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Research Paper

Plaque quantification from coronary computed tomography angiography in predicting cardiovascular events: A systematic review and meta-analysis

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ABSTRACT

Background: Plaque volumes quantified from coronary computed tomography angiography (CCTA) may offer improved risk prediction for future major adverse cardiovascular events (MACE) above current standards of care. This systematic review and meta-analysis examines the association between CCTA-derived plaque volumes and future MACE in stable coronary artery disease (CAD).

Methods: A systematic literature search was undertaken using PubMed, Web of Science and Cochrane Library databases. 504 publications were screened, identifying 38 studies for inclusion in the systematic review. 15 studies were eligible for meta-analysis. Separate meta-analyses were conducted for the most frequently investigated plaque volume variables.

Results: 35 out of 38 included studies showed an association between quantified plaque volumes and MACE. Low attenuation plaque (LAP) volume and total plaque volume (TPV) were most frequently independently associated with MACE. On meta-analysis, there was a significant association between MACE and TPV (pooled HR 3.93, 95 % CI 2.10–7.34, $p < 0.0001$), LAP volume (pooled HR 2.81, 95 % CI 2.01–3.93, $p < 0.0001$), calcified plaque volume (pooled HR 2.21, 95 % 1.5–3.24, $p < 0.0001$), non-calcified plaque volume (pooled HR 2.55, 95 % CI 1.30–4.98, $p = 0.006$), LAP burden (pooled HR 3.22, 95 % CI 2.12–4.87, $p < 0.0001$), calcified plaque burden (pooled HR 2.25, 95 % 1.56–3.24, $p < 0.0001$) and non-calcified plaque burden (pooled HR 3.42, 95 % CI 1.49–7.81, $p = 0.004$). Total plaque burden was significantly associated with MACE after exclusion of a small study driving considerable heterogeneity (pooled HR 3.81, 95 % CI 2.45–5.94, $p < 0.0001$).

Conclusion: Quantified plaque volumes are associated with MACE in patients undergoing CCTA for stable CAD. Future work is required in diverse populations with standardised methods to determine the clinical utility of plaque quantification in real world practice.

Abbreviations: Agatston units, AU; area under the receiver operating characteristic curve, AUC; calcified plaque volume, CPV; clinical risk score, CRS; coronary artery calcium score, CACS; Coronary Artery Disease Reporting and Data System, CAD-RADS; coronary computed tomography angiography, CCTA; fractional flow reserve, FFR; high risk plaque, HRP; Hounsfield units, HU; invasive coronary angiography, ICA; low attenuation plaque, LAP; low attenuation plaque volume, LAPV; net reclassification index, NRI; non-calcified plaque, NCP; non-calcified plaque volume, NCPV; percentage atheroma volume, PAV; pericoronary adipose tissue attenuation, PCATa; segment involvement score, SIS; segment stenosis score, SSS; total plaque volume, TPV.

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1. Introduction

Coronary computed tomography angiography (CCTA) is a first line investigation for suspected stable coronary artery disease (CAD) and permits visualisation of both the vessel lumen and plaque characteristics.[1] Current practice for diagnosing and treating stable CAD centres around obstructive plaque, yet it has been recognised for some time that the amount of non-obstructive plaque substantially increases cardiovascular risk.[2,3] The ability to quantify and characterise plaque could enable personalised precise risk assessment above current standards of care.

The prognostic importance of overall plaque burden is widely recognised and is used to refine risk and guide future management. The Coronary Artery Disease Reporting and Data System (CAD-RADS) 2.0 guidelines suggest using a subjective visual assessment of plaque burden, or more quantitative markers such as the coronary artery calcium score (CACS) or segment involvement score (SIS).[4] However, CACS does not detect non-calcified plaque and SIS does not consider the volume of plaque in each segment. With advances in machine learning models, plaque volumes can now be more readily quantified and characterised according to tissue density. Plaque quantification software reports either absolute plaque volumes or plaque volumes normalised to coronary vessel volume (typically reported as 'plaque burden' or 'percentage atheroma volume'). Plaque volume and burden can be considered essentially equivalent with burden having the theoretical advantage of normalising for vessel volume and therefore patient size. Plaque composition is characterised according to Hounsfield Units (HU) with typical thresholds for calcified (>350HU), non-calcified (≤350HU) and low attenuation plaque (LAP)(<30HU).[5] As the intensity of luminal contrast affects plaque attenuation values, scan-specific thresholds referenced to attenuation in the proximal coronary lumen have been proposed.[6]

The extent to which quantified plaque volumes are associated with future myocardial infarction (MI) and major adverse cardiovascular events (MACE) has been investigated in several studies using different software, methods of validation and clinical end points, making clinical interpretation and implementation challenging. We therefore conducted a systematic review and meta-analysis of studies examining the associations between CCTA plaque quantification and MACE in patients being investigated for stable CAD.

2. Methods

The study was registered with the PROSPERO international register (CRD42024518293) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7]

2.1. Search strategy

The PubMed, Web of Science and Cochrane Library databases were searched to identify eligible articles published before 18/6/2024. Results were restricted to English language articles. Medical Subject Heading (MeSH) terms were used where available. An example search strategy is presented in the supplementary material (Table 1). Additional articles were identified through screening the references of key publications. Abstracts were screened before full text articles were accessed to determine eligibility for the systematic review.

