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Clinical Applications of Cardiovascular Computed Tomography (CT)

Edited by
David C. Rotzinger

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Guest Editor

David C. Rotzinger



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Guest Editor

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About the Editor

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Preface

The aim of this Reprint is to provide clinicians, researchers and imaging specialists with a comprehensive overview of current evidence and emerging techniques in cardiovascular computed tomography. The contributions demonstrate how advances in image acquisition, tissue characterization and post-processing are improving diagnostic accuracy, prognostic assessment and procedural planning across diverse patient populations.

David C. Rotzinger

Guest Editor



Editorial

Clinical Applications of Cardiovascular CT: An Evolving Landscape

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In its three decades of existence, cardiovascular computed tomography (CT) has profoundly transformed patient assessment and established itself as one of the most recommended non-invasive imaging modalities in contemporary cardiology and radiology practice [1]. From its early application in coronary artery calcium (CAC) quantification using electron beam CT in 1990 [2] to its current role as a multiparametric toolset integrating morphology, physiology, and tissue characterization, cardiovascular CT continues to reinvent itself at a remarkable pace, while refining patient safety [3]. The multiplicity of data retrievable from a single-modality examination is well illustrated in a recent meta-analysis that underscored the prognostic value of coronary CT angiography (CCTA); in a compelling assessment including fractional flow reserve CT (FFR-CT), high-risk plaque features, fat attenuation index, total plaque volume, low-attenuation plaque, and radiomics-derived parameters, the authors advocated CT for improved cardiovascular risk stratification [4]. This is before even considering artificial intelligence (AI), which, while still largely research-driven, is increasingly finding its way into clinical workflows and is well positioned to reshape cardiovascular CT practice in the years ahead [5]. While these advances reflect the significant research effort dedicated to detecting, characterizing, and managing coronary artery disease, cardiovascular CT applications extend far beyond coronary CCTA alone.

Beyond cardiac applications, CT angiography has established itself as a non-invasive tool for morphologic assessment of arterial vessels. Advances in imaging acquisition and reconstruction have enabled high-resolution 3D images for diagnosis and risk assessment of vascular diseases in acute and chronic settings, as well as for treatment planning, providing both detailed vascular mapping and measurements for device sizing in complex procedures [6]. The panel of vascular disorders that CT angiography can help diagnose and manage has been expanding continuously, currently encompassing degenerative, inflammatory, congenital, neoplastic, and traumatic pathology [7].

Reflecting this expansive scope, this Special Issue of the Journal of Cardiovascular Development and Disease, entitled “Clinical Applications of Cardiovascular Computed Tomography (CT),” brings together a diverse collection of original research articles, reviews, case reports, and study protocols that highlight the true breadth and depth of the field. A short summary of each contribution can be found in Table 1.

Naturally, the cornerstone of cardiovascular CT remains coronary artery disease (CAD) assessment. Camacho-Mondragon et al. provide a comprehensive focused review of three major clinical applications of cardiac CT for the practicing cardiac imager: CAC scoring, coronary CT angiography (CCTA), and preprocedural planning for structural heart interventions (Contribution 1). The authors summarize technical requirements and patient safety before systematically addressing the prognostic value of CAC scoring across

diverse populations, the diagnostic and prognostic performance of CCTA, including high-risk plaque features and FFR-CT, and the indispensable role of CT in transcatheter valve procedures. Pushing the envelope further, the potential role of CCTA in acute coronary syndrome is discussed, an ongoing debate since the role of CT has evolved over the last few years and is increasingly integrated into major guidelines. Importantly, the review also covers emerging technologies, encompassing dual-energy imaging, photon-counting detector CT, and artificial intelligence, that are poised to further expand the clinical utility of the modality. This contribution serves as an accessible and timely reference for clinicians seeking to integrate cardiac CT into their daily practice.

Table 1. Summary of the ten contributions included in this Special Issue.

Authors	Title	Type	Sample	Main Findings/Conclusions
Camacho-Mondragon et al. (Contribution 1)	Clinical Applications of Cardiac Computed Tomography: A Focused Review for the Clinical Cardiologists	Review	N/A	Cardiac CT has evolved into a comprehensive multiparametric modality integrating anatomy, function, and prognosis; innovations (photon counting, AI, dual energy) are expanding its diagnostic and prognostic role.
Kyriakoulis et al. (Contribution 2)	Coronary Computed Angiography and Coronary Artery Calcium Score for Preoperative Cardiovascular Risk Stratification in Patients Undergoing Noncardiac Surgery	Narrative review	N/A	CCTA and CACS (alone or combined) reliably predict perioperative and long-term MACE, often matching or surpassing traditional stress imaging; integration with a revised cardiac risk index further improves risk stratification; routine use is not yet recommended, but selective use is supported by guidelines.
Hammerer et al. (Contribution 3)	Importance of Imaging Assessment Criteria in Predicting the Need for Post-Dilatation in Transcatheter Aortic Valve Implantation with a Self-Expanding Bioprosthesis	Retrospective single-center	585 TAVI patients	Peak aortic valve velocity (AV Vmax) and aortic valve calcium density—not total aortic valve calcium score—independently predicted post-dilatation. Post-dilatation did not increase short-/mid-term adverse events or mortality; it can be performed safely when indicated.
Aoki et al. (Contribution 4)	Extracellular Volume Fraction Analysis on Cardiac Computed Tomography Is Useful for Predicting the Prognosis of Hypertrophic Cardiomyopathy	Retrospective multicenter cohort	101 hypertrophic cardiomyopathy patients	LV-ECV and LVEF were independent MACE predictors; LV-ECV $\geq 37.6\%$ identified significantly higher-risk patients (AUC 0.79). CT-derived ECV is a useful quantitative risk tool, especially when MRI is contraindicated.
Lorusso et al. (Contribution 5)	Evaluating Epicardial Fat Density Using ROI-Based Analysis: A Feasibility Study	Retrospective feasibility study	171 patients undergoing CCTA	Significant regional variability in epicardial fat density (aortic bulb, apex, posterolateral wall) vs. global was found; ROI-based measurements do not reliably reflect global epicardial fat density; dedicated segmentation software remains necessary.
Tanaka et al. (Contribution 6)	Subtraction CT Angiography for the Evaluation of Lower Extremity Artery Disease with Severe Arterial Calcification	Prospective diagnostic accuracy study	32 lower extremity artery disease patients (640 segments)	Subtraction CTA markedly reduced uninterpretable segments (2.0% vs. 25.2%) and achieved higher accuracy (0.885 vs. 0.657); this is particularly valuable in critical limb ischemia with heavy calcification.

Table 1. Cont.

Authors	Title	Type	Sample	Main Findings/Conclusions
Capisizu et al. (Contribution 7)	A Pilot Study on the Role of Computed Tomography in the Management of Patients with Coronary Artery Anomalies in Romania	Retrospective pilot study	184 patients undergoing CCTA	Coronary artery anomaly prevalence was 8.7% (3.8% origin/course; 4.9% intramuscular bridging of LAD). Significant association with cardiac symptoms was present; there was no association with calcium score. This supports wider CCTA use for coronary artery anomaly detection.
Arrarte Terreros et al. (Contribution 8)	Thrombus Imaging Characteristics to Predict Early Recanalization in Anterior Circulation Large Vessel Occlusion Stroke	Retrospective cohort and prediction model	81 early recanalization and 322 persistent large vessel occlusion stroke patients (MR CLEAN Registry)	Intravenous thrombolysis administration, greater distance to thrombus (distal occlusion), and lower thrombus density predicted early recanalization (AUC 0.77). Thrombus imaging may optimize repeated-imaging workflow in transferred stroke patients.
Zhang et al. (Contribution 9)	Aorto-Esophageal Fistula Caused by Vascular Malformation: A Case Description and an Analysis of the Literature	Case report and literature review	1 patient (60-year-old male)	CTA precisely identified the anomalous vessel and fistula, guiding emergency endovascular repair. This highlights the essential role of CTA in diagnosing aorto-esophageal fistula and the need for early surgical intervention, given the high mortality.
Fahrni et al. (Contribution 10)	Investigating the Influence of High-Speed Gantry Rotation in Cardiac CT on Motion Artifacts in Aortic Stenosis Patients Not Premedicated with β -Blockers: The FAST-CCT Randomized Trial Protocol	Prospective single-center RCT protocol	Planned 142 patients ≥ 50 years (aortic stenosis work-up, no β -blockers used for CT)	Study protocol aimed to determine whether faster gantry rotation eliminates the need for β -blocker premedication and improves CCTA image quality, diagnostic accuracy vs. invasive coronary angiography, and radiation dose. Results pending.

Acronyms; AI = artificial intelligence; AUC = area under the receiver operating characteristic curve; CACS = coronary artery calcium score; CCTA = coronary computed tomography angiography; CTA = computed tomography angiography; DSA = digital subtraction angiography; ECV = extracellular volume; LAD = left anterior descending; LV-ECV = left ventricular extracellular volume fraction; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; RCT = randomized controlled trial; ROI = region of interest; TAVI = transcatheter aortic valve implantation.

Speaking of CAD prediction, preoperative cardiovascular risk stratification represents a clinically relevant yet underexplored application of CCTA and CAC scoring. Because of the scarcity of scientific data covering the specific setting of CAD in patients undergoing noncardiac surgery, no guidelines specifically recommend coronary imaging preoperatively. Kyriakoulis et al. present a narrative review examining the evidence supporting the use of CCTA and CAC score (CACS) in patients undergoing noncardiac surgery (Contribution 2). The authors demonstrate that both tools offer reliable perioperative and long-term major cardiovascular event (MACE) prediction, often matching or outperforming traditional imaging modalities such as dobutamine stress echocardiography and myocardial perfusion imaging. Notably, preoperative cardiac CT can help identify patients who carry an up to 12-fold risk of MACE during the 5 years following surgery. The review also highlights the emerging role of FFR-CT in this context and underscores the need for prospective comparative studies (CACS vs. CCTA and FFR-CT) to better define the optimal imaging strategy in the preoperative setting.

Beyond coronary artery disease, this Special Issue highlights the expanding role of CT in structural heart disease. Hammerer et al. investigated imaging predictors of the need for balloon post-dilatation (PD) following transcatheter aortic valve implantation (TAVI) in

a retrospective single-center cohort of 585 patients (Contribution 3). PD can be required to manage incomplete TAVI expansion, where the valve frame fails to reach its intended diameter. Potential complications of underexpansion mainly include ischemic stroke, valve hypoattenuating leaflet thickening (HALT), and paravalvular regurgitation. Hammerer et al. identified aortic valve maximal systolic transvalvular flow velocity (echocardiography-derived) and aortic valve calcium density (cardiac CT-derived) as independent predictors of PD, while demonstrating that PD was not associated with increased procedural adverse events or impaired mid-term survival. These results reinforce the value of multimodal preprocedural CT- and echocardiography-based assessment in anticipating procedural complexity and optimizing patient outcomes in structural interventions.

The prognostic capabilities of cardiac CT extend well beyond coronary anatomy. Aoki et al. investigated the effectiveness of conventional CT-derived extracellular volume fraction (ECV) analysis for predicting MACE in patients with hypertrophic cardiomyopathy (HCM) (Contribution 4). ECV was derived from CT numbers [HU] measured in the myocardium ($\Delta\text{HU}_{\text{m}}$) and blood ($\Delta\text{HU}_{\text{b}}$) as well as the hematocrit (Hct) according to the following formula: $\text{ECV} = (\Delta\text{HU}_{\text{m}}/\Delta\text{HU}_{\text{b}})/(1 - \text{Hct})$. In this multicenter retrospective cohort of 101 patients, left ventricular ECV on CT emerged as an independent predictor of MACE ($p < 0.001$), with an optimal threshold of 37.6% ECV yielding a sensitivity of 73% and specificity of 78%. This study is particularly noteworthy as it demonstrates that cardiac CT can provide tissue-level characterization, which is useful when MRI is limited by device incompatibility, arrhythmia, or claustrophobia. The ability to perform ECV analysis as an adjunct to standard coronary CT protocols, without additional contrast administration or extra ionizing radiation exposure, represents a meaningful advance in the multiparametric assessment of cardiomyopathies.

Epicardial adipose tissue (EAT) has gained increasing attention as a metabolically active compartment, with direct paracrine effects and bidirectional biochemical communication with the coronary vasculature and myocardium. However, full three-dimensional segmentation of epicardial fat is impractical, time-consuming, and incompatible with clinical workflows when performed manually. Lorusso et al. explored the feasibility of region-of-interest (ROI)-based epicardial fat density (EFD) measurement as a simplified alternative to full segmentation in 171 patients undergoing coronary CT (Contribution 5). Their results revealed significant regional variability in EFD across the aortic bulb, right posterolateral wall, and cardiac apex, with statistically significant differences compared to global EFD values they obtained using established semi-automatic segmentation software. While the study concludes that ROI-based measurements do not reliably reflect global EFD characteristics, it provides important methodological insights and highlights the need for dedicated segmentation tools to standardize EFD assessment in clinical practice. Future research integrating EFD with pericoronary fat attenuation index and plaque characterization may further enhance cardiovascular risk stratification.

The diagnostic versatility of CT is further illustrated by two contributions addressing less conventional applications. Tanaka and Yoshioka evaluate the performance of subtraction CT angiography (CTA) with volume position matching in 32 patients with lower extremity artery disease (LEAD) and severe arterial calcification (Contribution 6). When heavy calcification of the lower limb arteries is present, diameter stenosis assessment is typically challenging in the more distal vessels due to blooming artifacts. Tanaka and Yoshioka showed that compared to conventional CTA, subtraction CTA could overcome this limitation, dramatically reducing the proportion of uninterpretable arterial segments (2.0% vs. 25.2%) and achieving substantially higher diagnostic accuracy (0.885 vs. 0.657) against digital subtraction angiography (DSA) as the reference standard. These findings are particularly relevant for elderly patients and those with diabetes or end-stage renal

disease, in whom Mönckeberg-type medial calcification frequently renders conventional CTA non-diagnostic. Subtraction CTA thus emerges as a practical and clinically valuable tool in this challenging population.

Capisizu et al. report a pilot study on the prevalence and characterization of coronary artery anomalies (CAAs) detected by CCTA in a Romanian cohort of 184 patients with chest pain (Contribution 7). A prevalence of 8.7% was observed, consistent with contemporary CCTA-based series, with anomalies of origin and course accounting for 3.8% and intramuscular bridging of the left anterior descending artery for 4.9%. The most frequent symptoms associated with CAA were chest pain in 52.7% and shortness of breath in 36.8% of patients. The presence of cardiac symptoms was statistically significantly associated with CAA ($p = 0.045$). This study is notable as the first to characterize CAA prevalence by CCTA in a southeastern Romanian population, contributing to the growing body of evidence supporting CCTA as the gold standard for CAA diagnosis and anatomical characterization.

The application of CT imaging to cerebrovascular disease is represented by the work of Arrarte Terreros et al., who investigated thrombus characteristics on acute stroke CT as predictors of early recanalization in transferred patients with anterior circulation large vessel occlusion (LVO) (Contribution 8). Using baseline non-contrast CT and CT angiography data from 81 early-recanalized patients compared with 322 persistent LVO patients from the MR CLEAN Registry, the authors demonstrate that intravenous thrombolysis administration, thrombus distality, and lower thrombus density were independent predictors of early recanalization, with a model AUC of 0.77. These findings highlight the potential of CT-based thrombus characterization to optimize repeated-imaging workflows and reduce ineffective inter-hospital transfers, with direct implications for resource allocation and patient safety in acute stroke management.

A rare but instructive case of aorto-esophageal fistula (AEF) caused by a vascular malformation is reported by Zhang et al. (Contribution 9). The case illustrates the critical diagnostic role of CT angiography in identifying the bleeding source, characterizing the vascular anomaly, and guiding emergency surgical planning in a condition with extremely high mortality. The authors emphasized that CTA's non-invasive nature and high spatial resolution make it the preferred diagnostic modality when AEF is clinically suspected, avoiding the risk of precipitating fatal hemorrhage during endoscopy. This case expands the available literature covering the spectrum of primary AEF and reinforces the importance of attempting to map the vascular feeders in patients presenting with unexplained massive gastrointestinal bleeding prior to intervention.

Finally, this Special Issue includes a prospective randomized controlled trial protocol addressing a fundamental technical challenge in CCTA: motion artifacts. Fahrni et al. present the FAST-CCT trial, which aims to evaluate whether ultra-fast gantry rotation (0.23 s/rot) reduces coronary motion artifacts and improves diagnostic image quality compared to standard rotation speed (0.28 s/rot) in patients undergoing aortic stenosis work-up without β -blocker premedication (Contribution 10). This is a particularly relevant population, as β -blockers are frequently contraindicated in aortic stenosis, and motion artifacts remain a substantial limitation of CCTA in this setting. The trial's prospective, randomized design and rigorous power analysis position it to generate high-quality evidence with direct implications for clinical practice and scanner protocol optimization.

Taken together, the contributions assembled in this Special Issue reflect the remarkable versatility of cardiovascular CT across a wide spectrum of clinical scenarios, from primary prevention and preoperative risk stratification to structural heart disease, cardiomyopathy, peripheral vascular disease, cerebrovascular emergencies, and rare vascular malformations. They also underscore the ongoing technological evolution of the modality, from subtraction algorithms and ECV mapping to ultra-fast gantry rotation and AI-assisted image

analysis. As cardiovascular CT continues to expand its diagnostic and prognostic reach, the challenge ahead lies in translating these advances into accessible, cost-effective, and radiation-conscious clinical practice. We hope that this collection will serve as a valuable resource for clinicians, researchers, and imaging specialists and will stimulate further investigation into the many open questions that remain in this dynamic field.

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Study Protocol

Investigating the Influence of High-Speed Gantry Rotation in Cardiac CT on Motion Artifacts in Aortic Stenosis Patients Not Premedicated with β -Blockers: The FAST-CCT Randomized Trial Protocol

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Abstract: Background: Coronary CT angiography (CCTA) is increasingly used as a non-invasive tool to assess coronary artery disease (CAD). However, CCTA is subject to motion artifacts, potentially limiting its clinical utility. Despite faster (0.35 and 0.28 s/rot) gantry rotation times, low (60–65 bpm) heartbeat is recommended, and the use of β -blockers is often needed. Technological advancements have resulted in the development of faster rotation speeds (0.23 s/rot). However, their added value in patients not premedicated with β -blockers remains unclear. This prospective single-center, two-arm, randomized, controlled trial aims to assess the influence of fast rotation on coronary motion artifacts, diagnostic accuracy of CCTA for CAD, and patient safety. Methods: We will randomize a total of 142 patients aged ≥ 50 scheduled for an aortic stenosis work-up to receive CCTA with either a fast (0.23) or standard (0.28 s/rot) gantry speed. Primary outcome: rate of CCTAs with coronary motion artifacts hindering interpretation. Secondary outcomes: assessable coronary segments rate, diagnostic accuracy against invasive coronary angiography (ICA), motion artifact magnitude per segment, contrast-to-noise ratio (CNR), and patient ionizing radiation dose. The local ethics committee has approved the protocol. Potential significance: FAST-CCT may improve motion artifact reduction and diagnosis quality, thus eliminating the need for rate control and β -blocker administration. Clinicaltrials.gov identifier: NCT05709652.

Keywords: CCTA; motion artifacts; aortic stenosis; gantry rotation speed; 0.23; beta-blockers; high-speed; TAVI; protocol

1. Introduction

Cardiovascular disease, one of the foremost contributors to global mortality and morbidity, results in one person dying every 36 s in the United States alone [1]. Notably, coronary artery disease is the most prevalent type among various cardiovascular conditions [2].

1.1. Role and Challenges of CCTA

When assessing coronary artery disease, clinicians have several diagnostic options with different risks and degrees of invasiveness. Coronary catheterization with invasive coronary angiography (ICA) is the current gold standard and has the advantage of combining both diagnosis and therapy (coronary revascularization) within a single session [3]. However, not all patients with suggestive symptoms need a revascularization procedure, as other treatment options exist, such as lifestyle modifications, medical treatment, or surgery. Therefore, assessing coronary artery disease (CAD) with less invasive procedures can be beneficial, sending only selected patients to ICA and revascularization therapy [4]. In this context, different non-invasive tests can help diagnose flow-limiting atherosclerosis, including echocardiography, electrocardiogram, nuclear medicine tests, MRI, and CT. Of those, CT has recently gained interest due to ongoing technological advances [5], with several recent trials demonstrating its clinical value [6–8]. One major challenge with coronary CT angiography (CCTA) imaging, unlike extra-cardiac CT imaging, is that coronary arteries are small structures situated within the fast-moving heart, continuously affected by heartbeats. Without a technology to optimize the speed of anatomical sampling and, eventually, motion correction techniques, movement-induced distortion would critically undermine coronary artery analysis [9]. For CCTA to be feasible, images must be acquired using ECG gating synchronized with the heartbeats. CCTA image quality has improved dramatically in the last decade; nevertheless, some limitations persist, one of the most prominent being elevated (>65 bpm) or irregular heart rates. For this reason, oral or intra-venous β -blockers (including but not limited to Metoprolol or Esmolol) are frequently used before the examination to slow down and stabilize the heartbeat. While this procedure is generally safe, it can be time-consuming and still has limitations and contraindications, such as severe asthma, aortic stenosis, allergy, atrioventricular block, or severe chronic obstructive pulmonary disease (COPD) [10]. Additionally, when β -blockers are contraindicated, or a low and regular heart rate is not achieved, a wider acquisition window is typically required, increasing the patients' exposure to ionizing radiation.

1.2. Technical Advancements in Cardiac CTA

In this context, manufacturers have developed multiple technical solutions to help achieve motionless images [11]. On the software side, motion correction algorithms (MCA), typically operating in the image domain, prove valuable in improving image quality and interpretability [12]. On the hardware side, one of the most limiting factors is the speed at which images are captured, known as temporal resolution. This speed is mainly determined by the gantry's rotational velocity, which includes the tube and detectors of the CT scanner. Images are acquired by rotating the X-ray beam around the patient and using a number of tube-detector pairs operating simultaneously. Until recently, the rotation speed typically used in clinical settings ranged from 0.25 to 0.35 s/rot due to the challenges associated with increasing the rotation speed. Some of the main challenges of accelerating the gantry include the following:

- (a) Mechanical stress. The gantry, including the X-ray tube, detectors, and other components, must be designed and built to withstand the increased rotational forces and vibrations associated with higher speeds. This requires robust engineering and precision manufacturing to ensure the gantry can handle the increased load without compromising performance or longevity.
- (b) Heat dissipation. Faster rotation times mean shorter exposure times for each angular view, resulting in higher X-ray tube power requirements to maintain image quality. This increased power generation leads to higher heat generation, and effective heat dissipation becomes crucial. Designing tubes that can deliver higher currents and equipped with efficient cooling mechanisms to dissipate the excess heat and prevent overheating is essential for maintaining optimal system performance and preventing damage.

- (c) Data acquisition and processing. Faster rotation speeds generate a larger amount of data in a shorter period of time. This increases demand on data acquisition and processing systems, including detector speed, readout capabilities, data transfer rates, and computational power. The system must handle the increased data volume and process it efficiently to reconstruct high-quality images within the desired time frame.

Most recent technical advances overcoming these physical constraints due to acceleration led to faster rotation speeds, up to 0.23 s/rot.

2. Materials and Methods

2.1. Rationale, Aim, and Design of the Study

This prospective study is conducted in a single Swiss tertiary hospital. It aims to evaluate whether faster gantry rotation speeds in coronary imaging (FAST-CCT) improve the rate of diagnostic images and reduce motion artifacts in patients referred for aortic valve stenosis evaluation. Our institution's routine protocol for cardiac CT in the work-up of aortic stenosis utilizes a gantry speed of 0.28 s/rot.

Fast gantry rotation CCTA is performed using a 256-multi-detector RevolutionTM Apex CT system (GE Healthcare, Waukesha, WI, USA), with gantry rotation speeds of either 0.23 (fast) or 0.28 s/rot (standard). Acquisition and reconstruction parameters are detailed in Table 1.

Table 1. Acquisition and reconstruction parameters. DLIR H = deep learning image reconstruction at high strength.

	Standard Protocol	Fast Protocol
Tube voltage (kVp)	100	100
Tube current (mA)	500–1000	500–1000
Noise index	20	20
Rotation time (s/rot)	0.28	0.23
Acquisition mode	Axial	Axial
Injection phase	Arterial	Arterial
Phases of cardiac cycle	20–80% (prospective)	20–80% (prospective)
Collimation (mm)	256 × 0.625	256 × 0.625
FOV (mm)	220–250	220–250
Matrix size (pixels)	512 × 512	512 × 512
Slice thickness (mm)	0.625	0.625
Slice incrementation (mm)	0.6	0.6
Reconstruction kernel	Standard	Standard
Reconstruction algorithm	DLIR H	DLIR H

For this purpose, a monocentric prospective randomized controlled trial with two arms is designed. The study flowchart is provided in Figure 1.

2.2. Sample Size, Inclusion, and Exclusion Criteria

We conducted a power analysis based on the assumption that standard CCTA in patients undergoing aortic stenosis treatment yields 70% analyzable vessels as previously published [13], and fast rotation CCTA is supposed to provide an improvement in the order 20%, i.e., 90% analyzable segments [14]. The sample size analysis showed that in order to achieve 80% power under the assumed diagnostic CCTA rates, the study should include 62 participants in each arm. Considering an expected weighted kappa of 0.82 [15] for inter-observer variability in the qualitative scoring of vascular motion, the adjusted sample size was 71. Consequently, we intend to have 142 participants with complete datasets.

Inclusion criteria: Participants will be patients holding a clinical indication to undergo cardiac CT due to known or suspected aortic valve stenosis. Participants will be over 50 years old and have signed an informed consent form.

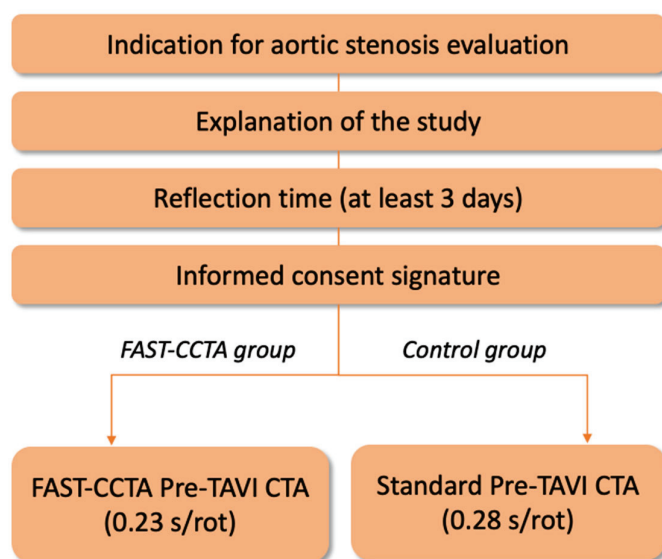


Figure 1. Study flowchart.

Exclusion criteria: Patients unable to hold their breath, deaf, or incapable of discernment. Estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m². Severe allergy to iodinated contrast medium, manifest thyrotoxicosis. Presence of acute conditions including hemodynamic instability or cardiogenic shock, acute pulmonary edema, exacerbated chronic obstructive pulmonary disease, acute coronary syndrome, pulmonary embolism, or aortic syndrome. Pregnant and breast-feeding women. Patients with prior coronary artery bypass grafting (CABG). Patient psychiatric or psychological conditions undermining the ability to understand study procedures and provide informed consent. Vulnerable subjects.

2.3. Characteristics of Participants, Randomization, and Blinding

Most patients screened for aortic stenosis are septuagenarians, even in lower-risk trials [16]. Women of childbearing age are unlikely to undergo aortic stenosis work-up. For this reason, we set the minimum age for eligibility at 50 years. The study population is limited to subjects scheduled to undergo transcatheter aortic valve implantation (TAVI) or surgical aortic valve replacement because (a) CT-based coronary artery analysis is not required in the standard of care during aortic stenosis assessment since patients undergo ICA, and (b) CT is performed without β -blockers.

Randomization will be performed using the sequentially numbered, opaque sealed envelopes (SNOSE) method with a 1:1 allocation. The randomization list will be electronically generated using R (The R Foundation for Statistical Computing Platform, version 4.1.2) and placed in envelopes before the first patient is included.

The study will be single-blinded to minimize biases for the radiologist reading the images for the study's purpose. The radiologists reporting the CT for clinical needs (aortic valve assessment) will not be blinded to the assigned group.

2.4. Processes and Interventions

Patients are enrolled as follows. Each time a cardiac CT appointment for aortic stenosis assessment is required, the investigators will contact the patient unless the inclusion/exclusion criteria are unmet. All patients potentially eligible for the study will be approached by phone. The investigators will comprehensively explain the study type, its purpose, CT examination specifics, planned study duration, and anticipated risks and benefits. Interested patients will be sent the patient information sheet via email or regular mail, allowing them ample time to make an informed decision regarding their participation in the investigation. On day 0, subjects will have the opportunity to ask any questions about the study, and those willing to participate will proceed to sign the informed consent

sheet. Subsequently, after randomization, the participants will undergo cardiac CT with or without FAST-CCT based on their assigned group.

2.5. Measured Outcomes

The primary endpoint of this study will be to evaluate the rate of CCTAs with coronary motion artifacts hindering interpretation in patients undergoing cardiac CT before aortic stenosis treatment, with fast (0.23 s/rot) vs. standard (0.28 s/rot) rotation speed. Two radiologists blinded towards the gantry rotation speed will assess motion artifacts on coronary segments with a diameter of at least 1.5 mm, using an ordinal scale as previously published [17]: “excellent (no artifacts; score = 4), good (minor artifacts, good diagnostic quality; score = 3), adequate (moderate artifacts, acceptable for routine clinical diagnosis; score = 2), or poor (severe artifacts impairing accurate evaluation, segment classified as non-evaluable; score = 1)”. Examples of each qualitative motion artifact rating score are provided in Figure 2. The rate of CCTAs with coronary motion artifacts hindering interpretation will thus be defined as (CCTAs with any segment score = 1/total CCTAs). The rationale behind the choice of this primary endpoint is that only CCTAs without motion artifacts can provide clinical value.

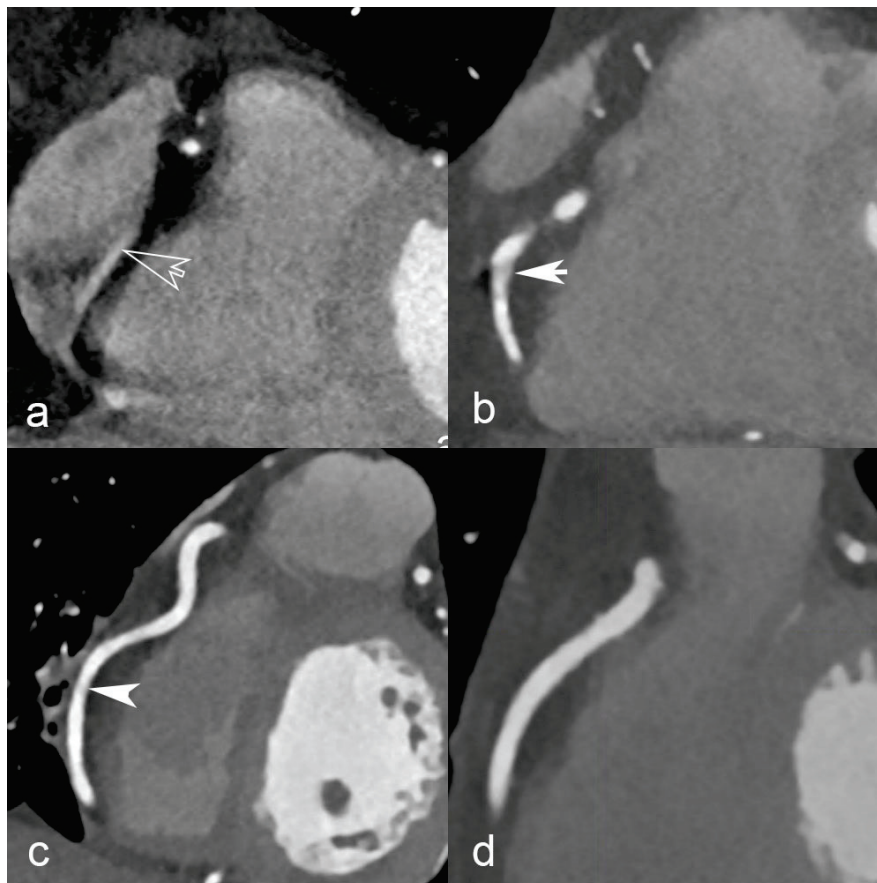


Figure 2. Examples of coronary CT angiography images illustrating the range of motion artifact magnitudes. Each panel corresponds to a qualitative rating on a 4-point scale: (a) poor, open-headed arrow indicates severe artifacts impairing accurate evaluation, segment classified as non-evaluable; score = 1, (b) adequate, white arrow indicates moderate artifacts, acceptable for routine clinical diagnosis; score = 2, (c) good, white arrowhead indicates minor artifacts, good diagnostic quality; score = 3, and (d) excellent, no artifacts; score = 4.

The secondary endpoints (comparison between arms) will be the following: difference assessable coronary segments rate; diagnostic accuracy against ICA; motion artifact magnitude per segment; quantitative image quality measured with contrast-to-noise ratio

(CNR); patient ionizing radiation dose; TAVI sizing efficacy. Assessable coronary segments will be defined with the same score as the primary endpoint. For the diagnostic accuracy against ICA endpoint, coronary stenoses will be assessed and compared with stenoses values from the ICA reports. TAVI sizing efficacy will be assessed by evaluating motion artifacts as either present or absent. These artifacts are defined as an annular double contour with unclearly defined measurement targets for diameter, perimeter, and area. Finally, in the overall study cohort, multivariate analysis will be conducted to assess predictors of unsuccessful CCTA. The rationale behind choosing these secondary endpoints is that they all measure quality (or safety). CNR will be calculated using the following formula:

$$\text{CNR} = \frac{|\text{mean CT number}_{\text{lumen}} - \text{mean CT number}_{\text{fat}}|}{\sqrt{\frac{1}{2}(\text{SD}_{\text{lumen}}^2 + \text{SD}_{\text{fat}}^2)}} \quad (1)$$

where “lumen” is obtained from a region of interest in the coronary lumen, and “fat” is obtained from a region of interest in the pericardial fat.

2.6. Data Management

Trial data is securely stored on a REDCap database, a broadly used HRA-compliant data collection application [18], assuring traceability of data editing with hourly automatic backups (audit trail). Data will be coded and archived for at least 10 years after study termination or premature termination of the study.

2.7. Safety Considerations

Patients screened for inclusion will all have a clinical indication for a cardiac and aortic CTA as part of the aortic stenosis work-up. This applies to enrolled participants and those who decline to participate, ensuring an equal administration of intravenous iodinated contrast media and radiation dose for all cases. However, patients enrolled in the fast rotation group may potentially experience lower radiation dose exposure.

Device deficiencies (DDs) and adverse events (AEs), including serious adverse events (SAEs), will be diligently collected, thoroughly investigated, and documented in both the source document and electronic case report form (CRF) maintained on the REDCap throughout the entire investigation period. Patients who agree to participate will not be subjected to any additional procedures or follow-up visits.

2.8. Type of Data

The following clinical and laboratory data will be collected: serum creatinine (and estimated glomerular filtration rate); height, weight, body mass index (BMI); dyslipidemia; current or past smoking; hypertension; diabetes; family history of CAD; hypersensitivity reaction to iodinated contrast medium; heart rate before and during CCT acquisition.

Cardiac CTA and ICA imaging data will be stored electronically in a picture archiving and communication system (PACS).

Radiation exposure data, including dose measurements, will also be collected for patients in both groups.

2.9. Statistical Analysis

The null hypothesis postulates no statistically significant difference in the coronary artery non-interpretability rate due to motion artifacts in both study groups. Conversely, the alternative hypothesis suggests a statistically significant difference in the study groups' coronary artery motion artifact rate.

Statistical analysis will be conducted using R (The R Foundation for Statistical Computing Platform, version 4.1.2). The results will be presented as the number of subjects (percentage), mean ($\pm$ SD), or median (IQR) for non-normally distributed data unless otherwise specified. Data normality will be assessed using the Shapiro–Wilk test. The rate of diagnostic CCTA in each arm will be compared using the chi-squared test. Additionally,

further bivariate statistical analyses will be conducted employing chi-squared, Wilcoxon two-sample, or Student's *t*-tests where appropriate.

In the overall cohort, factors associated with unsuccessful coronary artery analysis will be assessed through binomial logistic regression, with the following independent variables: gantry rotation speed, heart rate, body mass index (BMI), age, sex, and coronary artery calcium score. The significance level will be two-sided, $\alpha = 0.05$. Interobserver agreement for qualitative ratings will be evaluated using weighted kappa coefficients and interpreted as follows: ≤ 0.4 , poor; 0.4–0.75, fair to good; > 0.75 , excellent.

2.10. Ethical Considerations and Declarations

The study protocol (version 2, 2 February 2023) was approved by the ethical committee of the Canton de Vaud (CER-VD) on 31 May 2023 (protocol number 2023-D0002). The study complies with the principles of the Declaration of Helsinki and was registered on ClinicalTrials.gov (NCT05709652). Only participants who give written informed consent will be included.

2.11. Study Status and Timeline

The study is not open yet. The recruitment is expected to begin in 2023 and be completed by the end of 2025.

3. Discussion

3.1. Rationale of the FAST-CCTA Study

Technological advances in gantry maximum rotation speed are on the rise. Improved rotation speeds have been shown to result in improved image quality and motion artifacts [19–26]. With a rotation speed of 0.35 s/rot, Kojima et al. defined an upper heart rate limit of 60 bpm for image quality in CCTA with ultra-high-resolution CT [27]. Few studies are focused on the benefit of improved gantry rotation time. In a retrospective study including 160 patients, Beeres et al. found that 0.28 s/rot and 0.33 s/rot reduced motion artifacts but resulted in more streak artifacts, image noise, and reduced image quality for whole chest CT scans [28]. In a preliminary study including 50 consecutive patients with elevated (> 70 bpm) heart rates without β -blockers, Belsack and al. found subjective improvements in image quality with 0.23 s/rot [29]. To our knowledge, there are no peer-reviewed published data of prospective studies on the impact of FAST-CCT on coronary motion artifacts in the absence of β -blocker premedication.

This study is anticipated to have a significant clinical impact given the potential improvement in the rate of diagnostic-quality images and the feasibility of performing CCTA without the need for β -blocker premedication. The results are expected to be scientifically robust due to the study's prospective design, randomization, and power analysis.

3.2. Limitations of the Study Design

There might be a bias due to patient selection. As our study includes patients referred for aortic valve stenosis assessment, the population will predominantly consist of elderly patients with a likely high prevalence of coronary artery disease. These patients are more prone to poor image quality than younger patients' normal coronary arteries. However, this is not a concern, as it would lead to an underestimation, rather than overestimation, of the benefits of improved gantry rotation on image quality. Another limitation of the selected population is the range of heart rates, which may differ from the general population undergoing routine CCTA.

3.3. Dissemination

Once terminated, study results will be submitted for publication in a peer-reviewed scientific journal. We intend to communicate the results to the public via scientific media outlets if the results are compelling enough. We will implement substantial amendments only following a formal agreement by the external ethics committee.

Author Contributions: G.F.: bibliography, writing, and editing of the draft. G.G., A.T., S.F., A.-M.J., H.L., D.R., O.M., C.P. and S.D.Q.: draft editing and validation. D.C.R.: principal investigator and sponsor representative, concept, study design, management, and draft editing. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study protocol (version 2, 2 February 2023) was approved by the ethical committee of the Canton de Vaud (CER-VD) on 31 May 2023 (protocol number 2023-D0002).

Informed Consent Statement: Only participants who give written informed consent will be included.

Data Availability Statement: This protocol presents no patient data.

Conflicts of Interest: D.C.R.: consultancy for GE Healthcare. O.M.: research grant & honoraria for Edwards and honoraria for Abbott. S.F.: honoraria for Abbott & Edwards. The other authors declare no competing interest.

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Case Report

Aorto-Esophageal Fistula Caused by Vascular Malformation: A Case Description and an Analysis of the Literature

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Abstract

Aorto-esophageal fistula (AEF) is a condition with an extremely high mortality rate that often causes massive gastrointestinal bleeding, commonly resulting from esophageal perforation due to foreign bodies or aortic aneurysmal malformations. This case report introduces an elderly male patient who experienced hematemesis for longer than 16 h without obvious cause. The patient did not receive relief from endoscopic compression hemostasis. Through computed tomography angiography (CTA), a tortuous and thickened vessel was found in the descending aorta of the patient, which entered the esophagus. The diagnosis was AEF caused by vascular malformation, which has not been previously documented in the literature.

Keywords: aorto-esophageal fistula; computed tomography angiography; surgery

1. Introduction

Aorto-esophageal (AEF) is a rare and potentially fatal condition. The first confirmed case was reported in 1818, and successful treatment of AEF was not achieved until 1980 [1]. Due to diagnostic challenges and high misdiagnosis rates, AEF often leads to life-threatening gastrointestinal bleeding with a poor prognosis. Early recognition, accurate diagnosis, and prompt intervention are critical for improving patient outcomes. This article presents a rare case of primary AEF caused by vascular malformation, accompanied by a literature review. The mortality rate of AEF is extremely high. Early diagnosis and surgical treatment are of great help to the survival and prognosis of patients.

2. Case Report

A 60-year-old male was admitted to Shuangliu First People's Hospital in Chengdu, Sichuan Province, with a chief complaint of hematemesis for longer than 16 h without obvious cause. The patient had no infection or trauma and had not swallowed any hard foreign objects such as pig bones, duck bones, metals, etc. Endoscopy revealed massive fresh blood and clots in the esophagus, with a jet-like bleeding site located 30 cm from the incisors. Hemostatic clips (10 in total) were deployed but failed to control the hemorrhage, which continued to gush through the gaps between the clips. A Sengstaken–Blakemore tube was then placed for tamponade, but the gastric cavity remained filled with blood, obstructing further visualization. During the procedure, the patient experienced cardiac arrest for approximately 20 min. After resuscitation, the patient was transferred to the West China Hospital of Sichuan University for further management.

Chest computed tomography angiography (CTA) demonstrated discontinuity in the mid-esophageal wall, with swelling of the surrounding soft tissue swelling, effusion, and gas accumulation. A tortuous vascular structure (diameter: 0.5 cm) originating from the descending thoracic aorta extended into the esophageal lumen (Figure 1). The esophageal cavity also exhibited a high-density shadow, which progressively increased, suggesting active bleeding (Figure 2). Laboratory tests revealed severe anemia (RBC: $1.83 \times 10^{12}/L$, Hb: 58 g/L, Hct: 0.18 L/L), thrombocytopenia ($91 \times 10^9/L$), and hypoalbuminemia (26.0 g/L).

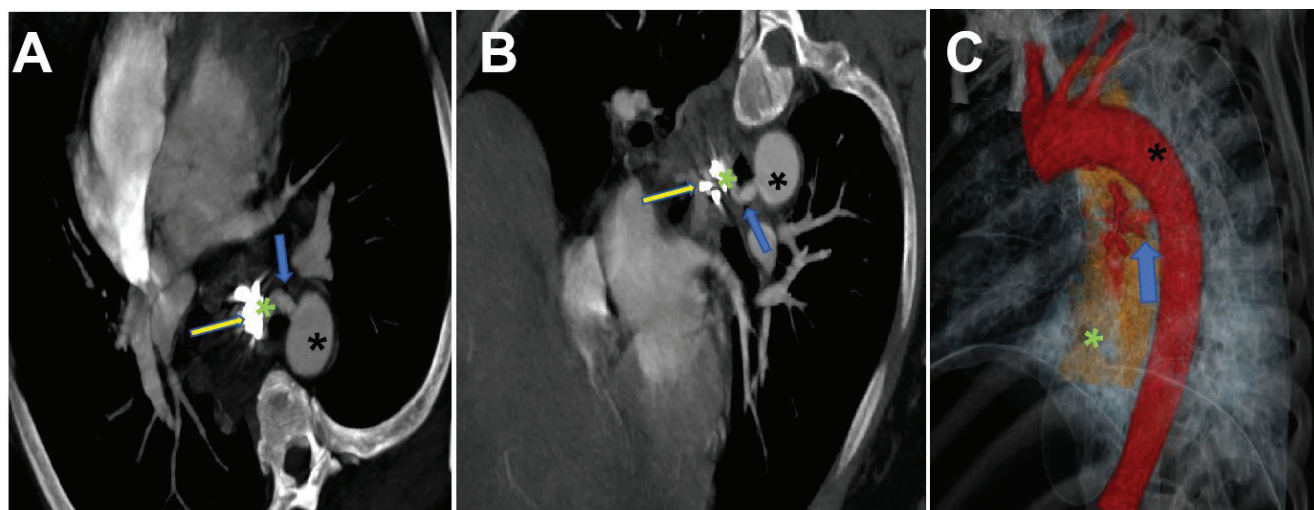


Figure 1. Axial MIP reconstruction (A), oblique coronal MIP reconstruction (B), and volume-rendered (VR) reconstruction (C) demonstrate a branching vessel (blue arrow) originating from the proximal descending aorta (black *) communicating with the esophagus (green*). High-density hemoclip artifacts are visualized within the esophageal lumen (yellow arrow). The VR image reveals significant blood pooling (blue arrow) in the esophageal cavity (green *).

