Vascular and Intravascular Imaging Trends, Analysis, and Challenges, Volume 2

Plaque characterization

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Plaque characterization

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To our families and friends for their infinite patience, love and support.

Contents

Preface

Atherosclerosis is the leading cause of cardiovascular disease (CVD) and stroke. These diseases impose an immense financial burden and have the greatest impact in terms of morbidity. CVD is the cause of one in every three deaths in the USA and accounts for almost 45% of deaths in European countries. On average, per year, CVD causes 7.4 million deaths, while stroke causes 6.7 million. Between 2000 and 2030, it is estimated that about 35% of all CVD deaths in India will occur among 35- to 64-year-olds, which has been attributed to atherosclerosis. These facts raise different questions, such as: What are the most appropriate methods for calcium detection and its quantification for coronary and carotid arteries? What are the advantages and disadvantages of these methods and the risk stratification strategies? How can a combination of machine-learning and deep-learning techniques improve accuracy? How is rheumatoid arthritis (RA) associated with carotid atherosclerosis? How are plaque-based biomarker and carotid artery disease image-based phenotypes associated with HbA1c? How can the disease risk stratification accuracy and the speed of computation be to improved? Are there solutions to issues associated with multi-center clinical trials and routine vascular screening? How to establish a connection between the synthesis routes of micro-electro-mechanical systems (MEMSs) and their application to synthesize a multi-layered vascular bed with micro-scale level refinement?

In this book, we are pleased to witness several advanced clinical and medical imaging works that cover a wide spectrum of clinical disease issues, clinical intervention techniques, imaging modalities for plaque visualization and inspection, automatic analysis and clinical parameter extraction techniques, and advanced tools for the navigation of and intervention in both coronary and carotid lesions.

The book is organized into five sections: the first part is comprised of four review papers. The first paper presents a state-of-the-art review covering the methods for calcium detection and its quantification for coronary and carotid arteries, the advantages and disadvantages of these methods, and the risk stratification strategies. The review also presents different kinds of statistical models and gold standard solutions for the evaluation of software systems useful for calcium detection and quantification. The second and third review papers present comparisons between various methodologies used for tissue characterization, classification and measurement using OCT. The review also presents different ways to predict and stratify the risk associated with CVD based on plaque characterization and measurement. Based on comparative analysis between different schools of thought, a combination of machine-learning and deep-learning techniques has been verified to provide the best classification accuracy using OCT images. The review also discusses the physics of image acquisition using different imaging modalities followed by tissue characterization using three paradigms based on (i) optical feature measurement methodologies, (ii) machine-learning algorithms and (iii) deep-learning techniques. Quantification of vulnerable plaque components and risk stratification using the above mentioned paradigms are also discussed. The fourth review provides a brief

understanding of the pathogenesis of RA and its association with carotid atherosclerosis imaged using B-mode ultrasound techniques. Lacunas in traditional risk scores and the role of machine-learning-based tissue characterization algorithms are discussed, which could facilitate cardiovascular risk assessment in RA patients.

As manual ultrasound (US)-based methods adapted for lumen diameter (LD) and carotid intima–media thickness (cIMT) measurement are tedious, error-prone and cause variability, an intelligence-based, novel, robust and clinically strong deep-learning (DL)-based strategy is the need of the hour. The second section of this book demonstrates the superior performance of DL systems over conventional methods and is comprised of two clinical papers. In the first chapter in this section, an automated DL-based system is presented, which consists of a combination of two systems: the encoder and decoder for lumen segmentation. The encoder employs a 13 layer convolution neural network (CNN) model for rich feature extraction and the decoder employs three up-sample layers of a fully convolutional network (FCN) for lumen segmentation. In the second chapter, a combination of DL and machine-learning (ML) paradigms are used for cIMT measurement. The first stage consists of a convolution-layer-based encoder for feature extraction and a FCN-based decoder for image segmentation. This stage generates the raw inner lumen borders and raw outer intra-adventitial borders. To smooth these borders, the DL system uses a cascaded second stage that consists of ML-based regression. The final outputs are the far wall lumen–intima (LI) and media–adventitia (MA) borders which were used for cIMT measurement. In both studies, the experimental results demonstrated the superior performance of the DL system over the conventional methods in the previously published literature.

The third section of this book investigates the association of plaque-based biomarker and carotid artery disease image-based phenotypes with HbA1c and comprises two clinical chapters. The first chapter investigates the association of carotid ultrasound echolucent plaque-based biomarkers with HbA1c, measured as an age-adjusted grayscale median (AAGSM) as a function of chronological age, total plaque area and conventional grayscale median (GSMconv). The study concluded that echolucent plaque in patients with diabetes can be more accurately characterized by risk stratification using AAGSM compared to GSMconv. In the second chapter, the association between six types of carotid artery disease image-based phenotypes and HbA1c in diabetes patients is explored. A set of six phenotypes (intima–media thickness measurements (cIMT (ave.), cIMT (max.), cIMT (min.)), bidirectional wall variability (cIMTV), morphology-based total plaque area (mTPA) and composite risk score (CRS)) were measured in an automated setting using AtheroEdge™. Among the six carotid phenotypes, all except for bidirectional wall variability showed a strong association with HbA1c. mTPA and CRS were equally strong phenotypes as cIMT. The CRS phenotype showed the strongest relationship to HbA1c.

The fourth section of this book presents studies performed to improve the risk stratification accuracy and the speed of computation. Further, a reliable, accurate, fast, completely automated, anytime-anywhere solution for multi-center clinical trials and routine vascular screening is discussed. This section comprises three

clinical chapters. Several machine-learning systems have been previously developed for plaque wall risk assessment using morphology-based characterization. Even though these systems have the ability to perform risk stratification, they lack the ability to achieve higher performance due to their inability to select and retain dominant features. The first chapter introduces a polling-based principal component analysis (PCA) strategy which, when embedded with an ML-based framework, selects and retains dominant features and thus results in superior performance. As fast intravascular ultrasound (IVUS) video processing is required for calcium volume computation during the planning phase of percutaneous coronary interventional (PCI) procedures, the second chapter introduces the idea of embedding segmentation methods with nonlinear multiresolution techniques. To achieve this, four different segmentation methods for calcium volume measurement, namely threshold-based, fuzzy c-Means (FCM), K-means and hidden Markov random field (HMRF), are embedded with five different kinds of multiresolution techniques (bilinear, bicubic, wavelet, Lanczos and Gaussian pyramid). Among the 20 different combinations of multiresolution with calcium volume segmentation methods, the FCM embedded with wavelet-based multiresolution gave the best performance. Finally, the third chapter presents a completely automated, novel, smart, cloud-based, point-of-care system for (a) carotid LD, (b) stenosis severity index (SSI) and (c) total lumen area (TLA) measurement using B-mode ultrasound, which thus provides an anytime-anywhere solution for multi-center clinical trials and routine vascular screening.

The last section of this book is devoted to MEMSs, a kind of miniaturized system commonly being used in the domain of sensor technology and drug delivery devices in the healthcare industry. Although there is a significant amount of potential in the manufacturing routes of MEMS synthesis, their use tends to be limited to semiconductor device industries. In this section a very careful amalgamation has been carried out to form a connection between the synthesis routes of MEMSs and their application to synthesize multi-layered vascular bed with micro-scale level refinement. This technique can be used as a potential method for re-defining the construction of the multi-layered tissues of many organs.

In summary, this collection of chapters gives an overview of research on vascular and intravascular analysis, discussing in detail different scientific and clinical questions, and proposes advances in clinical treatment and medical imaging automatic analysis. We aim to give an overview of the active topics and problems in this field and encourage the community to continue in their search for scientific and clinical answers as to which are the most precise, objective, effective and efficient strategies for atherosclerotic diagnosis, treatment and follow-up, as it remains one of the most important health problems of humanity.

Petia Radeva
Jasjit S Suri

Editor biographies

Petia Radeva

Dr Petia Radeva (PhD 1993, Universitat Autònoma de Barcelona, Spain) is a senior researcher and full professor at the University of Barcelona. She received her PhD degree from the Universitat Autònoma de Barcelona in 1998. She is the head of the Computer Vision and Machine Learning Consolidated Research Group at the University of Barcelona and the head of MiLab of the Computer Vision Center (www.cvc.uab.es). Her current research interests include the development of learning-based approaches (in particular, deep learning methods) for computer vision and image analysis. Radeva has been an AIPR Fellow since 2015, and became an ICREA Academia researcher in 2014 for her outstanding research achievements. In 2015 she received the Aurora Pons Porrata award for her scientific merits as well as the Antonio Caparros award for the best technology transfer.

Jasjit S Suri

Jasjit S Suri, PhD, MBA, is an innovator, visionary, scientist and an internationally known world leader in the field of biomedical imaging and healthcare management. Dr Suri is a recipient of the Director General's Gold Medal (1980), was named a Fellow of the American Institute of Medical and Biological Engineering by the National Academy of Sciences, Washington, DC (2004), and received a Marquis Life Time Achievement Award (2018). Dr Suri is a board member in several organizations.

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Section I

Review on wall quantification, tissue characterization and coronary and carotid artery risk stratification

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Vascular and Intravascular Imaging Trends, Analysis, and Challenges, Volume 2

Plaque characterization

Petia Radeva and Jasjit S Suri

Chapter 1

Coronary and carotid artery calcium detection, its quantification and grayscale morphology-based risk stratification in multimodality big data: a review

Sumit K Banchhor, Narendra D Londhe, Tadashi Araki, Luca Saba, Petia Radeva, Narendra N Khanna and Jasjit S Suri

Purpose of the review

Atherosclerosis is the leading cause of cardiovascular disease (CVD) and stroke. Typically, atherosclerotic calcium is found during the mature stage of atherosclerosis. It is therefore often a challenge to identify and quantify the calcium. This is due to the presence of multiple components of plaque build-up in the arterial walls. The American College of Cardiology/American Heart Association guidelines point to the importance of calcium in the coronary and carotid arteries and further recommend its quantification for the prevention of heart disease. It is therefore essential to stratify the CVD risk of the patient into low- and high-risk bins.