Inclusion criteria were as follows:

1. The study population comprised individuals receiving a CCTA scan for investigation of suspected or known stable CAD.
2. Coronary plaque volumes were quantified.
3. Coronary plaque volumes were related to acute coronary syndrome, myocardial infarction, cardiac death or a composite MACE outcome which may include additional variables such as revascularisation.

Table 1
Plaque markers with independent associations with major adverse cardiovascular events in the systematic review.

Plaque marker	Frequency
Low attenuation plaque volume	7
Total plaque volume	5
Progression of plaque volumes on serial scans	4
Non-calcified plaque volume	3
Total plaque burden	3
Low attenuation plaque burden	3
Non-calcified plaque volume	2
Calcified plaque volume	2
Calcified plaque burden	2
Fibrofatty plaque volume	1

Frequency of plaque markers found to have independent associations with MACE based on significance on multivariable testing or in significantly improving prognostic model performance on area under the receiver operating characteristic curve analysis. Where multiple studies report the same plaque markers on the same cohort, only the study with the largest cohort and longest follow up is counted.

Exclusion criteria were as follows:

1. CCTA scans performed in the context of acute chest pain.
2. Studies using plaque volume surrogates only, such as CACS or SIS.
3. Studies including individuals with prior coronary artery bypass graft or percutaneous coronary intervention.

2.1.1. Data extraction

Prespecified data from the studies included in the systematic review were extracted. Study quality was assessed using the Quality In Prognostic Factor Studies (QUIPS) tool[8] advocated in the PRISMA guidelines.[9] Database searching and data extraction were performed by two independent investigators. Any discrepancies were resolved by a third investigator.

2.2. Meta-analysis

The studies deemed eligible for systematic review were required to meet further criteria for inclusion in the meta-analysis.

Inclusion criteria:

1. The study reports hazard ratios for the association between plaque volumes and MACE.
2. Plaque volumes were analysed as a categorical variable using study specific thresholds for high and low risk groups.

Exclusion criteria:

1. If multiple studies reported on the same cohort, we only include the study with the largest cohort and the longest follow up. If multiple studies reported on the same cohort but investigated different plaque variables these were permitted because separate meta-analyses were carried out for each plaque variable. For example, separate studies reported hazard ratios for LAP volume,[10] total plaque volume,[11] and non-calcified plaque volume[12] on a single German cohort.
2. Not specified whether plaque volumes were analysed as a continuous, ordinal or categorical variable in multivariable testing.

For the eligible studies, we extracted the hazard ratios from the most adjusted model i.e. controlled for clinical risk factors, stenosis and CACS or SIS. Where multiple models were presented for different outcome definitions, the outcome definition excluding elective revascularisation was selected.

2.3. Statistical analysis

Hazard ratios and 95 % confidence intervals were extracted and log transformed. Separate meta-analyses were carried out for each plaque variable using a random effects model. Prespecified subgroup analyses were performed with systematic exclusion of studies including elective revascularisation in the MACE definition, studies reporting on a selective cohort (e.g. diabetic cohort), studies presenting unadjusted hazard ratios only, studies not controlling for clinical risk factors, and studies not controlling for surrogate markers of plaque burden, such as CACS or SIS. Statistical heterogeneity was assessed using the I^2 statistic and interpreted according to Cochrane guidance.[13] Publication bias was assessed using funnel plots and Egger's regression test. All statistical tests were two-sided with a p value < 0.05 considered significant. Analyses were performed on RevMan (Cochrane), SPSS (IBM) and R version 4.4.2.

3. Results

3.1. Eligible studies

A total of 504 records were identified through database searches (n = 494) and screening references of key articles (n = 10), of which 38 studies met eligibility for inclusion in the systematic review.[10–12,14–45] Full details of the methodology, including reasons for exclusion are shown in the study flow diagram (Fig. 1). Key data from the 38 eligible studies and risk of bias assessments are presented in the supplementary material (Tables 2 and 3, respectively).

3.2. Association between plaque volumes and MACE

Of the 38 eligible studies, 35 found that plaque volumes were associated with MACE outcomes.[10–12,14–22,24,26,27,30–38,40–42,44–49]

