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Prevalence and predictors of culprit plaque rupture at OCT in patients with coronary artery disease: a meta-analysis

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Aims The prevalence of plaque rupture at the culprit lesion identified by optical coherence tomography (OCT) in different clinical subset of patients undergoing coronary angiography and its clinical predictors remain to be defined.

Methods All studies including patients with OCT evaluation of the culprit coronary plaque were included. The prevalence of culprit plaque rupture (CPR) and thin-cap fibro-atheroma (TCFA) were the primary endpoints. The factors associated with these findings were studied in a subset of patients with different clinical presentations [ST-elevation myocardial (STEMI) vs. nonST-elevation myocardial infarction (NSTEMI) vs. unstable angina (UA) vs. stable angina pectoris (SAP)].

Results One hundred and fifty citations were initially appraised at the abstract level and 23 full-text studies were assessed. The mean prevalence of CPR and TCFA was 48.1% (40.5–55.8) and 48.7% (37.4–60.1), respectively. The prevalence of CPR and TCFA were higher in STEMI (70.4 and 76.6%) than in NSTEMI (55.6 and 56.3%) and UA (39.1 and 52.9%) or SAP (6.2 and 22.8%). In the overall population at meta-regression analysis, TCFA and current smoking were the only predictors of CPR (B 3.6:2.0–5.1, $P < 0.001$ and 0.06:0.02–0.1, $P = 0.002$, respectively). The factors associated with CPR were different depending on clinical presentation. Hypertension was the only clinical predictor for STEMI (B 3.3: 1.2.–5.3 $P = 0.001$), while advanced age (B 0.12: 0.02–0.22, $P = 0.021$), diabetes mellitus (B 0.04: 0.01–0.08, $P = 0.012$), and hyperlipidaemia (B 0.07:0.02–0.11, $P = 0.005$) were the predictors in NSTEMI and UA. No clinical predictor was found in SA.

Conclusions Our analysis showed high rates of CPR and TCFA detected by OCT in CAD patients, especially in those with ACS, although their prevalence is not negligible in stable patients. TCFA seems to be a strong predictor of CPR in all the ACS scenarios.

Keywords Optical coherence tomography • Plaque rupture • Thin cap • Acute coronary syndrome

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Introduction

Pathophysiology of acute coronary syndrome (ACS) deeply differs from stable angina, mainly due to peculiar features of plaque. Interestingly, most of the lesions triggering an acute ischaemic event, usually defined 'culprit lesions' are not angiographically severe, but present with mild stenosis.[1–5] However, when evaluated at autopsy or with intracoronary imaging, they often show a pro-thrombotic pattern, with thin cap fibro-atheroma (TCFA), soft plaques and thrombus, prone to rupture.[3]

The prevalence of culprit plaque rupture (CPR) is largely variable, depending on the clinical context, being more frequent in patients with sudden cardiac death compared with acute MI in post-mortem studies, and in patients with ST-elevation myocardial infarction (STEMI) compared with Non-ST-elevation myocardial infarction (NSTEMI) in *in vivo* studies.[3] Patients without CPR exhibit different mechanisms of instability including thrombus at the site of plaque erosion, intense vasoconstriction of epicardial arteries, or of coronary microcirculation.[4,5]

In the last years, optical coherence tomography (OCT)[6] has emerged as the most accurate instrument for intracoronary evaluation. Owing to a resolution of ~10–20 μm,[6,7] it is more accurate than intravascular ultrasound (IVUS)[8] and has been largely exploited in the evaluation and characterization of plaque features, both in stable and acute coronary artery disease.

In particular, different data[9–29] have been reported about incidence of plaque rupture evaluated with OCT across the spectrum of presentation. For physicians and interventional cardiologist evaluating these patients, the incidence and predictors of CPR might provide a more accurate evaluation of the cardiovascular risk. Consequently, we performed a meta-analysis to appraise prevalence and clinical predictors of CPR at OCT.

Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), the amendment to the Quality of Reporting of Meta-analyses (QUOROM)[30] statement along with recommendations from The Cochrane Collaboration and Meta-Analysis of Observational Studies in Epidemiology (MOOSE)[31–34] were exploited to perform the present study.

Search strategy

Three independent researchers (M.I., G.Q., and S.T.) searched on MEDLINE/PubMed, CENTRAL, and international congress reports for pertinent articles published in English according to the following strategy, with established methods and incorporating wild cards (identified by*) with the following terms: 'plaque rupture*', 'plaque erosion*', 'OCT', 'thin cap fibro-atheroma' 'plaque vulnerability'.

Study selection

Three unblinded co-authors (M.I., G.Q., and S.T.) discussed retrieved citations by at the title and/or abstract level, with divergences resolved after consensus.

If potentially pertinent, they appraised as complete reports according to the following explicit selection criteria that were (all had to be present) (i) human studies, (ii) ≥50 patients undergoing OCT at culprit plaque level (iii).

Exclusion criteria were (i) non-human setting and (ii) duplicate reporting (in which case the manuscript reporting the largest sample of patients with culprit plaque evaluation was selected, or if equal, the study with the largest number of overall patients), (iii) studies reporting mixed results for patients with ACS or stable angina (SAP), and (iv) intra-stent lesions.

We *a priori* chose to discard studies with <50 patients so as to not be influenced by low rates of plaque rupture due to the limited sample size.

Data extraction

Three unblinded reviewers (M.I., G.Q., and S.T.) abstracted the following data on the pre-specified electronic forms, with divergences resolved after consensus: authors, journal, and year of publication, location of the study group, baseline, angiographic and procedural features, CPR, and TCFA prevalence.