Recent findings

Calcium formation in the artery walls is multifocal in nature with sizes at the micrometre level. Thus, its detection requires high-resolution imaging. Clinical experience has shown that even though optical coherence tomography offers better resolution, intravascular ultrasound still remains an important imaging modality for coronary wall imaging. For a computer-based analysis system to be complete, it must be scientifically and clinically validated. This study presents a state-of-the-art review (condensation of 152 publications after examining 200 articles) covering the methods for calcium detection and its quantification for coronary and carotid arteries, the advantages and disadvantages of these methods, and the risk

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stratification strategies. The review also presents different kinds of statistical models and gold standard solutions for the evaluation of software systems useful for calcium detection and quantification. Finally, the review concludes with a possible vision for designing the next-generation system for better clinical outcomes.

1.1 Introduction

Atherosclerosis is the leading cause of CVD and stroke. These diseases impose an immense financial burden and have the greatest impact in terms of morbidity [1–4]. CVD is the cause of one in every three deaths in the USA and accounts for almost 45% of deaths in European countries [5]. On average, per year, CVD causes 7.4 million deaths, while stroke causes 6.7 million [6]. In India, due to a lack of healthcare facilities and awareness, CVD is more frequently observed in rural areas compared to urban areas [7]. Between 2000 and 2030, it is estimated that about 35% of all CVD deaths in India will occur among 35- to 64-year-olds [8], which has been attributed to atherosclerosis [9].

Atherogenesis is the process of plaque formation in the arteries [10]. During atherogenesis, plaques usually develop in the region where there is low endothelial shear stress. In this region, leucocytes such as monocytes and basophils attack the endothelium [11]. Monocytes migrate into the sub-endothelial region and become oxidised by low-density lipoprotein (LDL) cholesterol and become macrophages [12]. These macrophages become large foam cells containing oxidised LDL molecules [13, 14]. Foam cells, macrophages and intraplaque haemorrhages form a necrotic core; this lesion is called a fibroatheroma [15]. Microscopic calcium granules expand in this necrotic core and form a large lump of calcium deposits [16], as shown in figure 1.1. A fibrous cap separates the necrotic core from the vessel lumen [17]. If the plaque is small, the arteries will undergo positive remodelling and blood flow will be uninterrupted [18]. It has been observed that with an increase in the calcium content there is a decrease in the lipid core volume, leading to structural stabilisation of the plaque [19]. In contrast, the presence of juxtaluminal calcification elevates the local stress compared to when calcification is artificially covered with a 0.2 mm thick fibrous cap [20]. Progressive accumulation of lipids usually causes thinning of the fibrous cap [21], which may lead to plaque rupture. When the cap ruptures, platelets in the bloodstream attempt to heal the injury, which leads to the

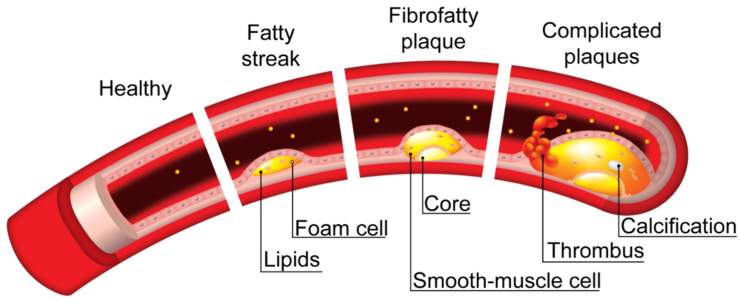

Figure 1.1. Calcified plaque formation in the arteries. (Courtesy of AtheroPoint™, Roseville, CA, USA.)

formation of a blood clot, or thrombus, which can block the artery [22]. If an artery is blocked, tissues are deprived of their blood supply, leading to cell death. If the coronary artery is blocked, the result is a myocardial infarction (MI). When a thrombus breaks off and travels through the bloodstream, it is called an embolus. If the embolus becomes lodged in a cranial artery, it leads to stroke [23].

In a prospective study of 40 patients, Joshi and his team [24] found a new way to detect plaque rupture non-invasively using F-sodium fluoride (F-NaF) PET radio-isotopes. Using coronary angiography and ultrasound, high F-NaF uptake was shown by both coronary and carotid arteries with microcalcifications and necrotic cores. The study demonstrates the need for more prospective trials to establish the relationship between high F-NaF uptake and plaque rupture [25], as the early detection of vulnerable plaque before rupture is very important.

Diabetic patients are at increased risk of atherosclerosis, particularly patients suffering from coronary artery disease (CAD) [26]. A large meta-analysis study carried out by Bulugahapitiya *et al* [27] involving 45 108 patients showed that patients with diabetes without prior MI had a 43% lower risk of CHD compared to patients without diabetes with prior MI. From a two-year retrospective analysis in Bangladesh consisting of 571 patients (333 in the diabetic and 238 in the non-diabetic group), Kabir *et al* [28] found that diameters of the left anterior descending (LAD), distal circumflex and right coronary arteries in diabetic patients were narrower than in non-diabetic subjects. As a result, the diabetic subjects needed longer stent lengths than non-diabetics. Another study carried out by Ertan *et al* [29] on 168 consecutive patients with CAD and 172 patients with normal coronary artery anatomy supported the previous work. The study showed that prediabetic patients have a smaller coronary size and diffuse coronary narrowing, and early detection of prediabetes may provide a more appropriate coronary lesion for percutaneous or surgical revascularization.

Atherosclerosis usually advances silently, and its clinical symptoms arise late in the CAD [9]. During atherosclerosis formation, the plaque usually consists of cholesterol, platelets and cellular waste products, while calcium builds up in the innermost layer of the artery [30]. Calcified plaques are only produced in the atheroma region, which lies in between the external elastic lamina (vessel region) and the internal elastic lamina (lumen region) [11], depicted in figure 1.2. Atherosclerotic

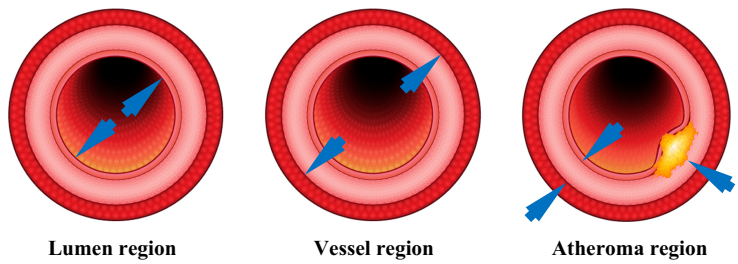

Figure 1.2. Atheroma region between the internal elastic lamina (lumen region) and the external elastic lamina (vessel region). (Courtesy of AtheroPoint™, Roseville, CA, USA.)

arteries limit the flow of oxygen-rich blood in the body and patients usually experience symptoms such as angina, shortness of breath, fatigue and lack of energy. However, in some cases, asymptomatic patients suffer from an MI or stroke without showing any preceding symptoms [31].

In the 20th century, researchers investigated the causes of atherosclerotic disease. Stryker [32] discussed five different cases of wall calcification in infants and suggested that calcification associated with fibroblast proliferation in the intima is the most frequent cause of coronary occlusion in infants. A similar relationship was seen in atherosclerotic diseases in childhood by Woolf [33] and Stary [34]. These studies indicate that the initial stages of atherogenesis can occur during childhood.

During their exploration of the origin of atherosclerotic disease, Hamby *et al* [35] found that patients with double- or triple-vessel disease are less susceptible to coronary artery calcification compared to patients with single-vessel disease. Furthermore, Kannel and Wolf [36] observed that atherosclerosis generally occurs not only as a result of genetic susceptibility, but also due to various other risk factors such as dyslipidemia, hypertension, adiposity, glucose intolerance, haemostatic factors, cigarette smoking, inflammatory markers and a sedentary lifestyle [37]. Even in the absence of these risk factors, patients with genetic hyperlipidaemia have shown an increased incidence of CAD. In the presence of other cardiovascular risk factors, lower levels of lipids can also cause atherosclerosis [38, 39]. Hirsch *et al* [40] found a spatial association between unesterified cholesterol and hydroxyapatite, which shows that there may be more than one mechanism of calcium deposition in atherosclerosis. One year later, Doherty and Detrano [41] showed that Gla-containing proteins and other proteins normally associated with bone metabolism play a significant role in the process of atherosclerotic calcification. Guyton and Klemp [42] suggested that the early core is associated with the accumulation of vesicular lipids rich in free cholesterol. However, later in core development, lipid deposits become more diverse. In such scenarios, early detection and risk stratification of calcium in the arteries is important, as there are few benefits of diagnosis at the advanced stages of atherosclerosis.

During atherosclerosis formation, different arterial beds usually share the same risk of stenosis [43]. For this reason, stenosis in one artery also boosts the chances of stenosis in other arteries [44]. Previous studies [45–47] have also shown that plaque accumulation in coronary and carotid arteries has the same genetic makeup, as shown in figure 1.3. Cohen *et al* [48] showed the relationship between carotid ultrasound parameters and CAD. The study analysed 150 patients, in which 71.3% of patients had carotid plaques and 57.1% had CAD. Independent of age and sex, carotid plaques with a mean intima–media thickness (IMT) greater than 0.75 mm were observed to be correlated with disease in at least one vessel in the coronary artery with odds ratios of 2.8 ($p = 0.03$), 2.19 ($p = 0.073$) and 2.22 ($p = 0.058$). A similar relationship between carotid atherosclerosis and coronary artery calcification in asymptomatic patients with type 2 diabetes mellitus (T2DM) was examined by Jeevarethinam *et al* [49]. In a cohort of 262 asymptomatic T2DM patients, cIMT and coronary artery calcium were examined. Using binary logistical regression,

