Reviews in Cardiovascular Medicine

*Rev. Cardiovasc. Med.* **2026**; 27(11): 54940
https://doi.org/10.31083/RCM54940

*Systematic Review*

# The Prognostic Value of Coronary Computed Tomography Angiography Plaque Characteristics to Predict Major Adverse Cardiovascular Events: A Systematic Review and Meta-Analysis

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Academic Editor: Yujie Zhou
Submitted: 16 June 2026 Revised: 12 August 2026 Accepted: 24 August 2026 Published: 17 November 2026

**Abstract**

**Background:** Coronary computed tomography angiography (CCTA) provides a non-invasive assessment of plaque morphology and burden, offering prognostic information beyond traditional risk factors. Recent studies suggest that CCTA-derived plaque features such as low-attenuation plaque, positive remodeling, and napkin-ring sign (NRS) may predict major adverse cardiovascular events (MACE) independent of stenosis severity. To date, no comprehensive synthesis has evaluated the full spectrum of plaque variables in relation to MACE risk. Our objective was to compare and determine which CCTA plaque characteristics, including severity, composition, high-risk morphology, and disease extent, showed the greatest MACE association. **Methods:** We conducted a systematic review and meta-analysis using Medline, Embase, Emcare, Google Scholar and Web of Science databases for articles published between 1946 and September 2025 which reported hazard ratios (HRs) evaluating the association between CCTA plaque characteristics and ≥2-point MACE. Eligible studies included adult patients with suspected or known coronary artery disease (CAD) and ≥1-year follow-up. Pooled HRs were generated using random-effects models. **Results:** 72 studies (n = 143,453) met the inclusion criteria. Obstructive stenosis ≥70% showed a strong association with MACE (HR 5.84, 95% confidence interval (CI) 3.86–8.85), followed by ≥50% stenosis (HR 5.04, 95% CI 3.44–7.39), and non-obstructive plaque remained significant (HR 1.54, 95% CI 1.19–1.98). High-risk plaque (HRP) features, including napkin-ring sign (HR 3.28, 95% CI 2.19–4.91), positive remodeling (HR 3.03, 95% CI 1.64–5.61), spotty calcification (HR 2.30, 95% CI 1.40–3.75) and low-attenuation plaque (HR 2.34, 95% CI 1.87–2.93) were also strongly associated with MACE beyond stenosis severity. Risk progressively increased with multivessel involvement (1-vessel: HR 4.18, 95% CI 1.60–10.93; 2-vessel: HR 7.34, 95% CI 2.15–25.10; 3-vessel: HR 10.91, 95% CI 3.50–33.99). Importantly, considerable between-study heterogeneity and evidence of publication bias were observed in selected analyses, while leave-one-out sensitivity analyses demonstrated stable pooled effect estimates. In the hard MACE subgroup of 25 studies, effect estimates were attenuated but remained directionally consistent, with reduced heterogeneity. These findings demonstrate that beyond luminal narrowing, HRPs and disease extent provide significant prognostic value. **Conclusion:** CCTA-derived plaque characteristics, particularly HRP features and multivessel disease, were consistently associated with MACE across studies. These findings highlight the prognostic value of CCTA and support integrating plaque vulnerability and burden into cardiovascular risk stratification.

**Keywords:** coronary artery stenosis; coronary artery disease; coronary angiography; CT angiography; major adverse cardiac events; atherosclerotic plaque

## 1. Introduction

Coronary artery disease (CAD) is the leading cause of major adverse cardiovascular events (MACE) such as myocardial infarction, unstable angina, stroke, and cardiovascular death [1]. Coronary computed tomography angiography (CCTA) is an established non-invasive modality for detecting CAD. Over the last decade, there has been increasing interest in CCTA-derived plaque characteristics, including composition, morphology, and distribution, to provide prognostic information independent of traditional clinical risk factors [2].

Numerous studies have demonstrated that high-risk plaque features such as the napkin-ring sign (NRS), low-attenuation plaque (LAP), positive remodeling, and spotty calcification contribute to plaque vulnerability and potential rupture [3,4,5]. Furthermore, CCTA-derived features, such as plaque calcification type and plaque burden, correlate with MACE in cohort studies. Even non-obstructive plaque, especially that which contains high-risk features, is linked to MACE [6,7].

Previous literature syntheses have explored the link between plaque characteristics and MACE. Nerlekar et al.

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[8] conducted a 2018 review that does not include the numerous published studies from the last decade. In 2023, Gallone et al. [9] conducted a similar review but combined multiple imaging modalities in their analysis. Recently, Bell et al. [10] conducted a more focused review on the prognostic value of quantified plaque volumes for MACE but did not include high-risk plaque features. These studies do not evaluate all commonly reported CCTA-derived plaque features or analyze the prognosis for hard MACE outcomes. There is a need for a prognostic study that incorporates a wide range of literature and compares various plaque characteristics to identify which variables are most strongly associated with MACE.

This systematic review and meta-analysis aimed to evaluate the association between CCTA-derived coronary plaque features and the risk of 2-point MACE in patients with suspected or diagnosed CAD. Specifically, we aggregated hazard ratios across a broad spectrum of plaque variables, ranging from stenosis severity (e.g., obstructive vs. non-obstructive), composition (e.g., calcified, non-calcified, mixed), high-risk morphology (e.g., NRS, LAP), and disease extent (e.g., 1-, 2-, or 3-vessel disease).

## 2. Methods

### *2.1 Study Design and Search Strategy*

We selected a systematic review & meta-analysis methodology as we anticipated a diverse literature base with aggregable quantitative data. We searched Medline, Embase, Emcare, Google Scholar and Web of Science from 1946 to September 2025 using the following keywords: computed tomography angiography, MACE, prognosis, coronary artery disease, calcified plaque, obstructive plaque, etc. (**Supplementary Material 1**). An academic health sciences librarian reviewed the search strategies. We searched Google Scholar to identify any significant articles missed in the initial search. This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (**Supplementary Material 2**) [11]. Methodological decisions were additionally informed by the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis guidance for systematic reviews [12]. Our review protocol was not prospectively registered in PROSPERO. To minimize potential selection bias, the review team predefined the research question, eligibility criteria, data items for extraction, plaque feature definitions, subgroup analyses, and statistical methods before conducting the literature search.

### *2.2 Eligibility Criteria*

Studies were eligible for inclusion if they (1) involved adult patients undergoing coronary CCTA for suspected or known CAD; (2) reported associations between specific CCTA-derived plaque characteristics and subsequent MACE; (3) incorporated a MACE definition with at least 2 of the following endpoints: myocardial infarction, acute coronary syndrome, cardiovascular death, all-cause mortality, stroke, revascularization, unstable angina, cardiac-related hospitalization, arrhythmia, and cardiac arrest; (4) provided hazard ratios (HRs) for MACE stratified by plaque feature presence or severity; (5) conducted analyses at the per-patient level; (6) were randomized controlled trials (RCTs) or observational studies with follow up time of at least 1 year; and (7) reported univariate HRs or multivariable HRs controlling for relevant clinical confounders such as age, sex, traditional cardiovascular risk factors, or calcium score. Studies were excluded if they (1) reported data solely at the per-lesion or per-segment level; (2) lacked extractable hazard ratios; (3) enrolled populations with exclusive comorbid conditions (e.g., only diabetic or chronic kidney disease cohorts); (4) assessed characteristics that were not evaluated in this study (e.g., calcium score); (5) defined plaque characteristics significantly different from our definitions; and (6) not randomized or observational cohort in study design (e.g., case-control). When multiple studies reported on the same data points from overlapping cohorts, only the most comprehensive and recent study with the largest sample size and longest follow-up was retained.

### *2.3 Screening*

Each article's title and abstract were independently screened by two reviewers (among AS, LL, and WK) using Covidence (Veritas Health Innovation Ltd, Melbourne, VIC, Australia) [13]. Reviewers were trained on a set of 40 articles to ensure consistent application of inclusion and exclusion criteria. Two reviewers then independently reviewed the full texts of all papers that met the inclusion criteria, based on title/abstract screening. Disagreements were resolved through consensus or by involving a third author (MS).

### *2.4 Data Extraction and Management*

Data items to be collected were specified before conducting the literature search. Items for data extraction included the study design, clinical rationale for CCTA, patient baseline characteristics, definitions of plaque morphology, high-risk plaque (HRP) features, and MACE, as well as HRs showing the risk of MACE associated with plaque features. We defined plaque morphology and HRP features according to the definitions reported by each study. Table 1 (Ref. [14,15]) presents the standardized definitions of plaque features based on what was consistently reported in our included studies and aligned with the Society of Cardiovascular Computed Tomography (SCCT) and coronary artery disease-reporting and data system (CAD-RADS) 2.0 consensus statements. Data from eligible studies were extracted, grouped, and synthesized by four reviewers (AS, WK, BB and LL), and the synthesis was verified by a second reviewer (AS, WK, BB). Data were collected across

**Table 1. Plaque characteristic definitions**.

| Plaque characteristic | Definition |
|---|---|
| Obstructive Plaque ≥50% Stenosis | Coronary lesion causing ≥50% luminal diameter reduction, measured visually or via semi-automated software. Often the clinical threshold for hemodynamically significant CAD. |
| Obstructive Plaque ≥70% Stenosis | Coronary lesion with ≥70% luminal narrowing, used to identify high-grade obstructive disease, especially in proximal or major epicardial vessels. |
| Non-Obstructive Plaque <50% Stenosis | Coronary plaque causing <50% luminal narrowing, often included in risk models for subclinical or early atherosclerosis. |
| Moderate Stenosis 50–70% Stenosis | Coronary lesion causing 50%–70% luminal diameter reduction, measured visually or via semi-automated software. |
| Calcified Plaque | Coronary plaque with attenuation ≥130 Hounsfield Units (HU) and composed predominantly (typically ≥50%) of calcium on CCTA. Reflects advanced or stabilized atherosclerosis. |
| Non-calcified Plaque | Plaque with attenuation <130 HU and composed primarily of fibrous or lipid-rich components, without visible calcification. Commonly associated with vulnerable or early-stage plaques. |
| Mixed Plaque | Plaque containing both calcified and non-calcified components, with neither comprising more than 50% of total plaque volume. Indicates transitional plaque composition, often associated with instability. |
| Napkin-Ring Sign | Low-attenuation core (<30 HU) surrounded by a high-attenuation rim on cross-sectional CCTA imaging. Suggests necrotic core with thin fibrous cap; highly specific for high-risk plaque. |
| Low-Attenuation Plaque | Non-calcified plaque with mean attenuation <30 HU, indicating lipid-rich necrotic core; frequently used in risk stratification. |
| Spotty Calcification | Small foci of dense calcification (<3 mm in diameter) within or at the margin of non-calcified plaque, associated with plaque instability. |
| Positive Remodeling | Outward expansion of the vessel wall in response to plaque, defined as remodeling index ≥1.1. |
| ≥1 High-Risk Plaque Feature | Presence of any one of: low-attenuation plaque (<30 HU), positive remodeling (RI ≥1.1), napkin-ring sign, or spotty calcification. |
| ≥2 High-Risk Plaque Features | Presence of two or more high-risk plaque features from the above list. |
| ≥3 High-Risk Plaque Features | Presence of three or more high-risk plaque features from the above list. |
| 1-Vessel Disease | ≥50% stenosis in one major epicardial coronary artery (LAD, LCx, RCA, or left main equivalent). |
| 2-Vessel Disease | ≥50% stenosis in two major epicardial coronary arteries. |
| 3-Vessel Disease | ≥50% stenosis in three major epicardial coronary arteries (LAD, LCx, RCA). |

Table 1 shows the general definitions used across the included studies of the CCTA-derived plaque variables evaluated in this meta-analysis and that aligned with the SCCT and coronary artery disease-reporting and data system (CAD-RADS) 2.0 consensus statement [14,15]. Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; RI, remodeling index; LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; SCCT, Society of Cardiovascular Computed Tomography.

multiple Excel spreadsheets covering study characteristics, patient populations, and quantitative data.