Discrepancy among the studies about software off-line image analysis and cut-off distance to define the thin cap atheroma were reported in results.

Endpoints definition

Among the selected studies CPR was defined as the presence of fibrous-cap discontinuity and a cavity formation in the plaque. Moreover, the thinnest part of the fibrous cap was measured three times or two quadrants, and the average value was calculated and defined as TCFA according the criteria exposed in Supplementary data online, *Table SA*.

Thus according to the above-mentioned definition the prevalence of plaque rupture and of thin cap atheroma were the co-primary endpoints (reported, respectively, as the ratio between ruptured plaques/total analysed plaques and total thin cap plaques/total analysed plaque). Impact of clinical features on plaque rupture was tested at meta-regression analysis in the overall population and different clinical subset of patients such as STEMI, NSTEMI, unstable angina (UA), mixed results of ACS and stable angina (SA).

Internal validity and quality appraisal

Three unblinded reviewers (M.I., G.Q., and S.T.) evaluated the quality of the studies on pre-specified electronic forms, with divergences resolved after consensus. According to the MOOSE and the Newcastle–Ottawa Scale (NOS), we separately abstracted and appraised study design, setting, data source, as well as (in keeping with the Cochrane Collaboration approach) the risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low-, moderate-, or high-risk of bias, as well as incomplete reporting leading to inability to ascertain the underlying risk of bias).

Data analysis and synthesis

Continuous variables are reported as median (first; third quartile). Categorical variables are expressed as *n*/*N* (%). Statistical pooling for incidence estimates of CPR and TCFA was performed according to a random-effect model with generic inverse-variance weighting, computing risk estimates with 95% confidence intervals, using RevMan 5 (The Cochrane Collaboration, The Nordic Cochrane Centre and Copenhagen, Denmark). Study bias were appraised by graphical inspection of funnel plots. Hypothesis testing for superiority was set at the two-tailed 0.05 level. Hypothesis testing for statistical homogeneity was set at the two-tailed 0.10 level and was based on the Cochran *Q* test, with I^2 values of 25, 50, and 75%, representing mild, moderate, and extensive statistical inconsistency, respectively. Meta-regression analysis was performed with comprehensive meta-analysis, reporting results as Beta.

Results

Three hundred and fifty-two results were initially appraised at the abstract level and 23[9–29] full-text studies met the criteria for inclusion into the present meta-analysis (*Figure 1*).

