Cardiovascular Calcification

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Chapter 1
Plaque Collagen Synthesis and Calcification: Working Together to Protect Against Instability and Rupture

Rachel Nicoll

Introduction

Cardiovascular disease (CVD), is a leading cause of mortality and morbidity and often remains undetected until patients are hospitalised with a clinical event [1], with the Framingham risk score predicting only 60–65% of individuals at intermediate risk, the group who comprise the majority of acute coronary syndrome (ACS) patients [2, 3]. A systematic review carried out by the US Preventive Services Task Force concluded that the addition of a range of non-traditional risk factors would not improve traditional risk factor predictive ability for CVD morbidity and mortality [4], suggesting that there is still much to be learned about atherosclerosis. Arterial calcification, which has long been viewed as subclinical atherosclerosis, merely complicates the situation. While a high CT calcium score is predictive of the unstable angina and myocardial infarction (MI) of ACS, yet a calcified plaque is rarely the culprit plaque [5].

Little attempt has been made to acknowledge or resolve this paradox and knowledge gap. Moreover, numerous *in vitro* and animal studies have tried and failed to find the one unifying mechanism for the initiation and development of a pathogenic arterial calcification. Furthermore, much of the research into arterial calcification has focused on promotors and inhibitors of calcification, and while more of these are discovered with each passing year, it does not appear to lead towards an understanding of the root cause of arterial calcification or its purpose [5, 6]. This chapter puts forward the hypothesis that arterial calcification is ultimately a protective mechanism, whose development is closely bound up with collagen status.

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Arterial Calcification in Atherosclerosis

Arterial calcification is commonly seen in atherosclerosis, with coronary artery calcification (CAC) being the most studied form. It is now possible to image both macrocalcification (assessed by Agatston score) and microcalcification (assessed by uptake of 18F-sodium fluoride in PET/CT scans). Microcalcification, thought to be the initial manifestation of macrocalcification, has been detected in the earliest stages of plaque development and correlated with macrophage presence in early-stage atherosclerosis [7]. Microcalcification has been observed to form in the spaces between collagen fibres and in regions of collagen fibre degradation, with lower collagen content associated with increased microcalcification area [8–10]. Histopathology studies showed that increased microcalcification was found in culprit plaques and rupture sites in coronary and carotid arteries [11, 12] and following an MI [13, 14] and could identify culprit plaques in carotid arteries, predicting symptomatic disease [15, 16]. Nevertheless, the absence of any microcalcification has been observed with large areas of stable macrocalcification [9, 13] and increased microcalcification is frequently seen with zero CAC [13]. Although a high Agatston score predicts cardiovascular (CV) events, a heavily calcified plaque is usually stable and is rarely the culprit plaque [17, 18]; the culprit plaque in ACS is almost always a thin-capped fibroatheroma (TCFA), whose cap is not calcified [19]. Furthermore, many of the elderly have extensive macrocalcification suggesting that it may have survival value [20].

Because CV calcification is understood as sub-clinical atherosclerosis, it would therefore follow that statins would be an effective treatment [5]. However, a meta-analysis showed that CAC progression was unaffected by statins [21], while others have shown that in fact statin use independently predicted calcium progression [22], suggesting that they may cause progression [23, 24]. No pharmaceuticals have so far been shown to prevent or reduce calcification safely, although administration of vitamin K1 (phylloquinone) is protective against calcification, as well as MI, heart failure and all-cause and CV mortality [5].

Atherosclerotic plaque formation is now largely understood as a response to endothelial injury [25] and many researchers now also consider arterial calcification to be a continuation of that response [5]. It has been shown that atherosclerotic plaque will regularly form at a site of shear stress, typically a bifurcation [5], and there is growing evidence that this is also the site of maximal arterial calcification [26]. Peak shear stress was increased in non-calcified TCFAs with a larger necrotic core and also in ACS patients [27, 28] and increased with the size of the lipid pools, particularly where there is also microcalcification [28, 29]. Animal studies have confirmed that development of arterial calcification requires a pre-existing injury [30, 31], while histopathology studies have also shown that plaque CAC extent may correlate with the presence of healed plaque rupture [32], suggesting that the CAC development represents an attempt to protect the endothelium by stabilising vulnerable plaque [20]. Finite element modelling showed that microcalcification, larger

necrotic core size and a thinner fibrous cap combine to increase stress [33], promoting plaque rupture and causing cardiovascular events [34], while macrocalcification of the fibrous plaque cap reduced plaque stress [29, 35].

Summary: Macrocalcification is seen mainly in stable plaques and is thought to develop in response to endothelial injury, particularly shear stress or prior rupture. Microcalcification, the likely forerunner of macrocalcification, is seen in the early stages of plaque development and can identify high risk lesions and culprit plaques following MI. No pharmaceuticals can safely prevent or reduce arterial calcification, although vitamin K1 (phylloquinone) is protective. Statins appear to induce calcification progression.

Collagen and Its Synthesis and Degradation

Collagen is a long, fibrous protein, comprising around 30% of all the body's proteins [36]. Bundles of collagen fibres are the main structural proteins in the extracellular matrix which supports tissues and provides cells with their external structure [37]. There are several different varieties of collagen, of which type I collagen is the most common, comprising >90% of all body collagen, and is found particularly in bone and the vasculature because of its great tensile strength. Collagen is synthesised principally from the amino acids glycine (c30%) and proline (c17%), mediated by vitamin C (ascorbic acid); in the arterial wall it is the vascular smooth muscle cells (VSMCs) which principally synthesise collagen. Vitamin C deficiency results in impaired collagen synthesis and development of scurvy, while defective collagen synthesis prevents the formation of strong connective tissue [38]. Animal and *in vitro* studies have shown that arterial wall VSMCs cultured in ascorbic acid demonstrated increased proline incorporation and collagen synthesis [39]. One of the principal promotors of collagen synthesis is transforming growth factor beta (TGF-β) [40], which stimulates proline transport in VSMCs [41]. Vitamin C levels appear to be inversely associated with TGF-β [42], suggesting that where vitamin C levels are adequate for collagen production, there is less need for induction via TGF-β. In healthy arteries, collagen is synthesised in medial layer VSMCs whenever there is an inadequate amount of collagen or a weak extracellular matrix, as part of a negative feedback loop, i.e. synthesis will stop when levels are adequate.

The collagen peptide bonds can be broken by release of collagenases, leading to collagen degradation. Collagenases are a type of matrix metalloproteinase (MMP), which are proteolytic enzymes derived from macrophages and other inflammatory cells and are therefore frequently seen in atherosclerotic plaque, particularly in the foamy macrophages of the plaque shoulder but rarely in the fibrous cap [43]. In older subjects, a biomarker for collagenase independently predicted higher carotid intima-media thickness, a marker of sub-clinical atherosclerosis [44], while in mice with induced atherosclerosis, an MMP inhibitor markedly increased plaque collagen content, producing thicker collagen fibres [45]. Collagenases can also cause

VSMC apoptosis leading to reduced collagen synthesis [46]. Upregulated MMPs, collagen loss and circulating degraded collagen fragments have been observed in several disease states as well as CVD, including conditions as diverse as arthritis and tumour metastasis [8, 45]. In general, low levels of TGF-β mRNA correlated with high expression of collagenases [47]. Plaque collagen content is therefore the net result of a balance between degradation and synthesis.

Serum levels of carboxy-terminal telopeptide of type I collagen (ICTP), a marker of degraded collagen, were positively and independently correlated with the necrotic core area in patients with coronary artery disease (CAD) [48]. Patients with acute MI or unstable angina had significantly higher levels of serum ICTP compared to those with stable angina or no coronary artery disease [49] and following acute MI, ICTP was an independent predictor of all-cause mortality [50]. In postmenopausal females or carotid endarterectomy patients, higher levels of baseline ICTP predicted CV events and CV and all-cause mortality [51, 52].

Summary: Collagen is synthesised in the arterial wall by VSMCs in response to requirements, provided there are sufficient cofactors. It is degraded by collagenases, which are frequently seen in the more vulnerable areas of atherosclerotic plaque. ICTP, a marker for degraded collagen, predicts CV events and mortality.

Collagen and Endothelial Repair

Endothelial injury repair is a process that involves recruitment of mononuclear cells which trigger inflammation and enhanced uptake and oxidation of LDL, as well as extracellular matrix degradation, with the migration and proliferation of VSMCs from the medial to the intimal layer, leading to intimal thickening and atherosclerotic plaque formation [25]. Collagen is one of the principal factors involved in this healing response [53], which, together with elastin and proteoglycans, are the main fibrous structural proteins of the extracellular matrix of the arterial wall because of the tensile strength and elasticity of the tight association of collagen fibres [37, 46, 54]. Collagen is synthesised in the VSMCs immediately following arterial injury [55, 56] but if there is insufficient collagen in the vasculature to heal the injury, the migration of VSMCs provides a protective and stabilising plaque and allows further collagen synthesis [55]. No collagen was produced in the intima of arteries from healthy humans, although collagen synthesis was observed in the intima of atherosclerotic arteries [54, 57].

Risk factors for atherosclerosis, such as a pro-atherogenic diet, oxidised LDL and elevated homocysteine, are known to stimulate collagen production [58], probably through the damage they cause to the endothelial wall, while in angioplasty balloon-injured pigs on a cholesterol-rich diet, the administration of vitamins C and E markedly increased plaque collagen content and reduced vascular collagenases [59]. In patients with ischaemic heart disease, decreased collagen expression was observed in the aortic wall, as well as the coronary, indicating that collagen loss is systemic, rather than local [60].

Summary: Collagen is a key component of the healing process and is synthesised by VSMCs immediately following injury.

Collagen and Calcification in Atherosclerotic Plaque

As an atherosclerotic plaque develops, VSMCs migrate to the intimal layer from the media to form the basis of the plaque itself, while upregulated collagen synthesis enables collagen to form the plaque scaffold as a stabilising factor for plaque development, with the collagen fibres and proteoglycans providing structural integrity among the retained lipids [54, 55]. Collagen may comprise up to 60% of plaque protein [54]; the higher the proportion of collagen and the greater its cross-linking, the thicker the plaque cap and the stronger and more stable the plaque, protecting against contact between the necrotic lipid core and the circulation, thereby reducing vulnerability to rupture [46, 61].

Net collagen degradation, however, leads to plaque weakening, instability and possibility of rupture; collagen expression is significantly lower in plaque with a high content of pro-inflammatory macrophages, while a collagen-rich fibrous cap contains virtually no macrophages [25, 46, 54]. Collagen degradation is frequently seen in foamy macrophages of vulnerable plaque shoulders but rarely in the fibrous cap [43] and degraded collagen fragments have been detected at sites of plaque rupture [62]. TCFAs contained reduced collagen content, higher gene and protein expression of collagenases and increased collagenolytic activity [63]. In carotid plaque VSMCs, increase in collagenase expression was associated with decreased collagen content but the effect was up to fourfold higher in symptomatic versus asymptomatic patients; inhibition of collagenases restored collagen production and was more pronounced in symptomatic patients [64]. Differences are frequently observed between the body of the plaque and the plaque shoulder region. An animal model showed that the fibrous cap was rich in collagen and contained many VSMCs but virtually no macrophages, while the shoulder region held little collagen and few VSMCs but was filled with pro-inflammatory macrophages [54]. Plaque shoulder collagen degradation led to plaque mechanical weakening, which may mean that plaque destabilisation is determined by the balance of collagen synthesis and degradation [54].

Several factors may cause collagen breakdown or synthesis failure in atherosclerosis. There were significantly lower levels of collagen in all three arterial layers in smokers versus non-smokers [65], while in a study of aortic endothelial cells cultured in glycosylated collagen to simulate diabetes and then exposed to shear stress, no alignment of endothelial cells in the flow direction took place, whereas in those cultured in non-glycosylated collagen, the endothelial cells elongated and aligned in the flow direction [66].

Summary: High collagen synthesis in plaque leads to stability and luminal stenosis, while net collagen degradation results in unstable plaque which is more prone to rupture; CV risk factors are associated with lower collagen levels.

Pharmaceutical Influence on Plaque Collagen

Several pharmaceuticals can inhibit collagen synthesis, including calcium channel blockers and nitric oxide producers [54]. In suspected MI patients given thrombolytic agents streptokinase or tissue plasminogen activator, the breakdown of interstitial collagen was stimulated, possibly accounting for an increased re-thrombosis rate [67]. Over-expression of angiotensin II (which causes hypertension) applied to mouse carotid arteries subject to pro-atherogenic shear stress, was shown to trigger formation of vulnerable atherosclerotic lesions with a threefold decrease in collagen content; it also promoted the release of collagenases, which correlated with plaque collagen breakdown, ruptured plaque and severe intra-plaque haemorrhage [68]. A similar study showed that angiotensin II receptor upregulation reduced collagen accumulation by around 50% [69].

Other pharmaceuticals can improve collagen status. In subjects taking angiotensin converting enzyme inhibitor (ACE-I) therapy, there was a significant increase in collagen propeptide and mean collagen turnover, while atherosclerotic animals given ACE-1 therapy showed reduced risk of MI and stroke and increased extracellular matrix [70]. Furthermore, the diabetes drug rosiglitazone, a thiazolidinedione, can promote the stability of atherosclerotic plaques and reduce the lipid: collagen ratio, which correlated with reduction in plaque collagenases [71] and tamoxifen can increase collagen content, probably through upregulation of TGF-β, and suppress diet-induced lipid lesions in mice [72, 73]. Statin therapy has been shown to restore collagen production, thereby stabilising the plaque cap [74], probably through upregulation of TGF-β [75], and in endarterectomy patients given pravastatin three months prior to surgery, plasma collagen content was increased compared to a control group [76]. Pravastatin and simvastatin could also reduce net collagen degradation in hyperlipidaemic human and rabbit VSMCs, suggesting that this may be a mechanism by which statins stabilise plaque [77, 78]. As discussed above, statins also increase calcification progression, which researchers had been at a loss to explain. However, if both increased collagen and calcium progression can be viewed as beneficial, then the reason why both are associated with statin administration becomes clear.

Finally, the administration of collagen tripeptide decreased plaque area and reduced the number of macrophages [79]. It also led to a decrease in brachial artery pulse wave velocity, a marker for atherosclerosis [80], induced a significant reduction in the ratio of LDL to high-density lipoprotein (HDL) among those with a baseline elevated ratio and lowered advanced glycation end products (AGEs) [81], suggesting that sufficient collagen in the vasculature may reduce some of the known inducers of endothelial injury and atherosclerosis. Mucosal inoculation of collagen could also reduce plaque burden [82]. Since pharmacological agents that promote collagen synthesis or inhibit its breakdown may induce serious adverse effects [83], the administration of collagen peptides may be a preferred approach.

Summary: Several pharmaceuticals used in the treatment of CVD can reduce plaque collagen, while others, including collagen peptide and statins, can increase

it. The increase in both collagen and calcification may be one of the means by which statins benefit patients with atherosclerosis.

Interaction of Collagen and Calcification

Collagen has long been known to serve as a scaffold within atherosclerotic plaque, controlling size and growth, and to be a stabilising factor. 18F-NaF PET/CT scanning can now demonstrate how microcalcification development is also linked to collagen by allowing us to view microcalcification forming in the spaces between collagen fibres and in regions of collagen fibre degradation, with lower collagen content associated with increased microcalcification area [8–10], i.e. where there is abundant collagen, there is little microcalcification and vice versa. In atherosclerotic plaques, VSMCs which are deficient in collagen receptors show greater release of calcified extracellular vesicles and precipitation of minerals and collagen [10]. The microcalcification that forms within the fibrous cap tends to develop near or on the borders of the lipid pool/necrotic core [9, 23, 84].

An important study by Hutcheson *et al* showed that dense calcification was bordered by organised, mature collagen fibres, whereas microcalcifications were found in areas that were largely without mature collagen fibres [84]. Using hypercholesterolaemic mice, Hutcheson et al. went on to show that a large calcified mass will form in areas of low collagen density, while genetic inhibition of collagenases reduced the spacing between collagen fibres and the total area of calcification [84]. As an editorial by Miller pointed out, this appeared to be the first demonstration that manipulation of collagen content and density could alter the pattern of intimal plaque calcification [85]. Other researchers have shown that microcalcification areas merge following collagen degradation and will ultimately aggregate into a larger mass of macrocalcification, with the progression occurring from the outer rim of the necrotic core into the surrounding collagenous matrix [23, 86]. With further development of the plaque, the necrotic core can contain large areas of macrocalcification with microcalcification at the periphery [9].

The occurrence of stress directly adjacent to microcalcifications within the fibrous cap can induce plaque rupture [84], however, macrocalcification reduces peak circumferential stress [87]. Indeed, microcalcification is positively associated with plaque instability and rupture, while macrocalcification is positively associated with more stable plaque [84, 88]. Atherosclerotic plaque stability in fact depends on calcification density and the fibrous cap collagen content [9, 84] and plaque collagen directs the aggregation of calcifying extracellular vesicles, thus influencing calcification morphology [9]. An acute plaque rupture has been described as failure (degradation) of the collagen-rich fibrous cap [9, 84].

Summary: Microcalcification develops in spaces between collagen fibres and in regions of collagen degradation; the less collagen present, the greater the microcalcification area. Plaque stability depends upon calcification density and fibrous cap collagen content.

Discussion of the Hypothesis

It is hypothesised that both collagen and calcification serve the same purpose, to stabilise plaque following endothelial injury and protect it from rupture, and that calcification can develop where collagen synthesis is insufficient or there is excess collagen degradation.

We have already seen how collagen synthesis is key to the endothelial healing process and is indeed synthesised by VSMCs immediately following injury. A high level of collagen in atherosclerotic plaque is indicative of stability, although may cause luminal stenosis, while a high level of collagenases, leading to net collagen degradation, has been seen in vulnerable plaque or vulnerable areas of plaque. Several CV risk factors are inversely associated with collagen levels, while markers for degraded collagen can predict CV events and mortality. Microcalcification, which forms early in plaque development, is observed in rupture sites and in the culprit plaque of ACS, as well as in high risk lesions and the vulnerable plaque shoulder area; it could also predict CV mortality. Microcalcification is first found in the gaps between collagen fibres and in areas of collagen degradation and is ultimately thought to develop into the macrocalcification which is frequently found in the cap of stable plaques, typically at a site of shear stress. Statins, which protect against ACS, increase both collagen synthesis and plaque calcification, suggesting that this is an important means by which statins benefit patients with atherosclerosis.

It appears that the less collagen present, the greater the microcalcification area. This could be viewed as pathogenic, and indeed several researchers have considered it to be so [89, 90], however, that would make it a condition which is pathogenic in the early stages but becomes protective with increased quantities. Researchers once thought that the inclusion of VSMCs within plaques was also pathogenic but it is now viewed as beneficial to the development of atherosclerosis, as VSMCs also help to stabilise plaques. An alternative view is that microcalcification is the beginning of the protective macrocalcification and the pathogenicity derives not from the presence of microcalcification but from the lack of collagen, for which the microcalcification is attempting to substitute. Furthermore, if pathogenic microcalcification grows into protective macrocalcification, it would represent the first such occurrence of a small quantity of a substance being harmful while a large quantity is not; this defies the laws of toxicology. The hypothesis could also provide an explanation for why some stable angina is uncalcified [91] (because there is sufficient collagen to stabilise the plaque) and why a low Agatston score can predict increased CVD risk [92] (because the protective calcification process is only just beginning).

So if this hypothesis is correct, it suggests that in the presence of atherosclerosis risk factors and shear stress, collagen synthesis should be encouraged, firstly to bolster the integrity of the arterial wall and, if this fails, then to ensure an adequate amount of collagen synthesis and minimal degradation in order to provide a stable scaffold for the plaque. Administration of collagen tripeptide has demonstrated its ability to reduce plaque area and number of macrophages and has even been able to

lower certain risk factors. In addition, statins have demonstrated their ability to increase both collagen synthesis and arterial calcification progression, both highly protective measures. Several papers have now demonstrated the ability of vitamin K to decrease arterial calcification [5]. This does not negate the hypothesis but rather supports it, since administration of vitamin K can prevent collagen breakdown [93], confirming that where there is adequate collagen, calcification is no longer required. The US Preventive Services Task Force systematic review, which concluded that non-traditional risk factors would not improve traditional risk factors in the prediction of CVD morbidity and mortality [4], did not investigate either collagen breakdown or vitamin K deficiency.

Conclusion

Evidence has been provided to support the hypothesis that both collagen and calcification serve the same purpose, namely to stabilise atherosclerotic plaque following endothelial injury and to protect it from rupture. Collagen synthesis is the initial response to injury but if this proves insufficient, or there is net collagen degradation, then plaque calcification can develop to aid plaque stabilisation. This hypothesis also provides an answer to why statins increase calcification progression (because it increases plaque stability), a finding which had remained unexplored. To prove the hypothesis, clinical trials should be carried out administering statins in atherosclerosis patients, with and without collagen tripeptide, to determine whether there is additional decreased risk.

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Chapter 2
Cardiovascular Calcification and Carotid Intima-media Thickness in Atherosclerosis

Pompilio Faggiano and Eugenio Picano

Introduction: The Timeline of Atherosclerosis

Atherosclerosis is a big killer, top-ranked among non-communicable diseases and a major contributor to mortality and morbidity worldwide. Many accurate noninvasive functional tests have been developed for diagnosis, functional characterization and outcome prediction in these patients. However, these tests address advanced stage of the atherosclerotic disease in the specific coronary artery district and cannot detect preclinical, pre-intrusive and pre-hemodynamic stages of the atherosclerotic disease (Fig. 2.1). On the other side, prevention of cardiovascular disease is less costly than treating complications. Identification of disease in the asymptomatic stage has emerged as a public health and economic imperative.

Several risk scores have been proposed to classify asymptomatic subjects in high-, intermediate- and low-risk for subsequent cardiovascular events but none of them is fully adequate [1]. These risk scores are usually based on algorithms derived from longitudinal cohort studies confirming the association between traditional risk factors and atherosclerotic fatal and non-fatal events. However, it is widely recognized that most cardiovascular events occur in segments of population at low or intermediate risk, which represent approximately 80% of people living in western world. In a population with subclinical atherosclerosis in all 3 vascular beds (coronary, aortic, carotid), 35% had a low risk, 41% had an intermediate risk and only 23% had a high risk Framingham Risk score [1]. Laboratory and imaging

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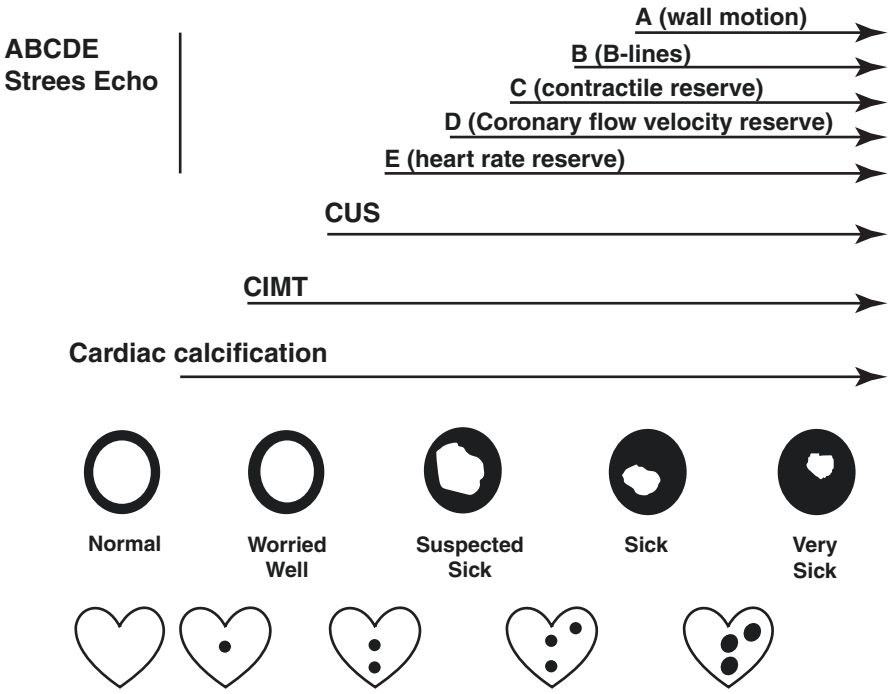

Fig. 2.1 The timeline of atherosclerosis. Cardiac calcification, carotid intima-media thickening and sub-hemodynamic plaque occur early in the natural history of atherosclerosis, well before the positivity during functional stress testing that assesses different pathophysiological targets with ABCDE protocol. Of these targets, regional wall motion abnormalities are the latest and probably the least important in predicting outcome in contemporary patients

biomarkers may be used to achieve a more efficient risk stratification allowing to titrate targeted and personalized preventive and therapeutic measures. To treat an asymptomatic subject at low risk with an aggressive diagnostic and therapeutic approach has a cost and an unwarranted risk, but to miss appropriate interventions in a patient at truly high risk means to omit potentially life-saving measures at a reasonable cost. This is especially true now, at a time when the impending economic crisis is further emphasizing the need to reduce useless health care expenditures. Both physicians and patients have become increasingly aware of the long-term risks of cardiac imaging due to the use of ionizing radiation and contrast agents such as iodine or gadolinium contrast. These toxic effects have to be considered in any diagnostic strategy based on imaging, since we are dealing with a low risk population and both ionizing radiation and contrast effects are cumulative. Screening with imaging for atherosclerosis is not a single snapshot assessment, but the patient has to be taken by hand and repeat the examination serially over time to assess natural history, evaluate the effect of therapeutic measures, and several times in the follow-up time during a lifetime. Any exam adds dose to dose and risk to risk.

For all these reasons, echocardiography remains the cornerstone of medical imaging for screening of atherosclerosis for its undisputed advantages of widespread diffusion, portability, versatility, and safety, with no need of iodine and gadolinium-based contrast agents [2, 3]. Echocardiography also has key advantages for economic and environmental sustainability, with lack of ionizing radiation significantly reducing the downstream cancer risk induction [4] and a low environmental footprint, estimated to be 100-times less than a cardiac magnetic resonance [5]. For screening atherosclerosis in its subclinical stage, the three major targets are cardiac calcification with transthoracic echocardiography (TTE), vascular pre-intrusive atherosclerosis with assessment of carotid intima-media thickness CIMT) and pre-hemodynamic disease (with carotid ultrasound, CUS, visualizing subcritical plaques unable to induce hemodynamic changes detectable by Doppler). Conceptually, they describe atherosclerosis decades before functional testing even when performed with the state-of-art ABCDE protocol [6, 7]. The A step is based on time-honored regional wall motion abnormalities which are the oldest, the most used and evidence-based but also probably the latest and least important of stress echo parameters in contemporary populations [8]. For risk stratification, wall motion is outperformed by step D (Doppler based assessment of coronary flow velocity reserve of left anterior descending coronary artery) [9], step C (contractile reserve estimated through changes in systolic blood pressure and end-systolic volumes) [10], Step B (pulmonary congestion by B-lines with lung ultrasound) [11] and step E (non-imaging, EKG-based assessment of heart rate reserve, an index of cardiac sympathetic reserve) [12]. The integration of stress echo with cardiac TTE and CUS allows to describe the full spectrum of atherosclerosis at all ages of life in each and every patient (Fig. 2.1).

Biomarkers of Atherosclerosis

Cardiac calcification, carotid intima-media thickness and hemodynamically subcritical carotid plaque are biomarkers of atherosclerosis. In 2001, a working group of the National Institutes of Health standardized the definition of a biomarker as a "characteristic that is objectively measured and established as an indicator of normal biological pathologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [13]. A biomarker may be measured on a biosample (such as a blood test, for instance, the C reactive protein as a biomarker of vulnerable plaque or D-dimer of vulnerable blood) or it may be an imaging test (for instance, echocardiogram for vulnerable myocardium). A simplistic way to think of biomarkers is as indicators of a disease trait (risk factor or risk marker), a disease state (preclinical or clinical), or a disease rate (progression). Biomarkers may also serve as surrogate end points. Although there is limited consensus on this issue, a surrogate end point is one that can be used as an outcome in clinical trials to evaluate the safety and effectiveness of therapies in lieu of measurements of true

Table 2.1 Ultrasound biomarkers for identifying the vulnerable patient (adapted and modified from [15])

	Methodology standardized	Methodology available/ convenient	Linked to disease progression	Additive to FHS risk score	Tracks with disease treatments
Arterial vulnerability					
• Structural markers (carotid IMT, plaque)	++	+	++	+	+
Myocardial vulnerability					
• Structural markers (cardiac calcification)	++	+	++	+	++
• Functional markers (ABCDE stress echo)	++	++	++	++	++

++ Good evidence, + some evidence, ? unknown or ambiguous data
IMT intima-media thickness, *FHS* Framingham heart study

outcome of interest. Surrogate end points (for instance, carotid intima-media thickness in hypertensives in lieu of major cardiovascular events) have the advantage that they may be gathered in a shorter time frame and with less expense than end points such as morbidity and mortality, which require large clinical trials for evaluation. A biomarker will be of clinical value only if it is accurate, it is reproducibly obtained in a standardized fashion, it is acceptable to the patient, it is easy to interpret by the clinician, it has high sensitivity and specificity for the outcome it is expected to identify, and it explains a reasonable proportion of the outcome independent of established predictors (in case of atherosclerosis, Framingham Heart Study risk score) [14]. As biomarkers of atherosclerosis, cardiac calcification, intima-media thickness and subcritical carotid plaque meet most of these criteria [15] (Table 2.1), although scoring system for cardiac calcification is not yet optimally standardized [16], methodology must be operator-independent for IMT, and plaque assessment will greatly benefit from neural network analysis and artificial intelligence-based plaque classification.

Cardiac Calcification

Coronary and cardiac calcification are not a passive, degenerative, age-related process but an active, inflammatory, disease-specific event that can be slowed, but not reversed, by appropriate treatment of risk factors [17].

It consists of an initiation phase and a propagation phase. In the initiation phase dominated by injury and inflammation the main site of damage is the endothelium or endocardium which develops an atheroma-like lesion with oxidized LDL and inflammatory cells, triggered by reduction of shear stress in valve leaflets leading to increased production of adhesion molecules such as VCAM and ICAM, reproducing at the valvular level the initiating events of atheroma formation in the blood vessel.

The subsequent propagation phase extends to the fibrosa layer and is dominated by tissue necrosis, apoptosis and calcification driven by pro-apoptotic and pro-calcific factors released by immune cells (such as macrophages and T cells) infiltrating the endocardium, fragmenting the elastic lamina and invading the fibrosa layer. In presence of an increased local concentration of pro-inflammatory cytokines and angiotensin 1, osteoblast-like cells and valvular interstitial cells develop an osteogenic phenotype, laying down a collagen matrix where apoptotic bodies are embedded facilitating the formation of needle-like crystals of hydroxyapatite. In the advanced propagation phase, calcification begets valve damage through increased mechanical stress and endocardial injury, and more valve damage begets more apoptosis and osteogenic differentiation in a self-perpetuating vicious cycle [17].

The main purpose of calcium screening is not to identify patients with obstructive coronary artery disease but to detect vessel wall atherosclerosis at a pre-obstructive stage. This information is usually obtained with the Agatston coronary calcification score with coronary computed tomography angiography, which is the most commonly used technique for detection of subclinical disease, prognostic stratification of asymptomatic individuals and implementation of preventive strategies [18, 19]. However, it use is restricted by cost, limited availability and radiation exposure. A convenient radiation-free proxy of coronary calcification can be obtained with cardiac calcification by resting TTE (Fig. 2.2). A semi-quantitative cardiac calcium score index can be derived from the assessment of calcification/fibrosis in mitral annulus [20], aortic root wall and aortic valve leaflets [21–23]. Each of these three parameters is associated to the extent of underlying coronary artery disease and cardiovascular mortality and morbidity. Their prevalence varies with increasing age and coronary risk, and is higher in diabetes mellitus and chronic kidney disease. The average prevalence in a middle-aged population is around 15%, slightly higher for aortic valve and slightly lower for mitral annulus calcification [17].

Aortic valve sclerosis is defined as focal areas of increased echogenicity and thickening of the aortic valve leaflets in the absence of aortic stenosis (velocity across the valve <2.5 m/s). Each aortic leaflet is usually scored from 0 (normal) to 3 (severely abnormal) as follows: 0 (normal thickness <2 mm and normal reflectivity); 1 (mildly abnormal: thickness >2 mm and/or increased reflectivity indicative of fibrosis); 2 (moderately abnormal: thickness >4 mm and/or diffuse or focal hyperreflectivity); 3 (severely abnormal: thickness >6 mm and/or marked reflectivity

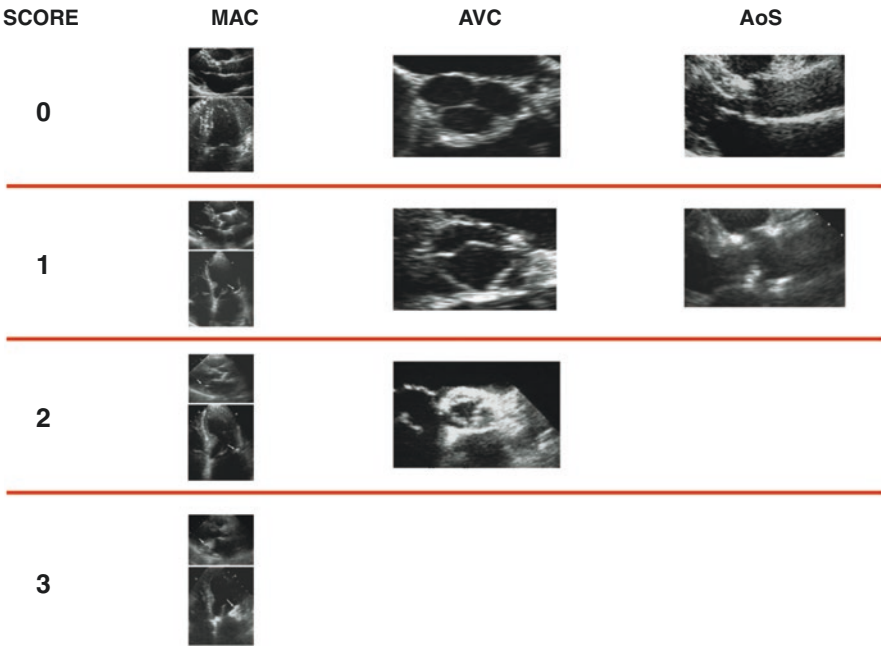

Fig. 2.2 A simple assessment of cardiac calcification through scoring of mitral annulus (left panel, from 0 = no calcium, to 3 = extensive calcification), aortic root (right panel, from 0 = absent, to 1 =, present) and aortic valve leaflets (from 0 = no calcium, to 3 = calcification of all three leaflets) calcification. Modified from Corciu et al. [24]

indicative of calcification). The highest score for a given cusp is assigned as the overall degree of aortic valve sclerosis [24, 25].

Mitral annulus calcification is defined as an intense and bright echo-producing structure located at the junction of the atrio-ventricular groove and posterior mitral valve leaflet, and is measured from the leading anterior to the trailing posterior edge. It is scored from 0 (normal) to 3 (severely abnormal) as follows: 0 (normal reflectivity); 1 (mildly abnormal: calcification thickness <5 mm); 2 (thickness 5–10 mm); 3 (severely abnormal: thickness >10 mm).

Ascending aorta calcium is defined as a focal or diffuse area of increased echo-reflectivity and thickening of the aortic root on the parasternal long-axis view. It is scored from 0 (normal, calcium absent) to 1 (abnormal, calcium present).

The cardiovascular ultrasound approach to calcification can be combined in a comprehensive cardiac calcification score index ranging from 0 (no detectable calcium) to higher values indicating severe and diffuse calcium deposits) [24, 25]. This method is appealingly simple but has some limitations. First, it is essentially qualitative since the cardiac calcification is generally defined as a nodular brightness of variable size exceeding that of normal surrounding tissue. The technique will

become more robust when the diagnosis will be based on operator-independent measurement of radiofrequency-based backscatter analysis or artificial intelligence based neural network analysis [26]. Second, as it stands the ultrasound approach does not allow a distinction between dense fibrosis and mild calcification. However, if we consider that sclerosis precedes and predicts calcification this is not necessary a drawback, since it allows to have insight into fibrosis, which is an earlier marker and an intermediate step of the calcification process. Third, the prognostic power of cardiac calcification in primary prevention is lost in patients with atrial fibrillation [27].

There is no consensus on details of scoring, with possibility to include papillary muscle calcification or assigning an individual score to each aortic cusp, and therefore the most severe score may vary to a maximum of 8 or 12. This index correlates nicely with coronary calcification evaluated with Agatston score (Fig. 2.3), allows a refined risk stratification compared to clinical Framingham score, and provides independent and incremental prognostic information compared to stress echo [28]. It allows therefore not only an early assessment of the atherosclerotic process, but also a dimension on derangement of calcium-phosphate metabolism which triggers inflammation and begets more calcification in a metabolic vicious circle [29]. Inappropriate or excessive calcification is important to identify patient vulnerability (more than plaque vulnerability) missed by the epicardial stenosis severity. The degree of coronary calcification is an excellent marker for atherosclerotic plaque burden, but it correlates poorly with luminal narrowing and does not affect the biomechanical stability of the plaque [30]. In other words, it is the inappropriate

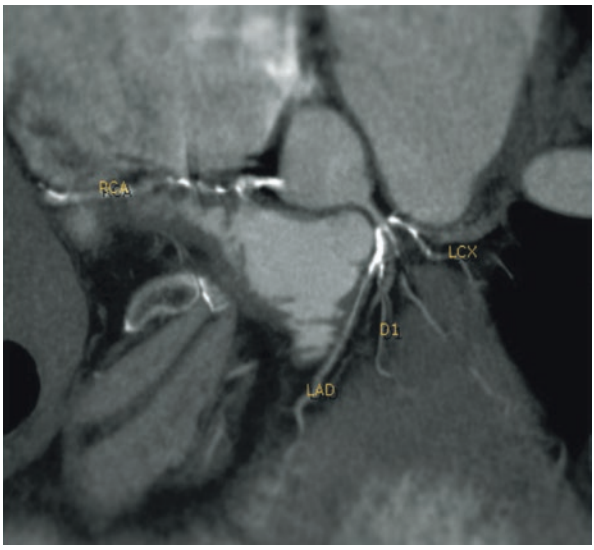

Fig. 2.3 Coronary artery calcification by coronary computed tomography. Calcification is detectable in proximal left anterior descending (LAD) and first diagonal (D1), proximal left circumflex (LCx) and diffusely in the right coronary artery (RCA)

calcification that counts, not where we detect it, and cardiac calcification detected by TTE may be equally effective that coronary calcification (detectable by coronary computed tomography angiography and in the blind zone of TTE) [17].

Carotid Intima-media Thickening (CIMT)

Pre-obstructive atherosclerosis is obtained with CIMT assessment, which if increased predicts subsequent events in asymptomatic subjects [31]. Albeit conceptually different and performed in different operational theaters by different subspecialists (Table 2.2), both cardiac calcification and CIMT precede and predict clinical manifestations of atherosclerotic disease [32, 33]. However, 80 to 90% of subjects with cardiac calcification or increased CIMT will never develop clinical disease in the subsequent decade, and 10 to 20% without calcification and with normal CIMT will develop the disease [33].

CIMT is defined as a double-line pattern visualized by echo 2D on both walls of the common carotid artery in a longitudinal view. Two parallel lines are used to measure it, and consist of leading edges of lumen-intima and media-adventitia interfaces.

The required equipment is a high resolution 2D system with >7 MHz transducer, with measurement performed in triplicate on the far wall of the common carotid artery on a 10 mm in length straight arterial segment, with inclusion of carotid bifurcation in the image plane serving as a landmark to provide accurate serial measurements [34]. CIMT measurements should be taken at a distance of at least 5 mm below the distal end of common carotid artery with an automatic or semi-automatic border detection program, either online or offline, at end-diastole (R wave). Mean values of right and left carotid arteries are combined and averaged to have a more reproducible measure. A CIMT value >0.9 mm is considered a marker of asymptomatic damage, but values are age-dependent (higher in elderly) and sex-dependent (lower in females) and the risk is importantly increased in patients falling in the highest quintile (>1.4) [34]. An increase of CIMT is already detectable at a pediatric age in the offspring of patients with premature myocardial infarction [35].

Table 2.2 Assessment of inappropriate cardiovascular calcification and pre-obstructive atherosclerosis

	Echocardiography	Carotid scan
Key variable Clinical measurement	Cardiac calcification Eyeballing	Intima-media Thickness Automatic border detection
Measured parameter	Calcium score index	IMT (mm)
Normal values	0	<0.10
Mildly abnormal values	1 to 3	10–11
Abnormal values Severely abnormal values	4 to 6 ≥ 7 (up to 10)	12–13 ≥14
Prognostic value	Additional to FRS	Additional to FRS

Carotid Pre-hemodynamic Plaque

Vascular Duplex scan of the carotid artery identification of the vulnerable plaque. This vulnerability can also occur at a pre-hemodynamic stage, when the stenosis is subcritical and unable to provoke any change in Doppler profile which remains normal until stenosis exceeds 50% of diameter reduction. Yet, as it is the case for coronary plaques, subcritical carotid plaques and calcification has a powerful capability for risk stratification and the shape and morphology of the structure is even more important than its severity. Carotid artery plaque further adds to CIMT for the cardiovascular risk assessment, and is a more powerful predictor than CIMT. It is defined as a focal structure that encroaches into arterial lumen of at least 0.5 mm or 50% of the surrounding CIMT value or demonstrates a thickness >1.5 mm [36]. Quantitative measures of plaques such as plaque number, plaque thickness, plaque area, and 3-dimensional assessment of plaque volume are more sensitive than plaque presence in refining risk. Limited but encouraging data are present suggesting that plaque features such as composition, irregularity and vascularity are even more important than plaque presence and severity in determining outcome [36].

Vulnerable plaques are prone to rupture, and their rupture can trigger unfavorable pathology events such as distal embolism, thrombosis and plaque progression mirrored in clinical events such as (in coronary arteries) unstable angina, myocardial infarction and death and (in carotid arteries) transient ischemic attacks and stroke [37]. At histology, the vulnerable plaques are rich in lipids and hemorrhages, poor in fibrosis and with thin fibrotic cap, show only spotty calcification and possibly irregular plaque surface border and neovascularization [38]. These histologic features leave ultrasound fingerprints clearly identifiable in vitro with different parameters such as acoustic attenuation, backscatter, angle dependence, frequency distribution and spatial texture distribution [39–43] and can be recognized by in vivo imaging systems by simple visual [44], more objective video-densitometry [44–45] (Fig. 2.4), and quantitative backscatter analysis [45–47], both noninvasively with Duplex scan of the carotid with 2D images also amenable to artificial-intelligence based neural network analysis [48] and invasively with virtual histology and radiofrequency-based intracoronary ultrasound [49, 50]. Whatever the approach (transcutaneous, transesophageal or intravascular), wherever the district (carotid, aorta or coronary arteries), and whichever the image analysis (visual, video-densitometric, neural.network analysis or radiofrequency backscatter signal) the ultrasound appearance of the vulnerable plaque can be distinguished from the low-risk stable plaque and identifies a group at higher risk of subsequent cardiovascular events [51–55].

The carotid unstable plaque is associated with a systemic (not only local) plaque instability, present in different districts (coronary and carotid) and on different sides (both ipsilateral and contralateral to symptomatic side) and is associated with unfavorable events in the follow-up [56]. Hypoechoic or dishomogeneous plaques, with spotty micro-calcification and large plaque burden [57, 58], with plaque neovascularization by contrast-enhanced ultrasound [59] and surface irregularities by fractal analysis, are more prone to clinical complications than hyperechoic, extensively

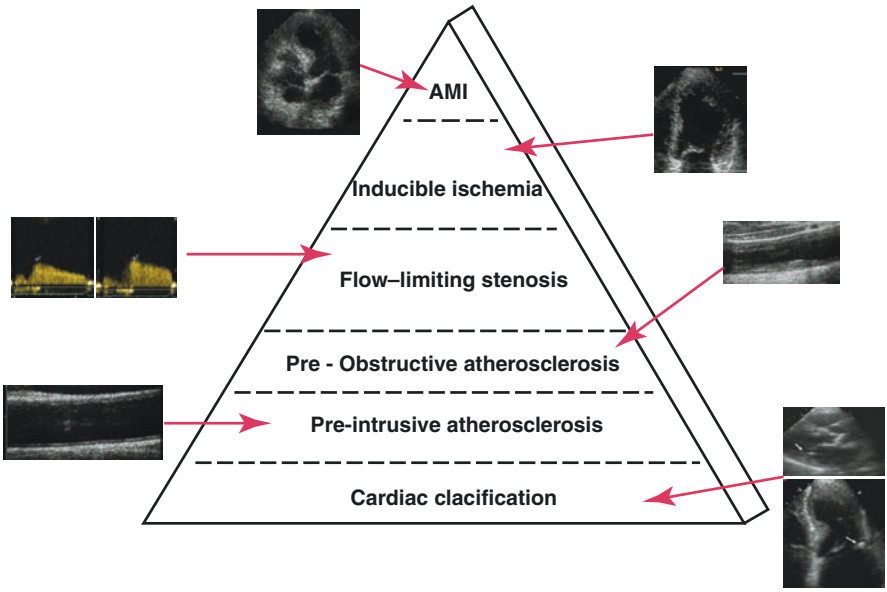

Fig. 2.4 A visual and videodensitometric assessment of carotid plaque morphology. Unstable, soft, lipid-rich plaques are less echogenic and more dishomogeneous than stable, fibrotic plaques. These texture features can also be more objectively described with simple textural analysis with quantitative descriptors of plaque echogenicity such as median gray level or plaque texture such as entropy (lower panels). Stable plaques show higher median gray levels and lower entropy values, related to the spatial disorder of the image. Modified from Mazzone et al. [45]

Table 2.3 Ultrasound texture and morphology as a predictor of plaque instability

	Low-risk	High-risk
Plaque border profile Echo density	Smooth Iso, Hyperechoic	Irregular Hypo-, anechoic
Plaque luminal border[a]	Regular	Irregular
Plaque neovascularization[a]	Absent	Present
Spotty microcalcification	Rare	Frequent

[a]By contrast-enhanced ultrasound

calcified, homogeneous plaques with limited plaque burden, smooth surface and absence of neo-vascularization (Table 2.3). Plaque ultrasound morphology is important, together with plaque geometry, in determining the atherosclerotic prognostic burden in the individual patient. A complex-type plaque coronary morphology at carotid or coronary ultrasound—for any given coronary stenosis—makes the myocardium more susceptible to induced ischemia during SE. With this integrated approach, SE, baseline resting echocardiography for cardiac calcification and carotid scan for intima-media thickness and carotid stenosis [60] can team up with invasive studies for comprehensive risk stratification of most variables, including those in the blind spot of functional imaging and SE [61].

Different Targets for Different Tools

Cardiac calcification, carotid intima-media thickness and carotid plaque describe different time points of the same atherosclerosis phenomenon, and also evaluate partially different aspects of the same disease. In fact, not all patients with stress-induced ischemia have carotid dìsease, and not all patients with cardiac or cardiac calcification will progress to hemodynamically and clinically significant disease. On the other side, atherosclerosis is a multifactorial phenomenon, and different windows of vulnerability may underlie the same clinical phenotype. Calcification is a systemic metabolic disorder; intima-media thickness is due to smooth muscle cell proliferation; a vulnerable plaque is more a disease of inflammatory cells and lipid metabolism. The three parameters show partially independent prognostic value in predicting events and this once again indicates that our monolithic view of ischemia must be restructured and re-built to provide a more integrated assessment of the complex pathophysiology of atherosclerosis. The possibility to improve risk stratification and re-classify the global cardiovascular risk of asymptomatic subjects by addition of noninvasive imaging of subclinical atherosclerosis to traditional risk scores such as Framingham risk score or European score allows to optimize the number of statin-eligible subjects and, in particular, to improve statin allocation [62]. Again, the opportunity to show in asymptomatic subjects the objective evidence of preclinical atherosclerosis (carotid plaque) may allow to improve cardiovascular prevention strategies [63].

Clinical Guidelines

Owing to the importance of asymptomatic organ damage as an intermediate stage in the continuum of vascular disease (Fig. 2.5), and as a determinant of overall cardiovascular risk, signs of organ involvement should be sought carefully by appropriate techniques if indicated, for instance in hypertensive patients.

In this setting, measurement of carotid intima-media thickness is reasonable for detecting hypertensive or diabetic patients at high cardiovascular risk [64].

Recent ESC guidelines 2019 do not mention cardiac calcification by echocardiography for lack of evidence and only mention coronary artery calcium by computed tomography which “may be considered as a risk modifier in the cardiovascular assessment of asymptomatic patients with diabetes mellitus at moderate risk” (class of evidence IIb, level of evidence B). On the contrary, CIMT has not shown incremental value over the coronary artery calcium score to predict coronary artery disease or cardiovascular events. In contrast, detection of carotid plaque has shown incremental value over CIMT to detect coronary artery disease in asymptomatic diabetes mellitus (Table 2.4). Additionally, echolucent plaque and plaque thickness are independent predictors of cardiovascular events (coronary artery disease, ischemic stroke, and peripheral artery disease).

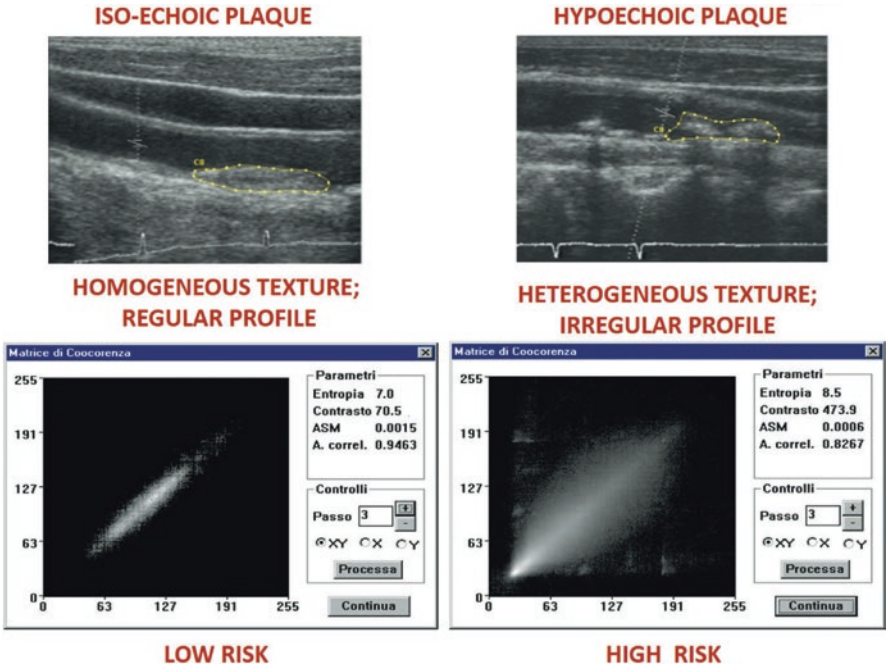

Fig. 2.5 The pyramid of atherosclerosis. The ultrasound imaging tools devoted to each of the segments of the disease: from the asymptomatic, clinically silent large base of the pyramid (cardiac calcification and CIMT by ultrasound) to the clinically obvious tip of the pyramid, represented by the baseline regional left ventricular dysfunction. *AMI* acute myocardial infarction

Table 2.4 Guidelines recommendations on use of cardiovascular ultrasound for screening purposes

Test	COE	LOE	Source
CAC by CT may be useful in asymptomatic DM at moderate risk	IIb	B	ESC 2019 (Cosentino et al.)
CIMT screening is not recommended	III	AQ	ESC 2019 (Cosentino et al.)
Detection of atherosclerotic plaque of carotid or femoral arteries may be considered as a risk modifier in pts. with DM at moderate-high CV risk	IIb	B	ESC 2019 (Cosentino et al.)

CAC coronary artery calcium, *COE* class of evidence, *DM* diabetes mellitus, *LOE* level of evidence. Source: European Society Cardiology 2020 guidelines [64]

Gaps of evidences are important, and there is need of studies using imaging techniques (including tissue characterization of atherosclerotic plaque) in prospective cohorts. Calcium, intima-media thickness and sub-hemodynamic plaque presence and structure can be combined to address noninvasively 3 key features of incipient atherosclerosclerosis: calcium, wall thickening and plaque vulnerability.

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Chapter 3
Heart Valve Calcification

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Left heart valve calcification is the commonest form of valve disease in the West. Valve calcification varies in its severity from mild spotty calcification to severe calcification, particularly in the aortic valve which results in severe valve stenosis and the need for valve replacement in order to protect the overall cardiac function.

Valve Calcification and Atherosclerosis Risk Factors

Valve sclerosis is an age-related phenomenon, particularly in men and those carrying risk factors for atherosclerosis [1–3]. While mild sclerosis has no implication on valve function, the development of progressive leaflet calcification may eventually cause valve dysfunction, stenosis or regurgitation, which when severe requires valve replacement. Aortic stenosis is the commonest pathology, affecting an average age of patients undergoing aortic valve replacement of 65–85 years [4]. This relationship however, is not mutually exclusive, since most people around the same age and even older, may present with either only mildly sclerosed aortic valve or a completely normal healthy valve, for age [5]. Also, evidence exists regarding a modest relationship between valve calcification (VC), particularly aortic valve in athletes, irrespective of development of aortic stenosis. The likely explanation of this phenomenon is the leaflet inflammation resulting from strenuous valve opening and closing with high sheer stress because of the raised aortic pressure during exercise.

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Valve calcification has also been shown to be related to other important atherosclerosis risk factors. Hypertension is a well-known associate with mitral annular calcification, irrespective of its impact on valve function, stenosis or regurgitation [6]. As for the aortic valve calcification, systemic hypertension is commonly seen in many patients with VC although it is not a predictor of valve dysfunction [7, 8]. Dyslipidemia is another important atherosclerosis risk factor which has been intensively investigated for its predisposition to aortic calcification and valve stenosis. Based on the scientific evidence that calcification is a manifestation of healed atherosclerosis, trials tested the potential improvement of aortic stenosis severity parallel to the fall in LDL-Cholesterol with statins [9–12]. Although early observational studies suggested a beneficial effect of statins on aortic stenosis severity [9, 10], randomized clinical trials [11, 12] and recently a meta-analysis [13] refuted such idea, having shown a clear dissociation between the rate and extent of fall of LDL-Cholesterol with statins and progressive worsening of aortic valve stenosis over time. In contrast, it has been hypothesized that statins may favour calcification in the aortic valve as they do on coronary plaques, with different hemodynamic effects, progression of aortic valve stenosis in the former and plaque stabilization in the latter. Diabetes is a third risk factor for atherosclerosis and has been highlighted as a potential risk for coronary calcification but its direct relationship with VC has not been established. The evidence behind any close relationship of the rest of the atherosclerosis risk factors and calcification including smoking and obesity remains weak.

Assessment of Valve Calcification

Recognition of even small calcium deposits on valves and other cardiac structures is clinically important. Incidental findings of calcified cardiac valves or aortic wall, seen on chest X-ray or CT, should alert physicians to the presence of atherosclerotic disease. The extent of valve calcification on CT can be expressed quantitatively by applying the well-established Agatston score, conventionally used for assessing coronary artery calcification (CAC) [14]. However, its use for routine follow up of patients is limited because of the associated radiation exposure [15]. Echocardiography, the most patient friendly cardiac investigation represents a more suitable approach for detecting VC, being noninvasive and more economical. It should be mentioned that the echocardiographic approach to VC has been only semiquantitative; by summing the number of calcified sites and the estimated size of each calcification it is possible to estimate the overall extent of calcification [16, 17]. Despite being semiquantitative in nature and having good relationship with CT, studies have shown a good inter- and intra-observer concordance in the evaluation of VC [18, 19]. Echocardiography based VC is generally defined as a nodular brightness (of variable size) or diffuse brightness exceeding that of normal valve tissue, thus the conventionally estimated VC scores usually include some sclerotic lesions. Nevertheless, since sclerosis is considered a precursor of calcification and

sclerotic nodules often contain areas of focal calcification, this should not, by any means, devalue the ultrasound method of estimating severity of VC. In searching for VC, tissue harmonic imaging should be used carefully since it gives better visualization of valves, but could be on the expense of making them appear thicker or even give a false appearance of sclerosis [20]. Despite these limitations there is a robust evidence that assessment of VC during routine echocardiography can be reproducible, safe and reasonably accurate.

Grading Valve Calcifications

Currently, there is no validated method using ultrasound to quantitatively assess the extent of VC, i.e. a calcium score similar to Agatston coronary calcium score obtained on CT. Some studies have simply marked the presence or absence of mitral annular calcification (MAC) and aortic valve calcification (AVC). Others assessed the presence of calcification in different areas and factored in the size of calcium deposits. Similar to the Agatston score for CAC, in which greater amounts of calcium deposition predict worse outcome, it is probable that an echocardiographic cardiac calcification score can predict events in a graded fashion. Proposed scores have generally examined the number and extent of calcifications in 4 sites: aortic valve, mitral annulus, ascending aorta, and papillary muscle [17, 21, 22]. The higher the score, the greater the overall burden of calcification. Using an echocardiographic approach which comprehensively assesses calcification of aortic and mitral valves, papillary muscle, and ascending aorta, could predict (1) coronary and total cardiac calcium burden assessed by CT; (2) the presence of coronary artery disease by angiography [22, 23] and (3) cardiovascular outcome [24–26].

Coronary Artery Calcification and Severity of Valve Calcification

Observations have reported a potential relationship between coronary artery and VC, hence a number of studies assessed the prevalence of coronary artery calcification in symptomatic individuals with CT evidence for left heart valve calcification, AVC, MAC or both. The most recent CT study of 282 consecutive patients with calcification in either the aortic valve or mitral annulus, calcium scoring of the coronary artery, aortic and mitral valve was measured using the Agatston score [27]. AVC was more prevalent than MAC (64% vs. 2.5%, $p < 0.001$), with 34% having both. Absence of CAC was noted in 12.7% of the study population. The combination of AVC and CAC was observed in 53.5%, MAC and CAC in 2.1%, and combined AVC, MAC and CAC in 31.6%. The median CAC score was higher in individuals with combined AVC and MAC, followed by those with AVC and the

lowest was in the MAC group. The same pattern was more evident in individuals with combined AVC and MAC, where 70% had CAC score > 400 and only 6% had CAC score of zero. These results were irrespective of gender. There was no relationship between AVC and MAC but only a modest correlation between CAC and AVC score ($r = 0.28$, $p = 0.0001$), MAC ($r = 0.36$, $p = 0.0001$) and with combined AVC and MAC ($r = 0.5$, $p = 0.0001$). This study concluded that AVC score of 262 had a sensitivity of 78% and specificity of 92% for the prediction of presence of CAC. Accordingly, AVC or MVC on transthoracic echo is predictive of coronary artery disease on CT.

The relationship between Aortic valve calcification and CAC was further investigated in great detail with an objective of identifying possible degrees of valve and root calcification in patients with aortic stenosis. A two-centre study from Scandinavia [28] sought to investigate the hypothesis that CAC is likely to correlate with aortic root calcification (ARC), based on shared process of atherosclerosis and tissue similarity, more than its relationship with valve calcification, as shown above. In a sample volume of 211 consecutive patients (age 72.5 ± 7.9 years, 91 females) with aortic stenosis requiring aortic valve replacement in the two Heart Centres, CAC, AVC and ARC were studied using conventional multidetector cardiac CT pre-operatively and calcification was quantified using the Agatston scoring method. CAC was present in 92%, AVC in 100% and ARC in 82% of patients. CAC correlated with ARC ($rho = 0.51$, $p < 0.001$) but not with AVC. The number of calcified coronary arteries correlated with ARC ($rho = 0.45$, $p < 0.001$) but not with AVC. 29/152 patients had echocardiographic evidence of bicuspid aortic valve morphology and 123 trileaflet aortic valve, who were older ($p < 0.001$) but CAC was associated with trileaflet valve disease even after adjusting for age ($p = 0.01$). AVC score was modestly associated with BAV after adjusting for age ($p = 0.03$) but ARC was not. Of the total cohort, 82 patients (39%) had significant (>50%) coronary stenosis, but these were not different in the pattern of calcification from those without coronary stenosis. CAC was consistently higher in patients with risk factors for atherosclerosis compared to those without. These observations confirmed the study hypothesis that coronary artery calcification correlates with aortic root calcification, being a branch and tree related pathology, rather than aortic valve calcification.