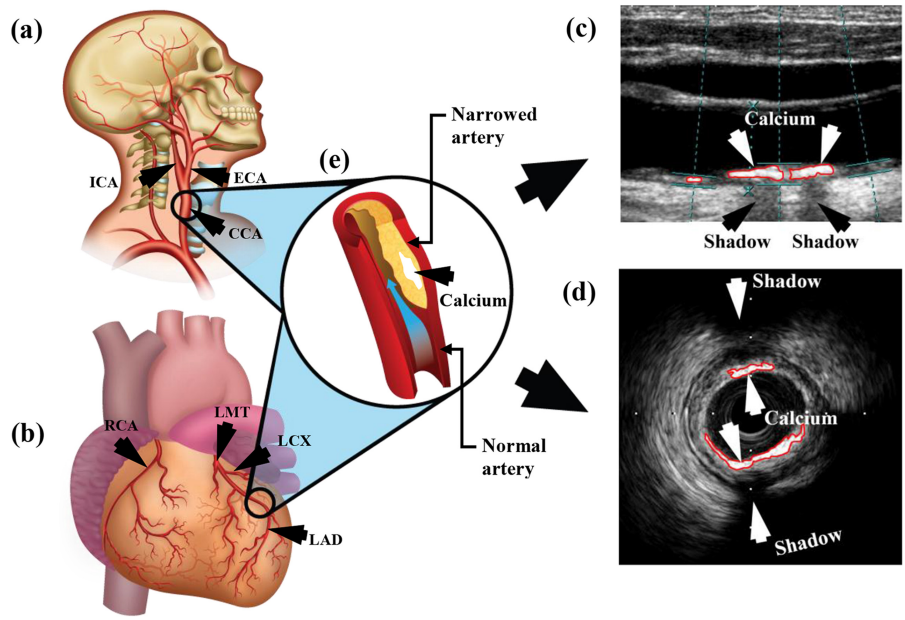

Figure 1.3. (a) and (b) Illustrations of the coronary and carotid artery, respectively. (c) and (d) Ultrasound images of the coronary and carotid artery, respectively, with calcium indicated by the arrows. (e) The calcified plaque narrows the cross section and causes abnormal blood flow in the arteries. (Courtesy of AtheroPoint™, Roseville, CA, USA.)

carotid plaques significantly predicted the severe coronary artery calcium (CAC) burden with an odds ratio of 3.26 (2.05–5.19). Recently, a total of 49 asymptomatic male marathon runners who underwent carotid ultrasound and CT angiography were assessed by Burgstahler *et al* [50]. The goal of the study was to evaluate the diagnostic accuracy of carotid ultrasound to predict coronary atherosclerosis. Between carotid ultrasound and coronary atherosclerosis, the study observed a sensitivity of 54.55% (95% CI 32.2–75.6), a specificity of 80.8% (CI 60.6–93.4), a positive predictive value of 70.6% (CI 44.1–89.9) and a negative predictive value of 67.7% (CI 48.6–83.3), with a positive likelihood ratio of 2.84 (CI 1.18–6.82) and a negative likelihood ratio of 0.56 (CI 0.34–0.92). Therefore, when a patient is diagnosed with calcium accumulation in the carotid artery, they should immediately undergo coronary atherosclerosis tests.

In support of these studies, the American College of Cardiology/American Heart Association (ACC/AHA) [51] and the European Society of Cardiology/European Society of Anaesthesiology (ESC/ESA) [52] guidelines also point out the importance of calcium in the arteries and further recommend its measurement for the prevention of heart disease and stroke [53, 54]. Recent studies have evaluated the recommendations made by these two sets of guidelines. Nasir *et al* [53], in 2015, applied the ACC/AHA guidelines in a Multi-Ethnic Study of Atherosclerosis (MESA) study with 4758 participants. According to the guidelines, 50% of participants were recommended for statin therapy of which 41% of participants had no coronary

artery calcification. It was observed that patients with no calcium had a 10 year risk of 4.7% even when they had a 10 year atherosclerosis cardiovascular disease (ASCVD) risk of <20%. Thus, patients with a 10 year ASCVD risk between 5%–20% with no calcium can be stratified in the low-risk bin and can be deferred from taking statin therapy. This proves the importance of calcium measurement in the arteries. Recently, Mahabadi *et al* [54] showed the differences in the statin therapy recommendations based on the two guidelines (ACC and ECS) in an MESA study with 3745 participants. It was observed that calcium in the arteries was absent in 53% and 43% of the participants who met the statin therapy criteria recommended by the ACC and ESC guidelines, respectively. It was also observed that participants with a higher calcium score had a higher rate of CHD and CVD. The study concluded that, in addition to the guidelines, calcium score improves stratification of the participants into high-risk and low-risk bins.

A detailed analysis of the literature was performed using the PubMed and Google Scholar search engines. In the next section, we present a detailed survey of the different modalities used for detecting calcium in both the coronary and carotid arteries. In the second section, we discuss various studies carried out in the literature for quantifying calcium in both the coronary and carotid arteries. This section also includes studies carried out for fast calcium quantification using a multiresolution paradigm, and discusses the role of connected component analysis (CCA) for removing the false calcium signal in order to avoid overestimation during calcium quantification. The third section presents a detailed survey of the techniques used for performance evaluation and the methods used for validating the results. Finally, we present an exhaustive survey of various risk stratification studies using the machine-learning (ML) paradigm.

1.2 Calcium detection in coronary and carotid arteries

Imaging modalities are broadly divided into two categories: (a) non-invasive (such as computed tomography (CT), echocardiography and magnetic resonance imaging (MRI)) and (b) invasive (such as angiography, intravascular ultrasound (IVUS) and optical coherence tomography (OCT)). These imaging modalities play a vital role in the diagnosis, treatment and monitoring of patients suffering from CAD.

1.2.1 Calcium detection in coronary arteries

1.2.1.1 Using computer tomography

Studies have shown that CT, with recent advances in temporal and spatial resolution, plays an important role in assessing the coronary artery [55]. Sandercock *et al* [56] showed the usefulness of CT diagnosis and observed that, under certain defined circumstances, non-invasive methods including electron beam CT (EBCT) and multidetector CT (MDCT) can be employed for the detection of coronary artery calcium. EBCT is typically performed using echocardiography (ECG) triggering and MDCT using an x-ray tube in the presence of multiple detector rings. Modern MDCT scanners can achieve high temporal (75–150 ms) and spatial (0.5 mm) resolutions, even with a low patient heart rate [57]. Recently, in the

MESA study carried out by Bittencourt *et al* [58], 6781 patients underwent non-contrast cardiac CT to evaluate their calcium score. The results showed improvement in the prediction of CVD events, indicating that non-contrast cardiac CT can be considered a biomarker for the detection of myocardial infarction. It was observed that CT can provide a calcium score [59] in the artery but at the expense of a higher radiation dose, which could compromise patient safety [60].

1.2.1.2 Using echocardiography

Echocardiography has also been used for the detection of calcium in the aortic valves and aortic walls. Nucifora *et al* [61] used an echocardiography-derived calcium score (ECS) to predict the presence of severe CAC and obtained a high sensitivity and specificity of 87% for both. In a similar study by Pressman *et al* [62], global cardiac calcification (scored by echocardiography) showed a moderate correlation with CAC. The results showed that an echo score $\geqslant 5$ had a 60% positive predictive value for CAC > 400. Acharya further evaluated echocardiography images using a Gaussian mixture model (GMM) classifier to stratify CAD in patients [63]. The efficiency was close to 100%. These studies indicate the importance of echocardiographic evaluations for the detection of calcium in arteries.

1.2.1.3 Using angiography

Angiographic calcium can detect moderate calcification, but only during the cardiac cycle before contrast injection, whereas severe calcification, which affects both sides of the arterial lumen, can be detected without cardiac motion. In a comparative study of 183 patients, angiography identified less than half (45%) of the patients with any detected coronary calcification [64]. CAC can be easily detected using angiography, but this method has potential implications for percutaneous coronary intervention (PCI) outcomes [65, 66].

1.2.1.4 Using magnetic resonance imaging

In the late 20th century, MRI emerged as a radiation-free, safe technique for the diagnosis of CAD. A study carried out by Kaufman *et al* [67] investigated the impact of nuclear MRI on CVD. Three years later, Awad *et al* [68] used MRI to assess subcortical lesions in the elderly population. The study included 240 MRI scans among patients over 50 years of age. It was concluded that subcortical lesions can be used as an index of chronic cerebrovascular disease in elderly patients. Mohiaddin *et al* [69] also used MRI to measure both regional aortic compliance and total arterial compliance in 70 healthy volunteers, 13 athletes and 17 patients with CAD. Regional aortic compliance was higher than normal in athletes, whereas it was lower than normal in patients with CAD. Despite its benefits, the long acquisition imaging time in MRI can cause anxiety in some patients during image acquisition [70].

1.2.1.5 Using intravascular ultrasound

With the innovation of high-frequency sound waves (20–30 MHz), IVUS has emerged as a safer modality for the identification and location of calcium in stenotic arteries [71, 72]. The grayscale IVUS-based acquisition system consists of three

parts: (i) a catheter, (ii) a pullback device and (iii) a scanning console [73]. The IVUS catheter carries an ultrasound transducer at its tip, which can both transmit and receive ultrasound signals. Before starting acquisition, the catheter is first manually advanced to the distal end of the coronary artery. Typically, the catheter is first inserted along with a guide wire from the femoral artery up to the site of occlusion in the coronary artery. Then, using the pullback device, the catheter is automatically pulled back at a speed of 0.5 mm s^{-1}. The pullback device is connected to a computer via a cable. The reflected ultrasound amplitude is used to create cross-sectional images which are stored for post-processing [73]. The echogenicity of different plaques is different. Plaques can be characterised as hypoechoic, isoechoic or hyperechoic [74]. Lipids and thrombi are usually hypoechoic, whereas the fibrous cap and calcium are hyperechoic [75, 76].

In the literature, several theories have been proposed for using ultrasound scanned images for accurate quantification of lipid and calcified plaques [77]. Kovalski *et al* [78] proposed an algorithm that uses active contour principles to identify the lumen–intima (LI) border and the media–adventitia (MA) border. Later, the features were used to reconstruct the coronary artery in 3D. The 3D structure further helped in better understanding of coronary artery geometry and plaque deposition. Depending on the calcium location within the plaque, calcium can be further quantified as deep or superficial [79]. The potential of IVUS to estimate CAC was compared to histology by Friedrich *et al* [80]. This study showed high sensitivity (90%) and specificity (100%) for the detection of dense calcium. Mintz *et al* [81] and Tuzcu *et al* [64] further compared IVUS to CA and found that IVUS had a higher sensitivity in detecting calcification compared to CA. These studies showed a higher accuracy in detecting CAC compared to histology.