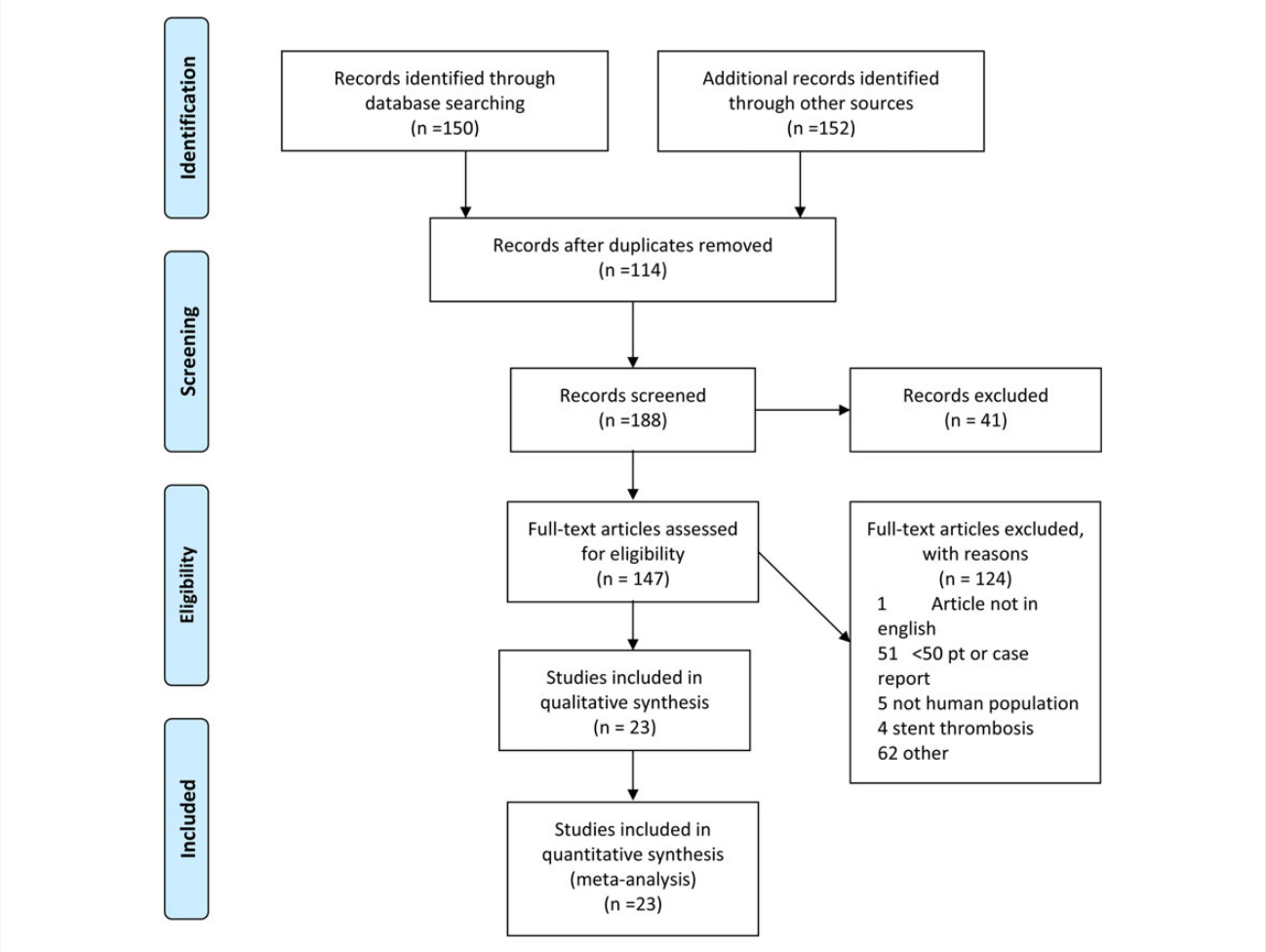

Figure 1 Article selection.

Table 1 Baseline features

Age (years)	64.1 ± 5.1
Gender female (%)	24.2
Hypertension (%)	65.1
Hyperlipidaemia (%)	59.9
Diabetes (%)	34
Smokers (%)	49
Previous PCI (%)	19.7
SA [*n* (%)]	17.1
UA [*n* (%)]	18.7
NSTEMI [*n* (%)]	9.8
STEMI [*n* (%)]	12.7
Mixed ACS (%)	41.0

ACS, acute coronary syndrome; NSTEMI, non-ST- elevation myocardial infarction; SA, stable angina pectoris; STEMI, ST-elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention.

Heterogeneity among studies in CPR evaluation was generally low to moderate ($I^2 = 58.4\%$), whereas TCFA evaluation ($I^2 = 83.4$) was extensive. This difference probably was mainly driven by different cut-off used for TCFA definition (Supplementary data online, *Appendix Table SA*).

By the included studies, we evaluated a total of 2711 culprit lesions, 12.7% in STEMI subset, 9.8% in NSTEMI, 18.7% in UA, 41% in mixed situation of ACS, and 17.1% SAP. Baseline study and overall population characteristics are reported in *Table 1*. The median age was 64.11 (60.1–67) years, 24.1% (20–30) being female and 34% (29.2–42) presenting with diabetes mellitus. As reported in *Table 2*, culprit lesion more often involved the left anterior descending coronary artery (41.1%: 36–48).

The prevalence of CPR and TCFA as assessed by OCT was 48.1% (40.5–55.8) and 48.7% (37.4–60.1), respectively. In particular, both CPR and TCFA were higher in STEMI patients (70.4 and 76.6%) than in NSTEMI (55.6 and 56.3%), UA (39.1 and 52.9%), and SAP (6.2 and 22.8% (*Figures 2–5*).

Culprit plaque predictors

In the overall population at meta-regression analysis, TCFA and current smoking were the only predictors of CPR (point estimate 3.56 LL 2 UL 5.11, $P < 0.001$ and point estimate 0.06 LL 0.02 UL 0.1 $P = 0.002$, respectively) (*Table 3*, *Figures 6* and *7*). Results of

meta-regression were confirmed even at sensitivity analysis using a second-order term for the independent variable.

The factors associated with CPR were different depending on clinical presentation.

In STEMI patients, hypertension and TCFA were the strongest factors associated with plaque rupture (point estimate 0.12 LL 0.04 UL 0.19, $P = 0.002$ and point estimate 3.27 LL 1.23 UL 5.3 $P = 0.001$, respectively) (*Table 4*). While in NSTEMI or UA patients also advanced age (point estimate 0.12 LL 0.02 UL 0.22, $P = 0.021$), diabetes (point estimate 0.04 LL 0.01 UL 0.08, $P = 0.012$), and hyperlipidaemia (point estimate 0.07 LL 0.02 UL 0.11, $P = 0.005$) were predictors of plaque rupture (*Tables 5* and *6*).

Finally, in SAP patients no clinical predictor was found, except for trend in TCFA (point estimate 4.16 LL −1.04 UL 10.28, $P = 0.11$) (*Table 7*).

Table 2 Angiographic features

LM (%)	0
LAD (%)	41.1
LCx (%)	18
RCA (%)	35.7
Stenosis at angiographic evaluation (%)	79
TIMI flow pre-PCI	2 ± 0.6
TIMI flow post-PCI	2.8 ± 0.2

LAD, left anterior descending; LCx, left circumflex artery; LM, left main; RCA, right coronary artery; PCI, percutaneous coronary intervention.

Discussion

To our knowledge, this is the first meta-analysis which investigated the prevalence and predictors of CPR detected by OCT in both ACS patients and SAP patients.

The main results of our analysis are as follows:

(1) Rates of thin cap atheroma and plaque rupture were higher in ACS patients, especially in those hospitalized for STEMI and NSTEMI, but their prevalence is not negligible in SAP patients.
(2) Thin cap fibro-atheroma seems to be a strong predictor of plaque rupture in all the ACS scenarios.
(3) Most of traditional cardiovascular risk factors are predictive of CPR, especially in NSTEMI and UA compared with STEMI patients.