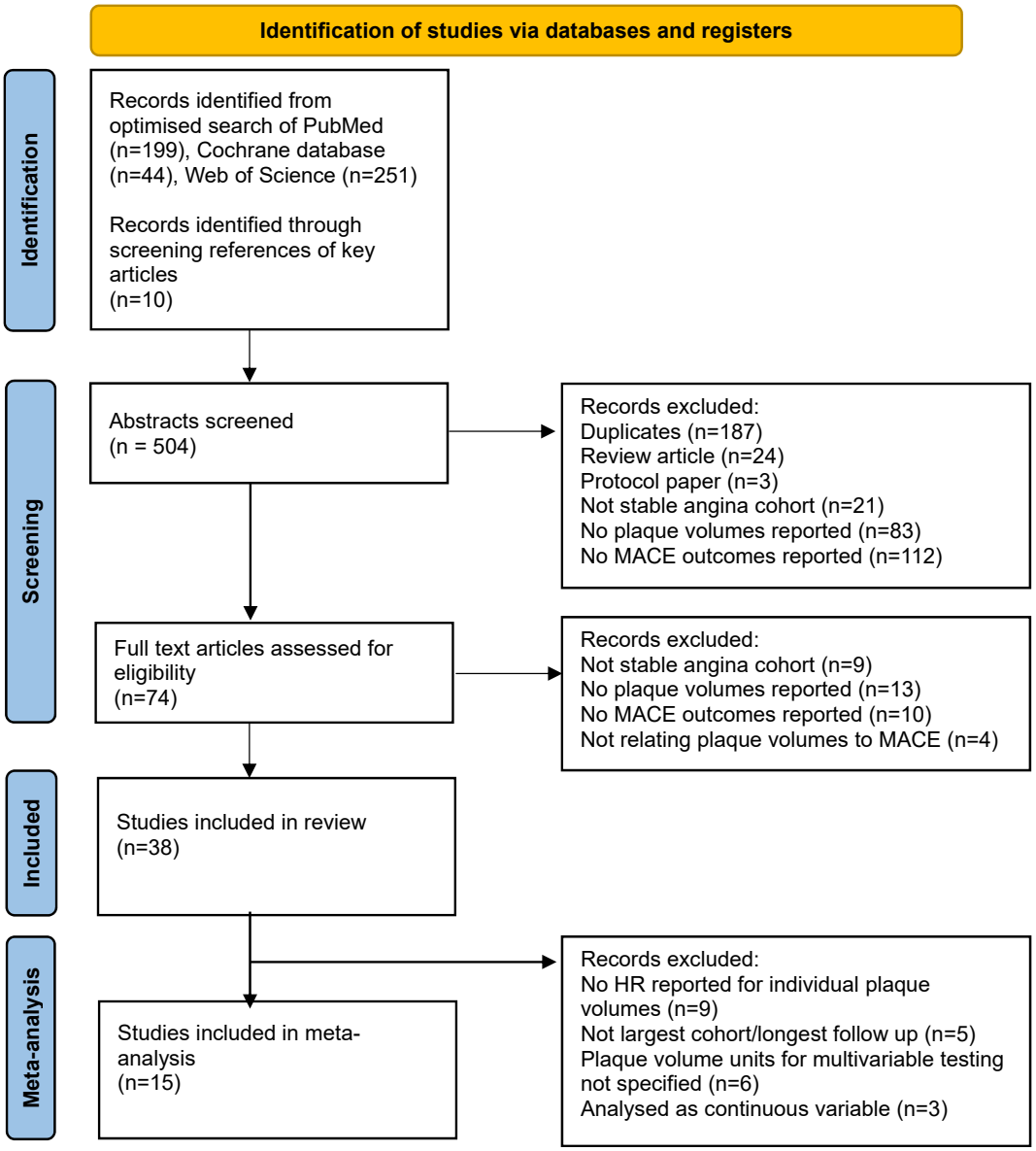

Fig. 1. Study flow diagram.
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram illustrating study selection process. Abbreviations: hazard ratio (HR), major adverse cardiovascular events (MACE).

Table 2
Plaque volume thresholds reported to identify populations at high risk for major adverse cardiovascular events.

Study	Software	High risk plaque volume thresholds	Derivation
Gitsioudis et al., 2015	Extended Brilliance Workspace 4.0, Philips	TPV ≥19.6 mm^3	Associated with future non-fatal MI and cardiac death
Hell et al., 2017	Autoplaque	NCP volume >146 mm^3 LAP volume >10.6 mm^3 TPV >179 mm^3	60th centile Associated with future cardiac death
Deseive et al., 2018	QAngio, Medis	LAP volume >2.67 mm^3	Associated with future MACE
Williams et al., 2020	Autoplaque	LAP burden >4 %	Associated with future MI
Van Diemen et al., 2021	Comprehensive Cardiac Analysis, Philips Healthcare	NCP volume >85 mm^3	Associated with future MI and all-cause death
Deseive et al., 2021	QAngio, Medis	Group 1: TPV 0 mm^3 Group 2: TPV <115 mm^3 Group 3: TPV >115 mm^3	Associated with future MACE (ACS, all-cause death, late revascularisation)
Kuneman et al., 2023	QAngio, Medis	TPV >169 mm^3 LAP volume >20 mm^3	Associated with future non-fatal MI and all-cause death
Nurmohamed et al., 2023	AI-QCT, Cleerly	Stage 0: PAV 0 % %NCPV 0 % Stage 1: PAV >0–5 % %NCPV >0–2.5 % Stage 2: PAV >5–15 % %NCPV >2.5–5 % Stage 3: PAV >15 % %NCPV >5 %	Based on correlation with invasively measured stenosis and fractional flow reserve.
Dundas et al., 2024	AI-QCPA, HeartFlow	TPV >564 mm^3 PAV >37.2 %	Associated with future MI and cardiovascular death

Abbreviations: acute coronary syndrome (ACS), low attenuation plaque (LAP), major adverse cardiovascular events (MACE), myocardial infarction (MI), non-calcified plaque (NCP), percentage atheroma volume (PAV), total plaque volume (TPV), percentage non-calcified plaque volume (%NCPV).