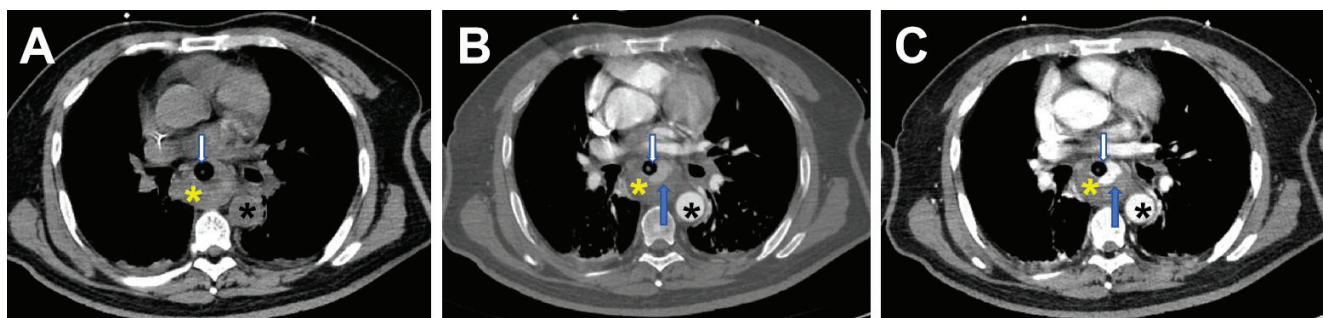


Figure 2. CTA examination: Non-contrast scan (A), arterial phase (B), and portal venous phase (C) images demonstrate a high-density enhancing shadow in the esophageal lumen (yellow *) on the non-contrast scan. During the arterial phase, a “crescent-shaped” higher-density shadow (blue arrow) is observed, which increases over time (C), suggesting active bleeding within the esophagus. A triple-lumen two-balloon tube is seen in the esophageal lumen (white arrow). Descending thoracic aorta (black *).

The patient underwent emergency thoracabdominal aortography+thoracic aortic stent placement surgery in the hybrid room under general anesthesia. Pigtail catheter angiography revealed a patent descending aorta, with a proximal branch vessel communicating with the esophagus, showing ill-defined patchy contrast staining in the adjacent esophageal region, while the descending aorta and its branches remained patent (Figure 3). After exchanging for a super-stiff guidewire, a Medtronic VAMF3232C200TE stent graft (Medtronic Inc., Parkmore Business Park West, Galway, Ireland) was used. The stent was deployed

with its proximal end distal to the origin of the left subclavian artery and its distal end in the lower thoracic aortic segment. Follow-up angiography demonstrated patent blood flow within the stent and no contrast extravasation (Figure 4), with no visualization of the previously noted descending aortic branch vessel.

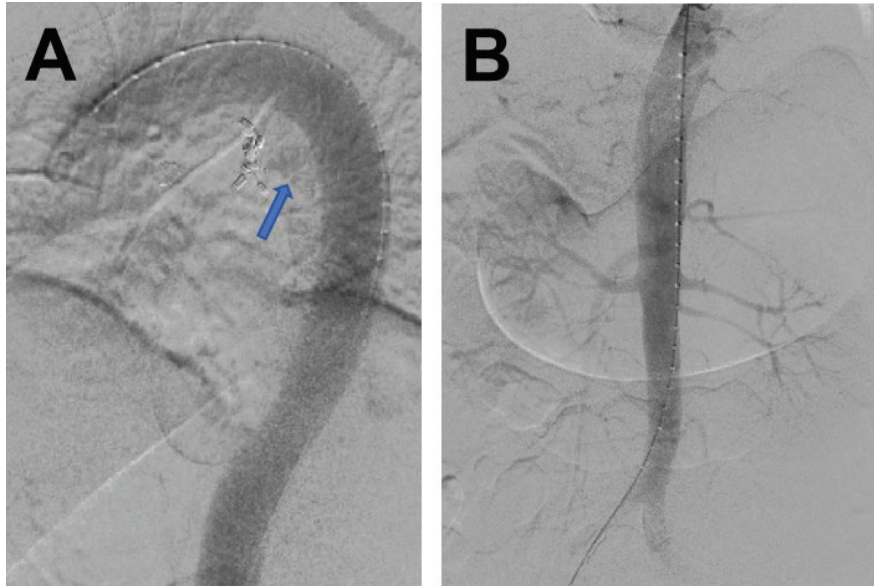


Figure 3. The descending aorta demonstrates patency throughout its course. At the proximal segment, a branching vessel (blue arrow) is observed communicating with contrast extravasation into the adjacent esophageal lumen (Panel A). The descending aorta and its major branches remain fully patent without evidence of obstruction or flow limitation (Panel B).

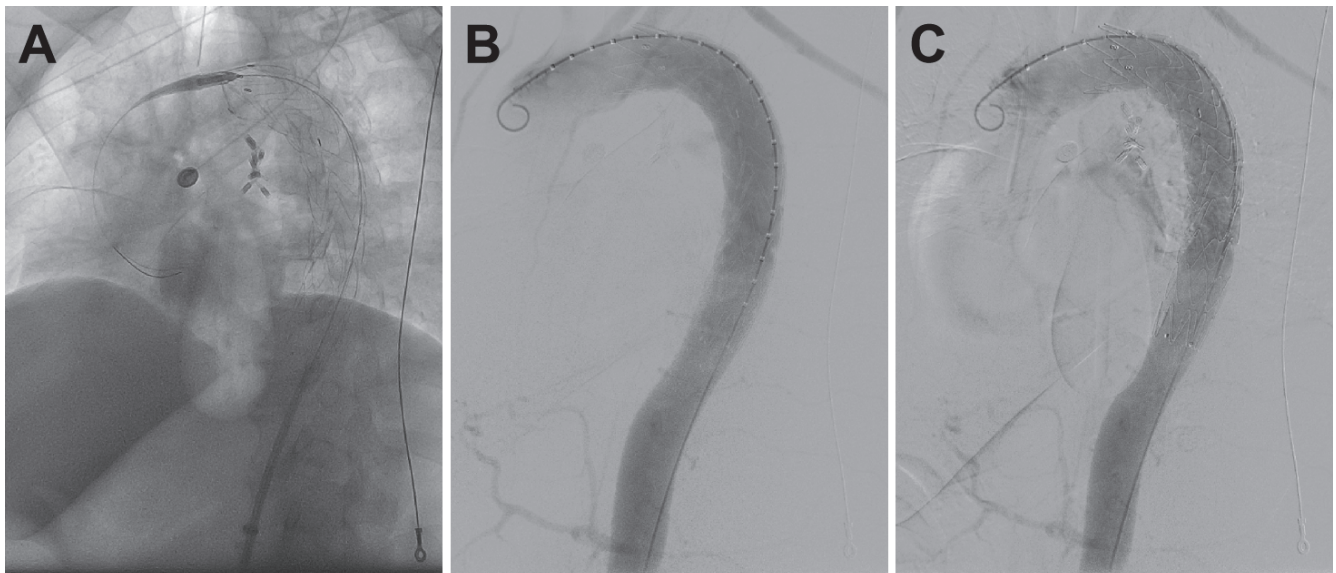


Figure 4. (A–C) Following endovascular stent deployment over the guidewire, follow-up angiography demonstrated Patent stent lumen with unimpeded blood flow and the absence of contrast extravasation.

The patient was postoperatively transferred to the intensive care unit for further management. Despite receiving packed red blood cell transfusions, fresh frozen plasma infusions, and intramuscular medications, the patient's hemoglobin levels continued to decline progressively. No clinical improvement was achieved, and the patient was declared deceased 12 h after the surgical procedure.

3. Discussion and Conclusions

AEF is a rare disease that can cause massive gastrointestinal bleeding. Based on its etiology, it can be classified into primary AEF or secondary AEF. Primary AEF refers to cases in which esophageal foreign bodies, diseases (including aortic aneurysms, esophageal cancer, bronchogenic carcinoma, etc.), or thoracic trauma impair the aortic wall, with aortic rupture being the most common cause. Secondary AEF mostly occurs in patients with a history of aortic surgery or adjacent organ surgery [2]. The development of AEF is related to the anatomical structure of the esophagus and thoracic aorta. Foreign bodies and esophageal cancers frequently occur at the site where the esophagus passes behind the left main bronchus and crosses with the thoracic aorta (the second esophageal constriction), and this is also the most common site for AEF formation [3]. Additionally, infections or atherosclerotic changes in the aortic wall at this location can lead to localized arterial dissection, aneurysms, or pseudoaneurysms. Combined with the reduced elasticity of atherosclerotic vessel walls and vascular compression on the esophagus, this may result in ischemic necrosis of the esophageal wall, ultimately forming an aorto-esophageal fistula [4].

The typical clinical manifestation of AEF is characterized by Chiari's triad: retrosternal pain, sentinel bleeding, and intermittent massive fatal hemorrhage [5]. Retrosternal pain may be caused by the expansion or penetration of arterial/esophageal lesions. The initial "sentinel bleeding" may present as intermittent or minor gastrointestinal bleeding, likely related to temporary hemostasis from blood clots blocking the fistula. As clots dissolve, dislodge, or become infected, or as continued bleeding increases pressure on the rupture site, larger ruptures may occur, leading to a fatal hemorrhage manifesting as massive hematemesis. However, some patients may experience fatal bleeding during their first episode [6–8].

AEF is challenging to diagnose, and few patients present with all three components of Chiari's triad. Hollander et al. [2] reported that 59% of patients experienced chest pain and 65% had "sentinel bleeding," while only 45% manifested the complete triad. Consequently, primary AEF is frequently misdiagnosed in clinical practice. Once massive bleeding occurs, mortality is extremely high, making early diagnosis crucial for a better prognosis. The literature indicates that endoscopy is the most sensitive and specific diagnostic method for AEF [9]. However, the role of endoscopy in diagnosing AEF remains controversial due to its complexity and risk of inducing fatal hemorrhage [10]. For patients with high suspicion of AEF, non-invasive methods like a CT scan or CTA may be preferable. The characteristic CTA findings in AEF typically include an incomplete aneurysm wall, contrast extravasation, and mediastinal free gas [5].

AEF has an extremely high mortality rate, and there are currently no reported cases of successful endoscopic hemostasis for AEF-induced massive gastrointestinal bleeding [11,12]. Surgery remains the primary treatment for AEFs, though there is no consensus on the optimal surgical approach [13–16]. Takeno et al. [17] analyzed the correlation between different surgical approaches and patient outcomes. Endovascular aortic repair is often preferred as the initial surgical option due to its minimal invasiveness and effective hemostasis. For an AEF caused by esophageal lesions, esophagectomy is the treatment of choice. Li et al. [18] found that conservative treatment of AEFs carries an extremely high mortality rate, with hemorrhagic shock, sepsis, and multiple organ failure being the main risk factors for death. The combination of aortic replacement and esophagectomy can significantly improve patient survival and prognosis.

The present patient presented with "hematemesis without obvious cause" and had no history of stent implantation, esophageal foreign bodies, ulcers, inflammation, or tumors. The absence of previous melena ("sentinel bleeding") or Chiari's triad made the case particularly misleading, leading to an initial misdiagnosis of conventional gastrointesti-

nal bleeding. The referring hospital performed an endoscopy to investigate the bleeding source, revealing jet-like arterial bleeding in the esophageal lumen that was unresponsive to hemoclip placement or balloon tamponade, prompting the transfer to our institution. Our chest CTA revealed a tortuous, enlarged vessel originating from the proximal descending aorta and traversing into the esophageal lumen, with a discontinuous adjacent esophageal wall and surrounding free gas, confirming the diagnosis of AEF. This represents a rare case of a primary AEF caused by a vascular malformation, previously unreported in the literature [17]. CTA precisely identified the bleeding source, vascular anomaly location, and its relationship with adjacent structures, providing crucial guidance for surgical planning. The non-invasive nature of CTA also avoided the risk of provoking or exacerbating bleeding during diagnostic procedures. Unfortunately, the malformed vessel originating from the thoracic aorta exhibited a high flow volume and pressure, and even after aortic stent placement, bleeding from the ruptured anomalous vessel persisted. Combined with the patient's massive blood loss prior to admission and brief cardiac arrest, and continuously decreasing postoperative hemoglobin levels, the patient rapidly succumbed despite resuscitation efforts.

Although AEF is clinically rare, its high mortality necessitates increased clinical awareness. Early diagnosis and prompt surgical intervention are critical for improving survival rates. Patients with gastrointestinal bleeding and risk factors for AEF (including a history of esophageal foreign bodies [retained or removed], esophageal cancer, esophageal stent placement, aortic dissection stent placement, or aortic aneurysms) should be carefully evaluated for possible AEF. A timely chest CT scan, aortic CTA, or even aortography should be performed for accurate diagnosis. Regardless of the etiology, early surgical intervention remains the best potential life-saving approach for AEF patients.

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Informed Consent Statement: Written informed consent was provided by the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Review

Coronary Computed Angiography and Coronary Artery Calcium Score for Preoperative Cardiovascular Risk Stratification in Patients Undergoing Noncardiac Surgery

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Abstract

Perioperative and long-term postoperative major adverse cardiovascular events (MACE) are a leading cause of morbidity and mortality in patients undergoing noncardiac surgery. In selected high-risk patients, when information about cardiovascular status may influence surgical decisions, preoperative risk stratification is reasonable, with stress imaging being the preferred method. Coronary computed angiography (CCTA) and coronary artery calcium score (CACS) offer direct anatomical assessment of atherosclerotic coronary arteries and help gauge the extent and severity of coronary artery disease. Strong evidence supports that CCTA and CACS, either alone or in combination, are reliable methods for assessing the risk of both perioperative and long-term postoperative MACE, often demonstrating equal or superior prognostic performance compared to traditional imaging tools. Moreover, integrating CCTA or CACS into standard preoperative imaging protocols further enhances perioperative risk prediction and improves the ability to accurately stratify patients. Future research is needed to better define the role of CCTA and CACS in preoperative cardiovascular risk evaluation of patients undergoing noncardiac surgery.

Keywords: coronary artery calcium score (CACS); coronary computed tomography angiography (CCTA); major adverse cardiovascular events (MACE); noncardiac surgery; preoperative risk stratification

1. Introduction

Cardiovascular perioperative complications are common and are associated with increased 1-year postoperative mortality [1]. The incidence of postoperative major adverse cardiac events (MACE) varies widely between different examined cohorts, ranging from 1.8% to 25% [2–4]. Older patients with existing cardiovascular disease or comorbidities (diabetes mellitus, kidney dysfunction, etc.) are at higher risk for perioperative cardiovascular complications and cardiac death [5–7]. Importantly, poor functional status and reduced exercise capacity—defined as metabolic equivalents (MET) of less than 4—have been consistently linked with increased risk of poor postoperative outcomes [8]. This

high-risk population should undergo preoperative risk evaluation to determine whether further strategies (guideline-directed medical therapy, revascularization, etc.) should be employed to reduce the risk and if the benefits of the surgery override the relevant risks. The ACC/AHA guidelines state that stress testing can help stratify risk and guide management in patients suspected of high-risk ischemia [8]. In a similar manner, the 2022 European Society of Cardiology (ESC) supports stress imaging in high-risk noncardiac surgery with poor functional capacity, high likelihood of coronary artery disease (CAD), high clinical risk according to the Revised Cardiac Risk Index (RCRI), or previous coronary revascularization [9].

Coronary computed tomography angiography (CCTA)—an important diagnostic tool for noninvasive anatomic evaluation of CAD—has been extensively investigated as an imaging modality for cardiovascular risk stratification. Both the Appropriate Use Criteria for Cardiac Computed Tomography (2010) [10] and the 2014 ACC/AHA guidelines [11] stated that there are no appropriate indications for using CCTA in preoperative evaluations for noncardiac surgery. However, in light of new evidence, the latest 2022 ESC guidelines and most recent 2024 ACC/AHA guidelines recognize the role of CCTA in assessing suspected CAD in select patients [8,9]. Indeed, numerous observational studies have demonstrated that CCTA as well as coronary artery calcium score (CACS) measurement are reliable options for perioperative risk stratification, yielding outcomes comparable to those of traditional imaging methods [12–15]. In this narrative review, we explore whether CCTA or CACS can effectively stratify the risk of patients prior to noncardiac surgery.

2. Perioperative Risk Stratification

2.1. CCTA

CCTA is recommended as the initial test for evaluation of patients with low-to-intermediate risk for CAD [16]. Thanks to its high negative predictive value (NPV), CCTA acts as a gatekeeper for invasive coronary angiography (ICA) [17].

In the surgical population, given that no existing evidence has demonstrated that preoperative revascularization reduces postoperative MACE and cardiac mortality [18], the 2024 ACC/AHA guidelines recommend against routine CCTA preoperative imaging and support the use of CCTA in select high-risk patients [8]. CCTA has shown comparable or even superior performance compared to tools like the RCRI and other imaging modalities, such as dobutamine stress echocardiography (DSE) or myocardial perfusion imaging (MPI), for accurately estimating cardiovascular risk and predicting postoperative MACE [19,20].

Previous studies have demonstrated a higher risk of MACE in patients diagnosed with obstructive CAD (stenosis > 50% or >70% on CCTA) [19,21–23]. Ahn et al. investigated 239 patients undergoing intermediate risk noncardiac surgery and reported a more than five-fold increase in postoperative events, including cardiac death, acute coronary syndrome, pulmonary edema, and arrhythmias, in patients with significant (>50%) coronary stenosis on CCTA [21]. Similarly, Hwang et al. reported an increased risk of perioperative major cardiac events in patients with significant stenosis. There was an exponential risk with higher stenosis severity (OR: 6.1, 95% CI: 2.7–14 for stenosis > 50% vs. OR: 8.4, 95% CI: 3.6–19.6 for stenosis > 70%) [22].

Significant stenosis on CCTA has also been found to have an additive value on the prognostic performance of RCRI, a commonly used risk model that uses six different clinical risk predictors of perioperative cardiovascular events [24]. Hwang et al. found that the combination of segment involvement score > 3, Duke jeopardy score > 0 and RCRI resulted in a significantly increased area under the receiver operating characteristic curve (AUC) compared to RCRI alone for diagnosing perioperative cardiac events (AUC: 0.757 vs. AUC: 0.631, $p = 0.003$) [22]. Furthermore, CCTA findings can significantly reclassify the risk of

perioperative major cardiac events in patients categorized as having RCRI risk levels 2 and 3. For those with significant CCTA findings, the odds of experiencing such events can increase 3- to 17-fold compared to patients with non-significant findings ($p < 0.05$). Based on these findings, the authors highlighted the usefulness of CCTA in further stratifying the risk of patients with an RCRI of 2 or 3 [22].

Li et al. investigated the impact of CCTA findings on surgery cancellation in a study involving 841 older patients (mean age 69.5 ± 5.8 years) with unknown or suspected CAD. Their findings revealed that the likelihood of canceling scheduled surgeries increased with the severity of coronary stenosis and the number of affected coronary arteries [23].

On the other hand, while CCTA possesses excellent ability to exclude nonsignificant CAD, false-positive findings due to calcium blooming artifacts and coronary lumen caliber underestimation are common [25]. Sheth et al. investigated the composite outcome of perioperative cardiovascular death and non-fatal myocardial infarction (MI) in patients with or at risk of atherosclerotic CAD undergoing noncardiac surgery [19]. The study found that combining CCTA findings with the RCRI, compared with RCRI alone, correctly reclassified as being at higher risk 17 out of 77 patients who experienced a perioperative event ($p < 0.001$). However, using CCTA also led to an overestimation of the risk of 98 out of 923 patients who did not experience a perioperative event. The last finding is of great importance since overestimation of the cardiovascular risk in patients scheduled for surgery imposes great risks, including redundant further cardiovascular evaluation and potentially detrimental surgery delay or even cancellation. Studies that have evaluated diagnostic and prognostic significance of preoperative CCTA are described in Table 1.

Table 1. Studies evaluating the preoperative use of coronary computed tomography angiography.

Author	Year	Study Design	Total Patients, <i>n</i>	Age, Years Mean $\pm$ SD	Type of Surgery	Objective	Key Findings	Follow-Up Period
Sampaio Rodrigues et al. [14]	2024	R	229	66 ± 5	OLT (patients with intermediate to high pre-operative cardiac risk)	Assess the predictive value of CCTA for postoperative cardiovascular events	CAD-RADS ≥ 3 but not CACS significantly increased MACE risk	4 years
Shalaeva et al. [12]	2022	P	199	62 ± 7	Partial foot amputations (patients with type 2 diabetes and peripheral artery disease)	Assess the predictive value of CCTA for 1-year all-cause mortality	Two- and three-vessel obstructive CAD on CCTA increased all-cause mortality risk; any obstructive CAD was associated with higher MACE risk	1 year
Walpot et al. [26]	2022	P	735	70 ± 9	Noncardiac surgery (patients with atherosclerotic risk factors or a history of congestive heart failure)	Assess if subendocardial attenuation using coronary CCTA predicts perioperative MACE	Normalized subendocardial attenuation independently and incrementally predicted 30-day MACE in a model including RCRI and CAD severity	1 month
Kim et al. [13]	2021	R	628	53 ± 8	OLT	Assess the predictive value of CCTA for late postoperative cardiovascular events	Mixed plaque, obstructive CAD, 1- and ≥ 2 -vessel CAD, and a CACS > 400 were significantly associated with MACEs within five years after liver transplant	5 years

Table 1. Cont.

Author	Year	Study Design	Total Patients, <i>n</i>	Age, Years Mean $\pm$ SD	Type of Surgery	Objective	Key Findings	Follow-Up Period
Li et al. [23]	2020	R	841	70 $\pm$ 6	High-risk noncardiac surgery (patients with significant CAD)	Assess the predictive value of CCTA for predictors of significant CAD and the event of cancelling scheduled surgery	Surgery cancellations increased with stenosis severity and the number of obstructed major coronary arteries; postoperative medication use increased with stenosis severity	NA
Messerli et al. [27]	2017	P	54	49 $\pm$ 7	Bariatric surgery	Assess the predictive value of CCTA for postoperative cardiovascular events	Absence of coronary stenosis on CCTA ruled out long-term MACE with a 100% NPV	6.1 years (mean)
Fathala et al. [15]	2016	R	93	60 $\pm$ 9	Intermediate- and high-risk noncardiac surgery	Assess the predictive value of CCTA for postoperative cardiovascular events	Normal or nonobstructive CCTA excluded significant CAD and predicted favorable postoperative outcomes	Hospital discharge
Shalaeva et al. [28]	2016	P	179	60 $\pm$ 8	Trans-femoral amputation (patients with type 2 diabetes and peripheral artery disease)	Assess the predictive value of CCTA for perioperative MACE	Patients with $\geq 50\%$ stenosis on CCTA had a higher 6-month MACE rate than those with normal or non-obstructive CCTA; patients with 3-vessel obstructive stenosis on CCTA had a higher 6-month MACE rate than those with two- or one-vessel obstructive CAD	6 months
Hwang et al. [22]	2015	R	844	67 $\pm$ 11	Noncardiac surgery	Assess the predictive value of CCTA for postoperative cardiovascular events	The addition of CCTA to clinical risk assessment improved perioperative risk stratification; absence of significant CCTA findings had high specificity and NPV for perioperative cardiovascular event risk, regardless of clinical risk	1 month
Sheth et al. [19]	2015	P	955	70 $\pm$ 9	Noncardiac surgery (patients with history or risk factors for CAD)	Assess the predictive value of CCTA for postoperative cardiovascular events	Compared to RCRI, CCTA improves risk estimation for perioperative cardiovascular death or myocardial infarction	1 month
Chang et al. [29]	2014	P	91	68 $\pm$ 9	Elective vascular surgery	Assess the predictive value of CCTA for postoperative cardiovascular events	No definitive conclusion was drawn on CCTA's role in preoperative risk evaluation due to low event rates	1 month
Ahn et al. [21]	2013	R	239	70 $\pm$ 10	Intermediate-risk noncardiac surgeries	Assess the predictive value of CCTA for postoperative cardiovascular events	Significant coronary artery stenosis ($>50\%$) and multivessel CAD were correlated with postoperative cardiac events; RCRI combined with CACS or multivessel disease predicted outcomes better than RCRI alone	1 month
Cassagneau et al. [30]	2012	P	82	53 $\pm$ 10	OLT	Assess the predictive value of CCTA for postoperative cardiovascular events compared to DSE	Normal or nonobstructive CCTA had a 95% NPV for MACE and 100% for clinical coronary events; CCTA had a prognostic value comparable to DSE	1 year

Table 1. Cont.

Author	Year	Study Design	Total Patients, <i>n</i>	Age, Years Mean $\pm$ SD	Type of Surgery	Objective	Key Findings	Follow-Up Period
Chae et al. [31]	2012	P	247	56 $\pm$ 7	OLT	Assess the clinical value of CCTA for postoperative cardiac events	3% of patients developed stress cardiomyopathy after surgery, but none experienced a cardiovascular event requiring emergency intervention	3 months
Jodocy et al. [32]	2012	R	54	56 $\pm$ 6	OLT	Assess the predictive value of CCTA for postoperative cardiovascular events	No cardiovascular events occurred during the follow-up period	9–15 months
Tognolini et al. [33]	2012	P	30	52 $\pm$ 15	Bariatric surgery	Assess the diagnostic value of coronary dual-source computed tomography (DSCT) in determining significant stenosis of coronary arteries	CCTA was more accurate than calcium scoring or traditional risk stratification in detecting severe CAD in this population	NA

Abbreviations: CACS, coronary artery calcium score; CAD, coronary artery disease; CAD-RADS, Coronary Artery Disease Reporting and Data System; CCTA, coronary computed tomography angiography; DSE, dobutamine stress echocardiography; DSCT, dual-source computed tomography; MACE, major adverse cardiovascular events; NPV, negative predictive value; OLT, orthotopic liver transplant; R, retrospective; RCRI, Revised Cardiac Risk Index; P, prospective.

2.2. Coronary Artery Calcium Score

CACS is a measure of atherosclerosis burden in the coronary arteries and acts as an indicator of CAD. Closely correlated with the severity of CAD, elevated CACS serves as an independent predictor for mortality and MACE in both symptomatic and asymptomatic patients [34,35].

CACS—alone or in combination with CCTA findings—has been also investigated as a method of preoperative risk stratification. The existing literature attests that an elevated CACS is associated with an increased risk of perioperative cardiovascular events. Studies that have evaluated diagnostic and prognostic significance of preoperative CACS are described in Table 2.

Table 2. Studies evaluating the preoperative use of coronary artery calcium score.

Author	Year	Study Design	Total Patients, <i>n</i>	Age, Years Mean $\pm$ SD	Type of Surgery	Objective	Key Findings	Follow-Up Period
Groen et al. [36]	2024	R	149	58 $\pm$ 9	OLT	Assess the predictive value of non-gated CACS to identify low-risk patients for whom further cardiac imaging could be safely withheld compared to SPECT MPI, CCTA, or ICA and its correlation with perioperative mortality	The NPV of no or mild calcifications on CAC for obstructive CAD on CCTA, and ICA was 100%; additional cardiac imaging could have been safely avoided in ~75% of patients by reviewing existing CAC data	1 month
Choi et al. [37]	2023	R	2554	68 $\pm$ 13	Intermediate- to high-risk noncardiac surgery	Assess the predictive value of coronary calcium estimates from existing non-gated chest CT imaging for perioperative major clinical events	Higher estimated coronary calcium burden values were linked to stepwise increases in perioperative MACE, with additional risk classification improvement when added to an RCRI model	1 month

Table 2. Cont.

Author	Year	Study Design	Total Patients, <i>n</i>	Age, Years Mean $\pm$ SD	Type of Surgery	Objective	Key Findings	Follow-Up Period
Shalaeva et al. [12]	2022	P	199	62 $\pm$ 7	Partial foot amputations	Assess the predictive value of CACS for 1-year all-cause mortality in type 2 diabetes patients with peripheral artery disease	Higher CACS was associated with an increased risk of all-cause mortality and MACE during follow-up	1 year
Yang et al. [38]	2022	R	4491	57 $\pm$ 11	Intermediate-risk lung cancer surgery	Assess the predictive value of prior non-gated CACS for perioperative cardiovascular events	CACS $\geq$ 1, and the number of calcified vessels were independently associated with perioperative cardiovascular events	Hospital discharge
West et al. [39]	2019	R	54	64 $\pm$ 6	OLT	Assess the predictive value of prior non gated CACS for clinically significant CAD compared to ICA	An Agatston score < 4 or Weston score < 2 excluded obstructive CAD, theoretically allowing 24% and 28% of patients, respectively, to avoid catheterization without missing significant cases	NA
Shalaeva et al. [28]	2016	P	179	60 $\pm$ 8	Trans-femoral amputation	Assess the predictive value of CACS for perioperative MACE in type 2 diabetes patients with peripheral artery disease	The postoperative event rate increased from 10% in patients with CACS 1–99 to 84% in those with CACS > 1000; patients with CACS = 0 had no MACE during the follow-up period	6 months
Kong et al. [40]	2015	R	443	52 $\pm$ 8	OLT	Assess the predictive value of CACS for early postoperative cardiovascular complications	CACS > 400 predicted early postoperative cardiovascular complications in OLT recipients	1 month
Ghadri et al. [41]	2012	P	326	71 $\pm$ 9	Elective noncardiac surgery	Assess the predictive value of CACS alone and in combination with SPECT MPI for postoperative cardiovascular events in patients with suspected increased perioperative cardiac risk	The cumulative MACE rate was highest in patients with abnormal SPECT and high CACS and lowest in those with normal SPECT findings and low CACS	40 days
Mahla et al. [42]	2001	P	51	69 $\pm$ 8	Elective vascular surgery	Assess the predictive value of CACS for perioperative myocardial cell injury	Cardiac troponin T elevations occurred only in patients with CACS > 1000; six patients with perioperative cardiac troponin T elevations had a 2.5-fold higher CACS than those without	7 days

Abbreviations: CACS, coronary artery calcium score; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ICA, invasive coronary angiography; MACE, major adverse cardiovascular events; MPI, myocardial perfusion imaging; NPV, negative predictive value; OLT, orthotopic liver transplant; R, retrospective; RCRI, Revised Cardiac Risk Index; P, prospective; SPECT, single-photon emission computed tomography.

In 2001, Mahla et al. examined the preoperative CACS, measured by electron beam computed tomography, in 51 patients undergoing elective vascular surgery. Six patients with elevated postoperative cardiac troponin T levels had a median CACS 2.5 times higher than the remaining 45 troponin-negative patients (2080 vs. 810; $p = 0.021$), suggesting a possible association between preoperative CACS and postoperative cardiac cell injury [42].

Choi et al. investigated 2554 patients having a non-gated chest CT performed within one year before surgery [37]. The authors employed an estimated coronary calcium burden (ECCB) score ranging from 0 to 9 with ECCB: 3–9 scores indicating severe disease ($\geq 50\%$ of the total artery length calcified) in one or two vessels. The authors found that higher coronary calcium burden was associated with a stepwise increase in the rate of postoperative major clinical events (MCE), defined as perioperative mortality and MI (ECCB 0: 2.9%, ECCB 1–2: 3.7%, ECCB 3–5: 8.0%; ECCB 6–9: 12.6%, $p < 0.001$). The odds for perioperative clinical events were twice as high in patients with ECCB > 3 compared to patients with ECCB < 3 (adjusted OR: 2.11, 95% CI: 1.42–3.12). Finally, the study demonstrated that implementing ECCB score in an RCRI model resulted in a significant improvement of the AUC for prediction of MCE (from 0.675 to 0.712, $p = 0.018$), with a net reclassification improvement of 0.428 (95% CI, 0.254–0.601, $p < 0.0001$). Of note, all-cause death rather than cardiac death was included in the composite primary outcome.

In another study of 4491 patients with lung cancer who underwent intermediate-risk surgery, the presence of coronary calcification (CACS ≥ 1) was associated with increased risk for perioperative cardiovascular events (OR: 1.75, 95% CI: 1.14–2.68) after adjustment for relevant variables [38]. Finally, in a meta-analysis of eleven studies including 3480 patients undergoing noncardiac surgery, a ten-fold increase in risk for perioperative MACE was seen in patients having severe coronary calcifications (CACS ≥ 1000 vs. CACS < 1000 , OR:10.4, 95% CI 1.6–69.7) [43].

In terms of prognostic performance, a previously used CACS cut-off of 113 demonstrated an NPV of 97% for postoperative cardiac events in patients undergoing intermediate-risk noncardiac surgery, highlighting the strong ability of CACS to identify patients at low risk for perioperative events [21].

It remains unclear whether preoperative CACS measurement has different predictive value in men versus women. This is an important gap, as prior large cohorts have shown that women with CACS > 100 have significantly higher cardiovascular mortality compared to men [44]. No available studies in the existing literature have directly compared CAC burden and postoperative outcomes stratified by gender, but most available analyses were adjusted for sex using multivariable Cox models, which may partially account for these differences. Notably, women are more likely to present with ischemic equivalents (e.g., fatigue, dyspnea, etc.), making symptom-based evaluation challenging [45]. In such cases, CACS and CCTA may provide more reliable risk assessment and improve diagnostic accuracy.

There are insufficient data in the literature to determine whether CACS, CCTA, or a combination of both is superior for risk stratification of perioperative cardiovascular events. While CACS possesses several advantages over CCTA (easier to perform, no risk for contrast induced allergy/nephropathy, etc.), it cannot adequately evaluate the coronary anatomy and the presence and the extent of non-calcified stenoses. Future comparative studies are needed to address this question.

Example images of calcified and non-calcified coronary arteries are shown in Figures 1 and 2, respectively.

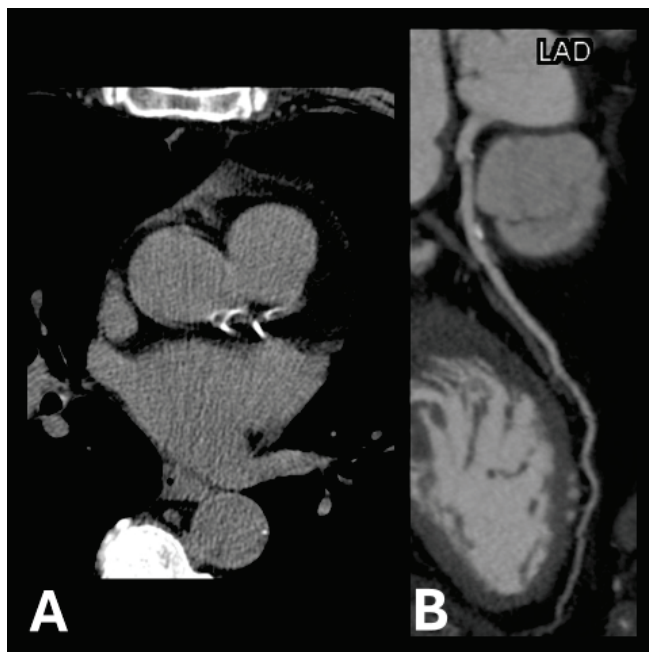


Figure 1. Examples of calcification plaque(s) in (A) left anterior descending artery and left circumflex artery and (B) left anterior descending artery.

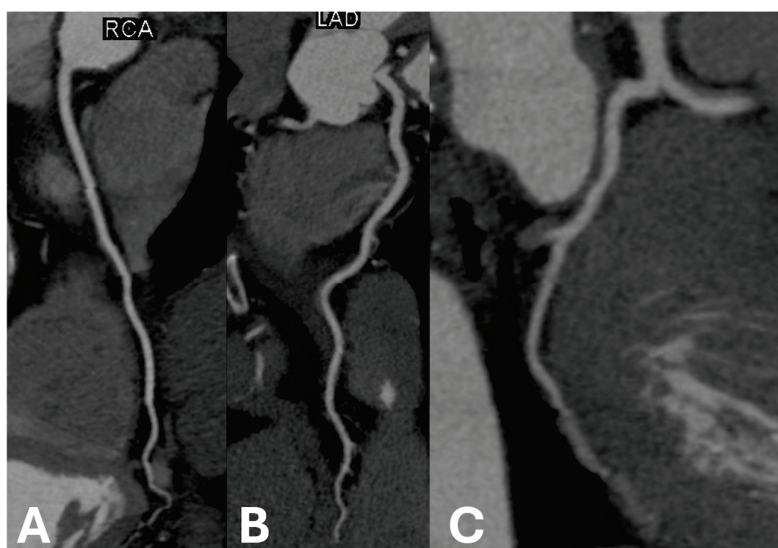


Figure 2. Examples of non-calcified coronary arteries in (A) right coronary artery, (B) left anterior descending artery, and (C) left circumflex artery.

2.3. Fractional Flow Reserve–Computed Tomography (FFR-CT)

FFR-CT is a noninvasive diagnostic tool with great correlation and agreement with invasive FFR and better performance than CCTA alone in diagnosing CAD [46]. Ma et al. investigated the predictive value of machine-learning based FFR-CT in patients scheduled for lung cancer surgery [47]. $\text{FFR-CT} \leq 0.8$ (compared to $\text{FFR-CT} > 0.8$) was associated with 10-fold increased odds for MACE in the perioperative period. Furthermore, when assessing the accuracy for prediction of MACE, FFR-CT outperformed CCTA findings (AUC: 0.737 vs. AUC: 0.524). Given its higher NPV for CAD, FFR-CT could potentially act as a gatekeeper for preoperative ICA when DSE or CCTA results are suspected to be false-positive.

3. Long-Term Outcomes

CCTA findings and CACS have been studied for risk stratification and prediction of long-term cardiovascular events, with coronary atherosclerosis burden emerging as a negative predictor. With a median follow-up of 4 years, Sampaio Rodrigues et al. reported a hazard ratio of 5.8 (95% CI 1.6–20.6) for MACE when significant CAD (stenosis > 50%) was identified preoperatively on CCTA [14]. Another study found a 12-fold increase (OR: 11.97, 95% CI: 5.79–24.75) in MACE for patients with severe coronary calcification (CACS > 400) or obstructive CAD in a follow-up period of 5 years [13]. Finally, when assessing the diagnostic value of CCTA, Cassagneau et al. found a 95% and 100% NPV of CCTA for MACE and coronary events (increase in creatine kinase or troponin, MI, postoperative coronary artery revascularization, etc.), respectively [30]. No significant differences were observed between the diagnostic performances of DSE and CCTA.

4. Revascularization Prior to Noncardiac Surgery

The usefulness of CCTA and CACS findings should be carefully considered given the lack of evidence supporting a strategy of routine revascularization before noncardiac surgery in stable CAD patients [48]. Two large trials (CARP and DECREASE-V) showed no benefit of prophylactic revascularization for short-term outcomes (death, MI, etc.) or long-term survival in vascular surgery patients [18,49]. Of note, left main CAD patients were excluded from both trials. A sub-analysis of the CARP trial, however, showed that revascularization in patients with anterior ischemia on stress imaging reduced long-term death and MI risk [50]. The 2024 ACC/AHA guidelines advise against routine revascularization before noncardiac surgery and recommend it only for traditional indications (e.g., unstable angina, left main disease, or high-risk anatomy) [8]. Perhaps, better stratification of preoperative cardiovascular risk, implementing clinical variables and imaging results, could help identify which patients might benefit from revascularization versus those who might be harmed by unnecessary procedures or delayed surgery.

5. Specific Types of Surgeries

Besides research on patients undergoing noncardiac surgery in general, there are also studies examining specific operation types. One population that has been particularly well studied is patients preparing for liver transplantation (LT) surgery. Patients with cirrhosis (especially metabolic-associated fatty liver disease-associated) are considered as high risk for CAD due to both traditional (obesity, metabolic syndrome, diabetes, and hypertension) and nontraditional risk factors (related to end-stage liver disease) [51]. LT recipients face a higher risk of cardiovascular death and ischemic events compared to the general population matched for age and sex [52]. For this reason and to select the most suitable candidates, LT patients undergo routine cardiac preoperative evaluation, commonly with stress electrocardiography, stress echocardiography, or MPI studies [53].

CCTA has been studied as an alternative imaging modality for preoperative evaluation of LT patients, with adequate ability of ruling out obstructive coronary stenosis [31,32]. More importantly, CACS has been shown to have great predictive ability of perioperative cardiovascular events. Kong et al. reported that patients with severe calcification (CACS > 400) had significantly increased odds for cardiovascular complications one month after LT (OR: 4.62, 95% CI: 1.14–18.72) [40]. Another study with 66 LT recipients undergoing both CACS measurement and ICA showed that a CACS of less than 400 (less than severe calcification) appeared to have a 100% NPV for obstructive CAD [36]. Consequently, the authors suggested there is no need for further CAD evaluation in patients with CACS < 400. A cutoff of 400 was also used by another study which reported a 100%

NPV and estimated that 24% of their cohort could have avoided catheterization without missing any obstructive coronary disease [39].

Regarding vascular surgeries, patients undergoing intermediate-risk surgeries like carotid endarterectomy or endovascular aneurysm repair and high-risk surgeries like open aortic surgeries are usually risk-stratified based on traditional testing with echocardiography and MPI [29]. Prior studies evaluating the role of ICA and selective revascularization in patients undergoing vascular surgeries did not show significant benefit in outcomes [18,54]. However, compared to LT, fewer studies on the use of CACS and CCTA have been performed in this population. In a recent retrospective study of patients undergoing open peripheral artery bypass surgery, patients with known CAD (history of myocardial infarction or revascularization) and those with subclinical atherosclerosis determined by a positive CAC had similar postoperative troponin elevation and heart failure events [55]. Chang et al. evaluated the use of CCTA combined with stress perfusion CT in patients undergoing various vascular surgeries [29]. While CAD was common in these patients, there were only a few cardiovascular events overall, and perfusion defects did not predict perioperative cardiac events. Lastly, Vallier et al. showed that postoperative myocardial injury was better predicted by CCTA when compared to functional testing [56].

Studies on other specific surgery populations, such as bariatric surgery [27,33] and foot amputation in type 2 diabetics [12,28] have been also demonstrated sufficient CCTA and CACS performance in predicting postoperative outcomes.

6. CCTA and CACS in Relation to Other Imaging Modalities

6.1. Dobutamine Stress Echocardiography (DSE)

Data comparing CCTA with other imaging modalities for preoperative assessment were limited until the publication of the PANDA trial in 2020 [57]. In this prospective observational study, 215 patients with more than one clinical risk factor for perioperative cardiovascular events received both DSE and CCTA prior to noncardiac surgery. The authors employed different models for prediction of events, implementing RCRI scores, CCTA findings ($\geq 50\%$ stenosis and/or $\text{CACS} \geq 203$), or DSE abnormal results. They found that combining CCTA findings with the RCRI score significantly enhanced risk stratification compared to the RCRI alone ($p < 0.001$), an improvement not observed with DSE. When DSE plus RCRI were compared head-to-head with significant stenosis on CCTA plus $\text{CACS} > 203$ plus RCRI, the latter model provided significantly better prognostic performance (AUC: 0.713 vs. AUC: 0.839, $p = 0.027$).

6.2. Single-Photon Emission Computed Tomography Myocardial Perfusion Imaging (SPECT MPI) and Stress Cardiovascular Magnetic Resonance Imaging (CMR)

Ghadri et al. assessed the added value of using CACS in combination with SPECT MPI. The study showed that using a cut-off of $\text{CACS} \geq 1314$ improved the risk discrimination both when perfusion studies were normal and abnormal. Most importantly, $\text{CACS} < 1314$ combined with a normal perfusion study predicted lower risk for perioperative events than a normal perfusion study alone. However, this study did not directly compare the predictive value of CCTA with that of SPECT MPI [41]. Similarly, the VISION-CTA trial showed that the predictive accuracy of SPECT MPI for MACE improved significantly when CCTA results (stenosis $\geq 70\%$) were integrated into the risk evaluation [20]. Addition of pathological CCTA results to SPECT MPI led to an increase in NPV for MACE from 75% (CI 34.9–96.8) to 100% (CI 79.4–100). These findings highlight the potential additive value of incorporating CCTA and CACS into routine imaging methods.

CMR is another tool for evaluating myocardial ischemia and has demonstrated higher diagnostic sensitivity than SPECT in detecting angiographically significant CAD [58]. In a

recent study of 669 patients undergoing MPI before intermediate- to high-risk noncardiac surgery, postoperative cardiac event rates were similar between patients who underwent stress CMR and those who had SPECT-MPI [59]. Due to the limited availability of supporting evidence, the 2024 ACC/AHA guidelines do not yet define a clear role for stress CMR in preoperative risk stratification [8]. Overall, there are insufficient data to conclude whether an anatomy-based approach (e.g., CCTA) or an ischemia-based approach (e.g., stress CMR or SPECT) provides superior prognostic value in the preoperative setting.

7. Conclusions

CCTA and CACS have consistently been shown to effectively predict the risk of both perioperative and long-term cardiovascular events. Future studies directly comparing CCTA with standard imaging methods are needed to clarify the optimal role of CCTA in preoperative cardiovascular evaluation for patients undergoing noncardiac surgery.