### *2.5 Statistical Analysis*

Data on HRs and 95% confidence intervals (CIs) for plaque characteristics associated with future MACE were collected and log-transformed, with HRs prioritized from the most fully adjusted models. Detailed information on each extracted HR and the covariates included in the respective models is presented in **Supplementary Material 3**. Analyses were performed using a random-effects model, generating pooled estimates with 95% CIs. Statistical heterogeneity was evaluated using the $I^2$ statistic and categorized as low (<25%), moderate (<50%), or high (>75%). Publication bias was assessed visually using funnel plots and statistically with Egger's test in RStudio 2025.09.1+401 (Posit Software, PBC, Boston, MA, USA). Sensitivity analyses were conducted by systematically excluding individual studies to determine their influence on the pooled results. A two-sided $p$ value of <0.05 was considered statistically significant. Pooled HRs were calculated using RevMan 5.4 (The Cochrane Collaboration, Copenhagen, Zealand, Denmark), and publication bias and sensitivity analyses were conducted in RStudio [16,17].

### *2.6 Subgroup Analysis: Hard MACE Outcomes*

To address variability in MACE definitions across included studies, a predefined subgroup analysis was performed, including only studies reporting hard MACE outcomes, defined as a composite of all-cause mortality, cardiovascular death, myocardial infarction, or stroke, excluding softer endpoints such as unstable angina or elective revascularization. This subgroup included 25 studies that met the criteria for hard MACE reporting. Pooled hazard ra-

tios were calculated using the same random-effects methodology as the primary analysis. Heterogeneity was assessed using the $I^2$ statistic.

### 2.7 Risk of Bias Assessment

Risk of bias was independently assessed by two reviewers using the Newcastle–Ottawa Scale (NOS) for cohort studies. The NOS evaluates three domains: selection of cohorts, comparability of cohorts, and outcome assessment. Because all included studies evaluated prognostic plaque characteristics within cohorts of patients undergoing CCTA, the "selection of the non-exposed cohort" item was considered not applicable, resulting in a maximum attainable score of 8 stars. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer.

## 3. Results

Our search identified 72 papers that met the inclusion criteria (Fig. 1). Table 2 (Ref. [4,5,6,7,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85]) shows the general characteristics of the included studies: 45 are prospective cohorts, 22 are retrospective cohorts, and 5 are post hoc analyses of RCTs. All studies show a follow-up time of greater than 1 year. The combined sample size of our meta-analysis was 143,453 patients, with the mean population size being 2049, ranging from 100 to 40,091 patients across all studies (Table 2). **Supplementary Material 4** further highlights details of scanner types and technical specifications of each study. Table 3 (Ref. [4,5,6,7,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85]) describes the patient characteristics, showing that all patients had either diagnosed CAD or suspected CAD with cardiac symptoms or risk factors. The mean age of the samples was 61.3, ranging from 52.9 to 70.7 years. Each of the study samples has a similar sex and co-morbidity distribution (Table 3). Table 4 (Ref. [4,5,6,7,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85]) describes the MACE components in each study. MACE was defined with diverse endpoints, with unstable angina and elective revascularization included as a MACE component in 35 studies. A total of 16 CCTA-derived plaque-related variables, commonly reported across studies, were included in the quantitative synthesis. Table 5 presents the results of our meta-analyses and subgroup analysis, including pooled HRs for each plaque variable. Most plaque variables were associated with MACE across the primary and subgroup analyses, however, several pooled analyses demonstrated substantial statistical heterogeneity ($I^2$ >75%), with evidence of publication bias. The hard MACE subgroup reduced heterogeneity significantly, and leave-one-out analyses demonstrated preserved magnitude of effect. Sources of heterogeneity are explored in the limitations section (4.2).

### 3.1 Stenosis Severity

Obstructive CAD was strongly associated with MACE. Stenosis ≥70% yielded the highest risk (HR 5.84), followed by ≥50% stenosis (HR 5.04). Moderate stenosis (50%–70%) also demonstrated increased risk (HR 2.46), though with fewer studies. Non-obstructive plaque (<50%) remained significantly associated with MACE (HR 1.54), though markedly less than that for obstructive stenosis, highlighting that risk persists even in the absence of flow-limiting disease (Fig. 2A–D).

### 3.2 Plaque Composition

All plaque types were associated with MACE. Mixed plaque exhibited the strongest association (HR 2.00), followed by non-calcified plaque (HR 1.33), and calcified plaque (HR 1.30) (Fig. 3A–C). These findings suggest that plaque composition represents a spectrum of risk, with mixed plaque potentially reflecting lesions containing both stable and vulnerable elements.

### 3.3 High-Risk Plaque Features

High-risk plaque features demonstrated strong and consistent associations with MACE. The NRS showed the highest risk (HR 3.28), followed by positive remodeling (HR 3.03), low-attenuation plaque (HR 2.34), and spotty calcification (HR 2.30) (Fig. 4A–D). The presence of ≥1 HRP (HR 3.25) and ≥2 HRP (HR 3.66) features further increased risk, supporting a cumulative effect of plaque vulnerability markers (Fig. 5A,B).

### 3.4 Disease Extent

A clear stepwise increase in MACE risk was observed with increasing disease extent. One-, two-, and three-vessel disease showed progressively higher HRs (4.18, 7.34, and 10.91, respectively), representing the strongest associations among all variables. Notably, three-vessel disease yielded the highest HR observed across all variables (Fig. 6A–C).

### 3.5 Subgroup Analysis

Our subgroup analysis restricted to hard MACE outcomes (n = 25 studies) demonstrated consistent but generally attenuated associations compared with the overall MACE analysis (Table 5 and **Supplementary Material 5**). Obstructive disease remained a strong predictor, with ≥50% and ≥70% stenosis significantly associated with hard outcomes, while non-obstructive plaque also retained

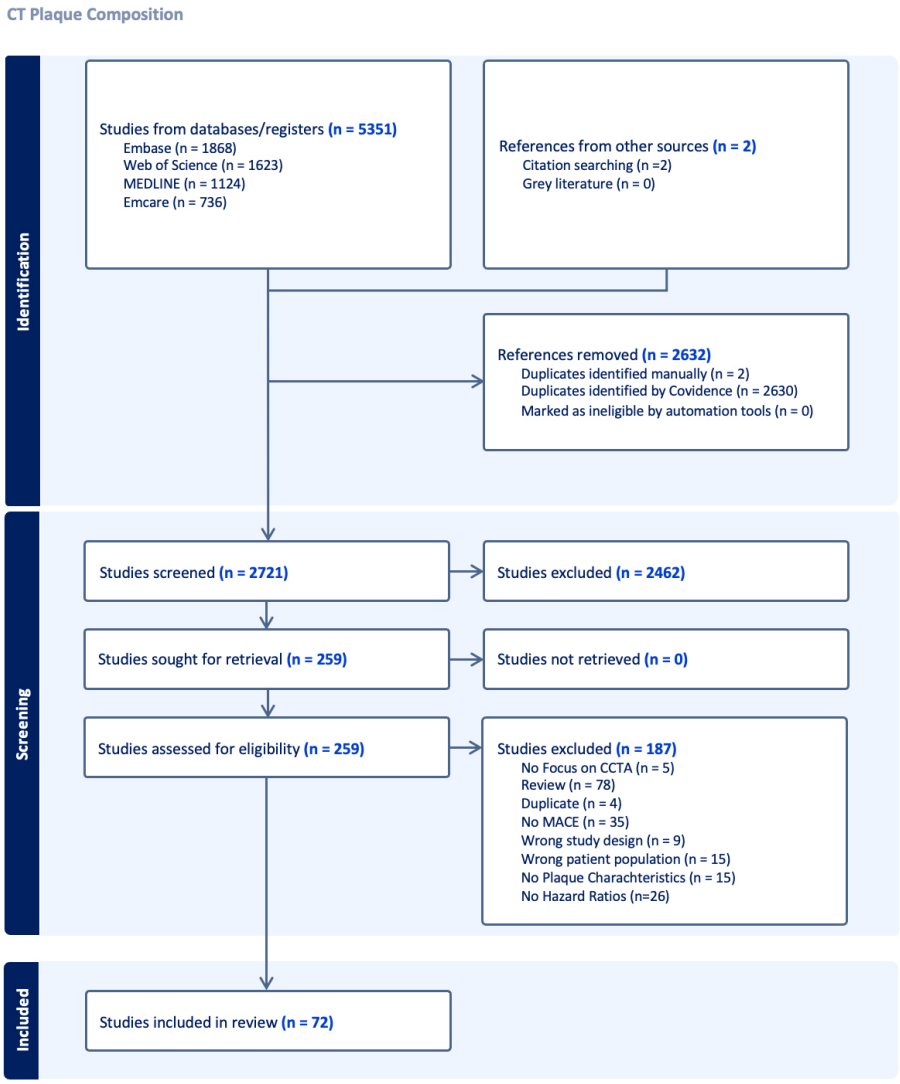



**Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of included studies**.

a modest but significant association. Plaque composition showed weaker effects: calcified and non-calcified plaque remaining significant, whereas mixed plaque was not. Among high-risk plaque features, the NRS and low-attenuation plaque remained significant predictors of hard MACE, while other features showed weaker or non-significant associations. The presence of ≥2 high-risk plaque features remained significant, suggesting a cumulative effect on vulnerability. Disease extent demonstrated the strongest and most consistent associations, with a clear stepwise increase in risk from 1- to 3-vessel disease, mirroring the primary analysis. Heterogeneity across several variables was reduced in the hard MACE subgroup, indicating improved consistency when restricting to clinically definitive endpoints.

### *3.6 Publication Bias Testing*

Publication bias was assessed using funnel plots and Egger's regression testing. Funnel plots visually showcased varying degrees of asymmetry across the different plaque characteristics (**Supplementary Material 6**). As shown in **Supplementary Material 6**, Egger's regression for small-study publication bias testing revealed statistically significant asymmetry ($p < 0.05$) for several outcomes, including obstructive plaque ≥50%, calcified plaque, non-calcified plaque, mixed plaque, LAP, and ≥2 high-risk plaque features. This suggests potential small-study effects or publication bias in these subgroups where smaller studies tended to report larger effect sizes. In contrast, Egger's test did not indicate significant asymmetry for non-obstructive plaque, NRS, spotty calcification, positive remodeling, or vessel-level analyses (1-, 2-, 3-vessel disease; all $p > 0.05$). This suggests that the association estimates for these plaque features were less likely to be influenced by small-study effects (**Supplementary Material 6**).

