Table S1. Quality Assessment.

Study	Study Type	Assessment Tool	Score/Confidence	Risk of Bias Summary	Study quality (per tool)
Nakahara et al. [1] 2017	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable - review paper	Not applicable
Budoff et al. [2] 2016	Observational cohort	NOS	7 / 9	Low risk - well-designed, defined metrics	High
Faulder et al. [3] 2024	Meta-analysis	AMSTAR 2	Not scored	Low risk - rigorous methodology	High
Channon et al. [4] 2022	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Cundari et al. [5] 2024	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Schuijf et al. [6] 2020	Prospective cohort	NOS	7 / 9	Low risk	High

Lima & Schuijf [7] 2020	Expert commentary	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Williams et al. [8] 2020	Prospective cohort	NOS	8 / 9	Low risk - robust core-lab methods	High
Yu et al. [18] 2025	Retrospective cohort	NOS	6 / 9	Moderate risk - single center	Moderate
Klüner et al. [9] 2021	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Rajiah et al. [10] 2022	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Nørgaard et al. [11] 2019	Expert consensus	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Manubolu et al. [12] 2024	Retrospective cohort	NOS	6 / 9	Moderate risk - moderate size	Moderate
Gallone et al. [13] 2023	Systematic review	AMSTAR 2	Not scored	Low risk - solid meta-analysis	High

Nørgaard et al. [14] 2022	Meta-analysis	AMSTAR 2	Not scored	Low risk	High
Mathew et al. [15] 2018	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Schuijf et al. [16] 2018	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Kimura et al. [17] 2015	Cost-analysis study	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
van der Bijl et al. [19] 2022	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Deseive et al. [20] 2018	Retrospective cohort	NOS	6 / 9	Moderate risk	Moderate
Yamaura et al. [21] 2022	Cross-sectional study	NOS	5 / 9	Moderate risk - cross-sectional	Moderate
Antoniades & Shirodaria [22] 2019	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable

Abdulkareem et al. [23] 2022	Retrospective cohort	NOS	6 / 9	Moderate risk	Moderate
Oikonomou et al. [24] 2019	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Vecsey-Nagy et al. [25] 2024	Retrospective cohort	NOS	6 / 9	Moderate risk	Moderate
Alyami et al. [26] 2023	Observational cohort	NOS	6 / 9	Moderate risk	Moderate
Alfakih et al. [27] 2018	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Coerkamp et al. [28] 2025	Prospective cohort	NOS	6 / 9	Moderate risk - preliminary cohort	Moderate
Cai et al. [29] 2023	Prospective cohort	NOS	7 / 9	Low risk - prospective design	High
Yu et al. [31] 2020	Prospective cohort	NOS	6 / 9	Moderate risk	Moderate
Pontone et al. [32] 2021	Editorial/commentary	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable

Imai et al. [33] 2019	Retrospective cohort	NOS	6 / 9	Moderate risk	Moderate
Min et al. [34] 2022	Cross-sectional study	NOS	5 / 9	Moderate risk	Moderate
Simantiris et al. [35] 2024	Narrative review	Not applicable (non-original data)	Not applicable (non-original data)	Not applicable	Not applicable
Oikonomou et al. [36] 2018	Post-hoc from cohort	NOS	7 / 9	Low risk - crisp-ct derived data	High
Khan et al. [37] 2023	Retrospective cohort	NOS	6 / 9	Moderate risk	Moderate

Notes:

• NOS categories: 0–3 = Low, 4–6 = Moderate, 7–9 = High.

• Inclusion threshold: NOS ≥5 (moderate or high) was set a priori owing to limited evidence and heterogeneity in CT biomarkers; a sensitivity analysis restricted to NOS ≥7 was performed to assess robustness.

• Non-original items (narrative reviews, editorials, consensus statements) are contextual and not included in the quantitative synthesis.

Table S2. GRADE Certainty of Evidence.

Outcome	# of Studies	Study Types	Certainty of Evidence	Comments
MACE (LAP, FAI, high-risk plaque)	12	7 prospective/retrospective cohorts, 3 post-hoc RCTs, 2 meta-analyses	Moderate	Downgraded for observational design; upgraded due to consistent HRs (~2–4) across SCOT-HEART, CRISP-CT, etc.
Myocardial Infarction	7	5 cohorts, 2 meta-analyses	Moderate	Adjusted HRs in SCOT-HEART; consistent moderate heterogeneity
Cardiovascular Mortality	5	3 cohorts, 2 systematic/meta-analyses	Low	Mostly secondary outcomes with less precision
Ischemia Detection (FFR-CT, Perfusion)	11	5 RCTs/post-hoc RCTs, 3 cohorts, 3 meta-analyses	High	Multiple RCTs/meta-analyses with robust AUC/accuracy data (AUC 0.86–0.88, sensitivity ~81–83%)