Valve Calcification and Statins Treatment of Dyslipidemia

Observation studies reported a potential cessation of the severity of aortic stenosis in patients receiving statins for lowering LDL-Cholesterol. Based on that, some clinical randomised trials were launched but results proved controversial. A meta-analysis of 14 studies (5 randomised trials and 9 observation studies) investigated such relationship [13]. In the 14 studies as a whole, no significant differences were found in all-cause mortality ($OR = 0.98$, $p = 0.91$), cardiovascular mortality

(OR = 0.80, P = 0.23) or the need for valve replacement (OR = 0.93, p = 0.45) between the statins and the control groups. LDL-cholesterol decreased in the statins groups in both <24 months and ≥24 months follow-up ($p < 0.001$ for both) but not in controls ($p = 0.35$ and $p = 0.33$, respectively). In the <24 months statins group, the annual increase in peak aortic velocity and peak gradient was less ($p < 0.0001$ and $p = 0.004$, respectively), but the mean gradient, valve area and calcification score were not different from controls. In the ≥24 months statins group, none of the above parameters was different from controls. In support of these results was another meta-analysis on the effect of statins on CAC which demonstrated that long term use of high dose statins is associated with worse calcification but less clinical events, suggesting therefore better stabilization of the atherosclerosis pathology and better tissue healing [29]. It is very likely that similar effect applies to aortic valve and root calcification. Thus, despite the consistent beneficial effect of statins on LDL-cholesterol levels, evidence is showing no effect on aortic valve structure, function or calcification and no benefit for clinical outcomes. In contrast, the exploratory analysis of Fourier trial have shown that the reduction in lipoprotein(a) levels with evolocumab, potentially responsible for aortic valve stenosis development and progression, determine a fall in aortic stenosis related events [30]. This needs to be further investigated in other trials.

Aortic Valve Calcification and Calcium Mineral

To better understand the process of aortic valve calcification identifying the type of calcium mineral formed in the leaflets is of significant importance. A Swedish study investigated the nature of the calcium mineral collected from 41 aortic valves surgically removed during valve surgery for aortic stenosis. The mineral composition of the calcium deposits was studied using Fourier transform infrared spectroscopy (FTIR). The calcified tissue was rinsed with deionised water and oven-dried at 50 °C before calcium deposits were dissected out from the underlying tissue and pulverised. After thorough grinding, samples were analysed on a Jasco Pike Miracle attenuated total reflectance system. The spectra from 600 to 4000 wave numbers were compared to a standard library to define the exact calcium composition. All analysed valves had either calcium phosphate or carbapatite [30]. No leaflet had calcium oxalate or any other mineral that could have shed light on different pathway. None of the patients had any other pathology related disturbed calcium/phosphate relationship e.g. parathyroid, suggestion that valve calcification is the primary pathology. The distribution of the calcium mineral was also interesting having involved the leaflet body and more diffusely the edges as has been previously described [31]. It is well known that aortic valve substitutes do calcify irrespective of their type, with the homografts showing such complication much faster than bioprostheses [32]. The calcification process starts within days of valve replacement. Such calcification has been shown to take stages, starting with the formation

of minor lipid deposition followed by amorphous calcium phosphate, a crystalline form of calcium phosphate then finally carbapatite [33]. This explanation is another evidence that refutes the process of calcium 'deposition' and favors the concept of calcium 'formation' on the leaflets.

Valvular Calcification in Predicting Cardiovascular Events

Cardiac calcification is a common finding with age, particularly in patients with risk factors for atherosclerosis. Cardiac calcification can easily be detected using echocardiography or CT, with calcium formed on the mitral annulus, aortic root or aortic valve leaflets, commonly described as aortic valve sclerosis. Cardiac calcification has been found to have an important relationship with a strong predictive ability of future clinical events. A review of the predictive ability of arterial and valvular calcification has shown an additive effect of calcification in more than one location in predicting mortality and coronary heart disease, with mitral annual calcification being a particularly strong predictor [34]. In individual arteries and valves there is a clear association between calcification presence, extent and progression and future cardiovascular events and mortality irrespective of symptoms and high risk patients, although adjustment for calcification in other arterial beds generally renders associations non-significant. Even in asymptomatic individuals, cardiac calcifications are frequently encountered on routine echocardiographic examination or CT scanning and their prevalence varies according to the site evaluated, age and presence of CV risk factors (e.g chronic kidney disease [35] or diabetes [36]). The most often affected sites are the aortic valve (with 24% prevalence in a general population) and mitral annulus (with 8% prevalence in the same population, and up to 15% with increasing age and number of risk factors or presence of chronic kidney disease) [37, 38]. A major issue in evaluating cardiac calcification prevalence and incidence is the lack of a clear and shared definition [39].

Over 20 years ago, the CV Health Study [40] reported aortic valve sclerosis in 29% of over 5600 subjects over 65 years of age. The presence of AV sclerosis was associated with double the risk of all-cause mortality and CV death, as well as an increased number of ischemic events including myocardial infarction (MI), angina pectoris, stroke and heart failure (HF) over a follow-up period of 5 years. The increased risk of all-cause mortality and CV death remained, after adjustment for age, gender and baseline factors (hypertension, current smoking, raised LDL cholesterol levels and diabetes) associated with aortic sclerosis (AVS). However, among subjects with CAD (history of MI, angina, coronary angioplasty or bypass graft surgery) events rates were higher in patients with AVS compared to patients without AVS. These findings suggest that AVS may not be a benign incidental finding but rather an independent marker of increased CV risk, particularly in the absence of CAD. Moreover, the presence of AVS, in patients admitted for chest pain but with normal cardiac enzymes was a strong predictor of obstructive CAD, independent of other atherosclerosis risk factors [41]. Other reports demonstrated a strong

association between mitral annulus calcification (MAC) and CAD [42, 43], and aortic atheroma [44] . Fox et al., in the Framingham Heart Study, reported an association between MAC and an increased incidence of clinical events [45], which remained even after adjusting for CV risk factors (hazard ratio [HR]: 1.5; 95% confidence interval [CI]: 1.1 to 2.0), CV death (HR: 1.6; 95% CI: 1.1 to 2.3), and all-cause mortality (HR: 1.3; 95% CI: 1.04 to 1.6). A multiethnic population study confirmed the same association, having found MAC thickness of >4 mm associated with ischemic stroke [46].

The prognostic role of cardiac calcification was also confirmed in a high-risk population of type 2 diabetics. Rossi et al. evaluated more than 900 subjects and observed approximately 45% having AVS, MAC or both. In this study, calcifications involving the aortic valve and/or mitral apparatus, predicted an increased risk of CVD and all-cause mortality; irrespective of traditional risk factors, diabetes-related variables, kidney function, and echocardiographic left ventricular variables [47]. Of interest in the LIFE (Losartan Intervention For Endpoint-reduction) study population, the risk of CV death, non-fatal stroke or MI was almost twofold in subjects with AV sclerosis [48]. In a population with suspected CAD study by Poggianti et al. AVS was found to be associated with endothelial dysfunction evaluated by flow-mediated vasodilation, an early stage lesion in atherosclerosis [49]. Cardiac calcification has also been found to worsen in a similar way as atherosclerosis does, such relationship has been reported between MAC and conventional CV risk factors [50] and resulted in worsening mitral regurgitation [51] or non-rheumatic mitral stenosis, particularly in the elderly [52]. Worsening of AVS over time has also been reported, with approximately 1/3 of those affected developing some degree of calcific aortic stenosis during mid-long-term follow-up [53].

Pathogenesis of Valve Calcification

Valve calcification process can be classified into 2 phases [54]; an early *initiation phase* dominated by valve tissue injury, lipid deposition, and inflammation, with many similarities to atherosclerosis and a later *propagation phase* where pro-calcific and pro-osteogenic factors drive disease progression. Histopathological studies of the early stages of MAC [55] and AVS [56] have shown focal subendothelial plaque-like lesions on the surface of the leaflet that extend to the adjacent fibrosa layer. These lesions generally contain “atherogenic” lipoproteins, including LDL, [Lp(a)] and evidence of LDL oxidation, inflammatory cell infiltrate and microscopic calcification [57, 58]. Mendelian randomization studies have highlighted Lipoprotein(a) [Lp(a)] strong association with calcific aortic valve disease [59]. Lp(a) transports oxidized phospholipids with a high content in lysophosphatidylcholine. Autotaxin transforms lysophosphatidylcholine into lysophosphatidic acid. Autotaxin is transported in the aortic valve by Lp(a) and is also secreted by valve interstitial cells. Autotaxin-lysophosphatidic acid promotes inflammation and mineralization of the aortic valve [60].

Early valvular lesions are likely to be initiated by endocardial disruption due to increased mechanical or decreased shear stress, similar to those happening in early atherosclerotic lesions [61]. The endothelium/endocardium, in these impact areas, responds by increasing the production of adhesion molecules such as ICAM and VCAM, that promote the adhesion and infiltration of monocytes and lymphocytes to participate in tissue repair, and induce expression of genes responsible for inflammatory cells infiltration and lipid deposition [62]. Extracellular lipid accumulation is usually seen in a small area in the endocardial region, with displacement of the elastic lamina and extension into the adjacent fibrosa. Micro-calcification co-localizes with sites of lipid deposition. The formation of these microcalcifications may be mediated by cell death and release of apoptotic bodies [63]. Such apoptotic bodies are similar to the matrix vesicles found in bone, which contain the prerequisite components for calcium crystal formation (including calcium and inorganic phosphate ions) and facilitate the formation of needle-like crystals of hydroxyapatite. When the homeostasis of valve tissue is disturbed, immune cells (such as macrophages and T cells) infiltrate the damaged area, and secrete various pro-inflammatory cytokines: tumor necrosis factor (TNF), transforming growth factor-1 (TGF-1), interleukin-1β (IL-1β) and matrix metalloproteinase (MMPs), thus perpetuating a cycle of calcium formation and valvular injury. Furthermore, the fibrotic process within the valve may be mediated by reduced nitric oxide expression following endothelial injury [64]. The renin-angiotensin system (RAS) is also believed to play a role through angiotensin 1 profibrotic effects [65]. Ultimately, valve calcification depends upon the presence of osteoblast-like cells that develop an osteogenic phenotype [66]. Pro-inflammatory cytokines released by macrophages (IL-1b, IL-6, IL-8, TNF-a, insulin-like growth factor-1, and TGF-b) [67, 68], activate various calcific pathways (Wnt3-Lrp5-catenin signaling pathway [69], the osteoprotegerin (OPG)/receptor activator of nuclear factor kappa B (RANK)/RANK ligand (RANKL) pathway [70] and Runx-2/NOTCH-1 signaling [71] causing valvular interstitial cell (VICs) osteogenic differentiation. These osteoblast-like cells then lay down a collagen matrix and other bone-related proteins, causing valvular thickening and stiffening before producing calcium. Additionally, apoptotic remnants of some VICs and inflammatory cells create a nidus for apoptosis-mediated calcification. Calcification of the valve induces compliance mismatch, resulting in increased mechanical stress and injury. This results in further calcification via osteogenic differentiation and apoptosis. A self-perpetuating cycle of calcification, valve injury, apoptosis, and osteogenic activation is established and drives the propagation phase of the disease.

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Chapter 4
Valve Calcification (Aortic and Mitral)

Jason Kho and Mario Petrou

Introduction

In 1663, French physician, Lazare Rivière performed autopsy on a patient with symptoms of progressive shortness of breath, irregular heartbeat and heart palpitations. He identified round caruncle-like masses that obstructed the left ventricular outflow tract (LVOT) associated with an enlarged left ventricle [1]. Physicians in his era also reported similar occurrences and further described an ossifying process of the aortic valve leaflets. These findings were initially presumed to be infective in nature as seen in endocarditis and rheumatic fever [1].

Hasse in 1846, challenged this aetiology and suggested that the calcification process could also be attributed to a degenerative process with ageing [1]. In 1904, Moenckeburg recognised aortic sclerosis as a potential precursor to aortic stenosis and proposed two mechanisms of secondary calcium deposition; ascending and descending. Ascending sclerosis occurs when degeneration within the valve leaflet layers facing the Valsalva sinuses propagates upwards towards the free margin while descending sclerosis occurs with downward sclerotic extension to involve both the cusps and commissures [1].

Cardiac valve calcification (CVC) is characterised by slowly progressive fibrocalcific remodelling of valve leaflets. Rheumatic heart disease is a common cause for CVC in developing countries while in the developed world, the formation of

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CVC is believed to be a combination of factors including age, gender, genetics, medical comorbidities and cardiovascular risk factors. Compared to mitral annular calcification (MAC), calcific aortic valve disease is associated with significant morbidity and has important clinical implications. Hence, calcific aortic valve disease will be the focus of this chapter with a small subsection to discuss the clinical manifestations and management of mitral annular calcification (MAC).

Epidemiology and Risk Factors of CVC

Calcific aortic valve disease is the most prevalent cause of aortic stenosis (AS) worldwide and poses a significant disease burden, with AS being the third most common cardiovascular problem after coronary artery disease and hypertension [2]. Prevalence of aortic sclerosis increases with age and the rate of progression to AS is estimated to be 1.8-1.9% of patients per annum [3]. Calcific AS has an estimated prevalence of 0.4% in the general population and increases to 1.7% in those aged >65 years in developed countries [4].

The calcification process can occur in either a normal trileaflet aortic valve or a congenitally abnormal bicuspid valve. Bicuspid valve is a known risk factor for calcification and accounts for nearly half of all surgically replaced aortic valves [5]. Moreover, these patients tend to develop calcific AS one or two decades earlier compared to those with a tricuspid valve [6]. Other risk factors of calcific aortic valve disease are those of atherosclerosis such as diabetes mellitus, hypertension and hypercholesterolemia [7].

The prevalence of MAC has been reported to be between 8% and 15% and increases with age [8, 9]. Risk factors are generally similar to those in atherosclerosis and calcific aortic valve disease with a few other specific risk factors including female gender, chronic kidney disease and congenital metabolic disorders such as Marfan syndrome and Hurler syndrome [10–12].

Anatomy of the Aortic Valve

The aortic valve is an avascular tricuspid structure situated at the LVOT and appended to the aorta by a fibrous annulus. The valve leaflets are named according to their location respective to the coronary arteries; right coronary cusp, left coronary cusp and non-coronary cusp. The leaflets are typically $\leq$1 mm in thickness and is made up of three layers. The outermost layers, fibrosa and ventricularis, face the aorta and LVOT respectively, with the spongiosa situated between those two layers.

The fibrosa is composed of circumferentially oriented Type 1 and 3 collagen fibres and has a load-bearing function while the ventricularis is made up of elastin-rich fibres in a radial orientation, providing good compliance (ability to expand under pressure) and allowing for the apposition of leaflets during diastole to prevent backflow of blood [13]. The spongiosa layer contains glycosaminoglycans which

provides lubrication as the fibrosa and ventricularis layers shear and deform during the cardiac cycle [14, 15].

At a cellular level, these leaflets are defined by three cell types. The vascular endothelial cells (VEC) form the outer layer and is in direct contact with luminal blood flow. These cells regulate valvular homeostasis by controlling permeability, inflammatory cell adhesion and paracrine signalling. Vascular interstitial cells (VIC) are the predominant cell population, interspersed between the fibrosa, spongiosa and ventricularis layers of the valve leaflet. Their function is to secrete extracellular matrix such as elastin, collagen and glycosaminoglycans which provide tensile strength and elastic properties to the valve. Smooth muscle cells (SMC) are the third cell type comprising <5% of the valvular cell population found at the ventricularis [14, 15].

Aetiology and Pathophysiology of CVC

For a long time, CVC was thought to be primarily caused by a degenerative process and passive calcium deposition. There is, however, emerging histopathological and clinical evidence to suggest that the pathophysiology involves an active and multifaceted process that involves chronic inflammation, lipoprotein deposition, extracellular matrix remodelling and osteoblastic transformation of VICs [16].

Cellular and Molecular Mechanisms

Valvular homeostasis is regulated by an intricate process involving the interaction between valvular cells and their environment. Under normal circumstances, an insult to the valvular surface activates a passive calcium-phosphate complex deposition process to initiate valve repair. In this process, the VICs transition to osteoblast-like bone-forming cells and the VECs undergo endothelial-to-mesenchymal transformation to form matrix vesicles and microcalcific nodules [17–20]. This procalcific process is counter-balanced simultaneously by circulating calcification inhibitors including matrix Gla protein (MGP), γ-carboxyglutamic acid-rich protein and Vitamin K-dependent protein, all of which inhibit bone morphogenetic protein (BMP) signalling [21]. Another potent circulating calcification inhibitor is Fetuin-A which binds to calcium and phosphate ions, stabilizing them and preventing cell uptake of the ions [22]. Dysregulation of this mechanism would lead to pathological cardiovascular calcification.

In patients with calcific aortic valve disease, MGP levels have been shown to be significantly depressed compared to patients with normal valves [23]. MGP activity depends on its carboxylation status and vitamin K availability. The use of warfarin, a vitamin K epoxide reductase and γ-carboxylase inhibitor, downregulates MGP activity and has been demonstrated to be a contributing factor to CVC [24]. Furthermore, deficiency in Fetuin-A has also been found to be implicated in aortic valve calcification [17, 22].

The role of BMPs is to stimulate osteoblasts and initiate calcium deposition and bone formation by activating Smad and Wnt/β-catenin signalling and upregulate the expression of Msx2, an osteochondrogenic transcription factor. These signalling pathways ultimately lead to the expression of master osteoblast transcription factor Runx2 [25]. Cells committed to an osteoblastic lineage, as in VICs, will secrete calcification-related protein in response to Runx2, causing valvular calcification [26]. The endothelial-to-mesenchymal transition of VECs can also lead to differentiation to osteoblast-like cells, resulting in a similar response to that of VICs which further contributes to the calcification process. Additionally, the presence of transforming growth factor-β, β-catenin signalling and transcription factor Msx2 are able to stimulate VECs to migrate into surrounding tissues and contribute further to calcification [20, 25].

Progenitor cells have been found to populate normal aortic valves and may also partake in the CVC process [27]. In porcine aortic valves, mesenchymal progenitor cells were found to possess the ability to differentiate into osteoblast-like cells [28]. An environment that favours calcification may be a further driving factor for osteogenic differentiation of these cells, contributing to CVC [29]. Endothelial progenitor cells, on the other hand, plays a role in repairing damaged endothelium by secreting proliferating factors and promoting the migration of resident endothelial cells [30]. Abnormal function of these cells would yield the repair process ineffective and cause abnormal calcification.

Aberrant Immune Response and Inflammation

The pathophysiology of CVC may involve an aberrant immunomodulatory response supported by the observation of leucocyte and macrophage infiltration in explanted calcified human aortic valve compared to the trace amount of macrophages found in normal aortic valves [17]. Inflammatory cell infiltration was observed more frequently at sites where VECs were activated, increasing the concentration of adhesion molecules and facilitating monocyte and macrophage recruitment to the valve [31–33]. Enhanced recruitment of inflammatory cells leads to the secretion of pro-inflammatory cytokines and the release of matrix metalloproteinases and cysteine endoproteases. These enzymes break down collagen and elastin causing disruption to the normal valvular architecture [18, 34].

There is also evidence to suggest that lipoprotein recruitment during endothelial injury and the retention of lipids encourage a chronic low-grade inflammatory process and may precede the pathologic mineralisation [35]. Oxidative stress and oxidisation of low-density lipoproteins have been found to be related to the degree of inflammation and fibrocalcific remodelling of the valves by stimulating fibroblasts to release matrix vesicles [36–38]. The production of reactive oxygen species in the vicinity of calcified areas also promotes the osteogenic potential of VICs and has the potential to activate the innate immune response [39, 40]. The adaptive immune response may also be activated concurrently during the calcification

process evidenced by the presence of activated CD8+ T cells [41]. Hence, it is very likely that both the innate and adaptive immune responses are actively involved in the calcification process.

Matrix Remodelling and Neovascularisation

In patients with CVC, there is evidence to suggest that abnormal matrix deposition and valvular fibrosis contribute to valve calcification. Activated VICs secrete extracellular matrix to maintain valve function and elasticity but the deposition of matrix substances is often haphazard which leads to altered biomechanical properties of the valve [3]. The resultant changes to valve stiffness may further augment phenotypic transition of VICs to osteoblast-like cells [42–44]. In addition, experimental models of aortic valve calcification have demonstrated raised pro-fibrotic signalling molecules such as transforming growth factor-β and thrombospondin-2, contributing to fibrocalcific remodelling of the valve leaflets [45, 46].

In contrast to a healthy avascular human aortic valve, calcified valves possess their own tiny vasculature [47]. Histological studies have identified a subgroup of cells that express pro-angiogenic factors Tie-2 and vascular endothelial growth factor (VEGF) receptor 2; these cells may represent activated VECs or VECs that have undergone phenotypic transitions [48]. The downregulation of angiogenic inhibitors also have an equally important role in neovascularisation of these calcified valves.

The presence of mast cells has been identified in calcified valves and plays a pivotal role in the release of VEGF (pro-angiogenic) while also releasing tryptase which degrades endostatin (angiogenesis inhibitor) [47]. Reduced expression of chondromodulin-I, an angiogenic inhibitor, has also been observed and is associated with increased VEGF and periostin. Periostin can stimulate the formation of capillary tube-like structures and have previously been implicated in calcified aortic valves [49]. Once neovascularisation is achieved, the vasculature network expedites the transfer of inflammatory cells and pro-calcifying molecules, further contributing to calcification.

Clinical Characteristics and Diagnosis of AS

Clinical Features

Patient evaluation should always include a thorough patient history and clinical examination, particularly auscultation of the heart sounds and looking for signs of heart failure. Patients with aortic sclerosis or mild to moderate AS are usually asymptomatic and the clinical suspicion for aortic valve disease is usually raised when a systolic murmur is heard on clinical examination.

A classical harsh crescendo-decrescendo systolic murmur is audible on auscultation, loudest at the aortic area (right sternal edge, second intercostal space) with the presence of a single second heart sound. The absence of radiation to the carotid arteries and a wide pulse pressure would suggest AS rather than aortic sclerosis. Symptoms occur particularly when patients have other comorbidities or in cases where there is severe AS leading to left ventricular dysfunction. The described symptoms are usually dyspnoea, syncope or angina.

Investigations

Electrocardiography (ECG) may be useful in demonstrating the impact of AS on the left ventricle. Although the findings are non-specific, there may be ECG evidence of left ventricular hypertrophy with a strain pattern (increased R wave amplitude in left-sided leads and increased depth of S wave in right-sided leads) and left atrial enlargement. Chest radiograph usually reveals a normal cardiac shadow since the left ventricular hypertrophy in AS is concentric but will manifest as cardiomegaly when systolic failure occurs.

A Doppler echocardiography is a useful modality in assessing the haemodynamic severity of AS by analysing the peak aortic jet velocity, aortic valve area (AVA) and the mean transvalvular pressure gradient (mean gradient). AS may be visualised as thickened valve leaflets with a restrictive opening causing increased peak aortic jet velocity and mean gradient. The resultant impact of AS on cardiac geometry and function, particularly the left ventricle can also be assessed simultaneously and may provide important prognostic information. Where a transthoracic echocardiography (TTE) is suboptimal, a transoesophageal echocardiography (TOE) should be considered. Particularly when performing the valvular procedure, TOE can be used to monitor the function and results of the valve post-implantation or repair [50].

Exercise testing may also be used in patients with non-specific symptoms or those who claim to be asymptomatic. It can also provide useful information for patients regarding appropriate levels of physical activity and participation in sports. In patients with AS and mitral regurgitation, exercise echocardiography may be used to evaluate prognostic impact of the disease [51]. An alternative for stress testing is by using low-dose dobutamine stress echocardiography which can assess coronary flow reserve (ratio of maximum increase in blood flow through the coronary arteries to normal resting flow) and severity of AS, particularly in low-flow low-gradient AS [52, 53].

Imaging modalities with multi-slice computed tomography (MSCT) and cardiac magnetic resonance (CMR) may also be utilised to evaluate severity of valve disease in patients with inadequate echocardiographic quality. The high resolution of MSCT allows calcium load to be quantified and scored using the Agatston modified method, which may be useful in predicting haemodynamic severity and clinical

outcomes [54, 55]. CMR is equally useful in predicting severity of disease by evaluating myocardial fibrosis and ventricular volumes and systolic function [50].

Invasive modalities include coronary angiography and cardiac catheterisation. Coronary angiography is indicated in suspected coronary artery disease, left ventricular systolic dysfunction or patients with one or more cardiovascular risk factors within the context of severe valvular disease to determine if concomitant coronary revascularisation is needed [50]. Cardiac catheterisation used to be the modality of choice before the advent of echocardiography. This modality allows the measurement of cardiac pressures and cardiac output to assess ventricular performance and severity of valve disease. It should, however, only be considered in patients where echocardiography is inconclusive or discordant with the clinical findings and where reclassification of the valve disease would change therapeutic management. This is due to its association with serious complications such as bleeding and cerebral embolism [56].

Spectrum of Severity in AS

Aortic sclerosis is the preclinical phase of calcific aortic valve disease. It is defined by echocardiographic evidence of focal areas of leaflet calcification causing thickening, without compromising valve function or cardiac blood flow [57]. Patients with aortic sclerosis are clinically asymptomatic but there is an independent association with increased risk of coronary events and cardiovascular death [58].

Mild to moderate AS is diagnosed on the basis of reduced AVA and increased peak aortic jet velocity and mean gradient across the valve. In severe AS, specific haemodynamic parameters on echocardiography would include a peak aortic jet velocity of ≥4 ms, a transvalvular mean pressure gradient of ≥40 mmHg and a calculated aortic valve area ≤ 1.0 cm^2 [50]. Patients may be asymptomatic even in severe AS and should undergo stress testing to delineate the disease severity.

While the majority of severe AS would manifest with the haemodynamic parameters previously described, a subgroup of patients may have low peak aortic jet velocity and mean gradient despite a small AVA. The most common cause is a low-flow state (low-flow low-gradient AS), where there is a reduction in stroke volume (≤35 mL/m^2) related to left ventricular systolic dysfunction. Two subtypes exist depending on the left ventricular ejection fraction; low-flow, low-gradient AS with reduced ejection fraction (<50%) and low-flow, low-gradient AS with preserved ejection fraction (≥50%). The diagnosis in patients with the latter disease where ejection fraction is paradoxically preserved is challenging and will require MSCT to evaluate the degree of valve calcification which corroborates stenosis severity [54, 55, 59]. Where ejection fraction is reduced, low-dose dobutamine stress echocardiography is recommended to distinguish true severe aortic stenosis from pseudosevere aortic stenosis (defined by increased AVA to >1.0cm^2 with flow normalisation) [50].

Finally, another group of patients will have echocardiographic evidence of small AVA ($\leq$1.0cm^2) but with normal flow (normal flow, low-gradient AS). These patients generally have only moderate aortic stenosis with better outcomes compared to those with high gradient AS or low-flow, low-gradient AS [54, 60–62]. Again, MSCT can be considered to quantify calcium burden to confirm severity of stenosis.

Management of AS

At present, aortic valve replacement (AVR) is the only available treatment for patients with symptomatic severe AS. This procedure may be performed surgically or percutaneously via a catheter, a procedure known as transcatheter aortic valve implantation (TAVI). While some studies and trials have suggested statins and angiotensin converting enzyme inhibitors (ACE-i) to be potential pharmacotherapeutic agents in preventing or slowing the calcification process, the evidence behind medical management remains inconclusive.

The decision for the need of an intervention is dependent on severity of disease and patient symptoms. Patients with symptomatic severe AS with evidence of left ventricular function compromise should be considered for intervention unless it has been deemed that the risks of the intervention outweigh any benefit, and especially so if it is unlikely to be of any benefit. Risk stratification tools such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and Society of Thoracic Surgery (STS) risk calculator may be used by the Heart Team in deciding between surgical AVR and TAVI in patients at high surgical risk [50].

Surgery

Since the first successful surgical AVR in 1960, the operative techniques and valve technology have advanced tremendously over the years [63]. Patient outcome and long-term survival have improved significantly despite increasing age and comorbidities of surgically managed patients [64, 65]. The type of valves used include bioprosthetic valves (made from porcine aortic valve or bovine pericardium) and mechanical valves.

Mechanical valves have better durability compared to their bioprosthetic counterpart but with the disadvantage of requiring lifelong anticoagulation due to its propensity for thrombosis. With advancing valve technology, however, durability of bioprosthetic valves has improved remarkably and is nearly comparable to that of mechanical valves. Bioprosthetic valves used to be advocated for patients in older age groups but are now increasingly used in younger patients to avoid anticoagulation. Bioprosthetic valves may be stented or stentless depending on whether the

leaflets are mounted to a metal or polymeric ring. Although stentless valves provide better haemodynamics, implantation is more complex and will require longer operative time and duration on cardiopulmonary bypass. Sutureless bioprosthetic valves are also becoming popular as it allows easier and quicker implantation.

Other operative strategies particularly for younger patients include the Ross procedure (also known as the Ross-Yacoub procedure). The procedure involves utilising the patient's own pulmonary valve to replace the diseased aortic valve followed by replacement of the pulmonary valve with a pulmonary homograft [66–68]. Alternatively, an aortic homograft may be implanted to replace the diseased aortic valve. These procedures are performed comparatively less than the traditional AVR with congenital aortic stenosis being the most common indication for the Ross procedure.

A minimally invasive operative strategy has also been developed by using a mini-sternotomy incision to gain access to the aortic valve and is a feasible option in patients who undergo an isolated AVR procedure. Although it is associated with a similar mortality, there is reduction in resource utilisation and post-procedural morbidity [65].

Transcatheter Aortic Valve Implantation (TAVI)

TAVI is a minimally invasive procedure involving the insertion of a bioprosthetic aortic valve by using a catheter. The catheter insertion may be transfemoral, transapical or transaortic to gain access to the native stenosed aortic valve. Most TAVI procedures are performed using the transfemoral approach as it is associated with lower mortality rates and quicker recovery.

Two types of transcatheter valves have been studied rigorously to date; balloon-expandable (BE) and self-expanding (SE) valves. The CHOICE trial, which compared the two valve types in high-risk patients with severe aortic stenosis, demonstrated that BE valves were more successful with less residual aortic regurgitation and conduction disturbances requiring permanent pacing [69].

TAVI is an AVR option particularly in high-risk patients unsuitable for surgery but is now being extended to patients in the intermediate risk groups. Although TAVI is a relatively safe procedure, some of the complications of TAVI include paravalvular aortic regurgitation, cardiac conduction disturbances and heart block requiring permanent pacemaker implantation, bleeding, acute kidney injury and very rarely, stroke, coronary obstruction and aortic rupture. Paravalvular aortic regurgitations remains the most notable complication due to its link to increased mortality with severity of the leak [70, 71]. Generally, TAVI has been a very successful therapy with outcomes comparable to that of surgical AVR and it is possible that this procedure will eventually be advocated to patients in the low risk categories.

Surgical AVR vs TAVI

The choice between surgical AVR and TAVI is becoming more challenging as TAVI is being extended to low-risk patients, and multiple factors including anatomical considerations and performing concomitant revascularisation or valvular procedures should be taken into consideration. The results from Placement of Aortic Transcatheter Valves (PARTNER) trial has greatly evolved the use of TAVI. Particularly in high-risk patients who would otherwise be unsuitable for surgery and intermediate risk patients, there were no significant differences in short and long-term outcomes between surgical AVR and TAVI. However, surgical AVR had the long-term advantage over TAVI by having fewer rehospitalisations and reinterventions, and particularly over transthoracic TAVI with fewer incidences of death or disabling stroke [70].

The use of TAVI in low-risk patients has recently shown superiority over surgical AVR in mortality outcome, stroke and rehospitalisation at 1 year and it is possible that the use of TAVI will continue to gain favour even in the low-risk cohort. Complication rates in this group remain similar to moderate and high-risk groups and the long-term outcomes remain to be evaluated [72]. It is likely with progressive improvement in valve technology, the complication rates will decrease, and it is possible that surgical AVR will only be reserved for a specific group of patients with complicated anatomy or where other concomitant cardiac procedures are being considered.

There is, however, a subgroup of patients where TAVI may be futile or of limited benefit. This may be the case in frail elderly patients where their quality of life and lifespan are limited by their performance status and coexisting medical comorbidities. In this patient group, the heart valve team may decide that the benefit of TAVI may be limited and a palliative care approach may be appropriate, taking into account the values and wishes of patients and family members when making this decision.

Balloon Aortic Valvuloplasty

Balloon aortic valvuloplasty (BAV) is reserved for haemodynamically unstable patients or patients with symptomatic severe AS who require urgent non-cardiac operation. It may also be used as a bridge to surgical AVR or TAVI or even as a diagnostic mean to decide whether AVR is appropriate in patients with multiple contributing factors to the clinical symptoms. The benefits provided by BAV are short-lived and is therefore, not a definitive therapy for AS [50]. BAV may also be used as a palliative approach as there has been previous evidence to suggest that BAV may provide a short-term benefit to quality of life and functional capacity [73].

Mitral Annular Calcification (MAC)

The term "mitral" was first suggested by Walmsley due to its resemblance to a bishop's mitre [74]. The mitral valve is seated between the left atrium and the left ventricle, preventing backflow of blood to the left atrium during left ventricular contraction. Its function is served by the orchestration of all its components (valve leaflets, papillary muscles, chordae tendinae and fibrous annulus) with the help of the atrial and ventricular musculature [75].

The mitral annulus marks the hinge line for the valvular leaflets and follows a D-shape, with the straight border of the anterior mitral leaflet forming part of the posterior aortic root. Where the aortic valve communicates with the anterior mitral leaflet via expansions of fibrous tissue forms the right and left trigonal structures. The right trigone is a route of passage for the atrioventricular bundle which explains the association between MAC/mitral valve disease with cardiac conduction disturbances [75].

MAC and its association with complete heart block was first described by Bonninger in 1908 [76]. To shed light on the pathophysiology of MAC, Dewitzky performed a detailed pathologic description of 36 cases and found a close resemblance to aortic valve calcification described by Moenckeberg in 1904 [77]. Moreover, MAC was a common autopsy finding in older people and was then considered to be primarily caused by rheumatic heart disease [78, 79].

Clinical Features

Mitral annular calcification (MAC) involves chronic calcification of the mitral valve fibrous annulus and has a tendency to affect the posterior mitral annulus. The anterior mitral annulus and leaflet are usually spared in MAC, in contrast to rheumatic mitral valve disease where the predominant pathology is that of the anterior leaflet and causes commissural fusion [80]. The pathophysiology observed in MAC draws similarity to those previously discussed in calcific aortic valve disease and shares associated atherosclerotic risk factors. Hence, concomitant calcific aortic valve disease and atherosclerotic cardiovascular disease are not uncommon with MAC. Other associated diseases with MAC include stroke, coronary artery disease, cardiac arrhythmias and endocarditis [81–86].

Patients with MAC are generally asymptomatic, and the disease is usually diagnosed incidentally. MAC does not typically contribute to haemodynamic disturbances or affect left ventricular or mitral valve function. However, extensive disease may lead to functional mitral stenosis, mitral regurgitation or a mixed disease process where both pathologies are manifested [87, 88].

Investigation and Diagnosis

Echocardiography is considered to be the principal imaging modality in diagnosing and characterising mitral valve diseases. MAC appears as an echo-dense, irregular, lumpy shelf-like structure affecting the posterior mitral valve annulus with acoustic shadowing on echocardiography. Occasionally, the anterior annulus or interannular fibrosa are also affected [89]. A rare variant of MAC known as caseous calcification is less echo-dense than the typical MAC and appears as a central echolucent area without acoustic shadowing.

Severity is generally divided into mild, moderate and severe depending on the echodensity and the extent of disease to involve the left ventricular inflow tract due to restricted mobility of the affected leaflet [89]. Due to its low specificity in distinguishing calcification from dense collagen, the use of echocardiography should be complemented by MSCT and CMR to quantitate the severity of the calcification [89].

Management of MAC

MAC does not usually require any intervention unless there is evidence of symptomatic concomitant severe mitral stenosis and mitral regurgitation. In fact, surgery should be avoided in patients with severe MAC due to an increased risk of complications such as left ventricular rupture and injury to the circumflex artery [90, 91]. Another indication for valve intervention may include recurrent thromboembolism despite anticoagulation or documented calcific emboli.

In patients with symptomatic severe mitral stenosis or severe mitral regurgitation, mitral valve surgery should be performed. The surgical approach involves decalcification of the mitral annulus followed by reconstruction and if possible, conservation and repair of the mitral valve or otherwise replaced with a prosthetic valve [90, 91]. The benefits of the operation should be carefully weighed against its risks as these patients tend to be older with multiple comorbidities. The use of percutaneous mitral commissurotomy (PMC) is not indicated in MAC since there is no commissural fusion and should be reserved for patients with rheumatic mitral valve disease.

Transcatheter mitral valve insertion (TMVI) may be considered in patients at very high-risk for surgery and deemed unsuitable for surgical intervention. Characteristics of MAC should be taken into consideration when performing this procedure. Circumferential calcification is preferred since it provides good anchorage for the prosthesis. The lack of this can lead to potential displacement of the anterior leaflet into the LVOT, increasing the risk of periprosthetic leak [89]. A heavy calcium burden also increases the risk of annular rupture and calcium embolization and stroke during the procedure [89]. At present, there is limited data to

evaluate the outcome and safety of TMVI and more studies are needed to compare its outcomes against surgical mitral valve replacement.

AF is a common complication in mitral valve diseases and MAC and predisposes patients to left atrial thrombosis and potential for embolism. Classically, warfarin is the only medication licensed for use in valvular AF with specific International Normalised Ratio (INR) targets depending on the valvular pathology. The direct oral anticoagulants (DOACs) have been gaining favour in recent years as no INR monitoring is required and there is emerging evidence to suggest these medications are safe to use in valvular heart disease. In fact, there is some evidence to suggest that it may reduce calcium deposition and progression compared to warfarin [92]. However, larger studies will be required to validate this finding.

Future Research

It remains challenging to decide which patients will benefit most from an early therapeutic intervention. The use of blood biomarkers such as B-natriuretic peptide (BNP) has previously been suggested to evaluate left ventricular function or left ventricular strain as an indirect measure of disease severity, particularly in asymptomatic patients [93, 94]. However, the cut-off value to identify patients at high risk of progression of disease is unclear with a previous study suggesting the use of BNP ratio (age and sex-adjusted measured BNP divided by expected value) instead. BNP ratio > 1 may be an independent predictor of mortality in AS, even in asymptomatic patients [94]. The limitations of the use of these blood biomarkers, however, are that they are often non-specific and should be used in conjunction with current investigative modalities. Further research is required to validate the use of these blood biomarkers in clinical practice.

Improved cardiac imaging with magnetic resonance is also promising in risk-stratifying patients. In severe AS, myocardial fibrosis has been documented on CMR and the quantification of myocardial fibrosis may be useful in recommending early therapeutic intervention, particularly in asymptomatic patients [6]. Further studies are needed to standardise CMR findings and their relationship to severity of disease and establishing a threshold at which valve intervention would be most beneficial in preventing further myocardial dysfunction. At present, the use of CMR is also limited by its cost and low availability but this will likely change in the foreseeable future.

While valve replacement is the mechanical solution to a calcified valve, strategies to improve clinical outcomes post-valve replacement are given little attention. Often, there is evidence of left ventricular dysfunction from chronic remodelling in response to valvular disease, and left ventricular function usually improves minimally after valve replacement. Research into adjunctive medical therapies to help improve left ventricular function and reverse the remodelling process could potentially reduce symptom experience and improve quality of life.

As previously discussed, there remains no effective pharmacotherapy to delay or halt the progression of calcification. While medications such as ACE-i and statins have previously been suggested, the evidence is weak and non-conclusive. In addition, the use of statins in randomised-controlled trials has previously shown no benefit [95–97]. The disease burden of CVC will continue to increase, and current research should, therefore, focus on effective prophylactic pharmacotherapy.

Conclusion

The disease burden of CVC will continue to increase globally due to better life expectancy and an ageing population. A pharmacotherapy to prevent or slow the progression of calcification has yet to be discovered and valve replacement remains the only effective treatment modality, particularly in calcific AS. Minimally invasive techniques with TAVI are increasingly being utilised and progressively replacing surgical interventions. The role of the heart valve team is crucial in deciding which patients will benefit most from an intervention by taking into account patient symptoms, cardiac function, coexisting medical conditions and their functional baseline. The future of TAVI is promising and by reducing the complications related to the procedure, it will eventually be an option for low-risk patients.

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Chapter 5
Calcification and Aortic Syndromes

Saeed Mirsadraee and John Pepper

Introduction

Vascular calcification is defined as the deposition of calcium crystals within the vessel wall, initiated as microcalcification and propagating towards macrocalcifications [1] and eventually encroaching entire segments of the vasculature [2].

Most individuals over the age of 60 years have progressively enlarging deposits of calcium mineral in their major arteries [3].

This vascular calcification reduces aortic and arterial elastance which impairs cardiovascular haemodynamics resulting in substantial morbidity and mortality [4] in the form of hypertension, aortic stenosis, cardiac hypertrophy, myocardial and lower limb ischaemia, congestive cardiac failure and compromised structural integrity. Aortic calcification introduces compliance mismatch that can promote mechanical failure due to stress concentration at the interface of calcium deposits and softer plaque components. It has been demonstrated that higher aortic calcium content in patients with thoracic and abdominal aortic aneurysm is associated with higher risk of all-cause mortality and cardiac mortality (odds ratio > 2) [5].

More than 10 years ago a paradigm change occurred in our understanding of the similarity of this process to bone development and metabolism, where endothelial, mesenchymal and haematopoietic cells interact and respond to mechanical, inflammatory, metabolic and structural signals governing skeletal mineralisation;

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their counterparts in the artery wall govern arterial mineralisation. With increasing age, the clinical burden of vascular calcification will continue to increase.

Aetiology of Vascular Calcification

Vascular calcification is the culmination of several distinct but overlapping pathological processes. These processes follow developmental programmes that recapitulate embryonic ossification, with modulation by inflammatory or metabolic phenomena. These programmes play out in vascular cells exhibiting lineage plasticity and inflammatory responses to chronic oxidative stress.

Calcification may be located in the neointima, within the atherosclerotic plaque or in the tunica media. Medial calcification is primarily associated with chronic kidney disease and diabetes. Towler has described chronic kidney disease as the "perfect storm" for vascular calcification [6].

Calcification at both sites often occurs in the same patient and even at the same arterial site. Histologically it may appear as amorphous lacking tissue architecture or chondro-osseous in which the tissue architecture is of cartilage or, when microvascular invasion occurs, as bone. Neointimal calcium deposits are found in a patchy distribution throughout the vascular tree, co-localising with atherosclerotic lesions. Small (5-10 μm) hydroxyapatite mineral crystals arise in early lesions in the third decade of life [7]. Medial calcium deposits are distributed more diffusely throughout the vascular tree, at sites with or without atherosclerosis, and are more often circumferential owing to the close association with elastic laminae.

Given the potential adverse consequences of uncontrolled biomineralization, calcium-phosphate metabolism is tightly regulated and mineralisation ordinarily is limited to skeletal bone by circulating and local inhibitors. Vascular calcification was previously thought to be a purely degenerative, passive process, without biological regulation. Certain aspects of both skeletal and vascular calcification, such as extracellular formation of calcium phosphate crystals, might be considered as passive because they are self-organised. In other respects, the process might be considered passive in that, when inhibitors are absent, such as in the matrix Gla protein (MGP)-deficient mouse [8], then unopposed activators, such as bone morphogenetic protein (BMP-2) drive osteogenic differentiation, giving the appearance of a spontaneous process. The current view is that vascular calcification is a biologically regulated process that, like osteogenesis, involves both activators and inhibitors.

Arterial Medial Calcification

The most extensive vascular calcification is found in patients with arterial medial calcification (AMC), a highly characteristic feature of Type 2 Diabetes mellitus (T2DM) and chronic kidney disease. AMC was once considered benign because it was neither stenotic nor thrombogenic. It is now recognised that AMC is associated

with a higher cardiovascular mortality and the risk of amputations in T2DM and in end-stage kidney disease. It is reported that media calcifications cause cardiovascular events through stiffening of the arteries, increased pulse pressure, isolated systolic hypertension, reduced coronary blood flow and left ventricular hypertrophy [9].

There is growing evidence for heterogeneous mechanisms within the category of medial calcification. For example, hydroxyapatite [10] is the predominant mineral in diabetic AMC but in Vitamin D toxicity, it is whitlockite [11]. Elastin degradation appears early in many forms of medial calcification. Several investigators have shown that elastin metabolites can activate and even nucleate cell-dependent calcium deposition. Matrix metalloproteinase 9 (MMP9), an elastase expressed by the vessel wall, appears to promote arterial calcium deposition in warfarin/vitamin K models of medial calcification [12]. Elastin degradation is a prominent feature of aortic calcification in Marfan syndrome [13]. Since an intact elastin matrix stabilises the vascular smooth muscle cell phenotype in vivo, changes in osteopontin expression and MMP9-dependent elastin degradation may contribute to medial calcification in diabetes.

In aging, medial calcification may develop by a distinct process of unknown aetiology or result from a confluence of specific processes. Aging is associated with mild degrees of several processes believed to affect vascular calcification including chronic renal disease, insulin resistance, atherosclerosis, hormone depletion, elastolysis and slowly manifesting genetic vulnerabilities. Any one or a combination of these may contribute to medial calcification in aging.

In hypertension, calcium handling is disturbed, which is associated with an increased activation of L-type calcium channels and sensitivity of the patients towards calcium channel blockers. Increased intracellular calcium induces the activation of receptors coupled to phospholipase C, leading to the generation of second messengers that trigger cytokines, reactive oxygen species and miRNAs, and also cellular derived extracellular vesicles (EVs) [14]. In addition, increased intracellular calcium activates the contractile machinery of VSMCs, leading to hypercontractility. Excessive intracellular calcium rapidly disintegrates both mitochondria and the structural components of VSMCs and results in calcium depositions within elastic fibres [15]. Consequently, elasticity of the vasculature decreases, further contributing to increased blood pressure and VSMC stiffening [16]. Specific calcium antagonists blocking L-type voltage-dependent calcium channels, reduce calcium movement into the cell and normalise blood pressure [17]. Furthermore, these calcium channel blockers also prevent calcification of the vasculature [10].

Intimal (Atherosclerotic) Calcification

Atherosclerotic calcification, the most common form of calcific vasculopathy, appears to result from induction of osteogenic differentiation in sub-populations of vascular cells by inflammatory factors such as modified lipoproteins and cytokines that are found in atheromatous components of plaque. Most clinical studies link dyslipidaemia with the presence, severity and progression of vascular calcification

[18], particularly when the duration of exposure to elevated cholesterol levels is analysed. Given the relevance of exposure duration, the association may be masked in cross-sectional studies that include patients on lipid-lowering agents whose current lipid level may not reflect the level of exposure over previous years. Hyperlipidaemia is known to promote calcification in mice [19]. In vitro, HMG-CoA reductase inhibitors (statins) reduce vascular cell calcification via Gas-6/Ax1 signaling [20]. But in recent randomised trials statins did not affect severity or progression [21].

The findings of Bone Morphogenetic Protein (BMP2) and Osteopontin (OPN) expression in human atherosclerotic plaque provided the first molecular evidence for an osteogenic signalling mechanism [22]. Atherogenic stimuli, such as inflammatory cytokines, oxidised lipids and monocyte-macrophage products, promote osteogenesis and matrix calcification in vascular cell culture [23]. High glucose levels also activate osteogenic programmes [24]. Aikawa and colleagues [25] used near-infrared fluorescence imaging to show that atherosclerotic mineralisation is linked with inflammation at its earliest stage.

Given the central role of inflammation in atherogenesis it is possible that vascular mineral itself may initiate, promote or perpetuate atherosclerosis by inducing inflammatory cytokines in monocytes that encounter and ingest hydroxyapatite crystals [26].

Vascular smooth muscle cells (VSMCs) in the medial layer of the vessel wall play a key role in arterial remodelling. They are the most abundant cell type in the arterial vessel wall and are pivotal in maintaining vessel structure and function [27]. VSMCs have a contractile phenotype which facilitates contraction and dilatation of the artery. In response to biological stress signals or vascular injury VSMCs respond by losing contractility markers and differentiate towards a synthetic VSMC phenotype. These synthetic VSMCs are able to produce extra-cellular matrix (ECM) components such as collagen. To remodel the ECM, synthetic VSMCs produce matrix metalloproteinases (MMPs) such as collagenases and elastases, that allow them to migrate to sites of injury [28].

Synthetic VSMCs also produce extracellular vesicles (EV) that have been found in both the intimal and medial layers of the vessel wall. VSMCs are known to release EVs upon switching towards a synthetic or osteogenic phenotype (Fig. 5.1). EVs derived from VSMCs share similarities with EVs from osteoblasts having calcium-binding capacities and osteoblast-like ECM production [29]. But it has been shown recently [30] that not all EVs promote calcification. Differences between mineralising and non-mineralising EVs eventually determine calcification of the ECM in the proximity of VSMCs. Better insight into the composition of EVs such as lipid content and RNA and protein profile might reveal the mechanism by which VSMC derived EVs contribute to vascular calcification and result in novel targets for treatment. In response to calcified ECM, neighbouring endothelial cells and VSMCs react and induce the production of osteogenic factors such as bone morphogenetic protein 2 (BMP-2) and protein 4 (BMP-4) [31]. Besides this expression of bone-associated proteins, the number of VSMCs decreases with age, and an increase of collagen-to-elastin ratio further increases the stiffening of the vessel wall [15].

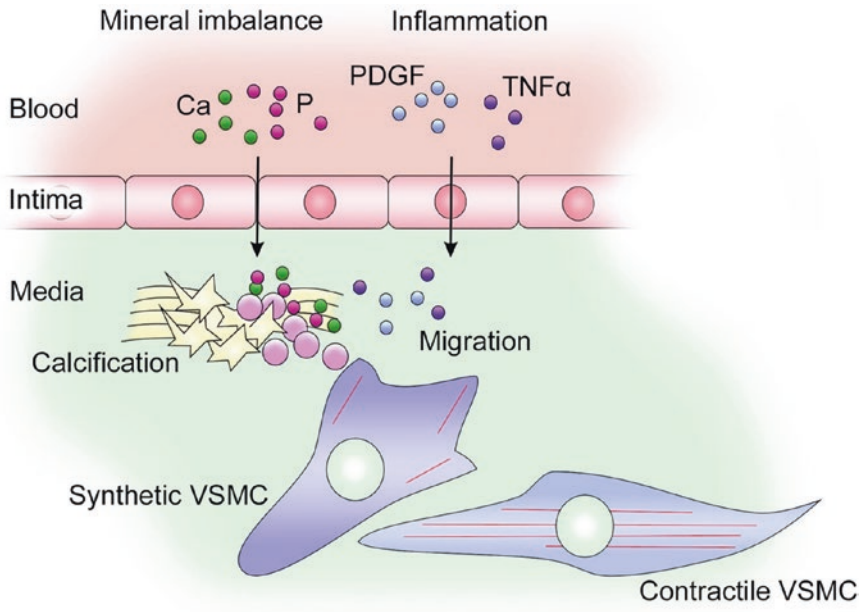

Fig. 5.1 Role of Vascular Smooth Muscle Cells (VSMC) in calcification. VSMCs are able to phenotypically convert from a contractile state to a synthetic state. Exosomes [large mauve dots] are produced by synthetic VSMCs and are active participants in calcification. Pro-inflammatory cytokines (TNFα) and growth factors (PDGF) as well as mineral imbalance stimulate exosome secretion by VSMCs

Regulation of Vascular Calcification

The clinical association of aortic calcification and osteoporosis often age-dependent, suggest a link between vascular and bone metabolism. There may be three causality vectors: firstly, vascular calcification promotes bone loss, secondly bone loss promotes vascular calcification and thirdly there may be a common aetiology.

Developmental Factors

A number of developmental regulatory factors, and their respective inhibitors, govern osteogenesis in skeletal bone and in both intimal and medial calcification. Master transcription factors such as, Msx2, Runx2, Osterix and Sox9, designate cells for osteoblast, as opposed to chondrocyte, lineages directly or indirectly through induction of downstream mediators such as type 1 collagen, alkaline phosphatase, osteopontin, tissue factor and osteocalcin.

Bone Morphogenetic Proteins

BMP2 and BMP4, potent osteogenic differentiation factors originally isolated from bovine bone, induce ectopic ossification in muscle tissue in vivo and mineralisation in smooth muscle cells in vitro. BMP acts through Runx2 which induces expression of type 1 collagen and alkaline phosphatase. BMP2 is antagonised by noggin, chordin and MGP. BMP4 is induced by tumor necrosis factor ligand superfamily member 11 (also known as receptor activator of nuclear factor κ-B ligand or RANKL) in rat smooth muscle cells. Another related protein, BMP7, inhibits calcification.

Matrix Gla Protein (MGP)

MGP, a BMP inhibitor, associates with conventional cardiovascular risk factors, but surprisingly, not with radiological coronary calcification. MGP is more highly expressed in calcified than in normal human arteries. The inhibitory role of this protein in vascular calcification was revealed with the unexpected phenotype of the MGP-deficient mouse which showed complete ossification of the aortic wall and major branches by calcified cartilage [8]. Later studies showed two mechanisms of MGP inhibition of calcification: direct binding of nascent crystals, and direct binding and inhibition of BMP2 [32]. MGP itself is inhibited by heat shock protein 70 as well as lack of vitamin K. MGP function depends on vitamin K-dependent gamma-carboxylation of glutamate residues, a process inhibited by warfarin. Accordingly, long-term warfarin treatment is associated with increased femoral artery calcification, and its possible contribution to other types of vascular calcification is under investigation.

RANKL

Expressed by osteoblasts, RANKL is an essential regulator of osteoclast differentiation. Deficiency of osteoprotegerin (OPG), a decoy receptor for RANKL, leads to medial calcification and acceleration of atherosclerosis in hyperlipidaemic mice. Unexpectedly, RANKL levels increase with age and reliably predict cardiovascular events. The OPG-RANKL system may govern differentiation of osteoclast-like cells at sites of vascular calcification.

In bone OPG may hold in check the pro-resorptive effects of RANKL, whereas, in the artery, OPG may hold in check inflammatory effects of RANKL. In support of this, OPG deficient mice have T-lymphocyte infiltration in their calcified arteries [33], T cells are associated with valvular calcification in humans. RANKL has been found in CD3-positive and F4/80-positive cells at the adventitial-medial junction in an atherosclerotic mouse model. Furthermore, ectopic mineralisation induced by

BMP2 treatment is not accelerated by the high turnover state of OPG deficiency. The importance of local RANKL-OPG signalling was highlighted by the finding that postnatal treatment with OPG failed to reverse the vascular calcification phenotype. Thus, rather than serving as the foundation of the bone-vascular axis, RANKL-OPG interactions may reflect tissue-specific immuno-modulation of OPG expressed in response to mechanical, endocrine and inflammatory cues.

Inflammatory Factors

Inflammation is closely associated with calcification. Macrophages, lymphocytes, and dendritic cells infiltrate plaque and release cytokines that regulate calcification. Perivascular adipose inflammation, and systemic inflammation associated with chronic kidney disease, might also contribute to intimal and medial calcification. A primary link between inflammatory and developmental mechanisms was identified as the tumor necrosis factor (TNF) activation of the Msx2-Wnt-β-catenin signaling cascade. An upstream pro-osteogenic pathway in osteoblast precursors of intramembranous bone is also activated in the vessels of diabetic, hyperlipidaemic mice.

Tumor Necrosis Factor

TNF induces the Msx2-Wnt-β-catenin signalling pathway, as do oxidant stress and hyperphosphatemia. TNF also promotes calcification in vitro by reducing expression of anti-apoptotic Gas6, and by inducing alkaline phosphatase via protein kinase A signalling. TNF may also act on alkaline phosphatase via NADPH-mediated generation of reactive oxygen species and induction of Msx2 expression. In vivo, targeted TNF overexpression in smooth muscle cells enhances Msx2-Wnt-induced calcification in LDL receptor-knockout mice, and the clinically used monoclonal antibody to TNF, infliximab, inhibits Wnt activation and calcification in these mice.

Gas6 and Axl

A prominent anti-apoptotic pathway in vascular smooth muscle cells is regulated by Axl tyrosine kinase and its ligand, Gas6, another Gla protein. Reduced expression of Axl and Gas6 correlates with progression of calcification in vitro, whereas restoration of the levels of these proteins prevents calcification [34]. These proteins are downstream effectors for a number of key regulators of vascular calcification, including inorganic phosphate, TNF, testosterone, and adiponectin. The role of Gas6 and Axl in cardiovascular diseases is probably complex, since they also mediate atherogenesis, platelet function and immune cell activation.

Fetuin A

Fetuin A, an abundant serum protein produced in the liver, binds and complexes calcium phosphate nanocrystals, to form calcioprotein particles and thereby prevents aggregation of calcium phosphate into insoluble mineral crystals and further growth. Fetuin A also promotes cellular uptake and removal of the complexes. As seen in bone, fetuin A accumulates at sites of vascular calcification. Other bone-associated proteins, including osteopontin, also bind calcium phosphate crystals. In vitro, fetuin A taken up by vascular smooth muscle cells reduces the ability of their matrix vesicles to calcify. Low fetuin A levels are associated with increased vascular calcification and mortality in patients with chronic kidney disease [35].

Crystals

Nanoscale hydroxyapatite crystals might have direct biological effects on cells through physicochemical interactions that trigger inflammation and apoptosis. These effects are known for pyrophosphate and urate crystals, but less appreciated for hydroxyapatite. A positive feedback loop may ensue when inflammation triggers mineralisation and mineralisation triggers inflammation. In osteoarthritis, crystals induce synthesis and secretion of matrix metalloproteinases and cell proliferation through ERK and calcium signalling.

Metabolic Factors

Excess lipids, phosphate and/or glucose, in the setting of chronic diseases, have direct and indirect effects on vascular calcification. Oxidant stress might be a central downstream mediator of these changes and their link with inflammatory and developmental processes described above.

Oxidant Stress

Oxidant stress alone, promotes vascular-cell calcification [36] and may account for the pro-calcific effects of inflammatory cytokines, oxidised lipids, and certain oxysterols. The classical oxidant stressor hydrogen peroxide (H_2O_2), promotes osteochondrocytic differentiation of vascular smooth muscle cells by up-regulating Runx2 [37]. The level of reactive oxygen species is increased at sites of calcification in human valves. Products of lipid oxidation, such as minimally-modified LDL and oxidised phospholipids induce osteogenic and apoptosis-mediated calcification of

vascular cells. The osteogenic differentiation induced by TNF and H_2O_2 is inhibited by insulin-like growth factor 1.

Hyperphosphatemia

Hyperphosphatemia, in addition to chemically promoting crystal formation is sufficient in vitro to increase osteochondrogenic gene expression in smooth muscle cells. Serum phosphate levels are regulated by phosphate itself, parathyroid hormone, and vitamin D, as well as by fibroblast growth factor 23 (FGF 23), which is released from bone osteocytes and activates its co-receptor Klotho in the kidney, to control phosphate elimination [38].

Vitamin D

High-dose dietary vitamin D reliably induces medial calcification; it is often used to generate vascular calcification in animal models. Although vitamin D generated in the skin by ultraviolet light is carried in the circulation by vitamin D-binding protein, dietary vitamin D is carried into the circulation via chylomicrons and then lipoprotein particles. When lipoprotein particles deposit in atherosclerotic plaque, the vitamin D they carry may be converted to the active form by the 1-alpha-hydroxylkase expressed in vascular smooth muscle cells and in monocytes and macrophages. This possibility could suggest the potential for vitamin D to promote atherosclerotic calcification and cardiovascular risk. Epidemiologically, both excess and insufficient vitamin D are associated with increased cardiovascular risk [39].

Insulin and Glucose

Studies in cultured smooth muscle cells have demonstrated that glucose directly promotes vascular cell calcification and insulin inhibits it. Despite the recognised increase in calcification observed in patients with diabetes, the role of glucose itself in humans remains to be determined.

Leptin and Adiponectin

The adipose-derived factors leptin and adiponectin promote and inhibit vascular calcification, respectively. Initially implicated in vitro, the potentially important and direct roles of these metabolic hormones were validated by the report of increased vascular calcification in leptin-treated, and adiponectin-knockout mice [40].