With the advancement in IVUS technology, integrated backscattered IVUS (IB-IVUS) and IVUS-Virtual Histology (IVUS-VH^{TM}) further enhanced CAC detection and quantification. To improve the quantitative assessment obtained by ultrasound signals, IB-IVUS uses the time domain information from radiofrequency (RF) signals [82]. Furthermore, IVUS-VH^{TM} adopted a spectral analysis of ultrasound signals for plaque characterisation to stratify different plaque components by using different coloured maps [83]. This showed a higher predictive accuracy (96.7%–100%) compared to histology [84].

1.2.1.6 Using optical coherence imaging (OCT)

In comparison to IVUS, OCT has a much better resolution (10–20 μm) as it measures the amplitude of the backscattered light and is one step ahead of IVUS in assessing coronary vessels [85]. A physical overview of an OCT system is shown in figure 1.4. Unlike IVUS, OCT provides fast data acquisition (2.5 s), yielding detailed images of the vessel lumen, neointimal tissue and strut distribution [86, 87]. Recently, Wang *et al* [88] evaluated OCT and IVUS against coronary angiography for the assessment of target lesion calcification. Of the 440 calcium lesions, coronary angiography detected 40.2%, IVUS detected 82.7% and OCT detected 76.8%, respectively.

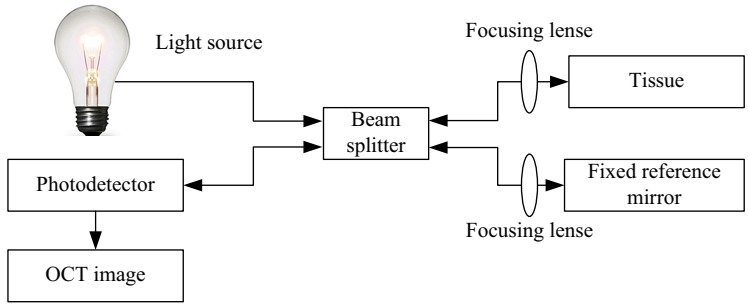

Figure 1.4. Physical overview of an OCT system.

1.2.2 Calcium detection in carotid arteries

1.2.2.1 Using computer tomography

With advancements in CT technologies, its application in carotid artery disease management has increased tremendously [89]. CT is usually employed for assessing calcium in the carotid arteries and has been shown to be a useful tool for plaque tissue characterisation [90] and in the prediction of stroke risk [91–93]. In *in vitro* [94] and *in vivo* studies [95], de Weert *et al* retrospectively evaluated the performance of 16 slice MDCT for the assessment of carotid plaque components (calcifications, fibrous tissue and lipid). These studies tried to quantify the atherosclerotic carotid plaque components and compared the results against histology. In an *in vitro* study [94], the calcified and lipid areas on MDCT and histology correlated well ($R^2 = 0.83$ and $R^2 = 0.68$, respectively). Similarly, in an *in vivo* study [95], the results showed a good correlation ($R^2 > 0.73$) between MDCT and histology, except for lipid core areas, which only had a good correlation ($R^2 > 0.77$) in mild calcified (0%–10%) plaques.

In another retrospective study consisting of 122 carotid arteries, Saba *et al* [96] observed no correlations between MDCT angiography-assessed carotid artery plaque volumes in the presence of ulceration. The same group [97] further evaluated the application of semi-automated techniques for the detection and measurement of carotid artery wall plaque. By carrying out a study using MDCTA in 22 patients, the authors demonstrated that the proposed semi-automatic method based on the level set model (LSM) can automatically measure the thickness of the plaque. By analysing 70 patients, the same group [98] tried to study the correlation between plaque in the carotid arteries (using a 16 detector row CT scanner) and cerebral microbleeds (CMB) in the brain (with a 1.5T MR imaging system). The results suggested an association between the presence of carotid artery fatty plaque, cerebrovascular symptoms and CMB, and concluded that the presence of CMB may represent an indication of the severity of cerebrovascular symptoms. Three years later, Saba *et al* [99] proposed an automatic mean shift-based algorithm for labelling calcified plaques in ICA using CT images taken from 75 patients. Independent of the number and size of calcium regions, the proposed approach provided reasonably accurate labelling of calcified plaques.

In the CT assessment of carotid plaques, the analysis of the attenuation value is a fundamental parameter in order to classify the type of the plaque components. In a retrospective study of 68 patients (192 slides), Saba *et al* [100] examined the attenuation values measured in Hounsfield units (HU) of the region-of-interest (ROI) before and after the administration of contrast medium. The study showed that the components of the plaque in ROI sampling, performed in the CT dataset acquired after the administration of contrast medium, had a greater degree of heterogeneity compared to the baseline measurement. This effect was observed because, during acquisition, different amounts of contrast were observed for different carotid artery plaque components.

1.2.2.2 Using magnetic resonance imaging

MRI is generally used to assess the soft tissue characteristics of carotid atherosclerotic plaques based on morphological features [101]. Most previous plaque characterisation work was focused on wall thickness measurements [102].

Merickel *et al* [103] used the functional and structural information of plaque and computed two different measurements. First, the authors computed the ratio of the plaque component volume with respect to the total wall volume. Later, they measured the difference in the cross-sectional area between the diseased lumen and the normal lumen. The first measurement provided an estimation of stenosis progression, while the second measurement provided an extent of blockage in the lumen. The study successfully demonstrated significant segregation between atherosclerotic tissues and calcified plaque.

In an *in vivo* study, Toussaint *et al* [104] showed that T2-weighted MRI can also discriminate lipid cores, fibrous caps and calcifications in human atheromatous plaques. The authors carried out an *in vivo* study on seven lesions from six patients, prior to surgery. Further, the authors repeated the same protocol *in vitro*. For each plaque component, the study observed a high correlation between *in vitro* and *in vivo* measurements by adapting the linear regression.

Coombs *et al* [105] showed the capability of a 3D MRI in identifying fatty plaque, fibrous plaque and calcified plaque. Twenty-one carotid endarterectomy tissue sections were analysed by both MRI and histology. The study observed different signal characteristics for different plaque components, leading to the conclusion that 3D gradient-echo MRI can distinguish and identify atherosclerotic plaque components.

Recently, Lee *et al* [106] showed the importance of high-risk carotid plaques in choosing the treatment strategy for carotid stenosis patients. From 2014 to 2016, the study collected data from 15 patients who underwent angiography for stenosis measurements. The authors further analysed intraplaque haemorrhage (IPH) using MRI. The results showed a significant relationship between IPH and ischaemic symptoms. Despite its benefits, challenges remain for patients with marked arrhythmia and metal implants [107].

1.2.2.3 Using B-mode ultrasound

A carotid B-mode ultrasound acquisition system is shown in figure 1.5. Using the rationale that variable echogenicity is produced by different tissues, Lal *et al* [77]

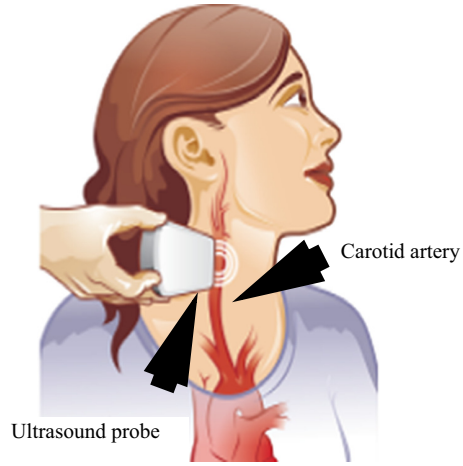

Figure 1.5. Carotid B-mode ultrasound acquisition system. (Courtesy of Atheropoint^{TM}, Roseville, CA, USA.)

used computer-assisted duplex ultrasound (DU) scanned images to quantify the echogenicity of blood, lipid, fibromuscular tissue and calcium. Pixel-based distribution analysis (PDA) was used to quantify these components in 10 healthy tissues and 20 carotid artery plaques from 19 patients. The results showed a strong correlation with the histologic readings and this proved that PDA can accurately quantify calcium components in control subjects.

Molinari *et al* [108] proposed an ultrasound-based technique for automatic characterisation of different plaque components (such as thrombi, lipids, fibrous tissue and calcium) in the carotid artery. For plaque boundary segmentation, an automated technique CULEX [109] was used. Twenty plaque specimen results were compared against histology. The results demonstrated that the proposed methodology can effectively identify plaque components. The studies showed that echogenicity produced by different plaque components in B-mode ultrasound images can be used as a biomarker for the accurate quantification of calcium components in the carotid arteries. Hitchner *et al* [110] further tried to estimate the role of IVUS in the characterisation of carotid plaque components. The study explored the relationship between microemboli and plaque tissues. In a group of 38 high-risk patients, microemboli were analysed by comparing the pre- and postoperative diffusion-weighted MRI images. Using univariate and multivariate logistic regression, the area of fibrous tissue and calcification was observed to be related to the microemboli.

Many studies have detected arterial calcification by ultrasound, but the diagnostic accuracy is still not well-validated. To validate the accuracy of ultrasound examination, Jashari *et al* [111] performed a comparative study of atherosclerotic calcification detection using two imaging modalities: carotid ultrasound and cone beam CT (CBCT). A pool of 88 patients (94 carotid arteries) who underwent pre-endarterectomy ultrasound examination were chosen for this study. Initially, atherosclerotic calcification was determined using carotid B-mode

ultrasound. Calcium was identified from its high echogenicity and posterior shadow. After endarterectomy, the calcium volume was computed using CBCT. To determine the accuracy, the calcium volumes acquired from both imaging modalities were compared. The results showed that carotid ultrasound could accurately (sensitivity of 96%) detect the presence of calcified atherosclerotic lesions having a volume $\geqslant 8$ mm^3.

In comparison to pixel intensity-based tissue characterisation (usually based on an intensity threshold), Pazinato *et al* [112] proposed image descriptors (such as statistical moments, texture-based, gradient-based and local binary patterns) for carotid ultrasound images to classify five different types of tissues, such as blood, lipids, muscle, fibrous material and calcium. The proposed classification consisted of the following pipeline: (i) image normalisation, (ii) multiscale feature extraction and (iii) machine-learning classification. The proposed descriptor was computed while using the pixel neighbourhood information. The study outperformed a standard threshold-based method by showing a 19% increase in accuracy. Thus, MRI is generally used for soft tissue component characterisation [113].