Different plaque metrics were found to have an independent association with MACE based on multivariable testing or by significantly improving prognostic model performance on area under the receiver operating characteristic curve analysis (Table 1). The methodology of cofactor entry into a model and their control were highly varied between studies (Supplementary Table 2). After exclusion of studies reporting on the same cohort, LAP volume and total plaque volume (TPV) were the most frequent plaque features independently associated with MACE (Table 1). Progression of plaque volumes on serial scans, non-calcified plaque (NCP) volume, NCP burden, calcified plaque (CP) volume, CP burden and fibro-fatty plaque (FFP) volume were also independently associated with MACE but less frequently. An incremental benefit of quantified plaque volumes in predicting MACE over surrogate markers for plaque volume such as CACS, SIS, CT-Leamann score and Leiden risk score was reported in 12 studies.[10–12,17,20,23,27,31,34,40,49]

Of 38 eligible studies, 3 did not find an independent association between plaque volumes and MACE.[28,39,43] The first study reported that total plaque burden was not independently associated with future MACE once CCTA-derived percentage stenosis was added into the model.[43] The second study followed the same cohort for an extended period of 4.9 years.[39] In patients without known CAD, only CACS was independently associated with future MACE after controlling for CAD-RADS class. In this cohort, MACE were predominantly revascularisation with few ACS or cardiac death events (Supplementary Table 2). A third study stratified their cohort by diabetes status and found no significant association between plaque volumes and MACE in either diabetics or non-diabetics.[28] Only TPV, NCP volume and CP volume were quantified. When LAP presence was included it was significantly associated with MACE in both diabetic and non-diabetic groups.

3.3. Plaque volume thresholds to stratify risk

Plaque volume thresholds stratifying patients into high and low risk groups vary considerably between software applications and studies (Table 2). Most studies derived these thresholds based on their association with future MACE. One study used a plaque staging approach (1–4) based on correlating total plaque burden by CCTA with invasively measured stenosis and fractional flow reserve.[46] This plaque staging approach correlated well with a composite endpoint of future MI, stroke, revascularisation and death.[31]

3.4. Plaque quantification methods

Plaque was quantified by semi-automatic software requiring manual correction in 37 of 38 studies, using 13 different software applications (Supplementary Table 4). Lin and colleagues used an alternative deep learning approach to determine TPV and LAP burden.[44] This method had excellent or good agreement with expert reader measurements of TPV and percentage diameter stenosis via CCTA, and TPV and minimal luminal area via IVUS. This method was significantly quicker than using semi-automatic software (mean analysis time 5.65 ± 1.67 s versus 25.7 ± 6.79 min).

3.5. Meta-analysis

Of the 38 studies included in the systematic review, 15 studies were eligible for meta-analysis (Fig. 1).[10–12,15,17,23,26,29,31,37,40,42,44,45,49] The eligible studies included 16,057 patients followed up for a median duration of 4.7 years (range median 1–10 years). There were 619 MACE outcomes comprising MI (n = 139), ACS (n = 41), cardiac death (n = 99), non-cardiac death (n = 50), all-cause death (n = 80), stroke (n = 13), and elective revascularisation (n = 186). Details of study design and baseline characteristics for studies eligible for meta-analysis are presented (Table 3 and Supplementary Table 5, respectively). Separate meta-analyses were carried out for each plaque variable (Fig. 2).

There were significant associations between MACE and TPV, LAP volume, LAP burden, CP volume, CP burden, NCP volume and NCP burden (Fig. 2). Total plaque burden was not associated with MACE when all studies were considered (pooled HR 2.48, 95 % CI 0.90–6.82, p = 0.08, I^2 93 %). Sensitivity analyses revealed that the considerable heterogeneity in this meta-analysis was driven by a small case control study (64 patients) reporting a small standard error for this variable.[17] While the adjusted HR was significant in this study (adjusted HR 1.10, 95 % CI 1.0–1.22, p = 0.04), the combination of the random effects model used for meta-analysis and high study weighting due to small standard error, led to a non-significant association between total plaque burden and future MACE. Exclusion of this study resulted in a significant association between total plaque burden and MACE (pooled HR 3.81, 95 % CI 2.45–5.94, p < 0.0001, I^2 0 %) with a magnitude of effect more in keeping with the TPV meta-analysis.

Subgroup analyses did not reveal any significant change in the summary estimates with exclusion of studies including elective revascularisation in the MACE definition, studies reporting on a selective cohort (e.g. diabetic),

Table 3
Design and key results of studies included in the meta-analysis.