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Review

Clinical Applications of Cardiac Computed Tomography: A Focused Review for the Clinical Cardiologists

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Abstract

Cardiac computed tomography (CT) has become a cornerstone in the non-invasive evaluation and management of cardiovascular disease, offering clinicians detailed anatomical and functional information that directly influences patient care. This review focuses on three primary clinical applications: coronary artery calcium (CAC) scoring, coronary CT angiography (CCTA), and preprocedural planning for structural heart interventions. CAC quantification remains one of the most powerful prognostic tools for cardiovascular risk stratification, with robust evidence supporting its use in asymptomatic and selected symptomatic individuals. CCTA provides a high-resolution assessment of coronary anatomy and plaque characteristics, guiding both preventive and acute care strategies. In structural heart disease, CT is indispensable for accurate device sizing, procedural planning, and complication avoidance in interventions such as transcatheter valve replacement or repair. Beyond these core applications, cardiac CT supports the evaluation of pericardial, myocardial, aortic, and congenital heart disease, and plays a role in pulmonary embolism risk assessment. Technological innovations—including artificial intelligence, dual-energy imaging, and photon-counting CT—are enhancing image quality, reducing radiation exposure, and broadening the modality's prognostic capabilities. Collectively, these advances are solidifying cardiac CT as an integrated diagnostic and planning tool with a significant impact on clinical decision-making and patient outcomes.

Keywords: coronary artery disease; cardiac computed tomography; structural heart disease

1. Introduction

Since its inception, computer tomography imaging has represented a breakthrough in medicine. The early application of this technology in cardiovascular disease, showcasing its usefulness, dates back to the early 1990s, with coronary calcium quantitation by Arthur S. Agatston representing a significant advancement [1]. Since then, the development of new technologies, such as electron beam CT and subsequently multidetector CT imaging, along with the introduction of ECG gating, has allowed for the non-invasive collection of three-dimensional, high-resolution anatomical and functional data of the heart, coronary arteries, and surrounding structures, with improved temporal and spatial resolution [2].

Initially used for detecting coronary artery calcium, coronary CT imaging has evolved to provide additional prognostic value about plaque burden, composition, and functional significance [3].

The scope of this review is to analyze the three major cardiac CT applications in clinical practice. These applications are as follows: (1) coronary artery calcium quantification (CAC); (2) coronary computed tomography angiography (CCTA); (3) evaluation and planning of structural heart disease interventions.

2. Coronary Artery Calcium Quantification

As was previously stated, coronary artery calcium (CAC) quantification was the first application of CT in cardiovascular disease. Despite certain limitations, due to its relatively wide availability, low cost, and its non-contrast nature, as well as its thoroughly documented prognostic value, it remains one of the most widely used tests in clinical practice to complete cardiovascular evaluation in primary prevention check-ups to this day [4].

2.1. Technique and Clinical Data

The assessment of coronary artery calcium (CAC) involves a non-contrast computed tomography (CT) scan, synchronized with electrocardiography (ECG) to quantify calcified coronary plaque burden. The procedure is rapid, typically completed in a single breath-hold, and does not require intravenous access, premedication, or special patient preparation [4].

Using contemporary imaging techniques, the radiation exposure is approximately 1 to 1.5 mSv, equivalent to the radiation of 2–3 mammograms or approximately 6 months of ambient background radiation [5]. After image acquisition, the total coronary calcium burden is quantified using the Agatston scoring method in a commercially available software, which is derived from the extent and density of calcified plaque within the coronary arteries [4].

Coronary calcium score is a continuous numerical variable. Studies suggest that it has a linear relationship to adverse clinical outcomes. The following classification is widely used as a mean of standardization. Classification: 0 (absent), 1–10 (minimal), 10–99 (mild), 100–399 (moderate), 400–1000 (severe), or >1000 (extreme), although gender and age-based sub-classifications have been shown to provide a more accurate prognostic value, particularly in individuals with scores classifying as “moderate” or young (<45) or older (>70) individuals, in which a score above the 75th percentile should be considered as significant in guiding primary prevention practices [1].

2.2. Rationale and Evidence of CAC Scoring in Cardiovascular Risk Assessment

Multiple algorithms have been proposed to help clinicians identify who is, and who is not, at high risk for CAD, such as SCORE-2 [6] (p2), SCORE-2 OP, Framingham risk scores (FRS), Pooled Cohort Equations, and carotid intima-media thickness, among others. However, coronary artery calcium (CAC) scoring consistently outperforms these tools. In the Multi-Ethnic Study of Atherosclerosis (MESA), involving 6814 asymptomatic adults across four ethnic groups followed for an average of 11 years, individuals with CAC > 300 had nearly a 10-fold increased risk of coronary heart disease (CHD) events compared with those with CAC = 0, even after adjusting for traditional risk factors [7].

The CAC Consortium, pooling over 66,000 asymptomatic individuals with a mean follow-up of ~12.3 years, demonstrated that annualized cardiovascular disease (CVD) mortality was 0.33 per 1000 person-years in patients with CAC = 0, compared to

8.0 per 1000 person-years in those with CAC ≥ 1000 (adjusted hazard ratio [HR] 5.0, 95% CI 3.9–6.5 versus CAC = 0; HR 1.7, 95% CI 1.4–2.1 versus CAC 400–999) [8].

The Dallas Heart Study, which included substantial representations of Black and Hispanic individuals, revealed that though Black participants had lower CAC scores on average, they still experienced disproportionately higher CVD event rates at any given CAC level, indicating potential disparities in calcium-risk thresholds [9].

In a post hoc analysis of the St. Francis Heart Study, a randomized trial of atorvastatin versus placebo in nearly 1000 asymptomatic individuals with elevated CAC (≥ 80 th percentile by age/sex), a median follow-up of 4.8 years showed that untreated eligible participants with CAC > 300 experienced event rates ≥ 17 per 100 person-years, whereas those with CAC < 100 had rates < 1 per 100 person-years. Statin therapy significantly reduced events, and combining CAC with clinical risk improved net reclassification ($p = 0.002$) [10].

The Rotterdam Study, conducted in an elderly European cohort, further confirmed that CAC significantly enhances CHD risk prediction beyond traditional models in older adults [11].

While many studies have focused on using coronary artery calcium (CAC) scoring to identify high-risk patients, evidence suggests that the absence of coronary calcifications (CAC score of zero) is associated with an exceptionally low 10 year cardiovascular event rate. This finding is particularly significant in individuals with a borderline or intermediate atherosclerotic cardiovascular disease (ASCVD) 10 year risk, potentially reclassifying these individuals as low risk and thus aiding in clinical decision-making in regard to holding off or starting statin therapy, and despite current guidelines' recommendation to test CAC scoring in patients 40–75 years old [12], younger patients represent another group in whom CAC scoring may provide relevant prognostic information; in a sub-analysis of the CAC consortium study, out of ~22,000 of adults aged 30 to 49 years undergoing CAC testing for clinical indications, 34% had detectable coronary calcium, and those with scores > 100 were found to have a 10 $\times$ increased risk of CHD mortality compared to those of the same age with a CAC of 0 [7].

Furthermore, recent studies have suggested that patients with higher CACS increase the prediction of abnormal myocardial strain by CT [13], although robust longitudinal data are lacking.

2.3. Relevance of Coronary Calcium Distribution

In the CAC consortium study, the largest CAC cohort to date, ~66,000 participants with no coronary artery disease enrolled between 1991 and 2010; findings suggest that after adjusting for total CAC and baseline risk factors, those with left main lesions and proximal multi-vessel calcium distribution had 20–30% higher CVD mortality. A notable exception to this finding were patients with extreme CAC scores (>1000) who had a mortality rate per 1000 person-years of 8.0, compared to 3.6 for those with CAC scores of 400 to 999. It is, however, worth mentioning that these findings might be challenged by clinical data from other cohorts and prospective studies. For example, in the MESA (Multi-Ethnic Study of Atherosclerosis), patients with CAC scores >1000 were at no higher risk of CHD death or MI than those in the 400–999 group (though with a much smaller sample size and shorter follow-up) [7]. The CAC Data and Reporting System (CAC-DRS), a new, validated scoring system, uses both total Agatston score and number (0–4) of the major coronary arteries affected, and is recommended by the SCCT/STR guidelines for coronary artery calcium scoring, and permits a standardized report to improve the communication with a clinical physician [14].

2.4. Relevance of Coronary Calcium Plaque Volume and Density

Another major caveat that clinicians should keep in mind when evaluating CAC scoring during an individual's risk assessment is the fact that data from several studies using other imaging techniques suggest that denser calcified plaque may be more stable over time [15], and that statin therapy actually increases calcium deposition in atherosclerotic plaque, protecting against plaque destabilization [16].

This discordance in findings could be explained by the fact that the overall CAC score is directly dependent on both plaque area (volume-dependent) and plaque density (derived from Hounsfield units), and there might be different phenotypes within similar CAC scores, with some patients with severe or extreme CAC scores having increased plaque density but not plaque burden, which paradoxically might be associated with lower CVD risk. Criqui et al. tested this hypothesis using data derived from the MESA cohort and found that CAC density was inversely related to CVD events at a given CAC volume, and that volume was more predictive when adjusted for CAC density, although more research is needed to precisely clarify the relationship between plaque burden, distribution, and density with cardiovascular outcomes, and how this may differ between age and gender groups [7].

2.5. Guideline Recommendations of CAC Assessment

Most guidelines endorse CAC as a risk modifier in individuals at borderline to intermediate, asymptomatic ASCVD risk, but they differ in details such as the age range, risk calculation models, and thresholds for statin initiation. Importantly, a CAC score of zero was consistently associated with down-classification of risk and deferral of pharmacologic therapy, while elevated CAC (e.g., ≥ 100 Agatston units or above the 75th percentile) often led to treatment intensification [17].

The 2019 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Primary Prevention of Cardiovascular Disease and the 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia recommend coronary artery calcium (CAC) scoring as a tool for refining risk assessment in adults aged ≥ 40 years with intermediate (7.5–20%) 10 year ASCVD risk, and also in selected patients at borderline risk. The ACC/AHA limits its benefit to individuals up to age 75. More recently, focused updates from the European guidelines highlight that while CAC is not recommended as a broad population screening test, its consideration improves both risk discrimination and reclassification. In particular, the presence of subclinical coronary atherosclerosis on imaging or an elevated CAC score should now be regarded as a risk modifier in individuals at moderate risk or in those around treatment decision thresholds, with a formal recommendation of Class IIa, Level of Evidence B [18].

In a recent study [19], 1903 statin-naïve adults aged 55–75 years without ASCVD or diabetes were chosen from the Rotterdam Study to assess the impact of guideline-directed coronary artery calcium (CAC) scoring on statin treatment recommendations. Using ACC/AHA (PCE and PREVENT) and ESC/EAS (SCORE2/SCORE2-OP) risk models, the authors determined eligibility for CAC scans, proportions of individuals reclassified after CAC, ASCVD incidence rates, and estimated 10 year numbers needed to treat (NNT10y). Results showed that ACC/AHA guidelines identified fewer CAC scan-eligible individuals (up to 18% of men and 12% of women by PCE) compared with ESC/EAS ($\approx 45\%$ of both sexes), but virtually all CAC-eligible participants under ACC/AHA were reclassified, while ESC/EAS reclassified about half. Event rates and NNT10y (11–26 with high-intensity statins) supported CAC's ability to refine risk, with up-risked individuals showing incidence rates similar to high-risk groups, and those with CAC = 0 showing very low event rates, reinforcing CAC as a valuable risk-modifying tool in primary prevention. An example of the clinical impact of elevated CAC score on clinical decision making is presented on Figure 1.

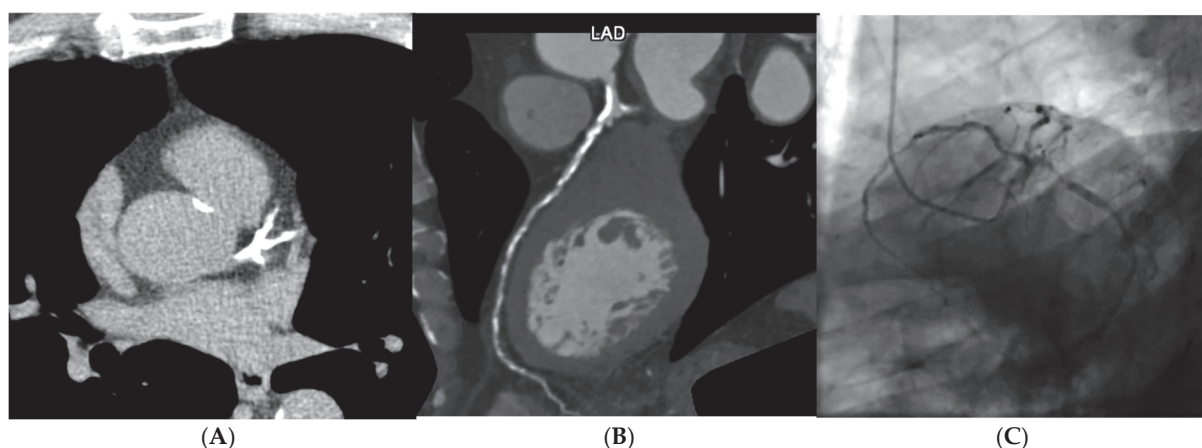


Figure 1. Screening finding of coronary calcium score of 2388 AU (A) on an asymptomatic patient leading to coronary computer cardiac tomography (CCTA) (B) showing extensive multivessel obstructive disease, which was then confirmed by (C) invasive coronary angiography.

3. Coronary Computed Tomography Angiography (CCTA)

Coronary computed tomography angiography (CCTA) is a contrast-enhanced, ECG-gated imaging modality used to detect and quantify both calcified and non-calcified coronary plaques. It also provides an estimation of the severity of luminal stenosis, aiding in the assessment of coronary artery disease severity and the high-risk factors to vulnerable plaques [3].

3.1. Technical Considerations and Contraindications

Before performing CCTA, an appropriate IV line (typically 18 gauge or 20 gauge in smaller patients) is needed to allow for rapid contrast injection (5–7 mL/s) during the scan [14]. Also, patients are often administered nitroglycerin to induce coronary vasodilation and beta-blockers (either orally or intravenously) to achieve lower heart rates, thereby optimizing image quality. The need for these medications varies depending on the type of CT scanner used, making pre-screening for contraindications essential (i.e., nitroglycerin contraindication in severe aortic stenosis) [3].

The scan is performed in a single breath-hold, typically lasting 5 to 10 s, and image acquisition occurs approximately 15 to 25 s after contrast injection; more precise timing can be determined using variations in bolus tracking, which monitors contrast attenuation in the ascending or descending aorta in real time [20].

Aside from a history of severe anaphylactic reaction to iodinated contrast, there are no absolute contraindications to CCTA [3]. However, certain scenarios require careful consideration to determine whether the potential benefits outweigh the risks; these include severe kidney impairment ($\text{eGFR} < 30 \text{ mL/min/m}^2$); uncontrolled tachycardia; severe obesity ($\text{BMI} > 40$); inability to comply with scan requirements (patients unable to follow breath-hold instructions or remain still during image acquisition); clinical instability, such as acute myocardial infarction or decompensated heart failure; pregnancy; presence of known severe, dense, calcific plaque or coronary stents with a diameter $< 3 \text{ mm}$ which are challenging to evaluate due to limitations in spatial resolution; and the impact of blooming artifacts from metallic struts that can lead to overestimation of stenosis or render the segment non-assessable [20]. All of these should be assessed in an individual risk-to-benefit ratio on a case-by-case basis [12].

3.2. Safety and Radiation Exposure

The radiation dose in cardiac CT depends on several scan acquisition parameters. The tube voltage, measured in kilovolts (kV), determines the energy of the emitted photons, while the tube current, measured in milliamperes (mA) or milliamperere-seconds (mAs), determines the number of photons produced [5,20]. Higher kV increases tissue penetration, whereas higher mA raises the total photon count, reaching the detector elements. Although increasing either kV or mA raises the radiation dose required for image acquisition, setting these values too low can result in excessive image noise and reduced diagnostic quality. Scanner settings should therefore be tailored to the patient's body habitus and the desired image quality. For example, in obese patients, where higher noise levels and photon attenuation are expected, a higher kV is generally preferred.

Recent advances in coronary computed tomography angiography (CCTA) have enabled substantial reductions in radiation exposure while preserving diagnostic image quality. Key strategies include prospective ECG-gating to limit exposure to specific cardiac phases, and high-pitch helical acquisition with dual-source CT, allowing whole-heart imaging in a single cardiac cycle with doses often <1 mSv. Heart rate control with beta-blockers facilitates longer diastolic imaging windows, and limiting scan range minimizes unnecessary exposure. Advances in iterative reconstruction algorithms improve signal-to-noise ratios, enabling lower tube current and voltage settings without degrading the image quality [5]. The combination of these methods has made sub-millisievert CCTA feasible. A prospective multicenter registry demonstrated that over the past decade, the estimated radiation dose from cardiac CT has decreased by approximately 78%. Specifically, the median dose-length product (DLP) for CCTA fell from 885 mGy·cm in 2007 to 195 mGy·cm in 2017 [21].

3.3. Diagnostic Precision

Coronary angiography (CA) is considered the gold standard for the assessment of epicardial coronary anatomy, though it is an invasive test, and while infrequent, it is not exempt from serious complications (bleeding, vascular injury, and even myocardial infarction) [7].

Comparison of the diagnostic performance of CCTA versus coronary angiography has been assessed in several trials. Recently, a meta-analysis including nine studies found that CCTA had a sensitivity of ~96% and a specificity of ~75% to detect a stenosis of >50%. However, it can be argued that in clinical practice, identification of functionally significant stenoses is a more desired benchmark, the PACIFIC (Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography with Invasive Coronary Angiography) assessed the diagnostic performance of several imaging techniques compared to an invasively assessed FFR < 0.8, and they found CCTA had only moderate sensitivity and specificity (0.83 and 0.81) to detect functionally relevant stenosis [22,23].

To overcome this, novel techniques that allow the calculation of FFR (Fractional Flow Reserve) derived from CT have been developed. In the PACIFIC study, FFR-CT showed a sensitivity and specificity of 90% and 86%, respectively [23]. FFR-CT details are presented in Section 3.6.

3.4. Prognostic Information

A relevant question regarding the use of CCTA is whether imaging findings translate to adverse clinical outcomes, particularly when a plaque is considered non-significant, and whether these findings lead to a change in the medical management of these patients. Several studies have assessed this inquiry; in the SCOT-HEART (Scottish Computed Tomography of the HEART) trial, a prospective, multicenter, randomized trial of 4146 patients

aged 18–75 years who had been referred by a primary-care physician to a dedicated cardiology clinic for patients with suspected stable angina due to coronary heart disease (CHD), patients were randomized 1:1 to receive either standard care plus CCTA or standard care alone. The patient population was intentionally broad to reflect a real-world setting and included a significant proportion of women (45%) and a median age of 57 years. The frequency of diagnosis of angina due to coronary artery disease (CAD) was lower, and diagnostic certainty was higher when CCTA was added, and nearly one in four patients in the CCTA group had their prescribed treatment altered at six weeks, compared with only one in twenty (5%) of those receiving standard care alone. Over a median follow-up of 4.8 years, the addition of CCTA to standard therapy reduced the composite endpoint of death from ischemic heart disease or nonfatal myocardial infarction by 41% (2.3% vs. 3.9%; HR 0.59; $p = 0.004$) [24].

While current CCTA technology and increased spatial resolution enable clinicians to diagnose and assess coronary atherosclerotic disease in its earliest stages, the main advantage of CCTA over coronary calcium is the ability to identify and categorize plaque features associated with acute coronary syndromes. These so-called “high-risk plaque features,” including low-attenuation plaque (which would be missed on standard calcium coronary assessment), positive remodeling (PR), spotty calcifications, and the napkin-ring sign have been linked to future acute coronary syndromes (ACS) [2]. Data from the SCOT-HEART and ICONIC studies show that these features are independent predictors of myocardial infarction (MI) even when stenosis severity is mild to moderate. For this reason, these high-risk features were added to the standardized report called CAD-RADS 2.0 [25].

In addition to plaque characterization, the non-invasive calculation of fractional flow reserve from CCTA (FFR-CT) has emerged as a valuable tool to functionally assess the hemodynamic significance of coronary lesions. The PACIFIC trial (Prediction of Advanced Coronary Artery Disease and Functional IsChEmia with CT) aimed to determine the diagnostic performance of FFR-CT compared to invasive FFR in 208 patients with suspected stable CAD, who underwent 256-slice coronary CTA, 99 mTc-tetrofosmin SPECT, [15O] H₂O PET, and routine three-vessel invasive FFR measurements. The trial found that FFR-CT had the highest per-vessel diagnostic accuracy with a sensitivity of 90%, a specificity of 86%, and an AUC of 0.92. This was similar to PET, but superior to coronary CTA and SPECT. However, in a more clinically relevant intention-to-diagnose analysis that included the one in four unevaluable cases, FFR-CT’s performance was significantly diminished. On a per-vessel basis, its AUC was 0.83, no longer superior to CTA alone, and on a per-patient basis, its AUC of 0.79 was significantly outperformed by PET’s AUC of 0.90 [23].

Quantitative CCTA analysis has allowed researchers to monitor plaque progression and treatment response over time, such as the stabilization of non-calcified plaques with statin therapy in the PARADIGM study [26]. A major concern in the assessment of plaque burden and characterization is interobserver variability. Furthermore, automated software tools like vascuCAP [27] and QAngioCT [28] are enhancing accuracy and reducing interobserver variability by providing 3D plaque characterization.

3.5. Emerging CCTA Technologies

Beyond anatomy, emerging tools such as fractional flow reserve derived from CCTA (FFR-CT), perivascular fat attenuation index (FAI), and wall shear stress (WSS) [29] enable the functional assessment of lesions and provide deeper insight into plaque physiology and vascular inflammation. For instance, FAI correlates with coronary inflammation and may predict future adverse cardiovascular events [30].

In patients with high-intensity inflammatory diseases like HIV, psoriasis, rheumatoid arthritis, and SLE, CCTA has uncovered an increased prevalence of non-calcified

plaques and vulnerable plaque features, which are often underdiagnosed using traditional modalities [31]. Longitudinal studies have shown that anti-inflammatory therapies can favorably modify plaque burden, further emphasizing the utility of CCTA in immune-mediated disease.

3.6. Functional Assessment

Currently, there are two CCTA technologies that enable the assessment of flow and coronary physiology: FFR-CT (Fractional Flow Reserve derived from Coronary CT Angiography) and CCTA perfusion imaging.

FFR-CT is a non-invasive technique that allows for the estimation of three-vessel FFR values using standard CCTA datasets. Because FFR-CT is calculated directly from existing CCTA imaging data, it does not require additional testing or radiation exposure. FFR-CT calculations are based on computational fluid dynamics (CFD) models applied to CCTA data to estimate coronary blood flow parameters, including pressure gradients, flow velocity, and volumetric blood flow within the coronary arteries [32]. Threshold to significant stenosis is $\text{FFR-CT} < 0.80$ (Figure 2).

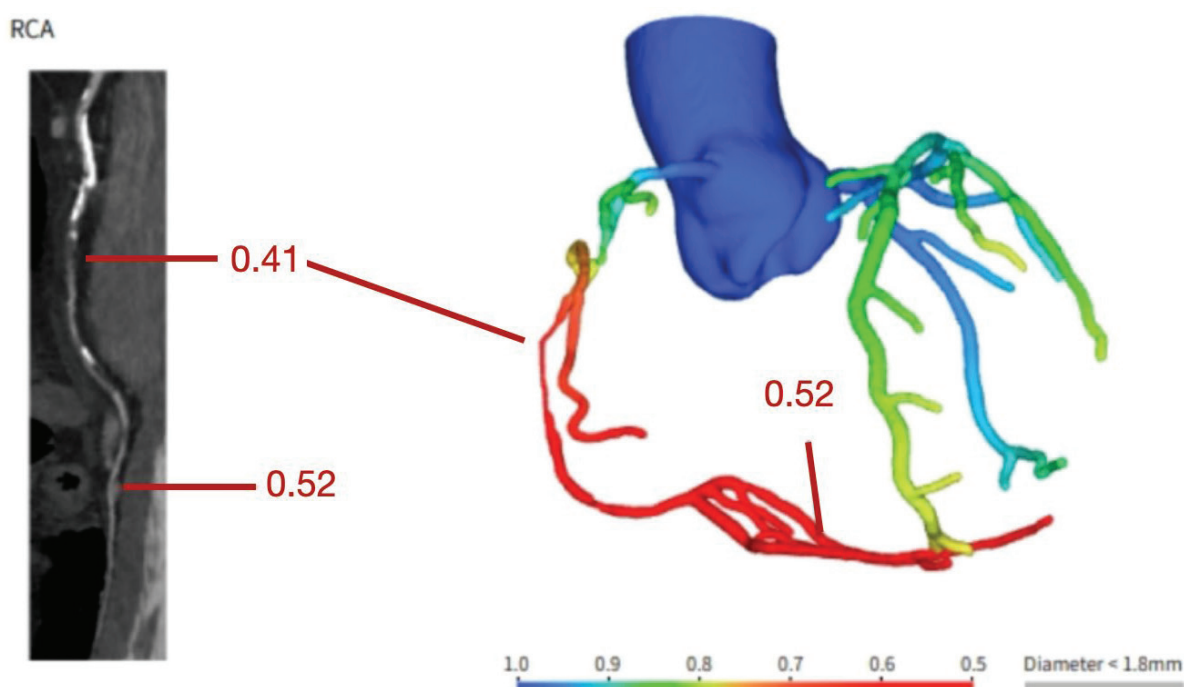


Figure 2. Coronary computer tomography fractional flow reserve assessment showing a functionally significant stenosis in the vertical segment of the right coronary artery.

A key advantage of FFR-CT is its ability to provide a lesion-specific assessment of myocardial ischemia, thereby aiding in clinical decision-making regarding coronary revascularization. In the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) [22] a prospective, multicenter study that enrolled 254 patients referred for clinically indicated invasive coronary angiography, FFR-CT was performed on 484 coronary vessels and found that the area under the receiver operating characteristic (ROC) curve for FFR-CT was 0.90 per patient and 0.93 per vessel, corresponding to an overall per-vessel diagnostic accuracy of 86%, using invasive fractional flow reserve (FFR) as the reference standard [33].

Another functional tool is myocardial perfusion assessment in CCTA, which evaluates the distribution of iodinated contrast material during its first pass through the myocardium. Perfusion defects appear as hypoattenuating areas containing reduced amounts of contrast

material. In static myocardial perfusion CT, assessment is often based on visual comparison of myocardial perfusion during pharmacological stress and at rest, which requires planning before the regular acquisition, since pharmacological stress images are not part of standard protocols. In contrast, dynamic myocardial perfusion CT acquires multiple sequential images during the first pass of contrast, enabling dedicated software to generate quantitative perfusion maps and objectively measure myocardial blood flow. With the advent of new multidetector CT scanners, both reproducibility and accuracy have increased, with reported sensitivity and specificity between 76 and 100% for static and dynamic CT perfusion imaging. This improvement offers incremental diagnostic value over coronary CCTA alone for the identification of hemodynamically significant CAD.

3.7. Impact of FFR-CT in Therapeutic Decision-Making

Several trials have assessed the impact of FFR-CT on clinical decision-making. The ADVANCE (Assessing Diagnostic Value of Non-invasive FFR-CT in Coronary Care) registry was a prospective, multicenter study that included 5083 patients across 38 centers, all of whom were referred for CCTA with FFR-CT assessment. The study found that incorporating FFR-CT into the CCTA workflow altered the initial treatment strategy in approximately two-thirds of cases. The authors also assessed the safety of deferring revascularization in patients with negative FFR-CT values (>0.80) [34]. Over a 90 day follow-up, none of the 1952 patients with negative FFR-CT experienced death, myocardial infarction (MI), unplanned hospitalization for acute coronary syndrome (ACS), or urgent revascularization. In contrast, 19 adverse events (ten deaths, four MIs, and five hospitalizations for urgent revascularization) occurred in the group with positive FFR-CT findings, yielding a crude risk ratio of 19.75 ($p < 0.001$) [34].

At one-year follow-up, there was a trend toward fewer major adverse cardiovascular events (MACE) in patients with negative FFR-CT ($p = 0.062$) and a significant reduction in cardiovascular death or MI compared to those with abnormal FFR-CT values ($p = 0.01$); specifically, patients with intermediate coronary stenosis who had a negative FFR-CT result (>0.80) demonstrated long-term clinical outcomes comparable to those with no or minimal stenosis (0–30%) on CCTA [34].

In the PROMISE trial, an observational cohort study that included 181 patients with stable chest pain, an FFR-CT value of ≤ 0.80 was found to be a significantly better predictor of revascularization or major adverse cardiovascular events (MACE) than severe ($>70\%$) stenosis on computed tomography angiography (CTA). The authors concluded that FFR-CT could improve cost efficiency by enhancing the selection of patients referred for invasive coronary angiography [35].

However, it is relevant to emphasize that when FFR-CT is used to guide treatment strategies, the evaluation of other clinical and anatomical factors is paramount, such as the high-risk features discussed previously. This tool is particularly valuable for assessing moderate coronary artery stenoses, especially those found in the proximal or mid segments, where the significance of a lesion is not always clear from anatomy alone [32] because FFR-CT values tend to decline along the length of an artery; particularly in vessels with multiple narrowings or diffuse disease, it is essential to match areas of pressure drop with specific plaque locations because focal stenosis have the benefit of revascularization contrary to diffuse lesions [32]. This alignment is only possible by directly comparing CCTA images with the 3D FFR-CT model, which helps identify the lesion responsible for significant ischemia.

While several studies use a simple cutoff approach to interpret FFR-CT, it is important to remember that its values fall along a spectrum, with lower readings associated with higher risk for hemodynamic compromise and adverse events [34,35]. In cases where

FFR-CT falls between 0.76 and 0.80, clinicians should integrate additional factors such as the exact lesion location, patient symptoms, presence of high-risk plaque features, and the magnitude of pressure drop across the lesion, to determine whether intervention is warranted [33].

FFR-CT presents several significant limitations. Currently, it requires dedicated technical personnel and incurs additional costs [32]. However, studies have demonstrated its cost-effectiveness by reducing the need for invasive coronary angiography and revascularization in selected patient populations [35]. Furthermore, the diagnostic reliability of FFR-CT is highly dependent on optimal image quality from the original CCTA. Artifacts such as motion, misalignment, low contrast resolution, or blooming from heavy coronary calcification can significantly impair accuracy [33]. Additionally, FFR-CT is not recommended for assessing stented coronary segments or in patients who have had prior coronary artery bypass graft (CABG) surgery, due to the limited validity of the method in those settings [35].

3.8. Results Reporting and Therapeutic Approach

In 2022, an update to the expert consensus document by the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR) and the North America Society of Cardiovascular Imaging (NASCI) on the coronary artery disease-reporting and data system (CAD-RADS) [25] was published. This way of reporting improved communication between the imager and the clinician and facilitated the collection of databases to further improve the classification of CAD. Key messages from this document are summarized in Table 1 and shown in Figure 3.

Table 1. CAD-RADS Categories (Adapted from Cury et al., 2022) [25].

Category	Degree of Coronary Stenosis	Further Investigations	Management Considerations
0	0%—No CAD	None needed	Assess non-atherosclerotic causes of symptoms. General preventive measures
1	1–24%—Minimal non-obstructive CAD	None needed	Assess non-atherosclerotic causes of symptoms. Risk factor modification, consider preventive pharmacotherapy
2	25–49%—Mild non-obstructive CAD	None needed	Assess non-atherosclerotic causes of symptoms. Risk factor modification, consider preventive pharmacotherapy
3	50–69%—Moderate stenosis	Functional assessment is recommended	Prior recommendations + other treatments, including antianginals per guideline-directed care
4A	70–99% single vessel stenosis	Invasive coronary angiography or functional assessment are recommended	Prior recommendations + other treatments, including antianginals per guideline-directed care
4B	Left main 50% or 3-vessel obstructive (70%) disease	Invasive coronary angiography is recommended	Revascularization should be considered + other treatments, including antianginals per guideline-directed care
5	100%—Total occlusion	Consider ICA, functional and/or viability assessment	Revascularization should be considered after viability/individual assessment + other treatments, including antianginals per guideline-directed care
N	Non-diagnostic study	Additional/alternative evaluation may be needed	Additional/alternative evaluation may be needed

The guidelines also emphasize the importance of assessing and reporting plaque burden, high-risk features, and functional tests as additional “modifiers” to anatomic parameters in clinical decision-making [25].

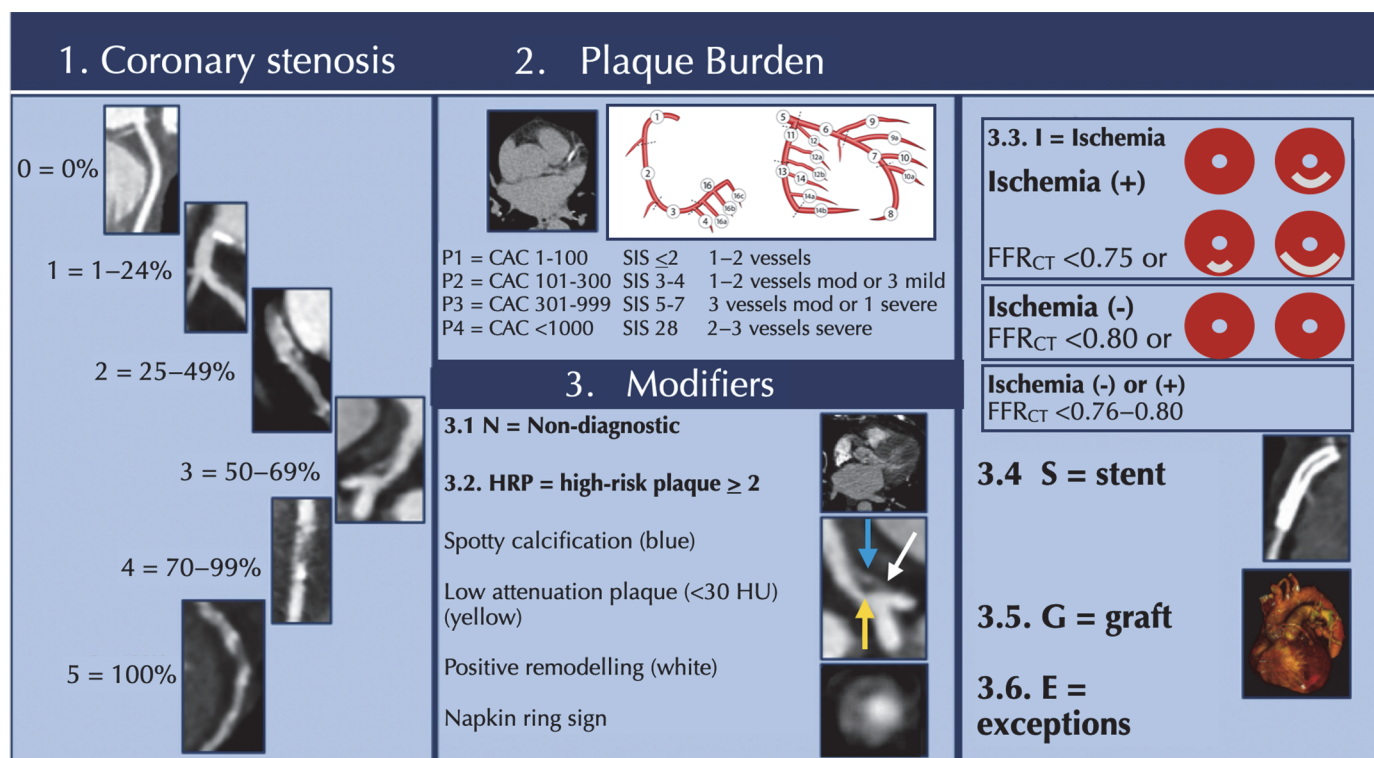


Figure 3. CAD-RADS 2.0 presented with examples and step-by-step configuration.

3.9. Role of CCTA in Acute Coronary Syndromes

Acute chest pain is among the most common causes of admission to the ER worldwide. Prompt and standardized assessment and identification of acute coronary syndromes in this context is paramount.

The development of structured clinical decision pathways, supported by both 2021 AHA/ACC chest pain guidelines [36] and 2025 AHA/ACC acute coronary syndromes guidelines [37], have been shown to decrease unnecessary testing and admissions while maintaining high sensitivity for detection of acute myocardial injury and 30 day MACE [37]. Several large randomized trials have assessed the usefulness of CCTA in acute coronary syndromes (ACS), such as the ROMICAT II, ACRIN-PA, CT-COMPARE, and CT-STAT, leading to its inclusion in these decision pathways, particularly in the context of intermediate-risk patients with acute chest pain, although some low-risk patients with inconclusive ECG and/or troponin findings may also benefit from anatomic testing with CCTA [38]. Table 2 depicts current guideline recommendations of CCTA in acute and chronic coronary syndromes.

Table 2. Guideline recommendations of CCTA in acute and chronic coronary syndromes.

Clinical Scenario	American Heart Association/American College of Cardiology	European Society of Cardiology
Acute Coronary Syndromes	Class I: CCTA may be considered for patients with lower risk NSTEMI-ACS as a non-invasive risk stratification, as part of a selective invasive strategy (1).	Class IIA: Incorporating CCTA or a non-invasive stress imaging test as part of the initial workup in patients with suspected ACS, non-elevated (or uncertain) hs-cTn, no ECG changes, and no recurrence of pain should be considered. Class IIIB: Routine, early CCTA in patients with suspected ACS is not recommended.
Chronic Coronary Syndromes	Class IIA: For patients with CCD and a change in symptoms or functional capacity that persists despite GDMT, and who have had previous coronary revascularization, CCTA is reasonable to evaluate bypass graft or stent patency (for stents ≥ 3 mm). Class IIA: For selected patients with suspected non-ischemic cardiomyopathy, CCTA may be considered as an initial diagnostic strategy.	Class I, Level B: CCTA is recommended as a first-line test for patients with low to intermediate pre-test probability of CAD.

3.10. Evaluation of Cardiac Structure and Function

Besides the utility of Cardiac CT in assessing coronary artery disease, it is also a useful tool for evaluating cardiac structural disease, including pericardial, myocardial, and valvular heart disease.

3.10.1. Pericardial Disease

Pericardial disease encompasses a diverse spectrum of congenital and acquired disorders, with highly variable clinical presentations that often necessitate targeted therapeutic approaches. In addition to primary pericardial pathology, the pericardium can be secondarily involved in a wide array of systemic and organ-specific diseases, including infectious, autoimmune, and neoplastic processes. Iatrogenic causes, such as those related to cardiac surgery or radiation therapy, also account for a substantial burden of pericardial-related complications [39].

Despite the well known role of echocardiography as first-line testing in the assessment of pericardial disease, a cardiac CT scan aids in the diagnosis in some pericardial abnormalities, particularly in patients with poor sonographic windows, and can even be superior in the assessment of certain characteristics (Table 3) [40].

Table 3. Comparison between echocardiography and cardiac CT in the assessment of pericardial pathology.

Pericardial Feature/Condition	Echocardiogram	Cardiac CT
Pericardial Thickness	Limited for precise measurement; may suggest thickening indirectly	High spatial resolution; precise measurement of pericardial thickness
Pericardial Calcifications	Poor sensitivity; typically, not visualized	Excellent for detecting and quantifying calcifications
Pericardial Inflammation	Can suggest inflammation (e.g., fibrin strands, increased echogenicity)	Limited unless contrast enhancement shows indirect signs
Pericardial Adhesions	Indirect signs (e.g., septal bounce), but not definitive	Can identify adhesions through restricted motion in multiphasic imaging
Pericardial Effusion Detection	High sensitivity; excellent for real-time detection	Good sensitivity, especially for loculated effusions
Pericardial Masses	Can detect large masses, but limited soft-tissue characterization	Superior soft-tissue contrast; good for mass localization and extent

Pericardial thickening and calcifications identified on cardiac CT are valuable in the assessment of patients with suspected constrictive pericarditis. Additionally, multiphasic imaging can aid in detecting pericardial adhesions in selected cases [39]. (Figure 4).

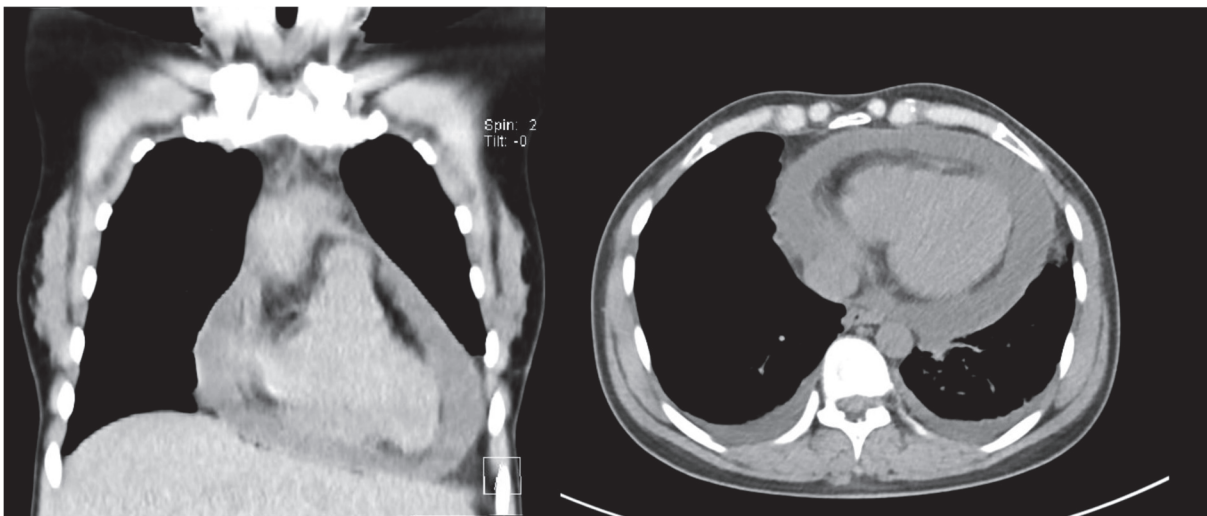


Figure 4. Non-contrast computer tomography showing severe pericardial effusion in a 36 year old female with unremarkable medical history. Pericardiocentesis was performed, diagnosing viral pericarditis.

3.10.2. Myocardial Characterization and Cardiac Function with CT

Cardiac CT is useful in assessing chamber morphology and size. End-diastolic images are used to measure the wall thickness of the left and right ventricles, as well as their overall size. The use of multidetector CT image acquisition (MDCT) enables the quantitative and qualitative assessment of left and right ventricular systolic function. Although there are variations in software between vendors, they typically employ retrospective ECG gating to measure left ventricular (LV) volume and left ventricular ejection fraction (LVEF) measurements. Evidence shows there is no significant difference between MDCT and cardiac MRI, the current gold standard for chamber morphology and ventricular ejection fraction [41,42].

The precision in assessing ventricular and valvular function strongly depends on the temporal resolution of the imaging modality used. Cardiac MRI, with its high temporal resolution (typically under 50 milliseconds), provides accurate quantification of left ventricular ejection fraction (LVEF), as well as valvular regurgitation. In contrast, conventional 64-slice single-source multidetector CT has a slower temporal resolution (around 150 milliseconds), which affects the ability to accurately image moving cardiac structures and often necessitates beta-blockade in patients with elevated heart rates, which may compromise functional accuracy [43]. The advent of dual-source CT has enhanced the temporal resolution to approximately 80 milliseconds, thereby improving the accuracy of LVEF evaluation and spatial resolution and often eliminating the need for beta blockers [42].

As temporal resolution continues to improve, CT is expected to allow an increasingly precise assessment of cardiac chamber function and valvular abnormalities. Despite MSCT's ability to estimate LVEF reliably, it presents notable limitations: chief among them is notably the high radiation exposure associated with retrospective ECG-gated acquisitions that span both systole and diastole. In several studies included in a recent meta-analysis, the average effective radiation dose ranged from 8 to 14 mSv [42]; although prospective ECG-gated protocols are now available and significantly reduce radiation exposure, they typically capture only a single cardiac phase, limiting their utility for full-phase functional assessment [44].

3.10.3. Valvular Heart Disease

In recent years, there have been significant developments in percutaneous techniques for replacement or repair in the field of valvular disease, which have changed current clinical practice worldwide. Along with major developments in these techniques, cardiac CT has emerged as one of the most important imaging techniques in preprocedural planning and postprocedural follow-up and assessment, and although echocardiography still remains the first-line imaging modality to assess valvular heart disease, transcatheter valve procedures depend significantly on CT imaging for planning the intervention, anticipating and identifying potential complications, and assessing prosthetic valve performance [45].

In the assessment of aortic stenosis, when there is uncertainty about the severity with echocardiography or when dobutamine stress echocardiography is inconclusive or contraindicated, non-contrast cardiac CT calcium scoring can be used to help confirm the severity of aortic stenosis (AS), as it offers a load-independent anatomical assessment. In men, calcium scores more than 2000 Agatston units, and more than 1200 in women, generally indicate severe aortic stenosis (AS) [46] (Figure 5).

Furthermore, direct measurement of the aortic valve coaptation area defect can be achieved through planimetry at the leaflet tips. This technique also enables precise assessment of aortic regurgitation by examining valve closure during diastole. Prior to transcatheter valvular aortic replacement (TAVR), CCTA can offer precise measurements of not only the aortic annulus but of the entire aortic root and offers essential information in

the assessment of vascular accesses [47] (Figure 6). The clinical impact of CT-based planning is supported by real-world evidence: Mylotte et al. reported that CT analysis frequently resulted in larger annular measurements than transesophageal echocardiography (TEE) alone, and that adherence to CT-based oversizing criteria was independently associated with a 21% lower incidence of paravalvular leak compared with TEE sizing (14% vs. 35%; $p = 0.003$) [48]. Similarly, in a prospective study of 266 patients, CT-based prosthesis sizing significantly reduced paravalvular leak rates (5.3% vs. 12.8%; $p = 0.032$) and in-hospital mortality (3.8% vs. 11.3%; $p = 0.02$) compared with sizing based on echocardiography and angiography [49]. Post-TAVR, cardiac CT is valuable in the evaluation of suspected prosthetic valve thrombosis, endocarditis, or structural deterioration, with characteristic findings such as hypoattenuated leaflet thickening (HALT) and reduced leaflet motion (HAM) providing important diagnostic information for targeted management. Likewise, Yin Ge et al. found that in a cohort of 80 candidates for mitral valve replacement who underwent pre-procedural cardiac CT, a substantial proportion were found to have unfavorable anatomy, resulting in the cancellation of the procedure [50].