**Table 2. General study characteristics.**

| First author, year | Study design | Total N | MACE definition | Follow-up period (days, months or years) | CT scanner used (slice & source) |
|---|---|---|---|---|---|
| Prospective | | | | | |
| Aldrovandi, 2009 [18] | P | 187 | Cardiovascular death, MI, Unstable Angina, Revascularization | Mean: 24 ± 2.8 months (~2.0 years) | 64-slice single-source |
| Andreini, 2012 [6] | P | 1196 | Cardiovascular death, MI, Revascularization | Mean: 52 ± 22 months (~4.3 years) | 64-slice |
| Andreini, 2020 [19] | P | 522 | Cardiovascular death, ACS, Revascularization | Mean: 37 ± 10 months (~3.1 years) | 64-slice |
| Ateş, 2021 [7] | P | 1138 | Cardiovascular death, All-cause mortality, ACS, Stroke | Median: 141.5 months (~11.8 years) | 64-slice dual-source |
| Benetos, 2020 [20] | P | 325 | MI, Cardiovascular death, Revascularization | Mean: 5.4 ± 1.7 year | 64-slice multidetector |
| Chan, 2024 [21] | P | 40,091 | MI, Heart Failure Hospitalization, Cardiovascular death | Median: 2.7 years | ≥64-slice |
| Cheruvu, 2016 [22] | P | 885 | All-cause mortality, MI, Unstable Angina, Revascularization | Mean: 5.6 ± 1.3 years | 64-slice single and dual source |
| Chow, 2010 [23] | P | 2076 | MI, Cardiovascular death | Mean: 16 ± 8 months (~1.3 years) | 64-slice |
| Chow, 2021 [24] | P | 8667 | MI, Cardiovascular death | Mean: 7.0 ± 2.6 years | 64-slice |
| de Azevedo, 2011 [25] | P | 529 | All-cause mortality, MI | Mean: 30.1 ± 11.1 months (~2.5 years) | 64-slice |
| Ferencik, 2018 [26] | P | 4415 | MI, All-cause mortality, UA Hospitalization | Median: 25 months (~2.1 years) | 64-, 128-, 256-, 320-slice dual source |
| Feuchtner, 2017 [4] | P | 1469 | ACS, MI, Unstable Angina | Mean: 7.8 years | 64- or 128-slice dual-source |
| Finck, 2020 [5] | P | 1615 | Cardiovascular death, MI | Mean: 10.5 years | 64-slice single- and dual-source |
| Hadamitzky, 2011 [27] | P | 2223 | Cardiovascular death, MI, UA Hospitalization, Revascularization | Median: 28 months (~2.3 years) | 16- and 64-slice single-source and dual-source |
| Hadamitzky, 2013 [28] | P | 1584 | All-cause mortality, MI | Median: 5.6 years | 16-, 64-slice single source, and dual source |
| Han, 2022 [29] | P | 4644 | All-cause mortality, MI | Median: 5.2 years | 64-slice multidetector |
| Hou, 2012 [30] | P | 4425 | Revascularization, Cardiovascular death, MI | Median: 1081 days (~3.0 years) | 64-slice multidetector |
| Kiriyama, 2018 [31] | P | 157 | Cardiovascular death, MI, Revascularization, UA Hospitalization | Mean: 45 ± 19 months (~3.8 years) | 64-slice multidetector |
| Lee, 2018 [32] | P | 1345 | Cardiovascular death, MI, Revascularization | Mean: 3.8 ± 1.6 years | NR |
| Lima, 2023 [33] | P | 199 | Cardiovascular death, ACS, Heart Failure Hospitalization, Revascularization, Arrhythmia, Cardiac arrest | Median: 6.8 years | 64-slice |
| Matsumoto, 2007 [34] | P | 810 | MI, Cardiovascular death, Unstable Angina | Mean: 1062 ± 544 days (~2.9 years) | 16-slice |

**Table 2. Continued.**

| First author, year | Study design | Total N | MACE definition | Follow-up period (days, months or years) | CT scanner used (slice & source) |
|---|---|---|---|---|---|
| Min, 2010 [35] | P | 172 | All-cause mortality, MI, Unstable Angina, Revascularization | Mean: 22.0 ± 4.5 months (~1.8 years) | 64-slice multi-detector |
| Miszalski-Jamka, 2012 [36] | P | 494 | MI, Cardiovascular death, Revascularization | Mean: 1308 ± 318 days (~3.6 years) | 16- and 64-slice |
| Mordi, 2016 [37] | P | 232 | Cardiovascular death, MI, Revascularization | Mean: 2.5 ± 0.9 years | 64-slice dual-source |
| Motoyama, 2009 [38] | P | 1059 | ACS, Unstable Angina | Mean: 27 ± 10 months (~2.3 years) | 16 and 64-slice |
| Motoyama, 2015 [39] | P | 3158 | ACS, Unstable Angina | Mean: 3.9 ± 2.4 years | 16-, 64, and 320-slice |
| Mushtaq, 2015 [40] | P | 1196 | Cardiovascular death, MI | Mean: 52 ± 22 months (~4.3 years) | 64-slice |
| Nadjiri, 2016 [41] | P | 1168 | Cardiovascular death, Unstable Angina, MI, Revascularization | Median: 5.7 years | 64-slice single-source |
| Nakanishi, 2014 [42] | P | 517 | ACS, MI | Mean: 4.1 ± 1.8 years | 64-slice multidetector |
| Oeing, 2023 [43] | P | 372 | Cardiovascular death, MI, UA Hospitalization, Revascularization, Arrhythmia, All-cause mortality, Stroke | Median: 4.88 years | 320-slice |
| Otsuka, 2013 [44] | P | 895 | ACS, MI, Unstable Angina | Mean: 2.3 ± 0.8 years | 64-slice multidetector |
| Otsuka, 2014 [45] | P | 543 | Cardiovascular death, MI, Unstable Angina | Mean: 3.4 ± 0.8 years | 64-slice |
| Petretta, 2012 [46] | P | 326 | Cardiovascular death, MI, UA Hospitalization, Revascularization | Mean: 26 ± 12 months (~2.2 years) | 64-slice multidetector |
| Plank, 2014 [47] | P | 711 | Cardiovascular death, MI | Mean: 2.65 years | 64- and 128-slice |
| Pundziute, 2007 [48] | P | 100 | Cardiovascular death, MI, UA Hospitalization, Revascularization | Mean: 16 months (~1.3 years) | 16- or 64-slice |
| Sato, 2024 [49] | P | 745 | Cardiovascular death, ACS, Revascularization | Median: 744 days (~2.0 years) | 320-slice |
| Senoner, 2020 [50] | P | 1430 | All-cause mortality, Cardiovascular death, ACS, MI | Mean: 10.55 ± 1.98 years | 64- and 128-slice |
| Sozzi, 2011 [51] | P | 192 | UA Hospitalization, MI | Mean: 5.0 ± 0.5 years | 64-slice single-source |
| Suruga, 2021 [52] | P | 243 | Cardiovascular death, ACS, Revascularization | Median: 1.8 years | 128-slice |
| Tommasino, 2024 [53] | P | 499 | MI, Cardiovascular death | Mean: 374.39 ± 104.28 days (~1.0 years) | 128-slice |
| van Werkhoven, 2009 [54] | P | 432 | All-cause mortality, MI, Revascularization, UA Hospitalization | Median: 670 days (~1.8 years) | 64-slice |
| Yamamoto, 2013 [55] | P | 453 | Cardiovascular death, MI, UA Hospitalization | 3.3 ± 1.2 years | 64-slice |
| Yamamoto, 2018 [56] | P | 2802 | All-cause mortality, ACS, MI, UA Hospitalization, Revascularization | Median: 24.5 months (~2.0 years) | ≥64-slice |

**Table 2. Continued**.

| First author, year | Study design | Total N | MACE definition | Follow-up period (days, months or years) | CT scanner used (slice & source) |
|---|---|---|---|---|---|
| Yorgun, 2013 [57] | P | 1115 | Cardiovascular death, MI, Revascularization, UA Hospitalization | Mean: 29.7 ± 13.2 months (~2.5 years) | 64-slice dual-source |
| Yu, 2021 [58] | P | 142 | All-cause mortality, MI, Revascularization, Heart Failure Hospitalization, UA Hospitalization | Median: 23.00 months (~1.9 years) | 64-slice dual-source |
| | | | Retrospective | | |
| Aldrovandi, 2012 [59] | R | 767 | MI, Cardiovascular death, Unstable Angina | Mean: 20 ± 4 months (~1.7 years) | 64-slice |
| Bittencourt, 2014 [60] | R | 3242 | Cardiovascular death, MI | Median: 3.6 years | 64-slice |
| Conte, 2017 [61] | R | 245 | All-cause mortality, ACS, Revascularization, El Revascularization | Mean: 98 ± 20 months (~8.2 years) | 64-slice |
| Driessen, 2020 [62] | R | 539 | All-cause mortality, MI | Median: 6.8 years | 256-slice |
| Dundas, 2024 [63] | R | 4430 | Cardiovascular death, All-cause mortality, MI, ACS, Revascularization | 1 year | Not Reported |
| Fujimoto, 2016 [64] | R | 628 | Cardiovascular death, MI, UA Hospitalization | Median: 677 days (~1.9 years) | 64- or 320-slice |
| Gu, 2018 [65] | R | 268 | All-cause mortality, MI, UA Hospitalization, Revascularization | Mean: 4.6 ± 0.9 years | 64-slice dual-source |
| Kawai, 2014 [66] | R | 676 | ACS, Cardiovascular death, Revascularization, Unstable Angina | Mean: 27.7 ± 15.4 months (~2.3 years) | 320- and 64-slice |
| Lee, 2016 [67] | R | 1077 | Cardiovascular death, MI, Unstable Angina, Revascularization | Median: 23 months (~1.9 years) | 64-slice |
| Lee, 2022 [68] | R | 220 | MI, UA Hospitalization, Revascularization | Mean: 554.3 ± 268.2 days (~1.5 years) | 64- or 128-slice dual-source |
| Maclean, 2022 [69] | R | 720 | MI, Cardiovascular death, Revascularization | Mean: 64.6 ± 19.1 months (~5.4 years) | 128-slice dual source, multi-detector |
| Meng, 2024 [70] | R | 516 | All-cause mortality, MI, Revascularization | Mean: 65.29 months (~5.4 years) | 64-slice dual-source |
| Mortensen, 2020 [71] | R | 23,759 | MI, Stroke, All-cause mortality | Median: 4.3 years | 64-slice |
| Motoyama, 2013 [72] | R | 253 | Cardiovascular death, MI, Revascularization, UA Hospitalization | Median: 24 months (~2 years) | 16-, 64-, and 320-slice |
| Munnur, 2022 [73] | R | 1257 | ACS, Unstable Angina | Median: 7.24 years | 320-slice |
| Nance, 2012 [74] | R | 458 | MI, Revascularization, Cardiovascular death, UA Hospitalization | Median: 13 months (~1.1 years) | First- and second-generation dual-source |
| Otsuka, 2022 [75] | R | 204 | Cardiovascular death, MI, Stroke | Median: 2.7 years | 320-slice |
| Pergola, 2022 [76] | R | 371 | All-cause mortality, ACS, Revascularization | Mean 25.4 months (~2.1 years) | 320-slice |
| Takamura, 2017 [77] | R | 339 | Cardiovascular death, MI, UA Hospitalization | Mean: 716.5 ± 262.6 days (~2.0 years) | 64- and 320-slice |

**Table 2. Continued**.

| First author, year | Study design | Total N | MACE definition | Follow-up period (days, months or years) | CT scanner used (slice & source) |
|---|---|---|---|---|---|
| Tesche, 2023 [78] | R | 361 | Cardiovascular death, MI, UA Hospitalization, Revascularization | Median: 5.4 years | 64-slice |
| Tomizawa, 2018 [79] | R | 317 | All-cause mortality, MI, Arrhythmia, Revascularization | Median: 25.8 months (~2.2 years) | 64-slice multidetector |
| Yang, 2025 [80] | R | 1052 | MI, Heart Failure Hospitalization, Stroke, All-cause mortality, Revascularization | Median: 6.8 years | 640-slice |
| | | | Other | | |
| Maclean, 2023 [81] | Post-Hoc | 1769 | Cardiovascular death, MI, Stroke, Revascularization | Mean: 4.9 ± 1.1 years | 64 and 320-slice multidetector |
| Meah, 2022 [82] | Post-Hoc | 404 | All-cause mortality, MI | 1 year | 64-slice |
| Tzolos, 2022 [83] | Post-Hoc | 1697 | MI, Cardiovascular death | Median: 4.7 years | 64- and 320-slice |
| Williams, 2019 [84] | Post-Hoc | 1769 | MI, Cardiovascular death | 5 years | 64- and 320-slice |
| Yamamoto, 2021 [85] | Post-Hoc | 2083 | ACS, Cardiovascular death, MI, UA Hospitalization, Revascularization | 2 years | ≥64-slice |

Table 2 shows the characteristics of the included studies, including the type of study, sample size, MACE definition, follow-up duration and CT scanner used. Abbreviations: P, prospective; R, retrospective; MI, myocardial infarction; ACS, acute coronary syndrome; UA, unstable Angina; MACE, major adverse cardiovascular events; CT, computed tomography.