First author & year	Study design	Indication for CCTA	Location	Number of participants	Plaque features analysed	Median follow up (years)	Outcomes	Plaque variables significant in multivariable analysis	Variables controlled in multivariable analysis
Gitsioudis 2015	Prospective cohort	Suspected CAD + diabetes	Germany	521	TPV	2.3 (mean)	Cardiac death (n = 3), non-fatal MI (n = 10)	TPV	CV RFs, eGFR, CACS, stenosis
Nadjiri 2016	Prospective cohort	Suspected CAD	Germany	1168	LAPV, NCPV	5.7	MACE (n = 52) including cardiac death (n = 6), MI (n = 10), late revascularisation (n = 36)	LAPV, NCPV	Morise score, CAD extent
Hell 2017	Case control study	Suspected CAD	USA	64	TPV, LAPV, CPV, NCPV TPB, LAPB, CPB, NCPB	5	Cardiac death (n = 32)	NCPV, LAPV, TPV	SIS
Deseive 2018	Prospective cohort	Suspected CAD	Germany	1577	LAPV	5.5	ACS (n = 18), all-cause death (n = 12)	LAPV	CRS, CACS
Williams 2020	Post-hoc analysis of RCT	Suspected CAD	Scotland (SCOT-HEART)	1769	TPB, LAPB, CPB, NCPB	4.7	Fatal or non-fatal MI (n = 41)	LAP burden	Nil
Andreini 2020	Prospective cohort	Suspected CAD + low or high clinical risk	Italy Switzerland	544	TPV, LAPV, NCPV	3.1 (mean)	MI (n = 8), cardiac death (n = 1)	NCPV	CRS, presence of obstructive multivessel disease
Jin 2021	Prospective cohort	Suspected CAD	International (PARADIGM registry)	874	TPV, CPV, LAPV,	4.3	Non-fatal MI (n = 1), cardiac death (n = 3), revascularisation (n = 106)	LAPV, %CPV, CPV	TPV, mean plaque burden, CV RFs, statin use
Desieve 2021	Prospective cohort	Suspected CAD	Germany	1577	TPV	10.5	MI (n = 18), cardiac death (n = 36), revascularisation for UA (n = 5)	TPV	Nil
Andreini 2022	Retrospective cohort	Suspected CAD + diabetes + high CV risk	Italy	265	TPV, LAPV, NCPV	3.8	ACS + cardiac death (n = 10)	NCPV	Age, gender, smoking status
Lin 2022	Post-hoc analysis of RCT	Suspected CAD	Scotland (SCOT-HEART)	1611	TPV, LAPB	4.7	Fatal or non-fatal MI (n = 41)	TPV	CRS, stenosis
Yamaura 2022	Retrospective cohort	Suspected CAD	Japan	376	LAPB, NCPB, CPB	2.2 (mean)	MACE (n = 15) including death (n = 2), ACS (n = 6), unplanned revascularisation (n = 7)	LAPB	CACS
Kuneman 2023	Retrospective cohort	Suspected CAD	Finland	494	TPV, LAPV, CPV, NCPV	6.1	Non-fatal MI (n = 14) All-cause mortality (n = 22)	LAPV	TPV, age, statin use
Huang 2023	Retrospective cohort	Suspected CAD	China	251	TPV, LAPV, CPV, NCPV, FFPV	1–6.6	MACE (n = 28) including non-fatal MI, UA, cardiac death, unplanned revascularisation	LAPV	FRS, CT-Leamann score, FFR-CT
Nurmohamed 2024	Retrospective cohort	Suspected CAD	Netherlands	536	TPB, NCPB, CPB	10	MACE (n = 112) including MI (n = 22), stroke (n = 13), revascularisation (n = 37), death (n = 44)	TPB, NCPB, CPB	CV RFs
Dundas 2024	Retrospective cohort	Suspected CAD and >30 % stenosis on CCTA	International (ADVANCE registry)	4430	TPV, LAPV, CPV, NCPV TPB, LAPB, CPB, NCPB	1	MACE (n = 55) including CV death (n = 15), non-CV death (n = 14), MI (n = 12), ACS requiring revascularisation (n = 27)	LAPV, TPB, NCPB, CPB, LAPB	CV RFs, stenosis, FFR-CT

Abbreviations: acute coronary syndrome (ACS), calcified plaque burden (CPB), calcified plaque volume (CPV), clinical risk score (CRS), coronary artery calcium score (CACS), coronary artery disease (CAD), coronary computed tomography angiography (CCTA), cardiovascular (CV), estimated glomerular filtration rate (eGFR), fibrofatty plaque volume (FFPV), fractional flow reserve computed tomography (FFR-CT), high risk plaque (HRP), low attenuation plaque (LAP), low attenuation plaque volume (LAPV), major adverse cardiovascular events (MACE), myocardial infarction (MI), non-calcified plaque burden (NCPB), non-calcified plaque volume (NCPV), risk factors (RFs), segment involvement score (SIS), total plaque burden (TPB), total plaque volume (TPV), unstable angina (UA).