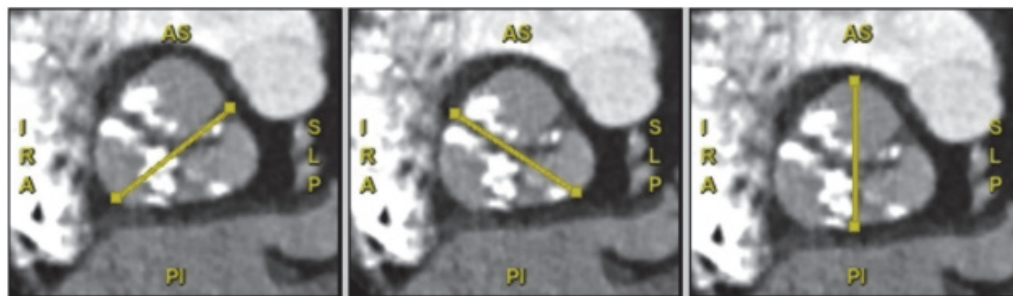


Figure 5. A 60 year old female with low flow low gradient severe aortic stenosis with severe valve calcification (2988 Agatston Units).

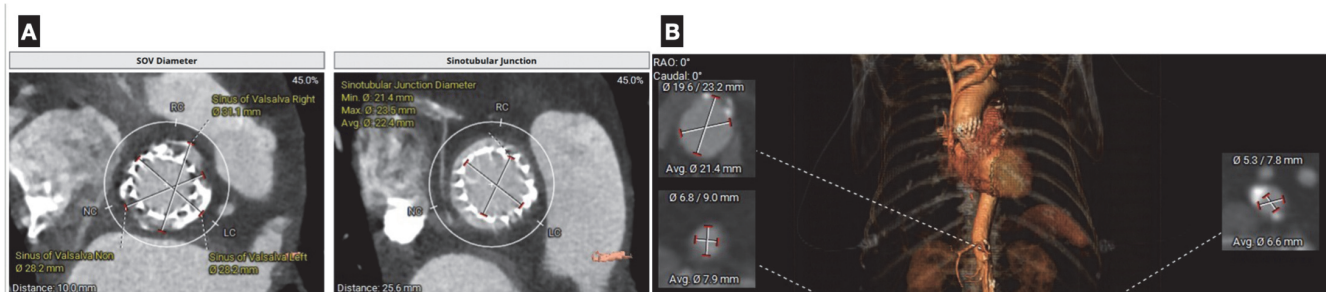


Figure 6. (A) Coronary computer tomography in planning of aortic valve-in-valve replacement. Measurement of aortic annulus size (diameter, area, and perimeter), is critical for selecting the appropriate prosthesis size to minimize the risks of paravalvular leak or annular rupture. Additional data, such as height of the coronary ostia, helps assess the risk of coronary obstruction during valve deployment. (B): Assessment of peripheral vasculature aids in the optimal selection of vascular accesses and minimizes the risk of vascular complications.

Post-procedure cardiac CT information in assessing prosthetic valve function and structure. Following TAVR, cardiac CT imaging may be appropriate in cases where there is clinical concern for valve thrombosis, endocarditis, or structural deterioration of the prosthetic valve. Valve thrombosis is typically suspected when echocardiography shows increased transvalvular gradients, especially if accompanied by symptoms of aortic stenosis [47]. Signs of leaflet thrombosis include hypoattenuated thickening of the valve leaflets (HALT) and limited leaflet motion, referred to as hypoattenuation affecting motion (HAM). This thickening often has a crescent-like shape, and is more pronounced at the base of the leaflet (Figure 7). These findings should be documented in terms of location, extent, and

thickness, and whether leaflet motion is restricted should also be noted. Differentiation between true HALT and beam hardening is important; true hypoattenuation is characterized by consistent localization within the leaflet tissue and correlates with restricted leaflet motion, whereas beam hardening artifacts typically appear as irregular streaks adjacent to the metallic stent and do not correspond to leaflet dysfunction.

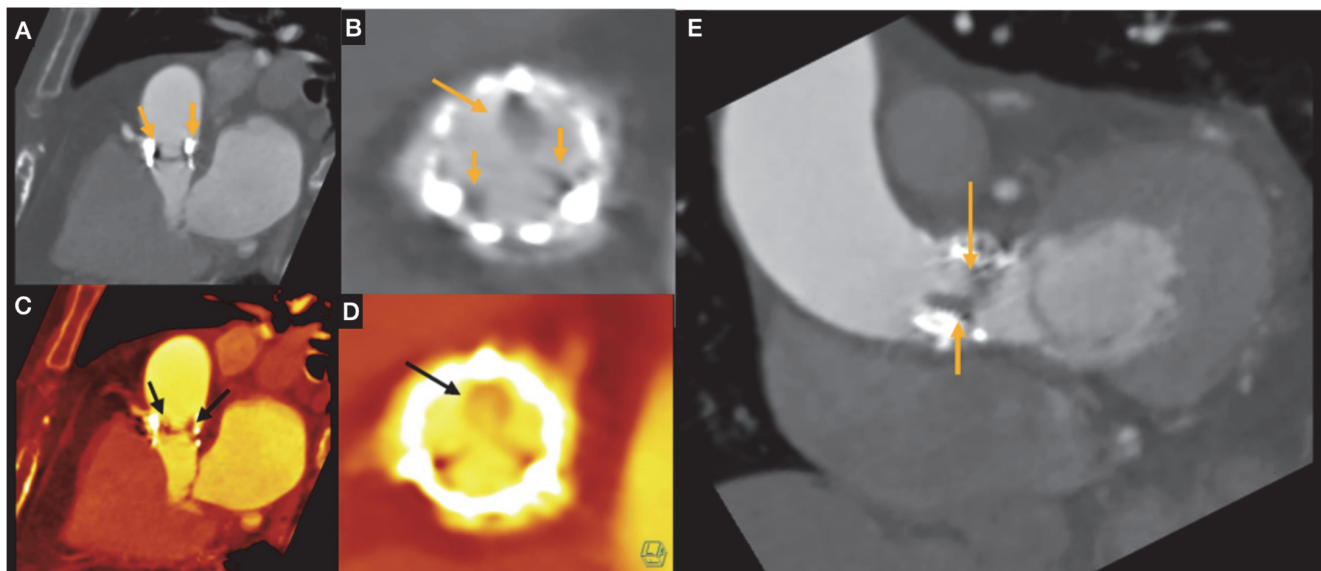


Figure 7. An 84 year old woman with a history of TAVI. She presents with dyspnea. Cardiac CT angiography revealed an aortic valve prosthesis with evidence of hypoattenuation and leaflet thickening (HALT), and absence of complete coaptation, with a calculated aortic valve orifice (AVo) area of 1.1 cm^2 (prosthetic valve dysfunction). Top images (A,B) show the valve stent and thickened leaflet in an oblique view (A), and a short-axis view of the valvular structure during systole (B), with arrows indicating areas of hypoattenuation consistent with HALT. Bottom images (C,D) display color-coded reconstructions to enhance structural contrast. Arrows highlight the valvular stent. The bottom-right image (D) demonstrates lack of leaflet coaptation, contributing to valvular regurgitation (arrow). (E) depicts an oblique view of the valve during systole, showing absence of excursion of one of the leaflets as compared to the other (arrows).

Valve thrombosis classification is based on the percentage of sinus of Valsalva thrombosis occupation seen in the MSCT as HALT, using grades 1 to 4, defined as >25%, 26–50%, 51–75% and >75%, respectively.

Most HALT cases with restricted motion are asymptomatic. Oral anticoagulation has been linked to a lower risk of developing HALT or HAM and can help reverse thickening when it occurs. However, the benefit of treating subclinical leaflet thrombosis remains uncertain, and it is unclear whether this approach reduces the risk of future valve degeneration. In a large real-world population undergoing TAVR and routine CTA screening 30 days afterward, HALT was detected in 12% of cases and was independently linked to increased long-term mortality [51].

In mitral valve replacement, left ventricular outflow tract (LVOT) obstruction is a potential complication of transcatheter mitral valve replacement (TMVR). During TMVR, a patient's native outflow tract can be altered, with the resulting LVOT sometimes referred to as the "neo-LVOT". Preprocedural CT imaging, which can simulate the neo-LVOT, is useful for predicting the risk of obstruction. Recently, a study of patients undergoing TMVR found that a neo-LVOT area smaller than 1.7 cm^2 at the end-systole posed a high risk of obstruction [52]. Other anatomical characteristics analyzed with MSCT are the presence and conformation of calcium at the level of the annulus (MAC), mitral anterior

leaflet length to recognize high-risk of LVOT obstruction, and annulus diameter to choose prosthesis size.

3.10.4. Aortic Diseases

Cardiac CT offers important information in the evaluation of aortic syndromes, including aortic dissection, intramural hematoma, and penetrating aortic ulcer. Its high spatial and temporal resolution, combined with rapid acquisition time, makes CT angiography (CTA) the first-line imaging modality in emergency settings. It enables precise visualization of the intimal flap, false lumen, branch vessel involvement, and extension of the dissection, which are critical for surgical or interventional planning. (Figure 8) [53].

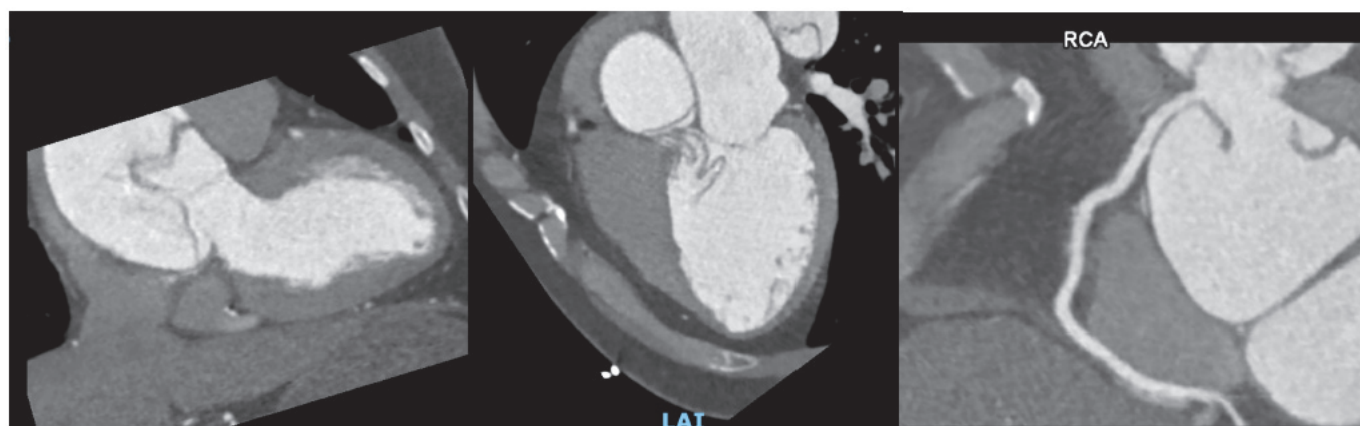


Figure 8. A 56 year old man presented to the emergency department with chest pain and ST elevation in right precordial leads. POCUS showed an aortic dissection flap with severe aortic regurgitation. This was confirmed on CCTA establishing right coronary involvement.

3.10.5. Congenital Heart Disease

In the assessment of congenital heart disease, cardiac computed tomography (CT) has a major role in anatomical assessment and surgical planning. Its ability to provide high-resolution, three-dimensional visualization of cardiovascular structures is especially useful in cases involving anomalous pulmonary venous return, complex aortic arch anomalies, coronary artery anomalies, and post-surgical repairs [54]. Furthermore, CT is valuable for long-term surveillance in postoperative CHD patients, including assessment of surgical grafts and conduits as well as in the longitudinal evaluation of the structural repercussions of hemodynamic alterations in this patient population [55] (Figure 9).

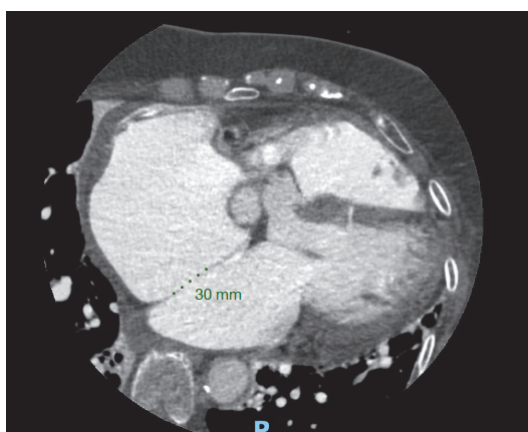


Figure 9. Coronary computer tomography showing a 30 mm atrial septal defect and a non-significant ventricular septal defect in an adult patient with non-relevant medical history who presented to the ER with dyspnea and atrial fibrillation.

4. Other Applications

In atrial fibrillation, pulmonary vein anatomy assessment is important in pre-procedural planning of ablation techniques, and while not first-line testing, it can aid in the identification of left appendage thrombus. A filling defect observed in the left atrial appendage could simply indicate sluggish blood flow; therefore, delayed contrast-enhanced imaging may be required to distinguish it from an actual thrombus.

In acute pulmonary embolism, CCTA is an essential tool, as it not only establishes the diagnosis with great precision but also provides important prognostic information by assessing signs of right ventricular (RV) failure, a key marker of severity in this context. Two validated imaging markers include an increased RV to left ventricular (LV) diameter ratio ($RV/LV > 1$), which suggests RV dysfunction, and a pulmonary artery to ascending aorta diameter ratio ($PA/Ao > 1$), which is associated with elevated pulmonary pressures. These findings are strongly linked to adverse outcomes and can guide clinical decision-making in patients with acute PE [56].

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is a very well acknowledged complication presenting after five years in up to 30–50% of patients undergoing heart transplantation, and it is a leading cause of allograft failure and death in heart transplant receivers [57]. Although both can coexist in a single patient, several key differences in pathophysiology and clinical presentations between CAV and atherosclerotic CAD should be noted; CAV can develop within one to two years after heart transplantation, progresses variably, and unlike focal, calcified native atherosclerosis has a more extensive distribution with CAV-related wall thickening typically affecting the whole length of the coronaries in a concentric fashion (concentric intimal hyperplasia). Another key difference between CAV and atherosclerotic CAD is that CAV lesions are typically non-calcified, whereas atherosclerotic CAD commonly exhibits substantial calcium deposition within plaques. In 2010, a consensus paper commissioned by the International Society of Heart and Lung Transplantation (ISHLT) board established a standardized CAV definition and classification system, and designated invasive coronary angiography (ICA) (with or without the use of intravascular ultrasound) as the accessible gold standard for surveillance with a recommendation of serial assessment every one to two years [58]. The rise in new CT technologies (such as photon counting CT) and protocols (with reduced radiation), along with evidence of excellent diagnostic performance, has spurred calls for updated recommendations. CCTA offers high sensitivity (up to 97%), specificity (up to 97%), and excellent negative predictive value (NPV up to 99%) for detecting significant stenosis in heart transplant recipients [59]. Beyond anatomical assessment, CCTA allows functional evaluation through CT-derived fractional flow reserve (FFR_{CT}) and facilitates quantitative plaque analysis, enabling earlier detection of diffuse and concentric intimal thickening that is typical of CAV. While considerations remain regarding radiation exposure, contrast use, and limited microvascular assessment, CCTA's comprehensive, multiparametric capabilities position it as a powerful tool for routine CAV monitoring and risk stratification in heart transplant follow-up, particularly compared to ICA, which is not devoid of complications, typically conveying greater radiation and contrast exposure [59].

5. Future Directions

Future directions in CCTA are rapidly advancing, particularly with the integration of artificial intelligence (AI), which enhances image acquisition, reconstruction, and diagnostic interpretation by reducing noise and improving efficiency [60]. AI algorithms are also being developed to detect coronary stenoses, assess plaque characteristics, and even predict major

adverse cardiovascular events based on CCTA data [61]. Myocardial viability assessment is another growing application, with studies showing that dynamic CT perfusion imaging and delayed iodine enhancement can identify viable versus non-viable myocardium, offering an alternative to nuclear or MRI-based techniques.

As discussed in previous section of this article, one of the major limitations of CCTA is the overestimation of stenosis severity in comparison to coronary angiography, particularly in the assessment of highly calcific plaques [3].

This is due to several limitations inherent to conventional energy-integrated detector CT imaging (EID-CT), a technology that uses layered scintillators to transform X-ray beams to visible light, and then, a photodiode array converts this light into electrical signals [62]. This layered and dual phase design leads to key shortcomings, chief among them being limited spatial resolution, which causes a voxel in the CT image containing both high-density calcium and lower-density surrounding tissues, resulting in an average high Hounsfield Unit (HU) value to the entire voxel, leading to size overestimation of calcium deposition [63]. Secondly, conventional energy-integrating detectors measure the total energy deposited by all incoming photons, not their individual energies. This lack of energy discrimination leads to the loss of spectral information, precluding fine discernment between calcium and soft plaque/normal tissue, and resulting in varying degrees of “blooming” artifacts that overshadow the coronary lumen [63].

New CT technologies have been developed to overcome these limitations; among these, ultra high-resolution photon-counting detector CT (UHR PCD-CT) represents a major advancement. Unlike EID-CT, photon-counting detectors register and count individual X-ray photons and measure their energy, enabling true spectral imaging at the detector level without the need for dual-source or dual-layer hardware [64]. This technology offers substantially improved spatial resolution, reduced electronic noise, and intrinsic spectral separation, allowing for more accurate differentiation between calcified plaque, non-calcified plaque, and lumen; these features translate into less blooming artifacts from calcifications, sharper vessel edge definition, and improved quantification of stenosis severity [62]. Additionally, the higher contrast-to-noise ratio of PCD-CT enables lower radiation dose protocols and better visualization of small cardiac structures, making it a promising tool for more precise, noninvasive coronary artery assessment in both heavily calcified and complex atherosclerotic diseases [65]. A prospective study compared coronary stenosis degrees and corresponding CAD-RADS [66] categories between UHR PCD-CT and EID-CT scans and assessed accuracy against an invasive coronary angiogram, CT angiography using both ultrahigh-spatial-resolution photon-counting detector CT (PCD-CT), and conventional energy-integrating detector CT (EID-CT) within 30 days, then had invasive quantitative coronary angiography (QCA) for validation. Among 278 plaques across 49 patients (202 calcified, 51 partially calcified, 25 non-calcified), the study found that PCD-CT measured a significantly lower percentage of diameter stenosis (PDS) compared to EID-CT for both calcified ($45.1 \pm 20.7\%$ vs. $54.6 \pm 19.2\%$; $p < 0.001$) and partially calcified lesions ($44.3 \pm 19.6\%$ vs. $54.9 \pm 20.0\%$; $p < 0.001$), while non-calcified plaque assessments were essentially identical ($\approx 39\%$). This reduction in overestimation led to a remarkable 49% of patients being reclassified to a lower CAD-RADS category when using PCD-CT. Importantly, in the subset of patients who underwent invasive angiography, PCD-CT stenosis measurements more closely agreed with QCA (mean difference $\approx 7.3\%$, limits of agreement -10.7% to 25.2%) versus the wider bias observed with EID-CT (mean difference $\approx 17.4\%$, limits -6.9% to 41.7%). These findings underline that UHR-mode PCD-CT not only reduces blooming artifacts but also enhances quantitative accuracy in calcified coronary lesions and meaningfully alters clinical stenosis grading [66].

Percutaneous coronary intervention planning is a novel topic, where specific characteristics assessed by CCTA, such as plaque calcium burden, plaque length and diameter, angiographic work projections; vessel ostium localization in post-coronary artery bypass grafting patients can reduce time, contrast and radiation in these interventional procedures [67].

These advances situate the CCTA not just as an anatomical tool but also as a comprehensive modality capable of functional and tissue-level cardiac assessment, showing that this tool has not reached its maximum potential [67]. The future of cardiac CT is currently focused on delivering significantly lower radiation doses through advanced acquisition techniques and detector technologies, while improving cost-effectiveness by incorporating machine learning and AI protocols, enabling faster, more accurate, and widely accessible cardiovascular assessment.

6. Conclusions

Cardiac computed tomography has evolved from a niche tool for coronary calcium scoring into a comprehensive, multiparametric imaging modality that integrates anatomical, functional, and prognostic information in a single examination. Coronary artery calcium quantification remains a robust, widely available method for risk stratification, guiding preventive strategies, and refining cardiovascular risk assessment across diverse patient populations. Coronary CT angiography provides high-resolution characterization of coronary anatomy and plaque morphology, identifies high-risk features predictive of acute coronary syndromes, and, when complemented by CT-derived fractional flow reserve or perfusion imaging, enables precise assessment of lesion-specific ischemia to inform revascularization decisions.

Beyond coronary disease, cardiac CT is indispensable for structural heart disease evaluation; preprocedural planning of transcatheter interventions; assessment of pericardial, myocardial, valvular, aortic, and congenital abnormalities; and risk stratification in acute coronary syndromes and pulmonary embolism. Continuous technological innovations—including dual-energy imaging, photon-counting detectors, and artificial intelligence—are enhancing spatial resolution, reducing radiation exposure, minimizing blooming artifacts, and expanding diagnostic capabilities toward tissue characterization and physiologic assessment.

Clinically, cardiac CT's expanding role supports earlier diagnosis, individualized treatment planning, and improved outcomes through better risk prediction and therapeutic targeting. From a research perspective, it provides a versatile platform for longitudinal studies on disease progression, therapy response, and prognostic modeling.

Despite major advances in scanner technology, image reconstruction, and dose-reduction algorithms, cardiac computed tomography (CT) continues to face important challenges. Radiation exposure, although significantly reduced with prospective gating, iterative reconstruction, and novel photon-counting techniques, remains a consideration in some scenarios, chief among them being younger patients or those requiring repeated imaging. Additionally, the high cost of advanced CT systems, specialized software, and expert interpretation can limit accessibility, especially in resource-constrained settings. These factors underscore the need for judicious patient selection and ongoing innovation to balance diagnostic benefit with safety and cost-effectiveness.

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Article

A Pilot Study on the Role of Computed Tomography in the Management of Patients with Coronary Artery Anomalies in Romania

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Abstract: Coronary artery anomalies may occur during embryogenesis and can lead to changes in the vascularization of the heart, possible ischemia, and an increased risk of sudden death. A retrospective study was conducted with the aim of assessing the prevalence of coronary anomalies in a Romanian sample of patients, investigated with computed tomography angiography for coronary artery disease. The objectives of the study were to identify the anomalies of the coronary arteries and to conduct an anatomical classification according to Angelini. The study also consisted of evaluations regarding coronary artery calcification in the sample of patients by the Agatston calcium score and assessments regarding the presence of cardiac symptoms and their association with coronary abnormalities. The results showed a prevalence of coronary anomalies of 8.7%, of which 3.8% were origin and course anomalies and 4.9% were coronary anomalies with intramuscular bridging of the left anterior descending artery. Recommendations for practice include the widespread use of coronary computed tomography angiography for the diagnosis of coronary artery anomalies and coronary artery disease in larger patient groups and encouraging this investigation across the country.

Keywords: coronary artery anomalies; computed tomography angiography

1. Introduction

The coronary arteries (CA) are blood vessels that originate in the aorta and provide vascularization to the heart muscle. Abnormalities may occur during embryogenesis and can lead to changes in the anatomy and function of the coronary arteries [1]. The prevalence of coronary artery anomalies (CAA) varies in the scientific literature between 1% and 5.6% [2]. This is due to the use of heterogeneous nomenclature and variable diagnostic methods, namely, coronary angiography and autopsies. The widespread use of coronary computed tomography angiography (CCTA) has led to a higher prevalence of coronary artery anomalies being reported (i.e., 7.9%) [2–4]. CAAs are often underdiagnosed because they are not routinely tested for, so early diagnosis is important as it could prevent cases of myocardial ischemia in the area corresponding to the anomaly and, even, sudden death. As such, nowadays, CCTA is considered the gold standard for the diagnosis and characterization of CAA [2,5–7].

The variable incidence of CAA in the scientific literature is also due to inconsistencies in the definition of anomalous variants. Angelini proposed several criteria for establishing what is considered normal anatomy; if this is excluded, the rest of the variants can be considered abnormalities [8]. There is also a numerical expression for some features, such as variations encountered in more than 1% of the general unselected population, but there

are other cases where a qualitative description is required [5,8]. Variations refer to simple variants in coronary anatomy, such as the type of coronary dominance, early branching, or the presence of the intermediate branch [9]. CAAs can also be classified functionally as ischemia obligatory or non-ischemic [8]. There are some considerations; for example, intramuscular bridges are included in several CAA classifications, although from a strictly epidemiological point of view they are found in 0.5% to 12% of the population [2]. Other abnormalities, such as separate origins of the LAD and LCX or an acute take-off angle, vary in incidence but generally have no hemodynamic consequences and are considered benign in most cases [2,5,8,9].

According to 2020 ESC guidelines and 2018 AHA/ACC guidelines for adults with congenital anomalies, CCTA is used for the diagnosis and anatomical evaluation of CAA [10,11]. For patient management, each coronary anomaly specificity must be considered, especially in high-risk anatomy, including ostial abnormalities with acute take-off angles, abnormal courses between large vessels, and intramural trajectories. Additionally, the presence of cardiac symptoms and functional investigation evidence of stress-induced ischemia contribute to recommendations for limiting sports activities and surgical correction [8,9].

To establish the possible causes of ischemia, the association of coronary atheromatous infiltration was evaluated by calculating the calcium score. Correlations between the CCTA result and the cardiological examination were sought, as was the association between the presence of CAA and the presence of cardiac symptoms.

In Europe, a first national multicenter study on CAA, MuSCAT in the Netherlands, started in 2020 and has been ongoing for the last three years, involving six centers and an established working protocol that included CCTA [12]. Other studies reported a prevalence of CAA of 7.9% in a single center in Zurich that investigated 1759 patients by CCTA over a four-year period [3]. Angelini et al. found a prevalence of 5.64% in a continuous series of 1950 coronary angiographies [7].

Regarding CAA in Romania, the current level of knowledge is limited, and the national prevalence has not been established. This study is important because, to our knowledge, it is the first to study the prevalence of CAA by CCTA in a southeastern region. However, a study conducted in the northwestern region of the country reported a prevalence of CAA of 10.3% in patients investigated by the CCTA over a period of 3.3 years [13]. Other CAA prevalence data were obtained by coronary angiography, which found a CAA prevalence of 0.5% [14] and 0.53% [15].

Thus, the aim of the retrospective pilot study was to investigate the prevalence of CAA in patients investigated with CCTA for coronary artery disease (CAD).

The specific objectives of the pilot study were:

1. identifying the characteristics of the Romanian patients with CAA;
2. identifying the particularities of coronary anomalies from an anatomical perspective;
3. establishing the association between CAA and calcium score;
4. determining the association between cardiac symptoms and the presence of coronary anomalies in the sample of patients.

2. Materials and Methods

2.1. Study Design and Participants

A retrospective study was conducted to establish the prevalence of coronary artery anomalies in a group of patients investigated with CCTA for CAD at Carol Davila Central Military Emergency University Hospital, Bucharest, Romania, between February 2021 and December 2022.

The inclusion criteria for the patients were: adults over 18 years of age with suspected CAD according to clinical assessment by the attending cardiologist, and patients with known CAD to assess clinical disease. The exclusion criteria were serum creatinine >1.2 mg/dl, pregnant patients, patients with a history of iodine allergy, patients with unstable angina pectoris, and patients with acute coronary syndrome (ECG changes, elevated cardiac biomarkers).

For categorizing CAA, an anatomical classification from Angelini was used, which includes four main categories of anomalies: anomalies of origin and course, anomalies of intrinsic coronary arterial anatomy and route, anomalies of coronary termination, and anomalous anastomotic vessels [1,8].

Out of 203 CCTA examinations, 184 were included; the rest were excluded due to poor image quality caused by patient movement, motion artifacts due to incorrect breath holding, or spontaneous heart rate irregularities during the CT examination.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Dr. Carol Davila's Central Military Emergency University Hospital, Bucharest, Romania, No. 433/12.01.2021.

2.2. Methodology

All patients underwent a clinical examination and resting electrocardiogram (ECG) prior to CCTA. Coronary anatomy was analyzed by CCTA, and examinations were evaluated for coronary artery origin location, acute angle, height of detachment, course, and intramuscular coronary track length. Coronary artery anatomical variants were established, and coronary anomalies were detected and classified according to Angelini's CAA classification. A semi-automated Agatston score was used to calculate the degree of coronary artery calcification in all patients. Data was retrieved from the patient's medical records and digital records on patient registration in the CT console. The presence of typical and atypical cardiac symptoms suggestive of coronary artery disease was established (angina pectoris, chest tightness, palpitations, dyspnea, or decreased effort tolerance).

2.3. Medical Investigations

2.3.1. Coronary Computed Tomography Angiography (CCTA)

The technique used for the diagnosis of CAA was coronary CT angiography, which consisted of a 128-detector CT system (Revolution EVO 128-slice, GE Healthcare, Milwaukee, WI, USA) and a dedicated angiographic protocol with retrospective cardiac gating. The protocol includes lateral and anteroposterior scouts. The calcium score was initially assessed, a Smart Prep slice 2 cm below the carina was obtained, and then the contrast acquisition was performed. The scan range was 2 cm below the carina, covering the whole heart to the base. The contrast medium was heated to 37 degrees, and 60 mL of iodinated contrast medium were administered at a rate of 5.5 mL/s, followed by 30 mL of contrast medium mixed with serum and then 30 mL of saline solution. A heart rate below 65 beats per minute was obtained by oral administration of beta-blockers approximately one hour before the examination or intravenously at the beginning and during the examination. For a better visualization of the coronary lumen, two puffs of sublingual nitroglycerin were administered at the beginning of the examination, which helped to relax the smooth muscles in the vascular walls.

For the evaluation of the coronary anatomy, image post-processing on a GE Medical System AW VolumeShare 7 station with Volume Viewer Applications CardIQ Function included automatic first coronal trajectory detection and automatic branch annotation. A 3D volumetric reconstruction was performed. The coronary pathway was validated by a physician who also verified the origin of the trunks and the path of the branches and made corrections and additions to the reconstructed pathway. Common images in axial, sagittal, coronal, and various oblique planes were used for the analysis of coronary origins and routes. Maximum intensity projection (MIP) images were used to identify the vascular anatomy but were limited in the analysis of anatomical details and stenoses. Multiplanar reconstructions (MPR) were analyzed with the possibility of making precise measurements. Multiplanar curve reconstructions (CPR) were also used for vascular lumen analysis with the possibility of continuous visualization of the vessel, even the ones with curved routes. Lumen measurements and stenosis analysis were also performed. Volume rendering (VR) 3D images were used to analyze the entire vascular tree anatomy.

2.3.2. Resting Electrocardiogram (ECG)

A resting ECG was used to measure the electrical activity of the heart. The rhythmic contractions of the heart were recorded, reflecting the electrical signal generated by the sinoatrial (SA) node, with the ECG signal's continuous P, Q, R, S, and T peaks at the corresponding moments of the cardiac cycle. The standard electrocardiogram consisted of 12 leads, with correct electrode placement being critical to interpreting the 12-lead resting electrocardiogram. The ECG calibration parameters were set up to record at the standard 25 mm/s and 10 mm/mV. Various cardiac conditions were detected, and ECG changes suggestive of cardiac ischemia were recorded [16,17].

2.3.3. Agatston Calcium Score

The Agatston score is a semi-automated tool used to measure the calcification of coronary arteries. It is routinely performed at the beginning of cardiac CT examinations using a low dose of radiation and an unenhanced CT scan. A density factor is calculated according to the density attenuation in Hounsfield units and the area of the calcification speck. Based on the total value of the calcium score, coronary artery disease (CAD) was graded into five categories: 0 calcium score (no CAD), 1–10 calcium score (minimal CAD), 11–100 (mild), 101–400 (moderate), and more than 400 (severe CAD) [18].

2.3.4. Anatomical Classification of the CAA

CAA were classified using an anatomical classification from Angelini (2007), and the main categories of anomalies included were: anomalies of origin and course, anomalies of intrinsic coronary arterial anatomy and route, anomalies of coronary termination, and anomalous anastomotic vessels [1,8].

2.4. Statistical Analysis

Statistical data analysis was performed using IBM SPSS Statistics 20. For the qualitative data, frequencies and percentages were used, whereas for the continuous data, it was the mean and the standard deviation. For the association between the sample of patients with CAA and other qualitative variables, the Chi-square (χ^2) test was used. The statistically significant threshold was a p -value < 0.05 .

3. Results

3.1. Romanian Patient Characteristics with CAA

The study included 184 individuals who underwent CCTA (87 males and 97 females, mean age 57.05 years). Further, 29 were young patients under 45 years old. The CAAs were present in 16 (8.7%). According to the χ^2 test, there was no statistically significant association between the age and gender of patients and the presence of CAA.

In the whole sample, there were 88 (47.8%) males and 96 (52.2%) females, while in the patients with CAA, there were 9 (56.2%) females and 7 (43.8%) males. In what concerns the age, there was a threshold division, namely, under 45 years and above 45 years. Thus, in the whole sample, there were 29 (15.8%) persons with an age under 45 years, while in the sample with CAA, the number of patients with an age under 45 years was 2 (12.5%). The vast majority of patients have ages above 45 years, and in the whole sample there were 155 (84.2%) patients within this range, whereas in the sample with CAA there were 14 (87.5%) patients.

3.2. The Particularities of Coronary Artery Anatomy, Coronary Artery Anomalies from an Anatomical Perspective

The CAA detected among the study patients were seven (3.8%) anomalies of origin and course and nine (4.9%) anomalies of coronary arterial anatomy with intramuscular bridging. Regarding the normal coronary artery anatomical variants among all patients, 147 (79.9%) presented right coronary artery dominance, 13 (7.1%) presented left coronary artery dominance, and codominance was found in 24 (13.0%) of the patients. The prevalence

of the intermediate branch in all patients was 76 (41.3%), while in patients with CAA, the prevalence was 5 (31.3%).

The age ranges were between 21 and 80 years for the whole sample, and for the patients with CAA, the age ranges were between 21 and 73 years. The CAAs detected were classified according to Angelini [8] and will be described in more detail as follows:

Two cases of anomalous origin of the left main coronary artery arising from the right sinus were found, as depicted in Figure 1.

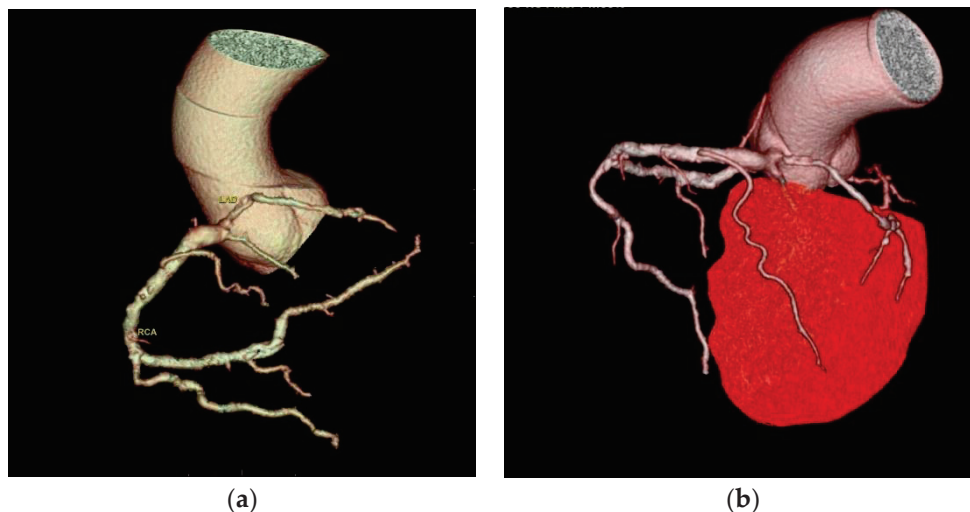


Figure 1. Anomaly of the origin of the left main coronary artery arising from the right anterior sinus. (a) CCTA volume rendered 3D images show the vascular tree anatomy, in which an origin anomaly is present. The left main coronary artery arises from the right sinus immediately above the right coronary artery with an anomalous course anteriorly to the left pulmonary artery towards the anterior interventricular sulcus, where it forms the anterior interventricular and circumflex arteries. The right coronary artery is well developed, with increased dimensions and the presence of a well-developed marginal branch and collateral circulation. Diffuse atheromatous infiltration of the left coronary tree is also present; (b) CTAA volume rendered 3D images show the vascular tree anatomy in relation to the left ventricle.

One case of right coronary anomaly originating from the left coronary sinus was found, with an anomalous course between the left pulmonary artery and the aorta, according to Figure 2.

Two cases of separate origins of LAD and LCX arising directly from the left coronary sinus were found, as illustrated in Figure 3.

One case of detachment of the left main coronary artery from the left coronary sinus at an acute angle was found (Figure 4).

One case of congenital cardiac malformation with transposition of the great arteries and associated variation of origin and course of the coronary arteries was found (Figure 5).

Nine cases of coronary anomalies with intramuscular bridging of the left anterior descending artery were found (Figure 6).

3.3. Identifying the Association between CAA and Coronary Calcium Score

Among all patients, 104 (56.5%) presented no calcium load, 6 (3.3%) presented a minimal calcium score (1–10 UA), 26 (14.1%) presented a mild calcium impairment (11–100 UA), 33 (17.9%) presented a moderate calcium score (101–400 UA), and 15 (8.2%) presented a calcium score of more than 400 UA. Among patients with CAA, 13 (81.3%) presented a calcium score of zero, and 3 (18.8%) had moderate calcium impairment. No statistically significant association was detected between the presence of CAA and the levels of calcium, as shown in Table 1.

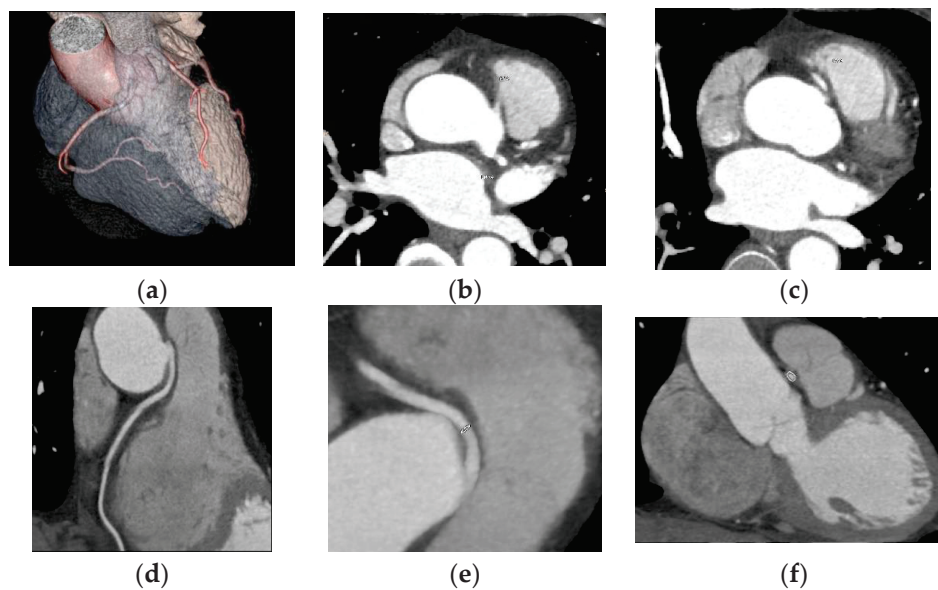


Figure 2. Anomaly of the origin of the right coronary from the left anterior coronary sinus, with a course between the pulmonary artery and the aorta. (a) CCTA volume rendered cardiac transparency images showing anomaly of origin and course; the right coronary anomaly originates from the left coronary sinus with an anomalous course between the left pulmonary artery and the aorta. Normal origin of the left main coronary artery from the posterior portion of the left coronary sinus with a normal trajectory. Intermediate filiform branch is present; (b) CCTA axial contrast-enhanced image at the aortic root showing anomaly of the origin and course; the right coronary abnormally originates from the left coronary sinus; (c) CCTA axial contrast-enhanced image at the aortic root showing RCA with an anomalous course between the pulmonary artery and the aorta; (d) CCTA curved planar reformatted image of the RCA; (e) CCTA curved planar reformatted image of the RCA origin; (f) CCTA vessel cross-section image of the RCA with an anomalous course between the pulmonary artery and the aorta.



Figure 3. Separate origins of the left anterior descending artery and circumflex artery from the left anterior coronary sinus. CCTA Volume rendered 3D images of the vascular tree anatomy, showing the LAD and LCX arise directly from the left coronary sinus. RCA with normal origin from the right coronary sinus and normal course.

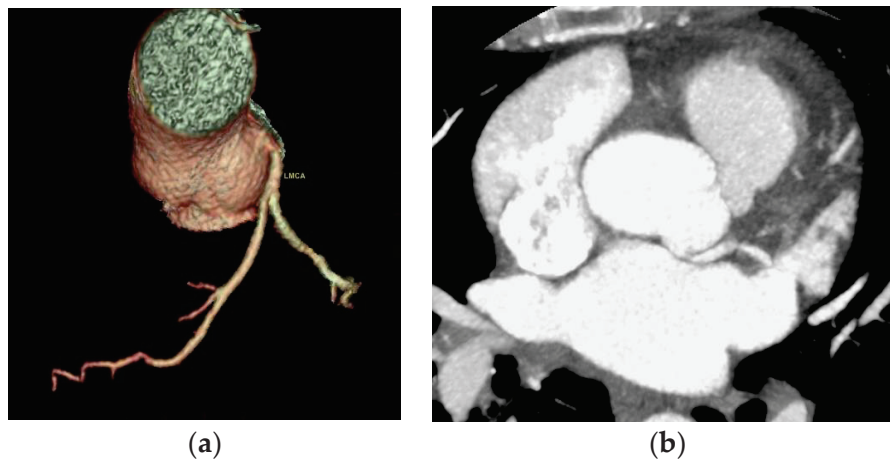


Figure 4. Acute take-off angle of the left main coronary artery. (a) CCTA volume rendered 3D images of the vascular tree anatomy show detachment of the left main coronary artery from the upper and posterior portion of the left coronary sinus at a sharp angle; (b) CCTA MIP axial contrast-enhanced image at the aortic root shows detachment of the left main coronary artery from the left coronary sinus at a sharp angle with the presence of posterior contact with the left atrium.

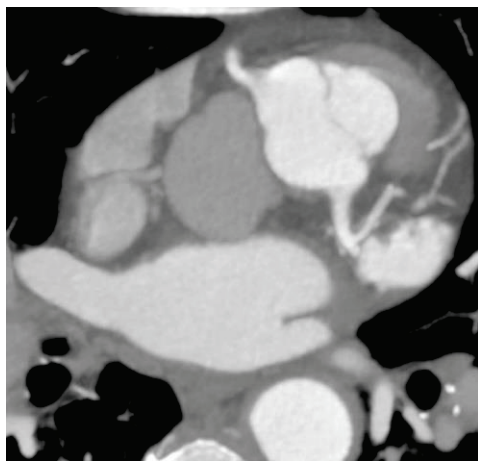


Figure 5. Congenital cardiac malformation with corrected transposition of the great arteries and abnormally rotated aortic cusps and origin of the coronary arteries. CCTA MIP oblique axial contrast-enhanced image at the aortic root shows congenital cardiac malformation with corrected transposition of the great arteries. The aorta is to the left of the pulmonary artery trunk; the aorta is in continuity with the left systemic ventricle, and the pulmonary artery is in continuity with the pulmonary ventricle. The malformation also involves aortic cusps that are abnormally rotated in the axial plane: two anterior sinuses, one on the right and one on the left, related to the patient, and a posterior one. The left main coronary artery arises from the posterior sinus, shows a posterior trajectory of 10 mm, and divides into the LAD and LCX. The LAD arises at a sharp angle and descends on the anterior face of the systemic ventricle. The RCA arises from the anterior right sinus and descends towards the anterior interventricular sulcus.