Genetic Pathways of Vascular Calcification

The genetic causes of medial calcification in the smooth muscle layer have been reviewed by Bowman and McNally [41]. As has been mentioned already vascular calcification is an actively regulated form of matrix mineral metabolism resulting in the deposition of calcium phosphate primarily in the form of hydroxyapatite (Ca 10 (PO_4) 6 (OH) 2) and hydroxyapatite crystals grow from extruded matrix vesicles. These vesicles are 100-200 nM particles that bud from the surface of osteoblasts, and contained within matrix vesicles are the beginnings of crystals. Matrix vesicles are the nidus around which bone formation occurs.

Vascular calcification has a heritable component. 40–50% of the variance of aortic and coronary calcification can be attributed to genetics. There are multiple contributing genes as well as environmental factors that mediate outcome. For vascular calcification, mechanisms affecting smooth muscle proliferation, endothelial function, response to reactive oxygen species, vitamin K metabolism, osteochondral differentiation, together with a growing list of physiological modulator molecules and environmental factors likely contribute to intimal calcification in atherosclerosis and medial calcification in the aorta. The genetic findings now focus on genes regulating extracellular phosphate metabolism, and one mechanism through which these genes exert their influence is via RAGE and S100 proteins.

RAGE is a receptor endogenously expressed in endothelial cells, macrophages, dendritic cells, smooth muscle cells and other vascular cells. RAGE is an immunoglobulin superfamily molecule whose multiple ligands have been shown to accumulate in disease conditions such as advanced glycation end products (AGE), the product of non-enzymatic glycation and oxidation of protein, S100 proteins, High Mobility Group Box 1 (HMGB1), amyloid beta and others. Once activated, RAGE initiates a cascade of downstream signals including activation of transcription factor NFκB, activation of ERK1/2 and MAPK [42]. There is substantial evidence for RAGE as a mediator of vascular disease [43] and interestingly, mice lacking RAGE have attenuated atherosclerosis seen in apolipoprotein-deficient mice [44]. More recent work has identified members of the calcium-binding EF-Land family of S100 proteins which are ligands for RAGE, as likely candidates involved in vascular disease and vascular calcification.

To date there are no reports of loss of function “Mendelian” mutation in the genes encoding RAGE and S100 A12 inhuman vascular disease. But a number of polymorphisms have been described, particularly in RAGE that have been linked to inflammatory states, especially diabetes. The CODAM (Cohort of Diabetes and Atherosclerosis in Maastricht) study linked the rs3134945 single nucleotide polymorphism (SNP) to higher glucose levels in diabetes [45]. A Finnish study associated a RAGE promoter polymorphism with protection in diabetic patients from coronary artery disease, myocardial infarction and peripheral vascular disease [46]. A coding polymorphism G28S was linked to diabetic nephropathy [47], although the same polymorphism was not associated with cardiovascular events in the general Framingham population. Together these data suggest that the RAGE pathway

mediates its effect most strongly in the diabetic population. A meta-analysis further reinforces the link between RAGE promoter polymorphism and protection from vascular complications in the type 2 diabetic population. Protein levels of soluble RAGE independently predict cardiovascular complications in type 1 diabetes, potentially reflecting the activation and production of RAGE in the context of accelerated vascular disease. Genetic control is only one means of regulating RAGE levels and therefore protein levels may be more predictive. The PREDICT (Personalised Risk Evaluation and Diagnosis in the Coronary Tree) study measured the blood expression levels of 23 different mRNAs, including S100A12, finding that this combination was effective at helping diagnose obstructive coronary artery disease in non-diabetic patients [48]. Thus, the RAGE and S100A12 pathway are broadly tied to inflammation and vascular disease. Further studies are needed to demonstrate whether genes encoding these proteins are specifically linked to vascular calcification as suggested by animal models.

In arterial calcification, as in many complex disorders, there are multiple contributing genes as well as environmental factors that determine outcome. Single gene Mendelian disorders are often useful for highlighting pathways that may not have been previously appreciated. For vascular calcification, mechanisms affecting smooth muscle proliferation, endothelial function, response to reactive oxygen species, vitamin K metabolism, osteochondral differentiation, together with a growing list of modulator molecules and environmental factors likely contribute to intimal calcification in atherosclerosis and calcification of the tunica media in arteries. The genetic findings now place focus on genes regulating extracellular phosphate metabolism, and one mechanism through which these genes exert their effect is through RAGE and S100 proteins.

Consequences of Vascular Calcification

Vascular calcification is associated with arterial stiffness. In chronic kidney disease, medial calcification of large arteries is directly responsible for the increased stiffness [49]. The presence of vascular calcification in the vessel wall contributes to ECM degradation and wall thickening [50]. Thus, vascular calcification contributes directly and indirectly to arterial stiffening and ultimately hypertension [51]. Atherosclerosis has also been associated with arterial stiffness and hypertension. Increased blood pressure and wall shear stress increase vulnerability and, consequently atherosclerotic plaques become prone to rupture [52].

For many years, calcification was considered to be a passive degenerative process, not amenable to intervention. This view has changed since statin treatment is associated with both increased plaque stability and decreased plaque calcification [53]. The apparent protective role of calcification in stabilising plaque contrasts with the predictive value of calcification for cardiovascular mortality and morbidity [54]. Medial calcification has been shown to change haemodynamics by inducing arterial remodelling processes and increasing arterial stiffness [55]. Medial

calcification strongly correlates with the phenotypical switching of VSMCs and a rise in blood pressure. Macro-calcification in patients who have had a CT scan were shown to have a 3 to 4 fold risk of developing fatal cardiovascular events [56]. In addition, micro-calcifications, which are precursors of macrocalcifications, have been shown to induce plaque vulnerability [57].

Cellular Processes of Vascular Calcification

Specific stimuli, such as elevated calcium or phosphate levels, induce the switching of VSMCs to an osteogenic phenotype where the cells acquire features of chrondrocytes and osteoblasts [58]. Osteogenic VSMCs show an increased expression of osteogenic markers, such as alkaline phosphatase, BMP-2 and runt-related transcription factor 2 (Runx2), but show decreased calcification-inhibitor protein expression [59]. VSMCs exposed to elevated calcium levels display an intracellular calcium overload that may induce microcalcifications, eventually resulting in macrocalcification which contributes to vascular stiffness and hypertension [60]. The process of calcification compromises the structural integrity of the vessel wall and hence its functional properties.

Oxidative stress is an important factor in the development of vascular calcification. Increased oxidative stress induces expression of Runx2, a key transcription factor associated with osteoblast differentiation [61]. Increased hydrogen peroxide levels have been found in the close vicinity of calcification nucleation foci together with an enhanced expression of oxidases [62]. High phosphate levels, present in chronic kidney disease, are associated with the extent of vascular calcification [63]. Advanced glycation end products, a feature found in diabetic patients, have been shown to induce vascular calcification via increased oxidative stress of VSMCs [64].

Imaging of Thoracic Aortic Calcification

Transthoracic Echocardiography

For many years thoracic aortic plaques have been identified by ultrasound techniques (transthoracic echocardiography). Echocardiography is a widely available, low cost and non-radiation technique and can be used to measure aortic dimensions, and to assess plaque mobility and characteristics (non-calcified from calcified atheroma). Transthoracic echocardiogram can be limited by poor echo windows in larger patients and poor visualisation of the aortic arch and descending thoracic aorta.

Severe calcification can confound the ECHO assessment due to reverberation artefact and acoustic shadowing [65]. Moreover, in distinction to the Agatston method for CT [66] ultrasound physics is not amenable to quantification of

calcification. Despite these limitations, echocardiographic assessment for thoracic aortic atheroma has been used to aid in the diagnosis of stroke, inform the probability of coronary artery disease and risk stratify for cardiovascular events [67, 68].

Transoesophageal Echocardiography (TOE), Atheroma and Stroke

TOE has an established role in the investigation of an embolic source of stroke due to three observations. Firstly, in an autopsy study of 500 patients, ulcerated plaques were found in the aortic arch in patients without an alternative cause for cerebral infarction [69]. Secondly, observational studies have shown that 20% to 30% of patients with embolic stroke have aortic arch atheroma on TOE [70]. Thirdly, case-control studies have demonstrated an association between thoracic aortic atheroma and stroke. In a study of 122 patients protruding atheromatous plaques (>5 mm) were associated with stroke after adjustment for traditional risk factors [71].

But the evidence to support causation between aortic atheroma and stroke is less compelling. In a prospective cohort study, aortic atheroma was not associated with cerebrovascular events after multi-variable analysis, although only 41 events occurred during a median follow-up of 5 years [72]. An observational study of 129 patients with thoracic aortic atheroma demonstrated an increased unadjusted risk for future embolic events if patients were not anticoagulated [73]. But larger observational studies with adjustment for confounding and randomised controlled trials are lacking.

Echocardiographic calcium may help in global risk stratification, but discrimination is poor and downstream changes in patient management are not defined. On a resting ECHO calcification for prognosis is therefore best relegated as a secondary assessment in a study performed for another indication.

Computed Tomography (CT) and Molecular Imaging

Aortic wall calcification can be identified on conventional angiography, and on CT scan. Calcium is best visualised on unenhanced CT due to the density difference between the calcium and the adjacent soft tissue or blood. Calcium can be quantified using a series of techniques for calcium volume and mass quantification, or by the standard Agatston technique. Contrast enhanced CT angiography will be best to differentiate calcium from non-calcified plaques and to measure aortic diameter, and to identify signs of acute aortic syndromes. The main risks of CT include exposure to ionising radiation, iodinated contrast associated nephrotoxicity and allergic reaction. MRI is a technique that can be used to investigate morphology of the aorta and for follow up. The technique, however, does not visualise calcium. On

computed tomography imaging (CT), intimal (atherosclerotic) calcification present as discontinuous lumps of calcium, whilst medial calcification is diffuse and linear in appearance (Fig. 5.2).

Sodium-Fluoride18 (NaF) positron emission tomography (PET) identifies the process of active bone formation in the aortic wall. Detecting early microcalcification using 18F-NaF PET/CT holds great promise [74] because it identifies necrotic material within vascular beds that drives further inflammation. Metabolic imaging and the emergence of novel radiotracers means that we can non-invasively identify metabolic activity related to inflammatory processes before structural changes manifest themselves. Much work remains to be done to bridge the gap between detecting aortic inflammation in at-risk individuals and predicting adverse clinical events. Novel radiotracers may hold the key to improve our understanding of vessel wall biology and how this relates to patients [75].

Recently, a rapid and efficient method for the detection of hydroxyapatite (HAP) has been developed which shows superiority to existing well-established methods. Sim AM and colleagues [76] have used a fluorescein-biphosphonate probe which is selective for HAP over other calcium minerals. This group have demonstrated

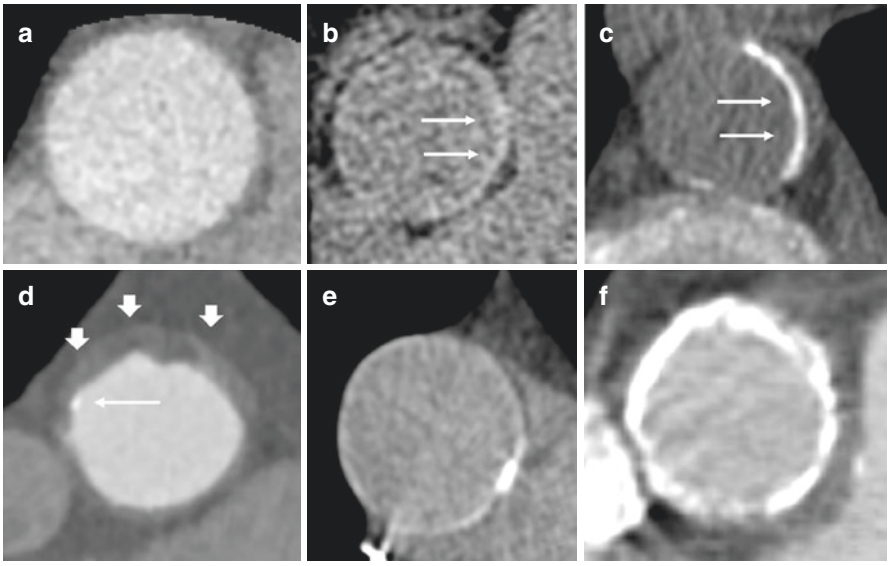

Fig. 5.2 CT variants of ascending aortic calcification. Axial contrast enhanced (**a**, **d**, **f**) and non-contrast (**b**, **c**, **e**) CT of the thoracic aorta. (**a**) Normal Aorta with no intimal or medial calcification; (**b**) Early medial calcium deposition as seen on non-contrast CT (arrow); (**c**) Established medial calcification that presents as diffuse, circular and linear calcification; (**d**) Intimal calcification (longer arrows): irregular and discontinuous calcified lump in association with non-calcified plaques (shorter arrows; (**e**) Often, medial and intimal calcification are seen simultaneously; (**f**) Porcelain calcification of the aorta (Image courtesy of Dr. Thomas Semple, Consultant Radiologist at the Royal Brompton Hospital, London, UK)

binding of this probe to vascular calcium in rat aorta and to areas of microcalcification in human vascular tissue beyond the resolution of computerised tomography in human atherosclerotic plaque.

Prognostic Implications of Thoracic Aortic Calcification on CT

There is a large amount of data regarding thoracic aortic calcification (TAC) and risk stratification arising chiefly from additional analyses of primary prevention cohorts that focused on coronary artery calcification. The results have been mixed and in studies of TAC notable differences apply to three areas.

The first relates to patient characteristics such as background risk and symptoms. The second applies to outcomes which vary from narrowly defined coronary events to more inclusive cardiovascular events to the least biased outcome, all-cause mortality. Thirdly, TAC itself has been disparately defined. For example, dedicated CTs for coronary artery calcification do not include the aortic arch and proximal descending aorta which are common sites of calcification. Furthermore, TAC can be expressed as binary or as a continuous variable with an Agatston score, extrapolating a method which was developed for coronary artery calcification. Finally, the relevance of TAC can be investigated independently or can be incorporated as part of an extra-coronary calcification score, which is similar to previous discussions regarding echocardiographic calcification.

Because of these considerations it has not so far been possible to construct a clinical prediction model for TAC. In the Multi-Ethnic Study of Atherosclerosis (MESA) trial, in an initial population of 6814 participants from 4 ethnic groups aortic wall calcification was present in 28.0% and approximately half of the participants had coronary artery calcification [77, 78]. Traditional cardiovascular risk factors were associated with aortic calcification, although hypertension and current smoking had the strongest associations [77]. At a mean follow-up of 4.5 years, only 1.9% had a myocardial infarction (MI), resuscitated cardiac arrest or cardiac death [79]. Similarly, in 3217 participants from the imaging cohort of the Framingham study, 42.5% had coronary artery calcification and 20.8% had TAC. During a mean follow-up of 8 years the event rate was low; 1.7% had a non-fatal MI or cardiac death [80]. By contrast, despite a similar enrolment period as MESA, the Heinz Nixdorf Recall (HNR) study had a prevalence of TAC of 63.1% and a prevalence of coronary artery calcification of 67.9% [81], which was likely due to higher baseline cardiovascular risk [82].

In the MESA and Framingham Heart studies after adjusting for clinical risk factors and coronary artery calcification, TAC was not independently associated with cardiac events. Likewise, in a report from the EISNER (Early Identification of Subclinical Atherosclerosis by Non-invasive Imaging Research) study, TAC did not

improve discrimination for cardiac events after adjustment for the Framingham Risk Score and coronary artery calcification [83]. The higher risk HNR study, which defined cardiovascular events as stroke, MI and cardiac death, found a trend toward a higher event rate (Hazard Ratio: 1.33; 95% CI: 0.87 to 1.81) after multi-variable adjustment [84].

The structure of the aorta is known to influence exercise systolic blood pressure response and this might have a predictive value especially in elderly individuals. Cho I-J and colleagues [85] retrospectively reviewed 702 individuals over the age of 60 years without obstructive coronary artery disease who underwent CT scan and exercise treadmill testing. The Thoracic Aortic Calcium Score (TACS) and Coronary Artery Calcium Score (CACS) were measured during the CT; during a median follow-up of 65 months there were 59 events (8.4%). In a multivariate Cox regression model independent factors for all events were: age, dyslipidaemia, and the fourth quartile on the Kaplan-Meier curve for thoracic aortic calcification (hazard ratio: 1.24; 95% CI: 1.03–1.49; p = 0.024). Among individual events the fourth quartile of TACS was the only independent predictor for stroke whereas CACS >400mm^2 was an independent predictor for obstructive coronary artery disease. The presence of aortic calcification was positively correlated with a rise in systolic blood pressure and a widening of the pulse pressure during exercise. These relationships remained significant after controlling for potential confounders including coronary artery calcification and resting blood pressure. In addition, aortic calcification was also related to adverse cardiovascular events, especially stroke whereas coronary artery calcification only predicted obstructive coronary artery disease events. Quantitative assessment of aortic calcification by use of TACS was feasible associated with exercise systolic blood pressure and proved a useful surrogate for long-term clinical outcomes other than coronary artery disease in elderly individuals.

Jolst BJ and co-workers in a multi-centre study in Germany assessed the hypothesis that severity of chronic obstructive pulmonary disease (COPD) independently predicts the extent of vascular calcification [86]. 160 smokers diagnosed with COPD and 40 smokers at risk (median age 60 years) underwent non-contrast, non-ECG-gated chest CT scans. The severity of COPD was a significant predictor of thoracic aortic calcification independent of other risk factors such as age or cigarette smoking. Thoracic aortic calcium scoring can be accurately performed on non-ECG gated CT images which are frequently carried out in COPD patients for a variety of clinical indications.

A retrospective study from Taiwan by Li and colleagues in 237 patients followed for 3 years showed co-existence of aortic calcification and cardiomegaly is associated with a faster decline in renal filtration as recorded by e-GFR, when compared to other patients with similar chronic kidney disease [87].

Therefore, among diverse primary prevention cohorts, TAC has not reliably demonstrated prognostic value for hard cardiac events independent of clinical risk factors and coronary artery calcification.

Calcified and Non-calcified Atherosclerosis

In primary prevention, CT scanning for risk stratification is obtained without intravenous contrast, in part because of the risks of contrast which include allergic reactions and renal damage. Moreover, the increased attenuation from contrast confounds assessment of the coronary artery calcification score. But the lack of contrast also precludes visualisation of non-calcified atheroma which may be especially prominent in the thoracic aorta (Figs. 5.2, 5.4). In a single centre study of 862 patients with ECG-gated, contrast-enhanced CT scans of the chest before cardiac surgery, the thickness and extent of aortic atheroma was measured in a semi-quantitative fashion [88]. Over a mean follow-up of 25 months, 119 patients died, and thoracic aortic atheroma was independently associated with all-cause mortality. Although contrast-enhanced studies in diverse cohorts are lacking, these results suggest that calcification alone is not the whole story in regard to the risk of thoracic aortic atherosclerosis.

The Porcelain Aorta

This has been defined as severe calcification that prevents safe aortic cross-clamping or cannulation [89]. In recent years CT has been used for pre-procedural planning and has facilitated a more standard definition by delineating the location and circumferential extent of atherosclerosis (Figs. 5.2, 5.3). Clinical trials in aortic stenosis have also been instrumental in this standardisation. According to the Valve Academic Research Consortium-2 consensus, a porcelain aorta is defined as "heavy circumferential calcification or severe atheromatous plaque of the entire ascending aorta such that cross-clamping is not feasible [90].

In an asymptomatic primary prevention population, porcelain aorta is rare. Investigations have focused on patients undergoing coronary artery bypass surgery, patients with severe aortic stenosis being considered for surgical aortic valve replacement (SAVR) or transcutaneous aortic valve implantation (TAVI) and patients with radiation-associated cardiac disease (RACD). In patients undergoing first time isolated coronary artery bypass grafting (CABG), a porcelain aorta is uncommon. Of 1800 consecutive patients with CABG at a single centre, only 23 had a porcelain aorta (1.2%) [91]. But these patients were diagnosed without CT scanning. The actual prevalence is probably higher, assuming that CT increases sensitivity beyond chest radiography and manual palpation. Epi-aortic ultrasound can also increase sensitivity and has been used to modify the approach at the time of operation [92]. A porcelain aorta is more common in patients with severe symptomatic aortic stenosis. In the inoperable PARTNER (Placement of AoRtic TraNscathEteR Valve) trial cohort, 15.1% of patients had a porcelain aorta, similar

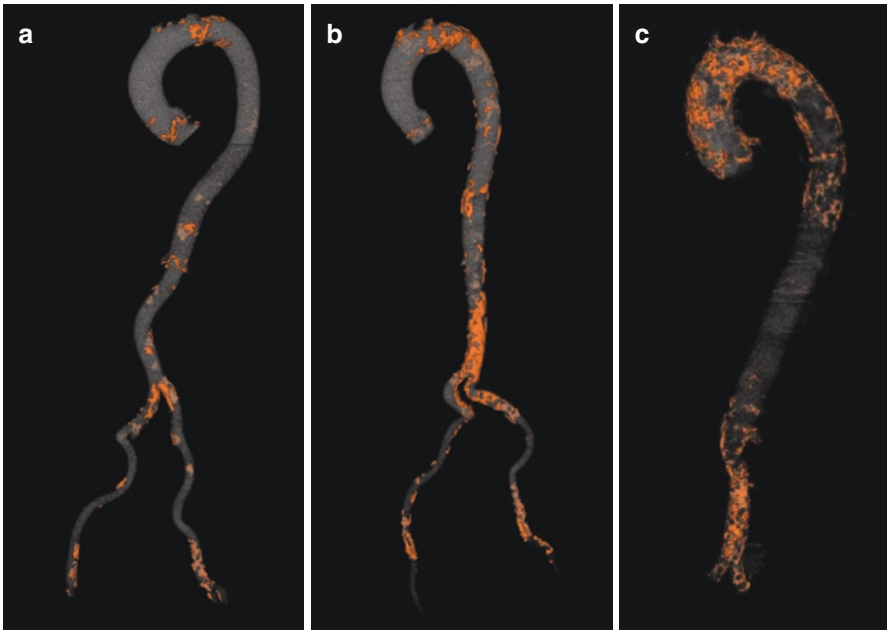

Fig. 5.3 Distribution of calcium in the aorta. Volume rendered CT angiography of the aorta (grey colour) in demonstrating various degrees and distribution of calcium (orange colour). (**a**) mild; (**b**) moderate; (**c**) severe calcification of the whole aorta (with porcelain calcification of the ascending aorta). Note that in all cases, the arch and infra renal aorta are particularly calcified

to the prevalence in a Canadian registry of high surgical risk patients with aortic stenosis (18.0%) [93, 94]. The prevalence decreases in a population of aortic stenosis patients with broader risk profiles and was 7.5% in one single centre study of 240 consecutive aortic stenosis patients [95].

It may be that the prevalence of porcelain aorta is lower than reported. Snow and colleagues [96] reviewed 175 consecutive CT aortograms in a large Transcutaneous Aortic Valve Implantation (TAVI) programme. They divided the aorta into 3 sections and each section into quadrants. These were individually scored using a 5-point scale. Results for each quadrant were summated for each segment to provide an indication of the distribution of calcification. Among these 175 patients they found only one (0.6%) who had a true porcelain aorta defined as contiguous calcification across all quadrants at any aortic level (Fig. 5.2). Intra-observer and inter-observer variation were minor for the ascending aorta (K = 0.85–0.88 and 0.81–0.96) respectively, while inter-observer variation in the transverse arch was slightly greater at 0.75. These findings are reassuring in an elderly patient population who are subjected to endovascular catheter manipulation in the aortic arch.

Imaging of Aortic Aneurysms

Recently Chowdhury and colleagues in a retrospective study have produced a well-validated assessment of calcium scoring in aneurysmal arterial disease [5]. Excellent reproducibility of score assessments within the arterial segments has been described. These data show that high scores are associated with poor outcomes and lend weight to the possibility of calcium scoring in clinical practice as a predictive tool of poor cardiovascular outcomes in patients with aneurysmal disease. A total of 319 patients (123 TAA and 196 AAA; median age 77 years, 77% male) were followed up for a median of 30 months. In the AAA group the calcium score was significantly related to all-cause mortality and cardiac mortality (OR 2.246; 95% CI 1.591–9.476; $p < 0.001$) and (OR 1.321; 95% CI 1.076–2.762; $P = 0.003$) respectively. In the TAA group, the calcium score was significantly related to all-cause mortality (OR 6.444; 95%CI 2.574–6.137; $p < 0.001$), cardiac mortality (OR 3.456; 95% CI 1.765–4.654; $p = 0.042$) and cardiac morbidity (OR 2.128; 955 CI 1.973–4.342; $p = 0.002$).

Interestingly, after regression analysis assessing the predictive power of aneurysm size and calcium score, it was only the score that proved significant to predict the outcomes irrespective of the size of the aneurysm. Aortic aneurysm calcification in either thoracic or abdominal territory is significantly associated with both higher overall and cardiovascular mortality. Calcium scoring, rapidly derived from routine CT scans may help identify high risk patients for treatment. The burden of aortic calcification is an accurate predictor of poor patient outcome. This warrants prospective validation.

Impact of Calcification on Acute Thoracic Aortic Syndromes (Fig. 5.4)

Acute aortic syndromes (AAS) describe a spectrum of life-threatening aortic pathologies with significant implications for diagnosis and treatment. The term AAS includes all of the following: aortic dissection (AD), intramural haematoma (IMH), penetrating atherosclerotic ulcer (PAU), and large unstable aortic aneurysm. A thoracic aortic aneurysm is considered unstable if it shows rapid enlargement or signs of impending rupture. An increase in size of >10 mm in 12 months or focal discontinuity of intimal wall calcification, the so-called “missing calcium sign”.

In the management of AAS hybrid procedures, branched and fenestrated endografts and percutaneous aortic valves have emerged as potent and viable alternatives to traditional surgery. In this context, multi-detector CT (MDCT) has become the gold standard in the emergency setting because of its intrinsic diagnostic value. Management of acute aortic disease has changed with the increasing realisation that endovascular treatments may offer distinct advantages in these situations.

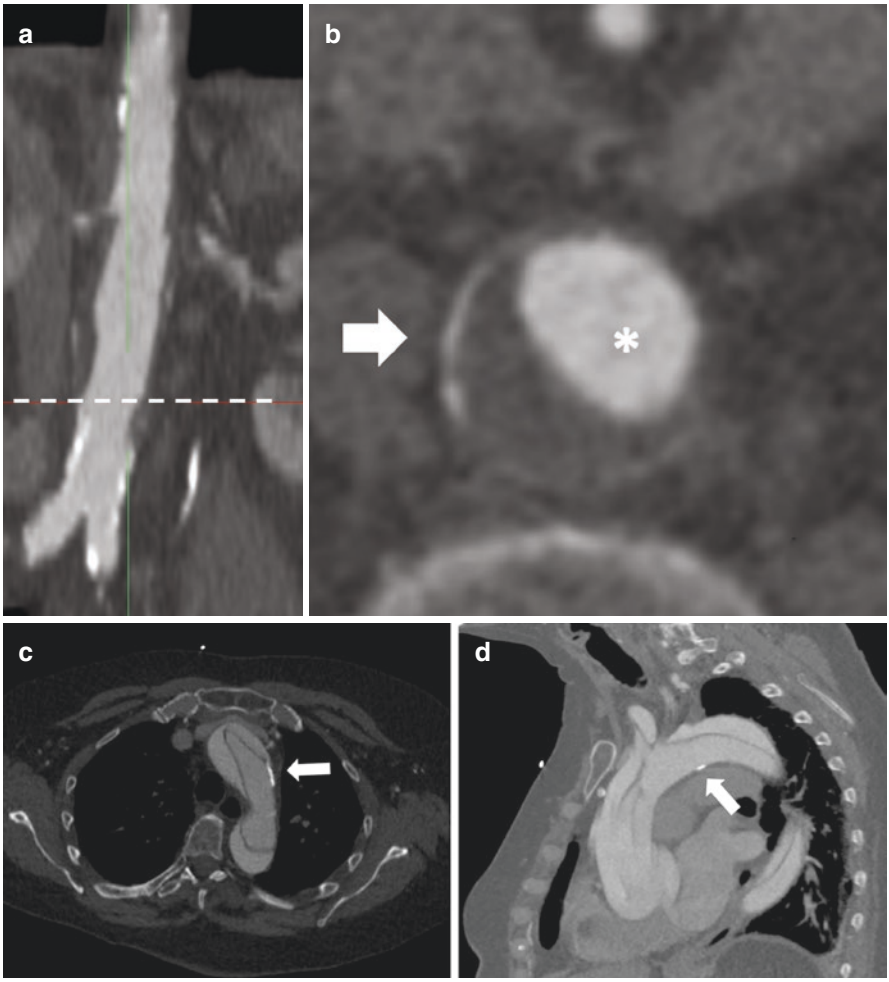

Fig. 5.4 Examples of various aortic pathologies on CT angiogram. (**a** and **b**) Diffuse atheroma of the abdominal aorta resulting in irregularity of the contrast lumen (coronal image **a**). Axial section at the level of the dotted line demonstrates extensive low attenuation atheroma between the aortic lumen (*) and the diffusely calcified aortic media (arrow). (**c** and **d**) Type-A aortic dissection. Axial (**c**) and double oblique multi-planar reconstructions show the intimal flap in the aortic arch and descending aorta. Note intimal calcifications, in this case not part of the flap (arrow). (**e**) Sagittal angiographic reconstruction of the thoracic aorta in a patient with Type-B dissection with no evidence of aortic calcification. (**f**–**h**) Intramural haematoma (IMH). Non-contrast axial CT of the aortic arch (**f**) showing dense thickening of the aortic wall (arrow) indicating fresh intramural haematoma. Post contrast (**g**), it is difficult to distinguish IMH from plaque. On sagittal reconstruction (**h**), calcification of the media is visualized (arrow). Dense pleural effusion indicates blood leak

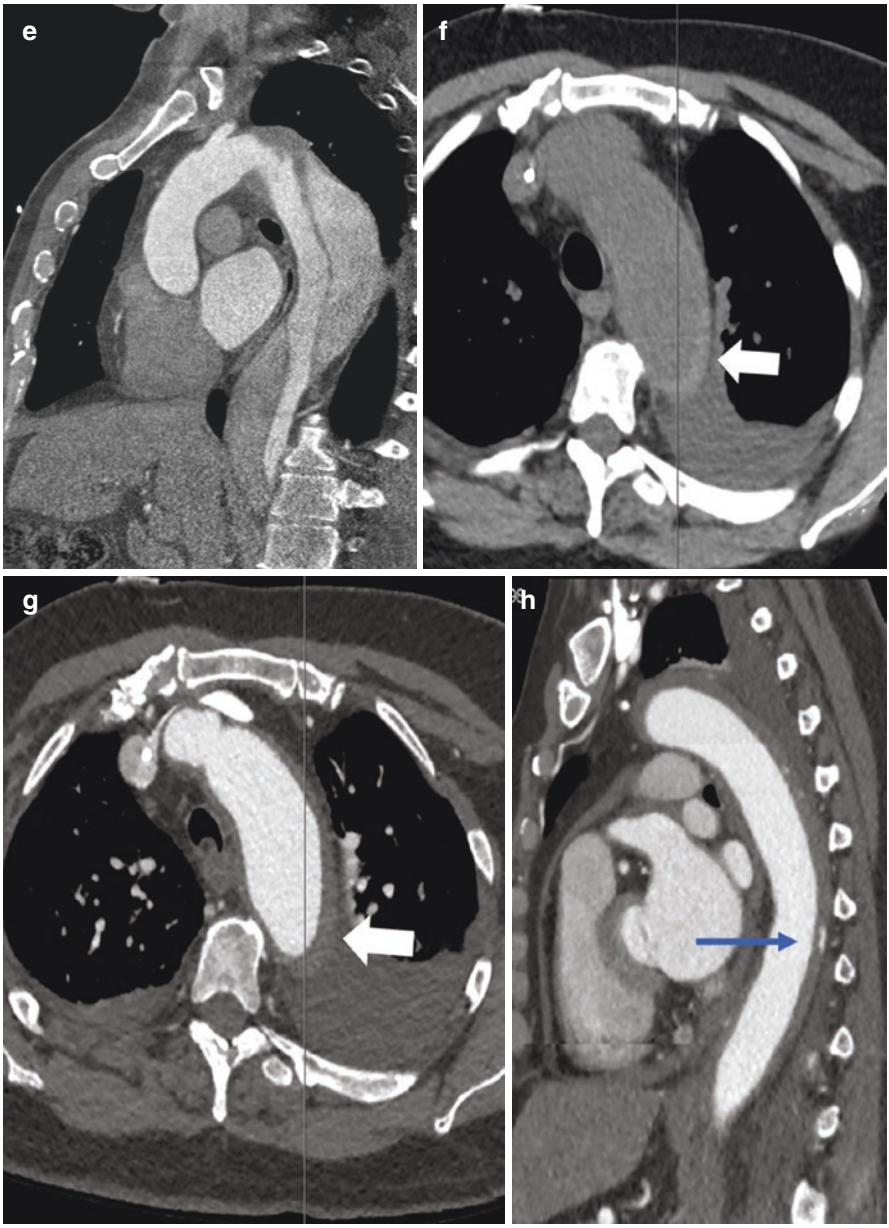

Fig. 5.4 (continued)

A study of 64 patients with type A and 32 patients with type B aortic dissection, significantly more calcification was observed in the ascending aorta and the aortic arch. However, aortic calcification was not an independent risk factor for dissection [97]. Another study of 344 patients with AAA showed that higher calcification was associated with risk of symptomatic non-ruptured and ruptured aneurysm [98].

Imaging of Aortic Dissection

Patients who present with acute chest pain will almost invariably undergo chest radiography (CXR). This is of minimal use in AAS as the sensitivity is 64% and specificity 86% for overt AD [99]. Importantly the CXR cannot be relied upon to definitively exclude acute aortic disease. Up to 20% of patients with AD will have a normal or near-normal CXR.

The diagnosis of AD by transthoracic ECHO is based on finding intimal flaps in the aorta. Transthoracic ECHO is restricted in patients with abnormal chest wall morphology, narrow intercostal spaces and obesity. These limitations can be overcome by TOE. A major advantage of ECHO is its portability which is useful in patients who are unstable. The disadvantages of TOE are operator dependency, limited acoustic window, an innate blind spot in the distal ascending aorta and proximal aortic arch due to air in the trachea and an inability to visualise the entire aorta.

A major advantage of MDCT over TOE is the ability to look beyond the aorta for alternative diagnoses such as pulmonary embolism. Because of its long acquisition time and inability to monitor patients who are acutely unwell in the MRI suite, MRI is mainly used for the follow-up of chronic AD. The choice of imaging modality for evaluating AD should adapt to local expertise and be individualised to the specific clinical situations.

Classic CT Findings of Acute Aortic Dissection (Fig. 5.4)

The pre-contrast phase is required to evaluate for displaced intimal calcifications which are suggestive of AAD, IMH and high-density blood in the pericardium, pleural space or mediastinum indicating aortic rupture (Fig. 5.4). The following is a summary of the important features of MDCT unenhanced phase in acute dissection:

1. Displaced intimal calcification along the true luminal aspect of the dissection flap in a Stanford Type B dissection.
2. Spontaneous high-attenuation intimo-medial flap in a right-sided aortic arch
3. Diffuse circumferential calcification of the ascending aorta (porcelain).
4. Calcified intimo-medial flap in a left-sided aortic arch extending into an “arteria lusoria”; aberrant right subclavian artery arising directly from the aortic arch.

5. Crescent of high attenuation within the wall of the aorta by acute false lumen thrombosis.
6. High-density intra-mural haematomas (Fig. 5.4): this is difficult to appreciate and easily overlooked.
7. High-density blood in the left pleural space and in the right mediastinum in aortic rupture.

Future Directions in Imaging and Drug Treatment

Advances in CT hardware and software post-processing evolution are opening a new era which will improve patient safety, reduce cost and improve patient care. Ongoing research in aortic computational flow modelling and molecular imaging is likely to map aortic disease at an earlier stage and to better risk stratify patients with established disease. With better understanding of predisposition and genetic risk, acute AD might soon become predictable and to some extent preventable by new biomarkers. The description of any particular dissection will be individualised by addressing specific features rather than using the simple classifications of the past. The ongoing advances in endo-vascular technology such as fenestrated and branched stent grafts directed to the most challenging segment of the aorta, the ascending and arch, will revolutionise the treatment of aortic disease.

Atherosclerosis, diabetes, aging, abnormal bone mineral homeostasis and chronic renal disease are major factors that contribute to the progression of vascular calcification. Several mechanisms such as the osteoblastic transition of VSMCs in response to oxidative stress have shed light on the active nature of vascular calcification, once thought to be a passive process. The fine interplay of regulatory factors such as parathyroid hormone, vitamin D3, FGF 33 and Klotho reflect the delicate balance between vascular calcification and bone mineralisation. Any disturbance affecting this equilibrium results in accelerated vascular calcification.

Biphosphonates share a similar mechanism of action as statins and hence several studies were undertaken in patients to see if the benefits proven to be obtained in animal models extended to the human as well. This yielded conflicting outcomes. The MESA trial was one of the first prospective studies which examined the use of bisphosphonates in preventing vascular calcification [100]. The participants were all women in ethnically diverse populations and across a wide age range, the mean being 63 years. There was a diffuse array of baseline co-morbidities. The results were age stratified, the primary end point being cardiovascular calcification. This study demonstrated that bisphosphonates reduce cardiovascular calcification in patients over 65 years, whereas an increase in cardiovascular calcification was seen in those under 65 years when compared to the control group of non-biphosphonate users. Whether the effect on cardiovascular calcification can be interpreted as a mortality benefit remains uncertain because mortality was not the primary end-point of the study.

Kranenburg and colleagues conducted one of the largest meta-analyses to date to ascertain the benefit of bisphosphonates in reducing vascular calcification and to see if it affects mortality [101]. 61 randomised controlled trials were used in this study, but each one had a different population and a different research question. The majority of the studies had a placebo administered as control whereas the rest used standard of care. There was a significant reduction in aortic wall calcification [102] and all-cause mortality with the largest benefit in patients with osteoporosis and breast carcinoma. Although this study revealed good outcomes in terms of all-cause mortality, the reduction in vascular calcification did not translate into a reduction in arterial stiffness, cardiovascular events or cardiovascular morbidity. This was partly due to inadequate sample size, duration of treatment and follow-up. Furthermore, adverse effects might have reduced the protective effect of biphosphonates on cardiovascular events and mortality. Further studies are required to establish the likely benefit of bisphosphonates on cardiovascular mortality.

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Chapter 6
Prognostic Value of Coronary Artery Calcium

Vahid Rezvanizadeh and Matthew J. Budoff

Introduction

Cardiovascular disease as the main leading cause of death in the world, remains as one of the most favorable topics in academic research. Given its importance, early diagnosis of cardiovascular disease helps to reduce mortality, morbidity, and related medical costs. During the past thirty years, Coronary artery calcification (CAC) has come a long path to be known as a robust indicator of subclinical atherosclerosis. Using CAC score helps clinicians to detect early stages of coronary artery disease. Also CAC score plays a significant role to assess the prognosis of atherosclerotic cardiovascular disease (ASCVD) events. Numerous studies have evaluated and validated power of CAC score as a strong predictive factor for ASCVD events. In this chapter, we will discuss the history of coronary artery calcium, utilization of CAC in the large cohort studies in both symptomatic and asymptomatic individuals, cost effectiveness of CAC scoring and the implication of CAC score of zero.

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History of Coronary Artery Calcium Score

Almost 46 years ago coronary artery calcification was evaluated in cardiac cine fluoroscopy studies. In 1974, Bartel AG et al. [1] performed cardiac fluoroscopy for 360 patients who were undergoing angiographic assessment. Among 154 patients with coronary calcification, 97% of them showed severe coronary stenosis in angiography.

In a report of 800 cardiac fluoroscopy and coronary cineangiography cases in 1980, Margolis et al. [2] demonstrated the prognostic and diagnostic value of CAC. Among 250 patients with detectable calcification in fluoroscopy, 236 of them (94%) showed >75% stenosis in at least one major coronary artery at angiography. Additionally, their study showed that survival rate in patients with coronary artery calcification (58%) is less than the patients without calcification (87%).

Electron-beam computed tomography (EBCT) with cardiac gating technique was developed in 1979. This imaging modality with fast and high quality image acquisition of coronary arteries substantially improved the CAC detection in the coronary tree. In 1990 Agatston et al. [3] used Electron Beam Computed Tomography (CT) to detect and quantify calcium in coronary arteries. They demonstrated that Electron Beam CT is more sensitive than fluoroscopy in detecting CAC in patients (95% versus 52% respectively). Given the high sensitivity in detecting calcium, they recommended that Electron Beam CT can be used as a standard screening tool for coronary artery calcification. Multi-Detector CT (MDCT) scanners provide better image quality with the use of more detectors. In 2009, Mao et al. [4] compared the coronary artery calcium scores quantified by MDCT with the older generation Electron Beam CT scanner (EBCT). They demonstrated that CAC scores quantified by MDCT scanner correlates significantly with CAC scores which are done by EBCT scanner.

Given the advanced image quality and consistency with older generation CT scanner, cardiac-gated MDCT became the preferred imaging modality to quantify CAC score. In addition, because of fast gantry rotation in MDCT, even non-gated Chest CT scan studies could provide CAC scores with high correlation with cardiac-gated studies, which makes CAC quantification available in different clinical settings. [5, 6]

Coronary Artery Calcium Score in Large Cohort Studies

Cohort studies with large study population and long-term follow-ups validated the importance of Coronary artery calcium score as a non-invasive indicator of subclinical atherosclerosis and its predictive capability for future cardiovascular event.

The Framingham Heart Study

The US Public Health Service initiated the Framingham Heart Study (FHS) in 1948 to examine the risk factors and prognosis of major diseases including cardiovascular and lung diseases [7]. Initially this prospective cohort study recruited 5209 men and women from Framingham city with age 30 to 62 years and free of known coronary heart disease. After twenty-three years, 5124 offsprings of the original Cohort and their spouses were enrolled in the Framingham Offspring Study [8].

In 1998 Wilson et al. using the Framingham study data, developed a multivariable risk assessment tool, which is known as Framingham Risk Score (FRS) to evaluate the cardiovascular event risk for every individual [9]. The Framingham Risk Score models categorized the population into three risk groups based on the 10-year risk of future cardiovascular events: less than 10% (low risk), 10–20% (intermediate risk) and >20% (high risk). The Framingham risk score emerged as main tool to cardiovascular risk stratify the population. The third generation cohort of Framingham Heart study enrolled 4095 participants including 1912 men and 2183 (53%) women with mean age of 40 years [10]. All participants of the third generation cohort went under clinical and laboratory assessments of vascular risk factors. They also utilized imaging modalities including MDCT for assessment of subclinical atherosclerosis.

In 2008, Hoffmann et al. [11] studied the normal distribution of coronary artery calcium in men and women in the Framingham Offspring and Third generation heart study. They recruited Participants who underwent non-contrast multidetector computed tomography (MDCT), including 48%women and mean age of 53 years. They provided the prevalence of absolute CAC scores (>0, >100 and >400) and relative age and sex strata (25th, 50th, 75th, 95th percentile) for three groups of participants. These three groups included healthy participants without any apparent cardiovascular disease and CHD risk factors (n = 1586), subjects at intermediate Framingham Risk Score (FRS = 6–20% 10 year risk CHD event risk) and the overall sample at risk (n = 1177). Their study provided specific normal distribution of CAC for age and sex, which is more helpful in clinical practice.

In 2018, Ferencik et al. using Framingham heart study (offspring and third-generation cohorts) studied 1268 subjects with CAC score >0 and free of prior coronary heart disease (mean age of 56.2 ± 10.3 years, 62% men). After median follow up of 7.4 years, total 42 major CHD (myocardial infarction or coronary heart disease death) events occurred. Their study emphasized that not only the CAC score, but also the distribution of CAC in the proximal segment of dominant coronary artery and number of coronary arteries with CAC are predictive for major CHD events [12].

The Rotterdam Coronary Calcification Study

In 1991, the Rotterdam Elderly Study [13] initiated as a prospective cohort of participants with age ≥ 55 years of the district of Ommoord in Rotterdam. The study aimed to determine etiology and risk factors of cardiovascular, neurogeriatric, locomotor and ophthalmologic diseases and provide the preventive strategies and recommendations. From 1997 to 2000, coronary artery calcification was assessed using electron beam scanner in 1795 asymptomatic participants with ages ranging between 62–85 years; and with a mean age 71 years. They also recorded traditional risk factors of cardiovascular events for all participants. Study participants were followed for a mean of 3.3 years. A total of 88 cardiovascular events including 50 coronary events were recorded. The relative risk of coronary events for CAC scores of 101 to 400, 401 to 1000, >1000 were 3.1, 4.6, and 8.3, respectively; compared with CAC score of zero. Their study demonstrated that the risk of coronary heart disease increases by higher calcium scores. In addition, they concluded that adding CAC scores could improve the risk prediction based on traditional cardiovascular risk factors and could play important role in primary prevention of coronary heart disease events in the elderly [14]. The Rotterdam Coronary Calcification study also emphasized that coronary artery calcification is the strongest independent predictive factor of coronary heart disease in the elderly population [14].

Vliegenthart et.al [15] using population-based Rotterdam study, concluded that the age-adjusted odds ratio for myocardial infarction (MI) in subjects with CAC score above 2000 is 7.7 for men and 6.7 for women (95% CI, 4.1–14.5 and 2.4–19.1, respectively), compared with subjects of CAC between 0–100. They concluded that this correlation exists in all age subgroups including subjects ≥70 years.

The Multi-Ethnic Study of Atherosclerosis (MESA)

The Multi-Ethnic Study of Atherosclerosis (MESA) [16] initiated in 2000 to investigate the prevalence, correlates and progression of subclinical cardiovascular disease (CVD). In this multicenter population-based cohort study of 6500 men and women free of clinical cardiovascular disease with age range of 45–84 years, four racial/ethnic groups were included: 38% White, 28% African-American, 23% Hispanic, and 11% Asian. At the baseline multiple measurements including coronary calcium score, standard CVD risk factors, measurement of ventricular mass and function using MRI, measurement of flow-mediated brachial artery endothelial vasodilation, carotid intimal-medial wall thickness and distensibility of the carotid arteries using ultrasonography were done. They followed participants with focus on cardiovascular disease events including acute myocardial infarction and other coronary heart disease, stroke, peripheral vascular disease and congestive heart failure; and mortality or interventions related to them.

In a study of 1461 asymptomatic adults from MESA with at least one coronary risk factor, Greenland et al. assessed the practicality of CAC score in risk stratification along with Framingham Risk Score (FRS). They followed up patients for a median of 7 years. Their study showed that high scores of CAC (300 or more) could modify predicted risk obtained from FRS especially in patients of intermediate-risk [17].

In addition, Taylor et al. in a study of 2000 healthy men and women ages 40 to 50 (from MESA study population) pursued the value of CAC score to predict incident premature coronary heart disease over measured cardiovascular risk factors. They evaluated participants with measured coronary risk variables (FRS) and CAC score detected with electron beam CT scanner. In mean follow-up of 3.0 ± 1.4 years total of 9 acute events occurred, only in men, 7 of them had showed coronary calcium in their scan. Their study demonstrated that in young men, the presence of coronary artery calcification plays as prominant independent prognostic factor to predict premature coronary heart disease events [18].

Detrano et al. assessed the correlation of CAC scores and future cardiovascular events in the MESA study [19]. During median follow-up of 3.8 years total 162 coronary events were recorded, of which 89 major events including myocardial infarction or death were resulted from coronary heart disease. Participants with CAC scores between 101 and 300 showed increased adjusted risk of a coronary event by 7.73, compared with participants with CAC score of zero. For the patients with CAC score above 300 this increase in adjusted risk compared with patients free of CAC, was 9.67. They also demonstrated that doubling the CAC score resulted in 15 to 35% increase of major cardiac events. There were no major differences in predictive value of calcium scores for coronary heart disease, between the four races included in the study.

In the MESA study, Kronmal et al. studied the association of traditional cardiovascular risk factors with the incidence and progression of coronary artery calcium [20]. Between this cohort's participants, 5756 participants had follow-up CAC measurements, with average of 2.4 years between scans. The average incident rate of newly detectable CAC was 6.6% per year. This annual incident rate was increased by age, which was more than twice in age > 80 years compared with age < 50 years. They showed that most of the traditional cardiovascular risk factors including age, male gender, hypertension, diabetes, body mass index and family history of heart attack are associated with CAC development and progression. Diabetes mellitus demonstrated strongest relation with CAC progression in African-American race, and weakest for Hispanic race. On the other hand, for other risk factors this relationship was similar in four different races.

Blaha et al. [21] compared the power of negative risk factors of CVD in the MESA study to see how these negative risk factors could help to re-classify patients in the proper risk group categories. Negative risk factors included CAC score of zero, Ankle Brachial Index (ABI) >0.9 and <1.3, carotid intima-media thickness (CIMT) <25th percentile, brachial flow-mediated dilation >5% change, NTpro-BNP <100 pg/ml, absence of carotid plaque, no microalbuminuria, no family history of CHD, absence of metabolic syndrome and healthy lifestyle, High sensitivity

C-reactive protein (hsCRP) <2 mg/L and Homocysteine <10 μmol/L. Their analysis demonstrated that CAC score of zero is the strongest negative risk factor for CHD and CVD. They concluded that CAC score of zero might help for the re-classifying patients in appropriate risk groups for CVD and thus preventing putting patients on unnecessary pharmacotherapy.

The Heinz Nixdorf RECALL Study

In 2000, The Heinz Nixdorf RECALL [22] (**R**isk factors, **E**valuation of **C**oronary Calcium and **L**ife style) study aimed to assess the silent atherosclerotic disease and related predictive risk factors for myocardial infarction and cardiac death in healthy middle-aged patients in Germany. They randomly recruited 4487 residents of the Essen, Mülheim, and Buchum cities (2027 men, 2248 women) with age 45 to 74 years, free of coronary artery disease. At the baseline, 95% of participants (4275) underwent Cardiac CTA scan using electron beam CT scanner. All participants were followed for mean 5.1 ± 0.3 years and underwent for second Cardiac CTA scan. They followed participants who were free of cardiovascular event at the second scan (n = 3281, 53% women) for another mean 7.8 ± 2.2 years, and recorded the cardiovascular events. Over a mean of 12.9 ± 2.2 years follow-up 85 hard coronary (i.e. 161 hard cardiovascular and 241 total cardiovascular events occurred [23]. Subjects with baseline CAC ≥ 400 experienced high rates of hard coronary and hard or total cardiovascular events and 10-year risks were 12.0%, 13.5% and 30.9%, respectively. On the other hand, participants with CAC score of zero in the baseline and second scan (double-zero subjects) experienced substantially less coronary and hard or total cardiovascular events and 10-year risks were 1.4%, 2% and 2.8%, respectively [23]. Their study also demonstrated that subjects with CAC score of 1 to 399 at the base line, who had CAC score of ≥400 in the second scan, experienced two-fold CVD events compared with participants whose CAC score remained less than 400.

Coronary Artery Calcium Consortium

CAC Consortium study in 2017, studied the role of coronary artery calcium and traditional risk factors for predicting CVD and CHD mortality [24]. Four institutions from three states including Minnesota, Ohio and California contributed in this study. This multicenter cohort study consisted of 66,636 subjects with mean age 54 ± 11 years, majority of male (67%) and predominantly white population (89%). All the participants who were free of coronary heart disease (CHD) underwent CAC scoring at the baseline from 1991 to 2010. All the CAC scans had clinical indication

and had referral by physicians. Investigators recorded Risk factors including Diabetes, Hypertension, Dyslipidemia, Family history of CHD and Current cigarette smoking. With 12.5 years median follow-up, 3158 deaths including 32% cardiovascular deaths occurred. Based on study results, patients with CAC scores of ≥400 had higher risk of CHD and CVD related mortality compared with the patients with CAC score of zero (Hazard ratio: 5.44 versus 4.15). CAC consortium study also demonstrated that in each risk factor burden (low, intermediate and high risk groups), higher CAC score is highly associated with higher all-cause mortality and higher proportion of CVD/CHD deaths. CAC score of zero in each risk factor burden showed low risk of all-cause mortality, which most was non-CVD/CHD related mortalities [25].

Coronary Artery Calcium Score in Asymptomatic Individuals

The coronary calcium score as an indicative of atherosclerosis could play substantial role in choosing the appropriate preventive strategy for cardiac events. CAC score can assist in patient-clinician decisions to modulate the intensity and type of prevention methods. For example within low-risk category of traditional risk factors patients with CAC score of zero would have different preventive strategy than the patients with CAC score > 400.

In a study of 1172 asymptomatic men and women (men 71%, age 53 ± 11 years), Arad et al. [26] sought to determine the prognostic accuracy of Electron Beam Computed Tomography (EBCT) Scan of coronary arteries for Coronary events. During an average of 3.6 years follow-up, 39 participants experienced coronary events including 3 coronary deaths, 15 nonfatal myocardial infarctions and 21 coronary artery revascularization. The mean CAC scores were significantly higher in the subjects with events, compared with subjects free of events (746 ± 935 versus 135 ± 432, $p < 0.0001$). In their study, CAC score ≥ 160 was associated with odds ratios of 15.8 for all coronary events and 22.2 for nonfatal MIs.

In a prospective study of 676 asymptomatic patients (mean age 52 years, 51% men) with follow-up of 32 ± 7 months after EBCT, the age and sex-specific calcium score (CS %) demonstrated best predictive value for hard coronary events. In receiver-operator characteristic curves for prediction of hard coronary events, the area under the curve of CS% alone was shown significantly larger than traditional risk factors and age combined (0.82 vs 0.71, $P = 0.028$) [27]. Their analysis also demonstrated that age and sex-specific calcium score adds incremental prognostic information to conventional risk factors for CAD.

Kondos et al. [28] studied the correlation of CAC and cardiac events in asymptomatic low to intermediate risk individuals. In cohort of 8855 asymptomatic men (74%) and women (26%) with age 30 to 76 years, they performed EBCT for CAC screening and recorded the traditional coronary artery disease risk factors. During

follow up of 37 ± 12 months 224 confirmed cardiac events occurred. Their analysis indicated that in women events correlates with existence of CAC (RR = 2.6, P = 0.037), but not with risk factors. For men presence of CAC correlated with cardiac events (RR = 10.5, P < 0.001) and this correlation was stronger than diabetes (RR = 1.98, P = 0.008) and smoking (RR = 1.4, P = 0.0025).

In a mean of 5.0 years follow up of 10,377 asymptomatic individuals undergoing cardiac risk factor evaluation and coronary calcium scoring with death rate of 2.4%, Shaw et al. [29] demonstrated that coronary calcium is an independent predictor for all-cause mortality (P < 0.001). Risk-adjusted relative risk for CAC scores 11–100, 101–400, 401–1000 and greater than 1000 were 1.64, 1.74, 2.54, and 4.03 respectively compared with CAC score of 0–10 (P < 0.001).

Arad et al. in the St. Francis Heart Study [30] followed up the 4613 asymptomatic participants of age 50–70 years with baseline utilization of EBCT, standard coronary disease risk factors and C-reactive protein. During 4.3 years follow-up, 119 atherosclerotic cardiovascular disease (ASCVD) events occurred. Overall, the subjects who experienced ASCVD events had higher baseline CAC scores compared with subjects without ASCVD events (mean CAC score 384 versus 10).

During 1995–2000 LaMonte et al. [31] recruited 10,746 asymptomatic participants (64% men) aged 22–96 years old. At the baseline, they quantified CAC scores using EBCT. During follow-up of 3.5 years, 287 events (CHD death, nonfatal myocardial infarction and coronary revascularization) occurred, 81 of which was hard events (CHD death and nonfatal MI). Their analysis suggested the incremental association of CAC scores with CHD events in asymptomatic subjects in younger (age < 40 years) and older (age > 65 years) population (P < 0.0001).

In a registry of 25,253 consecutive asymptomatic individuals (mean age of 56 ± 11 years, 54% men) who were referred by primary care physicians for CAC scanning to assess the cardiovascular risk, Budoff et al. [32] studied the effect of CAC scores in prediction of all-cause mortality. During mean follow-up of 6.8 ± 3 years, they recorded 510 deaths (2% death rate). Their analysis depicted CAC as an independent predictor of mortality in the multivariable model controlled for age, gender, ethnicity, and cardiac risk factors (model chi-square = 2017, P < 0.0001). Risk adjusted relative risk ratios for CAC scores of 11–100, 101–299, 300–399, 400–699, 700–999 and > 1000 were 2.2, 4.5, 6.4, 9.2, 10.4 and 12.5 fold, respectively when compared to CAC score of zero (p < 0.0001). Addition of the CAC scores to traditional risk factors had an incremental effect on concordance index (0.61 vs. 0.81, P < 0.0001).

In 2007, Detrano et al. [19] studied population-based sample of MESA study, including 6722 asymptomatic men and women with 38.6% White, 27.6% Black, 21.9% Hispanic and 11.9% Chinese. They collected data on traditional risk factors and CAC scores, and followed participants for median 3.8 years. Total 162 coronary events, including 89 major events (myocardial infarction or death from coronary heart disease) occurred during follow up. The adjusted risk of coronary events for subjects with CAC scores of 101–300 and > 300 were 7.73 and 9.67, compared with subjects with CAC score of zero (P < 0001).

Coronary Artery Calcium Score in Symptomatic Patients

Multiple studies have proven incremental value of CAC scores in prediction of cardiac events in symptomatic patients when added to traditional risk factors. The increased CAC score could be a sign of high probability of future cardiac mortality and morbidity.

Although CAC score could play a significant role in patient-clinician decisions regarding preventive strategies in asymptomatic patients, multiple studies also demonstrated importance of predictive value of CAC score in symptomatic patients.

In a multi-centric study [33] between 1989 and 1993, 491 symptomatic patients (57% men, mean age of 55 years old) underwent EBCT and coronary angiography. A cardiologist with no knowledge of subjects' angiographic data, interpreted the EBCT data. They followed-up subjects for 30 ± 13 months. During Follow-up, 13 coronary heart disease deaths and 8 nonfatal acute myocardial infarctions occurred and reviewed by three cardiologists with no knowledge of EBCT and coronary angiographic results. They divided CAC scores in 4 quartiles, CAC score of (0 to 2.1), (2.1–75.3), (75.3–397.1) and CAC score > 397.1. Number of cardiac events were 1, 2, 8, and 10 for first, second, third, and fourth quartiles, respectively. They concluded that CAC scores predicts coronary heart disease events in patients undergoing angiography.

In a cohort of 924 symptomatic patients in Germany (52% women, mean age of 59 ± 18 years) with no significant stenosis in angiography, Becker et al. [34] conducted cardiac CT using MDCT and followed subjects 36 months. CAC score of zero was reported in 20% of participants (188 patients). During follow-up period, they recorded 28 cardiac deaths and 50 myocardial infarctions. All of the 78 cardiac events happened for subjects with CAC scores >zero and none of the subjects with CAC score of zero experienced cardiac events.

Rozanski et al. [35] assessed the cardiac deaths and myocardial infarctions in a registry of 1153 patients (age 58.4 ± 10 years, 74% men) who underwent both CAC scan and myocardial perfusion scintigraphy (MPS). Their analysis demonstrated that increase in CAC scores correlates with increase in myocardial ischemia, although only 64 patients had ischemia during the 32 ± 16 months of follow-up ($P < 0.001$).

In a combined Positron Emission Tomography/Computed Tomography (PET/CT) study, Schenker et al. [36] assessed the correlation of CAC score and myocardial ischemia and outcomes in intermediate risk population. In a population of 621 symptomatic referred-subjects for rest-stress rubidium 82 PET scan (60% women), they also assessed the CAC scores. Abnormal scans in subjects with CAC score > 400 was more than 2 times higher, compared with subjects with CAC scores 1 to 399 (48.5% versus 21.7%, $p < 0.001$). During mean follow-up of 17 months, total 55 cardiac events including 33 cardiac death and 22 myocardial infarction occurred. Risk-adjusted survival analysis depicted that in subjects with or without ischemia on PET myocardial perfusion imaging, higher CAC scores correlates with higher event rates [36].

Cost Effectiveness of Coronary Artery Calcium Scoring

As a reliable predictive tool for cardiovascular diseases, CAC has attracted physicians and analysts to study this tool's cost-effectiveness. Using the data sets and results from the Rotterdam Coronary Calcium Study, the Multi-Ethnic Study of Atherosclerosis, and the Framingham Heart Study, All the cost-effectiveness studies concluded that CAC testing in asymptomatic individuals is cost-effective [37–41]. The main factors considered in these studies were the costs and side effects or discomforts of statin therapy. Van Kempen et al. [37] applied Markov model to assess cost-effectiveness of CAC scanning in asymptomatic individuals with intermediate risk of CHD in Rotterdam study. They concluded that CAC scanning could be cost-effective in men with intermediate risk of CHD, but not in women.