Our analysis, based on OCT findings, showed a different rate of plaque ruptures in CAD patients, with higher risk in STEMI patients (70.4%), followed by NSTEMI (55.6%) and unstable angina (39.1%). OCT is a feasible and safe imaging modality for patients with CAD and allows to identify the various microstructures of the atherosclerotic plaque such as plaque rupture, thin-cap fibro-atheroma, lipid core, and intracoronary thrombus.[6,7] Both autopsy studies and *in vivo* imaging studies identified plaque rupture as the main substrates of coronary thrombosis.[7,35] Likewise, IVUS[36] and angioscopic[37] studies reported similar rates of plaque rupture in ACS, ranging from 59 to 66%. It is still unclear why some plaque ruptures lead to a specific ACS (e.g. STEMI) and others cause different clinical scenarios (e.g. NSTEMI); certainly, not only plaque rupture, but also other mechanisms such as plaque erosion and calcified nodules contribute to thrombosis,[1] and, associated with various

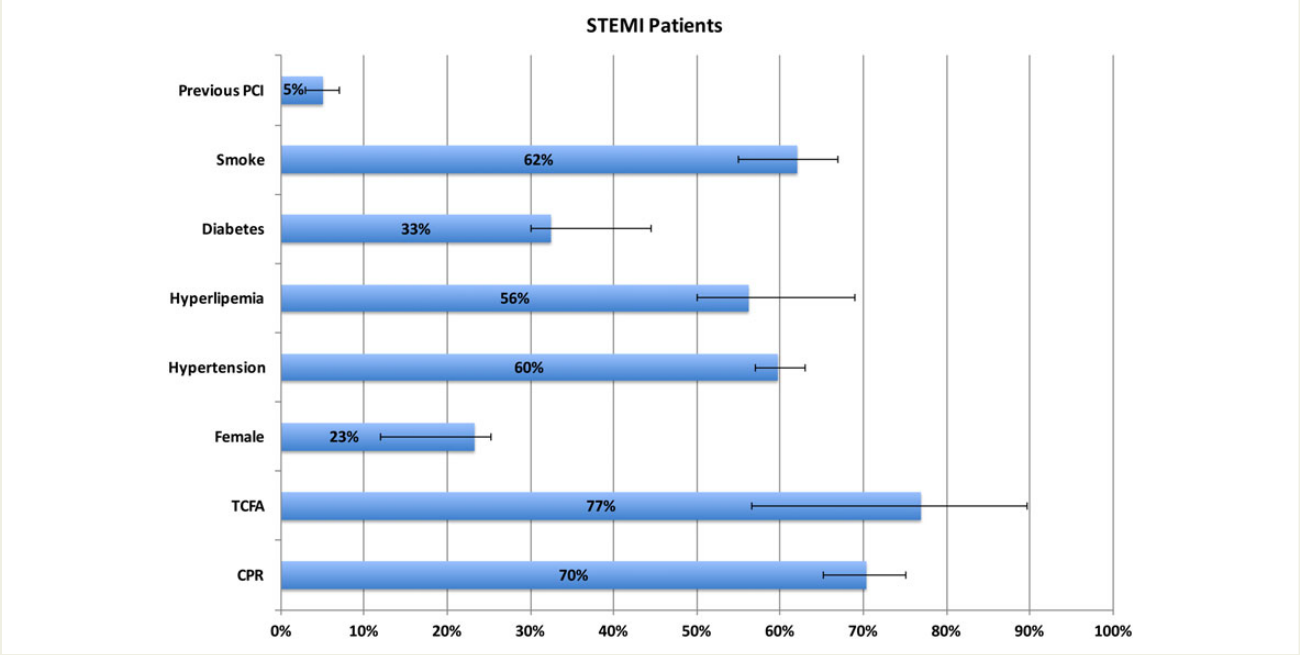

Figure 2 STEMI population characteristics. STEMI, ST elevation myocardial infarction; PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma; CPR, culprit plaque rupture.