1.3 Calcium area/volume quantification in coronary and carotid arteries

1.3.1 Calcium area/volume quantification in coronary arteries

For an optimal interventional procedure, a cardiologist must know the exact location, position and volume of the calcified plaque in the coronary arteries [114]. Several prospective cohort studies have tried to quantify the area/volume in the coronary artery using IVUS (see table 1.1). Weissman *et al* [115] measured plaque volume in 19 patients before and after atherectomy. The volume of the calcified plaque was calculated using the modified Simpson's rule [116]. To access calcium along the length of the vessel, Scott *et al* [117] presented a two-layered technique to quantify calcium in the coronary arteries. In this study, the total and calcified plaque luminal circumferential length was first measured, and then the plaque area was computed using the standard Simpson's rule [118]. The study accurately reflected coronary calcium as determined using histology. Previous studies lacked the automation of the calcium detection process.

In 2008, Santos Filho *et al* [119] proposed an automated calcium quantification technique by finding the optimised threshold using the iterative Otsu's method [120]. In their study, the calcified region was distinguished from other bright regions by identifying the presence of the acoustic shadow. Zhang *et al* [121] outperformed the Santos method by proposing an automated detection algorithm to detect calcification using snakes and contourlet transform. The study utilised a 2D Renyi's entropy algorithm to produce the ROI from which the contours of calcification were obtained. The study outperformed the Santo method by 2.76% and 14.53% in terms of sensitivity and specificity, respectively. Gao *et al* [122] showed that there were two reasons as to why the performance of previous methods was inferior for detecting and computing the calcium volume: (i) the detection of the ROI did not consider the concept of acoustic shadowing and (ii) refinement of the calcified plaque relied on

Table 1.1. Prospective studies on calcium computation in the coronary arteries.

Year	Authors	Modality	Techniques	Metric	*N*	Fr/ Video	Benchmark	Statistical analysis with CI	Entire video usage	Validation
1995	Weissman *et al* [115]	Coronary	Modified Simpson's rule	Volume	19	×	None	*t*-test (CI: 95%)	×	Manual
2000	Scott *et al* [117]	Coronary	Standard Simpson's rule	Area	6	≈ 195	None	*t*-test (CI: 95%)	×	Histology
2008	Santos *et al* [119]	Coronary	Adaptive thresholding	Area	14	×	Otsu *et al* [120]	×	×	Manual
2010	Zhang *et al* [121]	Coronary	Snakes and contourlet transform	Area	11	≈ 8	Santos *et al* [119]	×	×	Simulation
2014	Gao *et al* [122]	Coronary	RMM, MRF and GSA	Area	8	≈ 125	None	×	×	Manual
2015	Araki *et al* [123]	Coronary	Shape-based	Volume	100	≈ 2549	None	×	✓	Scoring
2016	Araki *et al* [114]	Coronary	FCM, K-means and HMRF	Volume	15	≈ 2040	Santos *et al* [119] and Araki *et al* [123]	*Z*-test and Wilcoxon test (CI: 95%)	✓	Scoring

N: number of patients; Fr/Video: number of IVUS frames per video; RMM: Rayleigh mixture model; MRF: Markov random field; GSA: graph search algorithm; FCM: fuzzy c-means; HMRF: hidden Markov random field; Manual: manual tracings of calcium; Histology: calcium determined by histology; Simulation: simulation of an IVUS image with calcium; Scoring: calcium scoring by trained expert; CI: confidence interval.

grey intensities. The authors provided an automated framework on 996 *in vivo* IVUS images acquired from eight patients. The technique was composed of the Rayleigh mixture model for performing pixel classification, the Markov random field for the detection of angular location, and the graph search algorithm to detect the borders of the calcified plaque. The study achieved a high sensitivity and specificity of 94.68% and 95.82%, respectively.

Besides Weissman *et al* [115] and Araki [123], the above mentioned studies had achieved accurate calcium area quantification but lacked volume computation. Weissman *et al* [115] study did not mention the number of frames utilised for the calcium volume computation. Further, the study did not perform calcium quantification. By utilising the entire IVUS video, Araki *et al* [123] used a shape-based approach for detection of the largest calcium region in each frame of the video. The study was performed on 100 patients resulting in an accuracy of 81%. The major drawback of this approach was selecting the largest connected calcium while ignoring the loosely unconnected small lesions. Since calcium is multifocal in nature, true calcium estimation is possible only if all the calcified components in the arteries are considered. By using the above concept, the same group [114] had utilised three segmentation techniques (fuzzy c-means (FCM), K-means and hidden Markov random field (HMRF)) for the automated detection of multifocal calcium regions in each frame throughout the IVUS video. K-means showed the best performance with an accuracy of 92.80%. As the number of IVUS frames per videos is usually large (~2040 frames/video), the proposed studies suffered from prolonged computational time.

High computation speed is a basic requirement of any automated calcium detection technique. By adapting multiresolution techniques (the so-called down sampling mode), it is possible to speed up the computation. Several prospective studies have tried multiresolution techniques for the detection and measurement of calcium in a coronary artery (see table 1.2). Recently, Banchhor *et al* [124] applied a set of five different multiresolution-based techniques (bilinear, bicubic, wavelet, Lanczos and Gaussian pyramid), on a set of four kinds of segmentation methods (threshold, FCM, K-means and HMRF). By carrying out a study on 38 760 IVUS frames acquired from 19 patients, the study observed an improvement in the mean computational time. It was observed that the FCM detection technique when embedded with wavelet-based multiresolution paradigm produced the best performance. Even though the study resolves the computational time issue, it did not take into account the noise in IVUS images. This leads to a bias of overestimation in the final detected calcium volume. To overcome this limitation, the same group [125] proposed an automated connected component analysis (CCA)-based approach to remove the noise, as shown in figure 1.6. The study was based on the assumption that isolated calcium size cannot be smaller than 100 pixel^2. Using the CCA-based approach, the study observed an improvement of 38.54% in the mean overall performance. The threshold-based classifier embedded with Lanczos multiresolution was found to be an optimal combination. Among the different automated techniques proposed, the quantification of coronary calcium volume using complete IVUS videos can assist the cardiologist during the planning of PCI procedures.

Table 1.2. Survey on calcium detection techniques using multiresolution paradigm in coronary arteries.

Year	Authors	*N*	F/Video	Objective	Multiresolution technique	Performance evaluation	Accuracy	Benchmark	Statistical analysis with CI	MR comparisons	Bias correction
2006	Liang *et al* [126]	Not mentioned	Not mentioned	Arterial wall strain	Gaussian pyramid	Correlation coefficient	N/A	None	×	None	None
2009	Srinivas *et al* [127]	Not mentioned	Not mentioned	Pre-rupture plaque	Wavelets	None	N/A	None	×	None	None
2010	Zhang *et al* [121]	11	≈ 8	Calcium area	Contourlet transform	MD, RMD, MSD, RDD, ARD, TD, LD, RARD, RTD and RLD	N/A	Santo *et al* [119]	×	None	None
2012	Katouzian *et al* [128]	5	1158 frames	LI border	Wavelets	TP, FP, RMSE	N/A	None	×	None	None
2012	Lazrag and Naceur [129]	Not mentioned	20 simulated, 30 real frames	Vascular boundary	Contourlet transform	None	N/A	Zhang *et al* [121]	×	None	None
2012	Lazrag and Naceur [130]	Not mentioned	Not mentioned	Speckle reduction	Wavelets	PSNR, NMSE	N/A	None	×	None	None
2015	Puertas *et al* [131]	Not mentioned	Not mentioned	Stacked sequential learning	Gaussian pyramid	Accuracy, overlapping, recall and precision	N/A	None	Friedman and Nemenyi test (CI: 95%)	None	None

(*Continued*)

2016	Banchhor *et al* [124]	19	≈ 2040	Calcium volume	Bilinear, bicubic, wavelets, Lanczos and Gaussian pyramid	PTI, PoM, MVS, DR and QAR	$PTI^{*}_{\forall S}$, $PTI^{*}_{\forall M}$, PoM^{*}_{VL}, PoM^{*}_{FL}, PoM^{*}_{DR} and PoM^{*}_{QAR}	Zhang *et al* [121], Lazrag and Naceur [130]	×	Yes	Yes

N: number of patients; F/Video: number of IVUS frames per video; MR: multiresolution, $PTI^{*}_{\forall S}$: percentage mean time improvement for multiresolution technique; $PTI^{*}_{\forall M}$: percentage mean time improvement for segmentation method; PoM: precision-of-merit; VL: volume level; FL: frame level; MVS: mean volume similarity; MVSIBC: mean volume similarity increase with bias correction; DR: degradation ratio; QAR: quality assessment ratio; CI: confidence interval; IMT: intima–media thickness; PSNR: peak signal-to-noise ratio; NMSE: normalised mean square error; MD: mean distance error; RMD: relative mean distance error; MSD: mean signed distance error; RDD: relative difference degree; ARD: arc difference; TD: thickness difference; LD: length difference; RARD: relative arc difference; RTD: relative thickness difference; RLD: relative length difference; TP: true positive; FP: false positive; RMSE: root mean square error; N/A: not available.

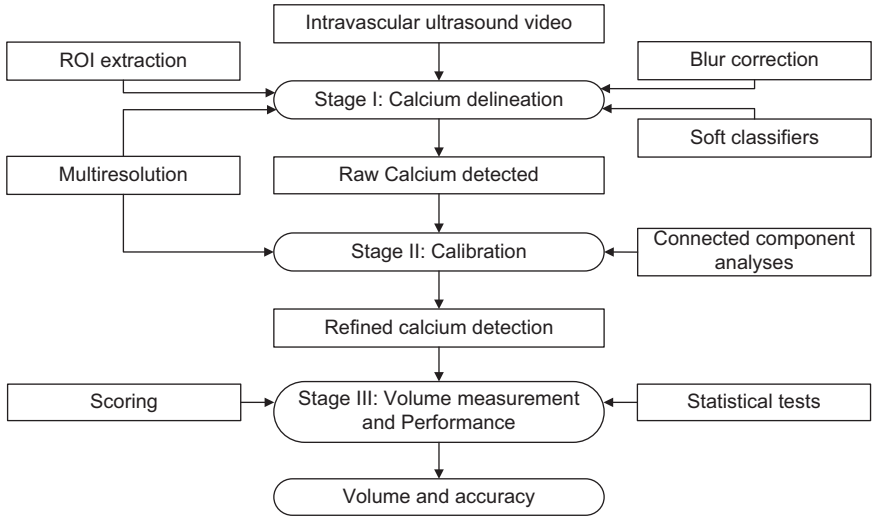

Figure 1.6. A well-balanced system for calcium detection using the CCA-based approach.