In a cost-effectiveness analysis Pletcher et al. [38] demonstrated that CAC testing can be cost-effective in intermediate risk patients only if either the cost of statin pills or the side effects are high. They concluded that if statin therapy is less favorable ($1.00/pill and disutility = 0.00384), using CAC score > 0 as indication of statin therapy would be cost-effective.

In another cost effectiveness study focusing on data from MESA study, Roberts et al. [39] compared CAC-based treatment with "treat all" strategy and treat based on Adult Treatment Panel III (ATP III) guidelines. They modeled clinical and economic outcomes for five and ten year's horizons. Their analysis depicted that it is more cost saving and effective to scan patients of intermediate-risk and treat those with CAC score ≥ 1. Treating the patients with CAC ≥100 was also preferred compared to the existing guidelines, when they considered the disutility and side effects of statin use.

On the other hand, Galper et al. [40] demonstrated that for primary prevention of CHD, treating all individual with moderate/high dose statin and all men with low-dose aspirin is more cost-effective than all risk stratification approaches. In their analysis, they compared treat-all strategy with ACC/AHA guideline, the Adult Treatment Panel (ATP) III guideline, and approaches based on CAC score and C-reactive protein (CRP). They also concluded that ACC/AHA guidelines, despite the more utilization of aspirin, are more cost-effective than ATP III guidelines.

In 2016, Kempen et al. using the data of Framingham Heart Study demonstrated that utilizing CAC testing prior to statin therapy in men is cost effective, while screening with hsCRP seems to be cost-effective in women. They recommended that the individual's disutility of taking the daily aspirin should play a key role in choosing the proper strategy [42].

A recent cost-effectiveness analysis by Hong et al. stated that the economic value of both "treat all" and "CAC based" strategies is similar, but considering the disutility of using daily statin the CAC strategy is favored. They suggested that individual's preferences should play key role in the context of shared-decision making of preventive strategies with patients [41].

Based on the results of these studies, utilizing CAC score in intermediate risk patients could be cost-effective. In addition, the power of CAC score to facilitate the patient-physician discussion about preventive strategies makes it more beneficial in clinical practice.

Coronary Artery Calcium Score of Zero

Among the CAC score spectrum, CAC score of zero always has demonstrated strong value as an indicator of favorable prognosis. CAC = 0 is one of the "negative risk factors" for future cardiovascular events [43]. Using CAC score of zero resulted in substantial downward shift in estimated cardiovascular disease (CVD) risk.

Studies in 2009 and 2012 demonstrated that CAC score of zero is a predictor of very low 10-year mortality rate; approximately 1% [44] and 2% [45] in both elderly and young patients. This favorable prognosis of CAC score of zero also has proved itself in different groups, including patients with multiple traditional risk factors (extremes of RF burden) [46], impaired lipid profile [47], elderly patients [45] and metabolic syndrome [48].

Handy et al. [49] sought the association of CAC score with non-cardiac diseases over median follow up of 10.2 years in 6814 subjects of MESA study. Their study showed that CAC score of zero decreases the risk of cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and hip fracture.

Additionally, studies compared the power of CAC score of zero with other negative risk factors. Blaha et al. [50] studying 6814 participants of Multi-Ethnic Study of Atherosclerosis (MESA), compared the negative risk factors including healthy lifestyle, no family history of coronary heart disease, hsCRP less than 2 mg/L, N-terminal pro-rain natriuretic peptide less than 100 pg/ml. Their study showed that among all negative risk factors, CAC score of zero is the strongest negative risk factors of CVD, with adjusted mean DLR (SD) of 0.41 (0.12) for all CHD and 0.54 (0.12) for CVD. Mortensen et al. [51] also pursued the same idea in elderly population, analyzing 5805 participants of Bioimage study (median follow-up of 2.7 years; mean age 69 years). Among the negative risk factors, CAC = 0 and CAC ≤10 were the strongest with mean DLRs of 0.20 and 0.20 for coronary heart disease; which means these patients had almost 80% lower risk than expected from traditional risk factor assessment. Altogether, these studies demonstrated that CAC score of zero is the strongest negative risk factor for future cardiovascular events.

Because of strong power of CAC = 0 in risk re-classification specially in intermediate-risk patients, it could play substantial role in choosing the preventive strategies. In a population of 950 participants from Multi-ethnic Study of Atherosclerosis (MESA) who were eligible for JUPITER trial, Blaha et al. [52] Compared CHD and CVD event rates in different CAC score groups. The coronary events rate in CAC =0 was 0.8 per 1000 person-years, while for CAC ≥ 100 this rate was 20.2 per 1000 person-years. The predicted 5-year number needed to treat

(NNT) for coronary heart disease was 549 for CAC score of zero, while for CAC ≥100 was 24. Additionally, the NNT for cardiovascular disease were 124 and 19 for CAC = 0 and CAC ≥100, respectively. This study demonstrated that subjects with CAC = 0 benefit significantly lower than CAC ≥100 participants, suggesting the role of CAC = 0 for risk stratification in choosing preventive therapy.

In a 9.4 years follow-up study of 13,644 asymptomatic patients (mean age 50 years; 71% men), Mitchell et al. [53] investigated the CAC ability to identify patients who benefit from preventive statin therapy. Their study showed that statin therapy correlates with reduced risk of major adverse cardiovascular event (MACE) in patients with CAC, but not in the CAC = 0 patients. The preventive effect of statin on MACE was highly correlated with CAC scores, as the NNT to prevent one MACE outcome were 100 and 12 for 1 < CAC < 100 and CAC > 100. In a recent study, Cainzos-Achirica et al. [54] studied utilization of CAC for guiding aspirin allocation as primary prevention. They demonstrated that using aspirin in CAC ≥100 and CAC ≥400 subjects is reasonable. On the other hand, in CAC = 0 subjects using aspirin seemed to have more harm than benefit.

ACC/AHA cholesterol management and primary prevention guidelines in 2018 and 2019 [55, 56] recommended measuring CAC when decision about statin therapy is uncertain in adults of 40 to 75 years without diabetes but with 70 mg/dL ≤ LDL-C levels ≤189 mg/dL and 10-year ASCVD risk between 7.5 and 19.9%. These guidelines recommended withholding or delaying statin therapy if CAC score is zero except for patients with family history of premature CHD, current cigarette smoking or diabetes.

While CAC = 0 could ensure clinicians regarding future ASCVD events, this question needed to be addressed that: "when is the best time to measure CAC again in CAC=0 patients?". Min et al. [57] studied 422 patients with CAC = 0 to identify the "warranty period" for remaining CAC-free in this group of patients. During the mean follow-up of 4.1 ± 0.9 years, 25.1% of CAC = 0 patients developed new detectable CAC scores. Incidence of CAC was non-linear and highest rate occurred in fifth year. They compared the results with a cohort of 621 patients with CAC > 0 at the baseline. Authors concluded that CAC > 0 is the strongest predictor of CAC progression, followed by diabetes and smoking. In 2012 Koulaouzidis et al. [58] studied 388 participants with CAC = 0. During follow up of 2.99 ± 1.35 years only 25% developed CAC progression, including 20.87% with CAC 1 to 10, 3.6% with CAC 11 to 50 and only 0.51% with CAC > 50. In a larger multicenter Korean study, Lee et al. [59] recruited 6268 participants with CAC score of zero. During median follow up of 109 months, 719 (11%) individuals developed detectable CAC. The CAC progression rate was 0.3% for the first year and increased to 16.7% for the fifth year. Their study demonstrated that risk of CAC score progression increases over time and correlates with the 10-years ASCVD risk. In a study of 6778 participants with median follow-up of 7.6 years, Budoff et al. [60] demonstrated that in participants with baseline CAC = 0, only 15.8% showed detectable CAC in the follow up CAC scan while 85.8% still remained CAC = 0. The median CAC score progression in subjects with baseline CAC = 0 was 2.2 Agatston units/year, compared with median progression of 28.9 units/years in participants with baseline CAC > 0. In a

recently published article, Dzaye et al. [61] pursued the same idea in the MESA study. They concluded that the CAC progression correlates with 10-years risk for ASCVD category of patients. In CAC = 0 patients with <5% of 10-years risk for ASCVD (low-risk patients), 20–25% develop new detectable CAC in 6-7 years, while for intermediate and high-risk groups these period of time are 3–5 years and 3 years, respectively. Based on the large studies with long-term follow-ups including variety of ethnicities and races, we could conclude that CAC score plays a strong role in risk-stratifying individuals regarding cardiac diseases. However, considering all factors including traditional risk factors along with CAC score and looking at all the patient's characteristics will always be the best strategy.

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Chapter 7
Value of Coronary Calcium-Screening for Risk Assessment in the General Population

Jan Engvall

Main Text

Risk assessment of future atherosclerotic cardiovascular events is the cornerstone in all preventive cardiovascular programs [1]. Preventive strategies may either be based on the general application of medication and life style adjustment, or using individual approach, based on various scores, to predict future cardiovascular risk, often denoted "personalized medicine" [2]. Several risk scores have been developed based on the data available at individual/local cardiovascular prevention clinic, such as the Framingham Risk Score [3], the Pooled Cohort Equation [1] and the European Risk Score [4]. The Pooled Cohort Equation was used to develop the Atherosclerotic Cardiovascular Disease (ASCVD) risk score, promoted by the American College of Cardiology to assess whether prophylactic statin therapy can be recommended to asymptomatic individuals, 40–79 years of age. These scores assist in predicting the potential risk for adverse cardiovascular events over 10 years. The scores build on age, gender, smoking, cholesterol, diabetes and systolic blood pressure. They work fairly well for individuals at high (>20%) and very low (<5%) risk, but a considerable number of those in the intermediate range may be misclassified and either receive recommendation for unnecessary use of statin treatment, or their risk may be under-estimated [3]. Using the ASCVD calculator, a 10 year risk of atherosclerotic cardiovascular (infarction and stroke) events >7.5% is considered high. Generally, it is recommended that this risk calculator replace previous risk assessments based on the Framingham Risk Score. However, risk calculators may overestimate the cardiovascular risk in certain populations such as Hispanics and blacks that may not have been included in large enough numbers in the derivation cohort.

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Other studies have assessed the clinical benefit of additional risk factors such as coronary calcium scoring (CAC), the ankle-brachial-index (ABI) and carotid intima-media-thickness (CIMT) [5]. The US Preventive Services Task Force (USPSTF) in 2018 found that neither of these additional indices merited to be added to the conventional primary prevention assessment, mainly because treatment-induced changes in these indices did not translate into a practical knowledge of the change of risk to the patient [6]. However, the Multi-Ethnic Study of Atherosclerosis, (MESA) [7], produced a new risk score based on support vector machine learning, which also included the result of calcium scoring. The American Heart Association (AHA) recommendations on the management of blood cholesterol in 2018 suggested measuring coronary artery calcification (CAC) as a possible tie-breaker when in doubt, for the above-mentioned risk interval [8]. However, the use of CAC has been opposed because of a perceived negligible clinical benefit, risk of inducing neurotic behavior and the risk of increased downstream testing due to incidental findings on the CAC scoring examination [9]. Neither has serial testing and calculating rate of change of CAC been shown to be fruitful, not the least because of the repeated radiation dose to the patient.

What is "calcium scoring"? Calcium deposition/formation in plaque, in the coronary arterial wall and in the fat surrounding the coronary arteries indicates an elevated risk of significant atherosclerotic coronary heart disease [10], Fig. 7.1.

Calcium deposits can also be found in valves and along the thoracic and abdominal aorta, signaling dystopic calcification comparable to what can be seen in lymph nodes affected with tuberculosis [11–14]. Ectopic bone production is at play, influenced by bone osteogenic protein as well as opposing anti-osteogenic factors [15]. Modern theories of inflammatory changes to the perivascular fat have some support in terms of imaging perivascular adipose tissue attenuation but studies definitely linking peri-vascular or vascular inflammation to the later development of coronary calcium have been lacking [16]. The presence of coronary calcification may complicate computer tomography of the coronary arteries (CTCA) and their lumen. In patients with extensive calcification, "blooming" artifacts from the presence of calcium may entirely prevent quantitative assessment of the iodine outline of the

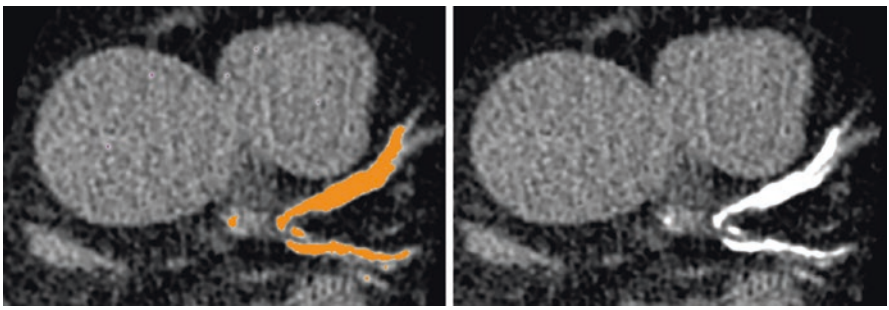

Fig. 7.1 Non-contrast calcium-scoring image of the mid left coronary artery. Original image right, colored areas left with Hounsfield intensity >130. Total Agatston score > 1000

coronary arterial lumen even if there are reports e.g. from the "MACHINE" consortium claiming that their software may deduce coronary CT-FFR despite the presence of calcium [17].

Calcium scoring has also been shown to be an effective add-on to nuclear myocardial scintigraphy. While myocardial scintigraphy has played an important role worldwide in excluding significant ischemia, small areas of what looked like reversible defects have been referred as manifestation of attenuation rather than real ischemia. In those cases, a coronary calcium score of zero has been used to disregard some of those patterns of perfusion defects related to attenuation with significant accuracy [18–22]. Based on this, manufacturers have now devised combined PET-CT scans which provide information on both coronary calcification and myocardial perfusion in one session.

Coronary calcification was first assessed using electron beam CT and the volume and density was quantified using the dimensionless Agatston score, which is built on the Hounsfield density of calcium (in excess of 130 Hounsfield units) times area, often referred to as "CAC" score [23]. However, the development of fast, widely available EKG-gated multi-slice, multi-detector CT has made CAC realistically available in many settings, for analysis based on physician referral as well as for "walk-in" calcium scoring in out-patient settings. A non-contrast EKG-gated scan covering the entire heart will collect the data in less than 15 min, at a radiation exposure of about 1 mSv. Newer methods utilizing iterative reconstruction may reduce radiation to below 0.2 mSv [24]. The Hounsfield number is dependent on acquisition at 120 keV. If using a different tube voltage, the calculated score will be affected, which needs to be accounted for since CTCA is often recorded at lower tube voltage in order to increase signal and reduce the amount of iodine contrast.

How is calcium scoring measured? The areas with calcium are segmented manually and the vendor software calculates the Hounsfield units, the area and the volume of the calcium deposits. Various semi- and fully automatic computer programs have been developed to aid in these calculations. Several studies have shown excellent performance of automatic calculations that produce an important useful addition to decision making and relieve the diagnosing physician from tedious manual work [20–22, 25].

Studies using standard CT images for the calculation of CAC, e.g. images recorded for lung cancer screening and images with iodine contrast, have been promising [26]. Such a possibility would greatly expand the available image material and make CAC assessment an integral part of any thoracic CT investigation. Various aspects on the presence of calcium have been analysed, such as the number of coronary arteries with calcium, the area and the volume of calcium, the Hounsfield density of the deposit and the relationship between CAC, coronary plaque and coronary stenosis [27–30], Figs. 7.2 and 7.3.

The presence of coronary calcification has been shown to have significant clinical prognostic value. Without exactly knowing the mechanism behind the development of calcium deposits, the absence of coronary calcification (score of zero) indicates a very low risk of future cardiac events, regardless of the presence or absence of traditional cardiovascular risk factors scored with either the Framingham

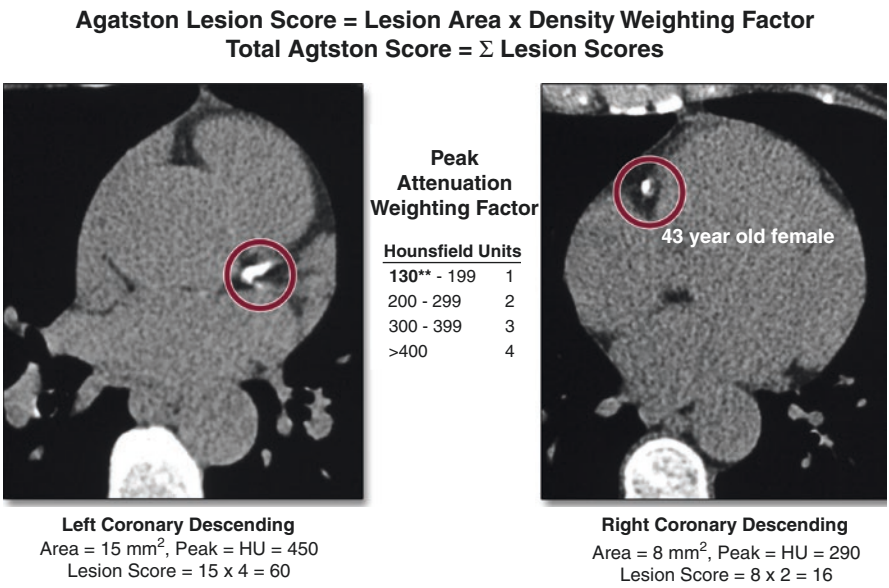

Fig. 7.2 Calculation of the Agatston score. Figure reprinted with permission from Blaha et al., JACC Cardiovasc Imaging. 2017;10(8):923–37

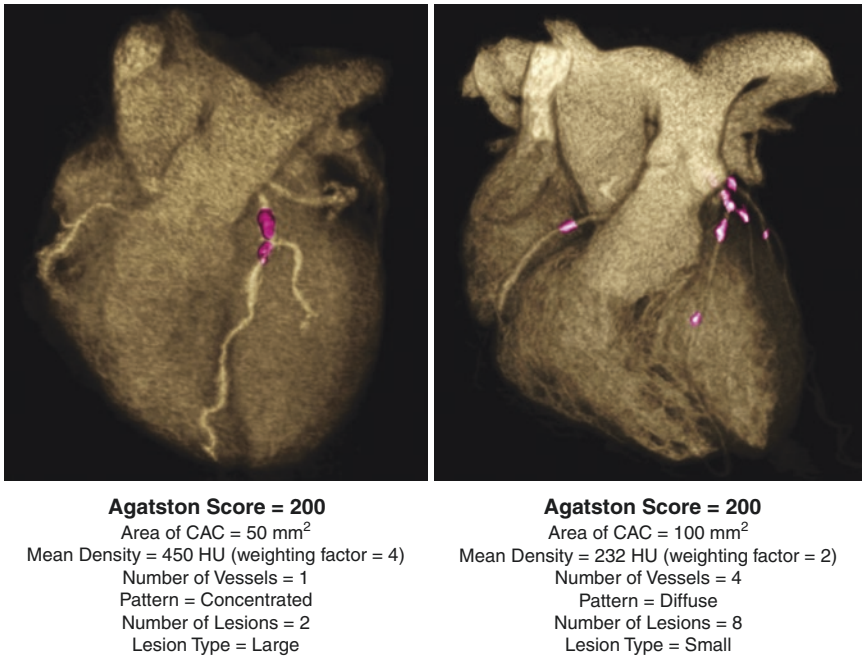

Fig. 7.3 Concentrated lesion, left, distributed lesions, right, with identical total Agatston score. Figure reprinted from Blaha et al., JACC Cardiovasc Imaging. 2017;10(8):923–37

Risk Score or the pooled cohort equation [31]. On the other hand, extensive coronary calcification and CAC scores >1000 indicate a substantial risk of coronary events (>11% per year) [32, 33]. Also, in asymptomatic population (e.g. in MESA, four ethnicities aged 45–84 years), the presence of coronary calcification has been shown to differ significantly between ethnicities, being highest in Caucasians. Coronary calcification has also been shown to have gender preference, being more prevalent in males, who may have equal average score to that in females at 10 years of age less [34]. Despite differences in the prevalence of coronary calcification between ethnic groups, the predictive power of CAC score is similar [3]. The presence of calcification is highly skewed in the population with a large number of individuals scoring zero. In the MESA study, 50% of enrolled individuals had CAC of zero and 10% had CAC >300. In a European context, the SCAPIS population study (50–64 years, 50% participation rate), CAC of any severity has been shown in 40% of participants and coronary plaques in 56% [29]. In the Heinz-Nixdorf study, increasing values of CAC, carotid intima-media thickness (CIMT) and ankle-brachial index (ABI) all contributed to the re-classification of coronary risk as determined from the Framingham Risk Score, with CAC score producing the largest number of reclassifications [5].

In addition to the overall coronary calcium score, the number of involved arteries has been shown to have a significant prognostic impact. With a similar total score, the presence of calcium along several coronary arteries and the number and size of CAC lesions correlated with worse prognosis while a higher density (Hounsfield number) seems to confer less risk [35], Fig. 7.3.

Also, the distribution of calcification seems to indicate different types of disease, with microcalcifications in plaque relating to more active atherosclerotic disease while coalescing large areas of high Hounsfield calcium seem to reflect well established stable disease [36]. Despite the significant role of CAC in coronary artery disease, most authors do not consider applying calcium scoring assessment to the general low-risk population, but reserve it for managing patients with intermediate risk profile in keeping with the position of the 2013 AHA/ACC guidelines on cholesterol and prevention which gives CAC a IIb indication [1–3]. Based on that, patients can be re-classified into those with clearly low risk while others are moved to a higher risk category mandating some intervention in terms of risk factor modification. This was shown in a report from the Rotterdam Heart Study, where patients initially classified as intermediate risk (22%, FRS 10–20%) where re-classified, 7% into the low-risk category and 5% into the >20% high risk category [37].

In symptomatic patients the role of CAC assessment of coronary disease differs significantly. In those patients, CAC scoring plays a very limited role as clearly seen in the latest European guidelines on stable coronary artery disease, where CAC scoring is only seen as a modifier of the calculation of pre-test probability of significant coronary artery disease [38]. In other cardiovascular diseases such as hypertension, calcium scoring may be seen as an additional factor in risk assessment and be used to modify antihypertensive treatment [39].

It must also be mentioned that in addition to the use of calcium scoring in assessing coronary artery disease and related risks, cardiac calcification assessment has

been extended to valves, mostly to assess aortic stenosis and also for the mitral valve [40, 41]. Higher scores relate to more severe aortic stenosis including valve leaflets and root, without measuring flow velocity or aortic valve area. This has been applied to the assessment of low flow low gradient aortic stenosis where many other measurements may underestimate the severity of the disease of the aortic valve. This topic will be dealt with in detail in the Chapters on Valve Calcification.

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Chapter 8
Calcification and Coronary Interventions

Giuseppe Venuti, Piera Capranzano, and Corrado Tamburino

Introduction

Severe calcified coronary artery disease (CAD) still represent a complex anatomical setting for interventional cardiologists. Moderate-to-severe calcifications complicating coronary plaques have been reported to range between 18% and 26% and are more commonly observed in patients with advanced age, arterial hypertension, dyslipidemia, diabetes and chronic kidney disease [1]. Obstructive calcium increases the overall procedural complexity of a percutaneous coronary interventions (PCI) as it requires more accurate lesion preparation and can lead to higher complication rates. In addition, coronary calcification may cause a drug-eluting polymer damage due to the friction between the drug-eluting stent and the calcium proximal to the stenosis [2], hampering the drug delivery and diffusion through the calcium [3], and may impair stent expansion and apposition [4]. Therefore, calcified CAD can be associated to higher rates of procedural failure or suboptimal results and still remains an important cause of stent under-expansion, which is a possible trigger for stent thrombosis (ST), in-stent restenosis (ISR), target vessel revascularization (TVR) and target lesion revascularization (TLR) [5].

Both adequate vessel preparation and meticulous stent optimization are pivotal to avoid stent under-expansion in calcified coronary lesions. Notably, it is already well established that intravascular imaging plays a crucial role in selecting the most appropriate strategies to prepare coronary calcified lesions as well as for stent optimization [6]. In order to achieve optimal lesion preparation and stent implantation, several PCI devices and technologies, including specialty balloon, atherectomy and lithotripsy, have been developed to treat calcified CAD.

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Invasive Assessment of Coronary Calcifications

Both coronary angiography and intravascular imaging assist in detecting coronary calcium. Although angiography has a relatively high positive predictive value in detecting calcium within coronary artery, it has low to-moderate sensitivity if compared with intravascular ultrasound (IVUS) and optical coherence tomography (OCT), which represent the gold standard for coronary calcifications assessment [7] (Fig. 8.1).

At fluoroscopy, calcium is classified as none or mild, moderate, or severe. Moderate calcification is defined as radio-opaque spots evidenced before contrast injection, only during the cardiac cycle. Severe coronary calcifications have been described as linear areas following the hypothetical silhouette of the coronary arteries usually involving both sides of the vessel, noted without cardiac motion [8]. However, it has been shown that coronary angiography is suboptimal to identify calcium and its sensitivity seems to be dependent on the degree of the arch of calcification [9]. Therefore, only greater amounts of coronary calcium are easily appreciated on fluoroscopy.

Calcific coronary plaque on IVUS appears as an echodense area that is brighter than the adventitia, with acoustic shadowing (Fig. 8.2). Calcium needs to be distinguished from fibrous tissue, which is also echodense and, sometimes, it may also shadow. A distinctive IVUS feature of calcium are reverberations, which are multiple reflections that are created from oscillation of ultrasound between the transducer and calcium causing concentric arcs at reproducible distances. Therefore, the

	Angiography	IVUS	OCT
Calcium Detection	▲	▲ ▲ ◢	▲ ▲ ▲
Calcium Localization	▲	▲ ▲ ▲	▲ ▲ ◢
Calcium Quantification	▲	▲ ▲ ◢	▲ ▲ ▲
Calcium Arch	✖	▲ ▲ ▲	▲ ▲ ▲
Calcium Length	✖	▲	▲ ▲ ▲
Calcium Thickness	✖	✖	▲ ▲ ▲

Fig. 8.1 Comparison of Imaging Techniques for Coronary Calcium Detection, Characterization, and Quantification

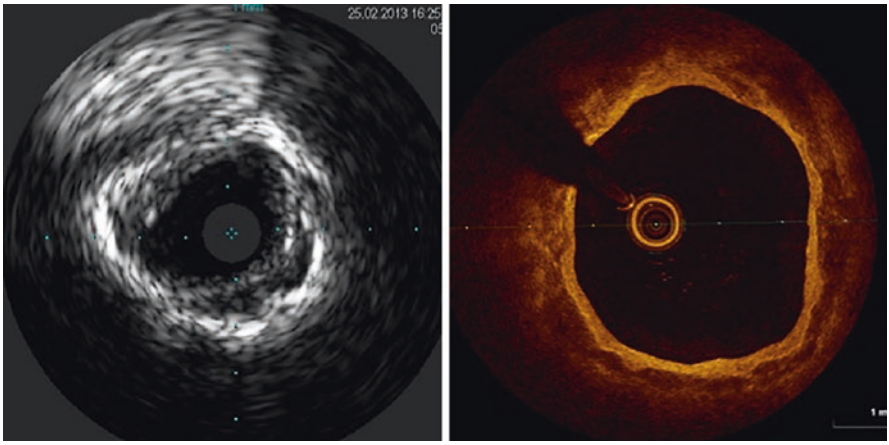

Fig. 8.2 Intravascular Ultrasound vs Optical Coherence Tomography for Coronary calcification

feature of echodense plaque with shadowing is highly sensitive for calcium, while reverberations are highly specific [7]. Regarding microcalcifications, these are usually missed on IVUS. Quantitative calcium IVUS analysis is performed according to the arch (degrees) and length (using motorized transducer pullback, if available); semiquantitative grading classifies calcium as absent or subtending 1, 2, 3, or 4 quadrants. Notably, calcium arch extension of more than >180° limits stent expansion and is related to smaller stent area and greater stent eccentricity; qualitatively, IVUS localizes calcium in term of lesion versus reference and superficial versus deep [1, 7]. Indeed, IVUS detects even the deeper deposits of calcium thanks to its higher penetration power. However, the major IVUS pitfall in calcium evaluation is that calcium thickness cannot be evaluated because of the acoustic shadowing.

The OCT has great accuracy in assessing coronary calcifications. Calcium on OCT is defined as a signal-poor or heterogeneous area with sharply and well delineated borders (Fig. 8.2). Compared with IVUS, OCT provides additional measurable parameters such as calcium thickness, area, and volume [7], which impact on stent expansion and response to balloon dilation [10]. Notably, the combination of large calcium angle (>270°) and thickness (>670 μm) predicts suboptimal or ineffective lesion preparation [11]. In addition, OCT provides accurate measurements of the minimal lumen area, lesion length and reference vessel diameters, as well as visualization of potential stent landing zones.

The use of intravascular imaging techniques for PCI guidance, compared to angio-guided PCI only, reduces the risk of cardiovascular death and improves outcomes [10, 12]. Therefore, information derived from intravascular imaging are crucial to select the most appropriate strategy for calcified lesion preparation as well as stent sizing and optimization in order to detect struts malapposition and stent underexpansion.

PCI Strategies for Calcified Coronary Stenosis: A Practical Algorithm

In the context of calcified stenosis, lesion dilatation by using semi-compliant (SC) balloons is usually ineffective and risky due to its high compliance leading more often to eccentric balloon expansion, which increases the likelihood of dissections and perforations occurrence. On the contrary, conventional non-compliant (NC) balloon, sized according to the distal vessel diameter (1:1 ratio or slightly undersized) represents the first choice for calcified lesions. However, high-pressure NC balloon inflations can may fail in lesion preparation of very resistant and calcified lesions. Therefore, several devices, ranging from dedicated balloons to atherectomy systems, have been implemented. These later devices include super high-pressure OPN NC balloons, cutting balloons (CB), scoring balloons (SB), chocolate balloons, rotational atherectomy (RA), orbitational atherectomy (OA), excimer laser atherectomy (ELCA) and the novel intravascular lithotripsy (IVL) coronary system. These devices alter plaque morphology with different mechanisms, creating fractures within the calcium and changing lesion compliance in order to increase the likelihood of maximal luminal gain and optimal stent expansion.

Calcified lesions can be classified in either de novo or ISR lesion and balloon crossable and uncrossable lesions (Fig. 8.3). Both lesion type and imaging insights need to be taken into consideration for procedural planning, including proper lesion preparation and device selection. If a calcific de novo lesion, after imaging, is suitable for atherectomy (superficial calcium arch >180°, length > 5 mm and

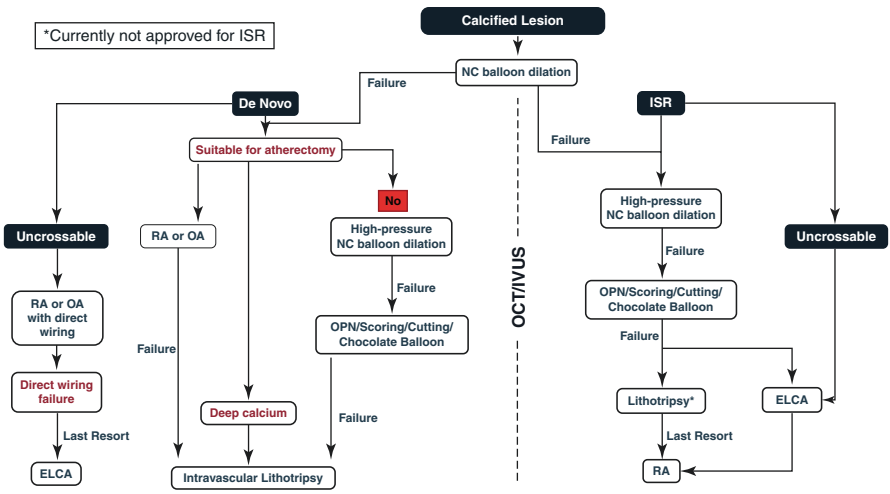

Fig. 8.3 Proposed algorithm for the Management of Coronary Calcified Lesions. *ISR* In-stent restenosis, *RA* Rotational Atherectomy, *OA* Orbital Atherectomy, *NC* non-compliant, *ELCA* excimer laser coronary atherectomy. *Intravascular Lithotripsy is currently not approved for the treatment of in-stent restenosis

thickness > 5 mm [8]), both RA and OA can be primarily used; differently plaque modification should be attempt through high pressure NC balloon inflations and/or dedicated balloons (OPN, SB, CB, Chocolate balloon). However, plaque modification provided by dedicated balloons and atherectomy may be limited because of deeper, thick or eccentric calcification, for which IVL has demonstrated to be effective.

Difficult balloon crossing through calcified lesion may be solved by increasing support using a larger size guiding catheter or using various techniques, such as buddy-wire technique, distal [13] or side branch [14] anchoring techniques, one or two guide extension catheters (mother-daughter or mother-daughter-granddaughter technique) [15]. If still uncrossable, calcified lesions are treated by either RA and OA. However, in case of failure of wire crossing, ELCA still remain as the last resort although it carries higher risk of vessel dissection or perforation (Fig. 8.3).

When treating calcified ISR lesions, NC balloon followed by either dedicated balloons or lithotripsy are preferred. In addition, ELCA remain a valid and effective tool for ISR lesions since energy emitted by laser atherectomy extends beyond the stent without compromising the metallic struts. Concerning RA, it carries higher risk of complications when used on ISR lesions, then, when indicated, RA represents the last resort (Fig. 8.3).

Dedicated Balloons for the Treatment of Calcified Coronary Lesions

Super High-pressure NC Balloon

The OPN NC super high-pressure balloon (SIS Medical AG, Winterthur, Switzerland) (Fig. 8.4a) is a rapid exchange balloon catheter, coming with a dedicated indeflator, compatible with 0.014″ coronary wires and 5 Fr guiding catheters. It is available for both lesion preparation and stent optimization, even though most evidence suggests its use mainly for stent post-dilation [16, 17]. The most distinctive feature of OPN is its dual layer balloon technology that permits balloon inflation up to very high pressures (its rated burst pressure is 35 atm) with uniform expansion, aiming for very low dog—boning effect and reduced risk of vessel injury. The device has been tested up to 50 atm in a real-world population with favorable results and an acceptable safety profile [18]. OPN device is available for a wide diameter range, starting from 1.5 mm to 4.5 mm with ½ mm intervals. Balloon lengths are 10, 15 and 20 mm. OPN balloon has a more favorable crossing profile (0.028″ for 2.0 mm device) than SB and CB but as the first inflation/deflation cycle is done, following delivery attempts may result difficult due to its overall growing in stiffness and bulkiness [18, 19]. Clinical evidences on these balloons mostly derive from case and retrospective studies reporting their acceptable safety and effectiveness [18, 20].

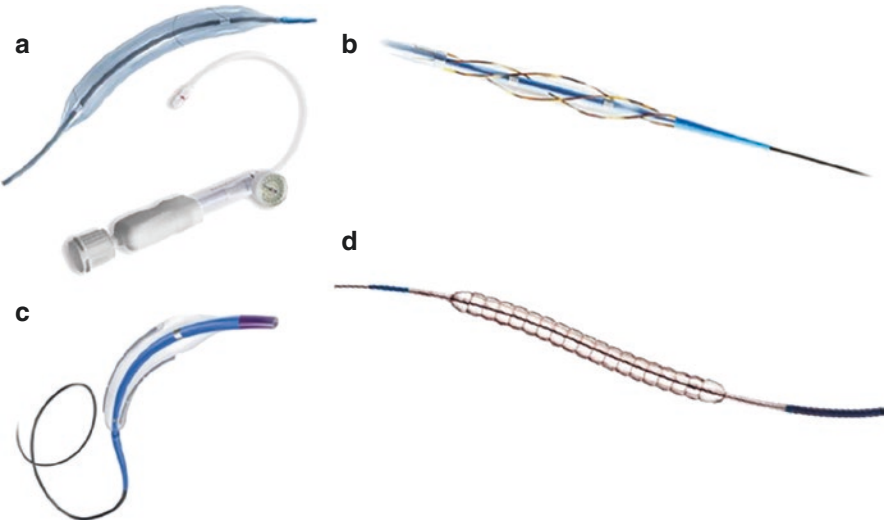

Fig. 8.4 Specialty Balloons. (**a**) Super high-pressure OPN non-compliant balloon (SIS Medical AG, Winterthur, Switzerland); (**b**) Angiosculpt (Biotronik, Berlin, Germany) Scoring Balloon; (**c**) Wolverine (Boston Scientific, Natick, MA, USA) Cutting Balloon; (**d**) Chocolate XD® (Teleflex, Wayne, PA, USA) PTCA Balloon Catheter

Scoring Balloon

SBs (AngioSculpt™ [Biotronik, Berlin, Germany]) (Fig. 8.4b) are 10 or 20 mm long SC nylon balloons surrounded by nitinol spiral scoring wires. The balloon is available in four diameters ranging from 2.0 up to 3.5 with ½ mm intervals. This device has a better deliverability, flexibility and crossing profile than CB (smallest SB crossing profile is 0.036″). With balloon inflation, the surrounding nitinol wires slide and rotate over the balloon with the radial forces exerted mainly along the surface of the nitinol frames, exerting the "scoring" effect on the target lesion. This mechanism helps to avoid significant balloon slippage and provides well-controlled balloon expansion, reducing vessel barotrauma and the risk of dissection and perforation. Notwithstanding SB was not initially thought to specifically tackle significant calcified CAD, it showed satisfying results in terms of efficacy and safety in different scenarios, including calcified lesions [21–23].

Cutting Balloon

The Wolverine™ (Boston Scientific Corporation, Marlborough, MA, USA) CB Dilatation Device (Fig. 8.4c) is a NC balloon catheter longitudinally armed with three (from 2.0 to 3.25 mm balloon diameters) or four sharp microsurgical blades

(from 3.5 to 4.0 mm balloon diameters) mounted on its outer surface. Available balloon working lengths are 6, 10 or 15 mm. Despite the structural improvements that have been accomplished comparing with CB previous generation (Flextome™ [Boston Scientific Corporation, Marlborough, MA, USA], Wolverine CB still carries a relatively poor flexibility and a high crossing profile (0.041–0.046″), which may prevent balloon delivery especially when approaching resistant stenosis with a very small lumen diameter. With inflation, the balloon expands radially, concentrating the force along the microblades that create longitudinal incisions within the plaque. Slow and gradual inflation/deflation cycles are suggested since the atherotomes allow effective plaque modification and vessel dilation at low inflation pressures. CB angioplasty did not proved to be superior to conventional NC balloon treatment for type A/B lesions but resulted more effective than plain balloon in reducing plaque burden and increasing acute lumen gain in more complex scenarios such as calcified lesions and ISR [24–26]. The most common troubleshooting and complications related to CB therapy are blade entrapment and vessel perforation [27].

Chocolate Balloon

The Chocolate Balloon (Chocolate XD® PTCA Balloon Catheter [Teleflex, Wayne, PA, USA]) (Fig. 8.4d) is a nitinol-constrained balloon used for pre-dilatation of de novo lesions, coronary ISR and bypass graft stenosis. Plaque modification is achieved by its "pillows" and "grooves" design made from the nitinol constraining structure, without scoring or cutting effects. The "pillows" are designed to provide predictable and uniform dilatation, and the "grooves" allow for stress relief, minimizing vessel wall trauma and decreasing the risk of vessel edges dissection. The device diameters cover a range from 2.0 mm up to 3.5 mm with ½ mm intervals. Balloon lengths are 10, 15 and 20 mm. 2.0 and 2.5 mm balloon diameters are compatible with 5 Fr guide catheters.

Rotational Atherectomy

In 1988, RA was described for the very first time in animal models [28] and, since then, has become most used atherectomy technology worldwide. It works on the "the differential cutting principle" provided by a rotating burr advanced over a dedicated guidewire. The differential cutting is the ability of selectively ablate hard, inelastic plaque (calcific or fibrotic) while not involving the surrounding elastic tissue that is "stretched away" from the ablating burr. If compared with balloon angioplasty, RA minimize dissections and vessel damage. Several observational studies have reported favourable intermediate and long-term outcomes with adjunctive RA

before DES implantation [29–34]. Then, RA emerged as an alternative strategy for vessel preparation when conventional balloon dilation remains ineffective, although there are still no randomized trials that demonstrate the long-term clinical benefit of its routine use [35–37].

The concept of the utility of a more aggressive debulking strategy for vessel preparation, (e.g. RA larger burr ablation, longer ablation run) has switched over the more contemporary philosophy of achieving lesion preparation by "plaque modification". Thus, the STRATAS and CARAT trials demonstrated as milder approach does not differ in terms of efficacy, while minimizing complications [38, 39]. Therefore, accumulating evidence as well as the growing expertise of the interventionalists achieved over the last decades, suggest the utility to use smaller burr and guide catheters/sheaths sizes, shorter ablation runs, the so-called "pecking motion" technique, with no sudden decelerations, which overall contribute to decrease the risk of complications without compromising the RA efficacy [35].

Common indications justifying the use of RA are lesion preparation for calcified or fibrotic de novo lesions (e.g. Fig. 8.5) that cannot be adequately prepared by conventional balloon inflation (undilatable) or are uncrossable. RA can be helpful in facilitating vessel preparation in more complex scenarios such as PCI of ostial lesions, bifurcations [40–43] and chronic total occlusion [44]. RA use is not routinely recommended in case of saphenous vein graft lesions and ISR [45]. However, RA has been showed feasible in selected ISR cases performed by experienced operators [46]. Furthermore, a retrospective analysis of 200 patients undergoing RA

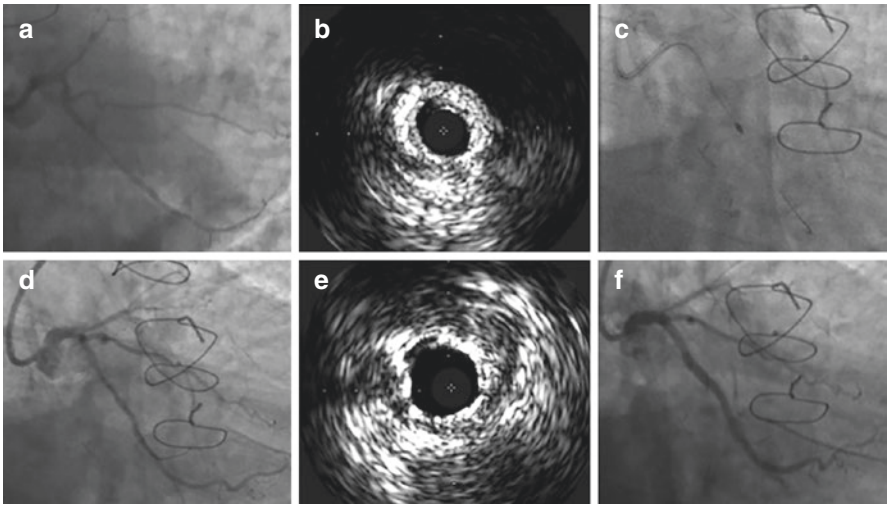

Fig. 8.5 Angiography showing left circumflex artery severely diseased (**a**). IVUS analysis showed a long calcified lesions suitable for atherectomy (**b**). 1.50 mm burr rotational atherectomy was performed with adequate plaque modification (**c–d**). Post-stenting IVUS and final angiogram showed good stent expansion and apposition (**e–f**)

suggests as RA followed by drug-coated balloon angioplasty may be valid for the treatment of severe calcified ISR requiring aggressive plaque modification [47]. Nonetheless, RA for stent ablation still remains the last resort therapy. Unlikely CABG patients needing left main (LM) PCI, where RA represent an excellent option [44], RA treatment for unprotected LM (ULM) artery, despite the efficacy, is related to worse long-term outcomes if compared to non-ULM PCI [48]. Further relative contraindications for RA treatment are: large dissections following previous vessel preparation attempts with conventional balloon; lesions with high thrombotic burden, due to the high risk of embolization caused by burr advancement; severe vessel tortuosity, due to the guide-wire bias and the demanding balloon and stent delivery after plaque modification; poor distal flow, in order to avoid further microcirculation impairment caused by the embolization of the debulking particles.

The Rotablator® (Boston Scientific, Natick, MA, USA) (Fig. 8.6a) was the first RA technology on the market. It consists of a rotating diamond-surfaced burr that is advanced, with high rotational speed, over a 0.09″ stainless steel dedicated 325 cm long guidewire, the so-called "rotawire" (available as floppy or extra-support models). The RA burr is available in eight size ranging from 1.25 to 2.5 mm with variable intervals. The burr is attached to a Teflon-covered drive shaft and then connected to the advancer, which has a controller knob on the upper face. Forward or backward sliding movements of the hand-controlled knob reflect directly on the burr. The advancer itself is connected to the RA console by a fiber optic cable and by a compressed gas connector, which enables the turbine within the advancer to rotate

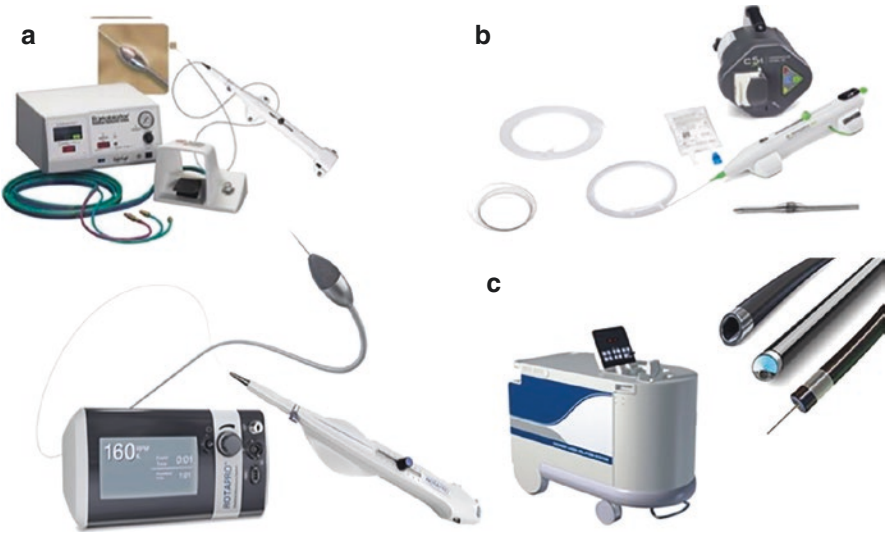

Fig. 8.6 Atherectomy Systems. (**a**) Rotablator and Rotapro (Boston Scientific, Natick, MA, USA); (**b**) Diamondback 360® Coronary system (Cardiovascular Systems Inc., St. Paul, MN, USA); (**c**) CVX-300 (Philips, Amsterdam, Netherlands) Excimer Laser system

the driveshaft at settled speed, then to the foot pedal incorporating the on/off pedal that activates burr rotation and the Dynaglide mode (used for burr placement and retrieval) switch button. During RA functioning, a heparinised saline solution continuously flows within the system in order to lubricate and to contrast the heat generated, preventing vessel injury. Recently, Boston Scientific launched the Rotapro system available for clinical use, which represents a remarkable technical improvement with higher manageability. The main change consists in foot pedal elimination with the integration of the on/off ablation and the Dynaglide buttons directly on the advancer.

The vascular access selected for RA treatment needs to provide adequate support to the system balancing a reasonable risk of bleeding. Since a standard 6 Fr guide catheter is sufficient for performance of RA with burr sizes up to 1.75 mm, radial access can be used effectively over femoral access [49, 50]. Transradial access can be pursued even in case of burr sizes needing a 7 Fr guiding system using the 7F glidesheaths (Slender®, Terumo) introducer or sheathless guide catheters. According to the STRATAS and CARAT trials, a maximal burr:artery ratio of 0.4 to 0.6 is suggested (e.g. a 1.5-mm burr fits for most epicardial vessels <3 mm in diameter).

Direct lesion crossing with the Rotawire may be very challenging, then is suggested to cross the stenosis with a conventional guidewire, which can be easily switched with the Rotawire using a microcatheter and the trapping balloon technique. If the microcatheter fails to cross, direct wiring with Rotawire with the Rotawire is necessary As the dedicated guidewire is placed distally, the burr is advanced over the Rotawire in Dynaglide mode (60,000–90,000 revolutions per minute [rpm] speed rotation mode) and positioned proximal to the target lesion. Once the foot pedal command initiates high-speed rotational (135,000–180,000 rpm), the burr is gradually advanced forwards and backwards by the advancer knob, following the pecking motion technique. Each run of 10–15 s has to be followed by a pause of 30 seconds preventing over-heating, increasing ischemia and slow/no-flow phenomena. As already mentioned, ablation is performed during saline inflation. It is important to avoid sudden decelerations (>5000 rpm) in order to minimize the risk of burr entrapment. Once the lesion has been fully crossed and after the recommended final polishing run, the RA system is retrieved in Dynaglide mode to proceed with further balloon dilations or stenting [44, 51].

Performing RA requires expertise and high operator skills in order to maintain high the standards of safety and efficacy. RA carries higher rates of serious complications and troubleshooting including burr entrapment, slow/no-flow, vessel dissection or perforation [35, 45]. Burr entrapment occurs with an incidence of 0.5–1% [52] and may be the consequence of oversizing the burr, excessive deceleration, inadequate rotational speed and allowing the burr to stop within and not proximal to the lesion. It happens due to the absence of the diamond-cover on the rear of the burr, which may allow the burr to lodge within a lesion and become entrapped. In case of burr entrapment, the first approach is to pull manually the system. If it is unsuccessful or judged too risky, alternative strategies [52] are (1) inflating a

balloon just proximal to the entrapped burr in order to mobilise it [53]; (2) deep guide catheter intubation or child-in-mother catheter advancement till the burr followed by a simultaneous traction on the burr shaft and counter-traction of the child-in-mother catheter [54]; (3) subintimal tracking and distal re-entry with balloon dilatation next to the burr. Sometimes an additional vascular access could be necessary [55]. When everything fails, the last option remains cardiac surgery [44]. Slow flow and no reflow are defined respectively as the acute absence of blood flow and the acute blood flow impairment (less than TIMI 3 flow but more than TIMI 0) within the target coronary artery. Their incidence ranges 0.0% to 2.6% in the most recent RA studies [44] and is limited by optimal antiplatelet and anticoagulant therapy, continuous flush of the RA system and optimal technique. They occur due to distal embolization of particles resulting from the ablation treatment, associated thrombi, platelet activation and aggregation, vessel spasm due to release of vasoactive mediators. Ischemia and hemodynamic instability may be experienced. Potential solutions are intracoronary bolus (injected with or without microcatheter) of nitroglycerine, adenosine, verapamil or nitroprusside. Coronary major dissections and perforations are, as well, feared complications during RA. Their incidence ranges from 1.7% to 5.9% and they should to be managed promptly because may led to acute myocardial ischemia including chest pain, ST-segment elevations, hemodynamic instability and cardiac tamponade [44].

Orbital Atherectomy

Orbital atherectomy technology utilises the Diamondback 360® Coronary system (Cardiovascular Systems Inc., St. Paul, MN, USA) (Fig. 8.6b) and consists in an eccentric diamond-coated crown mounted at the end of a drive shaft powered by a pneumatic drive console. As for RA, the principle underlying OA functioning is the "differential cutting" but, in contrast to RA, the crown is fully covered by diamond chips, which ablates with an orbital ("sanding") and bi-directional fashion (forwards and backwards), reducing the risk of burr entrapment. OA system uses a standardized crown of 1.25 mm that is advanced over a dedicated a 0.012″ guidewire (ViperWire Advance, Cardiovascular System) with a 0.014″ tip. OA system is 6 Fr guide catheter compatible. During the elliptical rotations, the crown is in contact with only one side of the vessel, thus continuous blood flow is provided and debulking debris are constantly flushed away reducing thermal injury, temporary heart-block and slow/no flow phenomenon. ViperSlide® (Cardiovascular Systems) lubricant is infused continuously during the treatment to reduce friction. Crown movements and speed are managed by the operator by the controller that is attached to the shaft. Despite the standard size of the crown, OA can treat vessels of various diameters by either setting the speed (low [80,000 rpm] for smaller vessel and high [120,000 rpm] for bigger vessel) or by regulating the rhythm of advancement (The

slower the burr is advanced with orbital atherectomy, the larger the orbit is). However, it is suggested to advance the burr 1–3 mm per second. Each OA run should be limited to less than 30 s with pause lasting for a minimum of duration equal to the preceding run before proceeding with a new one [56].

The OA use is recommended in case of de novo calcified lesions preparation [35] and not suggested in case of bypass graft, ISR, vessel dissections and thrombotic lesions.

The safety and the effectiveness of this technology have been proved by single arms non-randomized trials (ORBIT I and II) showing adequate plaque modification with successful stenting 98% of cases and infrequent occurring complication (dissections, perforations, slow/no-reflow and in-hospital MACE). The 3-year follow-up showed overall cumulative MACE rate of 23.5% and TVR rate of 10.2%. Other observational, real-word studies confirmed the feasibility of the technology [56]. OCT studies, comparing the impact on vessel preparation of OA versus RA atherectomy, reported as OA provides better plaque modification especially in vessel with large luminal area [57] and a deeper tissue modification with no increasing of occurring dissections and better final stent apposition [4]. However, direct randomized comparison between RA and OA is still lacking.

Laser Atherectomy

ELCA is an alternative technology used for vessel preparation. It uses pulsatile ultraviolet energy in order to photo-ablate the plaque. Laser ablation takes place thanks to three mechanisms: (1) photochemical, the energy breaks the molecular bonds between two carbon atoms; (2) photothermal, due to the increase of intracellular water that favors the rupture of cell membrane; (3) photomechanical, due to the generation of expanding vapor bubbles that explode and disrupt the plaque.

The CVX-300 (Philips, Amsterdam, Netherlands) excimer laser system (Fig. 8.6c) emits high-power ultraviolet pulses (wavelength 308 nm), which penetrate up to of 30–50 μm and vaporize thin sections of tissue without causing significant surrounding damage. The system consists in an excimer laser generator and dedicated monorail catheters, compatibles with conventional 0.014″ coronary guidewires. The laser catheters are available in 0.9, 1.4 (compatible with 5 Fr and 6 Fr guide catheters respectively), 1.7 (7 Fr compatible) and 2 mm (8 Fr compatible). Size selection is based on a catheter/vessel diameter ratio of 0.5:0.6. Current use of ELCA is mainly limited to uncrossable and undilatable lesions. Moreover, it represents a valid tool in case of ISR caused by incomplete stent expansion (laser energy does not compromise stent integrity but may extend beyond, ablating the underlying resistant tissue) [8]. In addition, ELCA has been demonstrated its feasibility for the in complex scenarios such as chronic total occlusions and saphenous venous graft

disease [58–60]. However, diffuse calcification seems to impact negatively on ELCA efficacy. Dissections and perforations are the most common complications in case of ELCA therapy.

Intravascular Lithotripsy

Coronary IVL delivers circumferential, pulsatile and mechanical energy focused on coronary calcium breakage leading to increased likelihood of optimal vessel preparation and good stent expansion and apposition [61, 62]. IVL technology transforms electric energy in mechanical energy in the form of circumferential sonic waves emitted by balloon-located transducers, which are able to penetrate towards and beyond the intimal layer. Therefore, IVL induces circumferential plaque modification and it is effective on both superficial and deeper calcium, minimizing soft tissue injury while aiding stent deployment. Unlikely atherectomy, post-IVL therapy calcium fragments remain in situ avoiding distal embolization and microvascular impairment [61].

The Shockwave C^2 Medical Rx Lithotripsy System (Shockwave Medical, Inc.; Santa Clara, CA, USA) (Fig. 8.7) is a three components device including the lithotripsy balloon catheter, the connector cables and an energy generator.

The device is mounted with a 12 mm (standard length), rapid-exchange, SC balloon available in different diameters ranging from 2.5 and 4.0 mm with increments of 0.25 mm. The balloon is 6 Fr guides and standard 0.014″ guidewires compatible, with a crossing profile filling a range from 0.043″ to 0.046″. The mechanical energy is delivered through two balloon-integrated, radiopaque emitters, which are located between the radiopaque markers and 6 mm apart from each other. IVL balloon

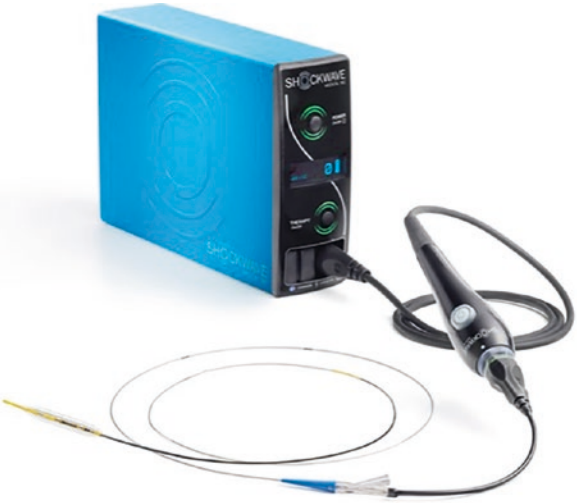

Fig. 8.7 Intravascular Lithotripsy Coronary System (Shockwave Medical, Inc.; Santa Clara, CA, USA)

preparation is similar to conventional balloon angioplasty. Therefore, the inflation port of the IVL balloon catheter is connected to a balloon indeflator filled with saline and contrast with 1:1 ratio, then the balloon needs to be de-aired completely and connected to the catheter emitter cable. Balloon sizing must be made accordingly to the reference vessel diameter (ratio 1:1). Once the device is delivered at the target lesion, the balloon is inflated up to the sub-nominal pressure of 4 atm for vessel apposition, then the therapy initiates by pushing the command button. Each IVL coronary balloon catheter can deliver 10 pulses (one pulse per second) of mechanical energy for each cycle for a maximum of 8 cycles of therapy (80 pulses in total). After lithotripsy, not mandatory NC balloons dilation could be used to enhance calcium breakage and lumen expansion.

For long calcified lesions requiring lithotripsy, balloon repositioning may be needed in order to treat the entire lesion length. If required, pre-dilatation with low-profile balloons or atherectomy can be performed in order to facilitate IVL balloon delivery or, in alternative, increasing the support of the entire system (e.g. guide-extension catheters, buddy-wire) can be sufficient. However, besides balloon delivery failure (e.g. vessel tortuosity, eccentric calcifications), IVL therapy can be inconclusive in case extremely resistant lesions, for which 8 energy cycles or more are not effective and, therefore, different strategies need to be pursued (if indicated).

Performing IVL therapy does not require dedicated training or proctoring, since device preparation and use are similar to those for conventional balloon treatment, making lithotripsy technology very easy to learn.

Intravascular lithoplasty has been developed for lesion preparation in case of stable, calcified de novo lesions prior to stent implantation (e.g. Fig. 8.8). Trials data reporting its efficacy and safety led to approval of the Shockwave C^2 Coronary Intravascular Lithotripsy catheter (Conformité Européenne [CE] mark received in May 2017) for clinical use in Europe. The DISRUPT CAD I and II were multicenter, single-arm trials questioning about IVL efficacy and safety for patients with severe, calcified coronary lesions in native coronary arteries before stenting. Those studies showed as lithotripsy therapy provides optimal vessel preparation with a significant gain in term of acute lumen area. Stent implantation was successfully performed in all lesions without significant intraprocedural complications and low in-hospital major event rates. MACE (cardiac death, myocardial infarction [MI] or TVR) rates were 5% and 7.6% at the 30-day follow-up for DISRUPT CAD I and II, respectively [63, 64].

Despite the absence of IVL trials data beyond the treatment of calcified de novo lesions in the context of stable CAD, case reports, case series and observational studies have been reporting positively on the feasibility of lithotripsy therapy for more complex scenarios (acute coronary syndrome, ULM calcified stenosis, chronic total occlusions, under-expanded stent due to underlying calcification, ISR due to abundant calcific neointima [e.g. Fig. 8.8]) speculating on the potential roles and future applications of the device [62, 65–71]. In addition, IVL has been reported as a potentially effective option when everything else fails [68]. To date, only a case of serious coronary perforation requiring covered stent implantation has been reported [72].