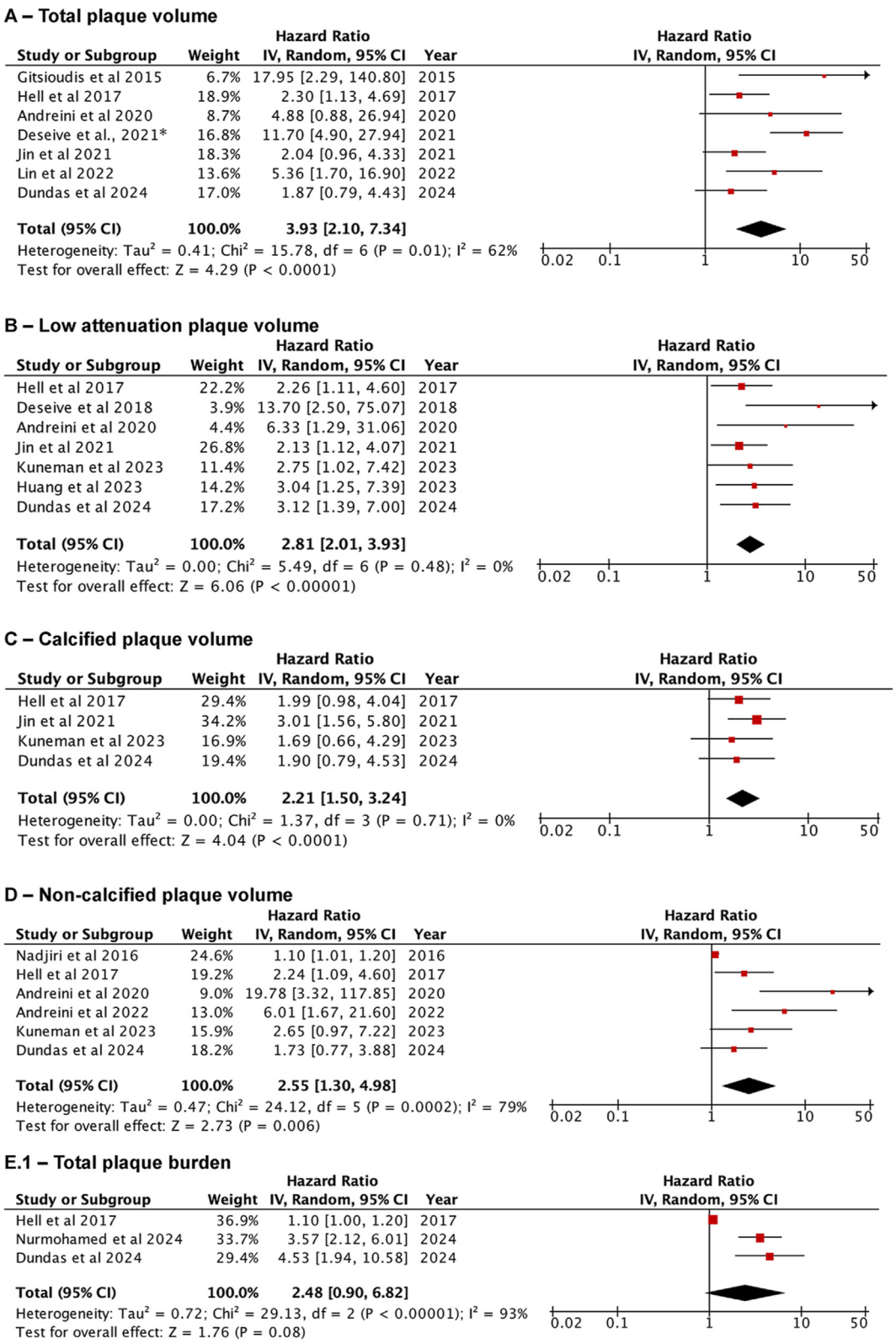

Fig. 2. Forest plots for individual plaque volume variables.
Forest plots display summary hazard ratios and 95 % confidence intervals for future MACE to according to different plaque volume variables. * Denotes studies where only unadjusted hazard ratios could be included in the meta-analysis.