Multiresolution techniques and the CCA-based approach can further improve the speed and accuracy of different calcium detection techniques.

1.3.2 Calcium area/volume quantification in carotid arteries

Several prospective cohort studies have tried to quantify area/volume in the carotid artery (see table 1.3). We have divided our calcium area/volume measurement strategy based on the modality chosen. Key authors in the CT-based paradigm are first discussed followed by key authors in the ultrasound-based paradigm.

1.3.2.1 CT-based measurements

Denzel *et al* [132] examined 92 CT-based internal carotid artery (ICA) endarterectomy specimens with stenosis greater than 70%. The results showed that the calcium scores computed, using the method discussed in Agatston *et al* [59], enabled precise *in vitro* measurements from ICA plaques (consisting of calcified plaques, lipid and combined plaques). The authors observed a high mean correlation ($R = 0.628$, $p < 0.001$) between the calcium score and radiological classification for slight, moderate and marked calcifications, but there was no *in vivo* validation of the plaque components. De Weert *et al* [133] also tried to estimate the volume of plaque and its components using MDCTA images. The authors analysed 56 carotid arteries using three observers. The observers manually drew the vessel contour based on the HU threshold. Since MDCTA cannot differentiate atherosclerotic plaque and tunica media, the technique can potentially lead to overestimation of plaque volume. Marquering *et al* [134] tried to explore the relationship between carotid calcium volume and degree of stenosis from CT angiography images using the Pearson correlation coefficient. The study observed a weak correlation between calcium volume and stenosis (a sensitivity of 47% and a specificity of 52%). The authors

Table 1.3. Prospective studies on calcium computation in the carotid arteries.

Year	Authors	Techniques	Metric	*N*	Fr/Video	Benchmark	Statistical analysis with CI	Validation
2004	Denzel *et al* [132]	Agatston	Scoring	89	92	None	CK test (CI: 95%)	None
2008	de Weert *et al* [133]	Manual	Volume	56	56	None	*t*-test (CI: 95%)	None
2011	Marquering *et al* [134]	Manual	Volume	90	159	None	*t*-test (CI: 95%)	None
2012	Molinari *et al* [137]	Bicubic	Area	NM	365 frames	None	*t*-test (CI: 95%)	None
2016	Anzidei *et al* [135]	ImageJ software	Volume	62	×	None	KS, MW, Wilcoxon, *t* and CK tests (CI: 95%)	None
2017	Gepner *et al* [136]	Agatston	Scoring	4955	×	None	×	None

N: number of patients; Fr/Video: number of IVUS frames per video; Manual: manual tracings of calcium; CK: Cohen's kappa; KS: Kolmogorov–Smirnov; MW: Mann–Whitney; CI: confidence interval.

concluded that the calcium volume measurement cannot estimate the degree of stenosis in the carotid arteries. Anzidei *et al* [135] examined the relationship between head and neck radiation therapy treatment (HNXRT) and the CT volume in carotid artery plaque, fatty plaques and mixed plaque components. A pool of 100 patients was analysed at baseline, and two years later, 62 patients (who underwent HNXRT) were reanalysed. In these two years, the volumes of carotid artery plaques (533 mm^3), fatty plaques (103 mm^3) and mixed plaque components (328 mm^3) were observed as 746 mm^3, 202 mm^3 and 419 mm^3, respectively. The study observed an increase in carotid artery plaque volume (particularly the fatty plaque component) with patients who underwent HNXRT.

Gepner *et al* [136] compared the CT carotid plaque score with the coronary artery calcium score. In a multi-ethnic cohort of 6814 patients, the results were analysed at baseline and after a follow-up of three years. For predicting CVD, the hazard ratios (HRs) for CAC scores and carotid plaque scores were HR = 1.78 (95% CI, 1.16–1.98; $p < 0.001$) and HR = 1.27 (95% CI, 1.16–1.40; $p < 0.001$), respectively. Similarly, for predicting CHD, the HRs for the CAC scores and carotid plaque scores were HR = 2.09 (95% CI, 1.84–2.38; $p < 0.001$) and HR = 1.35 (95% CI, 1.21–1.51; $p < 0.001$), respectively. The results showed that CAC scores proved to be a stronger predictor of CVD compared to the carotid plaque scores.

1.3.2.2 Ultrasound-based measurements

Not much has been proposed for the quantification of calcium area and volume using the ultrasound-based paradigm. The focus has been more on wall thickness

measurement, instead of component quantification. Keeping this in mind, Tsiaparas *et al* [138] proposed a multiresolution approach for carotid atherosclerotic tissue classification. Out of the four decomposition schemes (discrete wavelet transforms, stationary wavelet transforms, wavelet packets and Gabor transform), wavelet packets followed by Haar function produced the best performance (82.5% and 77.5%).

The scale-space strategy introduced by Suri's group dominates several fundamental carotid artery wall measurement paradigms. The basic idea was to apply a higher order Gaussian derivative filter to extract the edges of the wall (see Molinari *et al* [137]). This was accomplished in the multiresolution framework to ensure that the scales were not too high. By carrying out a study on 365 B-mode longitudinal carotid images, CAMES observed an 8.4% increase in the accuracy compared to their previous integrated approach using feature-based extraction and classifier (CALEX) [139]. The result proved CAMES as a clinical tool for accurate cIMT measurements in large multicenter clinical trials.

1.4 Metrics for performance evaluation for calcium detection algorithms and its validation

Metrics play an important role in evaluating the performance of calcium detection algorithms. Furthermore, it is important to discuss the types of strategies one can adopt to establish the gold standard when benchmarking calcium detection methods. These two factors are presented in this section.

1.4.1 Statistical metrics for performance evaluation

Any proposed calcium detection algorithm should have performance indices such as accuracy, reliability and robustness. To choose or compare, we must evaluate the performance by choosing the correct metrics. The basic evaluation measure is the supervised evaluation in which the output of the algorithm is compared against the ground truth (GT). The ground truth may be a set of binary images or calcium area/volume reflecting true calcium detection either derived by a human expert or from any prior established study.

Depending on the type of variable, the number of classes in the study and the distribution of the data, statistical tests commonly used in the literature are the *t*-test, *z*-test, Mann–Whitney test, Kolmogorov–Smirnov (KS) test, ANOVA test, Chi-squared test, Friedman test and Wilcoxon test [94, 98]. Bland–Altman plots are also used to display the average bias or the average of the differences between the two readings [140].

Given a set of GT images, the preferred performance evaluation metrics are the Jaccard index (JI), Dice similarity coefficient (DSC), signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). JI and DSC are the simplest ways to quantify the proximity between two binary images containing calcium regions. The JI and DSC always lie between 0 and 1, where 0 and 1 correspond to the lowest and highest similarity between the GT and the segmented binary image, respectively. If A is the

ground truth binary image and B is the segmented binary image, then the JI formula can be given as [125]

$$J_{AB} = \frac{|A \cap B|}{|A \cup B|} \text{ and } D_{AB} = \frac{2|A \cap B|}{|A| + |B|}, \tag{1.1}$$

where $|A \cap B|$ and $|A \cup B|$ indicate the sum of all the related and unrelated pixels between the GT and the segmented binary image, respectively. Similarly, $|A|$ and $|B|$ indicate the sum of all the pixels of the GT and the segmented binary image, respectively. Here, $0 \leqslant J_{AB} \leqslant 1$ and $0 \leqslant D_{AB} \leqslant 1$.

Araki *et al* [114] used these two metrics to quantify the degree of similarity between their proposed three automated detection metrics and the threshold-based method. Banchhor *et al* [124] used the same measure to compare segmented binary results obtained with and without the use of multiresolution techniques. SNR is a measure to compare the signal strength over the background noise and CNR is a measure to determine the image quality [141]. SNR can be mathematically given as [141]

$$\text{SNR} = \frac{S_L(i, j) - S_B(k, l)}{\sqrt{2}.\ \sigma_B(k, l)}, \tag{1.2}$$

where $S_L(i, j)$ is the mean signal strength in the ROI with a lesion at the location (i, j). $S_B(k, l)$ and $\sigma_B(k, l)$ are the mean signal strength and standard deviation of the background ROI without a lesion at the location (k, l), respectively. Similarly, CNR can be mathematically given as [142]

$$\text{CNR} = \sqrt{\frac{(\mu_L(i, j) - \mu_B(k, l))^2}{\sigma_L(i, j) + \sigma_B(k, l)}}, \tag{1.3}$$

where $\mu_L(i, j)$ and $\mu_B(k, l)$ are the mean signal strength in the ROI with a lesion at the location (i, j) and the background ROI without a lesion at the location (k, l), respectively. Similarly, $\sigma_L(i, j)$ and $\sigma_B(k, l)$ are the standard deviation of the signal strength in the ROI with a lesion at the location (i, j) and the background ROI without a lesion at location (k, l), respectively.

Unlike regional image-based performance, one can use performance metrics given the area or volume measurements. Typically adapted metrics are the correlation coefficient (CC), precision-of-merit (PoM), figure-of-merit (FoM) and receiver operating characteristic (ROC), The CC is a measure to predict the degree to which changes in one variable predict the change of another. PoM and FoM are measures to compare individual and mean readings, respectively [94]. Mathematically, PoM can be depicted as [143]

$$\text{PoM} = \frac{1}{N}\sum_{j=1}^{N} 100 - \left[\left(\frac{|\text{Auto}(j) - \text{Manual}(j)|}{\text{Manual}(j)}\right) * 100\right], \tag{1.4}$$

where $\text{Auto}(j)$ is automatically computed by any system and $\text{Manual}(j)$ values are obtained from manual measurements on the jth image of the database of N images.

