lower in-hospital mortality and lower likelihood of adverse clinical events. Further research is warranted to ascertain whether the superior short-term renal outcomes in STEMI patients with family history of CAD are related to differences in the management of diet and exercise or just due to the differences between association and causality in clinical epidemiology.
Patient characteristics

This meta-analysis found that female patients may be at slightly higher risk for CA-AKI after pPCI for STEMI, which is consistent with previous studies in humans.\(^{12}^{58}\) In animal studies, however, it has been shown consistently that females have a protective effect against the development of AKI.\(^{59}^{60}\) Ikeda et al found that oestrogen administered after resuscitation from cardiac arrest ameliorates renal injury in renal ischaemia-reperfusion mice, indicating the protective effect of exogenous oestrogen against AKI.\(^{61}\) In our meta-analysis, the predominance of males in the study populations may result in biased conclusions. Factors such as personal habits (eg, smoking and alcohol consumption), menopausal status, socioeconomic status and sex hormone use should also be taken into account.\(^{62}\)

There is still no conclusive evidence to explain the effect of sex in humans and in animal models of CA-AKI. Further research is necessary.

Diabetes is known to predispose to chronic kidney injury,\(^{63}\) but it might increase the risk for CA-AKI even in the absence of renal impairment.\(^{64}\) This meta-analysis could not determine whether the progression of diabetes and different phenotypes of diabetic nephropathy are associated with increased risk for CA-AKI. Only one of the included studies subgrouped diabetes patients by therapy. The authors reported that insulin-treated diabetes mellitus was significantly associated with increased risk of CA-AKI, whereas non-insulin-treated diabetes was not.

Figure 4  Angiography-related risk factors for CA-AKI. (A) Forest plot of OR for multivessel coronary disease. (B) Sensitivity analysis of multivessel coronary disease. CA-AKI, contrast-associated acute kidney injury.
Procedure-related and disease-related factors

The notion that use of contrast media are primarily responsible for the development of CA-AKI has been challenged in recent years. Caspi et al demonstrated in an observational study that the incidence of CA-AKI in STEMI patients undergoing pPCI was comparable to that in patients receiving fibrinolysis or no reperfusion. Non-randomised evidence suggests that computed tomographic angiography/perfusion are not associated with statistically significant increase in risk of AKI in patients with stroke, even those with known chronic kidney disease. However, in patients with pre-existing severe renal disease, the administration of contrast medium is often withheld in light of the high risk of renal damage. Our meta-analysis showed that contrast volume is associated with higher risk of CA-AKI. The same conclusion was reached in both low-osmolar and iso-osmolar non-ionic subgroups.

This meta-analysis showed that CA-AKI patients were more likely to have LM, LAD lesions, anterior wall myocardial infarction and multivessel disease. This can be explained by the greater likelihood of haemodynamic instability and poorer vascular conditions in these patients. It may be contributed to different revascularisation strategies or contrast volume usage. However, two previous meta-analyses of randomised controlled trials showed that the risk of CA-AKI was comparable among patients undergoing revascularisation of infarct-related artery only, multivascular intervention or complete revascularisation. Infarct size and cardiac microvascular disease may also be involved. One study included in our meta-analysis reported that patients presenting with CA-AKI have significantly larger infarct size and greater likelihood of microvascular injury. The underlying mechanism remains unclear.

Predictive value of laboratory parameters on CA-AKI

Current definitions of CA-AKI are mostly based on plasma creatinine level, but it alone is not a reliable indicator of renal function. For example, older patients and women tend to have lower muscle mass than young men do. Despite similar SCR values, the level of renal function differed markedly between these patients. Efforts have been made over the past few years to find out potential predictive factors for AKI, such as NGAL, cystatin C and kidney injury molecule-1. However, so far, none of them have been shown to be reliable and specific for prediction or diagnosis of CA-AKI. Because biomarker response differs during the progression of CA-AKI, stage comprehensive evaluation should be performed to estimate the degree of renal injury at different time points.

We found that lower hematocrit and higher serum glucose at admission were potential predictors of CA-AKI. However, because of the limited number of studies reporting these values, we did not obtain stable results. More studies are needed to confirm their predictive value.

Implications for clinical practice and further research

Previous studies have reported that older age, female sex, multiple comorbidities and haemodynamic instability are widely recognised as an independent predictor of hospital-acquired acute kidney injury in the elderly. In the present study, we extend these findings to STEMI patients. Thus, early efforts to identify and prevent CA-AKI should be emphasised for patients with aforementioned risk factors. The correlation between the family history of CAD, smoking history, different vascular lesions and CA-AKI need to be elucidated. Further research focused on this topic may help to better understand the pathogenesis of this complex complication and optimise current clinical interventions.

Limitations

We acknowledge several important limitations in this study. First, given the observational nature of the included studies, a causal relationship between risk factors and CA-AKI could not be established. Second, significant heterogeneity reduced the strength of the evidence, most likely as a result of disparities in patient populations, treatment strategies and diagnostic thresholds across the included studies. Thus, interpretation for some pooled outcomes with high heterogeneity should be cautious. Finally, all studies inevitably excluded some critically ill patients as most of these patients died in the hospital soon after admission. The data of these patients were not available for analysis, so we could not obtain a comprehensive picture of this complex complication.

Conclusions

CA-AKI remains a challenging problem in STEMI patients undergoing pPCI, with the overall incidence varying from 5% to 19%. Contrast volume was associated with increased risk of CA-AKI in both iso-osmolar and low-osmolar non-ionic subgroups. LM, LAD lesions and multivessel disease were also associated with higher risk of CA-AKI. Smoking and family history of CAD were negatively associated with incidence of CA-AKI, which needs to be investigated in further research.

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family history of premature cardiovascular disease on the outcomes of patients hospitalized for acute coronary syndrome from the GUSTO-IIb trial. 