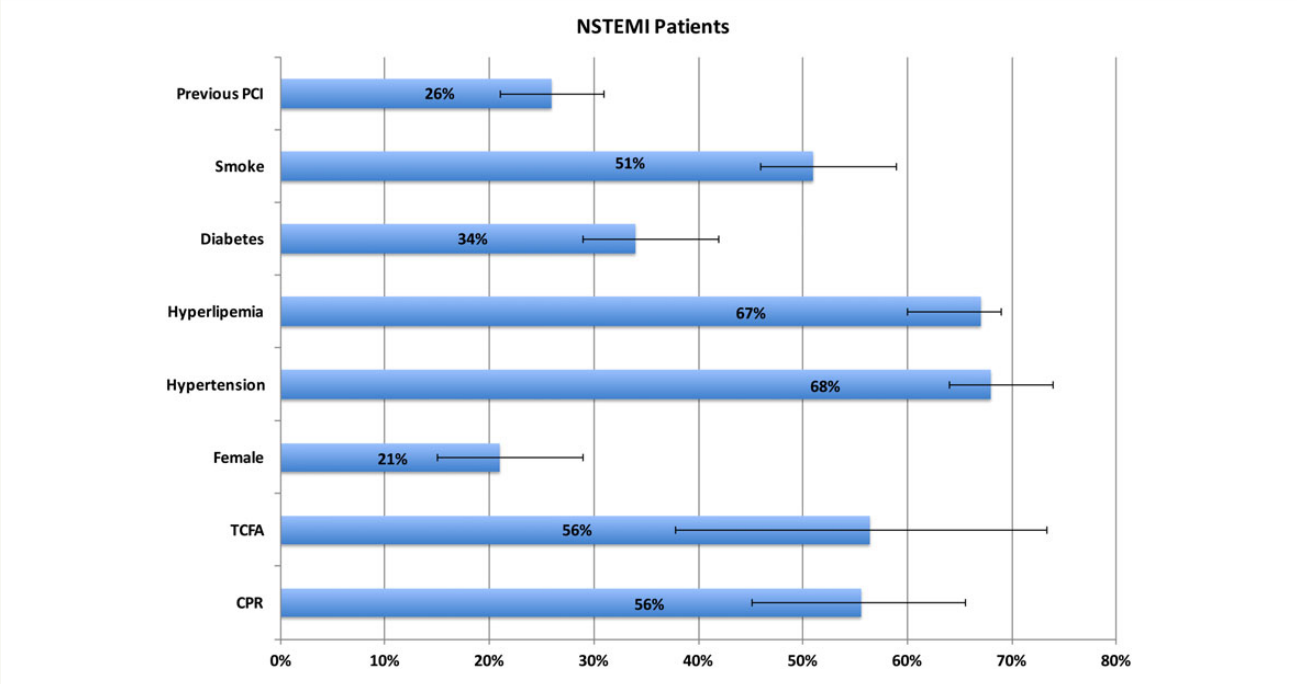

Figure 3 NSTEMI population characteristics. NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma; CPR, culprit plaque rupture.

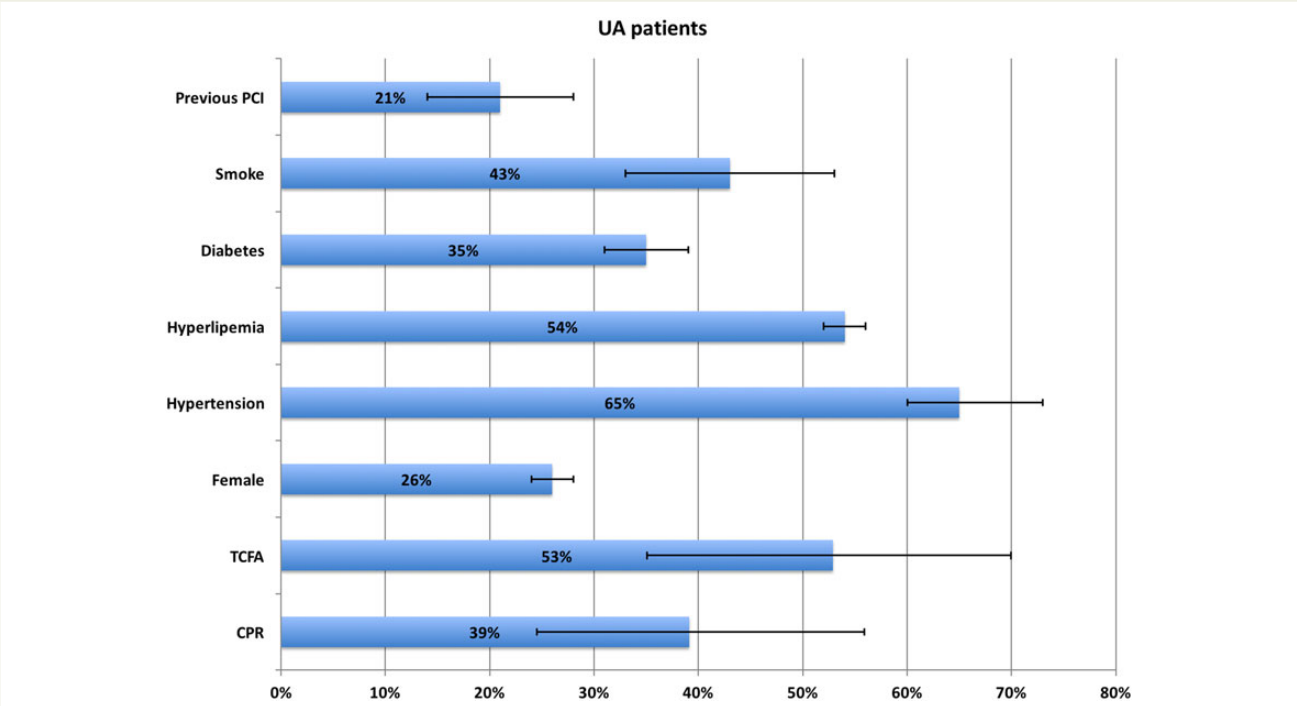

Figure 4 UA population characteristics. UA, unstable angina; PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma; CPR, culprit plaque rupture.