CAD Risk Reclassification (FAI, EAT)	6	4 prospective cohorts, 2 observational studies	Moderate	Consistent ORs (~1.5–2.3) and AUC (~0.76–0.88) across analyses
Epicardial / Perivascular Fat Analysis	8	5 retrospective cohorts, 3 systematic reviews	Low	Observational, narrative reviews with inconsistent quantification
Plaque Characterization and Burden	8	6 cohorts, 2 meta-analyses	Moderate	Consistent associations; e.g., adjusted HRs for LAP in multiple cohorts

Table S3. Study Characteristics.

Authors	Year	Study Type	Objective / Purpose	Key Findings
Nakahara et al. [1]	2017	Review	Review of coronary artery calcification and its role in CVD risk prediction.	CAC scoring independently predicts CV risk.
Budoff et al. [2]	2016	Observational	Assess CT angiography in identifying hemodynamic significance in lesions.	CT angiography helps in identifying hemodynamic significance.
Faulder et al. [3]	2024	Meta-analysis	Compare CT-derived FFR vs invasive FFR across studies.	CT-FFR correlates well with invasive FFR.
Channon et al. [4]	2022	Review	Overview of CCTA and related biomarkers including fat and flow.	Fat and flow biomarkers enhance CT utility.
Cundari et al. [5]	2024	Review	Review imaging biomarkers beyond anatomical plaque burden.	Biomarkers improve risk prediction beyond anatomy.
Schuijf et al. [6]	2020	Prospective Multicenter	Analyze INOCA using various modalities including CT perfusion.	CT perfusion and CTA provide complementary info.
Lima & Schuijf [7]	2020	Expert Commentary	Highlight multiparameter phenotyping for CAD risk stratification.	Combining CT perfusion and scar imaging improves prognosis.

Williams et al. [8]	2020	Prospective Cohort	Assess LAP on CCTA for prediction of MI in SCOT-HEART trial.	LAP is strong predictor of MI.
Yu et al. [18]	2025	Retrospective Cohort	Examine FAI in young patients and its link to MACE.	FAI is predictive of MACE in young CAD-suspected patients.
Klüner et al. [9]	2021	Review	Summarize how FAI is used for risk stratification.	FAI quantifies perivascular inflammation.
Rajiah et al. [10]	2022	Review	Practical guide for CT FFR interpretation and utility.	CT FFR feasible and clinically helpful.
Nørgaard et al. [11]	2019	Expert Consensus	Provide recommendations for CT-FFR interpretation.	Recommends how to report CT FFR results.
Manubolu et al. [12]	2024	Retrospective Cohort	Assess the relationship between EAT and coronary plaque burden.	Higher EAT associated with increased plaque burden.
Gallone et al. [13]	2023	Systematic Review	Summarize plaque characteristics associated with MACE.	High-risk plaque traits predict MACE.
Nørgaard et al. [14]	2022	Meta-analysis	Evaluate prognostic value of CT FFR via meta-analysis.	CT-FFR provides strong prognostic value.
Mathew et al. [15]	2018	Review	Discuss how CT FFR guides interventions.	CT-FFR useful for guiding PCI decisions.

Schuijf et al. [16]	2018	Review	Guide clinical application of CT FFR and perfusion.	Describes FFR and perfusion with CT.
Kimura et al. [17]	2015	Cost Analysis	Analyze cost-effectiveness of CT FFR in Japan.	CT FFR shown to be cost-effective.
van der Bijl et al. [19]	2022	Review	Describe PAT attenuation's diagnostic/prognostic roles.	High PAT attenuation predicts CAD events.
Deseive et al. [20]	2018	Retrospective Cohort	Quantify low-attenuation plaque volume and predict events.	LAP predicts future events and reclassifies risk.
Yamaura et al. [21]	2022	Cross-sectional	Identify determinants of LAP burden in asymptomatic patients.	LAP linked to LDL and other metabolic factors.
Antoniades & Shirodaria [22]	2019	Review	Describe perivascular attenuation maps and interpretation.	Perivascular maps reflect inflammation.
Abdulkareem et al. [23]	2022	AI-based Imaging Study	Use deep learning to quantify EAT and attenuation.	AI enables accurate EAT quantification.
Oikonomou et al. [24]	2019	Review	Review coronary inflammation and plaque features.	CT detects inflammation and predicts risk.
Vecsey-Nagy et al. [25]	2024	Retrospective Cohort	Relate low-attenuation burden to troponin in CCS.	Troponin release mediated by LAP.
Alyami et al. [26]	2023	Observational	Assess prevalence of non-calcified plaque on CTA.	Non-calcified plaque present in asymptomatic adults.