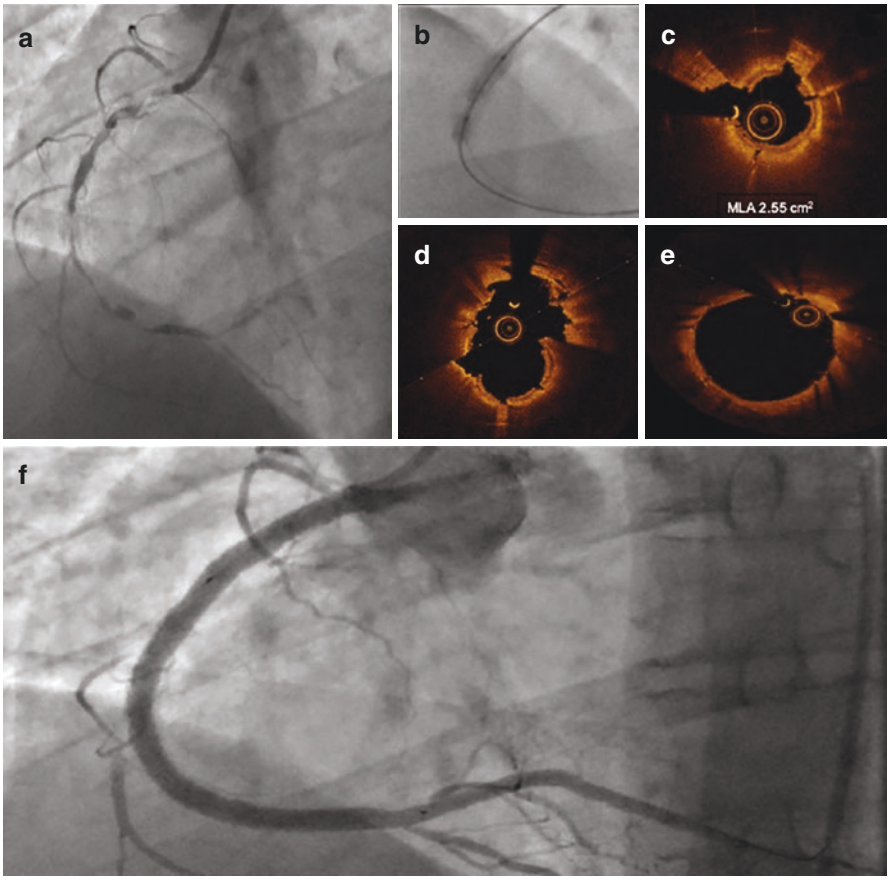

Fig. 8.8 Right coronary artery with severe calcified in-stent restenosis at the mid segment (**a**). Failed pre-dilatation with NC balloon "dog-boning" effect (**b**). Post Intravascular Lithotripsy OCT pullback showing circumferential calcium fractures within the calcific neointima (**c**); OCT analysis after NC balloon inflation showed full calcium breakage (**d**); Final Angiogram and OCT final pullback showed good stent expansion and apposition (**e**–**f**)

Conclusions

The presence of coronary calcification usually increases complexity in PCI, affecting acute and long-term outcomes. Intravascular imaging guidance is now crucial to achieve better results, especially in more complex lesions. Imaging techniques provide an accurate insight of calcium burden, distribution, location and thickness, which impact on the efficacy of the debulking strategy selected by the interventionalists. Therefore, the combination of intravascular imaging and dedicated devices is strongly suggested for a more standardized approach in calcified lesions. However, current use of specialty balloons and atherectomy technologies can be restricted due to the higher risk of complications, degree of technical difficulty and operator

experience. In addition, specialty balloons and atherectomy result can be limited by the presence of deeper calcium deposits. In this scenario, lithotripsy has been rising as the new tool in the box since its application does not require a dedicated training or proctoring and it is effective on deeper calcium.

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Chapter 9
Coronary Microcalcification

Federico Vancheri, Giovanni Longo, Sergio Vancheri, and Michael Henein

Introduction

Diagnosis, prevention, and treatment of myocardial ischemia have been traditionally based on the atherosclerotic plaque narrowing/occlusion of the epicardial coronary arteries, assessed by angiography. However, the extent of coronary obstruction is a poor predictor of subsequent coronary syndromes [1, 2]. The relationship between the degree of coronary stenosis and acute cardiovascular events is heterogeneous. Both mild and severe stenosis may result in myocardial infarction depending on the morphology of the plaque and thrombogenicity of the vascular environment [3–6]. Furthermore, many patients with clinical evidence for myocardial ischemia do not have obstructive atherosclerosis lesions on coronary angiography [7, 8]. Conversely, non-obstructive angiograms do not exclude coronary artery wall structural or functional abnormalities [9, 10].

Such discordance between the degree of coronary obstruction and subsequent acute and chronic myocardial ischemia may be explained by the complex nature of

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atherosclerosis. It is well documented that inflammation-induced endothelial dysfunction has critical role in the development of atherosclerosis [11, 12]. Impairment of endothelial function may lead to myocardial ischemia through its regulation of coronary macro- and microvascular tone, inflammatory cells adhesion in addition to platelet activity, and thrombosis, even in the absence of angiographically documented luminal narrowing [13–15].

Microcalcifications develop in the fibrous cap of the coronary fibroatheroma as an early healing response to intense local inflammation and immunological activity. However, they have also a critical role in destabilizing atherosclerotic plaques, leading to their rupture and superimposed thrombus formation.

Pathology

Although atherosclerosis has long been considered a lipid-storage disease, more recent research has shown that it is a dynamic process involving a complex interplay of inflammation, endothelial dysfunction, local hemodynamic forces such as arterial wall shear stress, intense immunological activity, arterial calcification, and remodeling, generally associated with cardiovascular risk factors [16–18]. As a consequence, the pathophysiology of atherosclerosis has shifted from vulnerable and flow-limiting atheroma with large lipid pool and thin fibrous cap, to a more chronic inflammatory process interrupted by periods of asymptomatic minor plaque rupture or erosion and subsequent healing [19].

Inflammation

Inflammation is the body's reaction to injury and infection. Along with blood flow dynamics, inflammation has a central role in the development of atherosclerosis, from early plaque formation to advanced calcification and plaque rupture [20–23]. The relationship between infection, as a proxy of inflammation, and the extent of atherosclerotic lesions, has been well described for a century (Fig. 9.1). Although the degree of inflammation may be higher in the culprit plaque of acute

Fig. 9.1 Relationship between arteriosclerosis and infections, based on 500 consecutive necropsies in connection with the clinical histories, published 1921. Table III shows that in cases without severe infections there is 1 severe arteriosclerosis among 9 patients between 40 and 50 years of age, 3 moderate cases among 12 patients between 50 and 60 years, and 3 moderate and 4 severe among 13 patients over 60 years. Table IV. In the group of septic infections are included all patients with a history of tonsillitis, rheumatic infection, or septic infections of wounds or bones. In the age group 40–50 there are 6 cases of moderate arteriosclerosis, 2 cases of chronic nephritis with hypertension and moderate arteriosclerosis, 5 cases of marked arteriosclerosis, with or without hypertension and nephritis. Among the 25 individuals over 60, there was only 1 with normal arteries

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Their Relation to Infectious Diseases

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TABLE III.

Relative incidence of general arteriosclerosis in cases without severe infections.

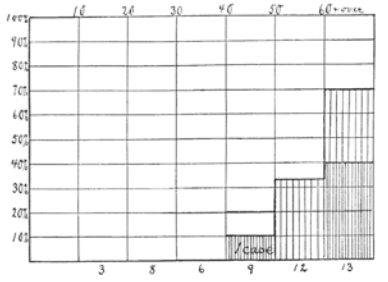
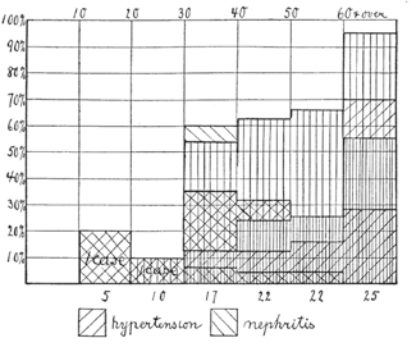


TABLE IV.

Relative incidence of general arteriosclerosis in septic cases

(Chronic streptococcal infections.)



CV events compared to other arterial sites, it is not limited to the culprit plaque but may be widespread and also involve both arterial sides in paired vascular beds, such as carotid and femoral systems [24, 25]. C-reactive protein (CRP), synthesized by the liver under pro-inflammatory stimuli, is not only an established marker of inflammation but has a causal role in the impairment of endothelial function in patients with coronary artery disease (CAD) [26]. In chronic systemic inflammation CRP binds to oxidized LDL and activates the complement system, inducing leukocyte recruitment, platelets aggregation and macrophage apoptosis, thus contributing to amplify and perpetuate the inflammatory response [27–29]. Inflammation-induced endothelial dysfunction is the earliest lesion in atherogenesis. The endothelium is considered the largest body organ functioning as a selective barrier regulating the exchanges of solutes and cells between blood and tissues. In addition, it is an endocrine organ modulating the vascular tone and homeostasis by releasing endothelium-derived vasodilators and vasoconstrictors [15, 30].

Wall Shear Stress

Although the endothelium of the entire vasculature is exposed to the atherogenic effects of inflammation and systemic risk factors, it is recognized that atherosclerotic plaques have a focal distribution, predominantly at or near side branches, the lateral wall of bifurcations and the inner side of curved segments [31, 32]. The topographic localization of atherosclerotic plaques is determined by local hemodynamic forces, such as wall shear stress (WSS) [33, 34]. This is the tangential force of the mechanical friction exerted by the flowing blood on the vascular endothelial surface, directed in the plane of the endothelial cells, in contrast to the arterial pressure which acts perpendicular to the endothelial cells [35, 36]. The WSS magnitude is a very small fraction of the arterial pressure (approximately 0.03 mmHg compared to 75 mmHg). Endothelial cells have specific receptors in the glycocalyx, a surface proteoglycan layer, which sense and distinguish laminar and disturbed blood flow patterns and translate WSS into biochemical signals which ultimately determine whether plaque formation is induced or inhibited.

In physiological WSS, the normal endothelium regulates vascular tone, platelet activity, leukocyte adhesion, angiogenesis, and endothelial permeability by producing nitric oxide which protects the arteries from atherosclerosis [30, 35, 37, 38]. Under normal circumstances the diameter of epicardial coronaries is regulated by WSS and endothelial function. In contrast, in the geometrically irregular arteries due to atherosclerosis, blood flow changes from the physiologic pattern of undisturbed laminar to nonuniform or turbulent flow which causes low WSS (Fig. 9.2). In the presence of additional risk factors for atherosclerosis, such localized hemodynamic force changes induces inflammation and has an essential role in plaques development, progression and instability [22, 39–41]. Intravascular imaging has shown that low WSS, associated with large plaque burden, can independently predict plaque progressive enlargement and luminal narrowing in patients successfully

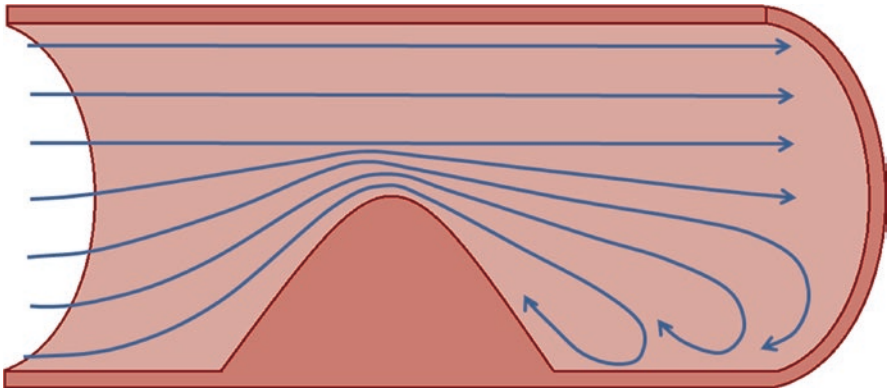


Fig. 9.2 Schematic figure illustrating the disturbed laminar flow characterized by reversed and recirculating flow. Low values of wall shear stress occur at the upstream of the plaque, high values at the luminal narrowing, and low, bidirectional pattern at the downstream shoulder of the plaque

treated with percutaneous coronary intervention after an acute coronary syndrome [42].

As the plaque develops, the stenotic lesion induces heterogeneous local WSS changes in direction and magnitude along its length, including low values occurring at the upstream shoulder of the plaque, high values at the site of luminal narrowing, and low-oscillatory (bidirectional) pattern at the downstream shoulder of the plaque [11, 43–46]. Although different WSS patterns usually coexist in the same plaque, they have been associated with different effects on the development and progression of atherosclerosis. Lesions with similar angiographic and hemodynamic severity can have largely different shear stress, thus accounting for differences in plaque vulnerability [47].

Both low and high WSS make the plaque more vulnerable through the upregulation of endothelial microRNAs [48]. These are small, non-coding post-transcriptional regulatory RNAs which have a role in all stages of the inflamed atherosclerotic plaque formation. In coronary segments that are subjected to low WSS, microRNAs suppress atheroprotective genes while promoting the proatherogenic ones [49]. Hence, low WSS arteries are most likely associated with inflammation, lipid accumulation, plaque development, matrix degradation, and positive arterial remodeling, leading to a rupture-prone feature [50–53]. In the same way, plaques that are exposed to high WSS at the site of maximal stenosis show an increased strain and activation of matrix metalloproteinases, favoring thinning of the fibrous cap and plaque vulnerability and rupture [54–56]. Therefore, it is conceivable to accept low and high shear stress as different phases of the same phenomenon: low WSS promotes the initiation and development of atherosclerotic lesions which in later stages are exposed to higher WSS making plaques more prone to rupture. The most frequent site of rupture is the plaque shoulder, where there is a junction between calcification and soft plaque, which may explain the vulnerability of mixed plaques.

In addition to WSS, the stress within the atherosclerotic lesion, proportional to blood pressure and inversely proportional to lumen stenosis, has a critical role in the

plaque rupture. This local haemodynamic factor increases at the upstream shoulder of a stenotic plaque, or in a non-stenotic plaque, usually associated with a thin fibrous cap, increased macrophages density, and microcalcifications [34]. A plaque ruptures when the wall stress exceeds the strength of the fibrous cap.

Remodeling

WSS has also an essential role in the arterial remodeling, which is the ability of arteries to adapt their shape, through a change in the external elastic membrane, in response to plaque growth or flow alterations [57, 58]. Normally, arterial lumen diameter and blood flow rate are strictly correlated in order to maintain WSS within normal range. In the presence of an eccentric atherosclerotic plaque which encroaches on the lumen, WSS increases at the site of luminal narrowing. This induces positive (outward) remodeling whereby arterial diameter increases, thereby reducing WSS to physiological baseline values, maintaining the appropriate lumen area (compensatory positive remodeling) in an attempt to maintain normal blood flow [57, 59]. Hence, even large plaques may be accommodated without producing symptoms. This may explain why coronary angiography, which opacifies only the arterial lumen, may underestimate the plaque burden. However, the positive remodeling may maintain the luminal size at the expense of perpetuating local low WSS. This arterial wall deformation induces further inflammation and lipid accumulation, and thinning of the fibrous cap, thus enhancing the progression of the plaque and its vulnerable characteristics [60].

The compensatory remodeling can occur until the plaque extend for about 40% of the arterial lumen area. With increasing plaque size, the arterial enlargement can no longer compensate, hence the lumen area reduces and the stenosis becomes evident. However, in conditions of intense inflammation, the plaque and the arterial wall expand beyond the compensatory remodeling (over-compensation). WSS decreases and promote further inflammation, plaque growth and expansive remodeling [41]. Although positive remodeling may be beneficial in limiting the arterial stenosis, postmortem and intravascular studies have documented that it is associated with high-risk plaque features [59, 61–63]. In contrast, coronary arteries with circumferential plaques usually present adventitial fibrosis and reduced external elastic membrane, promoting negative remodeling (arterial shrinkage) [64]. Lesions with this type of remodeling are more stable but show higher degrees of stenosis.

Plaque Development

As mentioned above, chronic exposure to low WSS alters the morphology and function of endothelial cells. The normal spindle-shaped endothelial cells become polygonal with an irregular and disorganized orientation [36]. The production of

nitric oxide is reduced and endothelial cells undergo apoptosis [65]. Endothelial damage results in increased permeability and subendothelial retention of small and dense low-density lipoprotein (LDL)-cholesterol which are produced with inflammation [66, 67]. These LDL sub-fractions derive from a shift in the lipoprotein metabolism towards particles with decreased affinity to the liver specific LDL receptor. Hence, their clearance is reduced and the presence in the circulation prolonged. Because of their small size, these particles enter the arterial endothelium and are susceptible to oxidation. The subendothelial retention of oxidized small and dense LDL-cholesterol is the earliest event in the formation of the atherosclerotic lesions, termed diffuse or pathologic intimal thickening [68, 69]. Lipid accumulation induces local inflammation and release of inflammatory peptides which attract inflammatory and immune cells such as macrophages, T-cells, and mast-cells [70–73]. Oxidized LDL-cholesterol molecules are adsorbed and catabolized by macrophages, forming lipid-laden foam cells, the hallmark cellular component of atheroma. Oxidized lipoprotein cholesterol is toxic to the macrophage, hence, depending on their amount, the lesion may resolve or progress. If inflammation persists, the large amount of oxidized lipoproteins cause apoptosis of the macrophages which coalesce resulting in a necrotic core [74].

In addition, the oxidized lipoproteins stimulate the immune system activating T-lymphocytes to release pro-inflammatory cytokines and enzymes, increasing the local vascular inflammation [75]. This inflammatory environment stimulates vascular smooth muscle cells (VSMC) to migrate into the intima and generate collagen and other fibrous products, leading to the formation of fibro-atheroma, whereas macrophages produce metalloprotease that degrade components of the fibrous cap [76].

Some VSMC undergo trans-differentiation into chondrocytes/osteoblastic-like cells, producing a calcified matrix [77]. Fibro-atheroma is the first clearly distinguishable plaque by histology and intravascular imaging, consisting of a lipid-rich necrotic core covered by a thick collagenous fibrous cap. The development of fibro-atheroma is considered a response to the endothelial damage, generally leading to a stable lesion [17, 78, 79].

In the early stage of fibro-atheroma, the debris of apoptotic dead cells are phagocytized by local macrophages (efferocytosis) reducing the spread of inflammation. In more advanced lesions, phagocytosis by macrophages becomes insufficient for the high rate of cell death. Hence, the necrotic debris of dead macrophages and smooth muscle cells are released and further stimulate the inflammation process [80, 81]. The inflammatory response can also directly activate platelets and the coagulation process, and promotes thrombus formation [82].

Intense inflammation makes the fibro-atheroma hypoxic, thus stimulating intra-plaque angiogenesis with fragile, capillary-like vessels arising from the vasa-vasorum of the adventitia [83]. The rupture of these vessels results in intra-plaque hemorrhage which provides a large amount of erythrocytes membranes carrying free cholesterol, which further worsens the inflammation and the likelihood of plaque rupture [83, 84]. Repeated episodes of intra-plaque hemorrhage can also result in substantial luminal stenosis.

Although the fibroatheroma is usually a stable lesion, the inflammatory cells, macrophages, lymphocytes, and VSMCs can phenotypically change from reparative to pro-inflammatory subtype. With extensive inflammation, macrophages exert a catabolic effect on the fibrous component of the plaque, through the release of matrix-degrading metalloproteinases. This process results in dissolution of collagen, thinning and weakening of the cap, producing a thin-cap fibro-atheroma (TCFA) consisting of a large necrotic core (>40% of plaque volume) with overlying thin fibrous cap, less than 65 micron thick, heavily infiltrated by macrophages [12, 85–87]. As the thickness of the fibrous cap is critical for the maintenance of the stability of the plaque, TCFA is considered a vulnerable plaque [88, 89]. In combination with other features of plaque vulnerability, such as high shear stress, microcalcifications, extensive infiltration of macrophages, and intra-plaque hemorrhage, TCFA are strongly associated with acute coronary events [17, 90–93]. All these factors affect the mechanical properties of the fibrous cap, resulting in reduced thickness and increased core size, thus leading to atheroma instability (Fig. 9.3).

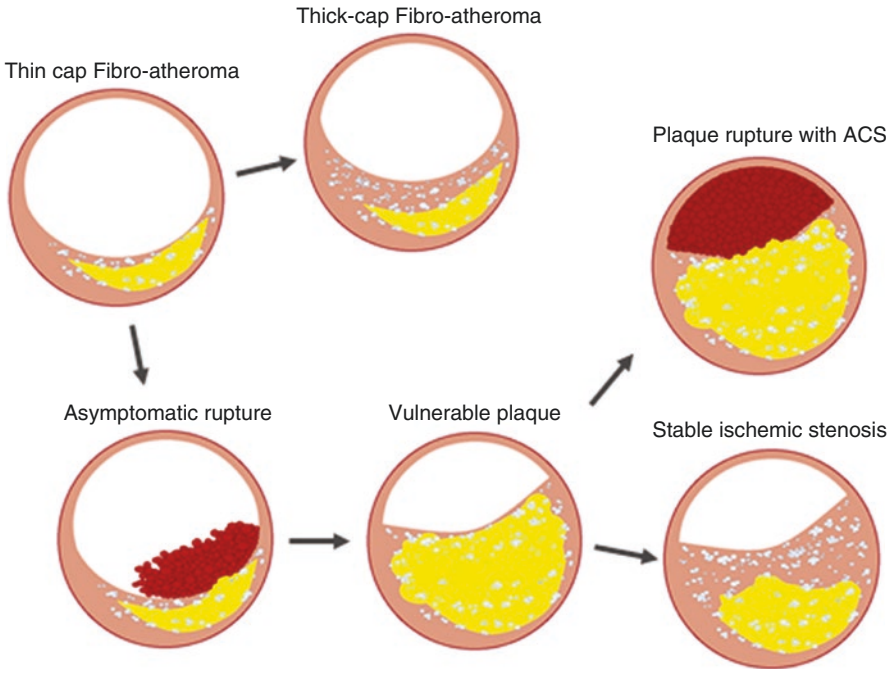


Fig. 9.3 The dynamic process of atherosclerotic lesions. Most thin-cap fibro-atheroma (TCFA) progress to thick-cap fibro-atheroma, while few undergo asymptomatic rupture. The majority of vulnerable plaques progress to stable lesions. Only few undergo rupture or erosion leading to acute coronary syndromes (ACS)

Plaque Calcification

Coronary artery calcification is closely associated with CAD irrespective of the presence of risk factors or symptoms, and is a strong predictor of future cardiac events [78, 94, 95]. However, the amount of coronary artery calcium (CAC) poorly correlates with luminal narrowing but strongly with atherosclerotic burden [96]. The extent of calcification in coronary arteries has different clinical implications.

The earliest calcification of atherosclerotic plaques develops within the necrotic core of the atheroma as a healing response to intense local macrophages inflammatory and immune cells activation [81]. Calcifications develop as an active process that resemble bone formation, controlled by enzymatic and cellular pathways [81, 97]. The death of macrophages and smooth muscle cells release vesicles and apoptotic bodies that serve as nucleating sites for deposition of crystalline structures such as hydroxyapatite [98–101]. Aggregation and fusion of such small crystals results in microcalcification, less than 50 microns in diameter, embedded in the fibrous cap. Microcalcifications can be visualized by confocal microscopy, which provides greater spatial resolution (0.5 microns) compared with the classical histological visualization methods (Fig. 9.4). Plaque calcification further stimulates

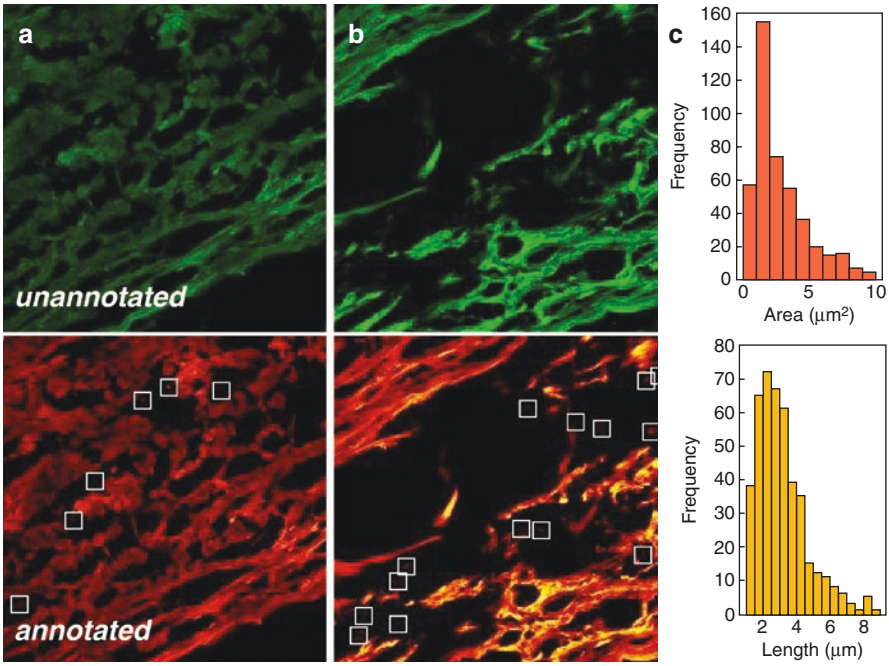


Fig. 9.4 Hematoxylin & Eosin stained samples of cardiac biopsies imaged under confocal microscopy at an excitation of 488 nm. (**a**) and (**b**) Show 2 fields of views before and after annotation using the custom written software CAS (Danial SH John, Angiology 2020. 71(10): 916–9). (**c**) Shows a distribution of the areas and lengths of the annotated micro calcifications in 16 such fields of views

macrophage infiltration, thereby enhancing the development of new calcification nucleating sites [102–104]. As long as inflammation persists there will be subsequent cycles of macrophages infiltration and calcification repair.

The link between inflammation and calcification has been also demonstrated by the observation that local arterial inflammation, assessed by positron emission tomography (PET), precedes the calcification in the same vascular site seen with conventional tomography [105]. However, the relationship between inflammation and calcification is complex. While densely calcified arterial sites are associated with low inflammation, already calcified vascular segments that subsequently developed additional calcification have significantly higher inflammation [105, 106]. These observations support the view that inflammation and calcification represent different phases of atherosclerosis. Inflammation seems to be the predominant process in early stages, promoting plaque development and calcification. Each episode of acute inflammation may induce progressive calcification [107]. In later stages, dense calcification is quiescent and does not provide a substrate for further inflammation, thus explaining the low grade vascular inflammation of pre-existing calcification.

Microcalcifications are more frequently observed in patients with acute coronary syndromes [102, 108]. Along with other features of plaque vulnerability, such as TCFA, large necrotic lipid core, and extensive macrophages infiltration, they strongly contribute to plaque instability [109]. In addition to further stimulating inflammation around the lesion, microcalcifications exert a local tissue stress within the fibrous cap that overlies the soft necrotic core [97, 110]. It has been shown that plaque rupture may derive from the mechanical stress produced at the interface between tissues with different stiffness. The presence of hard inclusions, as microcalcifications, within the much softer layer of the fibrous cap, results in a compliance mismatch in the vascular tissue properties. As a consequence, a large stress concentrates at the interface between microcalcification and fibrous cap which may lead to sudden rupture [111, 112]. The stress effect depends also on the combination of microcalcification size, shape and proximity to other lesions [113]. Laboratory simulation has shown that for a unidirectional force, as blood flow, even small differences in the tissue properties may cause a doubling of the local stress along the poles of the more rigid inclusion [114]. In accordance with this effect, biomechanical studies have shown that the risk of coronary plaque rupture is proportional to the extent of interface area and is biphasic [115]. In an early stage the microcalcifications are sparse and the risk is low. As their number increases, even the extent of the surface between rigid and soft regions increases, resulting in higher risk of plaque rupture. Moreover, the progressive aggregation of matrix vesicles forms progressively larger microcalcifications, eventually reach a critical size in the range of 5–60 microns, which has a high risk of plaque rupture [112]. Over time, pulsatile pressure fluctuations may weaken the region of stress concentration [116]. When tensile stress reaches a critical level, rupture may ensue, leading to thrombosis. As a coronary lesion gradually progresses, the majority of microcalcifications merge into

larger layers of calcium. Compared to multiple microcalcifications, the large calcified plaque has smaller interface area, hence the risk of rupture is reduced [117].

Not all microcalcifications have an adverse effect on plaque biomechanical stability. It has been observed that WSS increases by approximately 50% when calcium deposits are within the thin fibrous cap rather than in the base, thus increasing the risk of rupture [118]. Instead, calcifications in the lipid core or far from the fibrous cap act as floating debris which does not contribute to local tissue stress and may even stabilize the plaque [119, 120].

The Calcium Paradox

Most microcalcifications coalesce into larger masses giving rise to spotty calcifications, defined as calcium deposits embedded in a plaque, ranging between 1–3 mm in diameter and involving about one-fourth of the coronary circumference [100, 102, 121], During atheroma progression, microcalcifications eventually form dense calcified sheets, promoting the transition from high-risk lesion to more stable plaque with macroscopic calcification [122]. Other calcifications derive from asymptomatic rupture of unstable plaques subsequently healed [123, 124]. This is the pathophysiologic basis of the concept of the calcium paradox, which is the improved clinical outcome despite plaque progression characterized by increased dense calcium and plaque stability.

Unlike microcalcification, extensive plaque calcification is the result of a chronic healing process which makes the plaque stable, acting as a barrier to limit the spread of inflammation, similar to other inflammatory conditions such as tuberculosis. Hence, extensive plaque calcification reflects a more advanced, less inflammation disease which only rarely results in plaque rupture [3, 97]. Clinical studies support the concept of calcium paradox showing that the presence of dense calcified plaque is associated with lower risk of CV events when compared with the presence of calcified plaque with low computed tomography density, independent of coronary artery calcium (CAC) scores [94, 125]. The protective effect of extensive plaque calcification is further confirmed by the observation that the use of statins, which are known to reduce CV mortality through the reduction of vascular inflammation, is associated with increased plaque calcification and thickness of the fibrous cap, promoting the stabilization of the plaque [126–135]. In addition, clinical observations suggest that the severity of coronary calcification is significantly higher in symptomatic patients with stable angina, compared to those with sustained acute coronary syndromes, indicating that calcium confers stability to the plaque [136–139]. Although large calcified plaques are commonly associated with coronary stenosis, diffuse calcification may compromise myocardial perfusion causing ischemic symptoms even in the absence of significant luminal stenosis [140, 141].

The Vulnerable Plaque

Plaques thought to cause coronary thrombosis are described as vulnerable or high-risk plaques. Their identification is essential for effective prevention of acute coronary events [142]. About two-thirds of acute coronary events are attributed to TCFA rupture, and the remaining to plaque erosion [12, 143–145]. Their calcium content is small and in some instances may be described as mixed plaque, comprising a soft lipid rich core and partially calcified cap [146]. Uncalcified or mixed plaques are more likely to develop a thrombus than heavily calcified plaque [139]. In few cases, around 5%, a heavily calcified plaque forms a calcified nodule which protrudes into the lumen on which a thrombus may develop.

When the necrotic core underlying the fibrous cap is exposed to the circulating blood, the coagulation cascade involving platelets aggregation is activated causing arterial thrombosis [147]. Compared to plaque rupture, endothelial erosion is often associated with negative remodeling, smaller necrotic core and greater infiltration of smooth muscle cells, while inflammatory components are almost absent [12, 17, 148]. The histologic observation that in plaque erosion the acute thrombus is in direct contact with the intima, while the endothelium is absent and the media thicker than in the sites of plaque rupture, led to the hypothesis that coronary vasospasm might be involved in the pathophysiology of plaque erosion [87]. Superficial erosion occurs more commonly in women, diabetics and the elderly.

However, although pathologic data suggest that plaque composition, in terms of amount of necrotic core, thickness of the fibrous cap and calcification is the essential determinant of the atherosclerotic lesions progression and propensity to provoke clinical events, intravascular ultrasound imaging has now established that the atherosclerotic plaques usually identified as vulnerable TCFA do not always rupture and cause thrombosis. Prospective studies have shown that anatomic characteristics have limited accuracy in predicting future events [149, 150]. Indeed, only about 5% TCFA have been associated with coronary events during a 3.4 year follow-up period [151].

Atherosclerotic lesions have dynamic features with various possible pathways towards unstable evolution or stabilization [142, 152]. Plaques in various stages of development are observed in patients with CAD and their morphology may change over few months [153, 154]. Moreover, plaques with different composition may coexist in the same artery and each plaque may include regions with different atherosclerosis progression [155]. A large proportion of vulnerable plaques, such as TCFA, undergo progressive transformation from high-risk lesions to more stable plaques, showing extensive calcifications, while others undergo asymptomatic subclinical rupture with subsequent healing [151–153]. Hence, the few plaques that may trigger coronary events cannot be distinguished from the many others whose rupture and erosion are silent. However, high-risk plaques are expression of diffuse and severe atherosclerotic disease but not necessarily identify future culprit plaques [156]. In addition, plaque with high-risk features may occur at multiple distant coronary sites, especially when associated with widespread systemic inflammation

[157–159]. The relevance of the extent of disease is also confirmed by the observation that nonobstructive and obstructive CAD are associated with a similar rate of acute coronary events if the former has a more extensive disease, affecting a larger number of coronary segments [6]. These observations indicate that the development of plaque instability is not related simply to local vascular factors but may reflect more systemic factors, such as inflammatory state, altered coagulation or thrombogenic factors, endothelial dysfunction, and hemodynamic factors [11, 145, 160]. Accordingly, in recent years the search to reduce the risk of coronary events has shifted from the identification and treatment of vulnerable plaques to the global assessment of the vulnerable patient [19, 161, 162]. This implies that imaging aiming at the detection and treatment of individual plaques has a limited impact on cardiovascular prevention.

Imaging

Imaging Plaque Morphology

Invasive and non-invasive imaging modalities allow the assessment of coronary plaques, each providing different information about plaque morphology, vulnerability and extent of the atherosclerotic disease [163].

Coronary Angiography

Coronary angiography is a luminography that provides direct visualization of the extent and severity of arterial narrowing, making it a routine imaging method in symptomatic high-risk patients. In addition, it can provide access for other intracoronary studies, such as intravascular ultrasound or optical coherence tomography. Coronary angiography shows mainly the anatomy of the arterial lumen, while no information can be derived on the morphology of structures that are below the endothelium, and extent of arterial remodeling. Although large calcified plaques are well visualized, the sensitivity for smaller lesions is limited, due to the spatial resolution of about 100–200 μm [164, 165].

Also, the degree of anatomic stenosis has only limited correlation with coronary functional assessment as defined by fractional flow reserve (FFR) [166]. Coronary stenoses are more likely to cause a subsequent myocardial infarction when associated with an abnormal FFR producing ischemia, compared to lesions with similar angiographic appearance without myocardial ischemia [167]. In patients with stable angina, the diagnostic accuracy of angiography to detect a hemodynamically significant lesion has been shown to be about 60% [168]. In a large study of patients with multivessel disease, two-thirds of stenoses with an angiographic severity of 50% to 70% and also one-fifth of those between 71% and 90% were functionally

nonsignificant when compared with FFR [169]. Moreover, the positive remodeling which is a vulnerable lesion and allows apparently normal lumen size despite the presence of wall plaque, may be missed. Luminal narrowing can occur only after the atheroma expands to 45% of coronary cross sectional area [59, 170].

These observations may account for the elusive relationship between the severity of coronary artery stenosis and the site of subsequent myocardial infarction (MI). Old retrospective angiographic studies, performed months to years before MI, suggested that mild-moderate coronary stenoses were responsible for most MIs [171, 172]. However, these data were contradicted by postmortem findings which showed that the degree of stenosis of most patients who died of MI was more than 70% [173, 174]. Such discordance about the severity of culprit lesions may be explained by the variable time course of the progression of atherosclerotic plaques. Serial intravascular imaging studies have shown that months before MI most plaques which subsequently result in coronary events show vulnerable morphology with positive remodeling, hence appearing mild at angiography. However, in the days or weeks before MI, some of them go through a rapid progression into coronary occlusion [2, 175–177]. Because of these limitations, both the atherosclerotic burden and the prediction of coronary events may be underestimated by angiography.

Non Contrast Computed Tomography (CT)

Non-contrast electrocardiographic (ECG)-gated multidetector CT is extensively used for the quantitative assessment of coronary artery calcium (CAC), allowing the measurement of CAC score (Fig. 9.5). This is based on the Agatston score which

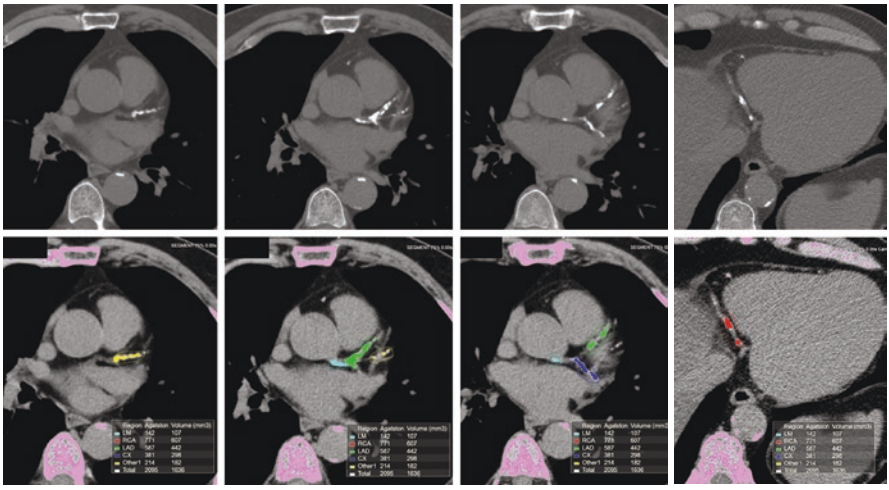


Fig. 9.5 Basal (non-contrast) CT shows extensive calcific atherosclerotic plaques within the coronary arteries (upper frames). Agatston score in the same vessels was calculated with a dedicate software (lower frames). Light blue: left main coronary artery. Green: left anterior descending. Yellow: diagonal branch. Blue: circumflex branch. Red: right coronary artery

measures the density of calcification in each coronary segment, multiplied by the area and summed for all arteries [178]. CAC score correlates well with the presence and extent of CAD and is an independent predictor of CV events [95, 179–184]. It is recommended as a CV risk stratification tool, to improve risk prediction in asymptomatic individuals at intermediate risk, providing prognostic information over traditional risk stratification [185–188]. The relevance of CAC in the prediction of acute events is also supported by the observation that in asymptomatic individuals free of clinical CAD, without conventional risk factors but elevated CAC score, the rate of all-cause mortality is significantly higher than in individuals with multiple risk factors but no CAC [189]. Also, the sensitivity of the combination of CAC score and conventional risk factors for predicting significant stenosis (>50%), measured by conventional angiography in symptomatic patients, has been reported considerably higher than for significant stenosis measured by computer tomographic coronary angiography (CTCA) [95].

A CAC score < 100 is usually associated with mild CAD, while a score > 400 generally correlates with extensive disease [190]. In individuals without known atherosclerotic disease, a CAC score of zero is associated with a high negative predictive value in excluding significant CAD [191]. However, although only 5% of individuals with zero CAC have significant stenosis, low CAC scores do not exclude obstructive CAD [192, 193]. Indeed, even in the absence of clinical CAD, a CAC score > 100 may be associated with a risk of events similar to patients with previous CAD [194, 195]. Observations from a large registry of asymptomatic individuals showed that, compared to zero CAC, the relative risk of all-cause mortality increased from 2.2 fold for a CAC score up to 100, to 12.5 fold for a score > 1000 [196].

The pattern of plaque calcification is also important. Although it is generally believed that CAC score reflects only calcified plaques, the use of contrast-enhanced computed tomographic angiography, which allows characterization of the plaque composition, has shown that higher CAC scores are more likely to be associated with mixed plaque burden which are the high-risk component of coronary plaque burden [197–199]. This may explain why these patients have a worse prognosis. In addition, these patients are more likely to benefit from statin therapy [200]. Instead, the majority of plaque burden in patients with low CAC score is calcified.

This supports the observation that the relationship of the CAC score with subsequent coronary events appear to be mainly based on the volume component of the score, while calcification density has an inverse relationship with risk of CAD [94, 201–203]. Density refers to the concentration of calcium in the plaques. High calcium density plaques have small lipid cores and are more stable. Low calcium density plaques are associated with large lipid cores and positive remodeling, making plaques more vulnerable. Hence, the inverse relationship of density with risk of CAD may reflect the protective role of stable large calcifications.

When interpreting changes in CAC score over time, statins use must be considered. In patients treated with statins, the progression of CAC may reflect plaque stabilization, rather than progression of the atherosclerotic burden [126, 129, 133, 134]. In these patients, the increase in CAC score is mainly due to calcified plaque progression, whereas without statins, it is associated with non-calcified plaque progression and increase in coronary plaque volume [204].

Although CT is used to quantify the extent of coronary calcification, the presence of microcalcifications can be significantly underestimated because even though these represent more than 80% of the total number of calcifications, their contribution to the total calcified tissue volume is less than 1% [119]. Moreover, the CT spatial resolution cannot distinguish vulnerable from stable atherosclerotic plaques. Hence, the total amount of calcification, quantified by CAC score, is a marker of CV risk rather than a marker of risk conferred by an individual plaque.

Contrast Enhanced Computed Tomographic Coronary Angiography (CTCA)

Although the CAC score measured by CT correlates well with the atherosclerotic disease burden, calcified plaques represent only one aspect of the total plaque burden. The intravenous administration of iodinated contrast agent allows accurate noninvasive evaluation of the presence and distribution of CAD (Fig. 9.6 and 9.7). In addition to the well documented visualization of coronary stenosis [205–207], CTCA can accurately characterize plaques into calcified, non-calcified or mixed, with sensitivity and specificity of more than 90% [168, 208–212]. The importance

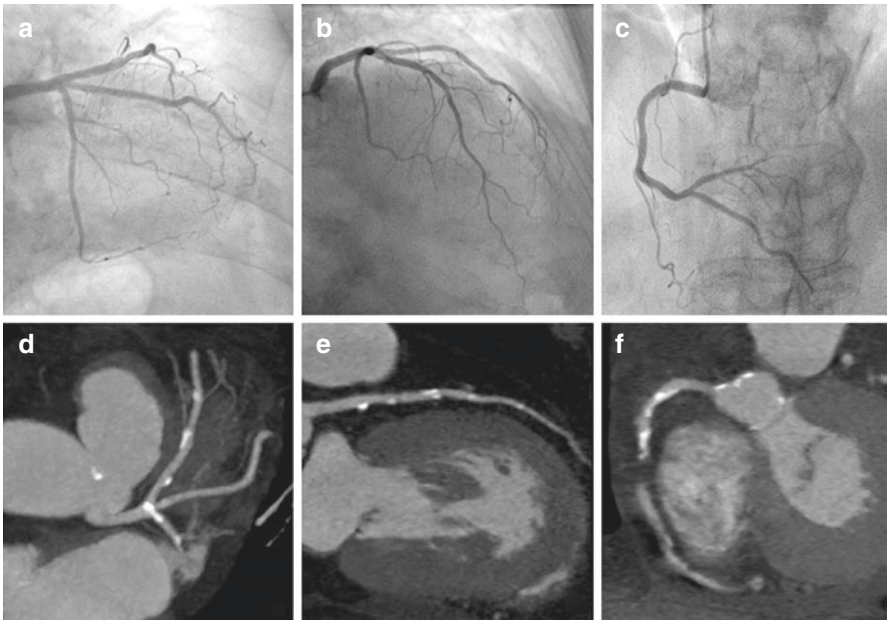


Fig. 9.6 Coronary angiography shows no significant narrowing of the left (**a**, **b**) and the right coronary artery (**c**); the corresponding CCTA depicts multiple calcific plaques, predominantly eccentric in the anterior descending coronary artery (**d**, **e**), in the circumflex branch (**d**), and in the right coronary artery. Note the trifurcation of the left coronary artery giving a large branch called ramus intermedius (anatomic variant)

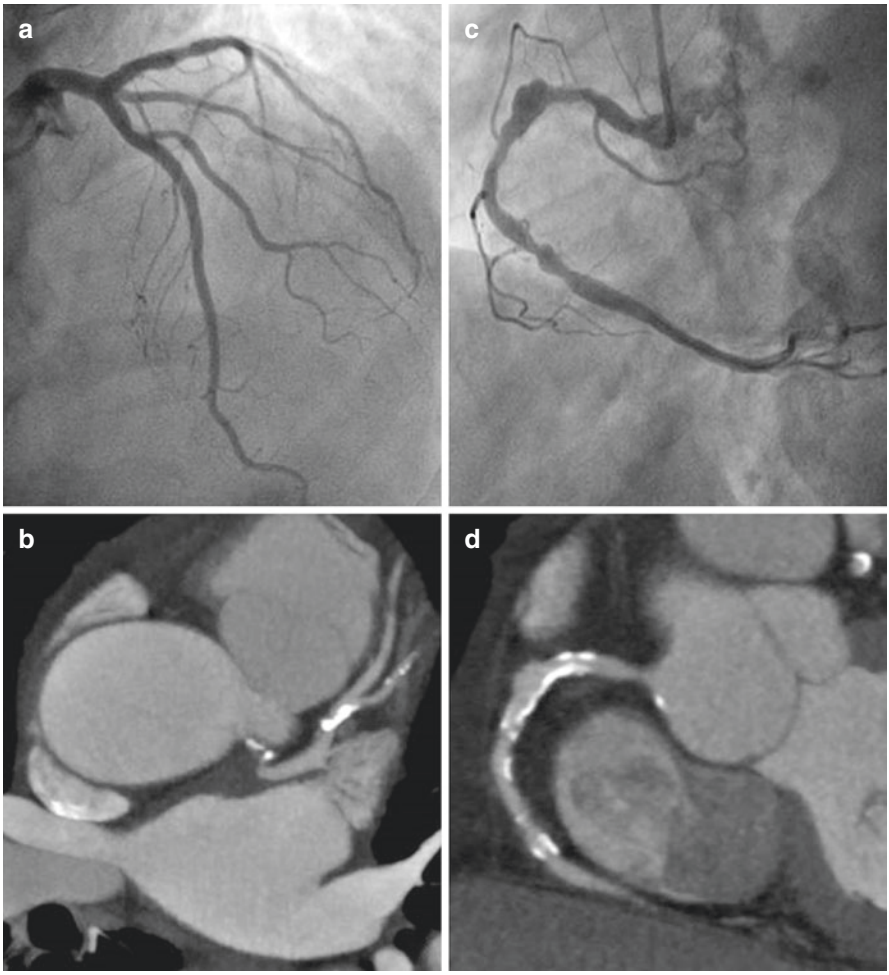


Fig. 9.7 Coronary angiography and the corresponding CCTA depict significant luminal stenosis in the proximal segment of the anterior descending coronary artery, at the origin of the first diagonal branch (**a**, **b**). Multiple stenoses in the proximal and middle segment and post-stenotic aneurysm in the proximal segment of the right coronary artery (**c**, **d**)

of reliable plaque morphological differentiation in a recent meta-analysis has shown that non-calcified plaque are more strongly associated with future acute coronary syndromes [208]. However, smaller components of the vulnerable plaque, such as microcalcifications, cannot be detected because their dimension is ten times less than the spatial resolution of CTCA (around 600 microns) [213]. CTCA is mainly appropriate for symptomatic moderate-risk patients without known CAD [214]. A negative result is associated with very low risk of coronary events (negative predictive value about 99%) [215–217]. Hence, the test is appropriate to rule-out significant CAD, thus reducing the need for invasive tests. Compared to intravascular

ultrasound (IVUS), CTCA shows excellent correlation between coronary stenosis and plaque area [210, 218]. The contribution of plaque extent to predict CV events in obstructive and non-obstructive CAD has been assessed with CTCA, showing that the extent of plaque provides additional prognostic value, regardless of the presence of obstructive or non-obstructive disease [6]. Indeed, patients with non-obstructive CAD who had extensive disease, showed similar rates of acute events as those with obstructive but less extensive disease.

Compared to conventional angiography, CTCA has been reported to have higher accuracy in identifying calcified and non-calcified plaques, and coronary positive remodeling [219, 220]. While more than 95% of arterial stenosis documented with angiography are confirmed by CTCA, only one-third of those detected with CTCA are identified by angiography.

The relationship between morphological plaque characteristics and patient clinical presentation has been investigated with CTCA in three population groups with different cardiovascular risk [221]. Plaque volumes and the proportion of necrotic core progressively increased with worsening risk profile, while the proportion of densely calcified plaques reduced. These observations confirm that high clinical risk profile is associated with potentially unstable lesions, while low-risk is associated with greater proportion of calcified and more stable plaques [208].

Cardiac Magnetic Resonance (CMR)

Based on advanced imaging technique, CMR provides non-invasive accurate soft tissue contrast imaging, visualization of coronary lumen and arterial wall morphology, atherosclerotic disease burden, and plaque composition and activity [222–224].

Coronary atherosclerosis characterization by CMR is based on electromagnetic signal intensity from protons in free water, triglycerides and free fatty acids in a strong magnetic field. Morphologic appearance of the atherosclerotic lesions depends on their free water concentration. Because calcification does not contain free water, densely calcified plaques appear as dark region on CMR. In contrast, plaques with low calcium density, usually associated with vulnerable features, appear with high intensity on MR.

Non-contrast enhanced CMR can identify some vulnerable plaque characteristics, such as vascular remodeling, inflammation, and intra-plaque hemorrhage due to high T1 weighted signal which is associated with methaemoglobin, a key constituent of acute coronary thrombus [225, 226]. While high-intensity intracoronary signals have been associated with early thrombus formation, high-intensity intra-wall signals have been related to the presence of macrophages and lipid-rich plaques, validated by intravascular imaging [227, 228]. However, there are several limitation which may impact the diagnostic use of CMR in clinical practice, including low spatial resolution of around 1.3–1.8 mm with most current techniques, visualization limited to proximal coronary segments, and the need for a separate CMR angiography to localize lesions.

Contrast enhanced CMR based on gadolinium contrast agent provides better spatial resolution (CMR angiography) and disease activity information. Indeed, the accumulation of gadolinium in the arterial wall is correlated with increased endothelial permeability and inflammation [223, 229]. CMR may assess significant narrowing in coronary arterial segments with ≥2 mm diameter, and detect ruptured coronary plaques in patients with acute myocardial infarction, with a high specificity [224, 229–231]. CMR has been also combined with positron emission tomography (PET) for the simultaneous assessment of anatomic details and disease activity [232, 233]. The advantage of this hybrid PET/MR system is the lower level of radiation exposure compared to PET/CT, thus allowing to monitor the progression of chronic atherosclerosis over time.

Intravascular Ultrasound (IVUS)

This catheter-based imaging modality allows direct cross-sectional visualization of coronary wall and atheroma [220, 234, 235]. IVUS imaging is based on ultrasound reflection by coronary calcification and is more sensitive and specific than angiography (Fig. 9.8). However, IVUS cannot penetrate calcium, hence the

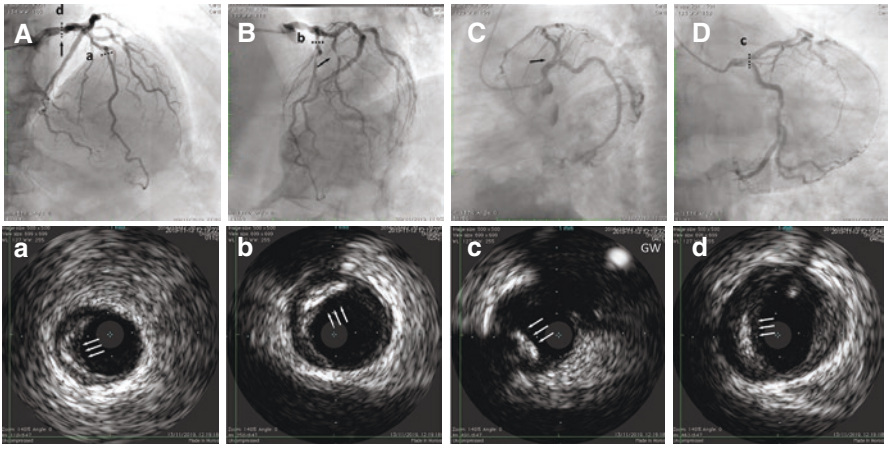


Fig. 9.8 Angiogram (**A**, **B**, **C** and **D**) and intravascular ultrasound (IVUS) pullback cross-section (**a**, **b**, **c**, and **d**) performed from left anterior descending (LAD) to left main coronary artery (LMCA) of a hypertensive male suffering from unstable angina due to sub-occlusive lesion on the first diagonal (**B** – black arrow). Another lesion located on the ostial LAD involving LMCA, was detected (**A** and **C** – black arrows) and a IVUS pullback was performed. LAD and LMCA minimal lumen areas (MLA) were 9.8 mm2 and 6.4 mm2, respectively. During IVUS pullback, several spotty calcifications, in mixed plaque, were detected on mid LAD (**a** – white arrows), proximal LAD (**b** – white arrows), ostial LAD (**c** – white arrows) and LM stem (**d** – white arrows). Drug eluting stent was implanted on diagonal while other lesions were considered not critical – after IVUS – and treated with medical therapy

assessment of plaque calcification is quantitatively expressed as arc (in degrees) and length. Calcified plaques appear echo-dense (hyperechoic) and brighter than the surrounding arterial structures. Grey-scale IVUS signal intensity features have been associated with plaque instability, such as ultrasonic attenuation (echo-attenuated plaque), associated with fibroatheroma containing large necrotic core; echolucent plaque, containing an intraplaque zone of absent echogenicity, associated with small necrotic core; spotty calcification associated with acute coronary events [122, 236].

However, the grey-scale IVUS axial and lateral resolution (about 200 microns), does not visualize some components of the vulnerable plaque, such as microcalcifications or the TCFA which are usually smaller than 60 microns. It is also limited by the inability to assess the composition and inflammatory state of the fibrous cap [237]. To improve the IVUS analysis of atherosclerotic plaque components, computer-assisted radiofrequency analysis of the reflected ultrasound signals have been developed in recent years to visualize color-coded plaque composition, including fibroatheroma, necrotic core, TCFA and dense calcification [122, 236, 237]. In addition to the greyscale IVUS, the analysis of intravascular ultrasound radiofrequency backscatter signal, also known virtual histology IVUS (VH-IVUS), provides a detailed analysis of plaque composition and has been validated in vivo and in postmortem specimens [149, 150, 238].

However, there are some doubts on the IVUS reliability and reproducibility for the accurate differentiation of plaque composition and prediction of future CV events, which may limit its use in routine practice [150, 151].

Optical Coherence Tomography (OCT)

OCT image reconstruction relies on a light source in the near-infrared range and measures the time delay of optical echoes reflected by the arterial wall (Figs. 9.9 and 9.10), allowing high-resolution cross sectional images of superficial plaque composition and microstructures [220, 239]. OCT has about ten times higher axial resolution than IVUS, between 10–20 microns. However, low penetration depth (1–2 mm vs 10 mm for IVUS), and attenuation of light transmitted through blood, red thrombus and a lipid or necrotic core, can limit the visualization of arterial border and plaque burden [239, 240]. OCT has shown high sensitivity and specificity for fibrous, fibrocalcific, and lipid-rich plaques and is considered the only imaging modality that can directly measure TCFA and quantify the presence of macrophages and cholesterol crystal in the atherosclerotic plaque [93, 241–244]. Imaging of contemporary presence of macrophages and microcalcifications in the same plaque with reciprocal distance smaller than 1 mm (termed co-localization), has been shown to be associated with more vulnerable plaque features [110, 245].

The integration of IVUS and OCT combines the deep penetration of IVUS with the high resolution of OCT, allowing more accurate measurements of cap thickness, necrotic core, and plaque burden [246].

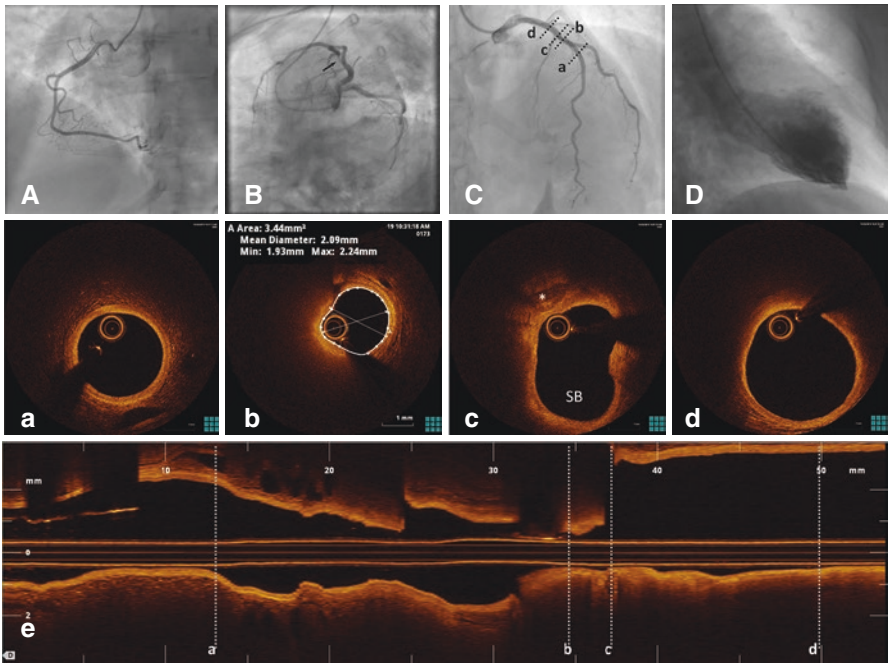


Fig. 9.9 Angiogram (**A**, **B**, **C** and **D**) and Optical Coherence Tomography (OCT) pullback (**a**, **b**, **c** and **d** [cross-section], e long-view) on left anterior descending (LAD) of a young female suffering from hypertension and diabetes, during an acute coronary syndrome. The angiogram shows no critical lesions on right (**A**) and left coronary artery (**B** and **C**). The ventriculography (**D**) shows akinesia of left ventricular apex associated to normal contraction at the ventricular base, typical aspect for Takotsubo syndrome (apical ballooning). However, a subcritical lesion on mid LAD (**B** – black arrow) was detected and an OCT pullback was performed. The minimal lumen area at the bifurcation segment was 3.44 mm2 (**E** and **b**) and a spotty calcification (**c** -white asterisk) was detected at the level of diagonal (SB) arising (**E** and **c**)

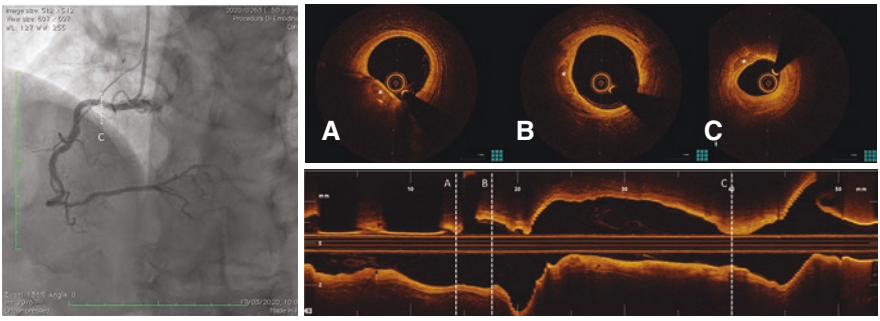


Fig. 9.10 Young male smoker patient was admitted for NSTEMI. Coronary angiography (left side) showed an intermediate plaque on proximal right coronary artery (**C**). The OCT pullback (right side) showed a diffuse fibro-lipidic plaque with some spotty calcifications (**A**, **B**, **C**, withe asterisk), and minimal lumen area (MLA) of 2.44 mm2 at the proximal segment (**C**)

Near-Infrared Spectroscopy (NIRS)

The limited ability of IVUS to accurately identify cholesterol-rich lipid core plaques, which are thought to be strongly associated with most cases of acute events, led to the development of NIRS for patients undergoing intravascular coronary imaging [247]. NIRS can detect lipid-rich plaques on the basis of the absorption pattern of near infra-red light by cholesterol molecules. The resulting image (chemogram) appears as a colourised ring around the IVUS image, ranging from red to yellow, according to the amount of cholesterol in the plaque [248–250]. The lipid core burden index (LCBI) can be automatically computed by dedicated software and has been histologically validated. Plaques with a high LCBI have been found strongly associated with subsequent major CV events [251–253]. Since NIRS provides only minimal anatomic visualization, it has been combined with IVUS in a single catheter so that information from the two modalities can be acquired simultaneously [254, 255].