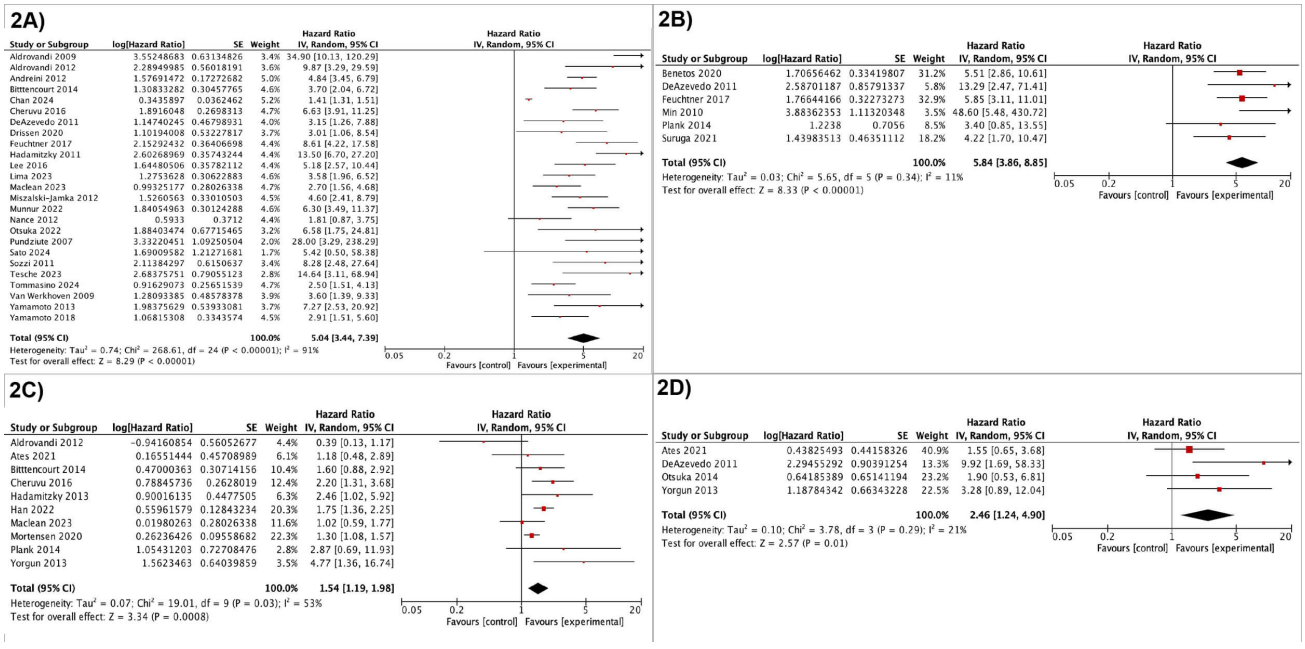



**Fig. 2. Forest plots for stenosis severity**. (A) Forest plot for Obstructive Plaque (≥50% Stenosis). (B) Forest plot for Obstructive Plaque (≥70% Stenosis). (C) Forest plot for Non–Obstructive Plaque (<50% Stenosis). (D) Forest plot for Moderate Stenosis (50%–70%).

### *3.7 Sensitivity Analysis*

Leave-one-out sensitivity analyses demonstrated that across all tested plaque variables, all pooled hazard ratios remained directionally consistent and statistically significant. This means no single study disproportionately influenced the meta-analytic results (**Supplementary Mate-**

**Table 3. Patient population characteristics.**

| First author, year | Patient population/indication for CCTA | Mean/median age (years) | % of men | Dyslipidemia (%) | HTN (%) | Diabetes (%) | Family history of CAD (%) | Smoker (%) |
|---|---|---|---|---|---|---|---|---|
| Aldrovandi, 2009 [18] | Suspected CAD but no known heart disease, which could include symptoms (chest pain, dyspnea), abnormal stress tests, or high cardiovascular risk profile | 62.5 ± 10.9 | 63.6 | 57.1 | 66.8 | 10.6 | 47.6 | 37.4 |
| Aldrovandi, 2012 [59] | Suspected or known CAD, had symptoms (chest pain, dyspnea on exertion), abnormal or equivocal stress test, or a high cardiovascular risk profile | 62 ± 11 | 64.6 | 51.1 | 63.2 | 14.5 | 51.7 | 34.7 |
| Andreini, 2012 [6] | Suspected CAD, without known CAD, indicated for new-onset chest pain, elevated risk profile, abnormal stress tests, or for comprehensive cardiac assessment when other cardiac diseases were excluded | 62 ± 11 | 62 | 45 | 59 | 11 | 33 | 29 |
| Andreini, 2020 [19] | Suspected but unknown CAD | 59 ± 8 | 58.2 | 60.3 | 52.1 | 12.1 | 31.2 | 24.5 |
| Ateş, 2021 [7] | Suspected stable ischemic CAD with equivocal non-invasive tests | 58 ± 11 | 54.3 | NR | 66.2 | 18.8 | NR | 34.2 |
| Benetos, 2020 [20] | Known or suspected CAD | 59 ± 11.5 | 61 | 45 | 54 | 10 | 40 | 35 |
| Bittencourt, 2014 [60] | Suspected CAD without prior CAD | 56 ± 13.3 | 57 | 56 | 55 | 16 | 28 | 22 |
| Chan, 2024 [21] | Stable chest pain evaluation to rule out obstructive CAD | 59 | 53.3 | 25.5 | 42.3 | 18.2 | NR | 12 |
| Cheruvu, 2016 [22] | Without prior CAD or any modifiable CAD risk factors | 55.6 ± 14.5 | 59.6 | NR | NR | NR | 31.3 | NR |
| Chow, 2010 [23] | Suspect CAD with symptoms, asymptomatic with multiple cardiac risk factors, abnormal stress-testing, or CCTA before non-coronary cardiac surgery | 58 ± 11.7 | 52.4 | 53.1 | 51.8 | 14.5 | 41.9 | 54.5 |
| Chow, 2021 [24] | Suspect CAD without prior CAD | 57.1 ± 11.1 | 52.9 | 54.7 | 50.1 | 12.8 | 44.9 | 37.9 |
| Conte, 2017 [61] | Suspected but unknown stable CAD | 63 ± 9 | 69.8 | 47.8 | 59.6 | 8.6 | 27.3 | 32.2 |
| de Azevedo, 2011 [25] | Suspected CAD with inconclusive results from prior non-invasive cardiac stress tests | 57.8 ± 12 | 61 | 56 | 60 | 12 | 24 | 13 |
| Driessen, 2020 [62] | Suspected stable CAD | 58.6 ± 9.2 | 55 | 37 | 47 | 17 | 54 | 35 |
| Dundas, 2024 [63] | Stable chest pain, suspected CAD | 67 | 65.9 | NR | 59.9 | 21.8 | NR | 54.9 |
| Ferencik, 2018 [26] | Stable chest pain, symptomatic outpatients without known CAD | 60.5 ± 8.2 | 48.3 | 67.2 | 64.1 | 20.6 | 32.7 | 51.2 |
| Feuchtner, 2017 [4] | Atypical chest pain, stable angina, or asymptomatic individuals with high CAD risk | 65.9 ± 11 | 55.8 | 51.3 | 51.4 | 9.7 | 32.2 | 33.3 |
| Finck, 2020 [5] | Suspected but not previously diagnosed CAD | 59 ± 11 | 66.6 | 53.3 | 59.3 | 7.4 | 31.6 | 33.9 |
| Fujimoto, 2016 [64] | Newly symptomatic patients without known CAD | 63.8 ± 7.8 | 58.3 | 79.6 | 69.7 | 22.1 | NR | 22.8 |
| Gu, 2018 [65] | Stable angina and recurrent or worsening symptoms | 52.9 ± 9.8 | 71 | 40.3 | 25.7 | 20.1 | 19.4 | 14.1 |
| Hadamitzky, 2011 [27] | Suspected CAD | 60 | 66.8 | 52.7 | 59 | 7.5 | 32.4 | 35.3 |
| Hadamitzky, 2013 [28] | Suspected CAD | 58.4 ± 11.1 | 68.9 | 53.4 | 59 | 7.7 | 33 | 34.8 |
| Han, 2022 [29] | Non-obstructive CAD | 56.7 ± 12.1 | 62.1 | 57.8 | 56.6 | 13.6 | 29.7 | 17.3 |
| Hou, 2012 [30] | Suspected CAD | 59.6 ± 11.3 | 62.1 | 27.6 | 57.4 | 14.5 | 35.1 | 30.9 |
| Kawai, 2014 [66] | Suspected CAD, patients undergoing both CCTA and ICA | 66.8 ± 10.3 | 74 | 61.8 | 74.1 | 31.8 | NR | 27.8 |
| Kiriyama, 2018 [31] | Chronic CAD who underwent both CCTA and stress myocardial perfusion imaging within a 6-month interval | 69 ± 9 | 76 | 71 | 82 | 34 | NR | 43 |
| Lee, 2016 [67] | Suspected CAD who underwent both single-photon emission CT and CCTA | 62 ± 10 | 63.2 | 45.3 | 42.1 | 55 | NR | 38.9 |
| Lee, 2018 [32] | Underwent repeated coronary CCTA >2 years apart. | 60.4 ± 9.4 | 57.1 | 37.7 | 52.2 | 19.8 | 29.3 | 36.8 |