Alfakih et al. [27]	2018	Review	Promote CTA over functional testing for CAD evaluation.	CTCA preferred over functional testing.
Coerkamp et al. [28]	2025	Observational	Assess whether FAI reclassifies CV risk on CCTA.	FAI improves CV risk reclassification.
Cai et al. [29]	2023	Prospective Cohort	Compare CT-FFR at different lesion sites.	Distal site FFRCT more accurate for ischemia.
Yu et al. [31]	2020	Prospective Cohort	Evaluate FAI in predicting ischemia severity.	FAI predicts hemodynamic lesion severity.
Pontone et al. [32]	2021	Editorial	Commentary on dynamic perfusion value in CT.	Dynamic perfusion enhances lesion detection.
Imai et al. [33]	2019	Retrospective Cohort	Link nonobstructive lesions with abnormal CT-FFR.	High-risk features in nonobstructive CAD lesions.
Min et al. [34]	2022	Cross-sectional	Correlate CTA plaque volume with invasive FFR.	CT plaque staging aligns with FFR.
Simantiris et al. [35]	2024	Review	Discuss perivascular fat as CAD risk factor.	FAI linked to subclinical atherosclerosis.
Oikonomou et al. [36]	2018	Post-hoc Analysis	Study inflammation detection via CCTA (CRISP-CT).	CRISP-CT: inflammation detected via CT predicts MACE.
Khan et al. [37]	2023	Retrospective Cohort	Evaluate EAT volume and ischemia in nonobstructive CAD.	High EAT volume linked to plaque and ischemia.

Table S4. Definitions and Cut‑offs Used Across Cardiac CT Biomarker Studies.

Biomarker	Core definition / HU window	Measurement region / protocol	Common cut-off(s) reported	Known variants across studies
Low-attenuation plaque (LAP)	Plaque voxels <30 HU (necrotic/low-density component) within coronary plaque volume [1,7]	Lesion- or vessel-level segmentation on CCTA; semi-automated plaque analysis	LAP burden >4% of total plaque volume; continuous per-doubling of LAP burden	Some studies use alternative HU thresholds (e.g., <60 HU); plaque segmentation tools and kernels vary
Positive remodeling index (RI)	Remodeling index = lesion EEM area / reference EEM area [21]	Cross-sectional area measured at minimal lumen and reference segment	RI >1.10 considered positive remodeling	Reference segment selection and EEM estimation methods vary
Napkin-ring sign (NRS)	Central low-attenuation core with a peripheral higher-attenuation rim on CCTA [3,11]	Qualitative visual assessment on thin-slab multiplanar reformats	Presence/absence (no numeric cut-off)	Interobserver criteria and window settings vary
Non-calcified plaque (NCP) / Fibrofatty/Fibrous	NCP typically defined by HU between ~−30 to 130 HU (tool-dependent) excluding calcified (>350 HU) [13,17]	Semi-automated plaque composition analysis; tool-specific bins	Study-specific (often continuous % volume or quartiles)	Attenuation bin edges differ across vendors; smoothing/kernel and kVp affect HU

Perivascular fat attenuation (PCAT) / Fat Attenuation Index (FAI)	Mean attenuation of adipose tissue (−190 to −30 HU) within a perivascular ring around the vessel [22,23]	PCAT sampled around proximal coronary segments (commonly proximal RCA over a fixed length); ring thickness or radial distance varies by protocol	High-risk FAI cut-offs reported near −70 HU (e.g., ≥−70.1 HU associated with higher cardiac risk)	Artery/segment length definitions vary (e.g., 10–50 mm proximal RCA; vessel-diameter–scaled rings); reconstruction and kVp impact HU
Epicardial adipose tissue (EAT) volume/attenuation	Adipose tissue between myocardium and visceral pericardium (−190 to −30 HU) [12,18]	3D segmentation within pericardial sac; non-contrast or contrast CT; attenuation as mean HU	No unified clinical cut-off; often analyzed as continuous or cohort-specific percentiles	Segmentation protocols vary (manual vs automated); contrast phase and tube voltage affect HU
CT-derived fractional flow reserve (FFR-CT)	Computationally derived pressure index along coronary tree from CCTA [16.17]	Per-vessel and per-patient reporting; distal to stenosis or lowest value in vessel	Ischemia typically defined as FFR-CT ≤0.80; 0.76–0.80 often considered borderline	Vessel-level vs patient-level thresholds; site-specific reporting conventions
CT myocardial perfusion (CT-MPI) dynamic	Quantitative myocardial blood flow (MBF) from dynamic stress CT perfusion [7]	Vasodilator stress; model-based deconvolution; per-territory MBF (mL/min/100 g)	Ischemia thresholds vary by vendor and protocol; often referenced to invasive FFR ≤0.80	Acquisition (kVp, rate), reconstruction, and modeling differences; absolute