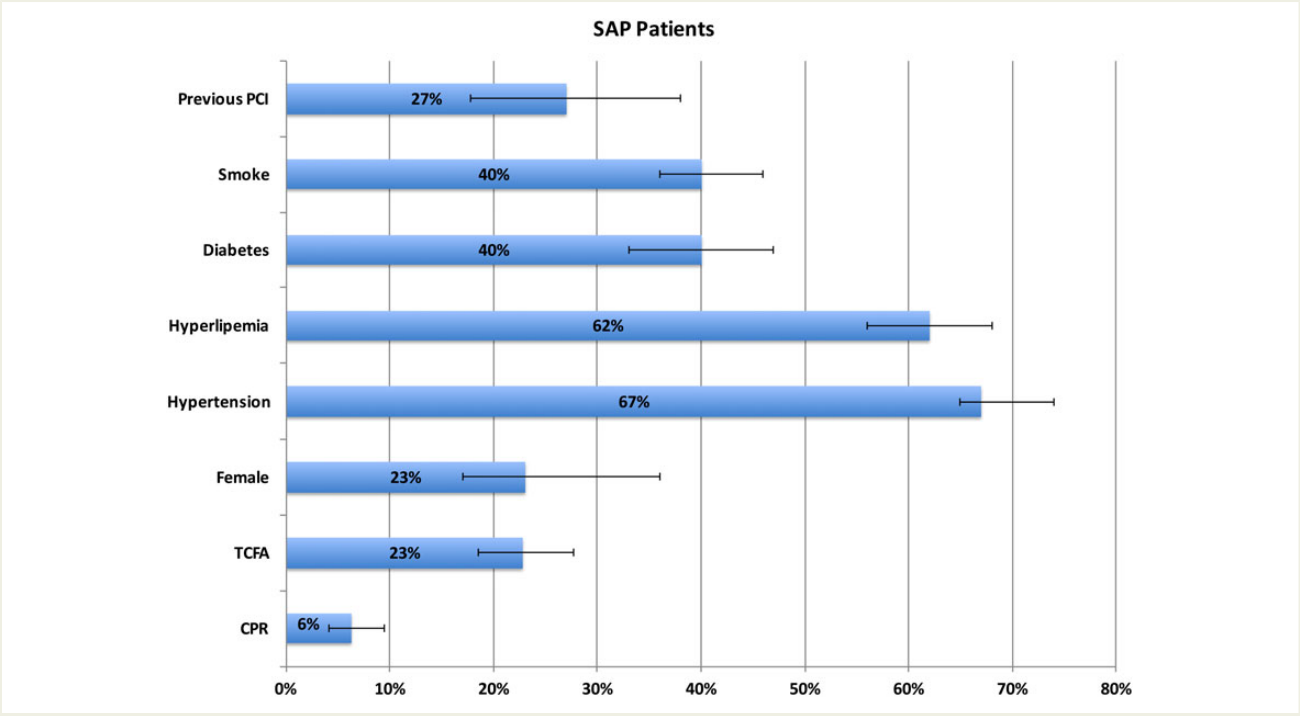

Figure 5 SAP population characteristics. SAP, stable angina; PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma; CPR, culprit plaque rupture.

Table 3 Predictors of culprit plaque rupture in overall population

	Point estimate	Lower limit	Upper limit	*P*-value
Hypertension	0.01	−0.03	0.04	0.79
Diabetes	−0.03	−0.08	0.02	0.26
Age	−0.04	−0.14	0.05	0.35
Sex	−0.03	−0.07	0.01	0.14
Hyperlipidaemia	−0.01	−0.04	0.04	0.88
Smoke	0.06	0.02	0.11	<0.001
Previous PCI	−0.01	−0.08	0.06	0.76
TCFA	2.08	1.56	2.6	<0.001

PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma.

combinations of systemic factors (e.g. hypercoagulability, activation of sympathetic nervous system,[4] increased systemic inflammation[38,39]) are responsible for different clinical presentations. Consistent with previous analysis,[40] we found a not negligible prevalence of plaque rupture in patients with stable CAD (6.2%), thus stressing the complex relationship between plaque rupture and coronary artery disease; possibly, the absence of the above-mentioned mechanisms is a key factor for a milder clinical presentation.

TCFA was appraised as a predictor of plaque rupture in the ACS subsets. Its pathological features include a large necrotic core, a thin fibrous cap, and macrophage infiltration into the cap.[41] The close relationship between TCFA and ACS was consistent with previous analyses. In the PROSPECT study, 596 TCFAs were identified in >600 high-risk patients,[42] while Vergallo,[43] in a OCT analysis, showed a higher rate of TCFA in patients with ACS and CPR compared with those without CPR. According to these results, with our analysis we could reiterate the concept of 'plaque vulnerability' in which TCFA seems to play a pivotal role.

As reported for CPR, the presence of TCFA was not always associated with an acute clinical event, as demonstrated by its significant prevalence in stable CAD subjects (52.9%); this is in agreement with a recent study, who showed a very high rate of plaque transition to thick-cap fibro-atheroma or fibrotic plaques and no clinical events at 1-year follow-up, suggesting a high dynamicity of the coronary plaque.[44]

Consequently, TCFA alone may not be enough to correctly stratify the risk of subsequent coronary events, but should be closely related to the burden of traditional risk factors, and should also be evaluated along with features of non-culprit coronary plaque.

On the other hand, despite OCT represents the intracoronary imaging modality with the highest spatial resolution, due to the low penetration power into the plaque tissue, the necrotic core composing the TCFA is seen as the signal-poor region with poorly defined borders and fast OCT signal drop-off.[45] Moreover, the presence of macrophage, often co-existent with the necrotic core, could be and adjunctive background noise of the image.[46] For these reasons as demonstrated by Manfrini *et al.*,[47] OCT could be unreliable to differentiate areas with heterogeneous composition because of its low signal penetration in particular situations such as large lumen diameter or large necrotic core. However, recently new algorithms