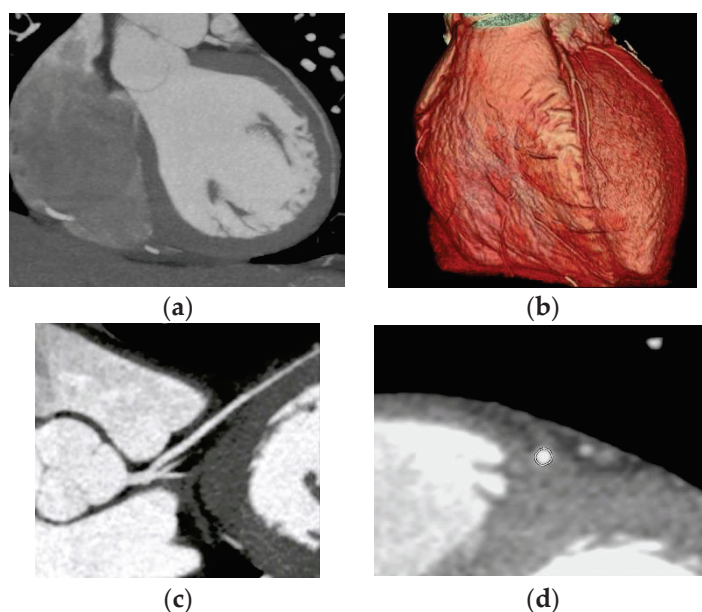


Figure 6. Intramuscular bridging of the left anterior descending artery. (a) CCTA oblique sagittal maximum intensity projection image of the LAD route shows intramuscular bridging of the left anterior descending artery in the second segment for a 30 mm distance and 3 mm depth; (b) CTAA volume rendered 3D images show the LAD in the atrioventricular groove entering an intramural route; (c) CCTA curved planar reformatted image of the LCA entering an intramural route; (d) CCTA vessel cross-section image of the LCA with intramural course.

Table 1. The association between CAA and coronary calcium score.

Variable	Whole Sample (n = 184)	Patients with CAA (n = 16)	
Coronary calcium levels	Frequency (%)	Frequency (%)	<i>p</i> value
No calcium	104 (56.5%)	13 (81.3%)	0.17 (NS)
Minimal	6 (3.3%)	0 (0%)	
Mild	26 (14.1%)	0 (0%)	
Moderate	33 (17.9%)	3 (18.8%)	
High	15 (8.2%)	0 (0%)	

Note: NS = not statistically significant.

3.4. Determining the Presence of Cardiac Symptoms and the Association with CAA

Among all patients, 94 (51.1%) presented cardiac symptoms, and among patients with CAA, 12 presented cardiac symptoms, and there was a statistically significant association between the presence of cardiac symptoms and CAA ($p = 0.045$).

Regarding the management of patients, the functional aspects of coronary anomalies were analyzed with the help of cardiac tests, mainly resting ECG. Among the study sample of patients, 23 (12.5%) presented changes suggestive of cardiac ischemia in the resting ECG, and among patients with CAA, 3 (18.8%) presented changes suggestive of cardiac ischemia in the resting ECG. In addition, no statistically significant association was detected between the presence of CAA and the presence of changes in the resting ECG ($p = 0.42$).

Among the 16 patients with CAA, 2 underwent revascularization treatment, and the remaining patients were discharged with close follow-up.

4. Discussion

The aim of this cross-sectional pilot study was to assess the prevalence of CAA in a Romanian sample of patients who were investigated with CCTA for CAD. The sample of patients with CAA consisted of 16 patients, mainly women with an age higher than 45.

In what concerns the prevalence of coronary anomalies in the scientific literature, it varies between 1% and 5.6%, but the use of CCTA has led to a higher prevalence (7.9%) of CAA being reported [2–4]. In this study, the prevalence of coronary artery anomalies obtained was 8.7%, similar to the one found in scientific literature. Among all patients, 7 (3.8%) had anomalies of origin and course, and 9 (4.9%) had anomalies of coronary arterial anatomy with intramuscular bridging.

Two cases of a left coronary artery originating from the right coronary sinus were found; this is a rare anomaly; the prevalence of coronary artery anomalies arising from the opposite site in the scientific literature is between 0.1% and 0.2%, with the left coronary arising from the right sinus being six times rarer than the right coronary artery originating from the left sinus [19]. This is considered an anomaly associated with a risk of sudden death estimated between 0.17% and 0.35% because of the larger myocardial territory associated with ischemic risk [19,20].

One case of CAA with a right coronary anomaly originating from the left coronary sinus and an anomalous course between the pulmonary artery and the aorta was detected; a dynamic compressive effect could not be excluded at this level. According to the anatomical classification of the CAA of Angelini, there are several possible routes for the anomalous location of the coronary ostium at improper aortic sinus: in the posterior atrioventricular groove, retroaortic, between the aorta and the pulmonary artery, intraseptal, anterior to the pulmonary flow, in the posteroanterior interventricular groove [8]. The CAA with a route between the aorta and the pulmonary artery is considered the highest-risk route and is associated with an increased risk of sudden death. Young people are the most vulnerable to sudden death; the risk decreases for middle-aged and elderly people [5,21,22]. One hypothesis for why this effect occurs is that, during exercise, the aortic root and the pulmonary trunk expand and compress the coronary that passes between them. Another hypothesis is that the course of the coronary artery is partially embedded in the aortic wall and is laterally compressed during exertion [5,22,23].

Two cases of separate origins of the LAD and LCX directly from the left coronary sinus were detected. Separate origins of LAD and LCX from the left coronary sinus is considered a benign variant, but some CAA classifications include it. It is considered a common CAA with a frequency between 0.41% and 0.67% [5,24].

One anomaly of detachment of the left main coronary artery from the left coronary sinus at an acute angle was encountered. In terms of route, the normal proximal orientation of the LM and RCA is 45° to 90° to the aortic wall, with a subepicardial extramural route to destination [5]. In scientific literature, the prevalence of acute angles of detachment of the coronary artery from the coronary sinus is 2% [2].

Coronary anomalies may coexist with other cardiac anomalies [1]. For instance, in 26% of cases, coronary anomalies are associated with aortic root anomalies [5]. In this study, one congenital cardiac malformation with corrected transposition of the great arteries was encountered. The CCTA has an increased capacity to diagnose cardiac malformations, coronary anatomy, and their relationship. In patients with transposition of the great vessels, the identification of coronary anatomy is fundamental for patient management and, eventually, for surgical intervention [25,26]. The cardiac malformation in this study is on the benign spectrum of the condition due to the presence of three separate sinuses and no malignant coronary course running between the aortic pathway and the right ventricular outflow tract.

In coronary intramyocardial bridging, a portion of the epicardial coronary pathway is covered by heart muscle; the artery most affected by this condition is the LAD artery [1]. Nine cases of coronary artery intramuscular bridging were detected, and the findings are consistent with the scientific literature; all cases included the left anterior descending artery.

Intramuscular bridges are frequently an incidental encounter in CCTA examinations, and only some of them associate systolic compression with a possible reduction in myocardial perfusion. Intramuscular bridges are sometimes associated with atypical angina pectoris. The impact of myocardial bridges on the risk of myocardial infarction is debatable. They are generally considered benign conditions, but the length and depth of the intramyocardial bridge may influence the degree of coronary dysfunction, with some studies showing an association of myocardial bridges with increased risk of myocardial infarction [27–29].

Identifying the association between CAA and coronary calcium score involves vessels with abnormalities of origin and route, which have a longer, more tortuous path and flow turbulence that cause damage to the vascular endothelium and tend to trigger the development of atherosclerosis. Thus, CAA of origin and trajectory contribute to myocardial ischemia [5,8,22,24]. In this study, 56.5% of the patients presented no calcium load, 3.3% presented a minimal calcium score, 14.1% presented a mild calcium impairment, 17.9% presented a moderate calcium score, and 8.2% presented a calcium score greater than 400 UA. The calcium score in patients with CAA was zero in 81.3%, and 18.8% had moderate calcium score values; no statistically significant association was detected between the presence of CAA and the presence of calcium levels.

Concerning the presence of cardiac symptoms and the management of patients with CAA, numerous studies have shown that CCTA is the gold standard method for investigating CAA [2,6,7].

There are many advantages to using CCTA to investigate CAA. Compared to coronary angiography, CCTA can provide further information regarding the relationship with other cardiac structures [2,30,31], is non-invasive [3,32], and requires less irradiation [33–35]. Furthermore, compared to coronary angiography and MR angiography (MRA), CCTA has better accessibility, time, and cost efficiency [30,31]. In this study, some of the patients were referred because of previous equivocal tests like coronary angiography and echocardiography. The results of several studies have shown that CCTA is a viable non-invasive method for detecting coronary anomalies, including in the case of equivocal coronary angiography [36].

For the management of CAA, international guidelines (2020 ESC guidelines and 2018 AHA/ACC guidelines for adults with congenital anomalies) recommend CCTA for the diagnosis and anatomical evaluation of CAA [10,11]. Under certain conditions, if there are symptoms and evidence of a stress-induced abnormality in association with the abnormality, surgical intervention is recommended, but for asymptomatic patients, surgical intervention is only considered. Special attention should be given to high-risk anatomy, including ostial abnormalities such as an acute take-off angle, a slit-like orifice, an ostium more than 1 cm above the sinotubular junction, and an abnormal course between large vessels that contribute to recommendations for limiting sports activities and surgical correction [10,11].

Thus, the presence of cardiac symptoms plays an important role in deciding the patient's management. In this study, among all patients, 94 (51.1%) presented cardiac symptoms, and among patients with CAA, 12 presented cardiac symptoms, and there was a statistically significant association between the presence of cardiac symptoms and CAA.

Functional aspects were analyzed with resting ECGs; in the study, 23 (12.5%) of all patients showed changes suggestive of cardiac ischemia, and among patients with CAA 3, 18.8% showed changes.

Among the 16 patients with CAA in the study, 2 underwent revascularization treatment. The remaining individuals were discharged with close follow-up.

There are limitations to the study from an imaging perspective, namely that the coronary CT angiography image quality is impaired by the impossibility of performing respiratory commands and by cardiac arrhythmias. There are contraindications and limitations to coronary CT angiography, such as pregnancy, chronic renal failure, or iodine allergy.

Other limitations relate to the pilot study, namely the number of patients. The outcomes of the study cannot be generalized to the entire population of Romania; future

directions involve continuing the study on a larger patient group with diverse socio-demographic characteristics.

The increase in the number of CCTA investigations, compared to coronary angiography, leads to an increase in the prevalence of detected coronary anomalies. Currently, there are no randomized multicenter prospective studies in the scientific literature, and the management of patients with CAA is performed by analyzing each individual case, considering symptoms, age, and the presence of risk abnormalities. More evidence based on multicenter studies and follow-up studies is needed to make the current recommendations more effective [37].

5. Conclusions

CCTA is a useful anatomical method to identify and characterize coronary anomalies. The prevalence of coronary artery anomalies obtained was 8.7%. According to Angelini's classification, various coronary anomalies have been detected; among all patients, 3.8% had anomalies of origin and course, and 4.9% had anomalies of coronary arterial anatomy with intramuscular bridging. CCTA also provides information about the presence of atherosclerotic disease; by calculating the calcium score, the atheromatous burden was determined.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on reasonable request from the corresponding author (A.S.C.). The data are not publicly available due to ethical restrictions.

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Article

Thrombus Imaging Characteristics to Predict Early Recanalization in Anterior Circulation Large Vessel Occlusion Stroke

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Abstract: The early management of transferred patients with a large vessel occlusion (LVO) stroke could be improved by identifying patients who are likely to recanalize early. We aim to predict early recanalization based on patient clinical and thrombus imaging characteristics. We included 81 transferred anterior-circulation LVO patients with an early recanalization, defined as the resolution of the LVO or the migration to a distal location not reachable with endovascular treatment upon repeated radiological imaging. We compared their clinical and imaging characteristics with all (322) transferred patients with a persistent LVO in the MR CLEAN Registry. We measured distance from carotid terminus to thrombus (DT), thrombus length, density, and perviousness on baseline CT images. We built logistic regression models to predict early recanalization. We validated the predictive ability by computing the median area-under-the-curve (AUC) of the receiver operating characteristics curve for 100 5-fold cross-validations. The administration of intravenous thrombolysis (IVT), longer transfer times, more distal occlusions, and shorter, pervious, less dense thrombi were characteristic of early recanalization. After backward elimination, IVT administration, DT and thrombus density remained in the multivariable model, with an AUC of 0.77 (IQR 0.72–0.83). Baseline thrombus imaging characteristics are valuable in predicting early recanalization and can potentially be used to optimize repeated imaging workflow.

Keywords: early recanalization; transferred patients; intravenous thrombolysis; endovascular treatment; acute ischemic stroke

1. Introduction

Current treatment options for acute ischemic stroke (AIS) patients with large vessel occlusions (LVOs) are intravenous thrombolysis (IVT) and endovascular treatment (EVT) [1,2]. IVT can induce rapid recanalization prior to EVT, may increase the rate of successful reperfusion with EVT, and can dissolve thrombi located in regions not reachable by EVT [2–4]. However, the administration of IVT before EVT increases the risk of hemorrhages and potentially increases the chances of thrombus fragmentation [5,6]. In

addition, IVT has been proven to be less effective in proximal large vessel occlusions (LVOs) compared to more distal occlusions [3], while EVT can successfully be targeted at proximal LVOs, especially those that are refractory to IVT [7].

In LVO-AIS patients transferred from primary stroke centers (PSCs), early recanalization (i.e., dissolution of the LVO on neuroimaging at the CSC, relinquishing the need for EVT) following IVT is reported to occur in 20–40% of all cases [8–10]. This underlines the importance of IVT in transferred LVO-AIS patients. Being able to predict the PSC at which patients will or will not recanalize early might improve treatment planification, leading to optimized resource expenditure and cost reduction [11,12]. In the case of the accurate prediction of early recanalization, futile inter-hospital transfers (and therefore capacity constraints at the CSC) could be limited. Determining which patients will not recanalize early can help with speeding up the workflow to the angio-suite room, by, e.g., avoiding the need to perform repeated imaging at CSC admission, which, on average, takes 20 min longer [13].

Thrombus characteristics, such as size or composition, play a major role in the recanalization process [14–19], and therefore, can be determinant of treatment effect and patient outcome. Such characteristics can be assessed on baseline radiological imaging. An early-stage assessment of these characteristics may guide treatment selection. The goal of our study is to identify predictors of early recanalization in transferred AIS patients based on baseline patient clinical and thrombus imaging characteristics.

2. Materials and Methods

2.1. Study Design and Patient Selection

We included patients with definite LVO at PSC who had early recanalization on repeated imaging at CSC. Our database consists of adult (≥ 18 years) stroke patients, who were referred to our CSC (Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands) for EVT between January 2016 and January 2021. We excluded late-window patients who presented at the CSC later than 6 h after symptom onset.

The patients were part of our regional prospective stroke database, in which all EVT referrals from the 11 PSCs in our region (catchment area ~ 3.4 million) were collected. Early recanalization was defined as the resolution of the proximal LVO (internal carotid artery (ICA); middle cerebral artery (MCA) M1 and proximal M2 segments; anterior cerebral artery (ACA) A1 and proximal A2 segments) or its migration to a distal location not eligible for EVT (distal M2, M3, distal A2, A3).

The reasons to undergo repeated imaging mainly include clinical improvement or deterioration [13]. Therefore, non-early recanalized patients from the repeated imaging group are suspected to be non-representative of commonly transferred LVO patients. Since baseline imaging data of patients transferred to our center without repeated imaging were not available, consecutive non-early recanalized transferred patients from the MR CLEAN Registry were collected for comparison. The MR CLEAN Registry is a multicenter prospective observational registry of all patients undergoing EVT for AIS in The Netherlands. Our hospital is part of this registry.

From the MR CLEAN Registry, we selected adult (≥ 18 years) stroke patients with an LVO of the anterior circulation that were referred to a CSC for EVT between March 2014 and November 2017, were presented at the CSC within 6 h after symptom onset and had baseline thrombus imaging measurements available. These patients had a persistent LVO, as confirmed by the first digital subtraction angiography run (for the transferred patients in the Registry, repeated imaging was not available).

2.2. Ethical Approval

For the regional database, this study was evaluated by the medical ethics review committee of the Amsterdam University Medical Centers, location AMC, who waived the need for obtaining written informed consent. The procedures followed were all in

accordance with institutional guidelines. A letter with detailed information about the study was sent to all patients meeting the inclusion criteria. The patient or legal representative had the opportunity to deny consent for use of their data via an opt-out form, conforming to the European Union General Data Protection Regulation.

The MR CLEAN Registry was approved by the central medical ethics committee of the Erasmus Medical Center Rotterdam, which served as the review board of all participating centers and granted permission to carry out the study as a registry (MEC-2014–235). All patients or legal representatives were provided with oral and written information on the registry and had the opportunity to withdraw consent to use their data.

2.3. Patient and Thrombus Imaging Characteristics

2.3.1. Regional Database

Clinical and imaging data of patients from between January 2016 and June 2019 were already available [8]. For patients included between June 2019 and January 2021, additional measurements and data collection were performed following the same procedures as stated previously [8].

The National Institute of Health Stroke Scale (NIHSS) was used to determine stroke severity at baseline. If not reported by the treating physician, the NIHSS was scored retrospectively from written neurological examinations, in accordance to previously published methods [20].

The workflow metrics collected were time from stroke onset to arrival at the PSC, time from stroke onset to imaging at the PSC, time from arrival to the PSC to initiation of IVT, time from arrival at the PSC to arrival at the CSC, and time from IVT initiation to arrival at the CSC.

Thrombus imaging characteristics included occlusion location, the distance from the terminus of intracranial carotid artery to the thrombus (DT), thrombus length, thrombus density, and thrombus perviousness.

The location of the intracranial LVO was assessed on CTA and subsequently compared with imaging from the PSC by experienced neuroradiologists from the CSC during routine clinical work-up. All included patients were eligible for EVT on baseline CT imaging with an occlusion of the ICA, the M1 vessel segment, the proximal M2 segment of the MCA or A1 segment, and the proximal A2 segment of the ACA. Also, the presence of an ipsilateral extracranial internal carotid artery stenosis/occlusion was scored as part of the routine clinical work-up. The method to measure DT, length, density, and perviousness has previously been described [8]. Baseline non-contrast CT and CT angiography data were coregistered using Elastix software [21]. Measurements were performed on ITK snap software, which permits on to simultaneously visualize and place markers on both CT scans [22]. Markers were manually placed along the occluded vessel centerline at the following locations: ICA terminus, proximal and distal thrombus borders, and proximal, mid, and distal parts of the thrombus (Figure 1). In case of curved and tortuous vessels, additional markers were placed between the ICA terminus and the proximal thrombus border. These measurements were performed by 3 trained observers: NAT, ISJS, and AAEB.

With these markers, DT and thrombus length were acquired by computing the Euclidean distance between adjacent markers. Thrombus density and perviousness were computed as the average intensities over a 1 mm-radius region of interest at the proximal, mid, and distal thrombus markers. Thrombus perviousness is a proxy of permeability and assesses how much contrast penetrates the thrombus.

If coregistration errors were present, DT and thrombus length were measured by placing markers in one of the CT scans and using the other one as a reference. Thrombus perviousness and density were only measured in good-quality thin-slice CT data (i.e., images without movement, metal and beam hardening artefacts, incomplete field of view, excessive noise, and poor contrast opacification).

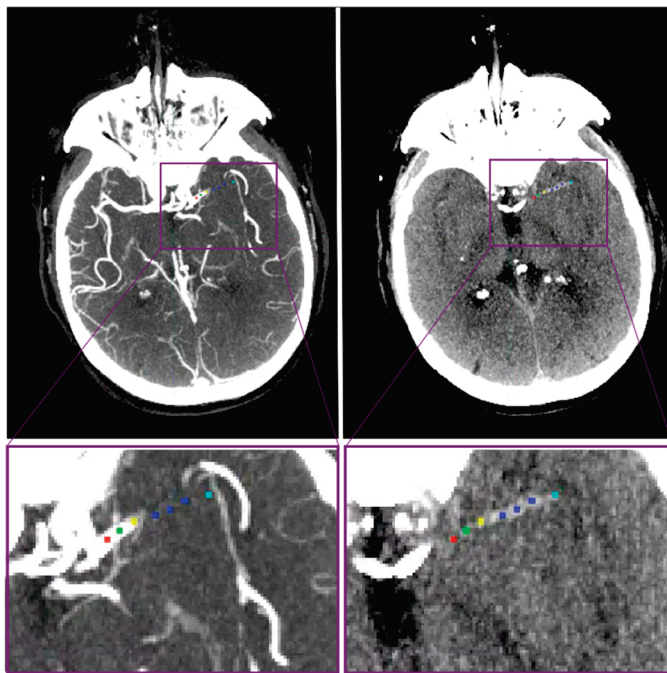


Figure 1. Thrombus imaging characteristics. Manually placed markers to compute thrombus characteristics. **Left:** thick-slab maximum intensity projection of a CT angiography showing a sudden stop of contrast due to the occlusion. **Right:** thick-slab maximum intensity projection of a non-contrast CT where the hyperdense artery sign of the thrombus is visible. Red marker: placed at internal carotid artery terminus (ICA-T). Green markers: placed between ICA-T and proximal border of the thrombus. Yellow marker: proximal thrombus border. Blue markers: proximal, mid, and distal parts of the thrombus. Cyan marker: distal thrombus border.

The modified Rankin scale score at 90 days, with a score ranging from 0 to 6 (0 being no symptoms and 6 being death) was also registered to assess differences in functional outcome. Good functional outcome was defined as an mRS between 0 and 2. A symptomatic intracerebral hemorrhage (sICH) was defined as hemorrhage resulting in neurological deterioration with an increase in NIHSS ≥ 4 [23].

2.3.2. MR CLEAN Database

The data collection and thrombus imaging characteristics methods from the MR CLEAN Registry have already been described in detail previously [24,25]. The followed patient workup is in line with the one described here (our hospital is one of the MR CLEAN centers).

2.4. Statistical Analysis

Our analysis consists of (1) comparing early-recanalized LVO (ER-LVO) and non-early-recanalized LVO (NER-LVO) patients and (2) building a logistic regression model to predict early recanalization using clinical and imaging data available at the PSC. To perform the statistical analysis in the group comparison, we used R (version 4.2.0). To build the prediction model, we used SciPy and Scikit-learn libraries from Python (version 3.6).

2.4.1. Group Comparison

We compared baseline patient clinical and thrombus imaging characteristics between ER-LVO and NER-LVO patients. Numerical data are presented as median and interquartile range (IQR) and categorical data as number and proportion (%). The Mann–Whitney U test was used to compare numerical data, and the χ^2 and Fisher’s exact tests for categorical data. Post-hoc analyses were adjusted with Bonferroni corrections for multiple testing. Statistical significance was set at $p < 0.05$.

2.4.2. Prediction Model

We built a multivariable binary logistic regression model to predict early recanalization using both clinical and thrombus imaging variables available at the PSC. We initially included all variables for which the difference had a $p < 0.1$ in the group comparison. The collinearity of these characteristics was assessed by computing Spearman's pairwise correlation coefficients (ρ) for two numerical (or categorical ordinal) variables, the Cramer's V coefficient for two categorical variables, and Point-biserial correlation coefficients (r_{pb}) for a binary and a numerical variable. Strongly correlated variables ($|\rho| > 0.6$, $V > 0.6$, $|r_{pb}| > 0.6$) were removed from the model. In addition, parameters were excluded from the model using manual backward elimination.

To fairly assess the predictive value of our model, we built the model on training sets and assessed the model's performance on testing sets. To minimize potential biases due to the data splitting, we validated the predictive ability of the models by computing the median of the area under the curve (AUC) of the receiver operating characteristics (ROC) curve for 100 5-fold cross-validations; i.e., 100 times, we split the database into 5 groups, and took each group as a testing set (20% of all data), while the remaining groups were used as a training set (80% of all data). Calibration curves (or reliability diagrams) were built using the whole dataset to compare the predicted and true probabilities of early recanalization. We additionally reported the sensitivity (true ER-LVO rate) and specificity (true NER-LVO rate) of the model. Patients with missing data were excluded.

3. Results

3.1. Patient and Thrombus Imaging Characteristics

We included 81 ER patients and 322 patients from the registry with a persistent LVO. (Supplemental Figure S1). In 43/81 patients, the thrombus completely dissolved, and in 38/81 patients the thrombus migrated to a more distal segment of the vasculature, too distal to be treated with EVT. Spontaneous recanalization (defined as early recanalization without IVT) occurred in 6/81 patients: 3 patients with complete thrombus dissolution, and 3 patients with a thrombus that was too distally migrated for EVT.

ER-LVO patients showed more often IVT administrations (93% vs. 78%, $p < 0.01$) and had lower NIHSS scores at CSC presentation (5 vs. 16, $p < 0.01$) than NER-LVO patients. The workflow-related time metrics show that in the ER-LVO group, the arrival at PSC to arrival at CSC time (157 min vs. 101 min, $p < 0.01$) and the IVT initiation to arrival at CSC time (126 min vs. 76 min, $p < 0.01$) were longer compared to the NER-LVO group. ER-LVO patients tended to be older (75 years vs. 71 years, $p = 0.05$) and had lower rates of hypertension (35% vs. 46%, $p = 0.08$), but these differences were not significant (Table 1).

A chart of thrombus imaging measurements in the early-recanalized group can be found in Supplemental Figure S2. For the registry patients, such a chart is presented in [25]. ER-LVO patients had fewer ICA occlusions (1% vs. 23%, $p < 0.01$ after Bonferroni correction) and more M2 occlusions (32% vs. 13%, $p < 0.01$ after Bonferroni correction). This was also reflected in the DT measure: ER-LVO patients had more distal thrombi (DT of 23 mm vs. 10 mm, $p < 0.01$). We also found that ER-LVO patients had shorter (16 mm vs. 18 mm, $p = 0.02$), more pervious (12 HU vs. 5 HU, $p < 0.01$) and less dense thrombi (43 HU vs. 50 HU, $p < 0.01$) compared to NER-LVO patients (Table 1).

We found that ER-LVO patients tend to have better functional outcomes (mRS 0–2, 52% vs. 38%, $p = 0.06$) and fewer occurrences of sICH (0% vs. 8%, $p = 0.07$), but these differences were not significant (Table 1).

Table 1. Baseline characteristics, thrombus imaging characteristics and patient functional outcome.

Baseline Clinical Characteristics *	ER-LVO, n = 81	NER-LVO, n = 322	p-Value
Age (years)—median (IQR)	75 (63–85)	71 (62–80)	0.05
Sex, female—no./total (%)	45/81 (56)	166/322 (52)	0.52
Medical history—no./total (%)			
Previous stroke	17/80 (21)	54/317 (17)	0.38
Diabetes mellitus	16/80 (20)	54/319 (17)	0.52
Hypertension	28/80 (35)	142/310 (46)	0.08
Atrial fibrillation	14/80 (18)	79/317 (25)	0.16
Pre-stroke mRS 0–2—no./total (%)	59/81 (92)	289/314 (92)	0.97
Systolic blood pressure ^α (mmHg)—median (IQR)	149 (130–166)	150 (133–164)	0.61
Diastolic blood pressure ^β (mmHg)—median (IQR)	82 (76–90)	80 (70–90)	0.31
NIHSS _{CSC} ^γ —median (IQR)	5 (2–10)	16 (12–20)	<0.01
IVT—no./total (%)	75/81 (93)	251/322 (78)	<0.01
Workflow related timing variables—median (IQR)	ER-LVO, n = 81	NER-LVO, n = 322	p-value
Onset [†] -to-PSC-door ^δ (min)	50 (35–96)	52 (39–97)	0.52
Onset-to-PSC-imaging ^ε (min)	67 (52–118)	67 (47–110)	0.72
PSC door-to-IVT ^ζ (min)	25 (18–33)	24 (18–33)	0.79
PSC door to CSC door ^η (min)	157 (122–240)	101 (81–128)	<0.01
IVT-to-CSC door ^θ (min)	126 (92–178)	76 (56–97)	<0.01
Thrombus imaging characteristics [‡]	ER-LVO, n = 81	NER-LVO, n = 322	p-value
Occlusion location—no./total (%)			<0.01
ICA	1/81 (1)	74/320 (23)	
M1	53/81 (65)	201/320 (63)	
M2	26/81 (32)	43/320 (13)	
A1/A2	1/81 (1)	2/320 (1)	
DT ^ι (mm)—median (IQR)	23 (14–32)	10 (0–21)	<0.01
Thrombus length ^κ (mm)—median (IQR)	16 (11–21)	18 (12–30)	0.02
Thrombus perviousness ^λ (HU)—median (IQR)	12 (4–21)	5 (–2–12)	<0.01
Thrombus density ^λ (HU)—median (IQR)	43 (36–52)	50 (44–56)	<0.01
Patient functional outcome	ER-LVO, n = 81	NER-LVO, n = 322	p-value
mRS at 90 days			<0.01
0	8/50 (16)	15/293 (5)	
1	12/50 (24)	40/293 (14)	
2	6/50 (12)	57/293 (19)	
3	3/50 (6)	46/293 (16)	
4	4/50 (8)	33/293 (11)	
5	5/50 (10)	15/293 (5)	
6	12/50 (24)	87/293 (30)	
Good functional outcome (mRS 0–2) at 90 days	26/50 (52)	112/293 (38)	0.06
sICH	0/81 (0)	13/322 (4)	0.07

Missing values: ^α 14, ^β 15, ^γ 22, ^δ 127, ^ε 52, ^ζ 185, ^η 126, ^θ 190, ^ι 10, ^κ 16, and ^λ 43. * Scored at PSC unless stated otherwise. [†] Witnessed stroke onset or, if unknown, time the patient was last seen well. [‡] Characteristics scored at baseline CT imaging (at PSC). BL, baseline; CSC, comprehensive stroke center; CT, computed tomography; DT; distance from intracranial carotid artery terminus to the thrombus; HU, Hounsfield units; IQR, interquartile range; IVT, intravenous treatment with alteplase; mm, millimeters; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PSC, primary stroke center; sICH, symptomatic intracranial hemorrhage.

3.2. Prediction Model

We considered the following variables available at PSC admission with a $p < 0.1$ in the group comparison: age, history of hypertension, IVT administration, occlusion location, DT, thrombus length, perviousness, and density. Correlation analysis showed that DT and occlusion location ($\rho = 0.66$, $p < 0.01$) were strongly correlated (Supplemental Figure S3)—therefore, we did not include occlusion location. The results before and after backward elimination can be found in Table 2. After backward elimination, we found that IVT administration (OR 4.3, 95% CI 1.2–15.4, $p = 0.03$), DT (OR 1.03, 95% CI 1.01–1.05 per mm, $p < 0.01$) and thrombus density (OR 0.94, 95% CI 0.90–0.97 per HU, $p < 0.01$) remained in the model (Table 2). The median (and IQR) ROC curve of the 100 5-fold cross-validations and calibration curves are displayed in Figure 2. The median AUC of the ROC curve was 0.77 (IQR 0.72–0.83). For a specificity of 70%, we achieved a sensitivity of 71%.

Table 2. Predictive model of early recanalization. Results of the multivariable binary logistic regression model before and after backward elimination.

Prediction model	Before Backward Elimination, n = 348		
	Characteristics Associated with Early Recanalization	Odds Ratio (95% CI)	p-Value
	Age (per year)	1.01 (0.98–1.04)	0.29
	Hypertension	0.45 (0.20–1.01)	0.05
	IVT administration	3.77 (1.04–13.64)	0.04
	DT (per mm)	1.03 (1.01–1.06)	<0.01
	Thrombus length (per mm)	1.00 (0.97–1.03)	0.98
	Thrombus perviousness (per HU)	1.01 (0.98–1.04)	0.40
	Thrombus density (per HU)	0.94 (0.90–0.98)	<0.01
	After backward elimination, n = 360		
	Characteristics associated with early recanalization	Odds ratio (95% CI)	p-value
	IVT	4.3 (1.2–15.4)	0.03
	DT (per mm)	1.03 (1.01–1.05)	<0.01
	Thrombus density (per HU)	0.94 (0.90–0.97)	<0.01

CI, Confidence Interval; DT, distance from intracranial carotid artery terminus to the thrombus; IVT, intravenous thrombolysis with alteplase; mm, millimeters.

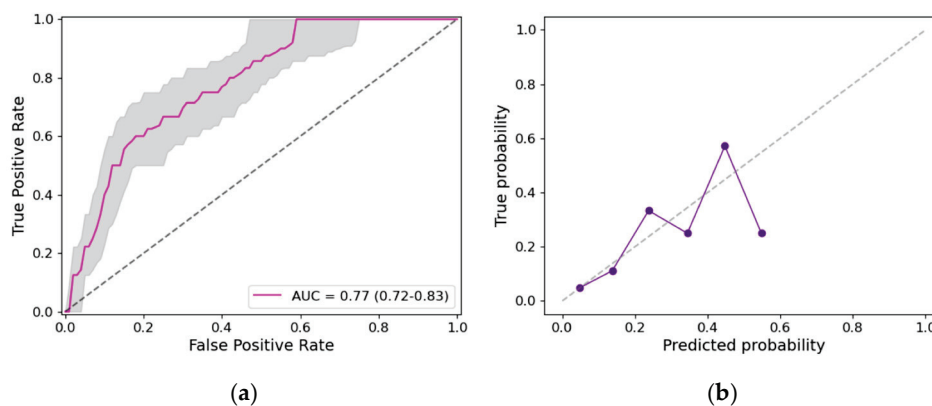


Figure 2. Model performance and calibration curves. (a) Median (magenta) and interquartile range (grey) of the ROC curve for 100 5-fold cross-validations. Median AUC was 0.77 (IQR 0.72–0.83). (b) Calibration curve showing the true probability over the predicted probability. AUC, area under the curve; ROC, receiver operating characteristics.

4. Discussion

In our study, IVT administration, longer door-to-door times, more distal occlusions, and shorter, more pervious, less dense thrombi were associated with early recanalization. Our model for early recanalization prediction based on clinical and thrombus imaging variables collected at PSC admission showed moderate discriminative ability. Assessing the imaging characteristics of the thrombus at an early stage may support clinical evidence and contribute to the optimization of transferred patients' workflow.

In an earlier study, we compared thrombus and patient characteristics between early-recanalized and non-early-recanalized LVO-AIS transferred patients that underwent repeated imaging from our regional prospective stroke registry [8]. In our current study, we have shown that thrombus imaging characteristics and IVT administration are significant predictors for early recanalization in transferred patients.

Our current study also shows an indication that early recanalization is time-dependent: ER-LVO patients had longer times between IVT administration and CSC presentation. This association needs to be further elucidated: rural areas with long inter-hospital transfer times might have higher rates of ER than a highly urbanized setting, like our region.

In respect to other workflow times, we did not show an association between onset-to-IVT time and early recanalization. In other research, a shorter onset-to-IVT time was associated with higher rates of recanalization [26]—thrombi are suspected to grow [27], become stiffer and contract over time, challenging IVT penetration [28]. One possible explanation for our contrasting result is our relatively fast onset-to-IVT times, with medians well below 100 min in both groups.

A significant number of patients undergo futile inter-hospital transfers, thus incurring extra costs [11], and this may cause unnecessary capacity problems for ambulance services, but also for neurointerventional teams who have to stand ready for every transferred patient. The predicted probabilities of early recanalization were shown to significantly affect the cost-effectiveness of transfers to a CSC [12]. Given the moderate predictive ability of our model at PSC admission, the transportation to a CSC (and therefore, EVT treatment) should not be ruled out for a potential ER-LVO patient.

The critical variables of the prediction model are expected based on common sense and previous literature. The value of the presented study partly resides in the actual quantification of the ER-LVO characteristics, and the future incorporation of such information in risk models. Such models should account for the information gain versus time loss, and could be used to better plan repeated imaging in transferred patients. Patients with a high likelihood of early recanalization could directly undergo repeated imaging to confirm the prediction. Notably, this is already done in the clinic: in 50% of cases, the reason to undergo repeated imaging is clinical improvement [13]; that is, a decrease in the NIHSS score between PSC and CSC admission. However, not all patients that have clinical improvements recanalize early. A prediction model like the one presented in this study supports this observation by accounting for multiple relevant variables simultaneously, including thrombus imaging characteristics. Determining ER-LVO patients at an early stage can reduce futile transfers to the angio-suite room and the associated invasive imaging and procedural risks. For patients expected in the NER-LVO group, the need for repeated imaging can be minimized, reducing the delay between the CSC door and the angio-suite room by 20 min on average [13]. A recent trial on patients directly presented at the CSC showed that direct to angio-suite workflow led to improved clinical outcomes and decreased costs compared to the conventional imaging workflow [29].

Limitations

This study has several limitations. The ER-LVO patients were selected from transferred patients undergoing repeated imaging. The reasons to undergo repeated imaging are not arbitrary and include clinical improvement (52%), clinical deterioration (24%) and other reasons (24%) [13]. Therefore, the non-early recanalized patients from the repeated-imaging database were suspected to not be representative of the commonly transferred patients

eligible for EVT. Thus, the MR CLEAN Registry database was used. Our main limitation is that the patients included in this study do not belong to the same study population, although both include stroke patients treated in The Netherlands, and our center is one of the MR CLEAN centers. In addition, the inclusion time periods are different (2014–2017 vs. 2016–2021).

The NIHSS scores at PSC admission were not available for the NER-LVO group. Due to the lack of thin-slice and good-quality images, a large number of patients had to be excluded for the thrombus imaging measurements, particularly for perviousness and density.

Stroke etiology, which was not included in our model, might be a relevant variable to consider in future prediction models of early recanalization.

A substantial amount of mRS scores were missing, especially in the ER-LVO group (38%). The main reason for this was because transferred patients in the ER-LVO group that showed clinical improvement were sent back to the PSC immediately; therefore, the contact information required to get an adequate follow-up was lacking. Additionally, the COVID-19 pandemic might also have affected the collection of ER-LVO follow-up data. The collection of 90-day mRS scores is part of the MR CLEAN Registry protocols, and therefore, fewer patient outcomes were missing (10%).

The predictive ability of our models is moderate, which might be limited by the number of patients included or by our ability to identify or measure the most relevant factors associated with early recanalization. In addition, our logistic regression model did not account for non-linearities in the model's features, and the use of more advanced prediction models (machine learning) could potentially improve the accuracy.

Two of the parameters that are included in the prediction model, DT and thrombus density, require manual measurements. Automated measurements could further help in the clinical workflow to make the model more practical to use.

5. Conclusions

IVT administration, longer door-to-door times, more distal occlusions, and shorter, more pervious, less dense thrombi are associated with early recanalization. Thrombus imaging characteristics, specifically thrombus distality and density, play a major role in the prediction of early recanalization. These characteristics can be used to predict early recanalization with moderate discriminative ability, and ultimately, to better plan repeated imaging workflow.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/jcdd11040107/s1>, Figure S1: Inclusion flowcharts; Figure S2: Early recanalization thrombus imaging characteristics inclusion flowchart; Figure S3: Correlation analysis.

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Institutional Review Board Statement: This study was evaluated by the medical ethics review committee of the Amsterdam UMC, location AMC, who waived the need for obtaining written informed consent (W19_366 # 21.072). The procedures followed were all in accordance with institutional guidelines. A letter with detailed information about the study was sent to all early recanalized

patients meeting the inclusion criteria. The patient or legal representative had the opportunity to deny consent for use of their data via an opt-out form, conforming to the European Union General Data Protection Regulation. The non-early recanalized patients are part of the MR CLEAN Registry, a multicenter prospective observational registry of all patients undergoing EVT for acute ischemic stroke in The Netherlands. This registry was approved by the central medical ethics committee of the Erasmus Medical Center Rotterdam, which served as the review board of all participating centers (MEC-2014-235). The requirement for written informed consent was waived, but all patients or legal representatives were provided with oral and written information on the registry, and had the opportunity to withdraw consent to use their data via an opt-out form, conforming to the European Union General Data Protection Regulation.

Informed Consent Statement: The requirement for written informed consent was waived, but all patients or legal representatives were provided with oral and written information on the study and had the opportunity to withdraw consent to use their data via an opt-out form, conforming to the European Union General Data Protection Regulation.

Data Availability Statement: All data relevant to the study are included in the article or have been uploaded as Supplementary Materials. The data that support the findings of this study are available upon reasonable request, after clearance by the local ethics committee.

Acknowledgments: See Supplementary Materials for details.

Conflicts of Interest: N. Arrarte Terreros is co-founder of inSteps, a start-up that focuses on in-silico stroke models. D.W.J. Dippel reports unrestricted grants from Stryker, Penumbra, Medtronic, Cerenovus, Thrombolytic Science, LLC, Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organization for Health Research and Development, Health Holland Top Sector Life Sciences and Health, and Thrombolytic Science, LLC for research, paid to institution. H.A. Marquering is co-founder of inSteps and Nico.lab, a company that focuses on the use of artificial intelligence for medical image analysis. C.B.L.M. Majoie reports grants from the European Commission during the conducting of the study; grants from CVON/Dutch Heart Foundation, TWIN Foundation, Healthcare Evaluation Netherlands and Stryker, outside the submitted work; and is a shareholder of Nico.lab. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Abbreviations

ACA	anterior cerebral artery
CI	confidence interval
CSC	comprehensive stroke center
CT	computed tomography
CTA	computed tomography angiography
DT	distance from intracranial carotid artery terminus to the thrombus
ER-LVO	early recanalized large vessel occlusion
EVT	endovascular treatment
HU	Hounsfield units
IQR	interquartile range
ICA	internal carotid artery
IVT	intravenous treatment with alteplase
IVT to CSC door	time from intravenous treatment with alteplase initiation to arrival at the comprehensive stroke center
mm	millimeters
MCA	middle cerebral artery
mRS	modified Rankin scale
NCCT	non-contrast computed tomography
NER-LVO	non-early recanalized large vessel occlusion
NIHSS	National Institute of Health Stroke Scale
Onset to PSC door	time from stroke onset to arrival at the primary stroke center
Onset to PSC imaging	time from stroke onset to imaging at the primary stroke center
PSC	primary stroke center
PSC door to CSC door	time from arrival at the primary stroke center to arrival at the comprehensive stroke center

PSC door to IVT

time from arrival at the primary stroke center to initiation of intravenous treatment with alteplase sICH, symptomatic intracranial hemorrhage

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Article

Evaluating Epicardial Fat Density Using ROI-Based Analysis: A Feasibility Study

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Abstract

Epicardial fat density (EFD) is implicated in cardiovascular diseases. This study aimed to assess the regional variability of epicardial fat density (EFD) using coronary computed tomography (CCT) and evaluate the feasibility of ROI-based measurements as an alternative to full segmentation. A retrospective analysis was conducted on 171 patients undergoing coronary CCT. EFD was measured on non-contrast scans acquired globally and in three predefined regions of interest (ROIs) for coronary calcium scoring: the aortic bulb, right posterolateral wall, and cardiac apex. Global EFD was quantified using semi-automated segmentation software (3D Slicer 5.6.2), while regional EFD values were manually determined. Statistical analyses were performed to compare global and regional EFD measurements. Global EFD averaged -83.92 ± 5.19 HU, while regional EFD showed significant variability. The aortic bulb had lower EFD values (-97.54 ± 12.80 HU) compared to the apex (-93.42 ± 18.94 HU) and right posterolateral wall (-94.99 ± 12.16 HU). Paired *t*-tests confirmed statistically significant differences between global and regional EFD values ($p < 0.000$). This study highlights significant regional variability in EFD across specific cardiac regions, suggesting that ROI-based assessments may not reliably reflect global EFD characteristics.

Keywords: cardiac computed tomography (CCT); epicardial adipose tissue (EAT); epicardial fat tissue (EFT); epicardial fat volume (EFV); epicardial fat density (EFD); region of interest (ROI)

1. Introduction

The adipose tissue of the heart is divided into two different layers: pericardial adipose tissue (PAT), located in the parietal layer of the pericardium, and epicardial adipose tissue (EAT), also referred to as epicardial fat tissue (EFT). EAT is a particular type of adipose tissue located around the heart, between the myocardium and the visceral layer of the pericardium [1–3]. Each layer has a different embryological origin and its own vascularization [4]; unlike PAT, EAT originates from the splanchnopleuric mesoderm, the same embryonic layer that gives rise to mesenteric and omental fat [5].

EAT is metabolically active and produces a series of pro-inflammatory molecules like cytokines (TNF- α , IL-6, monocyte chemoattractant protein-1) and adipocytokines which can have direct effects on the coronary vessels and on the myocardium itself [6–8].

These substances have protective and dangerous effects. EAT serves as a local energy reservoir, as mechanical protection for coronary vessels, and contributes to thermoregulation of the heart, particularly in metabolic stress. Furthermore, it is an immune barrier and protection of the coronary arteries; it also responds to energy needs, as it has a regulatory role in the release and absorption of free fatty acids.

However, EAT also has important implications in cardiovascular pathology. EAT's proximity to coronary arteries and the myocardium also enables direct paracrine interactions that can influence cardiovascular health. Its secretion of adipokines, inflammatory mediators, and free fatty acids may induce atherosclerosis and promote myocardial inflammation [9]. It has been demonstrated that an increase in epicardial fat volume (EFV) leads to hypoxia and dysfunction, characterized by enhanced lipolysis and consequent inflammation, resulting in alterations to the metabolic profile; when this dysfunction occurs, it may contribute to the development of coronary artery disease (CAD).

Numerous studies [10–13] demonstrate the role of EAT in the development of heart failure, atrial fibrillation, metabolic syndrome, and other cardiovascular disorders.

In this context, quantitative imaging techniques are indispensable for assessing EAT to potentially establish it as a non-invasive marker for cardiovascular risk.

While the overall EFV has been shown to correlate with cardiovascular risk, recent attention has shifted toward understanding the role of epicardial fat density (EFD), a measure of fat attenuation on CT scans. EFD reflects the composition of the fat, with higher density values indicating fat infiltration by connective tissue, fibrosis, or inflammatory cells [14]. These compositional changes may be more closely related to cardiovascular disease than fat volume alone [15,16].