**Table 3. Continued.**

| First author, year | Patient population/indication for CCTA | Mean/median age (years) | % of men | Dyslipidemia (%) | HTN (%) | Diabetes (%) | Family history of CAD (%) | Smoker (%) |
|---|---|---|---|---|---|---|---|---|
| Lee, 2022 [68] | CTA for suspected CAD within 6–36 months before PCI for acute MI or unstable angina, plus a control group of 62 patients without PCI | 65.5 ± 10.2 | 81.4 | 42.3 | 72.7 | 59.5 | NR | 19.1 |
| Lima, 2023 [33] | Symptomatic patients with suspected or known CAD | 58 ± 7 | 62 | 57 | 81 | 36 | 28 | 24 |
| Maclean, 2022 [69] | Low-risk patients with suspected ischemic symptoms | 58 | 62.1 | 27.6 | 24.3 | 5.3 | 6.8 | 18.2 |
| Maclean, 2023 [81] | Suspected stable angina referred to outpatient chest pain clinics | 58 ± 10 | 56 | NR | 35 | 11 | 44 | 34 |
| Matsumoto, 2007 [34] | Evaluation of typical and atypical chest pain | 61.3 ± 13.2 | 70.60 | 39.7 | 36.7 | 19 | NR | 16.6 |
| Meah, 2022 [82] | Suspected ACS who presented to the emergency department with acute chest pain | 63 ± 12 | 64 | 41 | 45 | 14 | 34 | 60 |
| Meng, 2024 [70] | Suspected or confirmed CAD who underwent CCTA at least twice (at least 12 months apart) and did not experience MACE between CCTA | 56.40 ± 9.56 | 67.4 | 62.6 | 63.6 | 22.3 | 27.1 | 46.5 |
| Min, 2010 [35] | Symptomatic patients with suspected or known CAD | 63.0 ± 12.3 | 57 | 24.4 | 49.2 | 21.9 | NR | 26.2 |
| Miszalski-Jamka, 2012 [36] | Suspected CAD for chest pain evaluation | 58.2 ± 9.8 | 52.4 | 63 | 78 | 11 | 34 | 10 |
| Mordi, 2016 [37] | Acute chest pain and troponin-negative results after inconclusive exercise treadmill tests (ETT) | 54.1 ± 10.9 | 42.2 | 53.4 | 41.4 | 7.3 | 22.4 | 13.4 |
| Mortensen, 2020 [71] | Symptomatic with suspect CAD | 57.4 | 44.6 | NR | 45.7 | 8.5 | NR | 20.7 |
| Motoyama, 2009 [38] | Suspected or known CAD | 64 ± 11 | 74 | 32 | 33 | 17 | NR | 20 |
| Motoyama, 2013 [72] | Suspected CAD, undergoing both CCTA and MPI within 3 months | 65.3 ± 10.6 | 72.4 | 48.9 | 59.9 | 26.6 | NR | 26.6 |
| Motoyama, 2015 [39] | Suspected or known CAD | 65.5 ± 11.1 | 69.8 | 48.1 | 55.5 | 22.9 | NR | 17.5 |
| Munnur, 2022 [73] | Suspected CAD | 60.9 ± 13.7 | 50.9 | 46 | 46 | 11.1 | 43.3 | 18 |
| Mushtaq, 2015 [40] | Suspected CAD | NR | 65.4 | 41.6 | 58.8 | 10.4 | 32.7 | 27.6 |
| Nadjiri, 2016 [41] | Suspected CAD without CAD diagnosis | 58.6 ± 11 | 68.9 | 53.3 | 61.6 | 8 | 30.6 | 34.5 |
| Nakanishi, 2014 [42] | Non-obese patients enrolled for evaluation of CAD progression | 65.7 | 71.2 | 58 | 76.6 | 37.1 | NR | 28.6 |
| Nance, 2012 [74] | Acute chest pain but without evidence of ACS who presented to the ED | 55 ± 10 | 36 | 45 | 69 | 21 | NR | 30 |
| Oeing, 2023 [43] | Symptomatic patients with suspected or known CAD | 62 | 67 | 68 | 78 | 34 | 44 | 37 |
| Otsuka, 2013 [44] | Symptomatic patients with chest pain and asymptomatic individuals with multiple CAD risk factors | 66 ± 10 | 66 | 55 | 66 | 49 | NR | 36 |
| Otsuka, 2014 [45] | Symptomatic patients with chest pain and asymptomatic individuals with multiple CAD risk factors | 65 ± 10 | 63.4 | 53.2 | 63 | 44.2 | NR | 19.9 |
| Otsuka, 2022 [75] | With or without known CAD | 64 | 53 | 63 | 70 | 20 | NR | 16 |
| Pergola, 2022 [76] | Asymptomatic patients or patients with stable (typical or atypical) chest pain, with a low to intermediate pre-test probability of obstructive CAD | 55.5 | 63.9 | 37.4 | 55.1 | 9.8 | NR | 31.2 |
| Petretta, 2012 [46] | Intermediate pre-test likelihood (15–85%) of CAD after analysis of traditional risk factors | 62 ± 12 | 67 | 38 | 51 | 12 | 40 | 27 |

**Table 3. Continued**.

| First author, year | Patient population/indication for CCTA | Mean/median age (years) | % of men | Dyslipidemia (%) | HTN (%) | Diabetes (%) | Family history of CAD (%) | Smoker (%) |
|---|---|---|---|---|---|---|---|---|
| Plank, 2014 [47] | Asymptomatic patients with high a priori risk of CAD | 61.8 | 59.90 | 46 | 46.7 | 8.7 | 36.1 | 27.7 |
| Pundziute, 2007 [48] | Suspicion of significant CAD | 59 ± 12 | 73% | 50 | 44 | 21 | 42 | 39 |
| Sato, 2024 [49] | Chronic coronary syndrome (CCS) patients with suspected CAD | 69 | 64.40 | 46.6 | 55.8 | 19.9 | NR | 16.9 |
| Senoner, 2020 [50] | Unknown CAD and low-to-intermediate atherosclerotic cardiovascular disease risk and with typical, atypical, nonspecific chest pain or asymptomatic | 57.9 ± 11.1 | 55.6 | 63.5 | 63.6 | 13 | 38 | 39.3 |
| Sozzi, 2011 [51] | First-time chest pain suspicious for angina, suspected but no previously known CAD and intermediate pretest likelihood of CAD | 59 ± 11 | 61 | 35 | 41 | 17 | NR | 22 |
| Suruga, 2021 [52] | Suspected stable CAD | 69 | 63 | 56 | 66 | 35 | NR | 22 |
| Takamura, 2017 [77] | Asymptomatic patients without known CAD but high risk for CAD (based on ECG, ETT, echo, or risk factors) | 63.4 ± 10.4 | 61.40 | 73.7 | 62.2 | 24.2 | 23 | 22.7 |
| Tesche, 2023 [78] | Non-diabetic patients with suspected CAD | 61.9 ± 10.3 | 64 | 45 | 55 | 0 | 25 | 32 |
| Tomizawa, 2018 [79] | CTA after PCI | 70.7 ± 9.5 | 60 | 75 | 82 | 39 | 21 | 38 |
| Tommasino, 2024 [53] | Suspected CAD with symptoms | 64.39 ± 9.9 | 78.3 | 56.1 | 73.1 | 22.6 | NR | 19.8 |
| Tzolos, 2022 [83] | Stable chest pain, suspected angina pectoris | 58 ± 10 | 57 | NR | 35 | 11 | 44 | 34 |
| van Werkhoven, 2009 [54] | Suspected CAD based on chest pain, a positive exercise ECG test, or a high-risk profile for cardiovascular disease | 58 ± 11 | 59 | 39 | 57 | 28 | 36 | 28 |
| Williams, 2019 [84] | Stable chest pain, suspected angina pectoris | 57.6 ± 9.8 | 56 | NR | 35 | 11 | 43 | 53 |
| Yamamoto, 2013 [55] | Suspected CAD (asymptomatic high-risk individuals, ischemia on tests, or chest symptoms) | 65.7 ± 11.3 | 63.6 | 53.2 | 61.4 | 41.3 | NR | 37.4 |
| Yamamoto, 2018 [56] | Suspected or known CAD | 67.0 ± 9.6 | 65.5 | 67 | 67.5 | NR | 40.3 | 47.3 |
| Yamamoto, 2021 [85] | Suspected CAD | 66.5 ± 9.7 | 61.6 | 64 | 65.7 | 26.1 | 40.3 | 44.9 |
| Yang, 2025 [80] | Patients with non-obstructive CAD presenting with chest discomfort | 61 ± 10 | 52.3 | 23.1 | 54.8 | 27.3 | 9.2 | 37.6 |
| Yorgun, 2013 [57] | Symptomatic patients with suspected CAD and mild–moderate stenosis | 58.4 ± 11.4 | 54 | NR | 65.7 | 19 | 15.1 | 34.3 |
| Yu, 2021 [58] | Chest pain, intermediate–high pre-test probability of CAD | 66.66 ± 12.72 | 67.61 | 46.48 | 69.72 | 28.87 | NR | 18.31 |

Table 3 shows the characteristics of the sample size included in each study of our meta-analyses, such as the age, % of men, and comorbidity rates. Abbreviations: CAD, coronary artery disease; NR, not reported; ICA, invasive coronary angiography; MPI, myocardial perfusion imaging; ED, emergency department; ECG, Electrocardiogram; HTN, hypertension; PCI, percutaneous-coronary intervention.

**Table 4. Reported MACE events and individual cardiovascular outcomes by study.**

| First author, year | Total sample (N) | Total MACE events (n) | MACE proportion (n/N) | Cardiac death (n) | All-cause death (n) | MI (n) | ACS (n) | UA (n) | Heart failure (n) | Stroke (n) | Revascularization (n) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aldrovandi, 2009 [18] | 187 | 20 | 0.11 | | | 3 | | 1 | | | 16 |
| Aldrovandi, 2012 [59] | 767 | 21 | 0.03 | 4 | | 12 | | 5 | | | |
| Andreini, 2012 [6] | 1196 | 259 | 0.22 | 18 | | 118 | | | | | 123 |
| Andreini, 2020 [19] | 522 | 22 | 0.04 | 1 | | 8 | 8 | | | | 13 |
| Ateş, 2021 [7] | 1138 | 149 | 0.13 | 57 | 149 | | | | 5 | 22 | |
| Benetos, 2020 [20] | 325 | 36 | 0.11 | 6 | | 7 | | | | | 23 |
| Bittencourt, 2014 [60] | 3242 | 195 | 0.06 | 56 | 144 | 45 | | 56 | | | 87 |
| Chan, 2024 [21] | 40,091 | 4307 | 0.11 | 1754 | | 1898 | | | 1727 | | |
| Cheruvu, 2016 [22] | 885 | 105 | 0.12 | | | | | | | | |
| Chow, 2010 [23] | 2076 | 31 | 0.01 | 11 | | 23 | | | | | |
| Chow, 2021 [24] | 8667 | 278 | 0.03 | 110 | | 104 | | | | | |
| Conte, 2017 [61] | 245 | 28 | 0.11 | 2 | 6 | 6 | 12 | 6 | | | 10 |
| de Azevedo, 2011 [25] | 529 | 37 | 0.07 | | 20 | 17 | | | | | |
| Driessen, 2020 [62] | 539 | 42 | 0.08 | | 23 | 19 | | | | | |
| Dundas, 2024 [63] | 4430 | 55 | 0.01 | 15 | 35 | 12 | 8 | | | | |
| Ferencik, 2018 [26] | 4415 | 131 | 0.03 | | 60 | 24 | | 47 | | | |
| Feuchtner, 2017 [4] | 1469 | 41 | 0.03 | | | 39 | 41 | 2 | | | |
| Finck, 2020 [5] | 1615 | 51 | 0.03 | 36 | | 15 | | | | | |
| Fujimoto, 2016 [64] | 628 | 26 | 0.04 | 1 | | 3 | | 22 | | | |
| Gu, 2018 [65] | 268 | 40 | 0.15 | | | | | 8 | | | 32 |
| Hadamitzky, 2011 [27] | 2223 | 47 | 0.02 | 4 | | 8 | | 4 | | | 31 |
| Hadamitzky, 2013 [28] | 1584 | 61 | 0.04 | | 48 | 13 | | | | | |
| Han, 2022 [29] | 4644 | 340 | 0.07 | | 195 | 145 | | | | | |
| Hou, 2012 [30] | 4425 | 363 | 0.08 | 40 | | 87 | | | | | 236 |
| Kawai, 2014 [66] | 676 | 66 | 0.10 | 9 | | | 17 | | | | 40 |
| Kiriyama, 2018 [31] | 157 | 9 | 0.06 | 1 | | 5 | | 3 | | | |
| Lee, 2016 [67] | 1077 | 71 | 0.07 | 2 | | 7 | | 23 | | | 39 |
| Lee, 2018 [32] | 1345 | 97 | 0.07 | 6 | | 3 | | | | | 79 |
| Lee, 2022 [68] | 220 | 158 | 0.72 | | | 27 | | 131 | | | |
| Lima, 2023 [33] | 199 | 73 | 0.37 | 9 | | | 14 | | 11 | | 31 |
| Maclean, 2022 [69] | 720 | 54 | 0.08 | 13 | | 15 | | | | | 26 |
| Maclean, 2023 [81] | 1769 | 74 | 0.04 | | | 41 | | | | | |
| Matsumoto, 2007 [34] | 810 | 28 | 0.03 | 6 | | 7 | 22 | 15 | | | |
| Meah, 2022 [82] | 404 | 25 | 0.06 | | 9 | 18 | | | | | |
| Meng, 2024 [70] | 516 | 114 | 0.22 | | 11 | 5 | | | | | 98 |
| Min, 2010 [35] | 172 | 18 | 0.10 | | | 1 | | 1 | | | 16 |
| Miszalski-Jamka, 2012 [36] | 494 | 40 | 0.08 | 9 | | 8 | | | | | |
| Mordi, 2016 [37] | 232 | 26 | 0.11 | | 2 | 4 | | 14 | | | 6 |
| Mortensen, 2020 [71] | 23,759 | 1054 | 0.04 | | 536 | 219 | | | | 299 | |