Although intravascular imaging using IVUS, OCT or NIRS, may have potential positive effects in the management of patients with CAD, further data are needed to support a strategy of preventive treatment of individuals lesions, particularly when they are not shown to cause myocardial ischemia.

Disease Activity Imaging

Positron Emission Tomography (PET)

Although structural imaging techniques provide an assessment of the plaque burden, they give no indication as to the extent of inflammatory plaque activity. Hence, they cannot accurately distinguish between patients with stable disease from those with increased disease activity, expressed by macrophages and microcalcifications which are associated with increased risk of developing acute CV events. PET can visualize the inflammatory components of the atherosclerotic process, thus providing a highly sensitive assessment of coronary disease activity, prediction of the high risk of events associated with plaque rupture, and monitoring the efficacy of drug treatment [256].

Specific radioactively labelled tracers targeted to pathological components of the atherosclerotic process, such as macrophages (^{18}F-fluorodeoxyglucose and 68-Gallium-dotatate targeting the somatostatin receptor on the surface of macrophages) and microcalcification (^{18}F-sodium fluoride), accumulate at sites of increased disease activity, releasing radiation which are detected by the PET scanner [225].

However, PET imaging has low spatial resolution and limited anatomic definition. Hence, it needs to be combined with an anatomic imaging modality, such as CT or MR to provide simultaneous assessment of disease activity and morphological information. Hybrid imaging systems that incorporate PET with CT or MR scanners within the same gantry, provide simultaneous imaging combining the

molecular specificity of PET imaging with the anatomic and functional characterization provided by CT or MR. [257, 258]

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a glucose analogue which is extensively used for malignancy staging as a marker of metabolic activity. Its uptake by macrophages has been recently used to image vascular inflammation because the glucose metabolic activity of the macrophages involved in the atherosclerotic plaque is higher than the surrounding cells [259]. ^{18}F-FDG PET has been most investigated in the carotid arteries and aorta, while its use in the assessment of coronary plaque inflammation is limited because a substantial proportion of FDG uptake can occur in the adjacent myocardium which has a high affinity to tracer uptake due to its high glucose metabolism. This makes it difficult to distinguish between arterial inflammation and myocardial uptake, thus limiting accurate plaque analysis, and requiring a special patient preparation to minimize the myocardial glucose uptake [222].

^{18}F-sodium fluoride (^{18}F-NaF) has been originally studied to identify bone metastasis and is now used to visualize coronary calcification [260]. Fluoride ions are incorporated into hydroxyapatite which is a central component of the osteogenic mineralization [256]. Coronary atherosclerosis is strongly associated with macrophages osteogenic activity in the early stages of atherosclerosis, which results in microcalcifications found in the lipid-rich necrotic core of atherosclerotic plaques. This allows ^{18}F-NaF to detect active microcalcification which are beyond the resolution of CT scan. The stronger affinity of the radiotracer with newly formed hydroxyapatite compared to the old crystals makes it possible to distinguish between actively inflamed coronary calcifications from stable ones. This is confirmed by the observation that large areas of coronary calcium detected by CT scan do not show increased ^{18}F-NaF uptake. Conversely, regions with absent or minimal CT calcium demonstrate intense ^{18}F-NaF uptake [261]. The preferential binding of ^{18}F-NaF uptake to microcalcification is also explained by high surface area of hydroxyapatite in microcalcifications compared to large macroscopic calcifications where hydroxyapatite is internalized and not available for binding [262]. This discordance between morphologic and nuclear imaging provide complementary information and may improve differentiating stable from vulnerable plaques [263, 264].

Adverse Effect of Coronary Atherosclerosis Imaging

With the exception of transthoracic ultrasound and CMR, coronary atherosclerosis imaging involves the intravenous or intracoronary administration of iodinated contrast media, or the use of ionizing radiation. A potentially serious complication is the contrast-induced nephropathy (CIN), defined as an acute rise in serum creatinine of $\geq$0.5 mg/dl (0.04 mmol/L) or 25% above the baseline value, occurring during the first 72 hours after the procedure [265]. In patients undergoing coronary angiography the incidence of CIN is between 2% and 15%, strongly related to preexisting clinical conditions such as renal insufficiency, diabetes, advanced age, extent of CAD, and congestive heart failure [266–268]. Although CIN is usually transient, few patients may develop persistent renal damage and an increased risk of cardiovascular events [269]. Compared to catheter-based intracoronary procedures, the

occurrence of CIN following intravenous contrast administration during contrast-enhanced CT is much lower and may be considered rare in patients with normal renal function [270–272].

The exposure to X-ray radiation due to coronary angiography is around 7 mSv, corresponding to more than double the 1 year background radiation on the earth [273]. CT scan also may represent a health concern, particularly in younger patients who are most likely to undergo sequential imaging for measuring CAC progression. This induces cumulative radiation exposure and risk of developing radiation-related malignancy. However, in recent years, new technologies have significantly reduced the level of radiation exposure. The development of CT scan angiography with prospective ECG-triggering, replacing the conventional retrospective ECG-gated, allowed significant reduction in radiation level which is now <3 mSv, comparable to the 1 year background radiation [273].

Compared to angiography and CT scanning, the dose of radioactive tracer given during a PET scan is small and patients are exposed to low levels of radiation during the test, around 5 mSv. When combined with CT scan, the radiation doses are much higher. MR/PET hybrid imaging system is therefore most likely to be useful when repeated imaging are needed.

Summary

Atherosclerosis is a dynamic process involving a complex interplay of inflammation, endothelial dysfunction and impairment of the vascular tone, arterial wall shear stress, intense immunological activity with migration of macrophages and smooth muscle cells into the intima, arterial remodeling and calcification. Inflammation stimulates calcification of the atherosclerotic plaque. The earliest calcification lesion is microcalcification which originates as aggregation of small crystals of hydroxyapatite, within a fibro-atheroma. Microcalcifications make the plaque unstable and are strongly associated with plaque rupture. Among invasive and non-invasive imaging modalities, optical coherence tomography (OCT) has the spatial resolution to allow the assessment of the smaller components of coronary plaques, including microcalcifications. Since microcalcifications are associated with inflammation, positron emission tomography (PET) identifies the extent of the inflamed areas.

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Chapter 10
Imaging Peripheral Arterial Calcifications

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Introduction

Vascular calcification (VC) results from crystallization of calcium/phosphate in the form of hydroxyapatite in the extracellular matrix of the arterial wall.

While localized intimal calcification, in concert with vascular smooth muscle cells (VSMCs), macrophages, and the necrotic lipid core, is implicated in pathogenesis of atherosclerosis [1, 2], extensive disseminated medial calcification is a common feature of peripheral arterial disease (PAD) [3].

Peripheral arterial disease refers to occlusion or narrowing of the upper and lower extremity arteries, causing insufficient blood flow to the limbs [3, 4].

Epidemiology

According to the European Society of Cardiology (ESC) approximately 202 million people are affected with lower extremity vascular disease (LEAD) worldwide; almost 40 million are living in Europe [5]. LEAD usually appears after the age of 50 years, with an exponential increase after the age of 65 years. This rate reaches 20% by the age of 80 years [5]. In most studies the proportion of symptomatic

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LEAD is 1:3 to 1:5 of all LEAD patients. The prevalence of chronic limb-threatening ischemia (CLTI) is at 0.4%, with an estimated annual incidence ranging from 500 to 1000 new cases per million, higher in diabetic patients [5]. There is a 23% increase in the total number of individuals with LEAD in the last decade as a result of the total population increase, global aging, increased incidence of diabetes worldwide and smoking in low and middle-income countries [6]. The mortality related to LEAD increased between 1990 and 2010 in Europe, reaching 3.5 per 100,000 individuals in 2010 in Western Europe [5].

Except for the subclavian arteries, the upper limb arteries are rarely affected by atherosclerosis. The prevalence of subclavian stenosis is estimated to be 2% in the general population but increases to 9% in the case of concomitant LEAD [5].

Mechanisms of Vascular Calcification

In the past, VC was considered only a passive process, the result of Ca2+ and P ions excess, inducing the precipitation and deposition of hydroxyapatite crystals [7]; it is currently accepted that vascular cells play an active role in osteoid formation and the ossification process to result in VC [8, 9].

There are multiple pathophysiological mechanisms resulting in VC, which can be summarized in:

- inadequate inhibition of the mineralization process;
- induction of osteogenesis;
- circulating nucleational complexes;
- cell death;
- elevation in serum $Ca2^{+}$ and P levels;
- migration and differentiation of macrophages and VSMCs into osteoclast-like cells [7, 9].

The reduction in inhibitors of mineralization expression, such as pyrophosphate and matrix GLA-protein (“loss of inhibition”) leads to spontaneous vascular calcification [9]. Furthermore, Kettler et al. (2003) suggest that fetuin/α2-HS-glycoprotein is a major inhibitor of apatite found in the circulation, and decreased fetuin levels have been correlated with elevated cardiovascular disease (CVD) mortality in hemodialysis patients [10].

Osteogenic mechanisms also play a role in vascular calcification, due to the presence of bone proteins such as osteopontin, osteocalcin, and BMP2, matrix vesicles, and outright bone and cartilage formation in calcified vascular lesions [9].

Price et al. (2001) speculate that the link between artery calcification and osteoporosis is increased bone resorption, leading to release of circulating nucleational complexes, and that in postmenopausal women this link involves the loss of the inhibitory effect of estrogen on bone resorption [11].

Cell death can provide phospholipidic membranous debris and apoptotic bodies that may serve to nucleate apatite, especially in diseases where necrosis and apoptosis are prevalent, such as atherosclerosis [9].

Two categories of VC have been described: intimal and medial (or Monckeberg's medial sclerosis).

Intimal calcification is associated with atherosclerotic plaques and thought to result from modified lipid accumulation, pro-inflammatory cytokines, and apoptosis within the plaque that induce osteogenic cell differentiation. Medial calcification is more common in the lower abdominal region, associated with PAD and results from the osteogenic differentiation of VSMCs within the medial layer of the vessel wall [7]. $Ca2^{+}$ accumulation begins as an amorphous mineral deposit and undergoes progressive remodeling, ultimately mineralizing into mature bone. Although medial calcification is generally not associated with luminal obstruction, and the decrease in the arterial vessel wall elasticity and compliance may lead to atherosclerosis, reduced perfusion and PAD [7].

Risk Factors

VC is a pathology characteristic of aging but is accelerated in chronic kidney disease (CKD), diabetes mellitus, and atherosclerosis [12]. Different localizations of PADs share common major risk factors for atherosclerosis [5]. Smoking is one of the strongest risk factors for PAD, particularly for LEAD, with a population attributable fraction estimated at 44% [13], and the risk increases with smoking intensity [5]; some studies estimates as high as a 4× greater risk among smokers than others [14]. Cessation of smoking among patients with intermittent claudication (IC) has been shown to improve various functional and physiological measures related to PAD, as well as reducing mortality [14]. Fowkes et al. (1992) found smoking to be associated with a significantly higher relative risk for PAD compared with other CVDs [15].

Diabetes is strongly associated with LEAD, with odds ratios (ORs) ranging from 1.9 to 4 in population studies [9, 15]. This risk is increased with diabetes duration. The prognosis of LEAD in diabetic patients is poorer than in non-diabetic patients, with a 5x increased risk of amputation, because distal arteries are more frequently affected, with the coexistence of neuropathy and higher risk for infection [16].

As for upper extremity artery disease (UEAD) significant associations were found with systolic blood pressure [17]. Hypertension is also associated with an increased prevalence of LEAD, with ORs in large epidemiological studies ranging from 1.32 to 2.20 [9].

A high prevalence of hypercholesterolemia is a significant contributor to LEAD. In most studies, total cholesterol is associated with prevalent LEAD in multivariable analyses [9]. HDL-C has been shown to be protective in all large epidemiological studies [9]. Obesity has been implicated in the causes of other risk

factors for PAD, such as hypertension, type II diabetes mellitus, and dyslipidemia but to date there is not a consistent positive association with PAD [14].

Inflammation is involved in atherosclerosis pathophysiology. Several markers of inflammation (e.g. high-sensitivity C-reactive protein, fibrinogen, interleukin 6) are associated with an increased risk of the presence, progression and complication of LEAD [2]. Some autoimmune/inflammatory conditions are at increased risk for LEAD (e.g. systemic lupus erythematosus, rheumatoid arthritis) [18].

Several studies have shown an association between CKD and PAD, particularly in the case of end-stage renal disease requiring dialysis [19].

Bowman et al. (2012) proposed a potential genetic role in VC, with gene mutations that regulate VSMC extracellular matrix phosphate production and protein promoters; adult onset vascular calcification is linked to mutations NTE5, enzyme that regulates extracellular phosphate metabolism, which appear to target vessels below the diaphragm muscle and spare the coronary and carotid vessels [20]. However, evidence on their clinical relevance is weak [5].

Clinical Features

Atherosclerosis of the upper extremity artery disease is mostly situated at the level of the brachiocephalic trunk and the subclavian and axillary arteries. Distal lesions are mostly related to non-atherosclerotic lesions [5]. Isolated subclavian stenosis is often asymptomatic and may be suspected because of unequal arm systolic blood pressure ($\geq$ 10–15 mmHg difference in systolic blood pressure) [21]. However advanced subclavian obstructive disease or vertebral vessels stenosis may result in flow reversal in vertebral artery, worsened by ischemia or steal symptoms. Subclavian steal syndrome may be suspected in cases of visual disturbances, syncope, ataxia, vertigo, dysphasia, dysarthria and facial sensory deficits occurring during efforts made by the arms [5]. LEAD has several different presentations, categorized according to the Fontaine classification [5]. Most patients are asymptomatic and a subset of these may have severe disease without symptoms, which can be related to their incapacity to walk enough to reveal symptoms (e.g. heart failure) and/or reduced pain sensitivity (e.g. diabetic neuropathy). This subgroup should be qualified as ‘masked LEAD’ [5]. LEAD can also be clinically masked in one leg when the other one has more disabling disease. A typical presentation in this patient with several comorbidities is toe necrosis after a wound. In symptomatic patients, the most typical presentation is IC; intermittent claudication consists of exertional calf pain that does not begin at rest and that resolves within 10 min of rest. Chronic limb-threatening ischemia (CLTI) indicates a more advanced stage and is defined by the presence of ischemic rest pain, with or without tissue loss (ulcers, gangrene) or infection. Arterial ulcers are usually painful and are often complicated by local infection and inflammation. When pain is absent, peripheral neuropathy should be considered [5]. Regular clinical examination is important in elderly patients, especially diabetic patients, to improve limb salvage [22]. Several studies show as

peripheral arterial calcification is significantly correlated with CAD extent in patients with PAD. Peripheral arterial calcification can be a useful marker for predicting multivessel-CAD [23].

Clinical Diagnostic Tests

The ankle-brachial index (ABI) is the preferred initial test for PAD screening and diagnosis [24] and is a ratio of Doppler-recorded systolic pressures in the lower and upper extremities.

In healthy people without PAD, arterial pressures increase with greater distance from the heart and this phenomenon results in higher systolic pressures at the ankle compared to the brachial arteries in people without lower extremity arterial obstruction [25].

The ABI should be measured with the patient in a supine position and appropriately sized blood pressure cuffs are placed over each brachial artery and at each ankle. The ABI is typically calculated for each leg, by dividing the highest of the two pressures in each leg by the highest of the left vs. the right brachial artery pressures [25]. The highest pressure in each leg is traditionally selected when calculating the ABI, because the highest pressure represents the greatest arterial pressure reaching the foot [25].

However, it has been demonstrated that the ABI calculation using the lowest of the dorsalis pedis and posterior tibial pressures in each leg maximizes sensitivity of the ABI for the diagnosis of PAD [26] but may be associated with lower specificity.

The normal ABI value is considered >90. An ABI $\leq$ 0.90 has 75% sensitivity and 86% specificity to diagnose LEAD [27]. However, when clinically suspected, a normal ABI (>0.90) does not definitely rule out the diagnosis of LEAD. ABI values <0.50 are associated with increased risk of amputation compared to higher ABI values in patients with leg ulcers and in patients with history of diabetes [25].

In case of a high ABI (>1.40) related to medial calcification, alternative tests such as toe pressure, toe brachial index (TBI) or Doppler waveform analysis of ankle arteries are useful [5]. The ABI is also a strong marker of generalized atherosclerosis and CV risk, in fact an ABI $\leq$ 0.90 is associated on average with a 2- to three-fold increased risk of total and CV death [5]. An ABI >1.40 due to arterial stiffening is also associated with a higher risk of CV events and mortality [5].

Vascular Ultrasound

One of the easiest radiological technique for arterial evaluation, specifically for peripheral vascular system, considering its availability, low cost and no use of ionizing radiation, is the ultrasound (US). This technique provides many details about vascular anatomy and blood flow [28, 29].

Vascular US is a diagnostic technique composed by:

- Conventional B-mode ultrasonography, used to morphologically evaluate the lumen and the blood vessel wall;
- Color Doppler Ultrasonography used to evaluate blood flow direction and velocity [30].

Technical Aspects and Approach

Medical US imaging is the result of ultrasound waves produced and received by piezoelectric crystals within the ultrasound transducer, whose frequencies range from 2 to 15 MHz. A linear probe is preferred for peripheral vascular evaluation. Image resolution and depth penetration depends on the ultrasound frequency and how ultrasound interacts with tissues.

For a correct US evaluation of peripheral vascular system, it is important to choose the appropriate probe frequency depending on the anatomic region of study interest. It is recommended to study arterial vessels in B-mode firstly, for a correct morphological interpretation, then proceed with the evaluation of color and spectral Doppler imaging. The acoustic window needs to be selected on the most superficial plane of target vessels. In B-mode it is important to examine blood vessel wall not only longitudinally but also perpendicularly, in order to precisely evaluate any pathological finding. Steering the sample volume is important to insonate the vessel of interest at an angle of up to 60 degrees [31]. The principle positions of vascular evaluation are (from proximal to peripheral):

– subclavian, brachial, radial and ulnar arteries for the upper limb;
– femoral (common, superficial and deep), popliteal, peroneal (when correctly detectable), anterior and posterior tibial arteries for the lower limb.

As explicated before, the vascular US investigation is completed by color doppler US: this colorimetric analysis is generated by blood cells, whose movement in blood flow is responsible for the transmitted US waves. Another important element in Doppler evaluation is the angle identified between the direction of blood flow and the principle axis of the ultrasound beam; in clinical practice, the US beam is aligned to make a 45- to 60-degree angle with the arterial lumen to obtain a reliable Doppler signal [32].

US Findings, Interpretation and Clinical Evaluation

In the context of peripheral calcifications in atherosclerotic patients, color doppler US allows not only a morphological arterial evaluation but it also may assess for hemodynamics, with grayscale, color flow and spectral Doppler imaging, focusing

on morphology of doppler wave and peak systolic velocity (PSV). Structures with strong reflecting power are depicted by white pixels; structures with weak reflecting power are depicted as dark shades of gray. Basing on this evidence, B-mode imaging shows brightness of the vessel wall (strong reflector) defined as hyperechoic; instead intravascular blood flow is dark, defined as anechoic (weak reflector).

The doppler analysis, usually performed in combination with the color mode, gives a characteristic spectral waveform, which is the result of the frequency shifts and velocities of blood flow; the flow direction relative to the US beam is referred to the baseline. A shade of gray is the representation of the amplitude of each velocity component. In normal arteries, the laminar blood flow generates a thin waveform, with a tri-phasic flow pattern and a clear area under this curve (called *spectral window*) [32]. The Doppler spectral waveform can be analyzed either by visual inspection or by listening to the auditory signal for vascular flow abnormalities. Other elements can be analyzed like PSV, diastolic velocity, mean velocity and Doppler indices such as systolic-to-diastolic ratio, pulsatility index and resistive index [32].

In patients with atherosclerosis, an initial B-mode ultrasonography can reveal an irregular profile of the arterial wall. This finding can be observed in longitudinal and transversal scanning mode [33]. Atherosclerotic plaques reduce vessel lumen diameter, causing mild, moderate, severe or occlusive stenosis. Depending on its composition, atherosclerotic plaque could be echographically defined:

- hyperechoic (the main composition of the atherosclerotic plaque is calcium); this finding is often accompanied to a "shadow cone" under the superficial layer of the plaque, whose presence makes the arterial wall evaluation incomplete and unassessable;
- hypoechoic or anechoic (the main composition of the atherosclerotic plaque is thrombotic material or in general non-calcified material). This finding has no "shadow cone" and makes the arterial wall evaluation reliable.

The morphological assessment is completed identifying significant stenosis when the vessel diameter is reduced by at least 50% (lumen reduction over 50% is usually clinically symptomatic). Then, the US investigation proceeds to the color doppler evaluation. Abrupt narrowing of the vessel lumen is associated with an increase in blood flow velocity through the stenotic segment. In addition, the spectral window is different from normal condition: healthy vessel segment has a clear spectral window, but in atherosclerotic vessels the spectral window is disturbed (suggesting the presence of turbulent blood flow, which is no more laminar) (Fig. 10.1). Following this, blood flow changes are:

- presence of a plug profile at the stenotic segment;
- the flow becomes disturbed or turbulent in the post-stenotic segment, with broadening or widening of the spectral waveform.

The spectral Doppler image displays these hemodynamic changes as high-resistance flow in the pre-stenotic segment, high-velocity flow with spectral broadening at the site of stenosis (the waveforms become monophasic or bi-phasic with

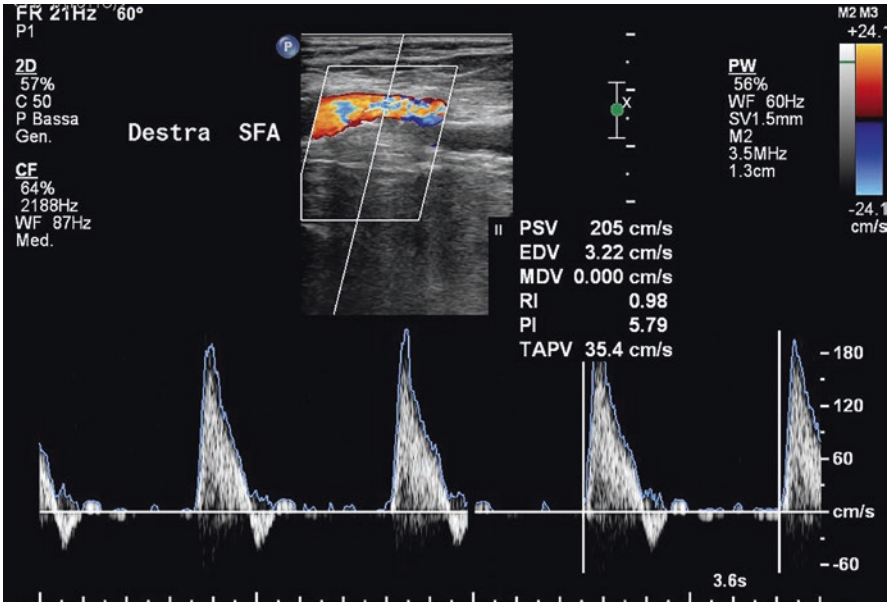

Fig. 10.1 Duplex ultrasonography of right superficial femoral artery. Spectral window shows a triphasic Doppler-wave with turbolent flow (the area under the first peak is not clear); PSV demonstrates a hemodynamically significant stenosis

increased PSV), and low-resistance monophasic flow with increased diastolic flow at the post-stenotic segment [33]. Distal to a hemodynamically significant stenosis, the waveforms become monophasic with a "*tardus-et-parvus*" pattern [34] (Fig. 10.2). Occlusion is seen as absence of flow on color flow imaging and spectral Doppler.

Pearls and Pitfalls

Imaging evaluation of peripheral arterial blood vessels should be preceded by accurate clinical non-invasive evaluation, with physiologic tests and a correct analysis of patient symptoms. Although US provides morphologic assessment of steno-occlusive disease, it lacks important information about the physiologic impact of the patients' disease.

US Color Doppler evaluation is a reliable tool that allows to assess a hemodynamically significant stenosis or not; if confirmed, patient could be eligible for a II level diagnostic investigation. In this context, it is important to pay attention to some aspects:

– Aliasing: artifact seen when blood flow velocity exceeds one half of the pulse repetition frequency (PRF). This can be solved increasing PRF (velocity scale)

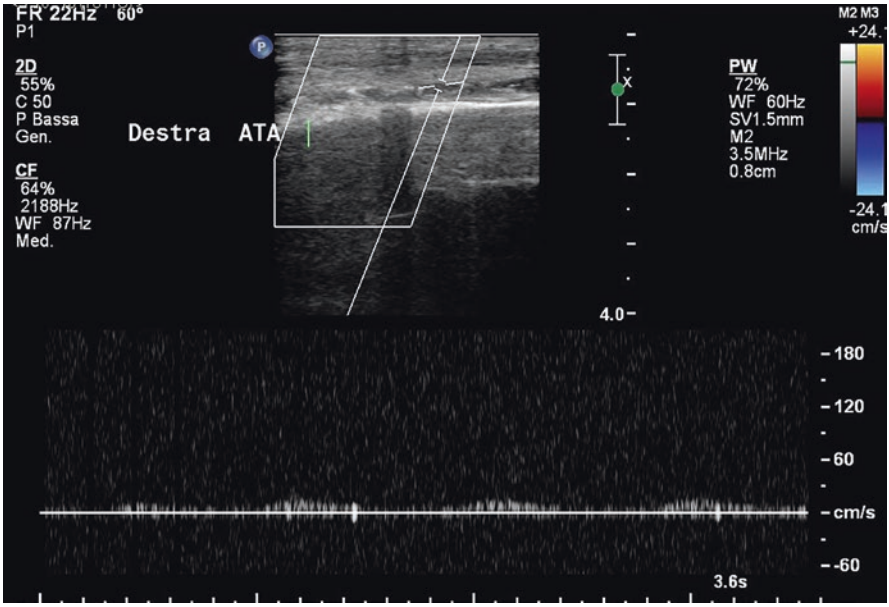

Fig. 10.2 Duplex ultrasonography of right anterior tibial artery. Spectral window shows a monophasic with a *"tardus-et-parvus"* pattern (the wave form is wide and flat suggesting a reduced blood flow)

and angle of insonation, decreasing probe frequency and moving baseline in spectral doppler in order to see complete waveform [35];

– Spectral broadening in normal vessels: an incorrect insonating angle with >60 degrees can lead to this artifact even if studying normal blood vessels. It can be solved decreasing the insonating angle <60 degrees and the sample size, and setting an optimal aperture size of the transducer [36];
– Flow direction artifacts: in curved blood vessels, there are more difficulties to correctly insonate and analyze blood flow. Regulation of beam steering could help to overcome this artifact, but it is also important to adjust scanning and probe position [37].

Limits

Even if US color doppler can give a great analysis of vascular peripheral system in atherosclerotic patients, helping in risk stratification of PAD developing, it is a diagnostic method not free from some limitations. It is highly dependent on:

– the expertise of the operator. A correct US study is insufficient without a great clinical interpretation of imaging data; the experience of the operator is important not only for the correct US exam execution, avoiding artifacts and wrong

scanning methods of spectral analysis and doppler evaluation, but also for the exact evaluation and interpretation of each finding;
– the patient compliance: an uncooperative patient leads to a more difficult examination, which could become a source of wrong and incomplete evaluations;
– the patient habitus (especially for abdominal vessels): an obese patient make the vessel evaluation and correct insonation vessels extremely difficult;
– the presence of anatomical variations: as aforementioned, vessel tortuosity, linked to congenital variations, gives an uncomprehensive evaluation of the peripheral vascular system, leading to a necessary second level imaging evaluation.

Multidetector Computed Tomography Angiography (MDCTA)

Computed tomography (CT) angiography (CTA) with multidetector CT technology is the current non-invasive gold standard for the evaluation of the upper and lower extremity arterial system because of its excellent spatial and contrast resolution. It represents a reliable alternative for the reference test, i.e. digital subtraction angiography (DSA). In order to optimize the scan protocol and to obtain high-quality images, it is necessary to know and understand each underlying acquisition parameter and it is imperative to achieve a valid enhancement of the entire arterial runoff.

Technique

Patient Positioning

Lower Extremity Arterial System

The patient has to comfortably lie in supine position, feet-first, with raised arms on the scanner table. Cushions are used to stabilize and align the legs and sometimes even adhesive tape may be required to hold the lower limbs together, especially when a non-cooperative patient must perform the CT scan, in order to avoid motion artifacts. Artifactual stenosis or occlusion of the dorsalis pedis artery (i.e., “ballerina sign”) may occur if an excessive plantar flexion of the feet is not avoided [36]. The patient has not to wear belts, metal buttons or zippers on his clothing, since this may affect the exam quality.

Upper Extremity Arterial System

The patient may be positioned in the supine or prone position, head-first, with the interested arm raised above the patient’s head, palm facing ventrally and fingers straightened and taped down. The contralateral arm, instead, is placed next to the

patient's body [37]. If bilateral upper extremities need to be scanned, both arms are raised.

Scanning Technique and Protocol

Modern multidetector CT (MDCT) scanners allow to obtain viable vascular images, due to thinner section collimation, shorter scan timing and advanced post-processing techniques [38, 39]. Every acquisition and reconstruction parameter, such as pitch, section thickness/reconstruction interval, relies on the scanner model.

The whole-body coverage for the lower extremity arterial system is about 1500 mm. A 120 kilovolts (kV) tube voltage is usually set [40]; some automated scanners may modulate two different energy levels, 120 kV or less (depending on the patient constitution-low body mass index) until the knee joint, with full field of view and 80–100 kV for the leg and foot tissues, with reduced field of view. Such parameters may improve spatial and contrast resolution on distal anatomical structures.

A standard acquisition protocol consists of [41]:

- a scout topogram to plan the study. The scan range, i.e. volume of interest (VOI), extends from the diaphragmatic domes to the toes.
- an optional (strongly recommended) non-contrast acquisition from the T12 vertebral body level to the pubic symphysis.
- a pre-monitoring phase, by using the bolus tracking technique; a region of interest (ROI) is positioned in the aorta, at the celiac trunk level with a preferred Hounsfield Unit (HU) threshold, usually from 100 to 150 HU, already set. Multiple fast low-dose sequential scans monitor the arrival of the contrast medium at the ROI level. When the chosen threshold is reached, the acquisitions starts automatically.
- the real CT angiography phase including the whole VOI.
- an optional caudal-cranial delayed phase, in case of previous surgical treatments (such as bypass), aneurysms or if distal vessels are not enhanced.

Breath-holding is required only during the acquisition through the abdomen and pelvis. The scanning time ranges between 20 to 40 s, depending on the number of detector rows and the collimation [42]. With cooperative walking patients, the exam may easily last 10–15 min of room time.

For the study of the upper extremity arterial system, the whole-body coverage is 500–1000 mm and two different energy levels (120 kV from the aortic arch to elbow and 80–100 kV from the elbow to fingertips) are used. A different protocol needs to be assessed [43]:

- a scout topogram ranging from the carina to the fingertips.
- an optional non-contrast acquisition.
- a pre-monitoring phase, by using the bolus tracking technique; a region of interest (ROI) is positioned in the aortic arch, with a preferred Hounsfield Unit (HU)

threshold, usually of 180 HU, already set. Multiple fast low-dose sequential scans monitor the arrival of the contrast medium at the ROI level. When the chosen threshold is reached, the acquisitions starts automatically.
- the caudal-cranial CT angiography phase including the whole VOI.
- a delayed phase, just above the elbow to fingertips.

Contrast Medium Injection

It is essential that an optimal and homogenous enhancement of the upper and lower extremities arterial system is achieved. Attenuation values >200 HU in the vessel lumen are considered eligible in MDCTA [44, 45]. CTA requires high contrast to noise ratio (CNR) to this end. During the study of the lower extremity arterial system, intravenous (IV) contrast medium (CM) is injected with a mechanical injector into an antecubital vein via wide gauge IV cannula (20 or 18 G), for the maximal flow rates of 4.0 and 5.0 mL/s, respectively. Instead, for the upper extremity arterial system, IV access (20 or 18 G) is usually obtained in the contralateral arm, unless a central venous access is required if bilateral upper extremities have to be studied [46]. CM with high iodine concentration (350–400 mg/mL) has to be preferably used. Other important factors that affect the resultant attenuation in the vessels are the iodine delivery rate (IDR-gI/s), injection rate (mL/s), total volume of CM (mL) and kV [47]. IDR is the product of the CM concentration (mgI/mL) and the injection rate (mL/s) and it represents the rate at which iodine is delivered into the arterial tree [48]; in the vascular imaging it has to range from 1.6 to 2.0 gI/s [49]. An injection rate of 4–5 mL/s is usually enough for achieving optimal arterial enhancement with current scanners, although a higher peak aortic enhancement is obtained with increasing injection rates [50]. The total volume of CM to be injected derives from the expected scan time given by scanner (in seconds) + 10 (constant) x flow of CM (in mL/s) and it usually ranges from 120 to 160 ml for a typical lower extremity arterial scan duration of 40 s, followed by 20–40 mL of saline flush, with the aim of compacting the CM bolus and optimizing the enhancement [41]. Poliphasic (bi- and tri-phasic) injection rates guarantee a more uniform enhancement and ensure lower CM volumes and lesser beam hardening artifacts both in upper and lower extremity arterial system [51]. In addition, by using peak tube voltages lower than 120 kV(p) and keeping the same iodine rate, a higher attenuation in HU of the target vessels is achieved (proximity with the k edge of iodine), thanks to the prevalence of the photoelectric effect rather than Compton effect. By reducing tube voltage from 120 to 70 kV(p) there is a 75% increase in HU attenuation [41].

Radiation Exposure

Radiation exposure is one of the major concerns in CT exams. The average patient dose reported in the assessment of peripheral artery disease (PAD) with CTA is 7.47 mSv [44, 52, 53]; however, it has to be remembered that the radiation risk is

almost redundant in this kind of patients because of their shorter life-expectancy rather than the latency period of a radiation-induced fatal malignancy [54–56]. Besides, there are several methods of dose savings that vary from the newer iterative image reconstruction (IR) techniques to the kV(p) reduction. The former is replacing conventional filtered back projection (FBP) techniques since they are less prone to increased image noise at lower radiation doses and the may lower radiation dose by up to 50% compared to FBP [57–60]. The latter consists of a dose drop of about 50% for each step of kV(p) reduction (120/100/80/70 kV(p)) [40].

Image Reconstruction

The raw data set is usually reconstructed by using an increment with 50% to 70% overlap, and the field of view (FOV) has to be selected as small as possible to increase spatial resolution [42]. A smooth kernel (B20 for Siemens CT scanners) is normally chosen and offers a suitable images quality.

CTA Findings and Interpretation

CTA allows evaluation of the length and severity of a stenosis or occlusion, and lesions can be categorized using the Trans-Atlantic Society Consensus (TASC II) classification for the management of aortoiliac and femoropopliteal occlusive disease [61]. Arterial calcifications are defined as hyperdensities of vascular wall. Calcified plaques are usually noticed in diabetic patients and in those with chronic kidney disease (CKD) undergoing hemodialysis and they may have variable effects; large calcified plaques can cause flow-limiting stenoses, whereas microcalcification may increase the chance of plaque rupture [62]. Calcifications may assume different shapes (bulky, protruding, horse-shoe) and may be circumferential or eccentric. They can affect the entire vascular tree, or they may be limited to bifurcation levels, due to blood shear stress. Occlusions may be seen as filling defects within the arteries. Linear endoluminal calcifications are also to be assessed since they may be an expression of a local previous intimal flap. Smaller vessel calibers combined with severe wall calcifications can make less accurate the luminal patency evaluation and determination of the degree of stenosis [63]. Imaging must provide the location and extent of steno-occlusive disease, patency of distal runoff and the presence of major collateral vessels.

Images interpretation is significantly improved using 2D and 3D techniques such as multiplanar reformation (MPR), curved planar reformation (CPR), maximum intensity projection (MIP), and volume rendering (VR), but it cannot prescind from axial-sectional imaging. Axial imaging is also mandatory for the assessment of extravascular abdominal or pelvic findings. Post-processing techniques may be time-consuming even for an experienced technologist, but at the same time they may facilitate and shorten reporting time.

MIP technique resembles conventional angiography, by providing a wide-ranging display of the arterial tree, including the status of collateral vessels, and permits easy detection of calcium and stents, but it cannot allow patency evaluation within of luminal a stent or calcified plaques [64] (Fig. 10.3). It is ideal to have an overall view of the vascular map that could be very useful for treatment planning. Although superimposing calcifications may be removed by the software, it is a time-consuming operation and voxels representing vessel lumen may be inadvertently removed when in close contact with bony structures [42].

MPR and CPR techniques offer the most reliable source in depicting vascular stenoses, especially when endoluminal stents and large eccentric calcified plaques are present [65]. MPR technique exploits transverse, sagittal, coronal and oblique reformations and it is extremely useful for the analysis of bifurcations. CPR

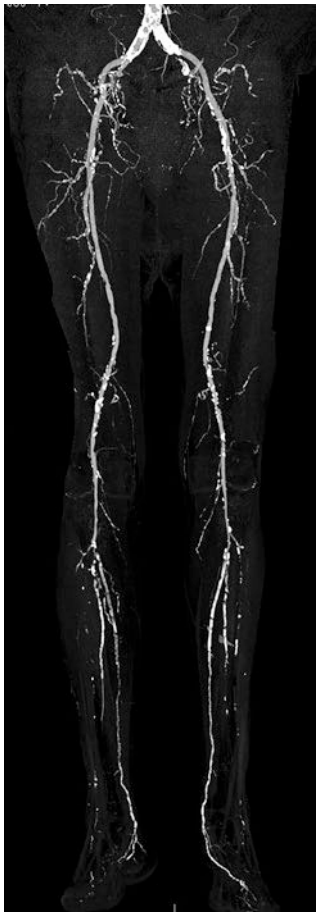

Fig. 10.3 Coronal thin section MIP of a CTA of the abdomen, pelvis and lower extremities after bone removal in a 64 years-old male patient, showing severe calcified plaques and high-grade stenoses

technique uses longitudinal cross-sections along a pre-determined vascular center line that may be manually or (semi-)automatically traced [66, 67]. The CPR projection does not require bone editing and should include at least two perpendicular longitudinal projections in order to effectively assess stenoses distribution and quantification.

VR technique creates fast 3D images, preserving depth information, unlike MIP. It may be useful for the rapid evaluation of peripheral CTA data sets and it may help clinicians by providing a vascular mapping overview. VR images should not be used for the lumen assessment since vessel calcifications and mechanical stents may completely obscure what is inside the vascular wall. A particular rendering technique, called cinematic rendering, may display photorealistic 3D images [68] (Fig. 10.4).

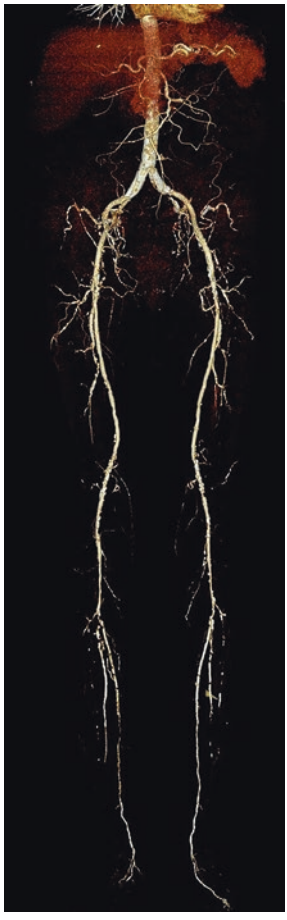

Fig. 10.4 Cinematic rendering technique of the abdomen, pelvis and lower extremities arterial anatomy showing calcifications as multiple and irregular hyperdensities although the lumen cannot be assessed with this technique

Clinical Considerations

A stenosis is considered hemodynamically significant if it has a > 70% diameter narrowing or has a hemodynamically significant gradient at rest or after a vasodilator challenge. Similarly, the presence of collateral vessels suggests hemodynamically significant stenosis or occlusion. Imaging provides precise pre-procedural planning information with regard to route of access and balloon selection. Particular attention should be paid to bulky and protruding calcified plaques localized in common femoral artery, since, in Transcatheter Aortic Valve Implantation (TAVI) procedures, such vascular district corresponds to the site of puncture for introducing the sheath. However, asymptomatic disease rarely requires revascularization despite the presence of arterial stenosis or occlusion. Thus, clinical conditions (such as intermittent claudication) has to guide treatment. The lower limb arterial calcification (LLAC) score, derived from non-contrast CT, correlates with the likelihood of diabetes, renal failure and cardiac mortality and morbidity [69]. Arterial wall calcifications have to be thoroughly investigated since they may have consequences for bypass surgery. Patients with Fontaine stage III/IV have more infrapopliteal calcified plaques compared to stage IIb [42]. Although literature reports a good to excellent inter-observer agreement for CTA [44, 70], arterial wall calcifications may decrease clinicians' confidence in vascular imaging [71] and may lead to the possibility of misinterpretations [72].

Pearls and Pitfalls

Visual interpretation of vascular abnormalities, even with the assistance of 2D and 3D techniques requires imaging expertise and familiarity. In extremely calcified arterial vessels, like in diabetic population, a sharp kernel (B46) is required; it is also selected when metallic stents are present, since it minimizes the "blooming" artifact, although this results in increased background image noise [73]. In detail blooming artifact derives from tiny, high-density structures such as arterial wall calcifications and metallic objects, which appear larger than their true size and it may lead to an overestimation of a vascular stenosis or suggest a spurious occlusion. The true vessel lumen may be studied by increasing the spatial resolution, by using IR and a high window level (WL) and wide window width (WW) of around 150 WC ± 250 WW to 200 WC ± 1000 WW [74]. Additionally, dual-energy CTA allows to characterize iodine, calcium, and other materials within tissues by their absorptiometric differences and it may automatically remove bone e calcified plaques [75, 76]. Generally, the diagnostic accuracy of CTA in tibial disease is lower compared with the aorta-iliac and femoral districts, particularly in the setting of heavily calcified vessels. Other interpretation pitfalls may result from misinterpretation of editing artifacts (e.g., accidental vessel removal) in MIP images and pseudostenosis and/or occlusions in CPRs due to inappropriate center-line definition [42]. In

patients with history of diabetes mellitus, Magnetic Resonance Angiography (MRA) should be assessed as the test of choice due to calcified arterial vessels and concurrent renal failure.

Magnetic Resonance Angiography (MRA)

Magnetic Resonance Angiography is a non-invasive accurate technique for the assessment of upper and lower extremity arterial disease [77, 78]. It does not use ionizing radiations and iodinated contrast agents, unlike CTA, and provides enough high spatial resolution images. Newer dynamic vascular sequences have led MRA closer to the DSA reference standard [77]. However, it is a rapidly evolving non-standardized technique that requires the knowledge of physical principle of quantum mechanics and of magnetic resonance (MR) sequences.

Technique

MRA of the upper and lower extremity arterial system may be performed with or without the use of contrast agents. It requires high-field MR scanner (1.5 T or 3 T) with dedicated phased-array receive coils in order to achieve sufficient spatial resolution and vessel contrast [79].

Patient Positioning

No substantial differences compared to CTA positioning are evidenced, both for the upper and the lower extremity arterial system. The only note concerns the study of the forearm and the hand since the patient has to be placed in a decubitus prone position with the arm of interest extended above the head ("Superman position").

MRA Techniques

Contrast-Enhanced MRA Techniques

– Contrast-Enhanced MRA (CE-MRA)

It is considered the modality of choice for MR vascular imaging [79]. Fast T1-weighted gradient-echo sequences with low flip angles are used after administration of IV paramagnetic gadolinium (Gd)-based contrast agents, due to the shortening of T1 relaxation in blood. Adequate acquisition timing of the center of k-space, during the peak vessel enhancement, has to be achieved. Such technique

has the advantage of creating subtracted images with a MIP visualization, of having short scan times and high spatial resolution with minimal flow-related artifacts. Image quality may be compared to that of DSA [80]. The main disadvantages of CE-MRA are artifacts related to stents and other metallic implants (off-resonance).

This technique involves the IV administration of 0.1–0.2 mmol/kg dose of a gadolinium-chelated contrast, usually Gadobenate dimeglumine (Multihance, Bracco Diagnostic, Princeton, NJ) at the rate of 1.5–2 mL/s, followed by 20 mL of saline flush, both for the upper and the lower arterial system. Bi-phasic injection protocol may be used and adequate timing of the bolus is crucial to minimize venous contamination. Background suppression may be obtained with subtraction.

– Time-Resolved MRA

Time-Resolved MRA techniques use preferential sampling of low spatial frequencies (center of k-space) with undersampling of higher spatial frequencies (periphery of k-space). View-sharing methods allow to obtain high temporal resolution by keeping the same spatial resolution [81]. Time-resolved MRA provides dynamic information (such as hemodynamically significant stenoses) and may acquire a pure arterial phase and minimize venous contamination that degrades image quality. Common nomenclature includes: TWIST (Time-Resolved Angiography with Stochastic Trajectories); TRICKS (Time-Resolved Imaging of Contrast Kinetics); 4D TRAK (4D-Resolved Angiography Using Keyhole).

Non-contrast MRA.

Several techniques may be applied with the benefit of not using contrast materials [82].

– Time of flight (TOF)

It is a flow-dependent obsolete technique that requires long acquisition times and it is susceptible to artifacts related to either slow or turbulent flow and stenosis overestimation [83].

– Phase contrast (PC)

PC-MRA depends on phase shifts caused by blood flow and it is commonly used for flow imaging and measurement of flow but rarely it may be applied for the evaluation of the upper and lower extremity arterial system.

– ECG-gated 3D FSE

Bright-blood 3-D FSE results from subtraction between systolic and diastolic images. ECG-gating takes advantage of differences in arterial and venous flow velocities during the cardiac cycle. During diastole arterial transit is minimal, resulting in high signal intensity on T2-W images, while in the systole phase, when the peak arterial flow is greatest, low signal intensity will be evidenced. Venous blood is bright throughout the cardiac cycle because of the relatively low resting flow [74]. The major limitations include cardiac arrhythmias and motion artifacts. Besides slow-moving blood may result in residual signal in the peak systolic images.

Flow-related dephasing of the arterial blood pool in diastole may also occur, resulting in improper vessel contrast and overestimation of stenosis.

– Balanced SSFP with arterial spin labelling

This technique uses two RF-pulses to tag protons in arterial blood, resulting in bright blood images. The first 180°-pulse is non-selective, by inverting the entire background regardless of location. The second 180°-pulse is spatially-selective and it is applied upstream of the arteries of interest to restore magnetization in the region from which the tagged blood flows.

– Quiescent-interval single shot MRA using 2-D SSFP (QISS)

QISS is a cardiac-gated inflow-based technique that uses modified single shot 2-D balanced SSFP pulse sequence. It provides diagnostic quality images of the upper and lower extremity arterial system, on both 1.5 T and 3 T magnets [84, 85]. It may assess peripheral vascular disease with sensitivity similar to CE-MRA but with significantly less specificity [85].

MRA Findings and Limits

Vascular calcifications are diamagnetic and with only few protons present, visualization is inadequate with standard MRI sequences [86]. Nevertheless, MRA is considered as an accurate test for PAD [87]. The sensitivity and specificity of CE-MRA exceed 95% for detecting 50% or greater luminal stenosis. It may also be used for surgical planning of peripheral artery bypass. Since vessel wall calcifications result in additional risk for morbidity and mortality, newer MR sequences that depict calcified plaques have been studied. By fusing image data from unenhanced QISS MRA and proton density–weighted in-phase 3D stack-of-stars (PDIP-SOS), a simultaneous evaluation of the vessel lumen and calcifications are assessed [88]. In addition, neutral contrast 3D magnetic resonance imaging (NCMRI) technique is able to detect vessel wall calcifications providing a CTA-like display [89]. As reported in the CTA evaluation, MRA must provide the location and extent of stenoocclusive disease, patency of distal runoff and the presence of major collateral vessels (Fig. 10.5). MRI has evidently many limits in its routinely use, first of all its limited availability and prolonged acquisition times. Secondly, any Gd-based contrast agent must be avoided in patients with an expected glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 given risk of nephrogenic systemic fibrosis [90]. However, it is known that the use of 3 T MRI scanners offer a higher signal-to-noise ratio (SNR), potential for lower doses of Gd and improved spatial resolution compared with 1.5 T. Another problem regards the effect of venous contamination that degrades image quality. Different tools may be used to prevent such complication: the use of bi-phasic injection protocols, extremity compression cuffs to slow arteriovenous transit and the use of time-resolved MRA techniques. Other contraindications include claustrophobia, the presence of pacemaker, metallic foreign bodies

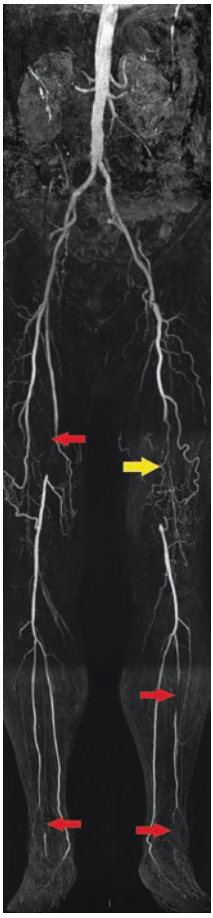

Fig. 10.5 Magnetic resonance angiography of the abdomen, pelvis, and lower extremities showing bilateral multiple segmental occlusions in right superficial femoral artery, right distal fibular artery, left mid and distal fibular artery (red arrows). Collateral vessels supplied by the left profunda femoral artery (yellow arrow) due to chronic occlusion of the left superficial femoral artery

and metallic stents. Current research is directed toward the discovery of new non-contrast sequences that could help in redefining e stratifying patients with PAD.

Catheter Angiography (CA)

Catheter angiography (CA) is an x-ray imaging technique focused on blood vessels using contrast medium injected through an introducer (needle, catheter or sheath) positioned within the vessel of interest. Its role has changed over time: with more recent developments in non-invasive vascular imaging techniques (US, CTA and MRA), the diagnostic approach of CA is decreased in favor of its therapeutic role. As a matter of fact, even if CA still remains the gold standard for vascular imaging, providing the best temporal and spatial resolution for assessing the blood vessels, its invasiveness, related also to several risk of complications, makes CA procedure

justified only because it represents an integral part of all therapeutic vascular interventions for patients [91]. In the context of atherosclerosis, CA is indicated in case of symptomatic patients with a diagnosed PAD that needs to be treated with endovascular approach.

Technical Approach

CA is a complex procedure that starts from pre-procedure patient evaluation, followed by selection of appropriate hardware and technical parameters during the procedure, and appropriate post-procedure care. Usually, CA is not a procedure that requires the use of antibiotics. An adequate premedication is needed in patients with known allergy to contrast medium or who are at risk of contrast medium-related allergic reactions. Vascular access needles, guidewires, dilators, sheaths and catheters are the basic tools for catheter angiography [92]. First of all, it is important to correctly clean the selected vascular access site with povidone-iodine or chlorhexidine solutions, as well as the site should be free of any local infection or skin interruption. After that, the vascular access site needs to be confirmed palpatory and local anesthesia is provided; above all, PAD may determine a not successful appreciation of arterial pulse, therefore it could be helpful for the operator an US preprocedural examination or by using bony landmarks. Obviously, it is necessary the patency of the vessel being accessed as well as the ability to catheterize the vessel of clinical interest selectively. There are two typologies of vascular access: antegrade access (along the direction of blood flow) or retrograde access (against the direction of blood flow). Independently from the access typology, vascular access refers to the original technique of percutaneous vascular catheterization as described by Seldinger, with the needle advanced at a 45- to 65-degree angulation toward the artery [92]. Commonly, needles used for vascular access are 18 gauge in diameter; they have a central sharp stylet which is able to puncture vessels through both the walls. The intra-arterial location of the needle is confirmed by the pulsatile flow through the hub of the needle. In order to reduce vessel trauma, it could be helpful using a 21-gauge micro-puncture needle, often preferred in patients in therapy with oral anticoagulant therapy (OAT) and new oral anticoagulant drugs (NOADs). A guidewire is advanced through the needle, and the needle is exchanged for a dilator. Dilators are tapered short catheters that have the role to displace soft tissues at the puncture site to facilitate easy passage of catheters and guidewires. At the end of the procedure, the arterial access sheaths or catheters should be removed; the operator, depending on patient coagulation parameters and/or the need of a new angiographic evaluation within 24 hours, could decide to temporary leave catheters inside the artery, protecting them with medications. After devices removal, the preferred haemostasis technique is the manual compression; when the vascular access is free from relevant calcifications but there is low patient compliance or the patient is affected from a coagulation system disorder, it could be necessary to use arterial closure devices.

Catheter Angiography Findings, Interpretation and Treatment Options

Despite CA is considered the gold standard for evaluation and endovascular treatment of peripheral arteries, it is an imaging technique that does not gives precise information about peripheral calcifications if compared to other imaging methods. With subtraction image reconstructions and the use of contrast medium, CA gives the best spatial and temporal resolution of vessel lumen, but it does not give any type of information about atherosclerotic plaques and vessel wall (Fig. 10.6). If there is a great amount of calcium in atherosclerotic plaques, it can be barely seen in diagnostic phase of procedure, but the major evidence is the vascular tract affected by a significant stenosis. Other indirect information given by stenosis due to arterial calcification are the patency of distal runoff, major collateral vessels, presence of dissection, suitability for endovascular intervention, suitability of distal vessels for bypass graft and presence of any arteriovenous communications. In general,

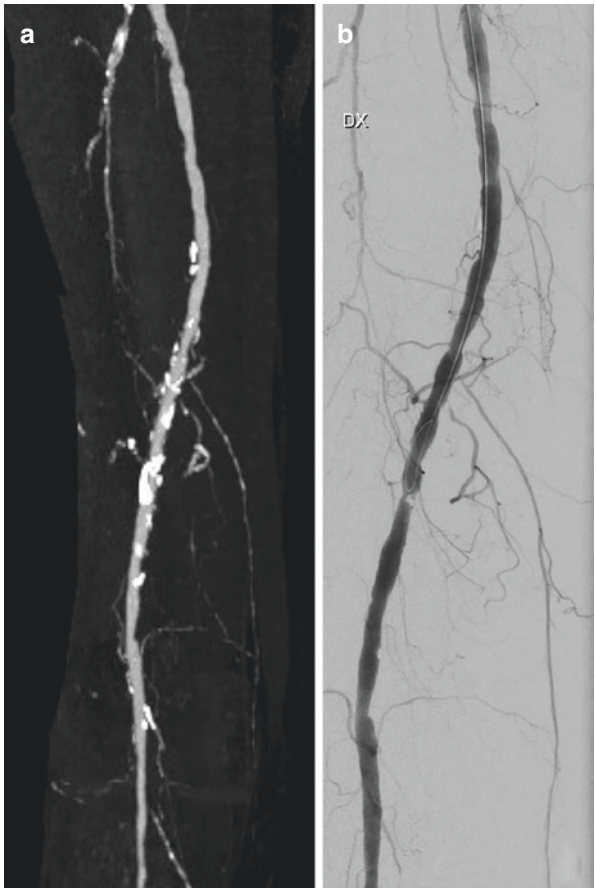

Fig. 10.6 Vascular calcifications in a 64 years-old male patient with diabetes and intermittent claudication. (**a**) Coronal thin section MIP of a CTA of the right superficial femoral artery runoff vessel demonstrating multiple dense calcifications, which obscure analysis of the lumen. (**b**) The same calcifications appear as intraluminal filling defects in CA

endovascular recanalization through CA is highly efficient in short, solitary, concentric, noncalcified, non-occlusive atherosclerotic plaques with patent distal runoff. About lower limb, the principle tract affected is the superficial femoral artery, usually well-treated with balloon angioplasty. If the results of balloon angioplasty are suboptimal or when angioplasty is complicated by flow-limiting dissection, bare metallic stents or stent grafts can be used. In case of chronic long segment occlusions, some techniques can be helpful to cross such plaques, including subintimal angioplasty or retrograde access through a distal runoff vessel. However, long segment chronic occlusions are best treated with surgical bypass grafts. The popliteal arterial district is usually treated with angioplasty without using stents because of the risk of stent fracture across the knee joint. Atherosclerotic tibio-peroneal and tibial vessels should be treated in case of limb salvage and/or non-healing ischemic ulcer. As regards the upper limb, CA is used for small vessels assessment of the hand. Atherosclerosis is a common cause of digital arterial occlusive disease but rarely symptomatic; when symptomatic, the disease is severe and is frequently associated to gangrene or fingers ulceration. CA of upper limb calcifications can evaluate luminal narrowing, irregularity of the luminal surface in the presence of ulcerated plaques, collateral flow and arterial occlusions. In case of proximal subclavian artery stenosis CA of the carotid arteries demonstrates the reversal of flow in the vertebral artery.

Limits, Contraindications and Complications

The principle limitation of CA is that the vessel wall and the atherosclerotic plaques characterization cannot be directly imaged. CA procedure has also its relative contraindications like severe allergic reactions to contrast medium, lack of vascular access and active inflammatory vascular disease. In addition, the invasiveness of CA makes this procedure not free from low but definite incidence of complications.

Another limit method-related is the use of contrast medium: its use could lead to hypersensitivity reactions [93]. To prevent vascular access site complications, patients should be followed up for 4 to 6 hours after angiography. These complications include access site haematoma, infection, pseudoaneurysm or arteriovenous malformation and arterial injury leading to thrombosis or dissection [94]. Other rare complications include intraprocedural arterial injuries (dissection, rupture, intramural haematoma, thrombosis), which can occur in diseased vessels or in oncologic patients under cancer therapy. Another common complication seen in older patients with diffuse atherosclerosis along all the vascular system is atheroembolism, as well as distal embolization of catheter or wire fragments after their accidental intraprocedural rupture. Prolonged catheterization could favor catheter thrombosis and distal embolism; the incidence of this event can be reduced with adequate, intermittent flushing of the catheter and systemic heparinization before the central-time procedure with prophylactic dosage.

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Chapter 11
Management of Peripheral Arterial Calcification

Magdy R. Moawad

Introduction

Vascular calcification (VC) is associated with a significant increase in cardiovascular morbidity and mortality. It can affect any segment of the peripheral arterial tree regardless of the size of the vessel. It is classified morphologically into intimal and medial calcification (Monckeberg's medial sclerosis) according to the arterial wall layer affected. The intimal calcification is related mainly to the underlying atherosclerotic process and influenced by all its risk factors such as hypertension, hypercholesterolemia, smoking, obesity and sedentary life. On the other hand, the medial calcification (MC) is not related to atherosclerosis and not influenced by risk factors.

Management of VC in peripheral arterial disease remains quite challenging. Since, MC commonly affects patients with diabetes mellitus and renal diseases, the mechanism of calcification, appropriate investigations and treatment options need be discussed in details. Pharmacotherapeutic drugs have a limited role in the prevention and treatment of VC, hence different surgical therapeutic options for symptomatic patients will be evaluated, including angioplasty techniques and appropriate use of vascular stenting as well as new emerging technology for occlusive arterial diseases such as atherectomy devices and lithoplasty. In addition, precautions and suspected complications related to endovascular repair of aortic aneurysm and common operative management particularly in VC will be dealt with.

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Management of Peripheral Arterial Calcification

Vascular calcification (VC) is associated with high cardiovascular morbidity and mortality. It is a predominant pathology in ageing, atherosclerosis, hypertension, diabetes, and chronic kidney disease. Atherosclerosis of the arteries was described as "degeneration of arteries into bone" by Falloppio in 1575 [1]. Although calcification and ossifications of arteries were recognised a few centuries ago, they were clinically dismissed and considered a passive process. In the late nineteenth century, numerous studies addressed the relationship between VC and osteogenesis. Lately, calcification has emerged as an active complex and highly regulated biologic process which resemble the mineralization of endochondral and membranous bone [2].

Prevalence of Vascular Calcification

Calcification occurs in arteries of all sizes including the aorta. Hirsch et al., have reported that atherosclerotic calcification in different vasculatures such as coronary, carotid, and aortoiliac vascular beds was found in 61% of asymptomatic patients presenting for preventative care [3] studies. And has also shown that more than two-thirds of patients over 70 years manifested calcification in all vascular beds. Notably, age and hypertension were the most crucial risk factors for systemic calcific atherosclerosis.