				MBF cut-offs not standardized
Radiomics / Texture features	High-dimensional features extracted from plaque/arterial wall CT voxels [13,21]	Segmentation of lesion/ROI; feature extraction with predefined radiomic pipeline	Study-specific thresholds; models reported via AUC/accuracy rather than fixed cut-offs	Pipelines, feature sets, and harmonization approaches differ widely

This table summarizes commonly used definitions, measurement protocols, and cut-offs reported across the included literature to illustrate variability and support standardization.

Notes:

1) HU-based thresholds are sensitive to tube voltage (kVp), reconstruction kernel, contrast timing, and vendor software; report acquisition/reconstruction parameters alongside any cut-offs.

2) For FAI/PCAT, segment length (e.g., proximal 10–50 mm RCA), radial sampling distance, and ring definitions vary by protocol; specify artery/length and method.

3) For FFR-CT, most studies define ischemia as ≤0.80; values 0.76–0.80 are frequently considered borderline. Report whether values are per-vessel (distal to lesion) or lowest per-patient.

4) For Dynamic CT-MPI, absolute MBF cut-offs are not standardized across vendors; report stressor, model, calibration, and any reference standard used (e.g., invasive FFR).

Abbreviations: HU = Hounsfield units; CCTA = coronary computed tomography angiography; EEM = external elastic membrane; RCA = right coronary artery; FAI = fat attenuation index; PCAT = pericoronary adipose tissue; EAT = epicardial adipose tissue; FFR-CT = CT-derived fractional flow reserve; CT-MPI = CT myocardial perfusion; MBF = myocardial blood flow.

Table S5. Summary of Findings by Biomarker (Diagnostic & Prognostic Performance).

Biomarker/Modality	Key Outcomes	Summary effect (range/anchor estimates)	Comments on consistency/applicability
Low-attenuation plaque (LAP)	Myocardial infarction (MI), MACE	HR ≈ 2.3–4.7 for higher LAP burden; LAP >4% → HR ~4.65; per-doubling LAP → HR ~1.60	Consistent independent predictor across cohorts; strongest for MI; measured as % of total plaque volume
Perivascular fat attenuation (FAI/PCAT)	Cardiac mortality, MI, reclassification	Mortality HR ~2.06–2.15 (derivation/validation); MI: RCA PCAT ~−70 HU → HR ~2.45; ΔAUC ≈ 0.05	Risk additive with high-risk plaque; thresholds and segment sampling vary; standardization ongoing
High-risk plaque (HRP) features	MACE, MI	OR ~1.6–2.5; AUC up to ~0.83	Includes LAP, positive remodeling, napkin-ring sign; effect sizes heterogeneous by feature
Quantitative plaque burden/volume	Ischemia, MACE	Higher burden in ischemic vs non-ischemic lesions; directionally consistent	Absolute thresholds vary by software/HU bins; standardized bins needed
Epicardial adipose tissue (EAT)	Plaque composition, ischemia	+~7% fibrofatty plaque per +1 HU EAT attenuation; volume-based links to ischemia mixed	Attenuation shows stronger link to composition than volume; acquisition phase impacts HU

FFR-CT (vs invasive FFR)	Ischemia (reference FFR ≤0.80)	Accuracy ~81%; Sens ~86%; Spec ~79; ≥90% accuracy when >0.90 or <0.49; weakest around 0.74–0.82	Improves specificity vs CTA alone; site-specific correlation r ~0.80–0.82; context-dependent utility
Dynamic CT myocardial perfusion (CT-MPI)	Ischemia (invasive reference)	Sensitivity ~90%+; Specificity ~80% (representative meta-analytic anchors)	Performance varies with vendor and protocol; absolute MBF cut-offs not standardized
Radiomics / texture features	Diagnosis, prognosis	Reported as AUC/accuracy (study-specific); no unified thresholds	Pipelines and harmonization differ; promising but investigational

This table synthesizes effect measures by biomarker and outcome. Abbreviations: HR = hazard ratio; OR = odds ratio; AUC = area under the ROC curve; MACE = major adverse cardiovascular events; HU = Hounsfield units; FFR-CT = CT-derived fractional flow reserve; MBF = myocardial blood flow; CTA = coronary CT angiography; PCAT = pericoronary adipose tissue.