The primary methods used for assessing EAT include echocardiography, cardiac computed tomography (CCT), and cardiac magnetic resonance (CMR). The quantification of EAT using CCT volumetric technique permits EFD measurement, but it is hindered by cost, technical expertise, time constraints, and lengthy segmentation times. Accurate measurements require numerous images with thin slice-thickness and specific segmentation tools which are not currently widespread; that significantly limits its feasibility for routine clinical practice [17].

This study aimed to explore whether EFD could be assessed without the use of specific segmentation software by comparing EFD values measured across the entire EAT and in three specific regions of interest (ROI)—the aortic bulb, right posterolateral wall, and cardiac apex. The ROI-based approach not only could improve feasibility by reducing processing time but also allow for targeted analysis of specific myocardial regions, which may better capture localized variations in EFD that are relevant for cardiovascular risk assessment.

2. Materials and Methods

2.1. Study Population

This study was conducted in alignment with ethical principles, adhering to the Declaration of Helsinki.

This retrospective study analyzed data from 200 patients referred to our institution for coronary CT angiography (CCTA) between January 2024 and October 2024, to explore whether EFD could be accurately assessed without segmenting the whole EAT. Informed consent was obtained from all patients.

This study was conducted retrospectively, with data extracted from previously acquired imaging. Strict inclusion criteria were applied to ensure consistency and reduce potential confounders.

Inclusion criteria for patient selection were as follows: (a) suspected CAD; (b) availability of comprehensive CCTA data including calcium score. Exclusion criteria were

as follows: known history of percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), open heart surgery, valve replacement, pericardial effusion, and those with pacing leads; poor image quality (Figure 1).

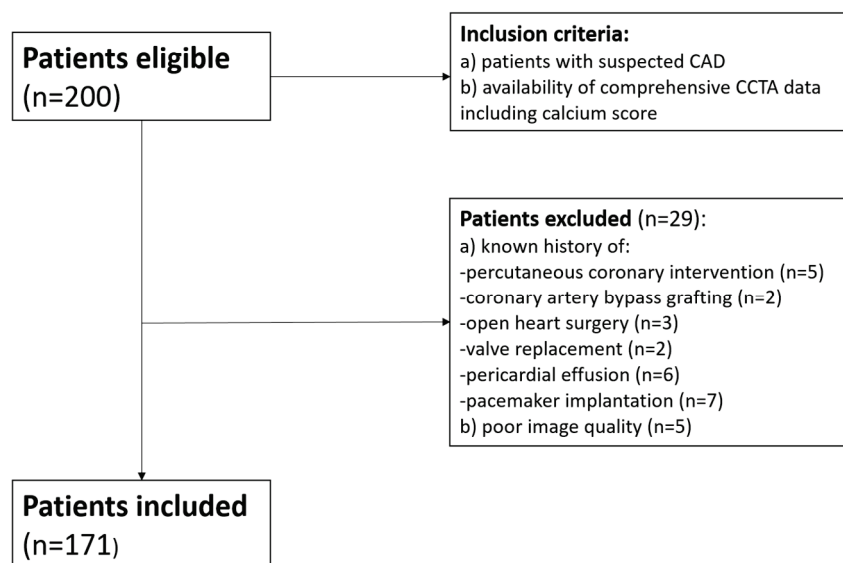


Figure 1. Inclusion and exclusion criteria applied in the study.

2.2. Scan Protocol

CCTA examinations were performed using a 256-row multidetector CT scanner (GE Revolution, GE Healthcare, Milwaukee, WI, USA). Nitrates were sublingually administered to all patients, after exclusion of contraindications, to induce vasodilation (Trinitrine, Natispray 0.3 mg). Patients with a heart rate > 75 bpm were treated with intravenous beta-blocker (metoprolol tartrate, Seloken 5 mg). A calcium channel blocker was used if there was contraindication to use beta-blockers. Prospective gated ECG-triggered non-contrast scan was acquired for coronary calcium scoring with following parameters: tube voltage of 120 kVp, tube current of 185 mAs, detector collimation of 0.625 mm, gantry rotation time of 0.28 s, pitch factor of 0, matrix size of 512 × 512 pixel, section thickness of 2.5 mm, and a Z-plane coverage of 16 cm enabling the imaging of the heart in 1 heartbeat. CCTA images were acquired using a prospective ECG-gated protocol with the following scan parameters: tube voltage of 100 kVp, detector collimation of 0.625 mm, gantry rotation time of 0.28 s, matrix size of 512 × 512 pixel, section thickness of 0.625 mm, and a Z-plane coverage of 16 cm the imaging of the heart in 1 heartbeat. All patients received intravenously 50 mL of iodine contrast medium (400 mg I/mL Iomeprol, Iomeron 400; Bracco Imaging, Milan, Italy) at flow rate of 5 mL/s through an 18-gauge antecubital access by using an automated injector, followed by saline chaser bolus of 30 mL at flow rate of 5 mL/s. Scan delay was determined using a bolus-tracking technique; images were acquired 6 s after the trigger attenuation threshold (150 HU) was reached into a ROI placed in the ascending aorta at the level of pulmonary arteries.

2.3. Images Analysis

Three radiologists with different experiences in CCTA analyzed the images to assess global EFD. Discrepancies in segmentation were resolved through consensus.

Global EFD was quantified on non-contrast scans acquired for coronary calcium scoring using dedicated free and open source-software (3D Slicer 5.6.2). The software semi-automatically segmented the epicardial fat tissue based on predefined density thresholds (−190 to −30 HU) [17]. For regional EFD analysis, three specific round-shaped ROIs were

manually delineated on axial CT slices, each with a surface area of 20 mm², when feasible. The ROIs were positioned at the following levels: (a) aortic bulb, defined as the region surrounding the ascending aorta at the level of the sinuses of Valsalva; (b) right posterolateral wall, located on the lateral aspect of the right ventricle near the right atrioventricular groove; (c) cardiac apex, defined as the most distal portion of the left ventricle. Each ROI was manually delineated to ensure they were positioned away from coronary vessels or other structures such as fibrous bands, and to avoid confounding the fat density measurements. Disagreements in ROI segmentation were addressed through mutual agreement. The mean HU value within each ROI was calculated using 3D Slicer (Figure 2).

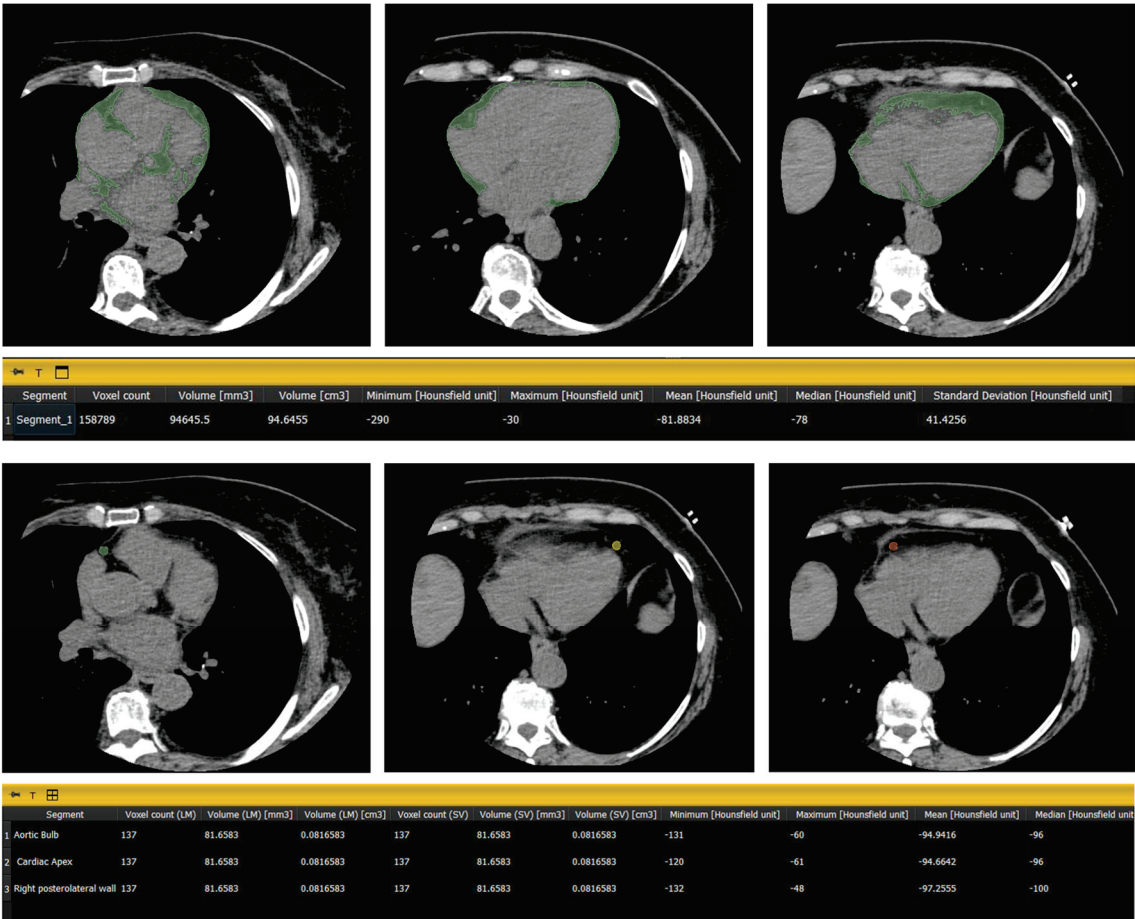


Figure 2. Example of epicardial fat analysis using 3D Slicer; complete segmentation of the total EFV and delineation of three distinct ROIs.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS software (version 26.0, SPSS Inc., Armonk, NY, USA). Descriptive statistics, including media and standard deviations, were used to summarize the data. The Shapiro–Wilk test was conducted to evaluate the data distribution. Paired t-tests were applied to compare the differences between the EFD values across the entire epicardium and the three ROIs. *p* values less than 0.05 were considered statistically significant. Statistical significance is closely related to clinical importance: statistically significant differences (<0.05) in the ROI may show areas affected by cardiovascular diseases and, therefore, areas that need more attention in clinical practice. The ROI values could be useful in the future to predict the risk of heart diseases and/or to choose personalized treatment.

3. Results

A total of 171 patients met the inclusion criteria out of the 200 patients retrospectively enrolled. The study population had a mean age of 62.34 ± 14.73 years, ranging from 17 to 88 years. The number of males and females in the study was 108/171 (63.16%) and 63/171 (36.84%), respectively.

The mean EFD measured for the entire epicardium was -83.92 ± 5.19 HU. This global fat density reflects the average attenuation of fat across the entirety of the epicardium and serves as a baseline against which regional EFD values can be compared.

The mean EFD values calculated at the aortic bulb region, at the apex, and at the right posterolateral wall were, respectively, -97.54 ± 12.80 HU, -93.42 ± 18.94 HU, and -94.99 ± 12.16 (Figure 3).

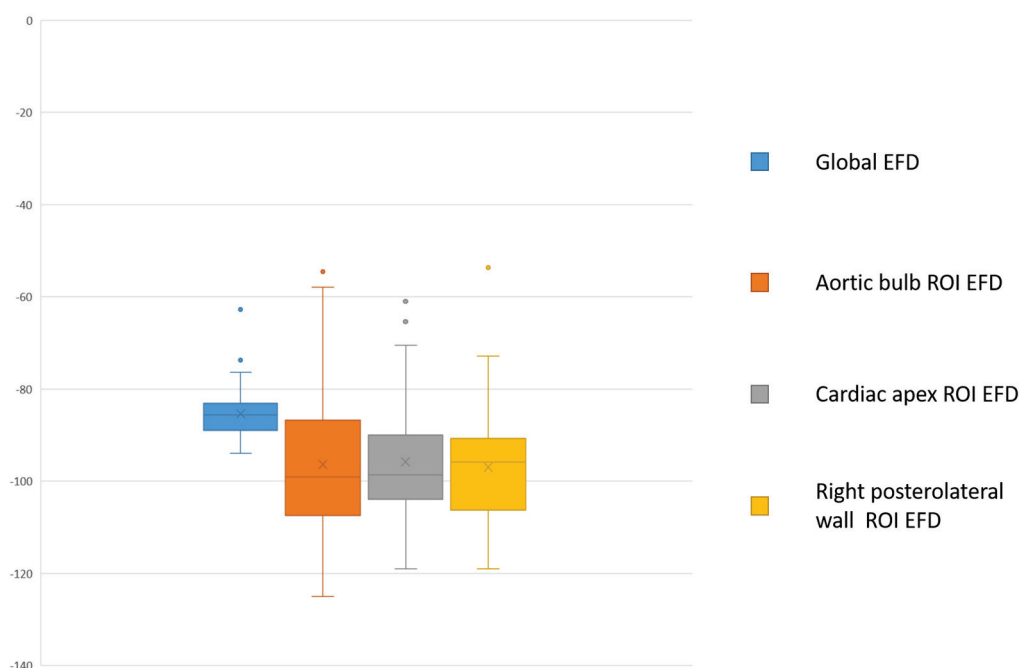


Figure 3. Box plot of mean EFD values calculated globally, at the aortic bulb region, at the apex and at the right posterolateral wall.

The placement of the ROI was not feasible at the level of the bulb and the posterolateral wall in 1 and 5 cases, respectively, due to the limited EFV.

The Shapiro–Wilk test result was 0.948 (p -value = 0.1) (Figure 4), meaning the data can be considered normally distributed.

Analysis of the three predefined ROIs revealed significant regional variability in EFD values.

The mean difference between global EFD and bulb ROI EFD is $13.63 (\pm 11.42)$, with a mean standard error of 0.88. The confidence interval (95%) ranges from 11.90 to 15.36, indicating that the difference is statistically significant. The t -value of 15.564 and the p -value of <0.000 confirm a highly significant difference between these two measurements.

The comparison between global EFD and apex ROI EFD revealed a slightly smaller mean difference of 9.50 ± 17.72 , with a mean standard error of 1.36. The 95% confidence interval spans from 6.83 to 12.18, demonstrating significant variability but still a statistically significant difference with the t -value of 7.011 and p -value of <0.000 .

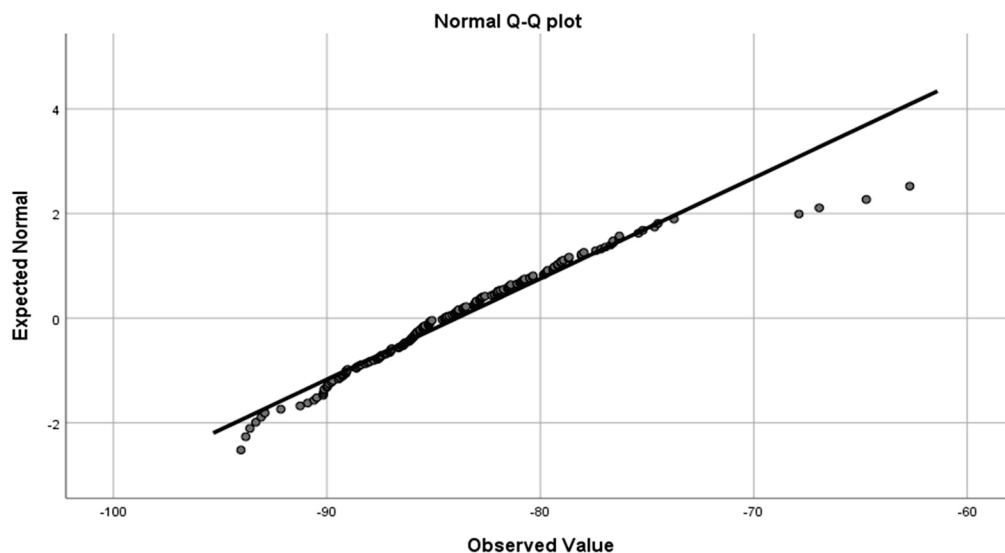


Figure 4. Normal Q-Q plot shows that data can be considered normally distributed.

For the comparison between global EFD and posterolateral wall ROI EFD, the mean difference is 11.04 (± 10.41), with a mean standard error of 0.81. The confidence interval (95%) ranges from 9.45 to 12.64. This difference is also statistically significant, supported by a t -value of 13.672 and a p -value of <0.000 .

Paired t -tests results are resumed in Table 1.

Table 1. Paired t -tests results for the comparison between global EFD and regional ROIs.

	Mean	S.D.	Mean Standard Error	Confidence Interval 95%		t	gl	p Value
				Inferior	Superior			
global EFD—bulbROI EFD	13.63155	11.41929	0.87582	11.90260	15.36051	15.564	169	0.000
global EFD—apex ROI EFD	9.50123	17.72049	1.35512	6.82620	12.17626	7.011	170	0.000
global EFD—postero-lateral wall ROI EFD	11.04425	10.40752	0.80778	9.44933	12.63917	13.672	165	0.000

4. Discussion

The interest in EAT is increasing in the scientific community as a possible non-invasive biomarker for cardiovascular risk [18]. EAT has dishomogeneous distribution around the heart: most are located at the base and apex of the heart, in the cardiac sulci, and around the coronary arteries; it is also thicker around the right ventricle than the left ventricle [19]. Several studies have demonstrated that pericoronary fat density, measured in Hounsfield Units (HU), is associated with the presence and severity of coronary artery disease (CAD). Higher pericoronary fat attenuation has been linked to increased vascular inflammation, which in turn correlates with greater plaque burden and the presence of high-risk plaques. Specifically, regions adjacent to significant stenotic lesions tend to show elevated fat density, likely due to the local inflammatory response associated with atherosclerotic progression. In contrast, non-stenotic or mildly diseased segments often exhibit lower fat attenuation, suggesting less inflammatory activity. Furthermore, fat density changes dynamically in response to plaque morphology; for instance, vulnerable plaques with a lipid-rich necrotic

core and positive remodeling tend to be surrounded by higher-density pericoronary fat compared to more stable calcified plaques.

Numerous studies in the literature revealed that the increase in EFV and EAT's alterations are related to CAD, atherosclerosis, and cardiac arrhythmias [20]. When the EF volume increases, it becomes hypoxic and dysfunctional, increases lipolysis and consequent inflammation which eventually results in a shift in its metabolic profile and alters the homeostasis.

A more precise correlation is represented by EFD: it describes the composition of EAT and its alteration is often related to inflammation, fibrosis, and infiltration of the connective tissues [21,22]. The use of non-invasive imaging methods for evaluating EFD, such as CCT, represents an important innovation for monitoring cardiovascular risk.

EAT functions as fatty tissue and it has an endocrine effect. Alterations of EAT promote the secretion of adipokine. In pathological conditions, it can promote the secretion of pro-inflammatory adipokine, reactive oxygen species, oxidative stress, and even autophagy, thus affecting cardiac function [23].

The quantification of EAT has traditionally relied on imaging modalities such as echocardiography, CCT, and CMR. Among these, CCT is considered the gold standard for assessing both the volume and density of EAT, offering high spatial resolution and the ability to quantify fat density using HU. However, quantitative evaluation of EFD is still limited by the need for complex segmentation software and the difficulty in obtaining repeatable and accurate measurements in daily clinical practice [14].

In this regard, our study focused attention on the possibility of evaluating EFD in an alternative and more accessible way compared to complete segmentation. The alternative method proposed in this study was a regional evaluation through predefined ROI, of pre-established dimensions (20 mm²) already used in the literature [24]. ROIs are easier to use and permit repeatable and accurate measurements.

Regional analysis of EFD through ROI would be very simple and useful. Through the ROIs, it would be easy to follow any alterations of EFD and therefore evaluate changes in the cardiovascular risk of each patient. The use of ROIs could be useful for the follow-up of patients with cardiovascular risk and to modify their therapy based on their cardiovascular risk condition.

CT scans for calcium score were used to position ROI at specific points:

1. Aortic bulb: The region at the base of the heart near the aortic root, chosen for its proximity to the aortic valve and proximal segments of coronary arteries, as well as its exposure to high mechanical stress; this region is critical due to its proximity to the coronary ostia and its role in hemodynamic regulation. The fat in this area is highly influenced by shear stress and systemic inflammation, factors known to contribute to the development and progression of CAD.
2. Right posterolateral wall: A region located on the right side of the heart, chosen for its relative distance from major coronary vessels and its association with arrhythmogenesis. The fat in this area is less exposed to high shear stress and its proximity to major venous structures, including the coronary sinus, could influence the local adipose tissue environment, making it an interesting site for evaluating differences in fat attenuation compared to more hemodynamically active regions.
3. Cardiac apex: The most distal part of the heart, located inferiorly and anteriorly. The fat in this location is less exposed to direct vascular inflammation from major coronary arteries, allowing for a comparison of regional variations in fat density. This approach may help to differentiate systemic inflammatory effects from localized vascular inflammation [14,25].

In our study, we used scans acquired for coronary calcium scoring. These scans were primarily used for screening purposes, as they identify calcifications of the coronary arteries, which are indicative of a patient's risk for cardiovascular events.

The absence of contrast agents ensures a more stable and accurate measurement of tissue density in HU, as contrast can alter tissue intensity and compromise the consistency of these measurements.

Calcium scoring scans are also performed with lower radiation doses compared to contrast-enhanced cardiac CT, making them safer for repeated use. Furthermore, they are generally more cost-effective due to the simpler procedure and absence of contrast material.

Our results showed that EFD varies significantly between different regions of the heart and across the three ROIs. The mean EFD for the entire epicardial fat is -84.75 ± 4.31 HU, in line with the values reported in the literature, while regional measurements in the three predefined ROIs, i.e., aortic bulb, right posterolateral wall, and cardiac apex, showed significant regional variability in the posterolateral wall and cardiac apex, but not at the level of the aortic bulb.

These regional differences demonstrate the distribution of EAT. More EAT is in the base of the heart (including the aortic bulb) and apex, but the right posterolateral wall, which is associated with greater mechanical activity and stress [20], also has a higher density than other areas. The variability in EFD values between regions suggests that some areas of the heart are more susceptible to infiltration of connective tissues or inflammatory processes and, therefore, more susceptible to cardiovascular pathologies. Regional differences in EFD may indicate localized inflammatory activity, which could influence the progression of atherosclerosis as plaque vulnerability, coronary artery stenosis, and visual plaque burden. The paired *t*-test results further emphasize this variability, underscoring their potential clinical relevance in assessing disease progression and cardiovascular risk, paving the way for future research. In addition, heterogeneity in EFD distribution, particularly around the atria, may contribute to atrial remodeling and fibrosis, potentially playing a role in the development of arrhythmias such as atrial fibrillation [10–13,21,22].

The variation in EFD between different ROIs could also be linked to differences in cardiac function and metabolic responses. The EFD measured at the aortic bulb was lower than the values measured at the other two regions (the apex and the right posterolateral wall). This could indicate that the fat surrounding the aortic bulb is more lipid-rich and less fibrotic or inflamed compared to the other regions. The aortic bulb is a region of high hemodynamic stress, which explains why the fat in this area is more metabolically active and less subjected to pathological changes such as fibrosis or inflammation.

Although measuring EFD using CCT is still difficult due to the necessity to use complex software and long segmentation times, the ROI-based approach, as demonstrated in this study, could offer a practical and more easily applicable solution in clinical settings.

Our study has some limitations. First of all, the relatively small size of our sample could limit generalization of the results. Studies on a larger sample and histological validation are needed to confirm these results and to establish more precise cutoff values for regional EFD measurements. Another limitation of this study is its retrospective design, which may introduce selection bias and limit the generalizability of the findings. Additionally, while the study demonstrated significant regional variability in EFD, it did not explain how these variations correlate with clinical outcomes. Future research should investigate if specific regional EFD values are predictive of cardiovascular events, such as myocardial infarction, heart failure, or atrial fibrillation. A potential limitation of this study is the lack of a formal assessment of inter-observer variability in ROI placement. Given the manual nature of this method, some degree of variability is expected, which could

impact reproducibility. Future studies should include systematic evaluations of observer agreement to further validate this approach.

In the future, studies with larger sample sizes and advanced imaging techniques—such as the use of artificial intelligence in more accurate segmentation and measurement of fat density—could enhance the use of EFD as a predictive biomarker for cardiovascular disease.

Additionally, monitoring changes in EFD over time could provide valuable insights into the mechanisms of cardiovascular disease progression and the effectiveness of specific therapies. To achieve a more accurate and comprehensive understanding of regional EFD's predictive value for conditions like heart failure and myocardial infarction, and to establish it as an early biomarker, larger-scale studies are essential.

5. Conclusions

This study highlights significant regional variability in EFD across specific cardiac regions, providing insights into the feasibility and limitations of ROI-based EFD assessment. The observed differences between regions, such as lower EFD at the aortic bulb and higher values at the apex and right posterolateral wall, indicate that localized measurements may not reliably reflect global epicardial fat properties.

To overcome these limitations, accurate EFD evaluation requires dedicated segmentation software capable of analyzing the entire epicardium. Such tools are essential for achieving precise and consistent measurements, which are crucial for integrating EFD into cardiovascular risk assessment and routine clinical practice.

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Institutional Review Board Statement: The present prospective clinical study was conducted at the University of Bari (Italy), in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki and the additional requirements of Italian law. Furthermore, the University of Bari, Italy, classified the study as being exempt from ethical review as it carries only negligible risk and involves the use of existing data that contain only non-identifiable information about human beings. The patients signed a written informed consent form.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CCT	Cardiac computed tomography
EAT	Epicardial adipose tissue
EFT	Epicardial fat tissue
EFD	Epicardial fat density
PAT	Pericardial adipose tissue
CAD	Coronary artery disease
HU	Hounsfield units

CMR	Cardiac magnetic resonance
CCTA	Coronary CT angiography
ROI	Region of interest
PCI	Percutaneous coronary intervention
CABG	Coronary artery bypass grafting

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Article

Subtraction CT Angiography for the Evaluation of Lower Extremity Artery Disease with Severe Arterial Calcification

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Abstract

(1) Background: Peripheral arterial CT angiography (CTA) is an alternative to conventional angiography for diagnosing lower extremity artery disease (LEAD). However, severe arterial calcifications often hinder accurate assessment of arterial stenosis. This study evaluated the diagnostic performance of subtraction CTA with volume position matching compared to conventional CTA, using invasive digital subtraction angiography (DSA) as the gold standard. (2) Methods: Thirty-two patients with LEAD (mean age: 69.6 ± 10.8 years; M/F = 28:4) underwent subtraction CTA and DSA. The arterial tree was divided into 20 segments per patient, excluding segments with a history of bypass surgery. Subtraction was performed separately for each limb using volume position matching. Maximum intensity projections were reconstructed from both conventional and subtraction CTA data. Percent stenosis per arterial segment was measured using calipers and compared with DSA. Segments were classified as stenotic (>50% luminal narrowing) or not, with heavily calcified or stented segments assigned as incorrect. (3) Results: Of 640 segments, 636 were analyzed. Subtraction CTA and conventional CTA left 13 (2.0%) and 160 (25.2%) segments uninterpretable, respectively. Diagnostic accuracies (accuracy, precision, recall, macro F1 score) for subtraction CTA were 0.885, 0.884, 0.936, and 0.909, compared to 0.657, 0.744, 0.675, and 0.708 for conventional CTA. (4) Conclusions: Subtraction CTA with volume position matching is feasible and achieves high diagnostic accuracy in patients with severe calcific sclerosis.

Keywords: CT/CTA; peripheral vascular disease; occlusion; stenosis/restenosis; arteriosclerosis; critical limb ischemia; subtraction

1. Introduction

Lower limb arterial disease (LEAD) is an ischemic condition caused by arteriosclerosis. LEAD not only significantly impacts quality of life but can also be life-threatening, particularly in patients who develop critical limb ischemia (CLI) [1]. While diagnosing LEAD is relatively straightforward, detailed lesion characterization is crucial for selecting appropriate treatment options.

Contrast-enhanced CT angiography (CTA) is a non-invasive alternative to conventional angiography. Doppler ultrasound and magnetic resonance angiography (MRA) play a central role in imaging studies for diagnosing LEAD. Moreover, CTA can visualize luminal stenosis and vessel wall calcification, aiding in selecting invasive revascularization

strategies, such as surgical bypass or vascular interventions [2]. It allows for precise grading of LEAD and detailed characterization of the vessel wall. However, CTA is limited in assessing luminal patency in severe arterial wall calcification [3,4].

Subtraction CTA is a promising alternative technique that may improve the visualization and characterization of arterial occlusive disease. Previous studies have demonstrated its effectiveness in diagnosing LEAD in the iliac artery [5]. More recently, its utility has been reported for the femoral artery and regions below the knee [6]. Understanding the state of blood flow disorders in the lower limbs has become increasingly important, especially in cases of severe ischemia, and advances such as dual-energy CT angiography have further strengthened diagnostic support [4].

On the other hand, in LEAD, comprehensive evaluation of the vascular tree of the entire lower limb is essential. Accurate evaluation of central and peripheral lesions simultaneously is crucial, as local evaluation alone is insufficient.

This study aims to evaluate the diagnostic performance of subtraction CTA compared with conventional CTA for assessing lower limb arterial stenosis in patients with severe arterial calcification. Using invasive digital subtraction angiography (DSA) as the gold standard, we evaluated the visualization ability of subtraction CTA from iliac artery lesions to below-the-knee artery lesions.

2. Materials and Methods

2.1. Study Design and Patient Population

This study was approved by our institute's research ethical committee (approved No H23-105) and performed under the Declaration of Helsinki. All patients provided informed consent. Thirty-two consecutive LEAD patients who underwent CTA and DSA were prospectively included at our institution. All patients underwent clinically indicated subtraction CTA of the lower extremities for therapeutic planning. Diagnostic invasive DSA was performed before intervention. Accordingly, all subtraction CTA examinations were performed before DSA. The clinical characteristics of the study population are provided in Table 1.

Table 1. Patient characteristics (n = 32).

Characteristic	Value
Age (y)	
Mean $\pm$ SD	69.6 $\pm$ 10.8
Range	51–87
Gender (n)	
Male	28 (87.5%)
Female	4 (12.5%)
Body	
Length (cm)	160.8 $\pm$ 6.0
Weight (kg)	56.1 $\pm$ 10.4
Body mass index	21.7 $\pm$ 3.7
Risk factors (n)	
Hypertension	27 (84.4%)
Diabetes	10 (31.3%)
Hypercholesterolemia	13 (40.6%)
Smoking	8 (25%)
Previous smoking history	8 (25%)
Chronic renal failure	10 (31.3%)
Hemodialysis	6 (18.8%)
Fontaine classification (n)	
I	1 (3.1%)
IIa	8 (25%)
IIb	17 (53.1%)
III	2 (6.3%)

Table 1. *Cont.*

Characteristic	Value
IV	4 (12.5%)
Duration between CTA and DSA (days)	
Mean $\pm$ SD	45.2 $\pm$ 22.0
Range	3–127

Values in parentheses are percentages. Abbreviations: SD: standard deviation, CTA: computed tomographic angiography, DSA: digital subtraction angiography.

2.2. CT Angiography

CT scanning was performed using a 64-slice scanner (Aquilion 64, Canon Medical Systems, Otawara, Japan) or a 320-slice scanner (Aquilion One, Canon Medical Systems, Otawara, Japan) in 32-slice mode with a slice thickness of 0.5 mm and a table feed of 13.5 mm/rot. The gantry rotation speed was 0.5 s/rot., the tube voltage was 120 kV, and the tube current was 75–125 mAs (variable tube current). Iterative reconstruction was applied during acquisition and reconstruction. Scanning was performed from the suprarenal abdominal aorta to the ankle joints. Automatic bolus tracking was used, with a threshold value of 170 HU set for a region of interest located in the abdominal aorta at the top of the scan range. After the acquisition of non-contrast images, 75 mL of Iopamidol (370 mgI/mL) or Iohexol (350 mgI/mL) was injected at 2 mL/s via an antecubital vein, followed by a 30 mL saline chaser.

The subtraction CTA protocol consisted of a pre- and postcontrast acquisition [5,7]. Controlled orbit helical scanning [7–9] was performed to synchronize the gantry rotation and the table movement to obtain the same orbit of the helical row dataset for both image acquisitions and minimize the difference in helical artifacts. In addition, a patient immobilization system was used for reducing motion artifacts (Figure 1).

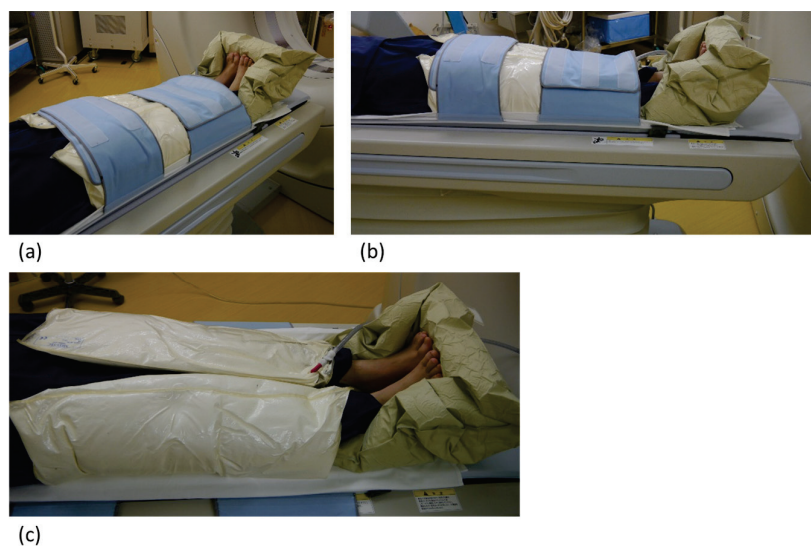


Figure 1. Patient immobilization system: Polystyrene bead bags were used for patient fixation. (a) and (b) illustrate the setup where the patient's lower limbs, including the ankles and feet, are immobilized. The thighs and lower legs are secured to the bed using broad hook-and-loop straps. (c) When vacuumed, these bags harden, ensuring effective immobilization of the patient during the examination.

Images were reconstructed with a 1 mm slice thickness and a smooth reconstruction kernel (FC03). Subtraction was performed separately on the left and right limbs to achieve higher precision using the built-in application of the CT system. The volume position

matching technique was used for the subtraction to minimize misregistration artifacts. The minimal unit of the position matching was 0.01 mm and 0.01 degrees for each X, Y, and Z volume axis. The position matching was performed with semi-automated, non-rigid registration by observing the reduction in artifacts. To avoid calculation errors, voxels with negative CT values were not subtracted. Negative CT values represent fat or air, and the subtraction of negative CT values could falsely result in high positive CT values in case of misregistration. Otherwise, intentional manipulation of CT values was not performed. Subsequently, the converted volume of non-enhanced CT data was subtracted from the volume of contrast-enhanced CT with the volume position matching technique (Figures 2 and 3).

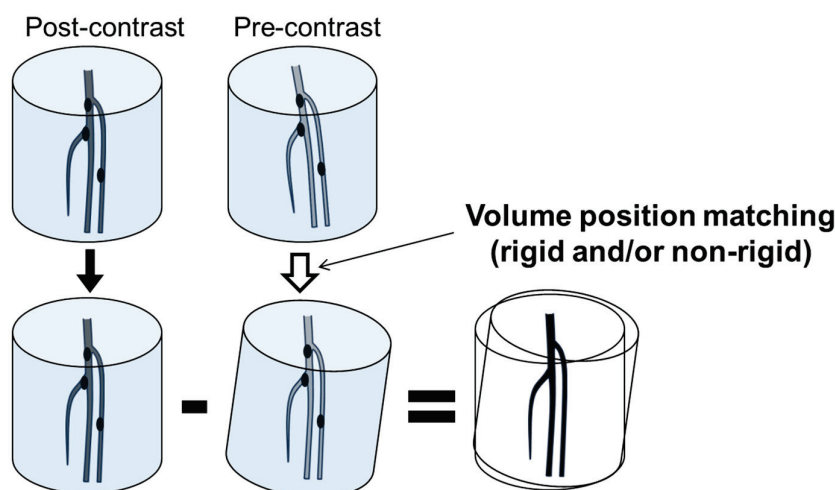


Figure 2. The basic concept of subtraction CTA with volume position matching.

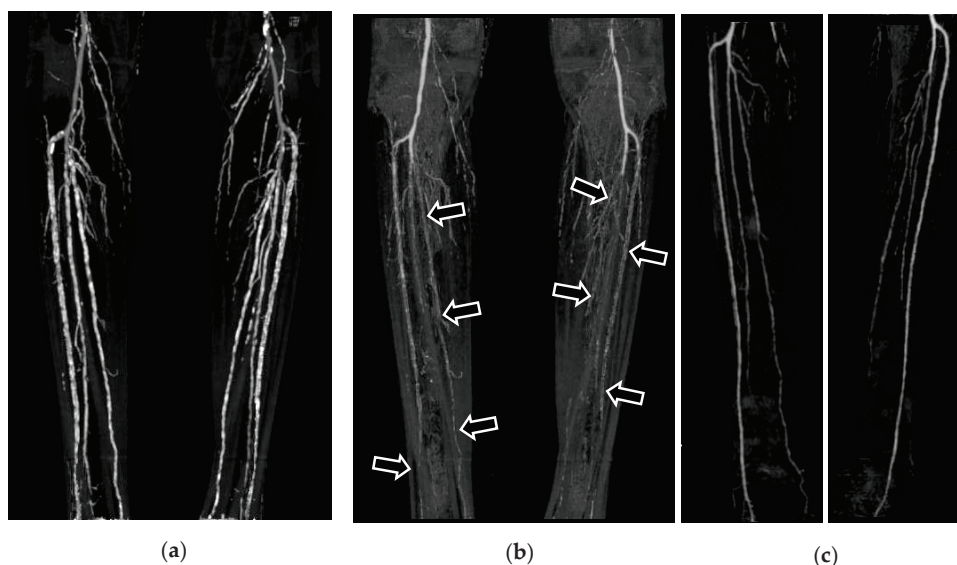


Figure 3. The difference between automatic and semi-automatic manipulation of subtraction CTA with volume position matching. (a) The non-subtracted MIP image shows diffuse arterial wall calcification. (b) The automatically subtracted CTA image, without manual manipulation, shows deletion of the vascular lumen due to misregistration of calcifications (black arrows). (c) The CTA image subtracted using a semi-automatic approach with manual adjustments accurately depicts the vascular lumen.

To minimize misregistration artifacts, subtraction images were calculated after aligning the vascular structures within the volume data.

All calculated data were reconstructed as maximum intensity projection (MIP) images (Figure 4). MIP images were reconstructed separately into three parts (aortoiliac, femoropopliteal, and below-the-knee regions) to take advantage of the spatial resolution. Conventional MIP images with non-subtracted data were reconstructed for comparison with subtraction CTA. All measurements were performed using MIP images because this study aims to provide angiographical images and assess their diagnostic accuracies.

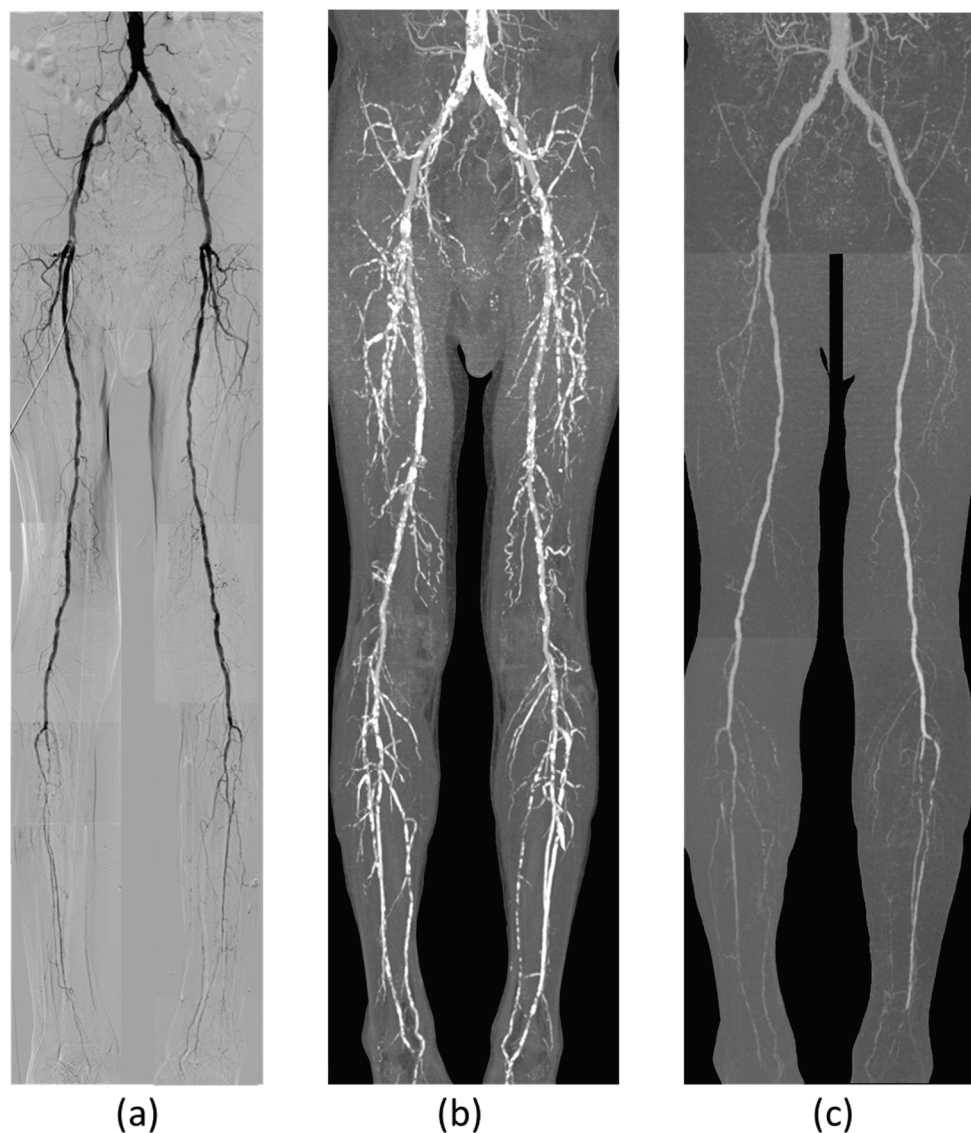


Figure 4. Visualization of DSA, conventional CTA, and subtraction CTA: (a) Composite image of bolus tracking DSA from the abdominal aorta to the ankle; (b) Composite MIP image of conventional CTA from the abdominal aorta to the ankle, showing clear visualization of arterial wall calcifications; however, evaluating luminal patency remains challenging; (c) Composite MIP image of subtraction CTA from the abdominal aorta to the ankle. Arterial wall calcifications are effectively eliminated, providing a clear visualization of luminal patency comparable to DSA.

2.3. Digital Subtraction Angiography

DSA was performed on all patients and used as a reference standard. Images were acquired using a digital angiography system (Philips Medical System, Allura Xper FD20/10, Best, The Netherlands). The “bolus chase” technique was used [10]. A 65–70 mL contrast medium (300 mgI/mL Iopamidol, Bayer Japan, Tokyo, Japan) was injected via a 4 Fr universal flush catheter (TEMPO4, Cardinal Health Japan, Tokyo, Japan) at 7 mL/s.

2.4. Image Analysis

Independent image analysis was performed on both CTA (conventional and subtraction) and DSA by a dedicated imaging clinical research organization (Micron Inc., Tokyo, Japan). Image evaluation was performed on a per-segment basis. The arterial tree was divided into 20 segments per patient, as follows: common iliac artery, external iliac artery, internal iliac artery, common femoral artery, superficial femoral artery, deep femoral artery, popliteal artery, anterior tibial artery, posterior tibial artery, and peroneal artery. One patient had undergone amputation of the right lower limb; therefore, three below-the-knee segments were not available. Also, one internal iliac artery segment was not evaluated on DSA due to overlapping by an external iliac artery; therefore, this one segment was also excluded. Segments were scored as assessable or not. Accordingly, 636 segments were available for evaluation (Figure 5).

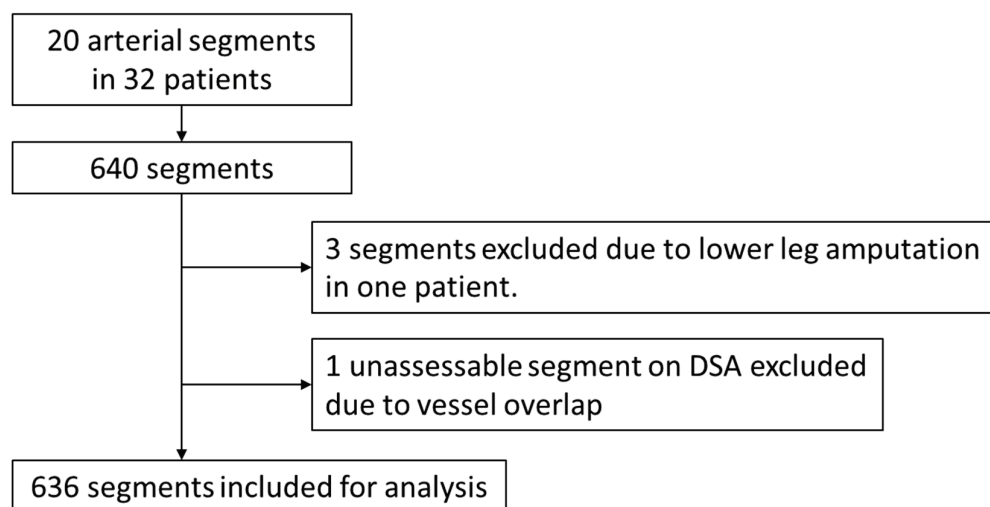


Figure 5. Flowchart of segment selection for evaluation.