The central tendency of the error can also be computed using FoM [143–145], which is given as

$$\mathrm{FoM} = 100 - \left[\left(\frac{|\overline{\mathrm{Auto}} - \overline{\mathrm{Manual}}|}{\overline{\mathrm{Manual}}}\right) * 100\right], \tag{1.5}$$

where

$$\overline{\mathrm{Auto}} = \frac{1}{N}\sum_{i=1}^{N}\mathrm{Auto}(i) \tag{1.6}$$

$$\overline{\mathrm{Manual}} = \frac{1}{N}\sum_{i=1}^{N}\mathrm{Manual}(i). \tag{1.7}$$

Here N represents the total number of images in the database.

ROC is a graphical representation of sensitivity and specificity where a higher AUC confirms superior performance [125]. ROC needs the computation of the true positive rate (TPR), false positive rate (FPR), positive predictive value (PPV) and negative predictive value (NPV). True positives (TPs) and false negatives (FNs) are defined as the number of times true calcium is correctly and incorrectly identified with respect to the manually computed calcium for the cut-off risk threshold. Similarly, true negatives (TNs) and false positives (FPs) are defined as the number of times true calcium is correctly and incorrectly identified for the cut-off risk threshold. TPR, FPR, PPV and NPV can be mathematically formulated as [125]

$$\mathrm{TPR} = \frac{\mathrm{TP}}{(\mathrm{TP} + \mathrm{FN})} \tag{1.8}$$

$$\mathrm{FPR} = \frac{\mathrm{TN}}{(\mathrm{TN} + \mathrm{FP})} \tag{1.9}$$

$$\mathrm{PPV} = \frac{\mathrm{TP}}{(\mathrm{TP} + \mathrm{FP})} \tag{1.10}$$

$$\mathrm{NPV} = \frac{\mathrm{TN}}{(\mathrm{TN} + \mathrm{FN})}. \tag{1.11}$$

1.4.2 Validation of calcium detection algorithms

Validation is an important component of a system as it explains how reliable the calcium detection methodology is. The two most common methods used for validation are: (i) giving a score to the evaluated results by an expert (scoring strategy) and (ii) comparing against histology. In scoring, the radiologist scores each calcium detected frame on a scale from 0 to 5 (where 5 indicates true calcium detection and 0 indicates false calcium detection) [124]. To avoid inter-observer

variability, the scoring should be performed by more than one expert. Also, each radiologist should repeat their tracings to avoid intra-observer variability. To avoid any bias, the current score should be performed blinded against the score done in the past. In the end, all the scores should be averaged to find the mean score for the computed automated values and GT, and compared between them, which forecasts the performance of the calcium detection algorithm. During scoring, factors such as the effect of lighting conditions, radiologist fatigue, experience and type of image resolution (DICOM versus JPEG) must also be taken into consideration [94].

The second most common method of validation is comparing the results of detection algorithms against histology. Scott *et al* [117], computed the coronary calcium from IVUS as a percentage of the coronary luminal surface. For the histology analysis, the arteries were decalcified and cut at 3 mm intervals, which is the smallest distance practical for processing tissue for light microscopy. Calcified areas were measured by computerised planimetry and the calcium volume was computed using Simpson's rule. The study found a high degree of correlation ($r = 0.84$, $p < 0.0001$) between the computed reading against the calcium area estimated using histological analysis.

1.5 Machine-learning-based risk stratification

Plaque risk assessment in diseased arteries is beneficial for cardiologists prior to any interventional procedures such as PCI. Further, procedures such as stent deployment or bypass shunting can be better planned [73] if plaque severity is known *a priori*. IVUS is more popular than other medical imaging modalities as it can provide an accurate tomography of the vulnerable plaque, which can be used for measurement of morphological features [53, 71]. Several studies have been conducted to stratify the vascular risk using a machine-learning (ML) paradigm (table 1.4).

1.5.1 Coronary risk assessment using ML-based approaches

Araki *et al* [158] demonstrated the use of the fusion of shape-based features with geometric-based coronary calcium volume for risk stratification on 92 patients with stable angina pectoris. Normalised calcium volume was computed using a geometric-based segmentation strategy. This strategy was used to isolate the calcium lesion by suppressing the non-calcium region. In comparison to shape-based features (AUC = 0.58), the fusion of the calcium volume features with shape-based features showed an improvement of 6.2%. Araki *et al* [154] further showed a CADx system for coronary risk stratification that utilised a support vector machine (SVM), which when trained using 56 plaque texture features yielded a classification accuracy of 94.95%. The major limitation of this study was a lack of feature selection adaptation; thus, it was never optimised. Later, the same group [155] modified their CADx system by using a dominant principal component analysis (PCA)-based polling technique for feature selection leading to an improvement of 3.48% (~98.43%) over their previous method. Recently, Banchhor *et al* [145] designed a CADx risk stratification tool by fusing plaque texture-based features with the wall-based measurement features (see figure 1.7). By using a PCA-based polling strategy, dominant features were selected from the

Table 1.4. Survey of risk stratification techniques in the literature.

Year	Authors	Arterial type	Data size	Feature type(s)	Total features	Feature selection technique(s)	Classifier(s)	Cross-validation accuracy
2003	Christodoulou *et al* [146]	Carotid	230	Tex	61	Mean, SD, Distance	MNN	73.1%
2005	Kyriacou *et al* [147]	Carotid	274	Tex, Wall	10	N/A	NN	71.2%
2007	Mongiakakou *et al* [148]	Carotid	54	SF, Law's	21	ANOVA	HNN	99.1%
2009	Kyriacou *et al* [149]	Carotid	274	Tex	10	N/A	SVM	73.7%
2012	Acharya *et al* [150]	Carotid	346	Tex	4	*t*-test	SVM, AdaBoost	SVM—82.4%, AdaBoost—81.7%
2012	Acharya *et al* [151]	Carotid	346	Tex, Wall	3	*t*-test	SVM	83%
2013	Acharya *et al* [152]	Carotid	492	DWT, HOS, Tex	7	*t*-test	SVM	91.7%
2014	Pedro *et al* [153]	Carotid	146	Rayleigh Mixture	16	N/A	EAI	77%
2016	Araki *et al* [154]	Coronary	2865	Tex	56	N/A	SVM	94.95%
2016	Araki *et al* [155]	Coronary	2865	Tex	56	PCA	SVM	98.43%
2017	Araki *et al* [156]	Carotid	407	Tex	16	N/A	SVM	FW—98.00%, NW—98.00%
2017	Saba *et al* [157]	Carotid	407	Tex	16	PCA	SVM	FW—98.55%, NW—98.83%
2017	Banchhor *et al* [145]	Coronary	4930	Only Tex, Tex fused with Wall	65	PCA	SVM	Only Tex—89.98%, Tex fused with Wall—95.41%

Tex: plaque texture-based; Wall: wall-based; NN: neural network; SF: statistical feature; SD: standard deviation; MNN: modular neural network: HNN: hybrid neural network; SVM: support vector machine; EAI: enhanced activity index; PCA: principal component analysis; DWT: discrete wavelet transform; HOS: higher order spectra; NW: near-wall; FW: far-wall; N/A: not applicable.

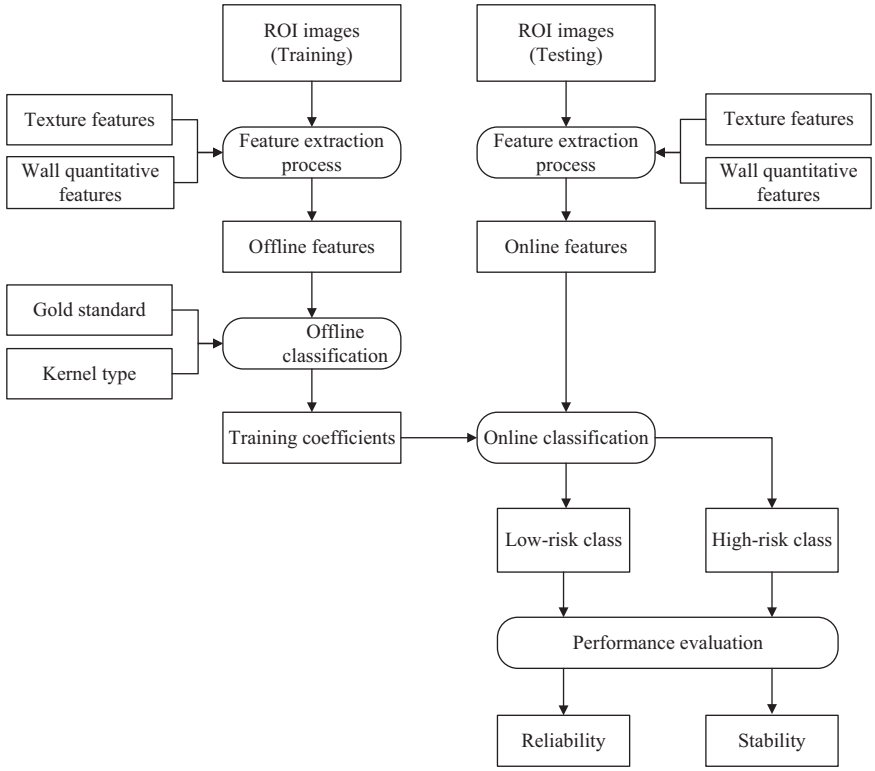

Figure 1.7. Improved coronary risk assessment system using a machine-learning paradigm.

pool of 65 different features. In an offline classification (using a training classifier such as SVM), the system used a combination of (i) training ground truth (or gold standard) risk labels (acquired from carotid plaque burden such as intima–media thickness) and (ii) dominant image-based training features extracted from training data sets to produce offline training coefficients [154, 155]. These training coefficients were then utilised to transform the online test features from the test images using the same SVM test classifier for predicting the risk of CAD patients and stratifying them into high- and low-risk bins. As compared to stand-alone plaque texture-based features, the proposed CADx system exhibited an improvement of ~6% in accuracy for coronary risk stratification into high- and low-risk bins.