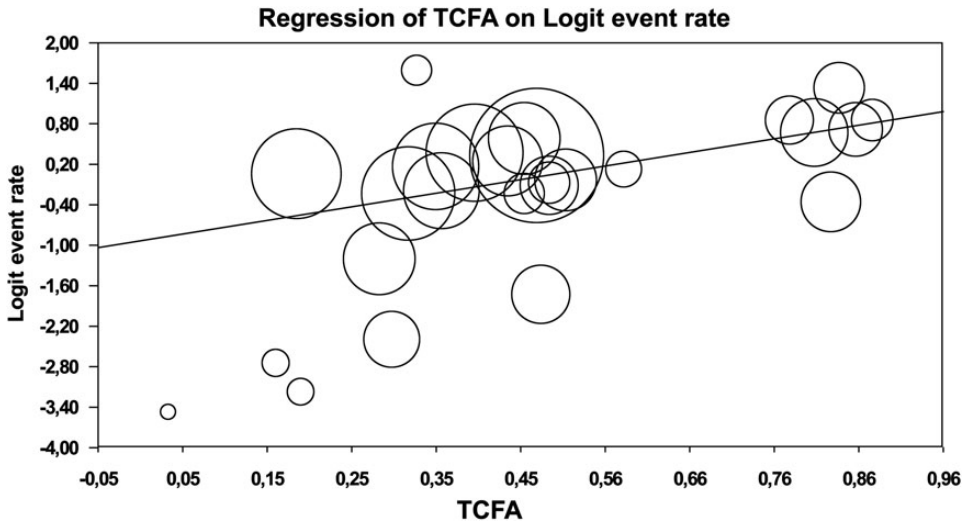

Figure 6 Meta-regression for TCFA as a predictor of CPR in overall population. TCFA, thin cap fibro-atheroma; CPR, culprit plaque rupture.

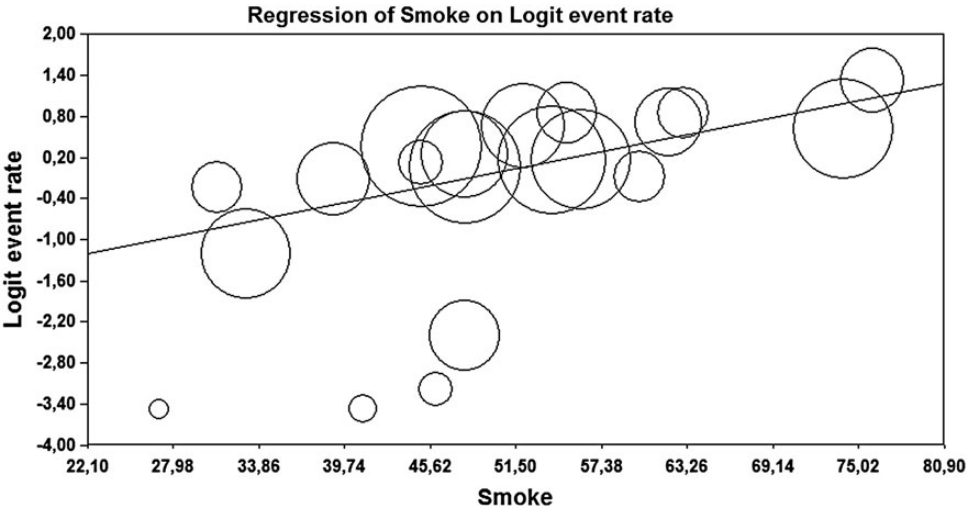

Figure 7 Meta-regression for smoke as a predictor of CPR in overall population. CPR, culprit plaque rupture.

are being developed to improve the identification of some types of vulnerable plaque and allow standardization of OCT image interpretation in misleading situation as above described.[48]

Actually interestingly, age, diabetes, and hyperlipidaemia resulted as predictors of CPR in the ACS setting, especially in the ACS population which is known to be characterized by a higher conventional cardiovascular risk.[49] On the contrary in STEMI patients, the association between traditional cardiovascular risk factors and CPR is less evident, thus explaining the higher unpredictability of this syndrome compared with the ACS. There may be different explanations, from the lower rates of risk factors in STEMI vs. NSTEMI patients, to the different physiopathology, related to the more diffuse and severe atherosclerotic disease in NSTEMI patients.

We reported rates and predictors of CPR in CAD patients: an adding prognostic value of OCT was shown by Niccoli *et al.*,[28] who pointed out a worse clinical outcome in patients with detection of CPR in culprit lesion compared with those with intact fibrous cap; further studies are needed in order to confirm this finding which could add significant information.in term of risk stratification and therapeutic options.

In conclusion, our meta-analysis showed high rates of CPR and TCFA detected by OCT in CAD patients, especially in those with ACS, although their prevalence in stable patients is not negligible.

TCFA seems to be a strong predictor of CPR in all the ACS scenarios.

Table 4 Predictors of culprit plaque rupture in STEMI patients

	Point estimate	Lower limit	Upper limit	*P*-value
Hypertension	0.12	0.04	0.2	0.003
Diabetes	0	−0.02	0.02	0.96
Age	0.02	−0.01	0.05	0.14
Sex	−0.03	−0.07	0.01	0.14
Hyperlipidaemia	−0.01	−0.03	0.01	0.36
Smoke	0.01	−0.03	0.05	0.65
Previous PCI	−0.02	−0.05	0.01	0.11
TCFA	3.27	1.24	5.3	0.002

PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TCFA, thin cap fibro-atheroma.

Table 5 Predictors of culprit plaque rupture in NSTEMI patients

	Point estimate	Lower limit	Upper limit	*P*-value
Hypertension	0.04	0.01	0.06	0.012
Diabetes	0.04	0.01	0.08	0.012
Age	0.13	0.03	0.22	0.021
Sex	0.02	−0.04	0.06	0.73
Hyperlipidaemia	−0.01	−0.05	0.03	0.75
Smoke	0.02	−0.01	0.06	0.13
Previous PCI	0.04	−0.01	0.1	0.1
TCFA	1.85	0.37	3.33	0.014

NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma.