The evaluation was performed by measuring the percent stenosis of the most severe lesion in each arterial segment using the caliper function. Segments were graded as either stenotic or not to calculate diagnostic accuracy. A stenotic lesion was defined as binary stenosis ($>50\%$). Unassessable segments due to heavy calcifications or stent placement were assigned as missing values and treated as incorrect data during statistical calculations.

2.5. Statistical Analysis

Statistical analyses were performed using R version 4.4.2 [11] and the pROC package version 1.18.5 [12] for receiver operating characteristic (ROC) analysis. In the ROC analysis, missing values were treated as incorrect responses. With 2000 bootstrap replicates, the Venkatraman method was employed to compare the area under the curve (AUC) of two ROC curves.

The diagnostic accuracies (accuracy, precision, recall, and macro F1 score) of conventional and subtraction CTA were calculated against DSA. The correlation coefficients of conventional CTA and subtraction CTA with DSA were calculated using correlation analysis for the overall dataset. All statistical analyses were performed with a significance threshold of 0.05 and a confidence level of 95%.

3. Results

Table 1 shows patient characteristics. Briefly, 84.4% of patients had hypertension, while other risk factors were also prevalent. 31.3% of patients had chronic renal insufficiency, and 18.8% of patients underwent chronic hemodialysis. Seventy-eight percent of patients were

Fontaine class II claudicants. Finally, CLI (defined as Fontaine class III or IV) was present in 18.8% of patients.

Iterative reconstruction (AIDR 3D) was used in the latter 20 patients, while the first 12 patients underwent CTA without iterative reconstruction. Details regarding the radiation dose of the entire examination are shown in Table 2. With iterative reconstruction, a reduced radiation dose of almost two-thirds was achieved while maintaining the image quality of CTA.

Table 2. Radiation dose of subtraction CTA.

Metrics	Overall (mGy·cm)	Without IR (mGy·cm)	With IR (mGy·cm)
Mean ± SD	1707.5 ± 1050.4	2962.7 ± 117.8	977.7 ± 69.7
Range	589.0–3672.6	1456–3672	659–1826

Abbreviations: CTA: computed tomographic angiography, IR: iterative reconstruction, SD: standard deviation

On conventional CTA, 160 arterial segments (25.2%) were unassessable (Table 3), with the majority (n = 152) being unassessable due to arterial calcification. In contrast, subtraction CTA rendered only thirteen arterial segments (2.0%) unassessable. In most instances, overlapping branches and misregistration of calcification interfered with the definitive evaluation of lesion severity.

Table 3. Characteristics of unassessable lesions on CT angiography.

Characteristic	Conventional CTA	Subtraction CTA
Total number of segments	636	
Unassessable segments	160 (25.2%)	13 (2.0%)
Calcification	152 (23.9%)	6 (0.9%)
Metallic stent	3 (0.5%)	0 (0.0%)
Overlap of branches	4 (0.6%)	5 (0.8%)
Unclear margin	1 (0.2%)	2 (0.3%)

Abbreviation: CTA: computed tomographic angiography.

Table 4 provides the correlations of percentage stenosis on conventional CTA and subtraction CTA with DSA. In quantifying lesion severity, subtraction CTA strongly correlated with DSA ($R^2 = 0.873$). A weak correlation was observed between conventional CTA and DSA ($R^2 = 0.358$), driven mainly by the high number of false positive segments due to calcifications. For both conventional and subtraction CTA, a discrepancy between stenosis on CTA and occlusion on DSA was observed for several segments.

Table 4. Diagnostic accuracy and ROC results of subtraction CTA and conventional CTA.

Region	Metrics	Conventional CTA	Subtraction CTA
Total	# of Missing Values	160 (25.16%)	13 (2.04%)
	Accuracy	0.657	0.885
	Precision	0.744	0.884
	Recall	0.675	0.936
	F1 Score	0.708	0.909
	Correlation with DSA (R^2)	0.358	0.873
	AUC (95% CI) *	0.594 (0.546–0.642)	0.913 (0.886–0.940)

Table 4. Cont.

Region	Metrics	Conventional CTA	Subtraction CTA
Iliac	# of Missing Values	98 (51.31%)	5 (2.62%)
	Accuracy	0.471	0.927
	Precision	0.741	0.971
	Recall	0.444	0.930
	F1 Score	0.555	0.950
	AUC (95% CI) *	0.343 (0.246–0.441)	0.933 (0.876–0.990)
Femoropopliteal	# of Missing Values	52 (20.31%)	6 (2.34%)
	Accuracy	0.707	0.891
	Precision	0.808	0.914
	Recall	0.768	0.934
	F1 Score	0.788	0.924
	AUC (95% CI) *	0.590 (0.500–0.680)	0.902 (0.851–0.952)
Below the Knee	# of Missing Values	10 (5.29%)	2 (1.06%)
	Accuracy	0.778	0.836
	Precision	0.633	0.689
	Recall	0.911	0.956
	F1 Score	0.747	0.808
	AUC (95% CI) *	0.830 (0.768–0.892)	0.903 (0.857–0.950)
CLI patients (6 cases, 111 segments)			
Total	# of Missing Values	49 (41.88%)	8 (6.84%)
	Accuracy	0.513	0.889
	Precision	0.571	0.892
	Recall	0.438	0.906
	F1 Score	0.496	0.899
	AUC (95% CI) *	0.443 (0.339–0.547)	0.854 (0.769–0.940)

* Indicates $p < 0.05$. Abbreviations: CTA: computed tomographic angiography, AUC: area under the curve, CI: confidence interval, CLI: critical limb ischemia

The diagnostic accuracy and AUC of ROC analysis of conventional CTA compared to DSA were 0.657 and 0.594, respectively. For subtraction CTA, these values were 0.885 and 0.913, respectively. A comparison of AUC showed a significant difference ($p < 0.05$) between conventional CTA and subtraction CTA. In patients with critical limb ischemia, the diagnostic accuracy of subtraction CTA was 0.889, although that of conventional CTA was 0.513. Details are provided in Table 4.

4. Discussion

This study demonstrated that subtraction CTA was superior to conventional CTA in cases of LEAD with severe arterial wall calcification. It exhibited high overall diagnostic accuracy, especially in CLI, suggesting that subtraction CTA may be a viable alternative to invasive angiography.

Arterial wall calcification is a common manifestation of arteriosclerosis and can be categorized into two types: intimal calcification of atherosclerotic lesions and Mönckeberg-type medial calcification. The latter is commonly observed in patients with diabetes and

end-stage renal disease (chronic renal failure) [13–15]. Critical limb ischemia frequently occurs in these patients, necessitating a detailed analysis of blood flow-limiting lesions to preserve the affected limbs. Furthermore, the prevalence and severity of vascular calcification are associated with cardiovascular disease and all-cause mortality in hemodialysis and peritoneal dialysis patients, providing critical prognostic information [16].

Multidetector CTA has been widely adopted for the initial diagnostic evaluation and treatment planning of patients with LEAD [17]. While CTA excels at detecting calcifications, the accurate assessment of arterial segments can be challenging due to “blooming artifacts” resulting from severe calcification.

Revascularization is essential not only for patients with claudication but also for patients with CLI to prevent tissue loss or avoid limb amputation [18]. However, determining the severity of the disease is crucial for establishing adequate inflow before restoring outflow, even in severely calcified arterial segments [19]. In this study, 18.8% of patients were on chronic hemodialysis because of renal insufficiency, and 18.8% of patients had CLI. Notably, half of the patients undergoing chronic dialysis also had CLI.

MRA has potential advantages in examining diffusely calcified vessels in patients with diabetes mellitus and chronic renal insufficiency. However, due to the risk of nephrogenic systemic fibrosis, contrast-enhanced MRA should be avoided in patients with chronic renal failure [20–22].

Although conventional CTA provides better spatial resolution than MRA, it has limitations in evaluating arterial segments with severe calcification [23].

Dual-energy CT angiography has been proposed for bone and plaque removal, and studies have shown promising correlations with invasive angiography [24]. However, dual-energy CT angiography’s accuracy in evaluating CLI calf arteries was insufficient. In addition, the specificity of dual-energy CT angiography was still significantly reduced in the presence of calcifications [25].

In this study, subtraction CTA successfully produced luminal images of lower extremity arteries comparable to those obtained through digital subtraction angiography, even for small peripheral arteries. Subtraction CTA effectively removed calcification and the associated blooming artifacts while preserving the structural detail of the lumen. However, structural misalignment between non-contrast and contrast-enhanced images—caused by respiratory motion, intestinal peristalsis, or involuntary leg movements—can generate artifacts and degrade image quality. We developed volumetric position matching software to address this and performed targeted image reconstruction for each limb. These enhancements minimized differences and achieved high spatial resolution. While the technique demands meticulous patient preparation, specialized scanning, and dedicated postprocessing, it facilitates improved image evaluation.

The main limitations of CTA include the need to administer iodinated contrast medium and high levels of radiation exposure [26]. In this study, the contrast volume was reduced to 70 mL. Although 60% of these patients were already undergoing dialysis, careful consideration is still required when deciding whether CTA is appropriate.

In one patient, insufficient contrast enhancement was observed. An additional scan of the below-knee arteries was performed immediately after the first contrast-enhanced scan; however, the contrast medium also failed to reach the ankle level in the second scan. The likely cause was increased microcirculation resistance due to severe arteriosclerosis, resulting in extremely slow arterial blood flow and an inability to complete the evaluation.

Subtraction CTA requires both non-contrast and contrast-enhanced images, leading to an increased radiation dose compared to a single contrast-enhanced CTA. However, non-contrast CT is necessary for LEAD patients to determine the extent and location of calcification for invasive revascularization. It is also helpful in distinguishing blooming

and beam-hardening artifacts caused by severe calcification, making it a key component of the imaging protocol. Recent advances in iterative reconstruction techniques and AI-based image processing are expected to reduce radiation doses, although further evaluation is required substantially.

5. Conclusions

Subtraction CTA is a practical and clinically useful diagnostic tool in evaluating peripheral arterial occlusive disease with severe arterial wall calcification.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Iwate Medical University (approved No H23-105).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to ethical considerations (protection of sensitive personal information).

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CTA	computed tomography angiography
LEAD	lower extremity artery disease
CLI	critical limb ischemia
DSA	digital subtraction angiography
MRA	magnetic resonance angiography
MIP	maximum intensity projection
ROC	receiver operating characteristic
AUC	area under the curve
SD	standard deviation
CI	confidence interval

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Article

Importance of Imaging Assessment Criteria in Predicting the Need for Post-Dilatation in Transcatheter Aortic Valve Implantation with a Self-Expanding Bioprosthesis

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Abstract

Background: Transcatheter aortic valve implantation (TAVI) has revolutionized the treatment of severe aortic valve stenosis (AS). Balloon post-dilatation (PD) remains an important procedural step to optimize valve function by resolving incomplete valve expansion, which may lead to paravalvular regurgitation and other potentially adverse effects. There are only limited data on the predictors, incidence, and clinical impact of PD during TAVI. **Methods:** This retrospective, single-center study analyzed 585 patients who underwent TAVI (2016–2022). Pre-procedural evaluations included transthoracic echocardiography and CT angiography to assess key parameters, including the aortic valve calcium score (AVCS); aortic valve calcium density (AVCd); aortic valve maximal systolic transvalvular flow velocity (AV Vmax); and aortic valve mean systolic pressure gradient (AV MPG). We identified imaging predictors of PD and evaluated associated clinical outcomes by analyzing procedural endpoints (according to VARC-3 criteria) and long-term survival. **Results:** PD was performed on 67 out of 585 patients, with elevated AV Vmax (OR: 1.424, 95% CI: 1.039–1.950; $p = 0.028$) and AVCd (OR: 1.618, 95% CI: 1.227–2.132; $p = 0.001$) emerging as a significant independent predictor for PD in TAVI. Kaplan–Meier survival analysis revealed no significant differences in short- and mid-term survival between patients who underwent PD and those who did not. Interestingly, patients requiring PD exhibited a lower incidence of adverse events regarding major vascular complications, permanent pacemaker implantations and stroke. **Conclusions:** The study highlights AV Vmax and AVCd as key predictors of PD. Importantly, PD was not associated with increased procedural adverse events and did not predict adverse events in this contemporary cohort.

Keywords: aortic valve stenosis; computed tomography; echocardiography; post-dilatation; TAVI

1. Introduction

Transcatheter aortic valve implantation (TAVI) has become a pivotal therapeutic approach for patients with severe aortic stenosis (AS), offering a minimally invasive alternative to surgery, characterized by reduced recovery times and expanded applicability to

older patients (e.g., >75 years), regardless of surgical risk, and patients who are ineligible for surgical intervention [1–3]. Despite the procedural advancements and improvements in patient outcomes, certain technical challenges remain, one of which is the need for post-dilatation (PD) after initial valve deployment [4].

PD in TAVI is an adjunctive step involving balloon expansion of the implanted prosthetic valve to correct suboptimal results from the initial valve placement. This procedure is primarily employed to address issues such as residual paravalvular regurgitation (PVR), incomplete valve expansion, or malpositioning [5]. While PD can optimize valve function by improving seating and reducing PVR, it is associated with several risks, including extended procedural duration, increased likelihood of cerebrovascular events, conduction abnormalities, valve embolization, and even annular rupture [5,6]. As a result, identifying the factors that drive the necessity for PD might have an impact on patient selection, procedural planning, and clinical outcomes. The reported frequency of PD in TAVI procedures varies widely, with rates ranging from 10% to 40% [5,6]. This variation can be attributed to differences in patient populations, valve designs, operator experience, and criteria for procedural success.

Echocardiography and multi-detector computed tomography (MDCT) are indispensable to evaluating the structural and functional characteristics of the aortic valve complex and the access vasculature before TAVI [7,8]. Key parameters, including the aortic valve calcification score (AVCS), annular dimensions, and left ventricular outflow tract (LVOT) morphology, could be crucial in predicting the likelihood of residual PVR and the requirement for PD. For instance, a high AVCS could potentially be associated with incomplete valve expansion and persistent PVR, making it a significant predictor for PD [9]. Additionally, the degree of leaflet calcification, as visualized by echocardiography and MDCT, could influence valve expansion dynamics [10].

Our retrospective study has two main objectives:

1. It aims to assess the incidence of PD in patients undergoing transfemoral TAVI with a self-expandable system and to identify imaging criteria derived from echocardiography and computed tomography that may causally contribute to, and therefore predict, the need for balloon PD;
2. We evaluate the clinical impact of PD by analyzing procedural outcomes and long-term all-cause mortality.

2. Materials and Methods

2.1. Study Cohort

This study included a cohort of 585 individuals who were eligible for TAVI at Paracelsus Medical University Hospital in Salzburg between 2016 and 2022. Patient eligibility for TAVI was determined by a multidisciplinary heart team comprising experts in cardiac surgery, interventional cardiology, and anesthesiology. The patient selection process for the study cohort was both retrospective and consecutive.

2.2. Ethics Declaration

The research followed ethical guidelines in accordance with the Declaration of Helsinki and Good Clinical Practice. Approval for the study was granted by the Ethics Commission of the State of Salzburg (Land Salzburg Ethikkommission, EK-Nr. 1082/2024). The informed consent requirement was waived by the ethics committee as this is a retrospective analysis using deidentified data.

2.3. Data Collection

Patient data were retrieved from the ORBIS electronic medical records system (Agfa Healthcare, Version 08043301.04110DACHL) and from a separate medical archive system (Krankengeschichtsarchiv System, Uniklinikum Salzburg, Softworx by Andreas SchwabTM, 2008). The collected information included patient charts, hospital admission and discharge summaries, as well as echocardiography and imaging reports associated with the TAVI procedures.

2.4. Transthoracic Echocardiography (TTE)

Routine transthoracic echocardiograms were performed 1 to 4 weeks prior to TAVI, using either the iE33 or Epiq 5 ultrasound systems (Philips Healthcare, Hamburg, Germany). These scans were conducted by clinicians with over 4 years of echocardiography experience. Severe aortic stenosis was classified in line with current European Society of Cardiology (ESC) guidelines, which define severity based on specific echocardiographic parameters, including an aortic valve maximum velocity (AV Vmax) of ≥ 4.0 m/s; an aortic valve maximum pressure gradient (AV MAX) of ≥ 60 mmHg; an aortic valve mean pressure gradient (AV MPG) of ≥ 40 mmHg; and a left ventricular ejection fraction (LVEF) of $\geq 50\%$. LVEF was determined using Simpson's method.

2.5. Computed Tomography Angiography and Calcium Scoring

Before intervention, patients underwent routine ECG-gated non-contrast computed tomography (CT) of the heart to assess the aortic valve calcium and ECG-gated CT angiography (CTA) of the entire aorta down to the femoral arteries. These scans evaluated the aortic annulus (measuring diameter, perimeter, and area), aortic valve calcium burden, vascular anatomy, and potential access routes. The imaging was performed using either 128- or 256-slice dual-source CT scanners (Revolution, General Electric Healthcare, Chicago, IL, USA or Somatom Definition AS+, Siemens Healthcare, Erlangen, Germany), with the tube voltage (80–120 kVp) and current modulation adjusted for patient size. A bolus of 100 mL of non-ionic iodinated contrast medium, followed by 70 mL of saline, was administered at a flow rate of 3.5–5 mL/s using bolus-tracking technology.

The Agatston score for aortic valve calcium (AVCS) and annulus measurements were determined by a radiologist who specialized in cardiovascular imaging using dedicated software (Impax 6, Agfa-Gevaert, Mortsel, Belgium; IntelliSpace, Philips, Amsterdam, The Netherlands). The AVCS was calculated by identifying calcified areas on non-contrast CT and applying the Agatston method, which multiplies the plaque area by a density factor based on the highest attenuation. Aortic annulus measurements were taken during mid-systole, with imaging planes manually adjusted to align with the annulus orientation. Semiautomated tools calculated annulus perimeter, diameter, and area, which were critical in selecting the appropriate TAVI prosthesis. AVCS was indexed to the patient's body surface area (BSA), calculated using the Dubois formula, as follows: $BSA = 0.007184 \times \text{height}^{0.725} \times \text{weight}^{0.425}$, receiving the aortic valve calcium index (AVCi). AVCS was also indexed on the annulus area by calculating the aortic valve calcium density (AVCd).

2.6. TAVI Procedure and PD

All 585 patients underwent transfemoral TAVI using either second-generation (CoreValveTM Evo-lutTM R; Medtronic Inc., Minneapolis, MN, USA) or third-generation (CoreValveTM EvolutTM Pro; Medtronic Inc., Minneapolis, MN, USA) devices. The procedure followed standard protocols. Diagnosis of AS, indication for valve replacement, anatomical measurements, and vascular access were determined by pre-procedural imaging, including

TTE, CT, and, when needed, transesophageal echo-cardiography (TEE). Aortic annulus measurements were used for choosing the correct valve size according to the instructions for use.

The indication for PD was determined jointly by the implanting physicians within minutes after deployment of the prosthesis, taking into account the following criteria:

1. Structural assessment of the valve prosthesis using rotational fluoroscopy: insufficient spontaneous expansion affecting the entire circumference (“underexpansion”) and/or localized infolding;
2. Functional assessment using angiography and instantaneous transvalvular pressure measurement: unacceptable paravalvular leakage and/or residual stenosis.

The following criteria were weighed against the risk of potential complications of PD and other objections to PD:

1. Valve dislocation/embolization: implantation height;
2. Annulus rupture: eccentric sub-/supra-/valvular calcifications;
3. Hemodynamic intolerance of rapid ventricular pacing: left ventricular dysfunction, arrhythmia;
4. Lack of benefit from PD: concomitant (coronary, valvular) heart disease or extracardiac disease, individual life expectancy, age.

Balloon PD was performed using a compliant balloon catheter (Osypka, OSYPKA AG, Rheinfelden, Germany). Balloon size was selected based on the size of the implanted valve and additional structural criteria (primarily the size of the anatomical annulus and valvular/subvalvular calcification). Balloon valvuloplasty was performed at the valve site under fluoroscopic guidance and rapid right ventricular pacing by temporary transvenous pacemaker or—if present—permanent pacemaker. It was carried out according to the instructions for use by short-time manual (i.e., “low pressure”) inflation (up to approximately 1 s) without a manometer. Therefore, the applied maximum pressure and the exact duration of maximum balloon inflation could not be assessed quantitatively.

2.7. Clinical Outcomes

The primary outcome of the study was overall survival, measured from the time of TAVI to a two-year follow-up. This outcome was used to assess the mid-term effectiveness of the procedure in extending the life expectancy of patients and the potential impact of PD on this. Secondary safety outcomes included the incidence of procedural adverse events, such as major vascular complications, defined according to the current Valve Academic Research Consortium (VARC-3) criteria [11] as: severe bleeding requiring vascular surgical intervention; large vessel perforation or dissection; significant bleeding necessitating the transfusion of four or more units of blood; and distal embolization causing irreversible end-organ damage. Additional secondary outcomes included the need for permanent pacemaker implantation and cerebrovascular events such as stroke.

2.8. Statistical Analysis

All statistical analyses and data visualizations were conducted using SPSS software (Version 25.0, SPSS Inc., Armonk, NY, USA). To assess the distribution of variables, the Kolmogorov–Smirnov–Lilliefors test was applied. Continuous variables following a normal distribution were reported as mean $\pm$ standard deviation (SD) and compared using an unpaired Student’s *t*-test. For non-normally distributed variables, data were expressed as median with interquartile range (IQR) and analyzed using the Mann–Whitney U test. Categorical variables were presented as frequencies or percentages and compared using the chi-squared test.

A univariate binary regression analysis was performed to identify echocardiographic and radiological variables potentially associated with the need for PD across the entire patient cohort. Metric data underwent z-transformation to enhance comparability. Factors with a p -value of ≤ 0.100 in univariate analysis were included in a subsequent multivariable binary logistic regression to determine independent predictors of PD, with backward elimination used to refine the model.

To evaluate the predictive power of aortic valve maximum velocity (AV Vmax) in determining the need for PD, a receiver-operating characteristic (ROC) curve was generated, calculating the area under the curve (AUC), sensitivity, specificity, and Youden Index (YI).

A Kaplan–Meier survival analysis was conducted to explore differences in 30-day to 5-year mortality between patients who underwent PD and those who did not, with corresponding log-rank tests and risk numbers included.

Finally, an additional binary logistic regression analysis was performed to assess whether PD was associated with an increased risk of adverse clinical events.

A p -value of < 0.050 was considered to indicate statistical significance in all analyses.

3. Results

The overall rate of post-dilatation in our study population was 11.5% (Table 1). The baseline characteristics (Table 1) highlight significant differences between patients who required PD after TAVI and those who did not. A smaller proportion of men underwent PD (40.3% vs. 50.6%, $p = 0.113$). Hemodynamic parameters were notably different, with the PD group exhibiting a higher AV MPG (47.0 ± 17.3 mmHg vs. 44.0 ± 11.8 mmHg, $p < 0.001$); aortic valve maximum pressure gradient (AV MAX) (82.0 ± 20.5 mmHg vs. 74.0 ± 19.0 mmHg, $p < 0.001$); and AV Vmax (4.6 ± 0.6 m/s vs. 4.3 ± 0.5 m/s, $p < 0.001$). Radiological factors, such as AVCS (4123.5 ± 2264.3 AU vs. 2813.5 ± 2060.0 AU), AVCi (2406.0 ± 1060.6 AU/m² vs. 1562.7 ± 1114.4 AU/m²), and AVCd (865.7 ± 299.3 AU/cm² vs. 598.2 ± 376.4 AU/cm²), demonstrated highly significant differences ($p < 0.001$ each) between the groups. Pre-dilatation of the native aortic valve immediately before implantation of the transcatheter valve prosthesis at operators' discretion was performed in 11 patients (2.1%) within the group without PD, and in 1 patient (1.5%) within the PD group (0.732). Due to these small numbers, we refrained from further analyses in this regard.

The binary logistic regression analysis (Table 2) revealed that, in the univariate model, AV MPG, AV MAX, AV Vmax, AVCS, AVCi and AVCd were significantly associated with an increased likelihood of PD. However, in the multivariable analysis, only AV Vmax with an odds ratio (OR) of 1.424, a 95% confidence interval (CI): 1.039–1.950; $p = 0.028$ and an AVCd with OR: 1.618, 95% CI: 1.227–2.132; $p = 0.001$ remained an independent predictor for PD, while other parameters, including AV MAX, AV MPG, and AVCS, lost their significance.

The AUROC curves for AV MPG, AV MAX, and AV Vmax were analyzed to predict PD (Figure 1). The AV MAX demonstrated the highest AUC (0.675, 95% CI: 0.608–0.742, $p < 0.001$) with a sensitivity of 0.72 and a specificity of 0.58, at a cut-off of 76.50 mmHg. This was followed by AV Vmax, which had an AUC of 0.670 (95% CI: 0.600–0.739, $p < 0.001$), a sensitivity of 0.72, and a specificity of 0.57 at a cut-off of 4.40 m/s. The AV MPG showed the lowest AUC of 0.657 (95% CI: 0.589–0.726, $p < 0.001$), with a sensitivity of 0.57 and a specificity of 0.68 at a cut-off of 48.20 mmHg. The YI, which represents the optimal balance between sensitivity and specificity, was highest for AV MAX (0.30), followed by AV Vmax (0.29), and AV MPG (0.25).

Table 1. Baseline characteristics of study cohort.

	Post-Dilatation+	Post-Dilatation –	<i>p</i>
<i>n</i> / <i>%</i>	67/11.5	518/88.5	-
Sex (male)— <i>n</i> / <i>%</i>	27/40.3	262/50.6	0.113
Age (years)—mean ± SD	80.4 ± 5.4	82.3 ± 5.0	0.004
Height (cm)—mean ± SD	166.4 ± 8.2	168.1 ± 9.8	0.172
Weight (kg)—mean ± SD	71.8 ± 14.2	73.1 ± 14.5	0.497
BMI (kg/m ²)—mean ± SD	25.9 ± 4.5	25.8 ± 4.4	0.825
BSA (m ²)—mean ± SD	1.8 ± 0.2	1.8 ± 0.2	0.463
LVEF (%)—median ± IQR	55.0 ± 15.0	55.0 ± 10.0	0.417
IVSD (mm)—median ± IQR	14.0 ± 3.3	13.0 ± 2.4	0.265
LVEDD (mm)—median ± IQR	4.6 ± 1.0	4.6 ± 0.9	0.660
AV MPG (mmHg)—median ± IQR	47.0 ± 17.3	44.0 ± 11.8	<0.001
AV MAX (mmHg)—median ± IQR	82.0 ± 20.5	74.0 ± 19.0	<0.001
AV Vmax (m/s)—median ± IQR	4.6 ± 0.6	4.3 ± 0.5	<0.001
Annulus Diameter (mm)—median ± IQR	25.0 ± 2.3	25.0 ± 3.0	0.850
Annulus Area (cm ²)—median ± IQR	467.5 ± 87.0	472.0 ± 124.3	0.797
AVCS (AU)—median ± IQR	4123.5 ± 2264.3	2813.5 ± 2060.0	<0.001
AVCi (AU/m ²)—median ± IQR	2406.0 ± 1060.6	1562.7 ± 1114.4	<0.001
AVCd (AU/cm ²)—median ± IQR	865.7 ± 299.3	598.2 ± 376.4	<0.001
Pre-dilatation performed— <i>n</i> / <i>%</i>	1/1.5	11/2.1	0.732

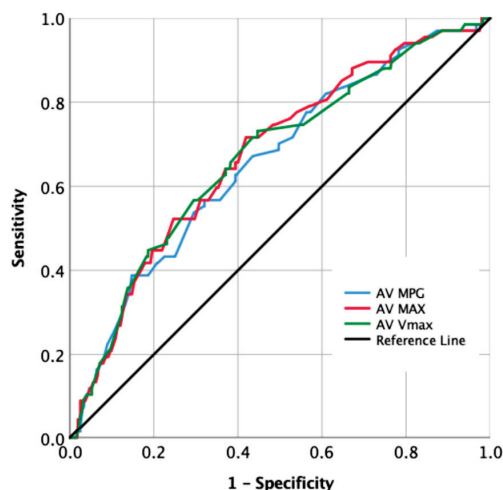
AVCd: aortic valve calcium density; AVCi: aortic valve calcium index; AVCS: aortic valve calcium score; AV MAX: aortic valve maximum pressure gradient; AV MPG: aortic valve mean systolic pressure gradient; AV Vmax: aortic valve maximal systolic transvalvular flow velocity; BMI: body mass index; BSA: body surface area; IQR: interquartile range; IVSD: interventricular septal thickness; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; SD: standard deviation.

Table 2. Univariate and multivariable binary logistic regression regarding echocardiographic and radiological parameters in the presence of post-dilatation after TAVI.

Post-Dilatation Binary Logistic Regression	Univariate		Multivariable	
	Odds Ratio (95% CI)	<i>p</i>	Odds Ratio (95% CI)	<i>p</i>
LVEF	0.789 (0.419–1.487)	0.464		
IVSD	1.036 (0.824–1.304)	0.762		
LVEDD	0.613 (0.147–2.561)	0.502		
AV MPG	1.607 (1.261–2.049)	<0.001	0.788 (0.470–1.321)	0.366
AV MAX	1.679 (1.314–2.145)	<0.001	1.187 (0.455–3.100)	0.726
AV Vmax	1.780 (1.361–2.328)	<0.001	1.424 (1.039–1.950)	0.028
Annulus Diameter	0.961 (0.725–1.274)	0.783		
Annulus Area	0.984 (0.743–1.304)	0.911		
AVCS	1.636 (1.269–2.111)	<0.001	0.953 (0.531–1.710)	0.872
AVCi	1.680 (1.293–2.184)	<0.001	1.248 (0.370–4.215)	0.721
AVCd	1.794 (1.387–2.321)	<0.001	1.618 (1.227–2.132)	0.001

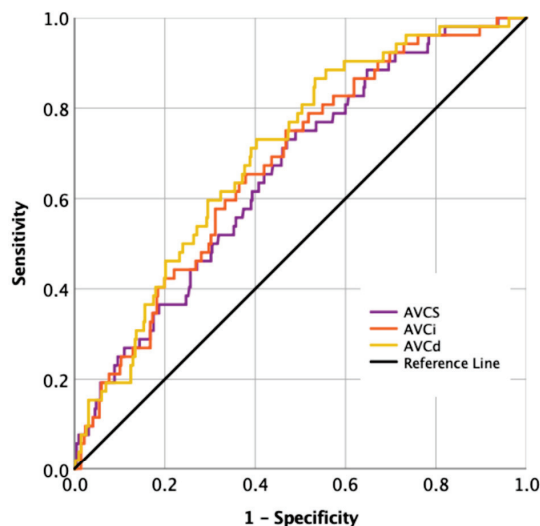
AVCd: aortic valve calcium density; AVCi: aortic valve calcium index; AVCS: aortic valve calcium score; AV MAX: aortic valve maximum pressure gradient; AV MPG: aortic valve mean systolic pressure gradient; AV Vmax: aortic valve maximal systolic transvalvular flow velocity; CI: confidence interval; IVSD: interventricular septal thickness; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction.

The AUROC analysis of AVCS, AVCi, and AVCd for predicting PD is shown in Figure 2. AVCd exhibited the best discriminative ability, with an AUC of 0.700 (95% CI: 0.632–0.769, $p < 0.001$), achieving a sensitivity of 87% and a specificity of 47% at a cut-off of 581.4 AU/cm². AVCi had a slightly lower AUC of 0.675, while AVCS presented the lowest AUC (0.659). AVCd also had the highest YI (0.34), suggesting that it is the most effective radiological predictor.



Value	Prediction	AUC	95%CI	P-value	Cut-off	Sensitivity	Specificity	Youden Index
AV MPG (mmHg)	Post-Dilatation +	0.657	0.589 — 0.726	<0.001	48.20	0.57	0.68	0.25
AV MAX (mmHg)	Post-Dilatation +	0.675	0.608 — 0.742	<0.001	76.50	0.72	0.58	0.30
AV Vmax (m/s)	Post-Dilatation +	0.670	0.600 — 0.739	<0.001	4.40	0.72	0.57	0.29

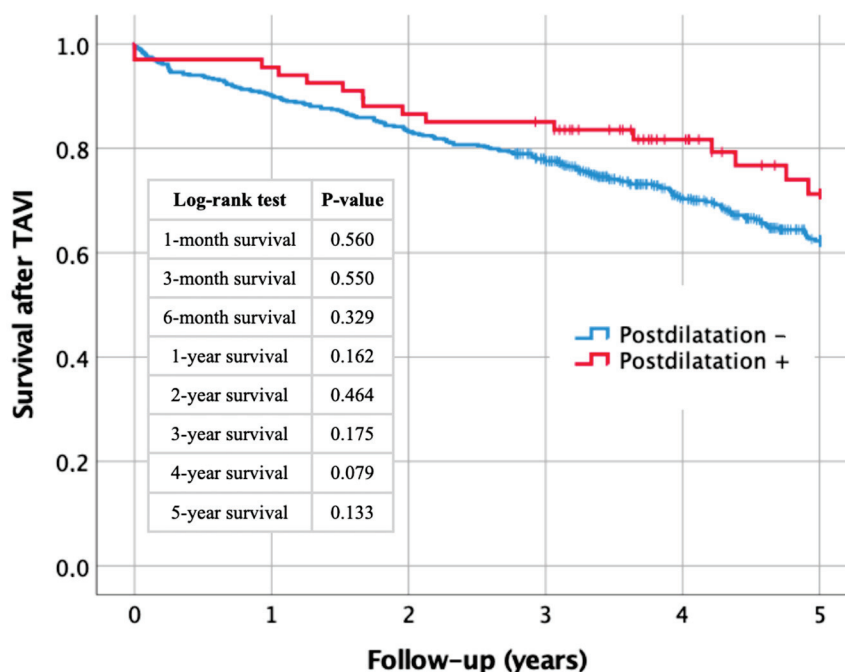
Figure 1. AUROC analysis of echocardiographic criteria for discrimination between the presence (+) or absence (–) of post-dilatation. CI: confidence interval; AUC: area under the curve; AV MAX: aortic valve maximum pressure gradient AV MPG: aortic valve mean systolic pressure gradient; AV Vmax: aortic valve maximal systolic transvalvular flow velocity.



Value	Prediction	AUC	95%CI	P-value	Cut-off	Sensitivity	Specificity	Youden Index
AVCS (AU)	Post-Dilatation +	0.659	0.586 — 0.732	<0.001	2981.5	0.73	0.53	0.26
AVCi (AU/m ²)	Post-Dilatation +	0.675	0.603 — 0.746	<0.001	1672.4	0.75	0.53	0.28
AVCd (AU/cm ²)	Post-Dilatation +	0.700	0.632 — 0.769	<0.001	581.4	0.87	0.47	0.34

Figure 2. AUROC-analysis of radiological criteria for discrimination between the presence (+) or absence (–) of post-dilatation. CI: confidence interval; AU: Agatston unit; AUC: area under the curve; AVCd: aortic valve calcium density; AVCi: aortic valve calcium index; AVCS: aortic valve calcium score.

A Kaplan–Meier analysis was performed to evaluate short- and mid-term survival in patients undergoing TAVI, comparing those who received PD to those who did not. As shown in the Kaplan–Meier survival curve (Figure 3), there is no statistically significant difference between the groups across the following time points: 1 month ($p = 0.560$); 3 months ($p = 0.550$); 6 months ($p = 0.329$); 1 year ($p = 0.162$); 2 years ($p = 0.464$); 3 years ($p = 0.175$); 4 years ($p = 0.079$); and 5 years ($p = 0.133$).



Number at Risk	0 months	1 month	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Post-Dilatation +	67	65	65	65	64	58	57	55	51
Post-Dilatation –	518	508	494	487	467	431	403	372	345
Overall	585	573	559	552	531	489	460	427	396

Figure 3. Kaplan–Meier curve with corresponding log-rank tests regarding overall short- and mid-term survival in patients with the presence (+) or absence (–) of post-dilatation after transcatheter aortic valve implantation.

The occurrence of major adverse events following TAVI is presented in Table 3. No significant differences were found between the groups for specific adverse outcomes such as major vascular complications (0.0% vs. 3.5%, $p = 0.121$), pacemaker implantation (7.5% vs. 13.1%, $p = 0.187$), or stroke incidence (1.5% vs. 2.7%, $p = 0.554$).

Table 3. Specific outcome of study cohort regarding presence or absence of post-dilatation.

	Post-Dilatation+	Post-Dilatation–	<i>p</i>
Major Vascular Complications after TAVI	0/0.0	18/3.5	0.121
Pacemaker after TAVI— <i>n</i> /%	5/7.5	68/13.5	0.187
Stroke after TAVI— <i>n</i> /%	1/1.5	14/2.7	0.554

TAVI: transcatheter aortic valve implantation.

The univariate binary logistic regression analysis (Table 4) revealed no significant associations between PD and individual outcomes, such as major vascular complications

(odds ratio, OR: 0.000, 95% CI: 0.000, $p = 0.998$), pacemaker implantation (OR: 0.534, 95% CI: 0.207–1.375, $p = 0.193$), or stroke (OR: 0.544, 95% CI: 0.070–4.207, $p = 0.560$), indicating no significant elevation in these specific complications.

Table 4. Univariate binary logistic regression regarding outcome parameters in the presence of post-dilatation after TAVI.

Post-Dilatation Binary Logistic Regression	Univariate	
	Odds Ratio (95% CI)	p
Major Vascular Complications after TAVI	0.000 (0.000–.)	0.998
Pacemaker after TAVI	0.534 (0.207–1.375)	0.193
Stroke after TAVI	0.544 (0.070–4.207)	0.560

CI: confidence interval; TAVI: transcatheter aortic valve implantation.

4. Discussion

4.1. Predicting the Probability of Post-Dilatation from Imaging Findings

Aortic valve calcium load: Aortic valve calcium has long been recognized as a potential predictor of TAVI procedural complications such as bioprosthesis underexpansion, paravalvular regurgitation, valve malpositioning, conduction disturbances, and annular rupture [12,13]. Since the underexpansion of bio-prosthesis, with or without paravalvular leakage, is the main indication for PD, the amount of aortic valvular calcium can be expected to predict the need for PD. While previous studies have suggested that a higher AVCS would increase the likelihood of PD, in our analysis, surprisingly, AVCS did not significantly predict the rate of PD. However, AVCd emerged as a stronger predictor, as shown by binary logistic regression and AUROC analysis. These results suggest that AVCd, which considers the concentration of calcium over the annulus area (“density”), may better reflect the mechanical challenges of valve deployment than the overall calcification score AVCS, which depends on local and systemic anatomical characteristics, including body size.

One possible explanation for the potentially diminished role of AVCS in predicting PD over the years could be improvements in self-expanding TAVI technology such as the then-current Evolut R and Evolut Pro devices used in this study. These devices apply consistent radial force even after deployment, which may allow for more complete valve expansion, even in heavily calcified settings. This could reduce the need for additional balloon expansion, even in the presence of significant calcification [3,14], which would make AVCS less predictive of PD.

Our findings contribute to a growing body of evidence suggesting that, while AVCS is useful in predicting outcomes, like paravalvular regurgitation, it may not be as predictive of the need for PD. The relevance of AVCd in this context underlines the need to reconsider the role of the absolute degree of calcification in procedural planning. Instead, future research could focus on identifying specific calcification characteristics, such as density or regional distribution within the aortic valve leaflets, which are likely to better predict PD risk, rather than relying solely on the overall calcification score.

Transvalvular flow velocity: Our study identified $AV V_{max} \geq 4.0$ m/s pre-TAVI as a significant independent predictor of the need for PD, with higher AV V_{max} values correlating with an increased likelihood of requiring PD. This finding supports the notion that elevated AV V_{max} may predict suboptimal valve deployment, necessitating PD to optimize valve function, minimize residual gradients [15], and reduce PVR [16]. The fact that AV V_{max} , but not AVCS, is associated with PD suggests that other factors not directly related to the absolute calcium load—such as fibrotic components in the AS,

or the distribution of valve calcification—play an important role in the development of underexposing and PVR, which represent the major indications for PD. Although AV Vmax shows (moderate) discriminative power in predicting the need for PD, as demonstrated by the AUROC analysis, its relatively low specificity suggests that it should not be used in isolation. Integrating AV Vmax with other echocardiographic parameters, such as aortic annulus dimensions, LVOT morphology, or LVOT calcium load, could enhance predictive accuracy. However, such an approach cannot be recommended at present and should be the subject of further studies.

4.2. Impact of Post-Dilatation on Procedural and Longterm Outcomes

Procedural outcomes: One of the most intriguing findings of our study was that PD was not associated with an elevation in adverse events. This counterintuitive result is contrary to the perception from earlier years in the TAVI era that PD could increase the risk of complications, including cerebrovascular events, conduction disturbances requiring pacemaker implantation, and annular rupture [6,17]. However, our findings align with studies that have reported similar outcomes [18,19]. For instance, a more recent study by Sanz Sánchez et al. [20] observed that PD in newer-generation self-expanding valves did not increase the risk of adverse events, suggesting that the more current generations of TAVI devices may offer improved safety profiles during PD.

Long-term outcomes: We found no significant survival difference between the group with PD and the group without PD over a period of five years. Despite concerns about premature valve degeneration due to the additional mechanical stress of the bioprosthesis during PD, there are few studies in the literature on long-term survival and other clinical endpoints after TAVI with PD. By far the longest follow-up period was again reported by Sanz Sanchez et al. [20], who tracked overall mortality over 6 years in a relatively large number of patients and also found no significant difference. The study also examined echocardiographic endpoints with regard to valve degeneration in the two groups—also without a significant difference.

4.3. Clinical Relevance

In line with previous studies, our study confirms the clinical experience of recent years that PD is not associated with a significantly increased risk in the context of contemporary TAVI procedures, provided that an appropriate clinical risk–benefit analysis is performed. The results thus support the concept of striving for an optimal implantation result—including PD, if necessary—which is particularly important in view of the increasing number of relatively young patients undergoing TAVI. In view of this, the pre-procedural assessment of the need for PD may no longer be as important as it was in previous years. However, particularly in high-risk patients, this will continue to be an aspect that will play an important role in the planning of TAVI—and in some cases possibly also in the decision for or against valve intervention. In this sense, our study can provide valuable information to those involved in heart team decisions.

4.4. Limitations

Despite providing valuable insights, our study has several limitations.

1. The retrospective design limits the ability to establish causal relationships between variables and the need for PD. Although significant associations were identified, prospective studies are required to confirm these findings and assess their real-world applicability. We focused on key echocardiographic and radiological factors, but other potential predictors, such as specific anatomical features or calcium distribution, were not analyzed;

2. The study was conducted at a single center with a relatively homogeneous patient population and small sample size, limiting the statistical power of our analyses and the generalizability to more diverse groups. Patient selection, procedural expertise, and device-specific factors might have influenced the outcomes. Larger, multicenter studies are needed to validate the findings and to establish whether they are transferable to other clinical and procedural settings;
3. The use of second- and third-generation self-expanding TAVI devices may not fully reflect the performance of newer systems, such as the Evolut Fx, currently in use; the findings are not generalizable to other self-expanding platforms with different designs and radial strengths such as the Acurate or Navitor systems. Of course, our results cannot be applied to balloon-expanded TAVI systems, which generally have significant lower post-dilatation rates compared with self-expanding systems due to their different deployment technology;
4. As a systematic limitation, it should be pointed out that the multitude of anatomical, morphological, functional and clinical criteria that contributed to the operators' decisions whether or not to post-dilate—which were inherently made intraprocedurally and under limited time resources—could not be assessed in this retrospective analysis.

5. Conclusions

In our study, AVCS as a measure of absolute valvular calcium load did not predict the likelihood of PD during TAVI procedure with a self-expanding bioprosthesis, whereas aortic valve calcium density and AV-Vmax were identified as significant predictors of PD. PD was not associated with an increase in adverse events. Our study therefore suggests that PD can be performed safely when indicated. Longterm mortality was also not affected by PD.

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Institutional Review Board Statement: The research followed ethical guidelines in accordance with the Declaration of Helsinki and Good Clinical Practice. Approval for the study was granted by the Ethics Commission of the State of Salzburg (EK-Nr. 1082/2024). The informed consent requirement was waived by the ethics committee as this is a retrospective analysis using deidentified data.

Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study and the use of deidentified data, as approved by the ethics committee.