In other studies, renal artery calcification was found in 14% of asymptomatic patients and conferred a 63% increased risk for all-cause mortality. However, a significant association between renal artery calcification and cardiovascular mortality could not be established due to the small number of cardiovascular deaths [4]. Other large cohort studies showed that calcification in the carotid, coronary, iliac arteries and the thoracic and abdominal aorta is present in 31% to 55% of asymptomatic patients. Although lower limb vascular calcification is very common in patients with peripheral arterial disease and critical limb ischemia and is more dominant in patients with renal disease or diabetes, the true prevalence of VC in symptomatic peripheral arterial disease patients remains undetermined.

Clinical studies have demonstrated that calcification of the thoracic aorta, carotid arteries, and iliac arteries are predictive of total mortality whereas the presence of coronary artery calcification (CAC) in asymptomatic individuals is a predictor of future cardiac events over and above Framingham risk score.

Considerable inconsistency of arterial calcification occurs according to the anatomical location, the vessel layer affected and the extent of the calcifications present [5].

Pathophysiological Aspects of Vascular Calcification

In-depth discussion of the different mechanisms that are involved in VC is beyond the scope of this chapter. Nevertheless, to better understand the strategies to prevent and limit calcium deposition in the arterial wall as well as the basis of some potential treatments, we will summarise the most important pathophysiological pathways.

Arterial calcification occurs as a result of multiple vascular insults that vary according to the layer of the arterial wall affected in different arterial beds which is initiated by diverse biochemical and cellular mechanisms. Under certain conditions, vascular smooth muscle cells (VSMCs) can transform into osteoblast-like phenotype. The membrane-bound vesicles released from transformed VSMCs and the apoptotic bodies derived from dying VSMCs act as nucleating structures for calcium crystal formation [6]. The ratio between pro-calcific factors and inhibitors determines whether calcification occurs. Broadly, the main mechanisms that are implicated in VC process include the elevation in serum Ca++ and P levels; the induction of osteogenesis in the presence of the inadequate inhibition of the mineralization process and the migration and differentiation of macrophages and VSMCs into osteoclast-like cells [7].

The following are among the most common factors implicated in the pathogenesis of vascular calcification:

1. The disturbed balance between Calcium and Phosphorus levels such as hyperphosphatemia and hypercalcemia
2. Hormonal disorders that affect the level of the Parathormone, Vitamin D3, Insulin and ESTRADIOL
3. Medication, for instance, Warfarin, Statins, Bisphosphonates, Vitamin K, Vitamin D, Selective estrogen receptor modulators (SERM), Denosumab and Sevelamer
4. Atherosclerotic calcification, in which deposition of lipids will develop in the subintimal layer. Inflammatory cells and Cytokines such as receptor activator factor NF-κB ligand and metalloproteinases are also involved in this process.
5. Medical calcification wherein vascular bone and cartilage-like cells will develop. The metabolite-induced vascular cell changes include the Apoptosis and Apoptotic bodies.
6. Loss of endogenous calcification inhibitors which act to protect the vascular smooth muscle cells (VSMCs) from calcification [8]. These factors will be described herein as they represent a crucial defence mechanism against VC and has an appealing therapeutic effect.

Inhibitors of Vascular Calcification

Regardless of the aetiology of VC, the endpoint is invariably the formation of hydroxyapatite (HA) deposits in the arterial wall. These inhibitor factors act by either directly interfering with molecular pathways and/or sequestering hydroxyapatite components impairing their assembly and deposition [8].

Inorganic Pyrophosphate (PPi)

Reduced circulating PPi concentration is commonly present during VC, as observed in haemodialysis patients [9]. and a recent study has shown that orally administered PP_i, also inhibits arterial calcification in ttw/ttw and Abcc6 mice [10].

Gla Proteins

Matrix Gla protein (MGP) and Gla-rich protein (GRP) are an extracellular matrix protein that binds to calcium ions with high affinity. They are synthesized by a variety of cell types including VSMCs and chondrocytes, where they function locally [11]. They are members of the vitamin K-dependent (VKD) protein family. Therefore, vitamin K is essential for their activation and that explains the induction and accelerated VC in a patient receiving warfarin therapy [12]. For MGP, its dephosphorylated and uncarboxylated form (dp-ucMGP) is a surrogate marker in CKD patients [13] and is associated with an increased incidence of cardiovascular diseases [14].

Fetuin-A

Fetuin-A is a glycoprotein secreted from the liver and adipose tissue and is present at high concentrations in human blood. It is the strongest circulating proteinaceous calcification inhibitor; it binds calcium and phosphate and acts as a systemic and local inhibitor of VC by preventing extracellular and intravesicular calcium phosphate growth and reducing calcium-induced apoptosis in VSMCs [15]. Low fetuin-A levels have also been found in CKD patients and these low levels been associated with poor long-term cardiovascular outcome [16].

Klotho

Klotho is a gene associated with anti-ageing properties, it directly inhibits phosphate uptake by VSMCs, and enhance phosphaturia. It seems that the kidney is the main producer and effector of Klotho in VC. Klotho deficiency predisposes VSMCs to transform into osteoblast-like cells and initiate mineralisation in response to phosphate uptake. Klotho can also prevent medial calcification through alternative mechanisms other than reducing phosphate. In CKD, serum Klotho levels decrease alongside disease progression. Hence, serum and urinary Klotho could serve as predictors of CKD progression but not mortality. Studies confirmed that decreased levels of circulating serum Klotho have been associated with increased arterial stiffness [17].

Osteoprotegerin (OPG)

OPG is a phosphoprotein endogenously expressed by contractile VSMCs. It is synthesized in osteoblasts, immune cells and in the media of most blood vessel cell and VSMCs, suggesting that OPG plays a role in the function of the vascular bed [18]. It is as also synthesized in many tissues including the cardiovascular system, kidneys, liver, spleen, brain, lungs, and bone marrow. It acts as a neutralizing decoy receptor for RANKL and TRAIL and it has a major function in regulating osteoclast differentiation via this pathway [19] thereby inhibiting bone resorption and inhibit VC.

Osteopontin (OPN)

OPN was first described by Young et al. (1990), as an important anti-apoptotic factor in smooth muscle endothelial cells. It inhibits VC provided it is phosphorylated. OPN expression in atherosclerotic plaques correlates with the severity of atherosclerosis and calcification [20].

Classifications of Vascular Calcification

Vascular calcification is classified as dystrophic or metastatic [21] It can be also morphologically classified into two distinct forms intimal or medial (or Monckeberg's medial sclerosis) calcification depending on the location of the arterial wall layer affected [22].

Vascular calcification has also been classified into three distinct types by Demer and Tintut [23]: firstly, inflammatory which is commonly in association with atherosclerosis and affecting the intimal layer leading to intimal calcification; secondly, metabolic disorders as in diabetes mellitus and chronic kidney disease and affecting the medial layer resulting in medial calcification and thirdly, calcification associated with genetic disorders such as pseudoxanthoma elasticum and generalized arterial calcification of infancy [24] which mostly affects the medial layer.

Intimal Calcification

Intimal calcification is a systemic process affecting the arterial intimal layer. It is related principally to atherosclerosis; therefore, it is predisposed by all recognised cardiovascular disease risk factors including: hypertension, smoking, high blood cholesterol, diabetes, sedentary life, emotional stress, and obesity. Intimal atherosclerotic calcification often occurs as a result of various healing responses to resolving tissue inflammation. It is characterised by extensive cellular necrosis, abundant fibrosis, apoptotic body formation, and cholesterol crystal accumulation that can support calcium phosphate formation [25, 26]. This results in atheromatous lipid-rich flow-limiting plaques and produce patchy discontinuous appearance of relatively large calcific deposits.

Whilst intimal calcification is quite common in older individuals with advanced peripheral vascular disease, there are no consistent findings and there is considerable variations. There is no relationship between the extent of calcification and the plaque complexity or size.

Atherosclerotic lesions can occur in any arterial bed however, certain vascular bed segments are more susceptible to plaque formation whilst others are spared. It preferentially affects the medium-sized arteries at bifurcations and curvatures where blood flow is turbulent and hemodynamic forces are disturbed [27]. Clinical data suggest a direct association between increased wall motion, shear stress, and plaque deposition [28] Table 11.1. Consequently, there are more susceptible regions of the vascular tree for plaque formation than others, for instance, lesions occurring at

Table 11.1 List of the most common factors affecting the haemodynamics of the plaque Localization

• Shear stress
• Hypertension
• Flow separation and stasis
• Oscillation of shear stress vectors
• Turbulence
• Increased lateral wall pressure
• Cyclic strain stress created by blood pressure

branches of arterial bifurcations such as branches of the aortic arch and the origins of the vertebral artery from the subclavian artery. It is now indisputable that atherosclerotic plaques are confined preferentially in areas of low shear stress and not in places of high shear stress. Carotid artery bifurcation is a good example as it is particularly susceptible to plaque formation mainly at the origin of the internal carotid artery. Coronary arteries, carotid bifurcation, infrarenal abdominal aorta, and iliofemoral arteries are particularly susceptible to plaque formation. However, the thoracic aorta, the common carotid artery, distal internal carotid, renal, mesenteric, and upper extremity arteries are particularly resistant. Interestingly, atherosclerotic arterial calcification may reduce arterial wall motion and cycling stretching and diminish subsequent plaque formation [29].

Medial Calcification

Medial artery calcification was originally described by the German pathologist Georg Monckberg in 1903 [30] and was considered to be of no clinical importance at that time. The most common variant of medial vessel calcification is Monckeberg's medial sclerosis. It chiefly affects the tunica media of the arterial wall which includes the smooth muscle cells and the elastic membrane, resulting in the loss of vessel elasticity [22]. Contrary to intimal calcification Medial sclerosis occurs in the absence of any compelling immune cell infiltration or lipid deposition where cytokine signalling is involved [31].

Medial calcification is common in medium and small muscular peripheral arteries of the lower limbs. However, it is occasionally found in different sites of the arterial tree regardless of the size of the vessel. It can be found in large vessels such as the aorta and the iliac vessels; medium-sized vessels like the renal and uterine arteries, and smaller vessels such as the mesenteric vessels. It can also affect the vessels rarely affected by atherosclerosis such as radial artery and epigastric vessels. On the other hand, it is rarely found in carotid arteries or coronary vessels. Medial calcification is a remarkable characteristic finding in chronic kidney disease and type 2 diabetes [32]. Medial vascular calcification does not spontaneously regress and it is not influenced by factors reducing the atherosclerotic process.

Although there are many attempts to produce a validated peripheral arterial calcium scoring system to classify the severity of vessel classification, this has not been well established. A peripheral arterial calcification scoring system (PACSS) was developed to facilitate and standardize management of this condition. This scoring system depends on an assessment by fluoroscopy and digital subtraction angiography. It classifies the severity of vessel calcification into 5 grades according to length and laterality of the target lesion. The intimal and medial layers of the vessel wall calcification at the site of the lesion is assessed by high-intensity fluoroscopy and digital subtraction angiography (DSA) in the anteroposterior projection (Fig. 11.1) [33].

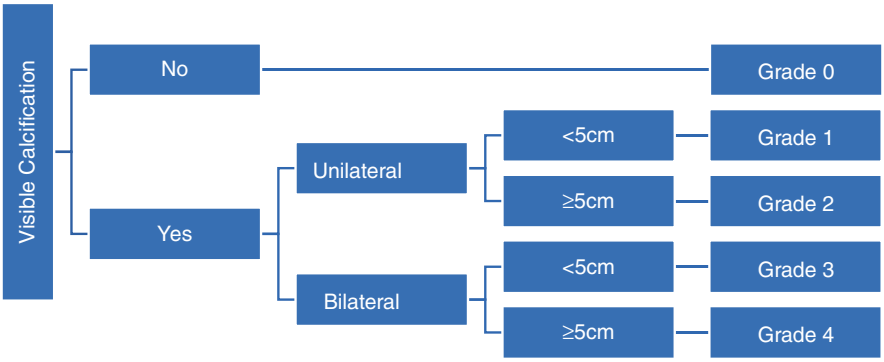

Fig. 11.1 Schematic diagram of the Peripheral Arterial Calcium Scoring System (PACSS). The subclassifications of each grade includes: (**a**) intimal calcification; (**b**) medical calcification; (**c**) mixed type

Imaging in Vascular Calcification

Despite recent advances imaging technology, there is no particular test of VC accurate enough to satisfy all diagnostic criteria required as marker for disease, since each method has its limitations and some have potential risks. Consequently, multiple complementary imaging modalities are used to evaluate the calcific vascular burden and its clinical effects on the vascular tree. Different non-invasive and invasive imaging modalities are available for vascular assessment with variable qualitative and quantitative capabilities.

Non-invasive methods are Duplex ultrasonography, plain radiographs, computed tomographic (CT) and magnetic resonance imaging (MRI). These are the most commonly used methods for diagnosis, surveillance programmes and follow-up following treatment.

Plain radiography is widely available and can detect macrocalcifications [34]. They are inexpensive and provide valid prognostic information, and, hence, is worth using as a screening tool for the presence of VC. However, it is less sensitive and lack quantitative accuracy compared with CT and MRI.

Duplex Ultrasound combines the use of B-mode imaging, Pulse Wave, Continuous Wave Doppler modes when assessing the hemodynamic function of the vascular system [35]. It has some ability in the differential of intimal and medial vascular calcification due to distinct patterns of advanced lesions. It is the most important and widely used non-invasive tool for investigating peripheral vascular disease. Yet, it is operator dependent and has its limitation in patients with ulceration, pain, swelling, heavily calcified arteries and obesity [36].

CT is currently considered the gold standard for the identification and quantitation of the cardiovascular calcification [5]. The arterial calcification scores generated by CT are a composite of both medial and intimal calcification, but still comparable to angiographic findings Fig. 11.2. The addition of 3D reconstruction

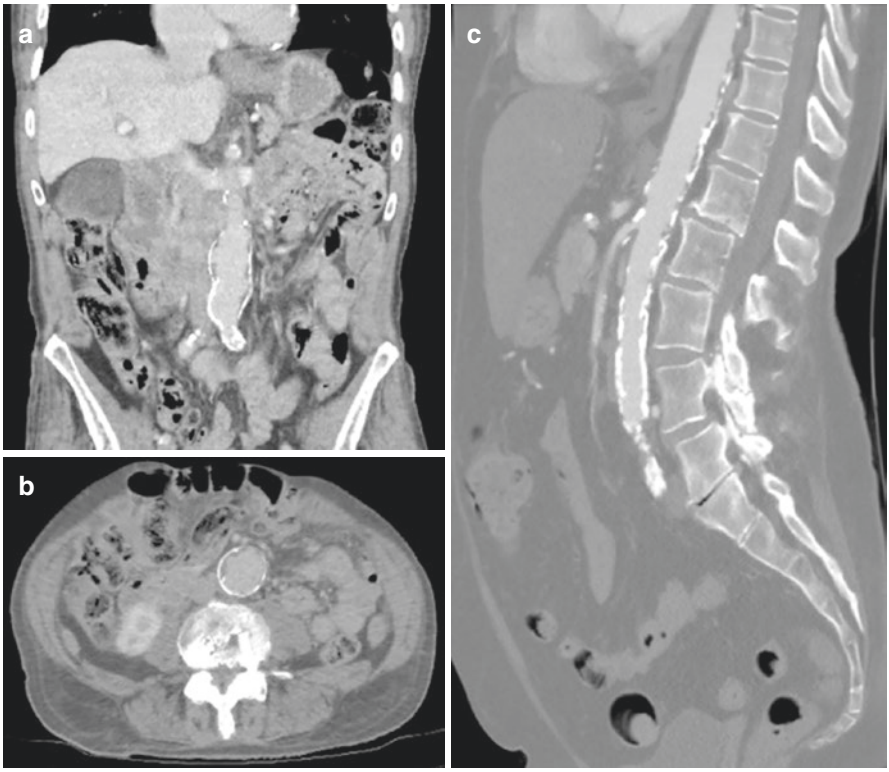

Fig. 11.2 (**a**) Coronal reformat shows the calcification over a long segment of the aorta. (**b**) Axial CT scan shows circumferential calcification of the abdominal aorta. (**c**) sagittal reformat demonstrating the calcifications of the abdominal aorta and the origin of the superior mesenteric artery

and the evolution of postprocessing computer modelling software allows more accurate depiction of the 3D vascular anatomy and relationships of intra-abdominal structures [37]. However, CT carries the draw back of high ionizing radiation and also has possible risks of an allergic reaction and contrast-induced nephrotoxicity with the use of high dose iodinated contrast agents in patients with chronic kidney disease and concomitant Diabetes. MRI offers a high quantitative assessment and superior soft-tissue resolution [38] but is susceptible to artefacts and also has risks of gadolinium-based contrast-induced nephrotoxicity.

Invasive investigations include angiography, intravascular ultrasound (IVUS) and recently optical coherence tomography. These techniques are typically reserved for instances where highly detailed measurements are required, for example, before surgical planning and during intervention procedures. Angiography remains the gold standard investigation for peripheral vascular disease. It can accurately detect any occlusion or stenotic lesion in the arterial tree and assist decision making for its amenability to interventional treatment. Intravascular ultrasound (IVUS) is usually used as adjuvant to other procedures, such as contrast angiography and balloon

angioplasty. It can be useful during balloon angioplasty and stent deployment when contrast agents are contraindicated. IVUS can play be an important role in the assessment of proximal and distal fixation points and the deployment of endovascular aortic stent (EVAR) for the treatment of abdominal aortic aneurysm (AAA) [39]. It is also a valuable tool in pre-diagnostic evaluation when contrast-enhanced computed tomography (CT) scans are inconclusive. Optical coherence tomography (OCT) is recently finding its way through the clinical arena in the management of peripheral diseases. It combines the principles of ultrasound with the imaging performance of a microscope [40] and has a high spatial resolution of 10–15 μm resolution, compared with a resolution of 100 to 150 μm for the IVUS [41]. OCT can differentiate between intimal and medial lesions and has potential use in the identification of carotid stenosis and distinction between stable and unstable atherosclerotic plaques.

Vascular Calcification and Diabetes

The prevalence of diabetes mellitus in the UK according to the Quality and Outcomes Framework for General Practitioners (QOF) is 3.55% [42]. The overall figure of peripheral arterial disease in patients with diabetes over 40 years of age has been estimated to be 20% [43]. This percentage increases to 29% in patients over the age of 50 [44, 45].

The entire vascular system is affected by diabetes and it is perhaps not astonishing that the Multi-Ethnic Study of Atherosclerosis (MESA) [46] has shown that T2DM is associated with other subclinical vascular diseases. The prevalence of thoracic aortic calcification is much higher in diabetics (38%) compared with non-diabetics and is not known to have metabolic syndrome (24%) [47]. Diabetes was also found to correlate with reduced aortic distensibility, especially in patients younger than age 65 [48].

The lower limb arterial disease in diabetic patients is more localized to the distal vessels being more prominent in the infrapopliteal vessels. Calcification and long occluded segments of the crural vessels are more predominant and occur more often rather than stenosis [49, 50]. A debate exists regarding potential involvement of the arteries below the ankle in the occlusive disease in diabetes [51].

Diabetes mellitus is a known cardiovascular disease (CVD) risk factor and was initially recognised by the Framingham Heart Study in 1979 [52]. It is the second most important risk factor for ischemic stroke after hypertension [22, 53]. A meta-analysis of 102 prospective studies with 698,000 individual (including data from MESA [Multi-Ethnic Study of Atherosclerosis]) demonstrates that diabetes confers an approximately two-fold increase in the risk of ischemic stroke, coronary heart disease, coronary death, and other vascular deaths [54].

Mechanism of Vascular calcifications in Diabetic Patients

Calcification is a perceived complication of atherosclerotic lesions in diabetic patients which correspond with expanded plaque burden. Diabetes plays an important role in the progression of the vessel calcification through numerous mechanisms including alterations in mineral metabolism, increased inflammatory cytokine production and release of osteoprogenitor cells from the marrow into the circulation [22].

The evolution of diabetes-related atherosclerosis follows the unvaried pathological row as atherosclerosis in nondiabetic patients [55]. The atherosclerotic disease develops 10 years earlier compared to non-diabetic patients. It also progresses faster with a high incidence of arterial occlusions. Atherosclerosis in diabetes is characterized by excessive intimal calcification related to the increased proinflammatory cytokines produced by the activated macrophages. it is also associated with the presence of macrophages, lipids, and proliferation of vascular smooth muscle cells [51].

The medial arterial calcification (MAC) prevents compensatory remodelling in response to atherosclerotic lesions which eventually speed up the disease progression [56] and has been hypothesized to be the cause of the clinical manifestations of diabetic angiopathy [57]. Moreover, the risk of thromboembolic complications increases due to the second invasion of the intimal layer [51]. Osteogenic differentiation with bone deposition commonly occurs in medial calcification contrary to its rarity in intimal calcification [58].

Although no absolute evidence exists, it seems likely that the MAC in diabetic PAD is due to diabetes rather than the arterial disease itself [59]. The main three factors implicated in the diabetic lower limb disease are neuropathy, ischaemia, and infection. The MAC has been associated with trophic foot ulceration and peripheral arterial disease PAD [59, 60].

Meema et al., have implied that there might be two unique sorts of medial calcifications. The first is a c kind, of slow onset, with thin medial calcification that is not compromising the lumen size, hence doesn't result in ischemia. The other kind is an aggressive form, where extensive medial calcification may disrupt the internal elastica toward the lumen, resulting in narrowing of the lumen [61].

It is evident that MAC is strongly associated with diabetes and is unrelated to the atherosclerotic changes [51]. Medial calcification in diabetes is a specific complication strongly associated with neuropathy rather than the duration of diabetes [62]. Ferrier and Ferner [63] described medial calcification as a characteristic finding in long-term diabetes. MESA has yield evidence that the relationship between subclinical atherosclerosis and glucose metabolism may initiate before the commencement of clinical diabetes (in Prediabetics) [52]. Importantly, lowering the HbA1c through the extensive glycaemic control did not alter or reduce the rate of peripheral arterial occlusion in the DCCT/EDIC study. However, it did reduce the incidence of peripheral arterial calcification [64].

Diabetic Foot and Arterial Calcification

Diabetic patients develop Peripheral arterial disease at a younger age compared to nondiabetics, irrespective of gender [51].

The main three factors implicated in the diabetic lower limb disease are neuropathy, ischemia, and infection. MAC has been associated with trophic foot ulceration and peripheral arterial disease [60]. However, there is an argument as to whether the ischemic foot changes in diabetic patients are related mainly to the atherosclerosis process with its specific characteristic changes or also by Diabetic macroangiopathy, a term for a nonatherosclerotic arterial disease which was first used by Lundbaeck [65]. The fundamental component of diabetic macroangiopathy is the MAC of the muscular arteries. The implication of microvascular disease to the diabetic foot remains debatable [51].

The concept of big artery disease and small artery disease was proposed by Ferrarasi et al. [66]. He implied that the arterial disease of lower limbs in diabetic patients is related to two types of failures; transmission failure and distribution failure. He also suggested the concept of big artery disease and small artery disease where the big artery disease involves all the arterial tree of the lower limb from iliac artery to the dorsalis pedis and plantar arteries and is predominantly liable to 'transmission failure' whilst the small artery disease affects the plantar arch and the small arteries arising from it including calcaneal branches tarsal metatarsal and digital branches. These vessels are responsible for the blood flow to the foot and are predominantly causative of the "distribution failure". In a meta-analysis of 15 studies, patients with diabetes were significantly more likely to have crural vessel disease and were significantly less likely to have aortoiliac arteries disease [67]. In general, there is no significant difference in Peripheral arterial disease presentation between type I and Type 2 diabetes mellitus.

MAC has appeared as a critical predictor of lower extremity amputation and mortality in patients with type II diabetes [32]. Likewise, Everhart reported that diabetic patients with medial calcification had a 1.5-fold mortality rate and a 5.5-fold rate of amputation. The relationship was noted disregarding glycaemic control and identified the duration of diabetes [68].

Vascular Assessment in Diabetic Foot Disease

The loss of arterial elasticity in peripheral lower limbs medium-sized vessels in diabetic patients renders them incompressible. For that reason, measuring the ankle brachial pressure ratio in diabetic patients is an unreliable indicator to exclude occlusive peripheral vascular disease. Alternatively, toe pressure measuring is a more reliable indicator compared to ankle Brachial pressure in diabetic patients as in most cases the toe vessels are spared from calcification.

MAC is easily detected on routine X-rays and has a distinguishable appearance which facilitates its differentiation from intimal calcification. It is characterized by

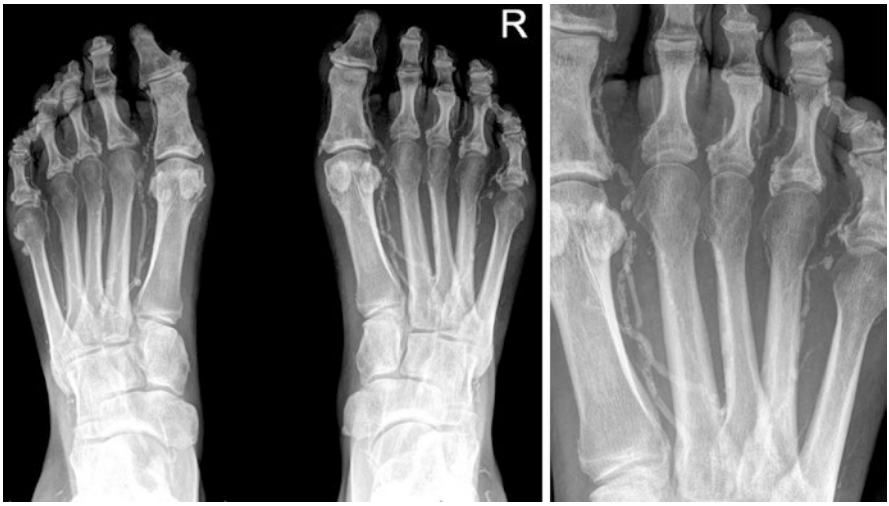

Fig. 11.3 AP view of metatarsal arteries. Plain X-Ray of the feet of a patient with diabetes mellitus on haemodialysis demonstrating typical appearance of medial arteries calcification in the first and fifth dorsal metatarsal arteries

the continuous lengthy calcification for more than one cm that gives the appearance of the pipe stem. More specifically if the 'ring sign' is present which demonstrates the circumferential calcification of MAC [59] Fig. 11.3.

CTA and MRA are of important value in planning for revascularisation treatment and to exclude osteomyelitis which often present in patients with longstanding of diabetic foot ulcers.

Vascular Calcification and Renal Disease

CVD is the principal cause of death in patients with kidney disease. More than 30 million adults are affected by chronic kidney disease (CKD) in the United States [69].

The increase in prevalence and severity of VC has longest been acknowledged as another important factor involved in the development of CVD in patients with CKD. Once VC has developed, it is most likely to progress resulting in worsening hypertension, myocardial infarction, and congestive heart failure [6] This increased risk cannot be entirely related to the recognized cardiovascular risk factors. It is evident that influencing these risks with controlling hypertension, statins, aspirin, and other proven interventions in patients without CKD may have less effect on reducing cardiovascular events in patients with CKD [70, 71]. The reason could be the excess risk conferred by non-traditional factors in the setting of derangements of metabolism present in CKD. One such risk factor proposed and investigated is the net positive calcium and phosphate balance thought to result in hydroxyapatite formation and accelerated VC [72].

Vascular calcification and coronary artery calcification (CAC) are very prevalent and progressive even in young adults with dialysis-dependent end-stage kidney disease (ESKD), in whom cardiovascular risk factors are not yet developed [72].

Notably, some medications such as calcium-containing phosphate binders, which increase oral calcium intake, may speed the process of VC. However, there is less progression of VC in patients with ESKD treated with non–calcium-containing phosphate binders such as lanthanum and sevelamer compared with calcium-containing binders [73].

On the other hand, some medications used in the treatment of secondary hyperparathyroidism in CKD such as calcimimetic agent and cinacalcet have proved to reduce VC progression in end-stage renal disease as they do not increase serum calcium levels [74].

Although VC is associated with increased cardiovascular mortality, data on whether its presence adds incremental predictive value to that incurred by traditional cardiovascular risk factors or whether interventions that reduce CAC result in cardiovascular event reduction are not conclusive in patients with ESKD. Because targeting VC has yet to be shown to improve cardiovascular outcomes in patients with ESKD, is calcification merely a disease marker, not an actionable target, in this patient population? [75, 76].

Management and Treatment of Vascular Calcifications

Overview of Nonoperative Management

Prevention of development and progression of atherosclerosis and calcification remains quite challenging. Recent studies have shown evidence that lifestyle changes such as stopping smoking, increasing exercise, healthy diet may reduce the overall risk of coronary artery disease and complications however it is not related mainly to the modification of the calcification process.

Medical Therapy

Despite the existing extensive research, the ideal treatment of VC remains undetermined and there is no definite effective medication exist to reduce the VC process. At present, there are just a few effective pharmacotherapeutic options to slow VC [77, 78].

Recent research studies have shown that nutritional supplements may have some beneficial effect in VC. Vitamin K has been identified as a likely factor in reducing the calcification process as it acts as an inhibitor of VC. Other dietary supplements such as vitamin B, C, D, E may also modulate this process through their ability to

activate MGP, which is a potent inhibitor of ectopic calcification [79]. Research also has shown a potential relationship between homocysteine and VC incidence and progression, a finding that may have a potential role for both coronary and extra-coronary calcification [80].

The main goal in reducing and preventing intimal vascular calcification process which eventually protects from any cardiovascular events is controlling the traditional atherosclerosis risk factors such as smoking cessation, blood pressure control, hypercholesterolemia, diabetes, obesity, and physical inactivity. On the other hand, controlling the medial artery calcification in diabetes, CKD, and metabolic syndrome disorders is quite challenging. It is mainly focused on the management of bone and mineral metabolism disorders [81]. Therefore, therapeutic benefits and risks should be considered carefully to avoid any unwanted effects on bone.

Pharmaceutical Treatment

Although many CV drug therapies such as calcium channel blockers and inhibitors of the renin–angiotensin–aldosterone system have shown promising effects on controlling VC in experimental animal studies, their effect in humans' studies is less promising and remain uncertain [82]. Calcium Chanel Blockers do not prevent existing plaques progression however it may reduce the development of new lesions through their ability to improve hemodynamics rather than a direct effect on calcification itself. Similarly, the effect of inhibitors of the renin–angiotensin system concerning CV complications are mainly related to the vasodilation effects and properties and not directly on calcification.

In reality, conventional treatment of hyperlipidaemia with statins irrespective of dosage, reduce the LDL Cholesterol levels and result in significant reduction of the arterial atheroma volume and increased plaque stability through promoting the plaque calcification [83].

Therapeutic strategies in the management of VC with bone and mineral metabolism disorders as in secondary hyperparathyroidism which is commonly associated with progressive renal failure and CVD are aimed to minimize hypocalcemia and hyperphosphatemia without producing hypercalcemia and suppressing parathyroid hormone activity. This can be managed by using active vitamin D analogues, oral phosphate binders, and Ca. mimetics [77].

Vitamin D Analogues and Calcium Mimetics

Although there is no clinical study that has yet examined the outcome of vitamin D therapy on VC, studies in mice with CKD receiving vitamin D receptor agonists have shown a significant reduction in aortic calcification [84]. Patients with CKD taking vitamin D supplements have shown improved survival and a significant

reduction in the incidence of cardiovascular events. In patients with end-stage renal disease associated with secondary hyperparathyroidism SHPT, treatment with cinacalcet (SensiparTM), a synthetic G-protein coupled receptor that controls calcium homeostasis by regulating the release of PTH results in fewer cardiovascular events compared with placebo [85]. Cinacalcet, in combination with low-dose vitamin D, also minimizes the risk of coronary and aortic calcification in hemodialysis patients [86].

Phosphate Binders

Calcium-based Phosphate binders are used in the treatment of hyperphosphatemia. They have shown significant interactions with bone metabolism and more increase in calcium burden in patients with extensive VC and hypercalcemia. Calcium free phosphate binders such as Sevelamer and Renvela produce a significant decrease in serum calcium levels without alteration of the phosphate levels. It has been suggested that this decrease in calcium levels is the main mechanism of reducing the rate of calcification. Other benefitable effects include decreasing the level of the low-density lipoprotein while increasing the high-density lipoprotein.

Surgical Therapy

Considering the limited options of the pharmacotherapeutic drugs in the prevention and treatment of VC, endovascular procedures and surgical options are considered in the management of symptomatic patients. Recently, new promising techniques and devices have emerged in the management of VC causing complex PAD and management of chronic ischemia and limb salvage. The choice between endovascular, open or hybrid intervention for revascularisation in symptomatic patients depends on multiple factors such as clinical severity, patient age and fitness, anatomic distribution and the extent of the disease [87].

Endovascular Management

Endovascular therapy is currently considered as the first line of treatment in PAD and limb revascularization [33]. More than 50% of disabling intermittent claudication and critical limb ischemia can be treated with endovascular interventions [88, 89] However, technical failure and restenosis are largely related to the calcification of the vessels which impact the short and long outcomes following this treatment [90–92]. We hereby summarise the available endovascular options and techniques in management of the calcified PAD.

Percutaneous Transluminal Angioplasty (PTA)

Percutaneous transluminal angioplasty (PTA) is considered the most common primary interventional therapeutic approach. The mechanism of balloon dilation for stenotic lesions involve adventitial stretching and plaque fracture leading to separation of the arterial media from the intima.

The instant resulting improvement in the luminal patency following PTA occurs as a result of some degree of dissection in most cases. This dissection is described as a tear in the inner wall of the artery which separates the lesion from the remaining arterial wall [93]. This tear can be limited to the intima or may include the medial and adventitial layers of the vessel. Notably, the severity of the dissection tends to be unreported clearly hence, the reported rate of dissection following PTA is varies significantly from 7.4% to 84% [94, 95].

The outcome of the PTA is affected by the type of lesion as severely stenotic lesions are likely to result in elastic recoil and restenosis. Contrarily, treatment of severely calcified lesions is likely to result in vessel dissection which may be flow-limiting, they are unlikely to develop late recoil or restenosis if a stent is used in addition to the angioplasty [83].

As the extent and degree of angiographic dissection following balloon dilatation influence the clinical outcome and the restenosis rate, the National Heart, Lung, and Blood Institute (NHLBI) angiographic dissection grading scale was created to categorize dissections in coronary arteries [96, 97]. Kobayashi et al. [98] proposed a simplified angiographic dissection grading system for the peripheral arteries (Table 11.2) and concluded that group C (sever dissection) present significant lower patency at 3 years (32.5%). They also concluded that the length of the lesion has implication on the outcome as severe dissection with long lesions had primary patency of 24.2%.

Prolonged balloon inflation should be considered in the treatment of non-flow limiting dissection, however, spot stenting or Tack [99] placement should be implemented in flow-limiting dissection or to provide mechanical support in critical locations.

The innovation of the drug-coated balloons (DBCs) has proven successful in significantly reducing the restenosis rate following balloon angioplasty. The prolonged inflation of the DBCs allows delivery of an antiproliferative drug impregnated on the matrix of the balloon surface which intends to inhibit the restenosis

Table 11.2 Simplified classification of post angioplasty angiographic dissection

Category	Width of Dissection
Group A,	No angiographic dissection
Group B,	Less than one-third of the lumen
Group C,	More than one-third of the lumen or spiral dissection

process by inhibiting intimal hyperplesia [100].However, the dense calcification of the lesions in the vessels may compromise the drug absorption process from the DBCs.

Different balloon behaviour and characteristics have been developed in attempting to minimise the risk of the dissection during the angioplasty. This included compliant and non-compliant balloons. Whilst compliant balloons are not advisable in treating severely calcified lesions, they are mostly used in lesions placed in curved parts of the vessel. On the other hand, non-compliant known as high-pressure balloons are preferred by most interventionists and are very useful in treating severely calcified lesions [101].

Evolution of technology has resulted in a variety of specific balloon characteristics such as cutting balloon which was introduced by Barath et al. [102] for percutaneous coronary intervention. The use of the cutting balloon has overcome the limitation of the conventional angioplasty in the treatment of severely calcified short lesions such as ostial infrapopliteal bifurcation lesions [103].

Vascular Stenting

The use of stents for peripheral arterial vascular lesions have complemented balloon angioplasty in selected cases. Clinical data has shown that using stents for short lesions <5 cm has no additional benefit compared to balloon angioplasty only. However, for intermediate and long lesions >6.4 cm, primary stenting is recommended [104]. Using stents allowes interventionalists to achieve very good results in providing inline flow through significant stenosis and occlusions in both critical and chronic limb ischemia. Stents are considered following balloon dilatation if there is more than 30% residual stenosis of the lesion on the post dilatation angiogram or if there is a systolic pressure gradient that exceeds 10 mmHg across the lesion. However, repeated PTA with a longer inflation time should be considered first. Stents may also be used to reduce the incidence of restenosis. Stents are necessary when moderate or severe dissection occurs, a false channel is made or if the acute occlusion is encountered during the angioplasty.

Generally, Stents are classified as bare metal or covered stents (Fig. 11.4), balloon expanding or self-expanding stents, and also Drug-eluting stents. Stents are varied in their characteristics such as flexibility, bending resistance and radial force. The choice of an appropriate stent is fundamental in impacting clinical outcome and the patency of the stent. The self-expanding stents are more flexible and easily trackable however they are not recommended in severely calcific lesions as they may not expand fully. Balloon-expanding stents are usually rigid to avoid elastic recoil of the lesion. They should not be used if there is any chance of external compression on the vessel as this will cause permanent stent deformition.

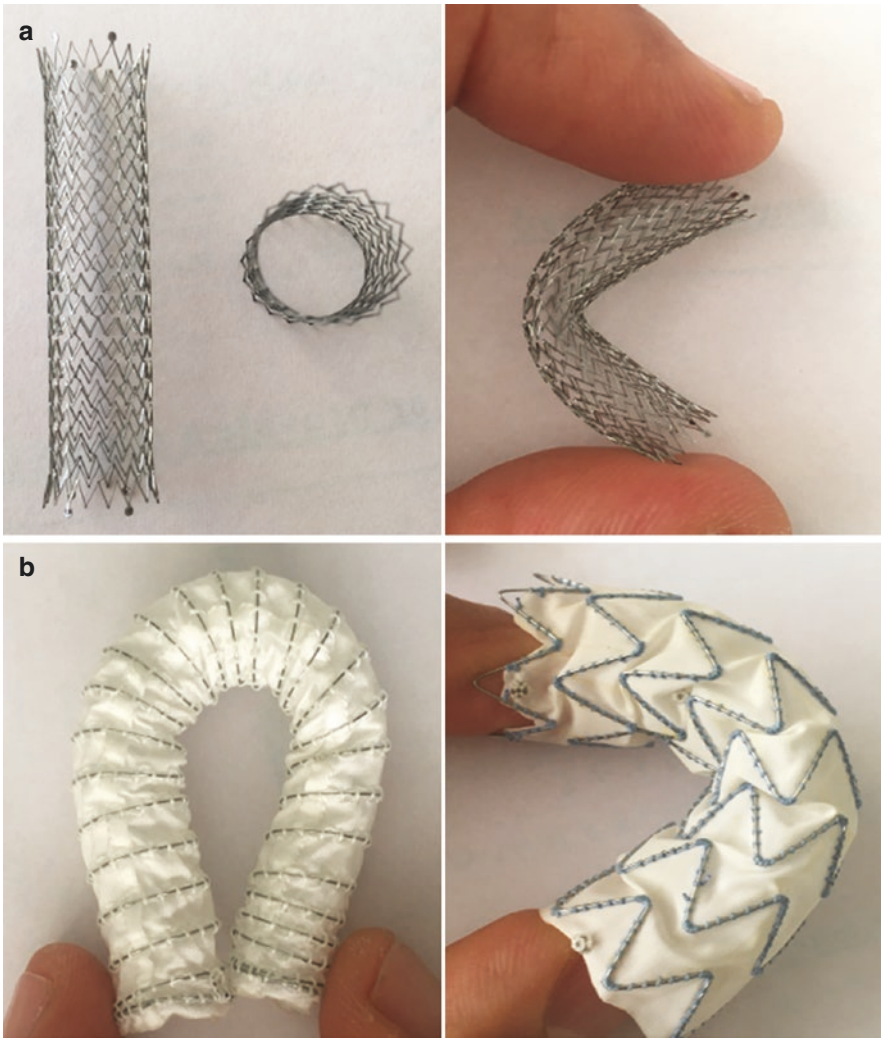

Fig. 11.4 Images demosnstrating the different types of stents (**a**) Bare Metal, (**b**) Covered stents. Note the flexibility of the stents

Subintimal Angioplasty

Endovascular management of chronic total occlusions (CTO) remains quite challenging and involve approximately 40% of peripheral arterial interventions. Calcified lesions are known to increase the difficulty of intraluminal crossing, hence, subintimal wire passage often occurs [105]. Subintimal angioplasty has

become an established approach for treating CTO as it is effective and a safe procedure. It was first described by Bolia in 1989 [106]. The concept of this technique involves intentional dissection and creating a new track between intima and media or adventitia layers to bypass the occluded segment of the artery, then re-entering the true lumen of the patent distal artery. Failure to re-enter the true lumen occurs in about 13–24% of the cases which eventually fail the procedure [107, 108]. The innovation of the re-entry devices such as The Outback LTD (Cordis Corporation, Fremont, California) and The Off-Road re-entry system (Boston Scientific, Natick, and Massachusetts), and Intra-Vascular Ultrasound (IVUS) guided Pioneer® (Philips, Minneapolis, Minnesota) have overcome this problem in most cases [109, 110].

To integrate the current evidence and assess the effectiveness and safety of subintimal angioplasty (SIA) with or without the use of re-entry devices (RED) for endovascular treatment of complete occlusion of the femora-popliteal segments, Kokkinidis et al. [111], have conducted a systemic review of 87 studies included 5161 lesions in 4665 patients where 46.7% of them had critical limb ischemia at the time of the intervention. SIA without RED is more commonly used (78.2%) compared to SIA with RED (21.8%). The total successful procedures were 80.9% (92.5% for using SIA without RED vs 88.3% for the RED subgroup). The overall complication rate was 9.1%. Perforations occurred in 1.6% and Embolization occurred in 2.9%.

Re-entry using the SIA alone could not be performed in about 25% [112], this rate can be significantly lowered by using the RED [113]. This systematic review demonstrates that SIA with or without RED is safe for short- and long-term clinical outcomes. However, current literature is indefinite regarding the safety and effectiveness of using RED in the management of the calcified lesions [114].

Atherectomy for Peripheral Arterial Disease

Stents have improved the outcome of revascularisation in most stenotic lesions and facilitated the management of occlusive lesions in peripheral vascular disease. However, they have their limitations and adverse long-term outcomes such as in-stent stenosis and stent fracture. Despite the current advancement in the balloon designs such as high-pressure balloon and different stent types, the management of heavily calcified lesions remains challenging.

The purpose of using atherectomy techniques is to debulk the heavily calcified plaque either by excision or ablation which will increase the luminal diameter and will prepare the complex lesions for the stent delivery and deployment. These techniques are used in conjunction with other endovascular modalities. Despite the cost of these devices, lack of outcome comparative data and randomised controlled trials comparing it with stand-alone stent therapy, limited the use of these techniques to mainly treatment of complex femora-popliteal disease [115].

Data analysis from the multicentre Excellence in Peripheral Artery Disease (XLPAD) registry (NCT01904851) demonstrated that in a cohort of 518 Below the Knee interventions with a 43% rate of atherectomy, there was a significant reduction in the 1-year clinically driven repeat endovascular and surgical limb revascularization rate with atherectomy [116]. Currently, there are four types of atherectomy devices; directional, rotational, orbital, and laser atherectomy.

Directional Atherectomy

This device shaves the atheromatous plaque in a longitudinal plane. The carbide cutting blade rotates at speed up to 8000 rpm. There are two known plaque excision system; the SilverHawk and TurboHawk. The latter is devised for treating severe calcification.

DEFINITIVE Ca (++) study [117] showed that the treatment of moderate to severely calcified lesions in femora- popliteal arterial segments were safe and effective when using these devices with the distal embolic device. The DEFINITIVE AR randomised controlled study compared the directional atherectomy device with the drug-coated balloon versus stand-alone drug-coated balloons but did not show a significant difference between the two methods of revascularization in the 1-year follow-up [118].

Rotational Atherectomy

This technique involves inserting a small drill into the artery. Once the device activated, it grinds the calcified plaque into very small particulates and create a smooth lumen in the vessel. These particulates can be aspirated by the device or removed by the body as 95% of them are smaller than red blood cells [119].

Orbital Atherectomy

The Orbital devices utilize centrifugal force and a standard 1.25 mm eccentrically mounted diamond-coated crown [120], allowing for 360° contact of the vessel wall. The treatment of variable arterial sizes can be achieved with one device size [121]. The main difference between rotational atherectomy and orbital atherectomy is that with increasing the rotational speed of the orbital device, the debulking area also increases. In a meta-analysis comparing Orbital versus rotational atherectomies in patients with calcified coronary artery disease, there was no significant difference between the two techniques except a significant reduction in fluoroscopy times with the orbital technique [121].

Laser Atherectomy

The newer devices as the XeCL excimer laser that emits in pulsatile fashion in the ultraviolet B region with shorter wavelengths (300 nm) and thus achieves higher efficacy with far less absorption depth (about 0.05 mm) and less damage to the deeper-lying tissues.

Dippel et al., demonstrated in a large prospective randomized EXCITE ISR study (Randomized Study of Laser and Balloon Angioplasty Versus Balloon Angioplasty to Treat Peripheral In-stent Restenosis) that using excimer laser atherectomy with adjunctive percutaneous transluminal angioplasty (PTA) has much better outcome compared to the PTA alone for treating peripheral in-stent stenosis [122].

Lithoplasty in Vascular Calcifications

Lithoplasty is a new emerging technology intended mainly to treat patients with calcific artery stenosis. The lithoplasty uses a localized circumferential high-speed sonic pressure waves applied through a low pressure inflated balloon catheter. The resulting shearing forces selectively target the highly-dense calcium deposits [123]. Subsequently, the deposits fracture, increasing vessel compliance. In recent systemic review, the short-term outcome of this technology appeared promising and successfully improved the vessel patency, with minimal wall injury and infrequent need for target lesion revascularization in the short term [124]. Currently, the safety and efficacy of this technology are uncertain and further research is required to determine the long-term outcome as well as its safety and efficacy.

Endovascular Repair (EVAR) of Abdominal Aortic Aneurysm and Vascular Calcifications

EVAR is considered the standard treatment for abdominal aortic aneurysm when anatomically suitable [125]. Currently, about 80% of patients are treated with this technique [126]. Short, conical neck and more than 60-degree angulation of the aneurysm are considered contraindications to the endovascular repair (EVAR). Heavy circumferential calcification and circumferential thrombus in the neck of the aneurysm are also considered a contraindication for EVAR [127] as they will interfere with endograft fixation resulting in type I endoleak. The low profile EVAR stent grafts deployment system and the advancement in the percutaneous closure devices such as the Perclose system have enabled the use of totally percutaneous access rather than open surgical approach “femoral cut-down” [128]. However, excessive calcifications are the major limiting factor in deploying this technique safely and effectively Fig. 11.5. Also, extensive circumferential distal aortic and iliac calcifications increase the risk of complications mainly iliac artery injury.

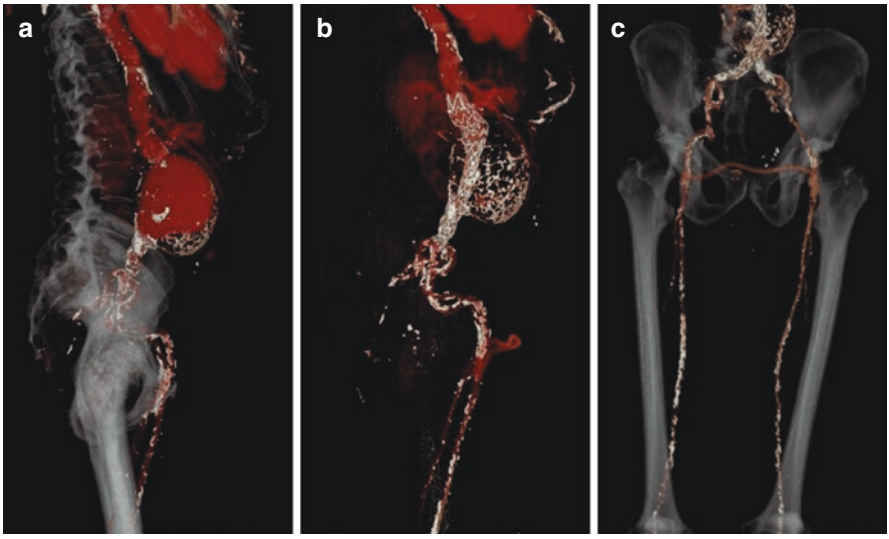

Fig. 11.5 CT shows a heavily calcified infrarenal abdominal aortic aneurysm treated with EVAR. (**a**) Large aortic aneurysm with evidence of heavily arterial calcification, (**b**) post endovascular treatment (EVAR) showing successful sac exclusion with no endoleak, and (**c**) an extra anatomical bypass (femerofemoral bypass) was required at later stage as patient had stent limb occlusion related to sever iliac calcifications

Operative Management

Conventional open surgical reconstruction for symptomatic significant stenosis or occlusive PAD is usually offered when endovascular revascularization attempts fail or if it is unfeasible. The choice of surgical procedure depends on many factors including patient fitness, location of the lesion/ lesions and availability and quality of autogenous veins. Generally, the surgical procedure may be endarterectomy which is the standard treatment for common femoral artery disease [129] or reconstructive surgery such as anatomical or extra-anatomical bypass. The general principle of infrainguinal bypass surgery is to bypass all hemodynamically significant lesions and to implant the bypass graft to the most proximal limb artery that has at least one continuous runoff artery to the foot. The Hybrid surgical approach was also deployed in specific cases with good results [130]. Applying vascular clamps on a heavily calcified arterial vessel to obtain proximal intraluminal control may result in vessel perforation and uncontrollable bleeding. Different techniques have been advocated to overcome this difficulty. The use of intraluminal occlusive balloon catheter through a haemostatic sheath minimizes blood loss and achieves good proximal control [131]. Precise balloon pressure and positioning are vital to avoid damage to the vessel and balloon bursting.

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Chapter 12
Arterial Calcification and Cerebral Disease: Stroke and Dementia

Fisnik Jashari, Per Wester, and Michael Henein

Introduction

Normal function of the brain relies on adequate perfusion by the cerebral circulation for the delivery of oxygen and nutrients, as well as the removal of waste products. Atherosclerosis is the dominant cause of cerebral blood flow disturbances. Atherosclerosis is the underlying pathology for coronary, carotid and intracranial artery disease leading to myocardial infarction and stroke, which are the most common causes of death and disability worldwide [1]. Due to the ageing of the population, the global burden of atherosclerosis, and thereby its clinical consequences will continue to rise in the coming decades. In addition to classical post-stroke sequel symptoms and signs such as motor and speech disabilities, stroke patients have an increased risk of cognitive impairment including dementia. Furthermore, atherosclerosis is considered an important cause of dementia in non-stroke patients, and seems to be an important factor in the pathophysiology of Alzheimer's disease, the most common cause of dementia [2].

Atherosclerosis can affect different and multiple arterial beds, with most predilection in the sites when arteries bifurcate. It starts as intimal thickening due to endothelial cell dysfunction that allows accumulation of lipid particles inside the wall, and progress through several stages, until it narrows the arterial lumen. The formed atherosclerotic plaques are histologically composed of different tissues;

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including fibrous elements, inflammatory debris, necrotic core and calcification. Calcium is an important component of the atherosclerotic plaque and its presence in different arterial territories including coronary, aorta, carotid and cerebral arteries has been found to be associated with increased risk of stroke and dementia [3].

Atherosclerosis and dementia are both progressive disorders with long subclinical phase. Therefore, early identification and application of preventive strategies before the onset of symptoms is of crucial importance. Arterial calcification is an important marker of atherosclerosis that can be detected by several imaging modalities in the preclinical stages. Likewise, there are several neuropsychological tests for the evaluation of cognitive performance that may be related to future cognitive impairment in subjects without dementia.

If subclinical atherosclerosis detected in middle age proves to be an important determinant of cognitive function in older age, increased efforts to prevent or potentially reduce the burden of atherosclerosis may result in delayed age-related cognitive decline and possibly dementia [4].

Stroke and Dementia: Epidemiology, Clinical Presentation and Diagnosis

Stroke ranks the second most common cause of death after ischemic heart disease worldwide and in high income countries as the second cause of lost quality-adjusted life-years (QALY) [5]. The incidence of stroke varies among different countries and increases exponentially with age. About 80–85% of strokes are caused by focal cerebral ischemia due to arterial occlusion, namely ischemic stroke, and the remaining 15–20% are due to hemorrhages. Mortality rates within one month for ischemic stroke generally range between 10 and 17% [6]. The likelihood of poor outcome after stroke is affected by many factors including patients age, comorbidities, the size of the brain infarct and level of consciousness. Acute stroke symptoms are characterized by sudden onset of focal neurological deficits including hemiparesis, hemidysesthesia, aphasia, dysarthria, hemianopia, ataxia, and neglect. Symptoms and signs usually affect one side of the body (unilateral), and consciousness is generally normal or impaired only slightly, except in the case of very large infarcts or hemorrhages in the hemispheres or stroke lesions in the posterior circulation [4].

Atherosclerosis and cardio-embolism are the leading causes of brain ischemia. Atherosclerosis usually affects large vessels and the vascular event follows atherosclerotic plaque rupture with superimposed thrombosis and embolization (artery-to-artery). During the acute phase of ischemic stroke, laboratory testing should exclude hypoglycemia which could mimic stroke. Complete hematological and coagulation test are also part of routine investigations. Clinical and electrocardiographic evidence for atrial fibrillation or acute/prior myocardial infarction are known potential causes of thromboembolism. CT and MRI scanning are very accurate in detecting

acute intracranial hemorrhage, with MRI having a much higher sensitivity than CT for acute ischemic changes, especially in the posterior fossa and in the first hours after ischemic stroke. However, non-contrast CT is more widely available, faster and less susceptible to motion artifacts compared to MRI. Patients in whom mechanical thrombectomy is considered, urgent CT or MRI angiography is important for identifying the site of arterial occlusion. Carotid duplex ultrasonography and transcranial Doppler ultrasonography have also been used to detect the site of arterial occlusion [7].

Dementia is defined as an acquired and usually progressive impairment of cognitive abilities that impairs the successful performance of activities in daily life. Memory is the most commonly lost brain function with dementia. Other mental functions may also be affected including; language, calculation, judgement, visuospatial ability and problem solving. Dementia is a devastating condition with a large societal impact, both for the suffering patient and next of kin as well as associated financial implications. Dementia affects more than four million Americans and results in a health care cost of >100 billion dollars annually. Its prevalence increases with age, particularly in patients having other diseases involving cerebral cortex, subcortical connections or both. Dementia is the fifth most common cause of death in the world and between 1990 and 2016, a 117% increase in the number of individuals living with dementia has been reported. The most common type of dementia is Alzheimer's disease (AD), accounting for up to 75% of cases, followed by vascular dementia which represents nearly 20% of all dementia cases [8, 9].

The most accepted diagnostic criteria for dementia, proposed by American Heart Association and American Stroke Association, are based on two factors: the presence of cognitive disorder by neuropsychological testing and history of clinical stroke or presence of vascular disease confirmed by neuro-imaging, that suggests a link between the cognitive disorder and vascular disease. Cognitive impairment or dementia after stroke is defined as any degree of cognitive impairment occurring within three months after the onset of stroke. However, many stroke patients develop delayed cognitive decline and dementia beyond three months or even after recurrent stroke. The recognition of cognitive impairment in the early phase after stroke may offer vital information to the clinician for early cognitive rehabilitation [10]. Dementia associated with cerebrovascular disease can be triggered by different pathologies including: (a) multi infarct dementia, (b) diffuse white matter disease (subcortical atherosclerotic leucoenceophalopathy) or (c) strategic infarct dementia [11]. Many patients with multi infarction dementia have a history of hypertension, diabetes, coronary artery disease or signs and symptoms of widespread atherosclerosis disease. Recently, the term vascular cognitive impairment (VCI) was introduced and refers to the contribution of vascular pathology to any severity of cognitive impairment, ranging from subjective cognitive decline, mild cognitive impairment and frank dementia of vascular origin, regardless of the pathogenesis (e.g., cardioembolic, atherosclerotic, ischemic, hemorrhagic, or genetic) [12]. It suggests that dysfunction of the neurovascular system and mechanisms responsible

for regulating cerebral blood flow, particularly those in the deep white matter are important components of the pathophysiological processes underlying VCI. In supporting the vascular mechanism for dementia, multi-infarctions have been documented coexisting with Alzheimer disease (specifically, the diffuse accumulation of amyloid-β plaques and neurofibrillary tangles composed of tau) [13]. Furthermore, with normal aging there is an accumulation of amyloid material in the cerebral arteries leading to the development of 'cerebral amyloid angiopathy' which is more prominent in Alzheimer patients. In addition to beta-amyloid and tau pathology, the role of vascular pathology in the etiology of dementia and Alzheimer's disease is increasingly being recognized. However, pure vascular dementia is more frequently associated with gait disturbance, hemiparesis and other focal neurological deficits. Also, in contrast to Alzheimer's disease known for memory loss, vascular dementia and vascular cognitive impairment are associated with disturbed executive functions. Most patients tend to develop a mixed form of Alzheimer disease and vascular cognitive impairment rather than either "pure" Alzheimer disease or "pure" vascular cognitive impairment (Fig. 12.1) [14].

The cognitive domains affected by stroke is related to several factors including stroke type, severity and duration of ischemia, location and volume of the lesion. Compared to patients with hemorrhagic stroke, those with ischemic stroke usually have higher survival rates, which explains why ischemic strokes lead to dementia more frequently than do hemorrhagic strokes [15]. Important lesion locations include dominant hemisphere and prefrontal–subcortical circuit that mediates executive function [2]. Lesions located in the frontal lobe can affect processing speed, reaction time, working memory and executive task measures. A single large cortico-subcortical brain ischemic lesion may present with acute cognitive deterioration, if located in an area that is functionally critical for cognition. Strategic infarct resulting in dementia is attributed to stroke lesion locations in the angular gyrus, the medial frontal lobe, and the inferomedial portion of the temporal lobe, all of which may be caused by large-vessel pathology. Bilateral hippocampal or thalamic infarctions and unilateral thalamic infarctions are other examples of strategically localized infarctions that are reported to cause dementia [16].

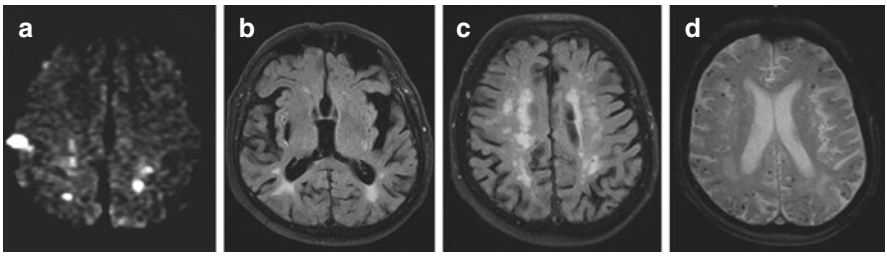


Fig. 12.1 (**a**) Different MRI imaging characteristics in patients with vascular dementia. MRI-DWI showing brain multi-infarction; (**b**) MRI-FLAIR, leukoencephalopathy in association with temporal lobe atrophy; (**c**) MRI-FLAIR Diffuse white matter lesions; (**d**) MRI-HEMO, cerebral amyloid angiopathy

Risk Factors for Cerebrovascular Disease and Dementia

The underlying etiology of dementia and cognitive decline is multifactorial and involves different pathologies which interact and accumulate over the course of years. In addition to beta-amyloid deposition and tau pathology, the role of vascular pathology in the etiology of dementia and Alzheimer's disease is increasingly recognized [17]. Atherosclerosis is highly frequent in the aging population and is considered the most important hallmark of vascular pathology. Apart from genetic and beta amyloid influence, stroke and dementia share many of the same risk factors. Hypertension, diabetes mellitus, hypercholesterolemia, smoking, sedentary life, obesity and atrial fibrillation all increase the risk of stroke and dementia. Cerebrovascular risk factors have been associated not only with vascular dementia but also with other types of dementia such as Alzheimer's disease (AD) which might be partly explained through promoting vascular oxidative stress and inflammation, which leads to altered cerebral blood flow (CBF) regulation, disruption of the blood brain barrier, and ultimately neuronal damage, worsening the coexisting neurodegenerative processes [18, 19].