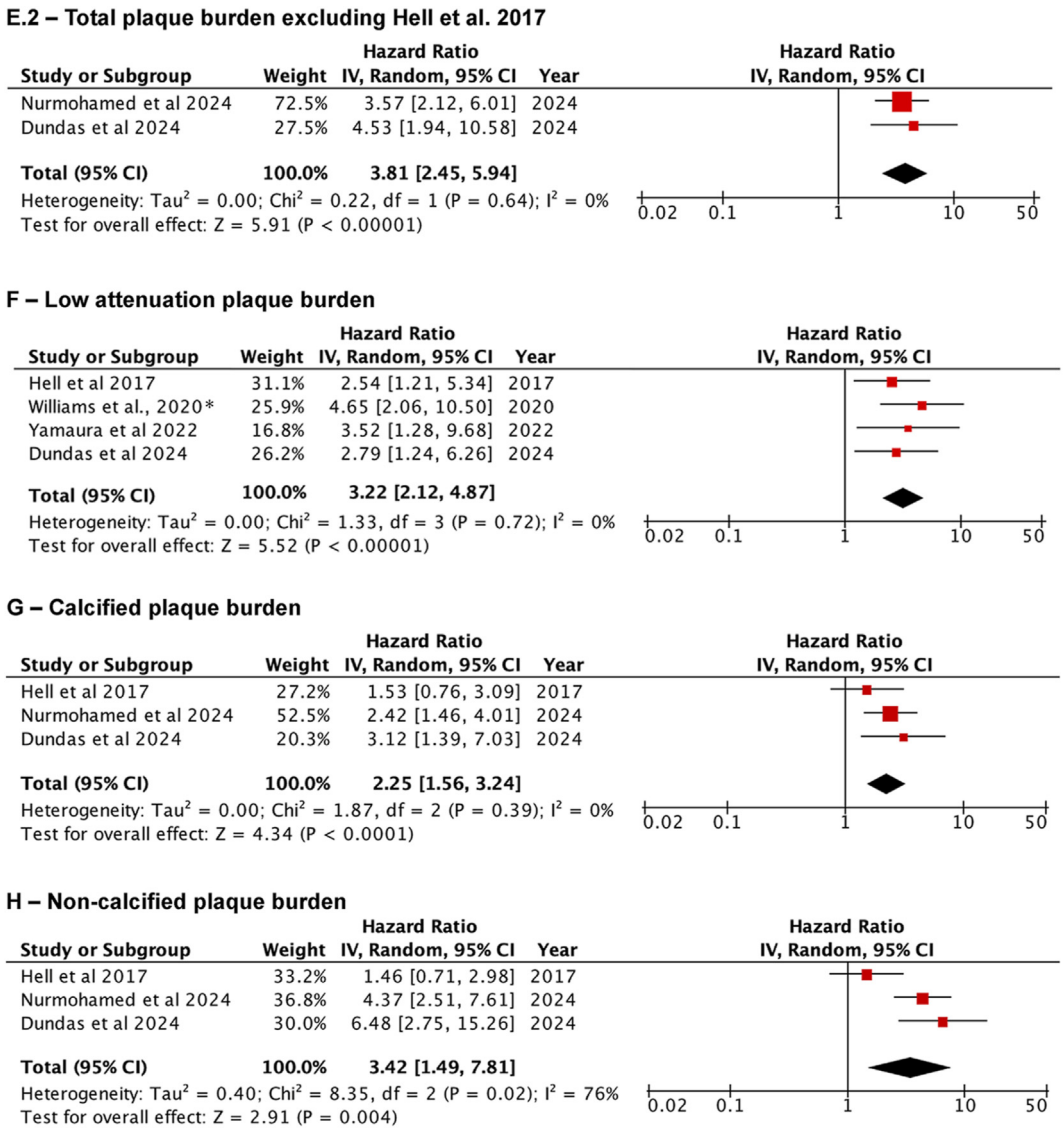

Fig. 2. *Continued*

studies presenting unadjusted hazard ratios, and studies not controlling for clinical risk factors (Supplementary table 6). When excluding studies not controlling for surrogate markers of plaque burden such as CACS or SIS, only LAP volume (pooled HR 3.4, 95 % CI 1.56–7.42, $p < 0.0001$) and LAP burden (pooled HR 2.85, 95 % CI 1.56–5.19, p=<0.0001) remained significantly associated with MACE. Only 6 out of the 14 studies were eligible for this latter analysis.[10,12,15,17,40] Publication bias testing identified the LAP and NCP volume meta-analyses as displaying small study effects (p value 0.002 and 0.03 respectively on Egger's test) (Supplementary Figure 1, Supplementary Table 7).

4. Discussion

4.1. Association between quantified plaque volumes and future cardiovascular events

In this systematic review, we found that 35 out of 38 included studies reported an association between quantified plaque volumes and MACE, in patients undergoing CCTA for suspected or known stable CAD. LAP volume and TPV were the most extensively studied plaque metrics and were most frequently found to have an independent association with future MACE. On meta-analysis, all plaque volumes were significantly associated with MACE, after exclusion of a single study driving considerable heterogeneity.

LAP is the CCTA marker of lipid-rich or necrotic core plaque which has long been recognised as a feature of the high-risk plaque.[50] On subgroup analysis including only studies controlling for surrogate plaque burden measures such as CACS or SIS, only LAP volume and LAP burden remained significantly associated with future MACE. This is biologically plausible as the proportion of vulnerable LAP likely increases the risk of an event beyond the total amount of plaque. However, only a limited number of studies were included in this subgroup analysis so these findings should be interpreted with caution. The LAP volume meta-analysis also showed evidence of publication bias. Regarding clinical application, CCTA-derived LAP volume has the highest variation of the plaque subtypes in observer and inter-scan variability studies[51] and its presence in plaques remains relatively infrequent.[52]

TPV is quantifiable with higher reproducibility and could be used in all patients with sufficient CCTA image quality.[51] TPV represents the overall amount of coronary atherosclerosis, encompassing calcified and non-calcified plaque, and thus intuitively reflects the risk of an acute plaque rupture occurring. On meta-analysis, TPV and total plaque burden have the highest pooled hazard ratios of all plaque components (3.93 and 3.81 respectively). However, it is difficult to determine the relative importance of individual plaque components based on meta-analysis or the frequency of independent association due to large variation in study design and in variables controlled for in multivariable models.