Data Availability Statement: The datasets analyzed during the current study were retrieved from the ORBIS electronic medical records system and a separate medical archive system at the University Hospital Salzburg. Due to patient privacy and institutional regulations, the datasets are not publicly available but are available from the corresponding author upon reasonable request and with appropriate ethical approval.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AS	Aortic Stenosis
AV	Aortic Valve
AV MAX	Aortic Valve Maximum Pressure Gradient
AV MPG	Aortic Valve Mean Systolic Pressure Gradient
AV Vmax	Aortic Valve Maximal Systolic Transvalvular Flow Velocity
AVCS	Aortic Valve Calcium Score
AVCi	Aortic Valve Calcium Index
AVCd	Aortic Valve Calcium Density
AUC	Area Under the Curve
AUROC	Area Under the Receiver Operating Characteristic Curve
BSA	Body Surface Area
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed Tomography
CTA	Computed Tomography Angiography
ECG	Electrocardiogram
ESC	European Society of Cardiology
IQR	Interquartile Range
IVSD	Interventricular Septal Thickness
LVEF	Left Ventricular Ejection Fraction
LVEDD	Left Ventricular End-Diastolic Diameter
MDCT	Multi-Detector Computed Tomography
OR	Odds Ratio
PD	Post-Dilatation
PVR	Paravalvular Regurgitation
ROC	Receiver Operating Characteristic
SD	Standard Deviation
TEE	Transesophageal Echocardiography
TTE	Transthoracic Echocardiography
TAVI	Transcatheter Aortic Valve Implantation
VARC-3	Valve Academic Research Consortium-3
YI	Youden Index

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Article

Extracellular Volume Fraction Analysis on Cardiac Computed Tomography Is Useful for Predicting the Prognosis of Hypertrophic Cardiomyopathy

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Abstract

Extracellular volume fraction (ECV) analysis on computed tomography (CT) is now available. The purpose of this study was to assess the usefulness of CT-derived ECV analysis for predicting outcomes in patients with hypertrophic cardiomyopathy (HCM). One hundred and one HCM patients (67 males, 66 ± 11 years old) who received cardiac CT between January 2009 and December 2021 were included. We measured left ventricular (LV) ECV (LV-ECV) on CT and investigated the relationship between LV-ECV and the major adverse cardiac events (MACE) after CT. Fifteen patients (15%) experienced MACE. The patients with MACE had a significantly higher LV-ECV, left atrial diameter, LV end-systolic diameter, and lower LVEF than those without MACE. The proportion of dilated phase HCM was significantly higher in the patients with MACE than those without MACE. LV-ECV and LVEF were significant predictors of MACE based on the multivariate analysis by Cox proportional hazards model. The optimal threshold of LV-ECV to predict MACE was 37.6% based on the receiver operating characteristic analysis. The patients with LV-ECV $\geq 37.6\%$ (30 patients) experienced significantly higher MACE than those with LV-ECV $< 37.6\%$ ($p < 0.001$). CT-derived ECV analysis suggested potential usefulness for predicting MACE in patients with HCM.

Keywords: hypertrophic cardiomyopathy; extracellular volume; computed tomography

1. Introduction

Hypertrophic cardiomyopathy (HCM) is recognized as a significant cardiovascular disorder that may result in life-threatening ventricular arrhythmia, syncope or sudden cardiac death, including among younger individuals [1]. The usefulness of transthoracic echocardiography (TTE) and magnetic resonance imaging (MRI) for risk stratification and the detection of high-risk patients with HCM is already known broadly [2,3].

Detection of late gadolinium enhancement (LGE) using cardiac MRI has been the gold standard in the qualitative evaluation of myocardial fibrosis in patients with cardiomyopathies. The recognition of the LGE pattern is useful for the differential diagnosis of

several types of cardiomyopathies, and the presence of LGE is a marker of worse prognosis in several myocardial diseases, including HCM [3]. Additionally, T1 mapping analysis on MRI is now available, and evaluation of native T1 values and extracellular volume fraction (ECV) using this mapping is also helpful in the quantitative analysis of myocardial fibrosis [4].

However, MRI has some limitations. MRI can be limited in individuals with non-MRI-conditional cardiac mechanical devices due to safety concerns. Furthermore, MRI is not suitable for individuals with severe claustrophobia, and patients with hemodialysis are not candidates for gadolinium contrast for LGE analysis. Even if cardiac mechanical devices are acceptable for MRI, obtaining clear images is not easy. This is due to frequent device checks before and after image acquisition and lower image quality caused by mechanical artifacts. Moreover, LGE imaging is complex in patients with arrhythmia and heart failure because of motion artifacts or difficulty holding their breath [5]. In contrast, cardiac computed tomography (CT) has fewer restrictions compared to MRI and can be used for more patients. Particularly in HCM patients, who often have ST abnormalities on ECG or chest discomfort, cardiac CT is commonly used to rule out coronary artery disease. Based on recent guidelines, cardiac CT is recognized as a valuable tool for screening coronary artery stenosis in individuals suspected of having myocardial dysfunction [6]. In addition, recent advancements in scanners enabled the acquisition of clear images even in patients with arrhythmia [7]. If late-phase scans are performed, they are helpful for screening intracardiac thrombus and detecting myocardial fibrosis occurring as late iodine enhancement (LIE), similar to the LGE [8]. Additionally, the ECV of left ventricular myocardium (LVM) (LV-ECV) is evaluable on those images, and the ECV values measured by CT correlate well with those of MRI [9].

Following recent reports on the utility of ECV analysis on MRI in predicting ventricular arrhythmia in cases with HCM [10], we speculated on the presence of a correlation between LV-ECV on CT and adverse events in HCM patients. To investigate this potential association, we evaluated the utility of CT-derived ECV analysis for predicting adverse events in the study cohort.

2. Materials and Methods

This study was a multicenter retrospective cohort study. This retrospective study enrolled HCM patients who underwent cardiac CT at Chiba University Hospital and Eastern Chiba Medical Center between January 2009 and December 2021. Patients were included if they underwent cardiac CT with late-phase acquisition using tube voltage consistent with non-contrast scanning protocols and completed a follow-up period of more than one month. Two cases were excluded because ECV analysis could not be performed due to significant gaps in the LVM images between the non-contrast and late-phase cardiac images. Patients who underwent CT at Chiba University Hospital between January 2016 and June 2020 were excluded because ECV analysis could not be performed due to different tube voltages between the non-contrast and late-phase cardiac images. We measured CT-derived ECV on LVM and collected comprehensive data, including patient characteristics, transthoracic echocardiographic findings, and other CT parameters. The relationship between these collected data and the occurrence of major adverse cardiac events (MACE) following the CT scan was subsequently investigated. MACE were defined as a composite of cardiac death, fatal arrhythmia, and heart failure hospitalization. The observation period was set until March 2023.

We compared patient background characteristics between the groups with and without MACE and assessed previously identified important factors for predicting MACE in HCM patients [11]. HCM was defined by cardiac findings demonstrating unexplained left

ventricular hypertrophy (LVH) measuring ≥ 15 mm (or ≥ 13 mm for individuals with a family history of HCM) [12,13]. Patients with secondary causes of left ventricular hypertrophy, specifically hypertension, Fabry disease, amyloidosis, mitochondrial disease, or congenital heart disease, were excluded. Patient background data, such as risk factors for coronary artery disease and administered medical treatments, were acquired from Chiba University Hospital and Eastern Chiba Medical Center. The risks of sudden cardiac death of patients were evaluated based on the previous study [14]. The institutional review board of Chiba University approved this retrospective analysis (reference number is 3822).

2.1. Protocol for Computed Tomography

CT examinations were conducted using either a 256-row detector CT scanner (Revolution CT Apex, GE Healthcare, Waukesha, WI, USA) or a 320-row detector CT scanner (Aquilion One or Aquilion One ViSion Edition, Canon Medical Systems, Otawara, Japan). Tube current for all scans was determined by the automatic exposure control system. A non-contrast ECG-gated cardiac scan, performed with a prospective ECG-gated technique, was acquired before the contrast administration. For the non-contrast scan, slice thickness was 0.5 mm and tube voltage was set to 100 or 120 kV on the 320-row CT, while the 256-row CT used a slice thickness of 0.625 mm and a tube voltage of 120 kV.

The early phase scan for coronary artery evaluation was performed using retrospective ECG gating, with dose modulation applied to reduce radiation exposure. As previously reported, conventional enhanced CT was conducted using a slice thickness of 0.5 mm and a tube voltage of 120 kV [15]. If a patient's heart rate was ≥ 65 beats per minute, 20 mg of metoprolol tartrate or 12.5 mg landiolol was administered before the scan, assuming no contraindications to β -blocker therapy existed. Two doses of sublingual isosorbide dinitrate were given immediately before scanning.

Contrast material was administered using a triphasic protocol, which was previously identified as providing higher diagnostic accuracy for detecting coronary artery stenosis on CT [16]. Intravenous access was secured in the right or left antecubital vein with a 20 or 22-gauge needle. A dual-syringe injector featuring a dual-flow option (Dual Shoot GX7, Nemoto, Tokyo, Japan) was utilized for administration. The protocol involved a first phase injecting 50–110 mL of undiluted iodinated contrast agent (300–370 mg/mL), followed by 0–50 mL of a 50% saline-to-contrast mixture.

A late-phase scan was performed 6 min after the injection of iodinated contrast medium, utilizing the prospective ECG-gating technique [17]. The CT scan was conducted using the same slice thickness and the same tube voltage as in the non-contrast scan.

This protocol is consistent with that used in our previous study [15].

2.2. Analysis of Cardiac CT Images Including ECV

ECV of the LV myocardium was calculated using the formula $ECV = (\Delta HU_m / \Delta HU_b) / (1 - Hct)$ with commercially available software (Ziostation 2, Ziosoft Inc, Japan). In this formula, ΔHU_m indicates the change in myocardial CT attenuation (in Hounsfield units), ΔHU_b the change in blood CT attenuation, and Hct the hematocrit [17]. An automatic three-dimensional non-rigid registration of the myocardium was performed between the non-contrast and late-phase CT images to generate subtraction images, facilitating ECV calculation. From these images, the change in CT attenuation (ΔHU) was measured [17,18]. A polar map illustrating the mean ECV value for each of the 16 American Heart Association LVM segments was generated (Figure 1A). LV-ECV measurements on CT were conducted by a board-certified cardiologist (Hi.T.) with 15 years of cardiac CT reading experience and another cardiologist (S.A.) with four years of experience. These observers also assessed for the presence

of LIE of LVM on the same workstation, resolving any disagreements through a consensus reading. Sample images demonstrating the ECV analysis on CT are shown in Figure 1.

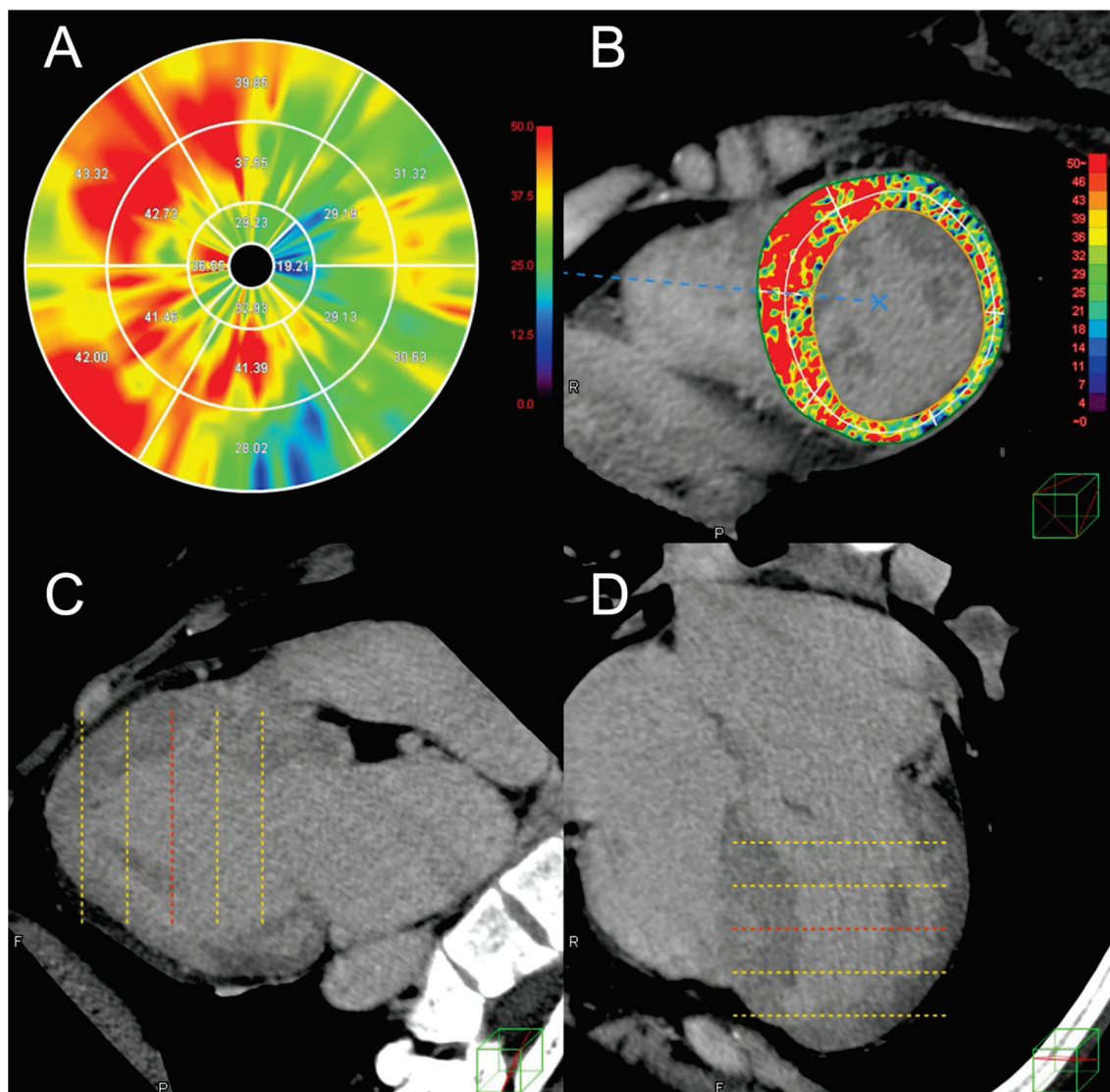


Figure 1. Extracellular volume analysis of left ventricular myocardium on computed tomography images in a case with hypertrophic cardiomyopathy. (A) A polar map displaying the segmental extracellular volume fraction (ECV) of left ventricular myocardium for each of the 16 American Heart Association segments. (B) A short-axis view with a color-coded ECV map overlaid. (C) Two-chamber and (D) four-chamber views of the late-phase computed tomography (CT) images used for the analysis. This case is of a 28-year-old female with HCM who was hospitalized for heart failure after the CT scan. The overall ECV of the left ventricular myocardium on CT was 37.6%.

For quantitative image quality analysis, regions of interest were manually drawn, approximately 0.1 cm^2 in areas of late iodine enhancement (LIE) and 0.5 cm^2 in the remote myocardium, in cases where LIE of LVM was present on CT (Figure 2). The contrast-to-noise ratio (CNR), an indicator of image quality, was also quantified. CNR is obtained by dividing the difference in CT attenuation between the late enhancement area and the normal myocardium by the standard deviation (SD) of CT attenuation in normal myocardium [15,18]. CNR was evaluated in all 40 patients (80%) with LIE on CT (by S.A.).

Significant coronary artery stenosis of $>70\%$ ($>50\%$ in the left main coronary artery) in 1 or more major epicardial coronary arteries, was evaluated based on the 15 segments model of the American Heart Association [19,20]. Coronary artery segments measuring at

least 1.5 mm in diameter were all evaluated. The significance and position of the stenosis was assessed by them using the same workstation. In cases of disagreement between the two observers, a consensus reading was performed to resolve the issue.

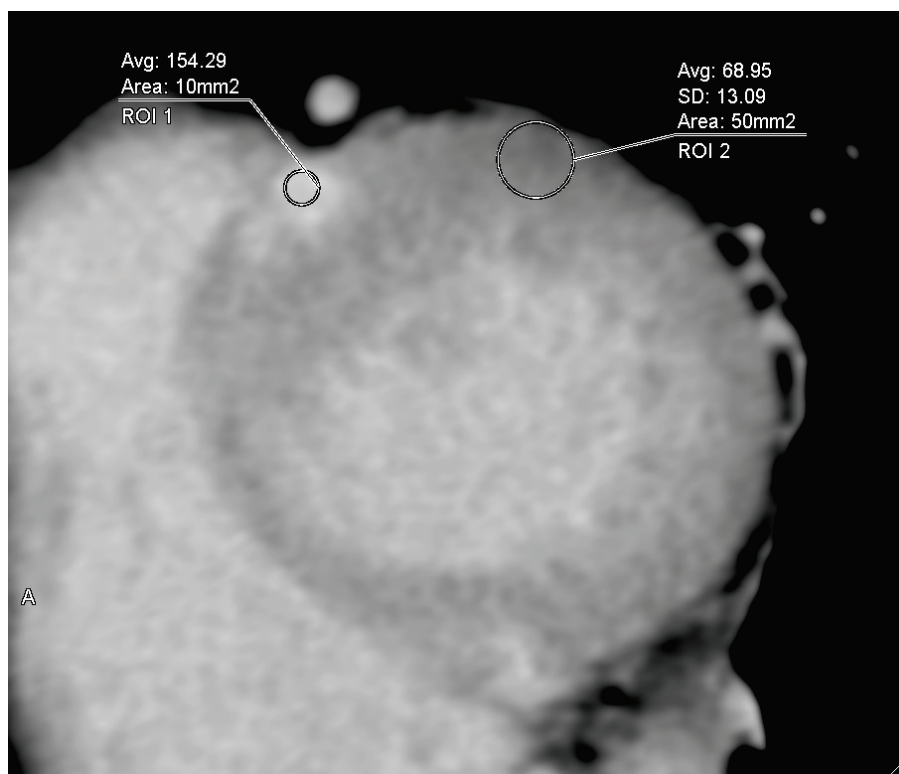


Figure 2. Evaluation of contrast-to-noise ratio in late-phase cardiac computed tomography images. Quantitative image quality analysis was performed by manually drawing approximately 0.1 cm² regions of interest on the late iodine enhancement (LIE) and 0.5 cm² on the remote myocardium in the cases with LIE of left ventricular myocardium on computed tomography (CT). Contrast-to-noise ratio (CNR), an indicator of image quality, was also quantified. CNR is obtained by dividing the difference in CT attenuation between late enhancement area and normal myocardium by the standard deviation of the normal myocardium CT attenuation.

2.3. Echocardiographic Measurement

TTE was conducted as part of routine clinical practice, employing EPIQ 7G and X5-1 transducers (Philips Medical Systems, Andover, MA, USA), iE33 and S5-1 transducers (Philips Medical Systems, Andover, MA, USA), Vivid E-9 and M5-Sc-D (GE Healthcare, Milwaukee, WI, USA) or Aplio 400 and PST-25BT transducers (Canon, Tokyo, Japan) by standard methods according to the recommendations of the European Society of Cardiology [21,22]. In parasternal long-axis views, LV diameters were assessed using direct two-dimensional (2D) measurements at both end-diastole and end-systole. LV ejection fraction (LVEF) was assessed using the Teichholz or biplane disk summation method. Additional standard measurements of cardiac size, function, and LV wall thickness were performed in accordance with the European Society of Cardiology [21].

The LV outflow tract (OT) flow was visualized in the apical long-axis color flow image, and a continuous wave Doppler cursor was directed toward the LVOT flow. The Doppler beam was assumed to be almost parallel to systolic flow in the LVOT. After that, the peak flow velocity and LVOT pressure gradient was estimated by utilizing the modified Bernoulli equation.

Significant valvular abnormality was defined as the presence of $\geq$ moderate valvular stenosis or regurgitation [15].

2.4. Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation, and categorical variables in numbers and percentages. Welch's t-test was used for continuous variables, and Fisher's exact test was used for categorical variables. Patient backgrounds were compared between patients with and without MACE. To identify significant predictors of MACE, univariable and multivariable Cox proportional hazards analyses were performed. Variables for multivariable analysis were selected using a stepwise method, adhering to a minimum of 5 (ideally 10) events per variable to avoid overfitting, as previously described [23,24]. Receiver operating characteristic (ROC) analysis was employed to determine optimal cut-off values for predicting MACE and evaluate their prognostic utility. Survival analysis was also performed to evaluate the prognostic predictive ability of the determined cut-off value. All statistical tests were two-sided, with a p -value < 0.05 considered statistically significant.

All statistical analyses were performed using the JMP software program, version 17.2.0 (SAS Institute Inc, Cary, NC, USA).

3. Results

One hundred and one HCM patients were enrolled in the study. The mean age of included patients was 66 ± 11 years old, and 66 (65%) were men. All patients were followed for 64 ± 55 months after cardiac CT, and 15 patients (15%) had MACE during the follow-up period. MACE included ten hospitalizations due to heart failure, two ventricular fibrillation, two sustained ventricular tachycardia, and one sudden cardiac death. No significant differences were observed in baseline backgrounds between the groups with and without MACE (Table 1).

Table 1. Characteristics of patients with and without major adverse cardiac events.

	MACE (+) (<i>n</i> = 15)	MACE (−) (<i>n</i> = 86)	<i>p</i> -Value
Age, years	63 ± 16	66 ± 11	0.42
Male, <i>n</i> (%)	8 (53)	58 (67)	0.38
Body mass index, kg/m ²	24 ± 4	25 ± 4	0.67
Atrial fibrillation, <i>n</i> (%)	7 (47)	20 (23)	0.11
Hypertension, <i>n</i> (%)	6 (40)	57 (66)	0.08
Dyslipidemia, <i>n</i> (%)	5 (33)	31 (36)	1.0
Diabetes, <i>n</i> (%)	2 (13)	17 (20)	0.73
Family history of SCD, <i>n</i> (%)	1 (7)	2 (2)	0.40
Syncope, <i>n</i> (%)	0 (0)	8 (9)	0.60
Previous NSVT, <i>n</i> (%)	5 (33)	23 (27)	0.76
eGFR, mL/min/1.73 m ²	63 ± 21	69 ± 16	0.32
Administration of β -blocker, <i>n</i> (%)	7 (50)	36 (43)	0.77
Administration of statin, <i>n</i> (%)	5 (36)	22 (26)	0.52
Administration of ACE inhibitor or ARB, <i>n</i> (%)	4 (29)	40 (48)	0.25
Follow-up period (month)	49 ± 46	67 ± 56	0.19

SCD, sudden cardiac death; NSVT, non-sustained ventricular tachycardia; eGFR, estimated glomerular filtration rate.

According to imaging parameters, patients with MACE had a significantly higher LV-ECV, left atrial diameter (LAD), LV end-systolic diameter (LVDs), and lower LVEF, than those without MACE ($42 \pm 8\%$ vs. $34 \pm 6\%$, $p = 0.002$; 48 ± 9 mm vs. 42 ± 7 mm, $p = 0.04$; 35 ± 10 mm vs. 28 ± 5 mm, $p = 0.025$; and $56 \pm 13\%$ vs. $67 \pm 7\%$, $p = 0.007$) (Table 2).

Table 2. Parameters on transthoracic echocardiography and CT in patients with and without MACE.

	MACE (+) (n = 15)	MACE (−) (n = 86)	p-Value
LVEF on TTE, %	56 ± 13	67 ± 7	0.007 **
Maximum LV wall thickness on TTE, mm	19 ± 5	17 ± 4	0.18
LA diameter on TTE, mm	48 ± 9	42 ± 7	0.04 *
LVOT gradient on TTE, mmHg	7 ± 4	9 ± 14	0.31
LVOT gradient > 30 mmHg on TTE, n (%)	1 (7)	5 (6)	1.0
LVDd on TTE, mm	50 ± 10	46 ± 6	0.15
LVDs on TTE, mm	35 ± 10	28 ± 5	0.025 *
Valvular heart disease (≥2+)	1 (7)	2 (2)	0.38
HCM SCD risk score, %	2.4 ± 1.1	2.0 ± 1.5	0.26
Significant coronary artery stenosis, n (%)	3 (20)	11 (13)	0.44
LIE on CT, n (%)	10 (67)	40 (47)	0.17
LV-ECV on CT (%)	42 ± 8	34 ± 6	0.002 **
DHCM, n (%)	6 (40)	2 (2)	<0.001 **

LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiography; LA, left atrium; LVOT, left ventricular outflow tract; LVM, left ventricular myocardium; ECV, extracellular volume fraction; CT, computed tomography; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; LIE, late iodine enhancement; DHCM, dilated phase hypertrophic cardiomyopathy. * $p < 0.05$, ** $p < 0.01$. p -value < 0.05 was considered statistically significant.

The percentage of dilated phase HCM was significantly higher in the patients with MACE than those without MACE (40% vs. 2%, $p < 0.001$). The results of univariable Cox proportional hazards model to predict MACE are shown in Table 3.

Table 3. Univariate Cox proportional hazards model for predicting MACE.

Variable	Univariable		
	Hazard Ratio	95% Confidence Interval	p-Value
LVEF (%)	0.90	0.86–0.94	<0.001 **
LV-ECV on CT (%)	1.15	1.08–1.23	<0.001 **
LAD	1.07	1.01–1.12	0.029 *
LVDs	1.13	1.06–1.20	<0.001 **
DHCM	8.12	2.9–23	<0.001 **

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; LV-ECV, left ventricular extracellular volume; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; DHCM, dilated phase of hypertrophic cardiomyopathy. * $p < 0.05$, ** $p < 0.01$. p -value < 0.05 was considered statistically significant.

According to univariate analysis, LVEF, LV-ECV, LAD, LVDs, and DHCM are significant predictors in MACE. Multivariable Cox proportional hazards model was performed using two variables because the number of events is small. LVEF and ECV as variables were selected by the stepwise method, which were considered important based on previous studies [25]. Multivariable Cox proportional hazards model shows LV-ECV and LVEF are both significant predictors of during the follow-up period. The hazard ratios for predicting MACE were 1.12 (95% confidence interval [CI]: 1.04–1.20, $p = 0.003$) for LV-ECV and 0.93 (95% CI: 0.88–0.98, $p = 0.006$) for LVEF (Table 4).

Based on receiver operating characteristic (ROC) analysis, the optimal threshold for LV-ECV to predict MACE was determined to be 37.6%. At this cut-off, the sensitivity and specificity were 73% and 78%, respectively, with a Youden index of 0.51. The area under the curve (AUC) for LV-ECV was 0.79 (Figure 3A). For LVEF, the optimal threshold identified by ROC analysis was 61.8%. This threshold yielded a sensitivity of 67% and a specificity of 81%, resulting in a Youden index of 0.48. The AUC for LVEF was 0.77 (Figure 3B).

Table 4. Multivariable Cox proportional hazards model for predicting MACE.

Variable	Multivariable		
	Hazard Ratio	95% Confidence Interval	p-Value
LVEF (%)	0.93	0.88–0.98	0.006 **
LV-ECV on CT (%)	1.12	1.04–1.20	0.003 **

HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; LV-ECV, left ventricular extracellular volume; LAD, left atrial diameter; LVDd, left ventricular end-diastolic dimension; DHCM, dilated phase of hypertrophic cardiomyopathy. ** $p < 0.01$. p -value < 0.05 was considered statistically significant.

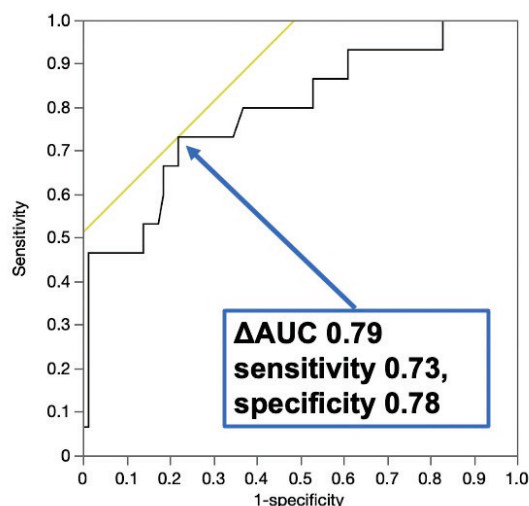
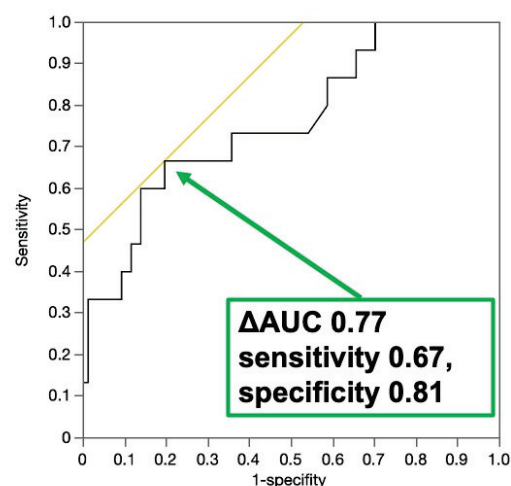
A**B**

Figure 3. Receiver operating characteristic analysis for prediction of major adverse cardiac events. Based on the receiver operating characteristic analysis, the best cut-off value of extracellular volume fraction for the prediction of major adverse cardiac events (MACE) was 37.6%, and the sensitivity and specificity of the prediction of MACE were 73% and 78% at the cutoff of 37.6% (A). The best cut-off value of left ventricular ejection fraction for the prediction of MACE was 61.8%, and the sensitivity and specificity were 67% and 81% (B).

During the follow-up periods, patients with LV-ECV $\geq 37.6\%$ ($n = 30$) experienced significantly more MACE than those with LV-ECV $< 37.6\%$ ($p < 0.001$) (Figure 4).

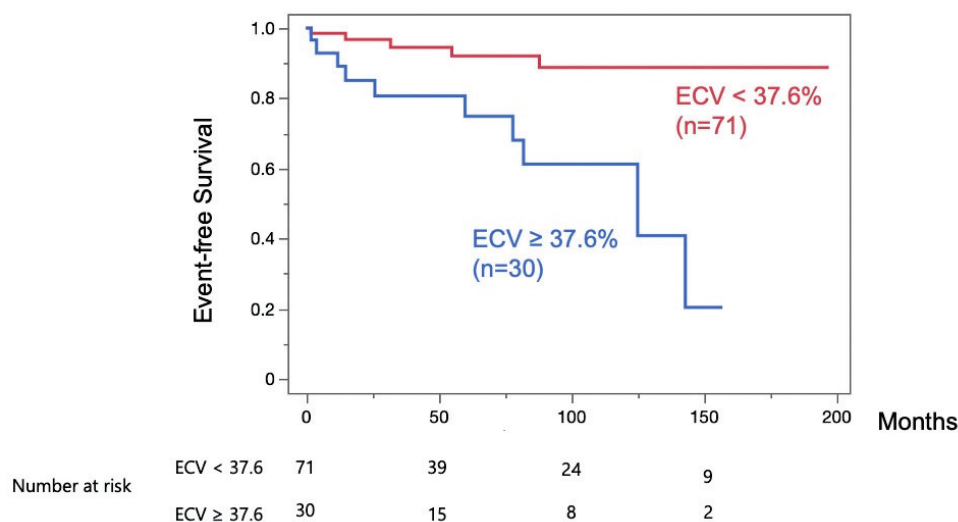


Figure 4. Kaplan–Meier curve of event-free survival. A significantly higher rate of major adverse cardiac events was observed in patients with left ventricular extracellular volume fraction (LV-ECV) $\geq 37.6\%$ ($n = 30$) compared to patients with LV-ECV $< 37.6\%$ throughout the follow-up periods ($p < 0.001$).

The radiation dose for the additional late-phase scan was 18.6 ± 7.5 mGy as measured by the Computed Tomography Dose Index (CTDI). (Cases prior to 2015 were excluded because effective dose data had not been recorded.)

CNR of 40 patients with LE of LVM on CT was 4.0 ± 2.0 .

4. Discussion

In this study, we evaluated the prognostic value of ECV on CT in patients with HCM. This study's findings indicate that ECV on CT could potentially predict MACE in patients with HCM. ECV on CT was shown to be a prognostic indicator independent of cardiac function. Performing an additional late-phase scan makes ECV analysis feasible. In addition to its established roles such as assessing coronary artery stenosis and cardiac structure, CT can also be useful for quantitative evaluation of myocardial tissue characteristics. These findings indicate that CT is useful for multifaceted evaluation of cardiac assessment in patients with HCM.

For the evaluation of myocardial tissue characteristics, a visual late-phase enhancement assessment is also possible. While contrast-enhanced MRI is considered the standard method, the accuracy of late-phase enhancement evaluation in LV using CT has improved in recent years. Previously, we reported LIE on CT as a marker of MACE in cases with HCM [26]. However, in the present study, no statistically significant difference was found in the presence of LIE of LVM on CT when comparing patients with MACE to those without MACE. One of the reasons for the phenomenon is the limitation of contrast resolution of CT for the detection of LIE of LVM. Visual assessment of LIE of LVM on CT is not stable because of the low contrast in several cases, especially the border zone is difficult to detect visually. Still, ECV analysis is supportive and superior to the visual assessment of LIE, and it significantly impacts the risk assessment in patients with HCM.

4.1. ECV Analysis in HCM

Cardiac MRI-derived ECV of LVM has been reported to be a useful marker associated with clinical outcomes [27]. Increased ECV on LVM shows a close correlation with a higher biopsy-proven myocardial fibrosis [28]. Therefore, higher ECV means severe degeneration of the LVM, which leads to LV dysfunction or ventricular arrhythmia [29]. The prognostic value of MRI-derived ECV in HCM has been increasingly recognized. Avanesov et al. reported that the combined use of the SCD risk score and MRI-derived ECV improved the diagnostic accuracy to identify HCM patients with syncope or non-sustained VT [10]. Li et al., in a study of 243 HCM patients, demonstrated that ECV was an independent predictor of major adverse cardiac events (a composite of cardiac death, heart transplant, and aborted sudden death) [25]. In line with these findings for MRI, our study demonstrates the prognostic utility of CT-derived ECV. In contrast, Mirelis et al. previously reported no correlation between ECV on CT and ventricular arrhythmia in HCM cases with an implantable cardioverter defibrillator (ICD) [30]. However, this discrepancy may be explained by differences in the study populations; their cohort consisted exclusively of high-risk patients with ICDs, whereas our study population had a lower risk profile.

4.2. Comparison of CT and MRI in ECV Analysis

While MRI is the established reference standard for quantifying ECV, multiple studies have demonstrated a strong correlation between CT-derived and MRI-derived values. Two meta-analyses reported similarly high correlation coefficients: 0.90 (95% CI: 0.86–0.95) [31] and 0.89 (95% CI: 0.86–0.91) [32]. Regarding reproducibility, both modalities have shown excellent inter-observer agreement in previous reports [33,34]. We have also previously reported a strong correlation between CT- and MRI-derived ECV using the same acquisition

protocol as in the present study [34]. However, each modality has a distinct profile of advantages and limitations.

MRI is contraindicated for patients with non-conditional mechanical devices or claustrophobia, and gadolinium contrast is avoided for patients with severe renal dysfunction [4]. Furthermore, acquisition time is longer, and image quality is poorer in cases with irregular heartbeats or breathing. Additionally, analysis using T1 mapping is not available at all facilities equipped with cardiac MRI because an upgrade of the latest machine or software is necessary.

Conversely, cardiac CT offers several clinical advantages. Its rapid acquisition time makes it a suitable modality for patients with arrhythmia or difficulty with breath-holding. Another key strength of CT is the ability to perform highly accurate coronary artery assessment. For HCM patients presenting with chest pain, a common clinical scenario, a single CT examination can be utilized to both evaluate for coronary artery disease and obtain prognostic data from ECV analysis. This approach of integrating myocardial tissue characterization into a standard cardiac CT protocol enhances the diagnostic yield from a single examination. Furthermore, CT serves as an essential alternative for patients with contraindications to MRI. On the other hand, CT has two main limitations. First, CT involves radiation exposure, although modern protocols minimize dose. Second, CT's contrast-to-noise ratio is lower than MRI, which can make subtle or patchy fibrosis harder to delineate. Therefore, the choice of modality should be tailored to the individual patient's clinical context, risk profile, and local resource availability.

4.3. Differences from Established Risk Factors and Clinical Utility of ECV on CT

Previous studies have reported factors such as a history of fatal arrhythmia, family history, NSVT, history of syncope, maximum wall thickness, and extensive LGE as risk factors for sudden cardiac death [35]. On the other hand, heart failure risk is thought to involve complex interactions with environmental factors, such as obesity and hypertension, which may not coincide with SCD risk factors [36]. In this study, several factors may explain why established risk factors were not significant predictors of MACE, but ECV on CT was significant.

First, our study cohort tended to consist of relatively low-risk cases with preserved LVEF and low SCD risk scores. Second, our sample size is small, and it may result in limited statistical power. Third, a large proportion of the outcomes were accounted for by heart failure hospitalizations.

Visual late-phase enhancement assessment using CT is limited in cases with subtle or diffuse myocardial fibrosis due to its low contrast resolution compared to MRI [37]. However, ECV may allow for quantitative evaluation of even subtle or diffuse fibrosis [38]. So, ECV on CT may have had significant detection ability even in this cohort with many low-risk HCM cases. Furthermore, LV-ECV reflects diffuse fibrosis, which may indicate myocardial damage caused by secondary myocardial stress. These findings suggest LV-ECV could be useful for comprehensive myocardial risk assessment from the early stages of HCM.

Most studies of ECV on CT have been observational. Prospective validation is needed before ECV on CT can guide major therapeutic decisions, such as ICD implantation. However, our findings highlight its immediate utility in risk stratification and patient management, particularly for individuals who might otherwise be overlooked. Asymptomatic or low-risk HCM patients, who are often younger, are particularly prone to discontinuing follow-up, creating a significant gap in care. The LV-ECV threshold of $\geq 37.6\%$ identified in our study can address this challenge by serving as an objective, quantitative marker of risk. For clinicians, this threshold can trigger more intensive management for this subgroup, such as more frequent monitoring or proactive medication adjustments. For patients, a specific

value illustrating their underlying myocardial fibrosis burden can be a useful communication tool. It helps them understand their long-term risk, thereby motivating adherence to follow-up and potentially preventing adverse events that might otherwise occur.

4.4. Decreased Radiation Dose and Increased Image Quality for LIE Analysis on CT

An additional radiation dose is required for ECV analysis performed using CT images. However, this is a reasonable trade-off for obtaining the useful clinical parameter. The radiation dose for the additional late-phase scan was 18.6 ± 7.5 mGy as measured by CTDI, which is comparable to standard chest CT examinations [39]. Advancements in multi-detector CT technology and new reconstruction techniques, such as iterative or deep learning reconstruction methods, have recently reduced radiation dose in late-phase cardiac imaging, while significantly improving image quality [8].

CT attenuation value increases when CT scanning is conducted with a lower tube voltage, but image noise rises because of the limited radiation dose; therefore, applying the technique to the cardiac LIE analysis on LVM has been almost impossible [40]. Meanwhile, in recent years, newer reconstruction techniques such as iterative reconstruction or deep learning reconstruction have emerged, and the maximum tube current has also improved. These technical improvements have reduced image noise in CT images taken with a lower tube voltage. Our previous report demonstrated that combining new-generation CT with iterative reconstruction enhances image quality for LIE on CT and improves its diagnostic accuracy [8]. In this study, CNR in 40 patients with LIE on CT was almost 4.0 ± 2.0 . In the previous studies, the CNR of LIE on CT in cases with old myocardial infarction was close to six and four, respectively. The CNR value of LIE in the present study appears comparable to those reported in these previous studies, despite differences in the underlying myocardial disease [17,41].

4.5. ECV Analysis in Cases with LVH

Notably, recent improvements in the image quality, enhancing the assessment of LIE with LVM on CT, have led to the approval of CT-derived ECV analysis as an alternative to MRI in the most recent guidelines for cardiac CT and cardiac amyloidosis issued by the Japanese Cardiovascular Society [42]. Differentiating cardiac amyloidosis from HCM is often difficult in patients with LVH, because their hypertrophic morphologies on echocardiography or ST abnormalities on ECG are sometimes similar, and additional imaging techniques are necessary as usual. Therefore, cardiac CT is valuable not only for evaluating coronary artery disease because of abnormal chest symptoms or ECG, but also for the screening of cardiac amyloidosis in patients with LVH. The additional late-phase cardiac scan is helpful for their differential diagnosis because their LIE patterns are different [3]. Another study has shown that ECV analysis using CT data is useful for predicting patient prognosis in cases with cardiac amyloidosis [43]. Extending this evidence, our study in HCM patients, from whom cardiac amyloidosis had been excluded, demonstrated that ECV on CT is an independent prognostic marker. Therefore, a late-phase CT scan can provide valuable information throughout the management of patients with LVH, including both diagnosis and risk stratification.

4.6. Screening for Intracardiac Thrombus in Cases with AF on Late-Phase CT Images

Almost one-third of all cases in this study had AF, and late-phase CT images are helpful for evaluating myocardial fibrosis and screening luminal thrombus [19]. However, ECV analysis performed with single-energy scans might be influenced by AF or other arrhythmia, including ventricular premature beats, because of the gaps in the positions of LVM between non-contrast and late-phase images. To decrease radiation dose, non-contrast or late-phase scans were acquired using a prospective ECG gating technique that targets

only limited cardiac phases (e.g., mid-diastolic). Nevertheless, in cases of AF, limiting the total scan time is challenging because predicting the timing of the next heartbeat is not possible. Therefore, scan times tend to be longer in patients with AF compared to those with normal sinus rhythm (e.g., end-systolic to mid-diastolic). To address potential motion, we selected the pair of non-contrast and late-phase images showing the fewest motion gaps from a relatively wide range of acquired cardiac phases for ECV analysis. Using this approach, we were able to report the utility of ECV analysis for predicting MACE in patients with dilated cardiomyopathy (DCM), despite approximately 20% of those cases having AF [15]. Other research groups have also reported on the utility of ECV analysis for identifying cardiac amyloidosis in patients with severe aortic valve stenosis, a population in which nearly half of the individuals had AF [44].

4.7. Future Perspectives

We believe that in the future, ECV on CT holds the potential for integration into risk stratification models and clinical guidelines for HCM. One approach is to combine ECV with other established markers to improve predictive accuracy. For instance, in an exploratory analysis of our data, we observed that combining LV-ECV with LVEF improved the predictive accuracy for MACE compared to LVEF alone (AUC increased from 0.76 to 0.84, sensitivity from 0.67 to 0.73, and specificity from 0.80 to 0.83). This supplementary analysis suggests that incorporating CT-derived LV-ECV as a marker of myocardial tissue characterization into established risk models such as the HCM Risk-SCD score may improve their predictive performance.

Furthermore, as the evidence base grows through larger, prospective studies, ECV on CT could be incorporated into clinical guidelines. Similarly to the recent inclusion of CT-derived myocardial assessment in the guidelines for cardiac amyloidosis, ECV on CT could become a recommended tool for risk stratification in HCM, especially for patients undergoing CT for other indications or those in whom MRI is contraindicated.

4.8. Limitations

Our study has several limitations that should be mentioned. First, this study was conducted as a retrospective analysis at a few centers and involved a relatively small sample size and events. Therefore, our multivariable analysis was limited to a few variables to mitigate the risk of overfitting. The results should therefore be interpreted with caution and require validation in a larger, independent cohort. Second, ECV analysis was performed using single-energy images, which needed the subtraction of late-phase and non-contrast images. Misalignment between these two phases could potentially lead to an under- or over-estimation of ECV on single-energy images when compared to analysis using dual-energy images from the latest CT scanners, which does not cause such gaps. Third, only a few high-risk HCM cases, e.g., dilated phase HCM or HOCM, were included, and forty percent of all cases were apical-type HCM in this study. The percentage of apical type HCM is relatively higher in Asian populations than in others, and apical HCM is originally thought to be lower mortality risk than others [45]. However, in recent research, it has also been reported that the mortality rate of apical HCM does not differ significantly from other types. Suggesting that the differences in subtypes may not have a significant impact on the outcome [45]. Fourthly, genetic tests have not been performed in almost all cases, and other differential diseases have not been completely ruled out. This is because, during the main follow-up period of this study, the availability of genetic testing for HCM was limited to specialized centers, which made the implementation of genetic testing in our cohort challenging. Fifth, only 33 patients in our cohort underwent both CT and MRI within one year, and in many of these cases, retrospective calculation of MRI-derived ECV was not

feasible. Therefore, a direct comparison between CT- and MRI-derived ECV in this cohort was not possible. Nevertheless, previous reports have demonstrated a high correlation between CT- and MRI-derived ECV, supporting the reliability of ECV on CT as a surrogate in our study [31–34]. Finally, all patients underwent cardiac CT because of the evaluation of coronary artery diseases based on the latest guideline⁶, so the other patients with HCM were excluded from this analysis; therefore, the results of this study should not be applied to all HCM patients.

5. Conclusions

LV-ECV on CT was a valuable prognostic indicator in HCM cases and helped predict MACE in HCM cases. LV-ECV on CT could serve as a quantitative risk stratification tool, particularly for patients in whom cardiac MRI is contraindicated or not feasible.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Chiba University (reference number is 3822, Approval Date: 17 August 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study using an opt-out method.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding author if the ethical committee agrees with the request.

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Abbreviations

The following abbreviations are used in this manuscript:

ECV	Extracellular volume fraction
CT	Computed tomography
HCM	Hypertrophic cardiomyopathy
LV	Left ventricular
LV-ECV	Left ventricular extracellular volume fraction
MACE	Major adverse cardiac events
LAD	Left atrial diameter
LVDd	LV end-diastolic diameter
LVDs	LV end-systolic diameter
LVEF	Left ventricular ejection fraction
TTE	Transthoracic echocardiography
MRI	Magnetic resonance imaging
LGE	Late gadolinium enhancement
LIE	Late iodine enhancement
LVM	Left ventricular myocardium

ECG	Electrocardiogram
HU	Hounsfield units
Hct	Hematocrit
ROI	Regions of interest
CNR	Contrast-to-noise ratio
SD	Standard deviation
LVOT	Left ventricular outflow tract
ROC	Receiver operating characteristic
CI	Confidence interval
AUC	Area under the curve
CTDI	Computed Tomography Dose Index
AF	Atrial fibrillation
DCM	Dilated cardiomyopathy
LVH	Left ventricular hypertrophy
SCD	Sudden cardiac death
NSVT	Non-sustained ventricular tachycardia
eGFR	Estimated glomerular filtration rate
DHCM	Dilated phase hypertrophic cardiomyopathy

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