Table 6 Predictors of culprit plaque rupture in UA

	Point estimate	Lower limit	Upper limit	*P*-value
Hypertension	0.02	0.01	0.03	0.026
Diabetes	0.05	−0.02	0.11	0.16
Age	−0.03	−0.06	0.00	0.09
Sex	−0.01	−0.22	0.21	0.96
Hyperlipidaemia	0.07	0.02	0.11	0.005
Smoke	0.06	0.01	0.08	<0.001
Previous PCI	0.01	−0.01	0.02	0.55
TCFA	3.93	1.17	6.69	0.005

PCI, percutaneous coronary intervention; TCFA, thin cap fribro-atheroma; UA, unstable angina.

Table 7 Predictors of culprit plaque rupture in SAP

	Point estimate	Lower limit	Upper limit	*P*-value
Hypertension	0.01	−0.02	0.03	0.74
Diabetes	−0.01	−0.10	0.08	0.75
Age	0.01	−0.10	0.11	0.9
Sex	−0.01	−0.22	0.21	0.96
Hyperlipidaemia	0.05	−0.09	0.20	0.47
Smoke	0.07	−0.03	0.16	0.18
Previous PCI	−0.03	−0.06	0.02	0.41
TCA	4.61	−1.05	10.28	0.11

PCI, percutaneous coronary intervention; TCFA, thin cap fibro-atheroma; SAP, stable angina pectoris.

Limitation

The present study has several limitations

First, it is not a patient level analysis, and does not derive data from randomized controlled trials, but only from observational. Therefore, the use of meta-regression analysis, although commonly exploited, may be viewed as hypothesis generating only and not as an analysis providing solid evidence of causal associations.

Second, different cut-offs were used for TCFA definition as shown in Supplementary data online, *Appendix Figure SA*.

Third, we found no predictors of CPR in stable CAD patients. This could be explained by the low rates of CPR and the small cohort of patients with SA.

Fourth, it was not possible to evaluate the influence of time from symptoms onset to the OCT because of the lack of these data in the selected studies.

Supplementary data

Supplementary data are available at *European Journal of Echocardiography* online.

Conflicts of interest: Dr Biondi-Zoccai has consulted for Abbott Vascular and St Jude Medical.

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IMAGE FOCUS

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Primary mitral valve sarcoma: multimodality imaging and therapy

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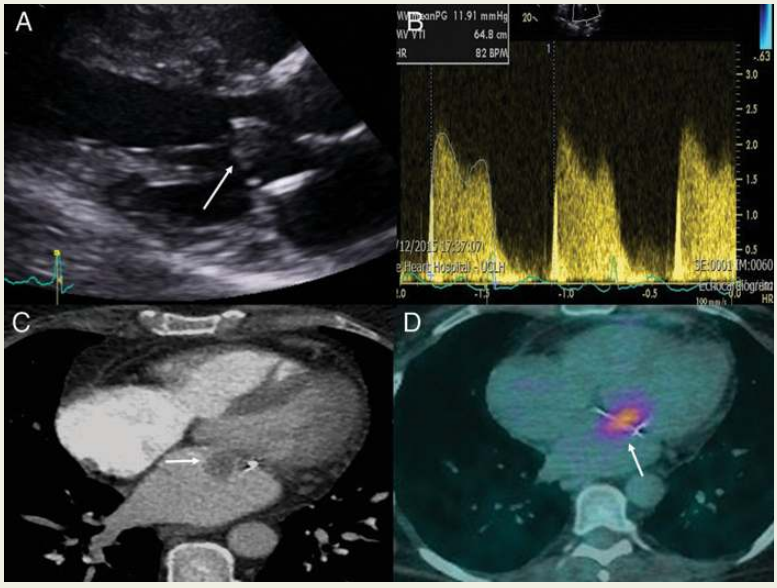

A 44-year-old lady underwent excision of a mass attached to posterior mitral valve leaflet. Histopathology showed high-grade sarcoma. After developing recurrence at the right gastrocnemius muscle and right atrium, she was treated with further courses of systemic chemotherapy (doxorubicin and ifosfamide followed by gemcitabine and docetaxel) and underwent radiotherapy to posterior right leg. Due to further progressive disease, she received a course of trabectedin chemotherapy. Recently, she presented with dyspnoea on exertion and peripheral oedema. Echocardiography demonstrated a 1.5 cm, highly mobile mass intermittently obstructing the mitral valve inflow (*Panel A*). Mean trans-mitral gradient was 12 mmHg (*Panel B*). The right ventricle was dilated with elevated pulmonary artery systolic pressures. Computed tomography of the thorax confirmed that the soft tissue mass was isolated to the mitral valve with no extension into other chambers/vessels (*Panel C*). Fludeoxyglucose positron emission tomography showed focal uptake of tracer within the mass confirming recurrent disease (*Panel D*). A course of palliative radiotherapy to the heart was delivered as there were no other systemic options.

Primary cardiac sarcomas are extremely rare malignancies. Although cardiac surgery with complete resection margins is associated with better survival than those with incomplete margins, recurrence is high and the overall prognosis of cardiac sarcoma is poor. Treatment with chemotherapy and radiotherapy may be associated with improved outcomes, although data are sparse. We report an unusual case of primary mitral valve sarcoma and demonstrate the value of multimodality imaging to identify anatomic features, haemodynamic consequences, and allow differentiation from other cardiac masses.

Conflict of interest: none declared.