Coronary calcification by non-contrast Agatston scoring has traditionally been used as a risk stratifier for future cardiovascular events.[53] On meta-analysis, CP volume and burden are significantly associated with MACE but are often outperformed in multivariable models by quantification of total plaque and LAP which account for more vulnerable plaques. For example, CP burden is significantly associated with MACE on multivariable testing but not when stratifying by median TPV.[42] Another study reported that the proportion of CP (CPV/TPV x100 %) was inversely associated with MACE on multivariate analysis.[26] This is consistent with observations that statin use is associated with an increase in plaque calcification and a decrease in NCP.[25,54]

Progression of plaque volumes may also be relevant for predicting future MACE with some studies showing that this is additive to baseline plaque volumes.[18,20,33,47,55] Unfortunately, due to the small number of studies and variable study design it was not possible to group these studies together for meta-analysis. Any incremental prognostic benefit from serial CCTA assessment would have to be carefully weighed against patient radiation exposure and costs.

4.2. Software variation

Several software applications were used for plaque quantification (Supplementary Table 4). While each application uses a similar semi-automated approach of vessel centre-line extraction and marking of endoluminal and outer vessel wall boundaries followed by manual correction, the outputs clearly differ.[5] This is compounded by challenges in differentiating the outer vessel wall from epicardial fat on manual correction, particularly in the presence of NCP. To our knowledge no studies have sought to compare outputs between software providers. Even for different users of a single software there is variation in the approach to plaque quantification.[10,43] These issues are manifest in the highly variable plaque volume thresholds used to define high and low risk groups (Table 2).

Another limitation of plaque quantification software is the time required to perform manual correction of vessel contours. For example, one software requires 9.7 ± 3.2 min for the automated analysis, but a total of 23.7 ± 6.4 min for automated analysis, quality assurance and report generation.[56] Deep learning models have the potential to dramatically reduce the time taken for plaque quantification, but these are trained using semi-automatic software outputs and are therefore subject to the same issues.[44]

4.3. Clinical application

Research in this sphere aims to improve risk stratification above current standards of care to guide preventative treatment. Our review demonstrates that plaque quantification does appear to offer incremental benefit over conventional risk factors and surrogate markers for plaque burden, however the magnitude of this benefit is variable and must be weighed against the associated time and costs. While quantified plaque volumes are unlikely to be relevant in guiding revascularisation, they may facilitate patient risk reclassification for those around the threshold for statin recommendation, and guide intensification of preventative medical therapy. At a personalised medicine level, determining more precise risk is becoming important given the expanding arsenal of novel therapies including aggressive lipid lowering, anti-inflammatory and anti-atherosclerotic diabetes agents. These medications may be clinically effective in certain cohorts, but plaque quantification could be used to determine cost-effectiveness, especially in intermediate-high risk groups already taking statins.

Future research should ensure that plaque quantification is demonstrably accurate and reproducible compared to an established ground truth. Clinically relevant plaque volume thresholds should be derived and validated across different populations. The relative importance of plaque volumes will need to be defined in the context of other prognostic CCTA markers such as pericoronary fat attenuation indices,[57] computational flow (or machine learning-based) shear stress, and CT-fractional flow reserve.[58] CCTA-derived imaging data should be integrated with traditional clinical risk factors and novel biomarkers to create useable personalised risk prediction models for future cardiovascular events. Given the time and costs associated with plaque quantification, randomised controlled and large real-world observational trials will be required to determine whether providing a greater depth of plaque analysis to clinicians influences decision making and patient outcomes compared to current standard of care. Hard clinical outcome measures including MI and cardiovascular death will be required at a large scale (population level) and over a longer term of follow up (5–10 years) than is traditionally used in cardiovascular trials to determine their impact.

4.4. Limitations

There are several limitations to the meta-analysis. First, three studies could not be incorporated into the meta-analysis as they analysed plaque volumes as continuous variables.[19,25,41] One of these studies reported hazard ratios for progression of plaque volumes and so could not be grouped with other studies for meta-analysis.[25] Second, study design was heterogenous with differences in scanning hardware, plaque analysis software, plaque quantification approaches, plaque volume thresholds used to define high and low risk groups, MACE definitions, and variables included in multivariable analysis (Table 3). Some of this heterogeneity is mitigated by using a random effects model and study specific definitions of plaque thresholds for high and low risk. Third, some studies include revascularisation in the MACE endpoint which is influenced by individual clinician decision making and patient preference, and biases analyses in favour of stenosis severity. However, subgroup analyses revealed no significant change in hazard ratios with exclusion of studies including revascularisation in the MACE endpoint. Fourth, subgroup analyses are limited by the small number of studies available for inclusion.

5. Conclusion

This systematic review and meta-analysis examines the association between quantified coronary plaque volumes and future MACE in patients undergoing CCTA for investigation of suspected or known stable CAD. The majority of studies report an association between quantified plaque volumes and future cardiovascular events which is supported by meta-analysis findings. Further work is required to standardise approaches and reproducibility for each software vendor, improve the speed of plaque quantification, define normal ranges and demonstrate the clinical and cost effectiveness of integrating plaque volumes into patient healthcare.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2025.05.003.

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