1.5.2 Carotid risk assessment using ML-based approaches

Not much has been demonstrated in carotid tissue characterisation compared to IVUS-based risk assessment strategies. Araki *et al* [156] proposed a CADx system using ultrasonic echolucent carotid wall plaque morphology by independently evaluating the near and far walls. Adapting the classification paradigm of SVM, the CADx system showed an accuracy of 98.05% and 97.53% for the far-wall and near-wall, respectively. Using the spirit of coronary risk stratification for feature

selection in [155], Saba *et al* [157] modified their CADx system by selecting dominant features using the PCA-based strategy. This brought an increase in the risk stratification accuracies of 98.28% and 93.92% to the far-wall and near-wall. For both coronary and carotid risk stratification, a PCA-based embedded system using greyscale morphology established a powerful paradigm for risk assessment and thus can be adapted to the clinical setting. In the future, a multimodal approach may be developed for validating detected calcium, which would be a useful diagnostic component for better CVD management.

1.6 Discussion

1.6.1 A note on the usage of calcium detection techniques in coronary and carotid arteries

Beyond traditional risk factors, the computation of calcium in both coronary and carotid arteries provides valuable prognostic information about the extent of cardiovascular disease. In section 1.2, we observed that previous studies had utilised two different techniques for calcium detection in coronary and carotid arteries, including non-invasive (CT, echocardiography and MRI) and invasive (angiography, IVUS and OCT) methods. MDCT offers increased spatial and temporal resolution and thus exhibits the potential for calcium detection and quantification. MRI is a radiation-free, safe technique and is generally used to assess soft tissue component characterisation [113]. Compared to other modalities, IVUS is safe, economic and easy to use with real-time diagnosis. Due to its optical properties, OCT has emerged as a valuable modality and has shown success in clinical demonstrations.

Even though there are advantages, both invasive and non-invasive modalities have some limitations. Previous studies have shown the utility of CT in the detection of coronary and carotid plaque components. Although CT provides calcium scores in the artery, higher radiation could compromise patient safety. From the literature, we have observed that many carotid studies have used MRI for accurate detection of soft plaque and its components. However, challenges remain for patients with marked arrhythmia and metal implants [107, 108]. It was also observed that grayscale IVUS-based studies required a shorter acquisition time and that near-real-time diagnosis is instrumental in detecting calcium in the coronary arteries. Clinical experience has shown that even though OCT offers better resolution, it has limitations in the estimation of the true vessel size for the assessment of plaque burden. OCT also lacks clinical standardisation; as a result, IVUS still remains important in the cardiologist's armamentarium [87]. Furthermore, PCI treatments involve risk to a patient's life, therefore, cardiologists usually diagnose arterial stenosis by observing all the imaging modalities adopted for the coronary and carotid artery.

1.6.2 A note on the usage of calcium quantification techniques in coronary and carotid arteries

Several studies in the literature have tried to quantify calcium in both the coronary and carotid arteries, as discussed in sections 1.3.1 and 1.3.2. In coronary arteries, initially the techniques [115, 117] were not automated, but later automated studies

slowly achieved high accuracy. The main limitation of the automated studies [119, 121, 122] is the lack of calcium volume quantification methods. Weissman *et al* [115] and Araki *et al* [123] did compute the calcium volume, but they either lacked quantification [115] or ignored quantification of multifocal small lesions [123]. The above two limitations were taken care of by Araki *et al* [114], whose study proposed K-means as the best approach in terms of accuracy (92.80%). The only limitation of Araki's study [114] was its computational time. This limitation was taken care of by Banchhor *et al* [124] by adapting multiresolution-based techniques. The results proved that best performance was achieved when the FCM detection technique was embedded with the wavelet-based multiresolution paradigm. Further, to improve the accuracy, the same group adapted a CCA-based approach. The study proved that the threshold-based classifier, when embedded with Lanczos multiresolution, produced the highest accuracy (94.06%) in quantifying the calcium volume in a complete coronary artery video.

On the other hand, in the carotid arteries, researchers have computed either plaque or calcium scores and tried to determine which score could be used for predicting stenosis in CVD patients. Denzel *et al* [132] and Gepner *et al* [136] proved that in comparison to the plaque score, the calcium score was a stronger predictor of stenosis in CVD patients.

1.6.3 A note on the use of statistical metrics for the evaluation of calcium detection algorithms

The statistical tests mostly used in the literature are: the *t*-test [115, 117, 133–135, 137], *z*-test [114], Wilcoxon test [114, 135], Friedman test [131], Nemenyi test [131], Cohen's Kappa-test [132, 135], Kolmogorov–Smirnov-test [135] and Mann–Whitney-test [135] with a 95% confidence interval. All these statistical tests are two-tailed tests and p-values < 0.05 are considered significant. According to the available data size and nature of the sample data, researchers must strategically choose their statistical tests in order to improve the accuracy, reliability and robustness of the results, and statistical significance [114, 124, 125, 140, 143]. Furthermore, logistic regression [144] must be performed to study the odds ratios of image phenotypes and the ranking order of the image phenotypes for the risk of associations.

1.6.4 A note on feature selection in ML-based risk stratification for the coronary and carotid arteries

Several studies in the literature have tried to perform risk stratification of CVD patients into high-risk and low-risk bins, as discussed in sections 1.5.1 and 1.5.2. In coronary risk assessment, earlier studies usually employed either texture features [154] or shape-based features [158] in their ML-based approaches. To obtain these features, a large dataset is important. In 2014, Araki *et al* [158] showed that the accuracy of risk stratification can be improved by fusing the shape-based features with the geometric-based coronary calcium volume features. Fusing more features can affect the risk stratification accuracy. Usually, among the pool of all features, only a set of dominant

features helps the system in stratifying the patient's risk. To overcome this limitation, Araki *et al* [155] used a PCA-based polling strategy and observed an improvement in accuracy with respect to their previous CADx system [154]. A study performed by Araki *et al* [155] proved the importance of dominant feature selection techniques. Recently, by adapting the classification paradigm of SVM, Banchhor *et al* [145] performed risk stratification on a large database (4930 US scans). The authors did prove that the fusion of texture-based and wall-based features along with the dominant feature selection using PCA-based polling strategy is highly accurate for risk stratification. This risk stratification approach using PCA-based polling strategy also showed promising results for carotid risk assessment using ML-based approaches. Saba *et al*, in their two studies [155, 157], proved that using a PCA-based polling strategy brought about an increase in the risk stratification accuracies in CVD patients.

1.6.5 Recommended interventions for CVD patients

Patients with coronary artery calcium (CAC) scores are mostly recommended to undergo a lifestyle change. The CAC score is measured using the Agatston method [59]. Recently, studies found that even in the absence of luminal narrowing [159] and in patients with low lifetime risk [160], CAC was the strongest predictor of incident CHD. Bittencourt and Riella [161] in 2016 discussed the limitation of CAC density which can be computed by dividing the Agatston CAC score by the CAC volume. The CAC density was found to be inversely associated with the incidence of cardiovascular events.

If the 10 year risk of atherosclerotic CVD is less than 20%, the patients are deferred to go for statin therapy [46]. Waheed *et al* [162] in 2016, also found that statin therapy is favourable in patients with high CAC. The study found that patients with low CAC might not benefit from statin therapy within 5 years. From a MESA study, Miedema *et al* [163] in 2014 observed that the use of aspirin had a favourable risk/benefit estimation if the patient's CAC score is greater than 100. The study concludes that patients with very low CAC score can receive harm from the use of aspirin. For heavy calcified plaque, apart from statin and aspirin therapy, rotational atherectomy also had emerged as a measure to open the narrowed arteries for increasing the blood flow. Li *et al* [164] in 2016 suggested that for a calcified plaque with severe calcified coronary lesions, rotational atherectomy (RA) using a cutting balloon is a more safe and effective measure compared to RA with a conventional plain balloon. In extreme cases, patients had to undergo interventional procedures such as shunting or stenting. Compared to coronary artery bypass grafting, coronary stenting is less expensive but in multiple diseased arteries, CABG is mostly preferred [165, 166].

Calcium measurement is not beneficial in every case. Recently, Messenger *et al* [167] showed that calcium scanning is associated with radiation equivalent to the dose of a mammogram. The study carried out by Nasir *et al* [53] and Mahabadi *et al* [54] also revealed that patients who are suffering from cardiovascular disease or who

are already taking some medical therapy and have a high calcium score receive no benefit if the calcium measurement is performed.

1.6.6 Atherosclerotic calcium in coronary and carotid imaging: ongoing challenges

The following are some of the key challenges observed during the quantification of calcium in coronary and carotid arteries. Obtaining a well-annotated dataset from various medical institutes is a challenging task, as it must pass through multiple guidelines and protocols from the institutional review board, which consumes an excessive amount of time. Calcified plaques are only produced in the atheroma region, which lies between the internal elastic lamina (IEL) interface and the external elastic lamina (EEL) interface (see figure 1.2). To prepare the ground truth, manual tracings of both the IEL and EEL borders are required. There are many crucial factors that can affect the performance of manual tracings. These factors include the operator's background and experience, image resolution, the type of hardware system specification used, the time of day, lighting conditions, operator fatigue, internet speed and the extent of changes needed during tracings [143]. Further, the video produced by an IVUS scanner consists of a very large number of frames (average of 2040 frames per video) [114], so manual tracing of all the frames is tedious and prone to error. Usually, studies validate their obtained results with histology (as a ground truth). Since histological studies are performed on human cadavers, this is a time-consuming, expensive [168] and extremely tedious process.

1.7 Conclusions

This state-of-the-art review provides an engineering perspective on calcium detection, its quantification, and morphology-based risk stratification methods in the coronary and carotid arteries. Different imaging modalities were covered, however, ultrasound was the primary focus. Thirty-four automated methods were covered and compared in the form of benchmarking tables. Speed issues were presented in the form of multiresolution paradigms. Verification and validation strategies were also presented. Finally, machine-learning-based risk stratification studies were discussed, indicating a need for a more robust multimodal approach for CAD systems. Finally, the review covered the ongoing challenges for improving collaborative efforts to undertake more meaningful basic research, leading to clinical delivery. Clearly, there is a need for multidisciplinary roles, and better and closer collaboration is needed between several departments.

Conflict of interest

None declared.

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Chapter 2

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Chapter 3

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