**Table 4. Continued**.

| First author, year | Total sample (N) | Total MACE events (n) | MACE proportion (n/N) | Cardiac death (n) | All-cause death (n) | MI (n) | ACS (n) | UA (n) | Heart failure (n) | Stroke (n) | Revascularization (n) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Motoyama, 2009 [38] | 1059 | 15 | 0.01 | | | | 15 | | | | |
| Motoyama, 2013 [72] | 253 | 11 | 0.04 | | | 9 | | 2 | | | 2 |
| Motoyama, 2015 [39] | 3158 | 88 | 0.03 | | | | 88 | | | | |
| Munnur, 2022 [73] | 1257 | 45 | 0.04 | 3 | | 34 | 45 | 8 | | | |
| Mushtaq, 2015 [40] | 1196 | 125 | 0.10 | 18 | | 118 | | | | | |
| Nadjiri, 2016 [41] | 1168 | 46 | 0.04 | 6 | | 10 | | 3 | | | 36 |
| Nakanishi, 2014 [42] | 517 | 43 | 0.08 | | | 13 | 43 | 30 | | | |
| Nance, 2012 [74] | 458 | 70 | 0.15 | 3 | | 11 | | 27 | | | 29 |
| Oeing, 2023 [43] | 372 | 97 | 0.26 | 5 | 23 | 7 | | 23 | 4 | 11 | 65 |
| Otsuka, 2013 [44] | 895 | 24 | 0.03 | 1 | | 4 | 24 | 19 | | | |
| Otsuka, 2014 [45] | 543 | 23 | 0.04 | 3 | | 12 | 23 | 11 | | | 11 |
| Otsuka, 2022 [75] | 204 | 11 | 0.05 | 2 | | 4 | | | | 5 | |
| Pergola, 2022 [76] | 371 | 58 | 0.16 | 13 | | | 45 | | | | 17 |
| Petretta, 2012 [46] | 326 | 34 | 0.10 | 13 | | 9 | | 12 | | | 12 |
| Plank, 2014 [47] | 711 | 6 | 0.01 | 2 | | 6 | | | | | |
| Pundziute, 2007 [48] | 100 | 26 | 0.26 | 1 | | 3 | | 4 | | | 24 |
| Sato, 2024 [49] | 745 | 20 | 0.03 | 1 | | 2 | 2 | | | | 17 |
| Senoner, 2020 [50] | 1430 | 57 | 0.04 | 25 | | 53 | | | | | |
| Sozzi, 2011 [51] | 192 | 30 | 0.16 | | | 2 | | 14 | | | 14 |
| Suruga, 2021 [52] | 243 | 24 | 0.10 | | | | 2 | | | | 22 |
| Takamura, 2017 [77] | 339 | 9 | 0.03 | | | 2 | | 7 | | | |
| Tesche, 2023 [78] | 361 | 31 | 0.09 | | | | | | | | |
| Tomizawa, 2018 [79] | 317 | 74 | 0.23 | 2 | 5 | | | | | | 68 |
| Tommasino, 2024 [53] | 499 | 62 | 0.12 | 3 | | 5 | | | | | 12 |
| Tzolos, 2022 [83] | 1697 | 37 | 0.02 | 2 | | 37 | | | | | |
| van Werkhoven, 2009 [54] | 432 | 21 | 0.05 | | 6 | 8 | | 7 | | | 7 |
| Williams, 2019 [84] | 1769 | 41 | 0.02 | | | | | | | | |
| Yamamoto, 2013 [55] | 453 | 15 | 0.03 | 2 | | 7 | | 6 | | | 19 |
| Yamamoto, 2018 [56] | 2802 | 49 | 0.02 | | 30 | 9 | 19 | 10 | | | |
| Yamamoto, 2021 [85] | 2083 | 73 | 0.04 | 3 | | | 17 | | | | 53 |
| Yang, 2025 [80] | 1052 | 183 | 0.17 | 9 | 25 | 60 | | | 44 | 16 | 38 |
| Yorgun, 2013 [57] | 1115 | 29 | 0.03 | | | 9 | 29 | 20 | | | |
| Yu, 2021 [58] | 142 | 15 | 0.11 | 3 | 3 | | | 4 | 1 | | 7 |

Table 4 shows the incidence of MACE and individual cardiovascular outcomes reported by each study that contribute to the study endpoint. Total MACE represents the composite endpoint as defined by each study. Individual cardiovascular outcomes are reported as provided in the original studies and may overlap. Blank cells indicate outcomes not separately reported. Abbreviations: MACE, major adverse cardiovascular events; MI, myocardial infarction; ACS, acute coronary syndrome; UA, unstable angina.

**Table 5. Hazard ratios from meta-analysis**.

| Variable | All MACE | | | Hard MACE | | |
|---|---|---|---|---|---|---|
| | Studies | Effect estimate | $I^2$ | Studies | Effect estimate | $I^2$ |
| 1. Obstructive Plaque (≥50% Stenosis) | 25 | 5.04 (3.44, 7.39) | 91 | 8 | 2.90 (1.79, 4.70) | 81 |
| 2. Obstructive Plaque (≥70% Stenosis) | 6 | 5.84 (3.86, 8.85) | 11 | 2 | 6.16 (1.64, 23.17) | 34 |
| 3. Non–Obstructive Plaque (<50% Stenosis) | 10 | 1.54 (1.19, 1.98) | 53 | 6 | 1.52 (1.26, 1.82) | 16 |
| 4. Moderate Stenosis (50–70%) | 4 | 2.46 (1.24, 4.90) | 21 | 2 | 3.32 (0.55, 19.85) | 71 |
| 5. Calcified Plaque | 17 | 1.30 (1.18, 1.42) | 55 | 7 | 1.23 (1.11, 1.37) | 15 |
| 6. Non–Calcified Plaque | 18 | 1.33 (1.15, 1.53) | 84 | 9 | 1.22 (1.02, 1.45) | 73 |
| 7. Mixed Plaque (Partially Calcified) | 13 | 2.00 (1.34, 2.99) | 95 | 5 | 1.15 (0.95, 1.40) | 70 |
| 8. Napkin–Ring Sign (NRS) | 11 | 3.28 (2.19, 4.91) | 48 | 3 | 2.57 (1.50, 4.39) | 20 |
| 9. Low–Attenuation Plaque (LAP) | 15 | 2.34 (1.87, 2.93) | 92 | 5 | 2.11 (1.60, 2.77) | 0 |
| 10. Spotty Calcification (SC) | 11 | 2.30 (1.40, 3.75) | 77 | 3 | 1.42 (0.93, 2.16) | 10 |
| 11. Positive Remodeling (PR) | 9 | 3.03 (1.64, 5.61) | 82 | 2 | 1.40 (0.27, 7.33) | 85 |
| 12. ≥1 High–Risk Plaque Feature | 17 | 3.25 (2.23, 4.75) | 85 | 3 | 1.12 (0.54, 2.30) | 75 |
| 13. ≥2 High–Risk Plaque Features | 14 | 3.66 (2.42, 5.54) | 84 | 1 | 1.93 (1.00, 3.72) | 0 |
| 14. 1–vessel Disease | 9 | 4.18 (1.60, 10.93) | 97 | 5 | 4.79 (1.71, 13.44) | 96 |
| 15. 2–vessel Disease | 7 | 7.34 (2.15, 25.10) | 97 | 5 | 6.36 (1.93, 20.99) | 96 |
| 16. 3–vessel Disease | 8 | 10.91 (3.50, 33.99) | 97 | 5 | 11.74 (3.26, 42.30) | 97 |

Table 5 shows the pooled HRs, the number of studies, and the heterogeneity of each variable measured. Abbreviations: HR, hazard ratio.

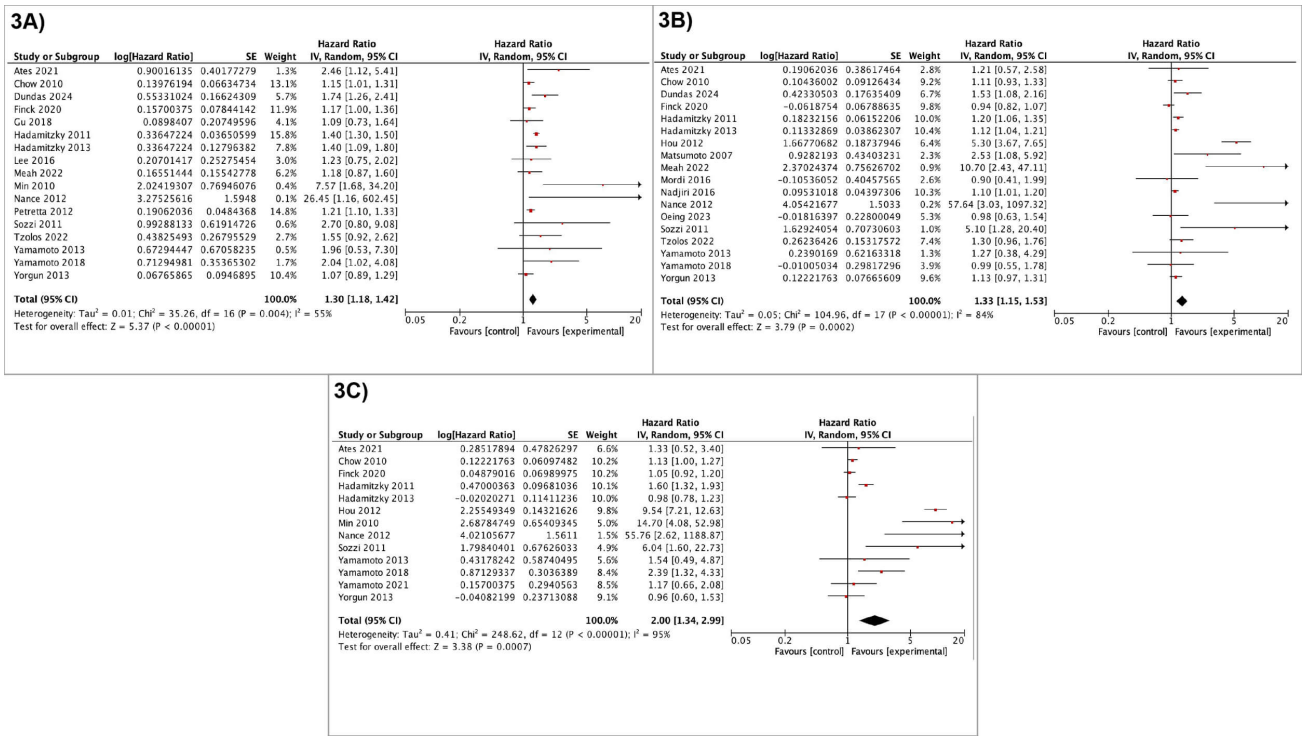



**Fig. 3. Forest plots for plaque composition**. (A) Forest plot for Calcified Plaque. (B) Forest plot for Non–Calcified Plaque. (C) Forest plot for Mixed Plaque (Partially Calcified).

**rial 7**). Across all plaque characteristics, HR variability was minimal, and heterogeneity remained largely stable, reflecting methodological rather than statistical differences. A few studies affected these parameters more significantly than others: in the moderate stenosis model, the exclusion of Ateş et al. (2021) [7] and de Azevedo et al. (2011) [25] decreased the heterogeneity by 21%; in the calcified plaque model, exclusion of Hadamitzky et al. (2011) [27] reduced heterogeneity by 35%; in the non-calcified plaque model, several papers affected heterogeneity, including Finck et al. (2020) [5], whose exclusion dropped the heterogeneity by 64%. Excluding these specific studies did not change the

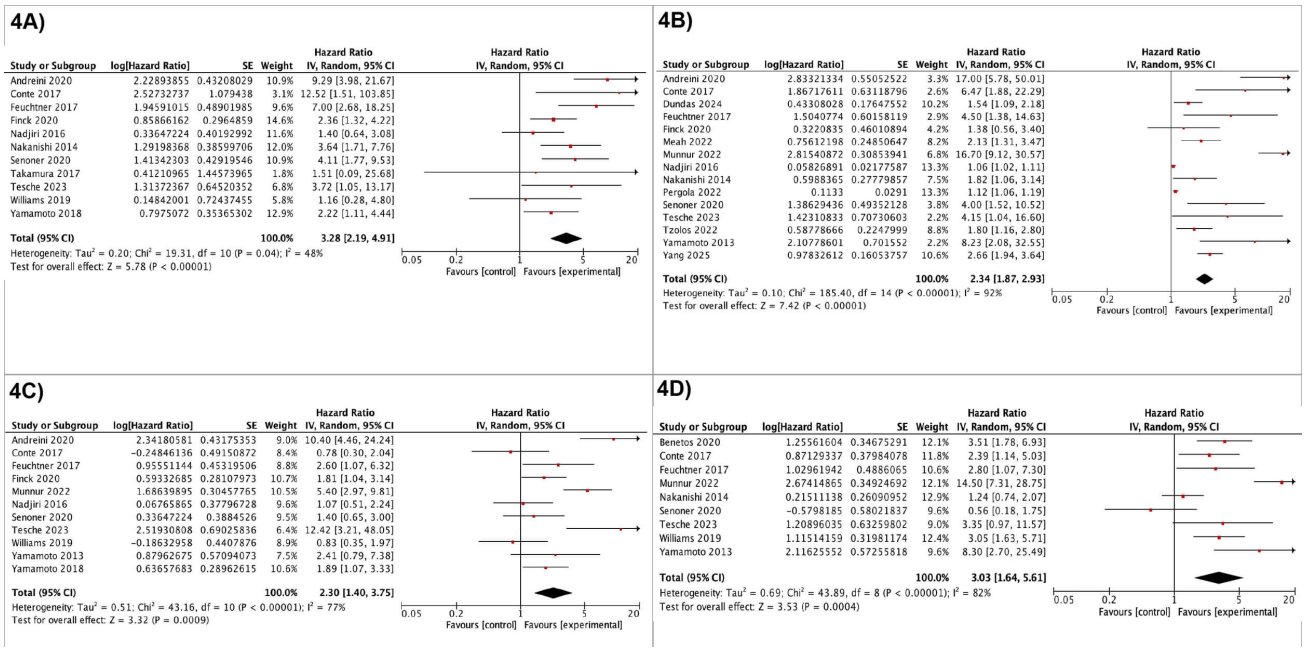



**Fig. 4. Forest plots for high-risk plaque features**. (A) Forest plot for Napkin–Ring Sign (NRS). (B) Forest plot for Low–Attenuation Plaque (LAP). (C) Forest plot for Spotty Calcification (SC). (D) Forest plot for Positive Remodeling (PR).

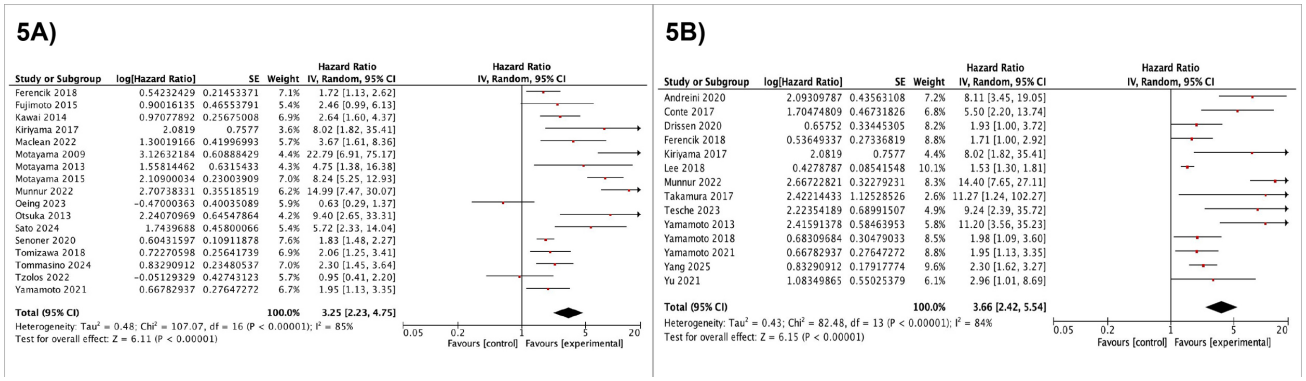



**Fig. 5. Forest plots for number of high-risk plaque features**. (A) Forest plot for ≥1 High–Risk Plaque Feature. (B) Forest plot for ≥2 High–Risk Plaque Features.

effect direction or significance, confirming overall model robustness. The sensitivity analysis shows that overall, the heterogeneity reflected genuine clinical and methodological diversity rather than influential outliers, even for plaque characteristics that demonstrated evidence of small-study effects.

### *3.8 Risk of Bias*

Risk-of-bias assessment using the NOSdemonstrated that most included studies were judged to be at low to moderate risk of bias, with scores ranging from 6–8 out of a total of 8 points (**Supplementary Material 8**).

## 4. Discussion

To date, this meta-analysis provides the most extensive synthesis of the prognostic ability of CCTA-derived plaque features. Our findings reinforce and extend prior literature on the association of future MACE with plaque characteristics and disease extent. The inclusion of a diverse range of plaque variables and metrics, spanning composition, high-risk morphology and overall atherosclerotic burden, enables more clinically relevant stratification of CAD risk. Importantly, although these associations were generally consistent across primary and subgroup analyses, several pooled estimates had substantial between-study heterogeneity, indicating that the magnitude of effect should be interpreted cautiously.

Our results demonstrate that both plaque composition and disease extent independently predict future MACE, supporting the prognostic utility of anatomic plaque assessment by CCTA. The strong association of obstructive CAD (≥70% stenosis; HR 5.84) with MACE aligns with cur-

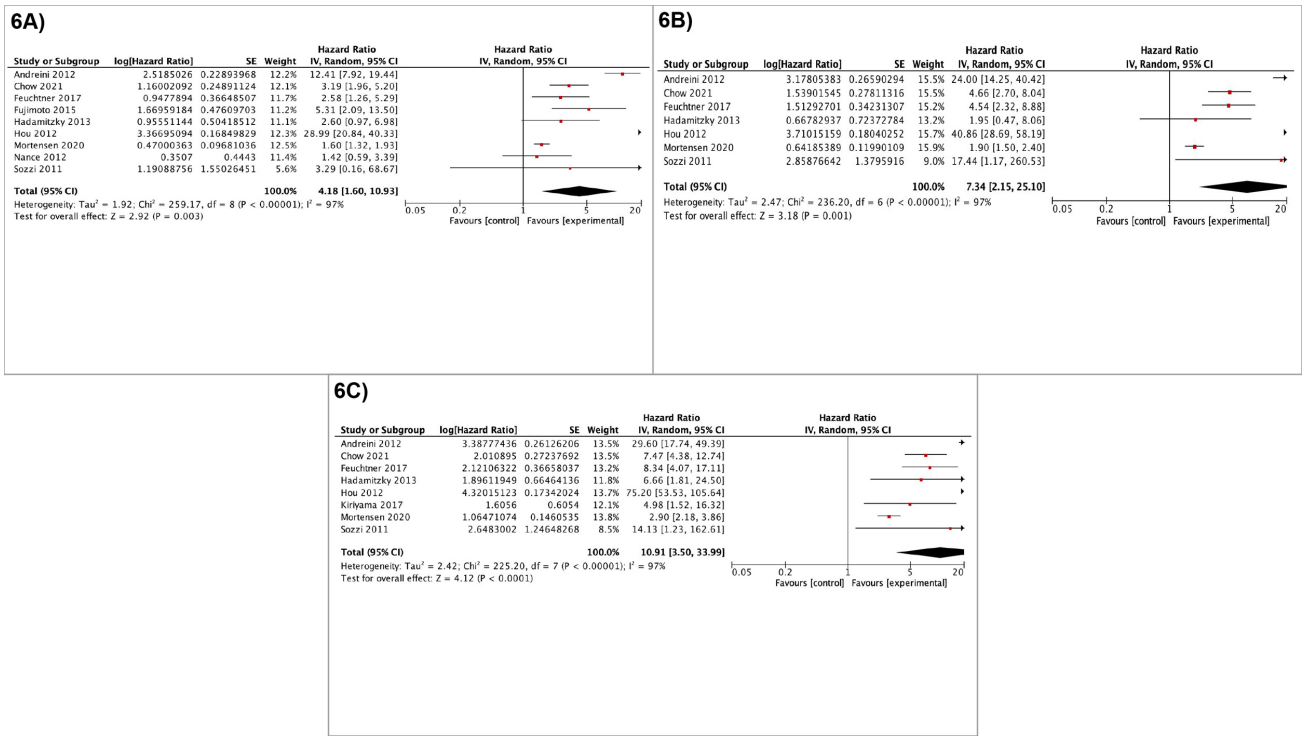



**Fig. 6. Forest plots for disease extent**. (A) Forest plot for 1–vessel Disease. (B) Forest plot for 2–vessel Disease. (C) Forest plot for 3–vessel Disease.

rent clinical guidelines that prioritize revascularization in such lesions, as they are more likely to be clinically significant [86]. However, non-obstructive plaque (<50% stenosis; HR 1.54) also demonstrated elevated risk, which is equally noteworthy, as these lesions are often not targets for revascularization in standard practice. Previous literature has shown that a substantial proportion of acute coronary syndromes arise from non-obstructive, rupture-prone plaques, underscoring the need to consider plaque vulnerability alongside luminal narrowing in clinical decision-making [87,88].

It is traditionally thought that calcified plaque reflects chronic, stable lesions, whereas non-calcified plaque is more prone to rupture [89]. Our findings show that calcified, non-calcified, and mixed plaques are all significantly associated with future MACE. Notably, mixed plaque had a stronger association than either type alone, likely reflecting lesions with both stable and unstable components. These findings suggest that the significance of plaque composition likely lies along a spectrum.

High-risk plaque features, including low-attenuation plaque, positive remodeling, spotty calcification, and the NRS, were strongly associated with MACE, with the NRS showing the highest HR of 3.28. These features reflect the biological vulnerability of atherosclerotic lesions: low-attenuation regions correspond to lipid-rich necrotic cores, positive remodeling represents compensatory vessel enlargement that can mask lumen compromise, spotty calcifications mark microcalcific instability, and NRS signals fibrous cap thinning over a large necrotic core. Independent of stenosis severity, these features demonstrate prognostic significance, suggesting that risk stratification should integrate morphological evaluation rather than rely solely on stenosis severity.

Further, we confirmed a stepwise increase in hazard ratios with greater vessel involvement, from 1-vessel disease (HR 4.18) to 3-vessel disease (HR 10.91). This demonstrates the cumulative impact of plaque burden, which increases the risk of destabilization and endothelial dysfunction.

Our subgroup analysis restricted to hard MACE outcomes demonstrated that, although effect sizes were attenuated compared to the overall MACE analysis, the direction and statistical significance of key associations were largely preserved. This indicates that the prognostic value of CCTA-derived plaque characteristics extends beyond softer endpoints and remains relevant for clinically significant outcomes such as myocardial infarction and death. Notably, obstructive coronary disease, high-risk plaque features, particularly low-attenuation plaque and NRS, and multivessel disease continued to show strong associations with hard events, supporting their biological role in plaque vulnerability and progression. The observed attenuation likely reflects the exclusion of more frequent but less severe events, resulting in a more specific and homogeneous outcome definition.

Importantly, our findings can be interpreted within a hierarchical framework of coronary artery disease. Steno-

sis severity reflects hemodynamic significance, whereas plaque composition represents structural characteristics of atherosclerosis. High-risk plaque features provide insight into biological vulnerability and rupture potential, and disease extent reflects the cumulative burden of atherosclerosis. Each of these domains contributes incremental prognostic information, supporting a multidimensional approach to CAD risk stratification using CCTA.

### *4.1 Clinical Implications*

Our results have several clinical implications. Firstly, CCTA can be used to improve cardiovascular risk stratification in patients with stable CAD and influence future management strategies [2,90]. Patients with non-obstructive plaques exhibiting multiple high-risk plaque features may represent a higher-risk subgroup that could benefit from closer clinical surveillance and optimization of guideline-directed preventive medical therapy (e.g., high-intensity statins, PCSK9 inhibitors) [91,92]. Current revascularization guidelines focus primarily on obstructive lesions and evidence of ischemia [92]. Emerging randomized evidence, including the PREVENT trial, suggests that preventive percutaneous-coronary intervention (PCI) of selected high-risk, non–flow-limiting vulnerable plaques significantly reduced MACE compared to medical therapy alone [93]. However, the applicability of these findings to routine CCTA-guided management remains uncertain [94]. Therefore, the present results should be viewed as hypothesis-generating and support the need for additional prospective randomized trials to evaluate whether management strategies guided by CCTA-derived plaque characteristics, including intensified preventive medical therapy or invasive approaches, can improve hard cardiovascular outcomes compared with current guideline-directed care.

Secondly, CCTA data can be used to personalize prevention strategies. Integration of plaque morphology and burden metrics into standardized reporting systems such as CAD-RADS 2.0, could improve early identification of patients at increased cardiovascular risk [14], enabling targeted lifestyle modification, optimization of preventive pharmacologic therapy, and individualized follow-up strategies [2].

Lastly, our study highlights the advantages of CCTA as a comprehensive assessment modality of atherosclerotic disease burden and plaque biology, rather than merely a tool for assessing luminal stenosis [90,93]. This supports CCTA's expanding role in screening, diagnosis, prognostic assessment, and follow-up imaging, especially in patients with HRP features, for whom serial imaging may help monitor plaque progression and guide individualized preventive management [90,95].

Future studies should assess the optimal management of patients with high-risk non-obstructive lesions, including intensified medical therapy and preventive endovascular intervention. Although our findings show that these plaque characteristics correlate with MACE prognosis, prospective, randomized studies are needed to determine whether modifying therapy based on HRP detection improves clinical outcomes. Future studies are encouraged to standardize the definition and quantification of plaque features to reduce heterogeneity and improve reproducibility across imaging centers and within research.

Most importantly, the feasibility of incorporating detailed plaque characterization into routine clinical assessment depends on advances in CCTA acquisition and analysis. Although CCTA is now a first-line non-invasive test for patients with a low-to-intermediate pretest probability of CAD [92], it is often primarily limited to stenosis evaluation and qualitative, rather than quantitative, plaque feature assessment, as many tertiary centers lack the specialized software, standardized protocols, and reader expertise needed for advanced plaque analysis [96]. Semi- and fully automated software can objectively quantify plaque burden, plaque composition, remodeling indices, and low-attenuation plaque on CCTA, thereby improving reproducibility compared to visual operator assessment alone [97]. Furthermore, artificial intelligence-based algorithms have demonstrated the ability to automate plaque segmentation, quantify high-risk plaque characteristics, and improve workflow efficiency [96,97,98]. Recent validation studies, such as the REVEALPLAQUE and CLARIFY trials, demonstrate that AI-assisted plaque quantification platforms improve reproducibility and risk stratification by providing automated measures of plaque burden and high-risk features [97,98,99]. Emerging technologies such as photon-counting CT may further improve spatial resolution and plaque tissue characterization, allowing more accurate detection and quantification of vulnerable plaque features [100,101]. Although these technologies were beyond the scope of the present review, our findings support the clinical relevance of the plaque characteristics that these evolving imaging platforms aim to identify more accurately. Future cost-effectiveness and multicenter implementation studies are needed before widespread adoption of detailed CCTA plaque characterization into routine clinical practice for CAD management.

### *4.2 Limitations*

This meta-analysis has several limitations. The most important limitation is the substantial statistical heterogeneity observed across many pooled analyses ($I^2$ frequently >75%, and exceeding 90% for some plaque characteristics), indicating considerable between-study variability. Although a random-effects model was used to account for this variability, such high heterogeneity reduces the precision of pooled estimates and warrants cautious interpretation. This observed heterogeneity reflects differences in study design, patient population, plaque definitions, statistical adjustment models, MACE definitions, imaging protocols, and image interpretation across the included studies.

The reduction in heterogeneity observed within the predefined hard MACE subgroup, together with stable leave-one-out sensitivity analyses, suggests that variability was driven largely by methodological differences rather than by single outlier studies.

Several methodological factors likely contributed to the observed heterogeneity. First, hazard ratios were derived from studies using different statistical adjustment strategies. Some studies reported fully adjusted HRs controlling for clinical risk factors and calcium score, while others provided only univariate estimates. The most adjusted hazard ratios were preferentially extracted whenever available. Inclusion of both adjusted and unadjusted HRs was necessary to maximize the available dataset but may have introduced residual confounding and contributed to between-study heterogeneity.

Secondly, definitions of key plaque features, including low-attenuation plaque, positive remodeling, and spotty calcification, were not fully standardized across studies. For example, low-attenuation plaque was variably defined as ≤30 Hounsfield Units (HU) or ≤38 HU, and positive remodeling cutoffs varied by site. These definitional differences, along with inconsistent approaches to classifying mixed plaque or identifying the NRS, may have influenced pooled estimates and contributed to between-study heterogeneity.

Another major contributor to heterogeneity was the lack of standardized MACE definitions across studies, with some including unstable angina and elective revascularization in their MACE definitions. Although these endpoints are clinically relevant, their inclusion may indicate stronger associations for stenosis severity, rather than purely reflecting plaque biology. Our hard MACE subgroup analysis improved clinical specificity and reduced heterogeneity; however, it substantially reduced the number of included studies for certain plaque characteristics, limiting statistical power and the precision of effect estimates. As a result, some associations did not reach statistical significance despite consistent directional trends. Future studies with standardized reporting of hard cardiovascular outcomes are needed to strengthen these findings.

Fourthly, CCTA imaging quality and interpretation are operator-, hardware-, and software-dependent, contributing to statistical heterogeneity. Differences in scanner generation, acquisition parameters, reconstruction algorithms, image post-processing software, and reader expertise may also have contributed to variability in plaque characterization and pooled effect estimates.

Beyond heterogeneity, several additional limitations should be acknowledged. Most studies were observational, limiting causal inference. Indications for invasive interventions or alterations in management for HRP are unclear, given the modest positive predictive value.

Furthermore, this review was not prospectively registered in PROSPERO. Nevertheless, the study eligibility criteria, data extraction procedures, and statistical analyses were predefined before the literature search. Protocol registration primarily enhances transparency rather than the conduct of the review itself.

Moreover, despite our extensive literature search, statistically significant Egger's test findings for certain plaque characteristics may reflect small-study effects, whereby smaller studies report larger effect estimates. These findings were not universal across all analyses and are presented in the results section. Furthermore, leave-one-out sensitivity analyses demonstrated that no individual study altered the direction or magnitude of the pooled effect estimates, supporting the overall robustness of the observed associations despite evidence of potential publication bias in selected analyses.

Finally, our risk-of-bias assessment using the NOS for cohort studies (**Supplementary Material 8**) indicated that most studies were at low to moderate risk of bias. This supports the overall methodological rigor of the evidence base, but risk-of-bias tools such as the NOS do not evaluate variability in plaque features, MACE definitions, or imaging protocols, which are all possible sources of heterogeneity. In addition, we did not perform a formal GRADE assessment of the overall certainty of evidence as this review synthesized a broad range of distinct prognostic plaque characteristics rather than a single prognostic factor or intervention. Therefore, the certainty of individual pooled estimates should be interpreted in the context of the observed heterogeneity, publication bias, and predominance of observational data.

Overall, despite the observed heterogeneity and methodological variability, the consistency of effect direction across most plaque characteristics, together with the stability demonstrated in sensitivity analyses, supports the overall robustness of the findings, although the magnitude of pooled effect estimates should be interpreted with appropriate caution. Future research should prioritize standardized CCTA acquisition protocols, uniform plaque feature definitions, consistent multivariable adjustment strategies, standardized hard MACE outcome definitions, and prospective evaluation of whether management guided by CCTA-derived plaque characteristics improves clinical outcomes.

## 5. Conclusion

In summary, our meta-analysis confirms that CCTA-derived plaque characteristics, particularly HRP features, obstructive stenosis, and multivessel disease, are powerful predictors of MACE. Nevertheless, considerable between-study heterogeneity and evidence of small-study effects for selected plaque characteristics warrant cautious interpretation and underscore the need for standardized imaging protocols, plaque definitions, and outcome reporting. Collectively, these findings support an expanded role for CCTA not only in diagnosing CAD but also in prognostic assess-

ment and cardiovascular risk stratification. Incorporating plaque vulnerability and burden alongside stenosis severity may enable earlier identification of high-risk patients and support patient-centered management.

## Abbreviations

CAD, coronary artery disease; CCTA, coronary computed tomography angiography; MACE, major adverse cardiovascular events; HRP, high-risk plaque; NRS, napkin-ring sign; LAP, low-attenuation plaque; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; NR, not reported.

## Availability of Data and Materials

The datasets analyzed during the current study are derived from publicly available studies, which are cited within the article. No new datasets were generated. Extracted data supporting the findings of this study are available in the Supplementary Materials and further from the corresponding author at request.

## Author Contributions

AS and MS participated in the study design process and idea creation. AS and LL were involved in the literature search. AS, WK, and LL participated in the screening process. AS, WK, BB, and LL were involved in the data extraction process. AS and MS were involved in the statistical analysis. All authors were involved in the manuscript writing and editing process. MS was involved in supervising all aspects of the project. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

Not applicable.

## Funding

This research received no external funding.


## Conflicts of Interest

The authors declare no conflicts of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/RCM54940.

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