Hypertension

Chronic arterial hypertension is a well-established risk factor for stroke, vascular dementia and AD. The Atherosclerosis Risk in Communities (ARIC) study showed that high blood pressure in middle age (around 48–67 years) is associated with declined cognitive function or dementia 20 years later [2]. Another study also demonstrated that subjects younger than 50 years with hypertension or prehypertension, if not treated, had increased risk for dementia. However, elevated blood pressure at 60 or 70 years old was not reported as a significant risk factor, even in those with severely raised blood pressure [20]. Middle age hypertension is associated with vascular dysfunction causing vascular remodelling, smooth muscle cells hypertrophy in the tunica media, endothelial dysfunction, atherosclerosis and increased blood-brain barrier permeability. Brain aging is considered to be induced not via neural aging, but via dysfunction of the neurovascular system. In addition, renin angiotensin system disruption plays an important role in the pathology of neurovascular dysfunction and dementia, not by affecting only the vascular system but also the causing astrocyte cell in central nervous system dysfunction.

A strong link exists between hypertension and cognitive decline, despite the inconsistent relationship between hypertension and dementia. A systematic review of meta-analyses, observational studies, and randomized controlled trials found that optimum treatment of hypertension reduces the risk of cognitive decline; however, another meta-analysis of longitudinal studies concluded the opposite [20]. Similar to data on the link between obesity and cognitive decline/dementia, studies proposed that late onset hypertension may be protective against cognitive decline.

Williamson et al. evaluated the effect of intensive blood pressure control on risk of dementia in 9361 randomized adults with hypertension. Intensive treatment to a systolic blood pressure goal of less than 120 mmHg compared with 140 mmHg did not result in significant reduction in the risk of dementia [21].

Diabetes Mellitus

Diabetes mellitus (DM) causes various microvascular and macrovascular changes that often culminate in major clinical complications. Diabetes is a well-established risk factor for all stroke subtypes and is also associated with worse outcome after stroke. Findings from the Emerging Risk Factors Collaboration showed that the risk of ischemic stroke is more than two times higher in patients with DM, adjusted hazard ratios 2.27 (1.95–2.65) [22]. Patients with type 2 DM have higher extent and severity of intracranial atherosclerosis and also more white matter lesions. Both types of DM are associated with increased risks of cardiovascular disease, but different pattern was observed. While individuals with type 1 DM are more likely to suffer coronary heart disease and peripheral arterial disease those with type 2 DM are more likely to have peripheral arterial disease, large-artery atherosclerosis and stroke [23]. According to data from the Greater Cincinnati/Northern Kentucky stroke study, the incidence of ischemic stroke is increased in all age groups, particularly patients with DM above age of 55 years in African Americans and below the age of 65 years in whites [24]. Furthermore, patients with DM are more likely to suffer from hypertension, myocardial infarction and dyslipidemia than individuals without DM [23]. Even impaired glucose tolerance has been linked to a greater risk of stroke [25]. A strong evidence exists suggesting that hyperglycemia at stroke presentation is associated with worse outcome, therefore current guidelines recommend treatment of hyperglycemia even though intensive acute glucose treatment has not shown beneficial [26].

The United Kingdom Prospective Diabetes Study (UKPDS) compared Type 2 DM patients on more intensive treatment (average HbA1c 7.0%) with traditional treatment (average HbA1c 7.9%) for primary stroke prevention and showed no significant reduction in stroke incidence ($p = 0.52$) [27]. As for secondary prevention, the Secondary Prevention of Small Subcortical Strokes Trial (SPS3) 37% of strke patients were noted to have diabetes mellitus and they were more frequently associated with intracranial atherosclerosis disease [28]. Insulin Resistance Intervention after Stroke Trial (IRIS) showed that pioglitazone, a thiazolidinedione, may be helpful for reducing vascular events after ischemic stroke. Recently, pioglitazone's benefit has been extended to patients with pre-diabetes, suggesting that it may be more widely adopted as a secondary prevention strategy in the future [29].

Based on meta-analyses, and a dozen of prospective observational studies, a lower cognitive performance and an increased risk of dementia among individuals with DM was observed. Also, a recent meta-analysis demonstrated that individuals

with mild cognitive impairment (MCI) and DM were more likely to progress to dementia compared to individuals with MCI and no DM. It seems that DM increases the risk of dementia not only through vascular pathways but also through interactions of other biological mechanisms related to diabetes itself. Of note, hyperglycemia is associated with functional changes in cerebral blood flow that are reversible when good glycemic control is restored. Studies suggest that the longer the duration of DM, the poorer the cognitive function. Of note, hyperglycemia is associated with functional changes in cerebral blood flow that are reversible with good glycemic control [30].

Dyslipidemia

Dyslipidemia is a clearly defined risk factor for stroke and intensive statins therapy showed clear protection from stroke recurrence. On the other hand, there are mixed results for the relationship between raised cholesterol and dementia, with some showing no association between cholesterol levels and vascular dementia [31]. While some observational studies suggest that statins reduce the risk of dementia, a Cochrane review and other systematic reviews found no or inconsistent evidence that use of statins reduces the risk [32]. At least, the effect has not been seen to date in randomised controlled trials and high quality cohort studies. Lipitor's Effect in Alzheimer's Dementia (LEADe) trial, included 640 randomized patients with mild Alzheimer disease, adding intensive lipid lowering therapy (atorvastatin 80 mg) to donepezil did not improve cognitive function over a 72-week period [33].

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia that develops with ageing. Untreated AF confers a five-fold risk for thromboembolic stroke. Recent studies have shown that AF is independently associated with other neurological disorders, including cognitive impairment and dementia, even after adjusting for prior ischemic stroke [34]. A meta-analysis of 14 studies including 85,414 participants showed that in patients with prior stroke AF was associated with a higher risk of incidence of dementia (Relative Risk, RR: 2.7) as well as those without prior history of stroke (RR: 1.4). The maintained association of the two conditions even after adjusting for independent history of stroke raised the question about the potential underlying mechanisms. Several proposed mechanisms include cerebral hypoperfusion, intermittent cerebral hypoperfusion during arrhythmia, inflammation, genetic factors, cerebral microbleeds, and recurrent silent cerebral micro infarcts. AF can be paroxysmal causing minimal symptoms, yet it contributes to cerebral hypoperfusion that can lead to cognitive decline and dementia. Because AF and dementia are

both strongly associated with advancing age, with each decade of life after the age of 40 years, conferring a two-fold higher risk, and sharing common risk factors, their association does not necessarily reflect pathophysiological connection. Several studies have evaluated AF and the risk of dementia, and showed its relationship with brain atrophy and brain volume loss even after adjusting for other risk factors and ApoE4. On the other hand, anticoagulation therapy have shown clear benefit for the reduction of stroke risk by two-thirds. Likewise, catheter ablation of AF resulted in a decrease in dementia risk. However, no difference in mini-mental state has been documented between patients with rate- and rhythm control over a 3-year follow-up. Patients with atrial fibrillation but without known cognitive dysfunction treated with oral anticoagulants (OACs) appeared to have a lower risk of developing dementia compared with patients not treated with OACs [35, 36].

Obesity

Middle age obesity, i.e. BMI >30, is associated with increased risk of stroke and cognitive decline, but there is inconsistent evidence regarding mid-late life obesity and dementia. Other data suggest lost association between obesity and cognitive impairment later on in life. In contrast, a recent large retrospective cohort reported a lower risk for dementia among individuals who were overweight, i.e., BMI 25–30, at middle age, while those who were underweight had an elevated risk. A recent meta-analysis showed that high waist-hip ratio is consistently associated with greater risk for dementia [37].

Smoking

The evidence associating smoking to all forms of stroke, irrespective of ethnicity is very convincing. Smokers have at least 2- to four-fold higher risk for stroke compared with lifelong nonsmokers or individuals who had quit smoking more than 10 years ago [38]. Stroke risk is increased even in patients exposed to passive smoking compared to those not exposed (odds ratio [OR]: 1.82; 95% CI: 1.34–2.49). When cigarette-smoking women with smoking spouses were compared with smoking women with non-smoking partners, a six-fold increase in the risk of stroke was observed in the first group [39]. Numerous mechanisms have been proposed to explain the increased risk of stroke and heart disease with smoking, including increased platelet aggregability, increased fibrinogen levels, reduced HDL-cholesterol, and direct toxic effects of several compounds on vascular endothelial cells. Cigarette smoke exposure has also been linked to the progression of carotid atherosclerosis as measured by ultrasound of the carotid wall as well as coronary and vertebrovasilar artery calcification measured by computed tomography [40, 41].

In a recent study, 1132 patients were assessed for dominant localization of calcification in carotid arteries (medial or intimal). Dominant intimal calcification was present in 30.9% compared to 46.9% with dominant medial calcification. Adjusted risk factors for dominant intimal calcification only were smoking (OR 2.09 [CI 1.27–3.44]) and hypertension (OR 2.09 [CI 1.29–3.40]) and for dominant medial calcification diabetes mellitus (OR 2.39 [CI 1.11–5.14]), suggesting that intimal and medial calcification represents a distinct etiology [42].

Atherosclerosis and Plaque Calcification Pathophysiology

The initial step in the pathophysiology of atherosclerosis is endothelial dysfunction that allows low-density lipoprotein particles (LDL) accumulation into the arterial wall. LDL particles then undergo oxidative modifications (oLDL) and trigger a local inflammatory response that signals the following steps in the lesion formation. This is followed by monocyte migration, accumulation into the intima when they convert to macrophages, which represent the early atherosclerotic lesion. Upon occupying the intimal space, macrophages will uptake oLDL by receptor mediated endocytosis and become lipid-laden foam cells leading to fibroatheroma formation [43]. Calcification, usually takes place later on, in more advanced stages of the disease and its severity increases with age. Plaque components that undergo calcification are: apoptotic cells, extracellular matrix and necrotic core. Sometimes all of these structures are completely calcified; so calcification may constitute most of the plaque volume. Vascular calcification is an important component in the atherosclerotic plaque formation. Uncertainty remains about the association between atherosclerotic calcification and the prediction of future vascular events. However, there is an undoubted correlation between atherosclerotic calcification and plaque progression and stability. Calcification is present in the plaques in different size, extent and shapes that may be important for its effect in plaque stability [44].

Large-scale studies have demonstrated that coronary and carotid atherosclerotic calcification increase with age [45]. Demer and Tintut hypothesized two different types of vascular calcifications; inflammatory and metabolic. While the former is localized in the intima together with necrotic lipid core, the latter, commonly seen in chronic kidney disease, is localized in the tunica media of the arterial wall (Fig. 12.2) [46].

A strong relationship exists between adverse cardiovascular outcomes and total coronary artery calcium score (CACs), evaluated by computed tomography (CT) [47, 48]. Nevertheless, coronary calcification, can be considered as an addition risk marker for plaque vulnerability, because coronary artery calcium score does not exactly predict the segment that will undergo rupture but identifies vulnerable patients at risk of ischemic events. In general, the presence of large amounts of calcification in the coronary arteries should be considered as a sign of combined metabolic and inflammatory disturbances and could contribute to the changes in

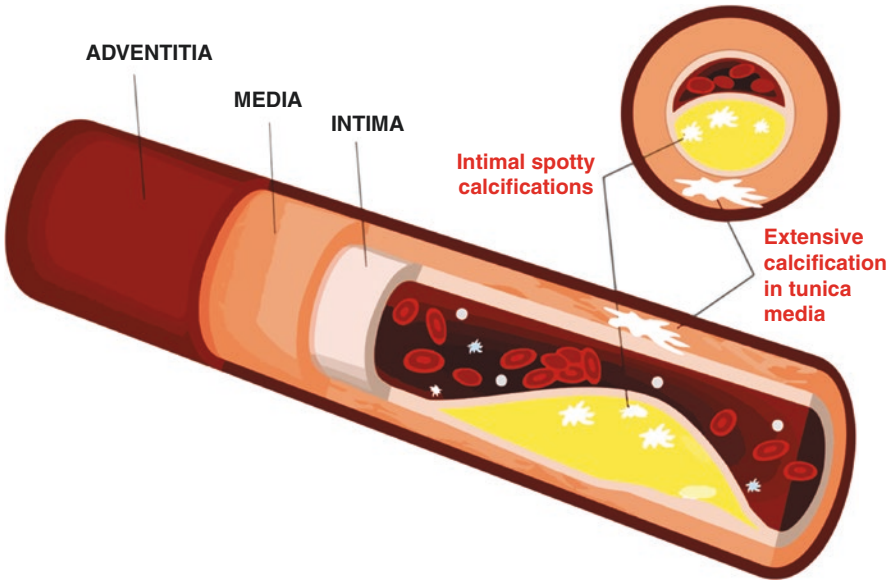


Fig. 12.2 Illustration of the arterial wall layers and calcium deposition into different location within atherosclerotic plaque and arterial wall. Micro-calcifications and spotty calcifications represent an active stage of vascular calcification correlated with increased inflammation. Patients with larger amount of calcifications (in the tunica media/adventitia) are often asymptomatic

mechanical properties of the arterial wall leading to the rupture of vulnerable adjacent less stenotic lesion. In support of this, presence of calcification in carotid artery has been found to have a protective role in the carotid artery but it was associated with future acute coronary syndromes. In brief, extensive arterial calcifications can be considered as an indicator of a vulnerable patient and intimal spotty calcification as a marker of vulnerable plaque [45, 48].

Imaging Atherosclerosis and Plaque Calcification in Carotid and Cerebral Vessels

Carotid and cerebral vessel atherosclerosis is an important cause and a predictor of stroke and dementia. Recent advances in imaging modalities have proved comparable to conventional angiography that requires radiation and evaluates only vessel lumen (Fig. 12.3). New imaging techniques use no or less radiation and in addition to vessel lumen they provide detailed information for arterial wall and plaque composition. Incidental atherosclerotic plaques and calcification can also be detected incidentally during brain CT (computed tomography), thyroid ultrasound or panorama imaging [49].

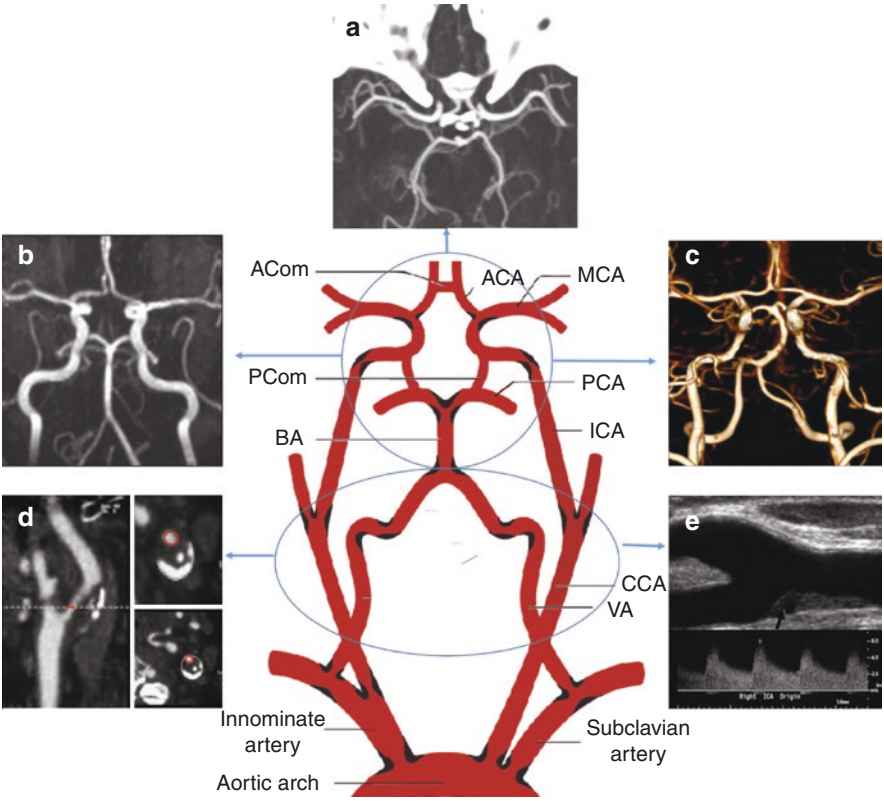


Fig. 12.3 Different imaging modalities used to diagnose atherosclerosis disease in cervical and cerebral vessels. (**a**) CT angiography of the main branches of the circle of Willis. (**b**) MR angiography imaging the distal branches of ICA, vertebrobasilar system and circle of Willis, (**c**) CT angiography with 3D reconstruction. (**d**) CTA in longitudinal and cross section view of the Carotid tree, depicting atherosclerotic plaque in the ICA. Duplex ultrasound of the carotid artery with plaque presence in the bifurcation. *ACA* anterior cerebral artery, *Acom* anterior communicating artery, *BA* basilar artery, *CCA* common carotid artery, *ICA* internal carotid artery, *MCA* Medial cerebral artery, *PCA* posterior communicating artery, *VA* vertebral artery

Ultrasound (US), magnetic resonance imaging (MRI) angiography and CT angiography allow visualization of carotid atherosclerosis disease in all phases of its development, including signs of subclinical atherosclerosis, degree of stenosis or even the most advanced plaque features (plaque composition, positive remodeling, intraplaque hemorrhage). Since atherosclerosis is a systemic inflammatory disease, plaque features in one vascular bed can add useful information and predict future events in other arterial systems. A stenotic plaque in the carotid arteries can predict future ischemic events in coronary arteries and vice versa. Because most of the ischemic strokes are caused by plaque rupture with subsequent artery to artery embolization, determining plaques prone to rupture (vulnerable plaques) should

theoretically assist in identifying patients at high risk for stroke [50]. The most accepted imaging features of plaque vulnerability include: thin cap fibroatheroma, large lipid core, intimal spotty calcification, positive remodeling and intraplaque neovascularizations [49].

The ability to precisely characterize significant carotid artery stenosis is fundamental for guiding treatment decisions. However, identification of other plaque features such as plaque composition and extensive calcification might be very important for deciding the time of intervention and the proper intervention technique to prevent peri- or post-procedural complications. It has been suggested that carotid artery stenting of soft (echolucent plaques in ultrasound) or in extensive calcified plaques is associated with higher risk of distal embolization and stroke [51].

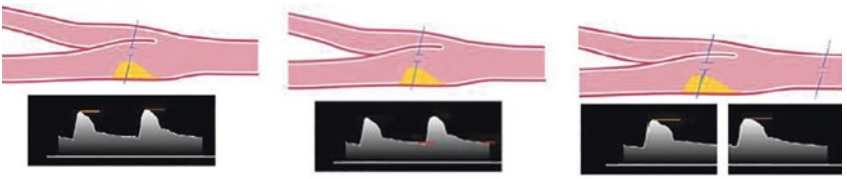
Duplex Ultrasound

Carotid artery ultrasound remains a long-standing and reliable imaging tool for assessing vascular morbidity at all stages. Over the last two decades, the procedure has undergone considerable upgrades in technology, approach, and utility.

Both greyscale and Doppler US (duplex ultrasound-DUS) can be used for evaluation of extracranial segments of the carotid arteries. The technique of greyscale US allows assessment of plaque morphology and vascular wall changes. Using carotid US also allows evaluation of carotid wall thickness (intima media thickness-IMT), aiding in the detection of subclinical atherosclerotic disease, and subsequent assessment of risk stratification. It also has the ability to differentiate between calcified and non-calcified portions of the plaque [52]. Compared to CT, Doppler US has proved accurate in detecting plaque calcification volume of as small as $1mm^3$ [53]. These non-calcified and hypoechoic portions of the plaques carry an independent risk for stroke, through plaque rupture. Using new techniques (grey scale median-GSM) plaque composition and even intima media complex can be quantified, with low plaque GSM associated with increased risk of stroke and TIA [49].

Doppler US examinations are known for the following advantages; safety, the ability to directly visualizing wall and plaque morphology as well as measuring flow velocities. It is also inexpensive, can be used bedside, is radiation free and needs no contrast. However, it is operator dependent so it needs good expertise. Depending on peak Doppler velocities as a sign of stenosis should be considered carefully, particularly in patients with contralateral carotid occlusion, since velocities are commonly over-estimated in the ipsilateral carotid stenosis. It should also be noted that Doppler US is restricted to the cervical portion of the internal carotid artery [54]. Some technical limitations should be carefully considered when using Doppler US. The interaction of the Doppler US beam with the moving red blood cells in the carotid vessels results in frequency shifts which are then used by the ultrasound system to estimate flow velocities (Table 12.1). Severe arterial tortuosity,

Table 12.1 Greyscale and Doppler criteria for diagnosis of internal carotid artery stenosis using ultrasound



Stenosis (%)	PSV_{ICA} (cm/s)	EDV_{ICA} (cm/s)	PSV ratio PSV_{ICA}/PSV_{CCA}
<50%	<125	<40	<2
50–69%	>125	41–100	2–4
70–89%	>230	>100	>4
>90%	>400	>100	>5

CCA common carotid artery, *EDV* end-diastolic velocity, *est.* estimated, *ICA* internal carotid artery, *PSV* peak systolic velocity. Adapted from Grant et al. [54]

high carotid bifurcation location, obesity, or extensive plaque calcification could all result in reduced sonographic accuracy [52].

Computed Tomography Angiography (CTA)

The anatomy of the right and left carotid arterial systems can be critically studied using CTA, from aortic arch to intracranial segments and the stenosis severity can be assessed. The technique is done using multiple views which can then be reconstructed, and the positive wall remodeling and plaque composition can also be evaluated [49]. Luminal area can form the basis of stenotic measurement. Accuracy of this method has increased with the current developments, since the detector row number has now been increased from 4 to 320. In the era of intracranial thrombectomy, primary stroke units recommend CTA evaluation during acute stroke in order to identify cases that could benefit from intervention within the first six and in some cases up to 24 hours after stroke initiation. In this way, the extra- and intracranial arteries are examined at once, and the results meet all clinical needs, both acute stroke treatment involving thrombectomy, and prevention involving carotid endarterectomy. CTA can be performed within 10 minutes. It is the most reliably used imaging modality and has been shown to be more accurate than MRA and duplex US for the assessment of the degree of stenosis [55]. Using CTA, one can also evaluate plaque morphology and identify different plaque compositions including spotty calcifications, as a sign of plaque instability [56]. The main disadvantages with CTA are radiation exposure, the need for contrast and a trained technologist and radiologist [49] (Fig. 12.4).

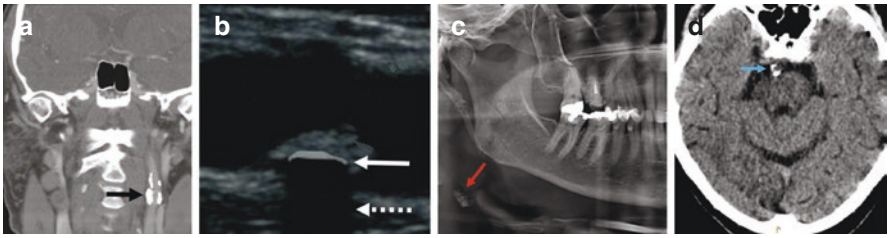


Fig. 12.4 Calcification detection on different imaging modalities. (**a**) Carotid artery calcification on carotid angiography. (**b**) Carotid artery calcification on ultrasound, calcified plaque (white arrow) producing posterior shadowing (white dotted arrow). (**c**) Calcified plaque on panorama radiography (red arrow) and (**d**) Vertebo-basilar calcifications on native brain CT (blue arrow)

Magnetic Resonance Angiography (MRA)

Magnetic resonance angiography encompasses the techniques used for both evaluation of carotid arteries: time-of-flight (TOF-MRA) performed without contrast and uses features of flowing blood, and the contrast enhanced (CE-MRA), which uses intravenous gadolinium. CE-MRA carries the advantage of being devoid of radiation, but is fraught for being expensive, requiring contrast, and is also time consuming [57, 58]. It should be mentioned that this technique lacks the accuracy for the detection of calcifications. TOF-MRA has a somewhat lower sensitivity and specificity than CE-MRA in arterial disease assessment. These methods have undergone notable development over recent years, however, despite these developments, invasive digital subtraction angiography (DSA) remains the gold standard [58]. Anzidei et al. [55] have compared the accuracy of three diagnostic methods, Doppler US, MRA and CTA for carotid artery stenosis degree compared with the gold standard method DSA (Digital Subtraction Angiography). A total of 336 carotid bifurcations were studied and area under the curve (AUC) for degree of stenosis was: Doppler US 0.85 ± 0.02, CE-MRA 0.994 ± 0.002 and CTA 0.997 ± 0.001 and the accuracy was 76% vs. 95% vs. 97% for Doppler US, MRA and CTA, respectively. In addition, CTA was the best imaging method for evaluating plaque morphology, calcification and ulceration [55].

Panoramic Radiographs (PR)

PR is a two-dimensional image that depicts teeth and facial skeleton and in 3 to15% of patients detects calcification in the area of carotid arteries. The prevalence of calcification detection increases with age and are its presence is often associated with carotid artery stenosis. Seventy-five percent of significant carotid stenosis are

associated with calcifications in panoramic radiographs. Calcification detection on PR can be used as a marker of atherosclerosis disease and cardiovascular disease prevention. It was confirmed that patients with calcifications on PR have higher prevalence of risk factors and higher risk of stroke in the future compared to patients without calcifications. Based on this it was recommended that patients with calcifications on PR should be referred for screening with carotid ultrasound to detect significant carotid stenosis and also to be advised for risk factors evaluation [59, 60] (Fig. 12.4).

Coronary Artery Calcification and the Risk of Stroke

Subclinical atherosclerosis, defined as any arterial wall changes not associated with organ ischemia, usually reflects lifetime exposure to cardiovascular risk factors such as hypertension and diabetes and also may be related to the development of cerebrovascular disease, cognitive impairment and dementia. Multiple studies have shown additive prognostic value of coronary artery calcification score (CACs) over other traditional risk factors [61, 62]. The prognostic value of CACs for incident stroke remains controversial with some studies suggesting an association and other studies denying it [63]. Wong et al. [64] investigated 2303 asymptomatic patients with CT scans who were followed up for 4.4 years. Although CACs was found to be associated with coronary events and overall cardiovascular events, it was not significantly associated with incident stroke. On the other hand, Gibson et al. [65] followed up 6779 patients for 9.5 years and Hermann et al. [66] followed up 4180 for 7.9 years, and both reported significant association between CACs and incident stroke. Recently, a meta-analysis was published addressing the prognostic value of CACs specifically for incident stroke including a large number of patients (n = 13,262) over mid-long term follow-up of 7.2 years [63]. Importantly, all studies enrolled patients without prior history of cardiovascular events and all were asymptomatic. The incidence of stroke was overall low (0.26%/year), which could be explained by the low-risk at baseline characteristics. Nevertheless, occurrence of first incident stroke was three times higher in patients with compared to those without coronary calcification. In addition, calcification volume proved an important predictor of stroke; patients with higher severity of CACs had higher incidence of stroke than those with less severe calcification. These findings support the prognostic value of CACs for prediction of incident strokes and this measurement could potentially be incorporated into future risk stratification approaches for the prevention of cerebrovascular events. The main disadvantage of CACs is radiation exposure; however, due to the rapid technological advancement, radiation associated with CACs testing has become significantly less with multi-detector computed tomography (0.7–1.0 mSv) [67].

Coronary Artery Calcification and the Risk of Dementia

Atherosclerotic plaque calcification has been strongly associated with magnetic resonance imaging markers of vascular brain disease, including cerebral micro-infarctions and micro-bleeds, white matter lesions, and worse white matter microstructural integrity [68, 69]. Several studies showed that the greater burden of CAC was independently associated with worse cognitive performance. In the Rotterdam Study (mean age 69.5 years), the greater calcified plaque in several locations, including the coronary arteries and aortic arch was associated with poorer performance on tests designed to measure a range of cognitive domains, including memory, processing speed, and executive function [70]. It was reported that a two-fold increase in CACs was associated with incident dementia, with a hazard ratio of 1.06 (95% confidence interval 1.08–1.41) after adjustment for cardiovascular risk factors [71]. Advances in MRI and post processing techniques allow automatic quantification of brain tissue volumes as a more precise measure of brain pathology. Furthermore, a novel MRI sequences such as diffusion tensor imaging (DTI) provide information on the microstructural integrity of white matter, which can independently predict cognitive function. In a large sample of community-dwelling persons aged 60 years and older, it was found that larger atherosclerotic calcification volume was independently associated with worse cognitive performance, smaller brain tissue volumes, and worse white matter microstructural integrity [72].

Cervical-Cerebral Vessel Calcification and the Risk of Stroke and Dementia

Vascular calcification is frequently observed during routine brain CT and CT angiography examination for patients suspected of stroke. Intracranial arterial calcifications have been shown to be independently associated with future stroke and also with stroke outcome. Intracranial artery calcification is very common and occurs in up to 83% of community dwelling elderly and up to 93% of stroke patients [73]. Calcifications can be either located in internal carotid artery or vertebrobasilar system. Studies have mainly reported intracranial carotid artery calcifications, but a significant amount of calcifications is also located in vertebrobasilar arteries, in up to 55% in ischemic patients and up to 25% in non-stroke patients [74]. Older age [RR 1.70 (95%CI 1.46–1.99) per 10 years], type II diabetes [RR 1.45 (1.03–2.06)] and obesity [1.57 (95%CI1.02–2.41)] are the most accepted risk factors associated with cervico-cerebral artery calcifications [75]. In addition, increased of IMT and ICA stenosis (>70%) at bifurcation were independently associated with intracranial artery calcifications [76].

Carotid artery atherosclerosis is an important risk factor for stroke and subsequent cognitive impairment [76]. Recent studies indicate that carotid atherosclerosis is an independent risk factor of cognitive decline and dementia also in individuals with [77] and without evidence of clinical stroke [78, 79].

In a study with 5888 participants >65 years older, cognitive decline was significantly greater in subjects with increased common carotid artery intima media thickness (IMT) >1.28 mm [80]. Also, In the Framingham Offspring study, a subgroup of 1971 asymptomatic participants who underwent carotid US examination and were followed up 4 years later with cognitive testing and brain MRI. Higher IMT was associated with significantly poorer performance on cognitive tests [81]. Rotterdam study confirmed that presence of plaques and high IMT were significantly associated with occurrence of both VaD and AD, even after adjusting for age [82]. Assessment of the calcification volumes using CT is novel, observer-independent, and has been shown to be strongly associated with lacunar infarcts, white matter lesions and worse cognitive performance [83]. Calcium formation has been observed to have different association in different vascular territories with cognitive performance and structural changes on MRI [84]. Calcifications located in cervical carotid arteries and intracranial vessels were strongly associated with cognitive decline compared to coronary and aortic arch calcifications [85]. Furthermore, calcification volume was inversely related to white matter volumes. This is of particular interest since executive function, information processing speed and motor speed are cognitive domains most frequently affected by white matter atrophy [86].

Vascular Aging in Cerebrovascular Disease and Dementia

Aging-related changes are major players in the pathogenesis of cardiovascular disease and dementia, including Alzheimer disease. Epidemiological studies have reported an independent correlation between the development of dementia and the incidence of cardiovascular disease in several populations, suggesting the presence of overlapping molecular mechanisms. Accumulating experimental and clinical evidence suggests that in addition to other inflammatory and metabolic changes, amyloid-beta (Ab) peptides may function as a link between aging, vascular changes and dementia. Induction of tissue inflammation and organ dysfunction by Ab deposition in arterial and cardiac wall is an important component of Alzheimer's disease amyloid hypothesis [87].

An equilibrium exists between Ab production and removal in various compartments inside or outside of the central nervous system [88]. The main mechanism of Ab deposition was supposed to be the defective peri-vascular drainage of neuronal derived Ab. Cerebral amyloid angiopathy (CCA) is a disease caused by accumulation of Ab1–40 in the circulatory system, whereas Ab1–42 is the main pathological hallmark in the development of Alzheimer's disease. Ab1–40 is a potent vasoconstrictor and suppresses endothelium-dependent responses, functional hyperemia, and cerebrovascular autoregulation. However, the accumulation of Ab1–40 was found not only in cerebral but also in carotid, aortic and coronary arteries, which has been associated with increased risk of cardiovascular disease. Ab1–40 is critically involved in vascular aging and arterial calcification that results in impairment of the vasodilating properties and enhancement of oxidative stress. Change of plasma Ab1–40 levels was independently associated with atherosclerotic plaques in carotid

artery and also with subclinical markers of atherosclerosis such as intima media thickness [89]. Plasma Ab1–40 was also associated with the severity of CACs in a sample of 3266 adults [90].

Overall, these findings indicate an effect of Ab1–40 in accelerated arterial aging, and arterial calcification atherosclerosis at various stages, and vascular beds, taking place long before the establishment of clinically overt cerebrovascular disease. An important feature of dementia is the long subclinical phase, during which subtle cognitive deficits develop that can only be measured using dedicated neuropsychological tests.

In Summary

Oxidative stress and inflammation appear to be the two primary pathological mechanisms of ageing-related endothelial dysfunction that is later followed by atherosclerotic arterial changes and subsequent cardiovascular disease.

Using different imaging modalities atherosclerotic plaques can be identified and its composition, including plaque calcification, can be easily identified. It was suggested that in addition to stroke, atherosclerosis is independently associated with increased risk of dementia.

Identifying high risk patients at a subclinical stage can lead to early intervention and cardiovascular risk factors modification. In addition, better understanding of the link between ageing and vascular changes can lead to significant advances in both preventative and therapeutic treatments aiming to decrease the risk of clinical events such as stroke and dementia.

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Chapter 13
Cardiovascular Calcification in Systemic Diseases

Paolo Raggi and Rekha Garg

Chronic Kidney Disease

Epidemiology of Cardiovascular Calcification in CKD

Numerous studies have shown a relationship between vascular calcification and increased risk of cardiovascular (CV) events in patients with CKD as well as increased prevalence of CV calcification (CVC) with declining renal function. In the MESA study, the prevalence and severity of coronary artery calcium (CAC) among 1284 subjects with non-dialysis dependent CKD was higher compared to 5296 subjects with normal renal function [1]. Similar results were reported in the Dallas Heart Study. Patients with CKD, defined as microalbuminuria and an estimated glomerular filtration rate (eGFR) <60 ml/min × min × 1.73 m^2, had an almost three-fold increase in risk of extensive CAC compared to patients with normal renal function (odds ratio of CAC greater than 100 units: 2.85; 95% confidence interval, 0.92 to 8.80 in CKD vs no-CKD subjects) [2].

Gorriz et al. [3] showed a stepwise age-independent increase in prevalence and severity of vascular calcification in a cohort of 572 non-dialysis dependent CKD patients. Using simple imaging tools such as planar X-rays of the abdomen, hips and hands, to detect arterial calcification, the authors reported calcifications in one or more territories in 79% of the study participants; in 47% of the patients CVC was graded as severe. At dialysis inception the prevalence of CVC is about 60% and it increases to about 80% in patients on maintenance dialysis (Fig. 13.1) [4, 5]. Unlike

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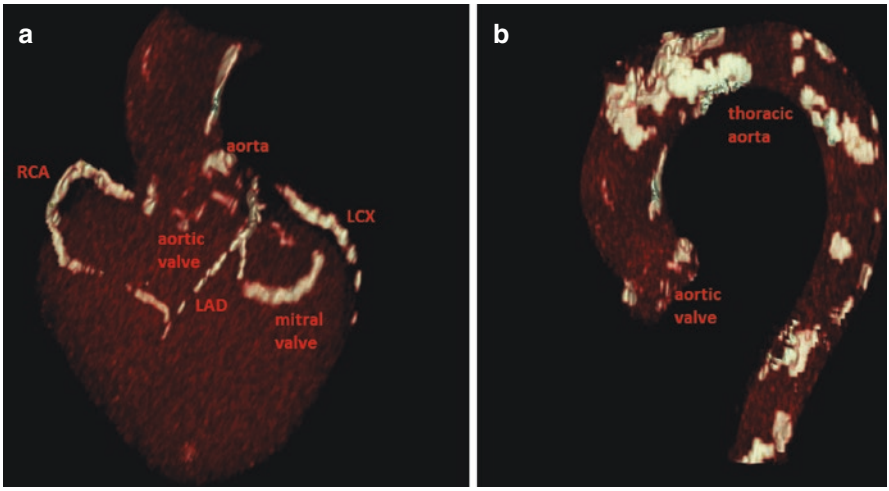

Fig. 13.1 Volume rendered images of the (**a**) heart and (**b**) thoracic aorta in a patient receiving maintenance hemodialysis showing heavy calcification of the coronary arteries, aorta and cardiac valves. *LAD* left anterior descending coronary artery, *LCX* left circumflex coronary artery, *RCA* right coronary artery (image courtesy of Dr. An de Vriese, AZ Sint-Jan, Bruges, Belgium)

the general population, there is no difference in markers of vasculopathy (namely thoracic aorta calcification, CAC or arterial stiffness) in patients receiving maintenance hemodialysis (HD) regardless of race or sex [6]. This suggests that dialysis is noxious for the CV system independent of clinical characteristics that may differentiate patients in the general population. Data on whether renal function restoration after kidney transplantation reduces the risk of CVC are limited and likely confounded by the concomitant use of various immunosuppressants [7].

Studies evaluating CVC using simple imaging modalities such as vascular ultrasound and planar X-ray in the radial, femoral, iliac arteries [8–11], abdominal aorta [12, 13], and CAC on chest CTs [14, 15] have all shown CVC as a marker of risk in CKD. In both subjects with normal renal function and patients with CKD, the MESA study showed an association between CAC and CV events independent of age, sex, race and comorbid conditions [1]. In addition, CAC was a better predictor of outcome than markers of arterial stiffness (ankle-brachial index) and carotid intima media thickness. Similarly, the Chronic Renal Insufficiency Cohort study of 1541 non-dialysis patients with CKD showed that CAC predicted myocardial infarction, congestive heart failure and all-cause mortality, independent of baseline CV risk evaluated by traditional risk score algorithms [16]. Inclusion of CAC in a risk algorithm led to a small albeit significant increase in the accuracy of cardiovascular events prediction.

Vascular calcification has been shown to be an independent predictor of all-cause mortality irrespective of demographic, risk factors or comorbidities in patients with CKD receiving maintenance HD or peritoneal dialysis (PD) and after kidney transplantation [17, 18]. A simple cardiovascular calcification index (CCI) that included

patient's age, dialysis vintage, calcification of the cardiac valves, and abdominal aorta was linearly associated with risk of all-cause mortality in patients on HD, such that the unadjusted hazard risk (HR) increased by 12% for each point increase in CCI ($P < 0.001$) [19]. Adjustment for confounders did not substantially change the strength of the association. In contrast, as seen in the general population, the absence of CVC is a harbinger of an excellent prognosis. Block et al. showed that within a few weeks to months of initiating dialysis, CAC predicted mortality after adjustment for age, race, gender, and diabetes mellitus with an increase in mortality proportional to the baseline score ($P = 0.002$) [5]. Conversely, the mortality rate was low at 5 years in patients without CAC (3.3/100 patient years without CAC vs 14.7/100 patients years for CAC > 400). In a series of 179 patients receiving PD, in the absence of CAC, subjects had a significantly lower risk of all-cause mortality, cardiovascular mortality and cardiovascular events, even after adjustment for demographic and comorbid factors [18].

Observational studies have shown that deposition of hydroxyapatite in the arterial wall is linked to a decrease in arterial compliance and subsequently increased CV risk [20, 21]. Di Iorio et al. reported a significant association of CAC and arterial stiffness (assessed via pulse wave velocity) as well as abnormal myocardial repolarization (assessed via QT dispersion on EKG) in 132 incident hemodialysis patients [22]. In studies of patients with CKD not receiving dialysis, worsening CKD stage was associated with a stepwise increase in arterial stiffness [23, 24]. Similarly, Raggi and coworkers showed that patients on maintenance HD with evidence of valvular, thoracic and abdominal aorta calcification have reduced aortic compliance [25]. Observational data confirmed the cardiovascular risk inherent with decreasing arterial compliance.

Similar to vascular calcification, the prevalence and severity of aortic and mitral valve calcification are higher in patients with CKD compared to the general population and associated with an unfavourable outcome. Valvular calcification leads to disturbed leaflet mobility, increased transvalvular pressure gradients, left ventricular hypertrophy (for aortic stenosis) and left atrium enlargement (with mitral valve stenosis and regurgitation) leading to poor outcomes [26, 27]. The increased risk associated with valvular calcification appears independent of its reported association with coronary artery or aortic calcification [28].

The debate on whether calcium deposition is a repair mechanism versus promoter of vascular damage is still ongoing. There are data suggesting that the mineral content of a plaque is a predictor of survival along with the extent of CVC. Bellasi et al. showed that a higher CAC density was independently associated with increased all-cause mortality with and without adjustment for confounders in a series of 140 consecutive HD patients [29]. These results are in conflict with data reported in the general population. In fact, an inverse association between plaque density and survival was reported in the general population by the MESA investigators [30]. Reverse epidemiology is a plausible explanation. Since most patients with CKD die primarily and prematurely of CV related events [31], patients receiving maintenance hemodialysis may not be comparable age- and sex matches for individuals with normal renal function.

Pathophysiology of Vascular Calcification in CKD

There is a linear relationship between CV mortality and decreased eGFR and increased proteinuria [31]. The all-cause and CV mortality rates for patients on dialysis are at least 15–20 times higher than the general age- and gender-matched population [32, 33]. This burden of CV disease is evident upon the initiation of renal replacement therapy when 40% of patients already have evidence of coronary heart disease and up to 80% have abnormalities in left ventricular structure and function by echocardiographic criteria [32, 34].

It has been postulated that accelerated CV senescence is one of the mechanisms responsible for development of CVC and CV risk in patients with impaired renal function [35]. Independent of age, CVC becomes more prevalent and severe as renal function declines [1]. A large body of evidence supports a biologically plausible, temporal [36] and dose-response [37] relationship between vascular calcification and CV risk in patients with CKD. Seminal findings by Goodman et al. demonstrated that CAC starts accumulating in young patients with end-stage renal disease (ESRD), decades before this pathology is observed in the normal population [38]. CAC scores in adult patients on HD have been reported to be over five-fold higher than age- and sex-matched individuals with established coronary artery disease, but normal kidney function [39]. A tendency for fast progression of CVC over 1 year has been reported in patients receiving HD [40]. Risk factors for greater progression of CVC in HD patients include age, diabetes mellitus, time since initiation of renal replacement therapy, and elevated levels of serum phosphorous and inflammatory markers. In addition to the extent of CVC, the rate of progression of CVC appears to be an important risk factor for CV events including mortality.

Intimal calcification is associated with the development and maturation of atherosclerotic lesions and is associated with traditional risk factors such as dyslipidemia, hypertension, diabetes and smoking and is not specific to CKD [41]. Medial calcification is more specific to CKD being associated with derangement of bone and mineral metabolism [42]. In addition, medial calcification is associated with vascular stiffening and arteriosclerosis observed with age and metabolic disorders including diabetes and ESRD. Beyond traditional risk factors, numerous non-traditional risk factors have been associated with CV aging and vascular calcification in CKD, namely inflammation, oxidative stress, metabolic derangements and accumulation of uremic toxins [35, 43].

Vascular calcification is considered an actively regulated process that may arise via a number of cellular mechanisms that include loss of calcification inhibitors, development of an osteogenic phenotype in vascular smooth muscle cells (VSMC), accumulation of protein aggregates and apoptotic bodies that serve to nucleate the development of hydroxyapatite, and disordered mineral metabolism.

In physiologic conditions, inhibitors such as pyrophosphate, matrix-GLA protein (MGP) or fetuin-A prevent transformation of amorphous calcium-phosphate complexes into insoluble crystals of hydroxyapatite and their precipitation in soft tissue including the blood vessels [42, 43]. In-vitro and in-vivo data also suggest the

role of micronutrients in vascular calcification propagation [44]. Preclinical data showed that VSMC incubated with high serum levels of calcium and phosphate undergo a osteochondrogenic phenotypic switch and become capable of secreting bone matrix in the context of the arterial wall, triggering calcification deposition and progression [42]. In addition, chronically elevated serum concentration of calcium and phosphate may lead to precipitation of mineral nanocrystals and the activation of resident macrophages, pro-inflammatory cytokine secretion and cellular apoptosis in an attempt to eliminate calcium-phosphate crystals [43].

An imbalance in pro- and anti-inflammatory cytokines leads to a state of chronic subclinical inflammation in CKD. The synthesis of anti-calcifying factors such as fetuin-A and the anti-ageing α-klotho [45] is reduced due to over-expression of pro-inflammatory cytokines such as interleukin 6 (IL-6) or tumor necrosis factor alpha (TNFα). Fetuin-A is a glycoprotein synthesized in the liver and essential for the formation of the highly soluble calciproteins (a complex of fetuin-A and plasma calcium-phosphate crystals) that keep calcium and phosphorus from forming crystal in the circulation. The protein α-klotho modifies the binding of fibroblast growth factor 23 (FGF-23) to its receptor in the kidney increasing urinary phosphate wasting [43]. Downregulation of α-klotho expression has been linked with accelerated vascular ageing. Furthermore, dysregulation of the α-klotho/FGF-23 axis has been implicated in the development and progression of CVC although the exact role of this complex is not fully understood [46]. FGF-23 and α-klotho control phosphate excretion through the kidneys and may have a direct vascular protective role by modulating different signaling pathways such as FGF-receptor 1 and mTOR [43]. Further elucidation of the contribution of the FGF-23/α-klotho complex to the development of CVC in patients with CKD is needed.

Oxidative stress and advanced glycation end products (AGEs) generation, for which oxidative stress is partly responsible, have been implicated in the pathogenesis of CVC [43]. AGEs promote RANKL activation in osteoblasts and calcium/phosphate removal from the bone. In addition, experimental data suggest that AGEs may induce VSMC osteogenic differentiation through p38/mitogen-activated protein kinase (MAPK) and Wnt/β catenin signaling. Finally, AGEs together with other uremic toxins synergistically trigger inflammation by inducing the synthesis of pro-inflammatory cytokines (IL-1, IL-6, TNFα) linked to endothelial dysfunction and vascular calcification [43].

As renal function declines, uremic toxins such as indoxyl sulfate (IS) accumulate and may directly affect the vasculature [43]. IS triggers the expression of the sodium-phosphate co-transporter Pit-1 that leads to the osteogenic differentiation of VSMCs induced by calcium and phosphorus. In addition, IS suppresses liver synthesis of fetuin-A further predisposing CKD patients to vascular calcification development. Finally, epidemiological observations suggest that patients with CKD are deficient in vitamin K (cofactor for MGP carboxylation and activation), and pyrophosphate (a major endogenous inhibitor of calcium-phosphate crystals formation), and are thus further predisposed to the crystallization of calcium-phosphorus in soft tissues [47].

Therapeutic Approaches

Several treatments have been implemented to target various steps in the deranged metabolism of bone and minerals in CKD. The primary ones consisted of normalizing Ca, P, and parathyroid hormone serum levels, minimizing Vitamin D use or considering calcium sensing receptor activating drugs ("calcimimetics") to control secondary hyperparathyroidism (see section on secondary hyperparathyroidism). Other approaches included administration of pyrophosphate (inhibitor of calcification), bisphosphates (inhibitors of bone osteoclastic activity), and Vitamin K (to favour the formation of active MGP) in patients with known CVC [48]. Only a few of these agents have demonstrated effectiveness in slowing progression of CVC.

Statins, primarily lipophilic, appear to accelerate rather than inhibit calcification progression probably due to the inhibition of vitamin K synthesis [49]. MGP is a potent inhibitor of calcification and requires activation through a Vitamin K-dependent pathway. One trial comparing Vitamin K antagonists vs direct oral anticoagulants has been reported, while two more ongoing trials are evaluating the effect of vitamin K supplementation on CVC progression. De Vriese et al. [50] randomized 132 maintenance hemodialysis patients to coumadin vs rivaroxaban or rivaroxaban plus Vitamin K supplementation. Despite a reduction in the serum level of decarboxylated MGP (i.e. inactive MGP) with rivaroxaban or rivaroxaban plus Vitamin K2 supplementation, there was no significant slowing of progression of coronary artery, valvular and aortic calcification. The VitaVasK study of 348 patients on maintenance HD will evaluate the impact of Vitamin K1 on progression of thoracic aortic calcification and CAC compared to placebo [51]. The IRIVASC-Trial will evaluate the impact of rivaroxaban compared to coumadin/phenprocoumon on coronary and aortic valve calcification in 190 patients with an eGFR >15 mL/min/1.73 m2, and either atrial fibrillation or pulmonary embolism. (https://clinicaltrials.gov/ct2/show/NCT02066662?term=IRIVASC&draw=2&rank=1; last verified April 6, 2020).

Phosphate and its associated effects on FGF23 and PTH have been linked to CVC [5, 52], and inhibitors of intestinal phosphate absorption, either calcium-containing or calcium-free, are commonly used to correct hyperphosphatemia in patients with advanced CKD [53]. Several studies showed that calcium-based binders in CKD [54–56] and calcium supplements in patients without renal dysfunction [57, 58] promote formation of CVC, while inhibiting bone formation [59, 60]. These results were accompanied by an increase in mortality in randomized clinical trials of patients with CKD stage 3 to dialysis [61–63], and in a meta-analysis of randomized trials comparing calcium-based binders to the non-calcium based binders lanthanum and sevelamer [64]. Calcium-based binders had a detrimental effect on CAC progression and were associated with a significant increase in mortality in patients receiving HD compared to non-calcium phosphate binders [64]. Thus, current guidelines on bone and mineral metabolism management in patients with CKD suggest limiting the dose of calcium-based phosphate binders for all patients with renal impairment [65].

Animal and laboratory experiments suggested that magnesium modulates the development of phosphate-induced calcification in a dose-dependent manner [66–69]. Small clinical studies showed that magnesium either directly slowed CAC progression or indirectly reduced the propensity for calcification in patients with moderate to end-stage CKD [70–72]. An open label randomized trial in 120 patients with stage 3–4 CKD showed that magnesium significantly slowed progression of CAC compared to standard of care (median change: 11.3%, IQR 0–30.8 vs 39.5%, IQR 19.0–81.3; $p < 0.001$) in patients [73].

There are a few new compounds under investigation that might impact development and progression of CVC. Sotatercept, an anti-anemia compound that inhibits the Activin A receptor, in preclinical data showed an increase in bone mineralization and reduction in deposition of hydroxyapatite in the vasculature [74]. The immunosuppressant everolimus appears to increase the synthesis of Klotho by inhibiting mTOR, while the chemotherapeutic agent bortezomib may exert some protective effect against CVC progression by increasing Wnt/B-catenin signaling [74]. Finally, several Wnt inhibitor antagonists (sclerostin, DKK1-secreted frizzeled related proteins) are in early stage of preclinical development [74]. SNF472 targets a novel pathway by selectively inhibiting the formation and growth of hydroxyapatite crystals, which are thought to be the final pathway in the development of vascular calcification. In the recently completed CaLIPSO, a double-blind, placebo-controlled phase 2b trial, SNF472 significantly attenuated the progression of CAC volume score (11% vs 20%, $p = 0.016$) compared to placebo in patients with ESRD receiving HD [75].

The pharmacological and surgical therapy of hyperparathyroidism are discussed in the next section.

Disorders of the Parathyroid Glands and Mineral Metabolism

The parathyroid hormone (PTH) is secreted by 4 small parathyroid glands located behind the thyroid gland. Until recently PTH was believed to be the primary regulator of phosphorus and calcium metabolism. However, a family of proteins known as phosphatonins described in the mid 1990s [76] is now thought to contribute very closely to the control of phosphorus metabolism along with PTH. The main actions of PTH include stimulating bone resorption, promoting phosphaturia, hydroxylation of 25-hydroxy vitamin D2 to its active form 1–25 dihydroxy vitamin D (Vit D3) in the kidney, as well as inducing calcium reabsorption from the distal renal tubule. Vit D3, in turn, promotes absorption of phosphorus and calcium from the gut and reabsorption of calcium from the distal tubule. The parathyroid glands are especially sensitive to calcium serum levels through the action of a cell membrane receptor known as *calcium sensing receptor* [77]. Of interest, this receptor is present in numerous other tissues and organs throughout the body. A low calcium level is rapidly detected at the parathyroid level by the calcium sensing receptor and it induces a powerful release of PTH. Several feedback mechanisms are operative

between serum calcium and phosphorus levels, PTH, Vit D3, calcitonin (produced in the medulla of the thyroid gland) and fibroblast growth factor 23 (FGF-23) such that the serum levels of calcium and phosphorus are tightly controlled (Fig. 13.2a) [79].

FGF-23 is produced by osteoblasts and osteocytes and it is the best-known member of the phosphatonin family. Its primary functions are inactivation of the enzyme 1-α hydroxylase in the kidney to slow the formation of active Vit D3, induction of the 24-hydroxylase enzyme (that results in the formation of inactive 1-24-25(OH)3 vitamin D3), and induction of phosphaturia in the kidney proximal tubule. Essential to the functions of FGF-23 is its soluble protein α-Klotho. This protein binds to the

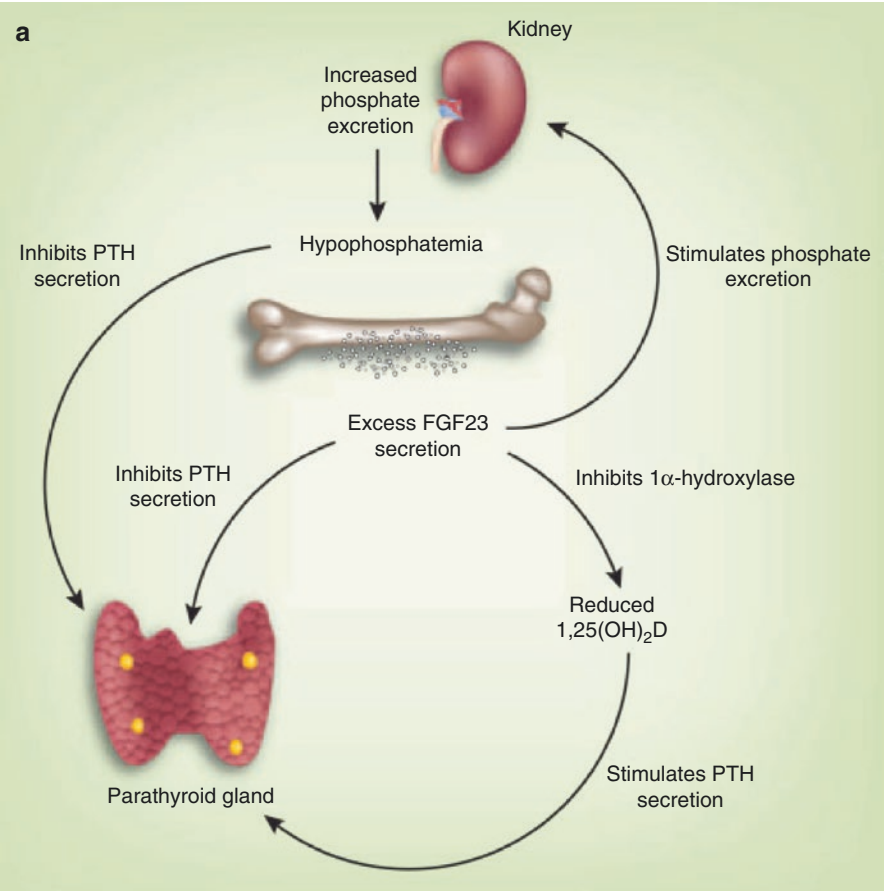

Fig. 13.2 (**a**) Physiological maintenance of serum calcium and phosphorus levels through the interaction of parathyroid hormone, vitamin D3 and FGF-23. (**b**) As kidney injury occurs and chronic kidney disease progresses several feed-back mechanisms are ignited. This results in hyperplasia of the parathyroid glands, reduced production of active vitamin D3 and α-Klotho with increased production of FGF-23 and parathyroid hormone. This cascade of events eventually leads to progressive bone resorption and weakening along with increasing soft-tissue calcification (reproduced with permission from Komaba H [78])

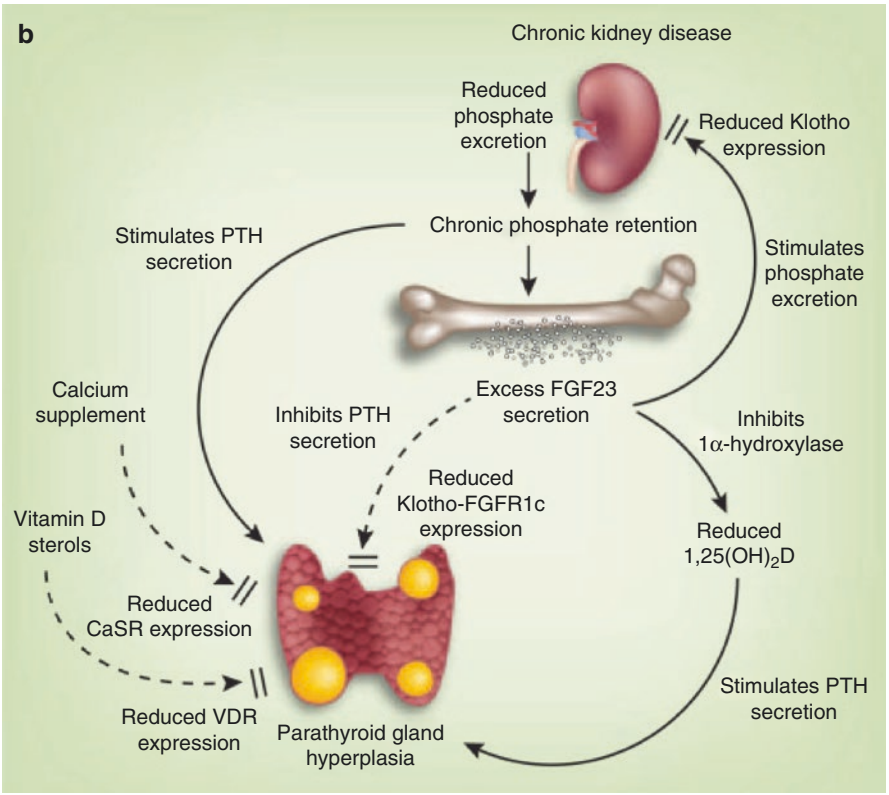

Fig. 13.2 (continued)

FGF-23 receptor increasing the affinity of the receptor for FGF-23 and rendering the latter more efficient. PTH and FGF-23 levels rise very soon after renal function declines below a glomerular filtration rate of 60 ml/min/1.73 m^2 [80], and are part of a complex cascade of events involved in the development of the mineral-bone- and vascular disorder typical of advanced stages of chronic kidney disease (Fig. 13.2b).

Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is characterized by high parathyroid hormone (PTH) and calcium serum levels with low serum phosphorus. It is usually due to an adenoma (80% of the times) or hyperplasia of a parathyroid gland, although it can also rarely be due to a carcinoma of one of the glands or be part of a hereditary multiple endocrine neoplasia syndrome [81]. More frequently encountered is secondary hyperparathyroidism (SHPT) that typically develops in patients with

advanced CKD. Other rare causes of SHPT include osteomalacia, rickets, and malabsorption. In CKD the high serum levels of parathyroid hormone (PTH) is due to hyperplasia of one or more parathyroid glands in response to the progressive retention of phosphate as renal failure declines, along with reduced activation of 25-hydroxycholecalciferol to VitD3. The loss of VitD3 eliminates an important negative feed-back on PTH suppression and causes reduced calcium absorption from the intestine along with reduced calcium retention at the level of the distal tubule. The declining serum calcium levels are detected by the calcium sensing receptor in the parathyroid glands chief cells and ignite a powerful release of PTH to restore balance. High PTH levels promote the maturation of osteoblasts into osteoclasts that act by removing calcium and phosphorus from the bone. Simultaneously, and likely preceding the rise in PTH, FGF-23 is released in a counter regulatory feed-back (Fig. 13.2b) [78]. Eventually the bone of patients with advanced CKD becomes resistant to the effects of minerals and hormones responsible for bone remodelling, while the parathyroid glands become progressively less responsive to the inhibitory effects of FGF-23. The end result is a progressive weakening of the bone architecture and loss of tensile strength leading to repetitive fractures. As many as 20–30% of patients with SHPT develop tertiary HPT most commonly in the setting of renal transplant, where patients continue to have elevated PTH levels even after receiving a renal allograft [82]. It is believed that prolonged hypocalcemia may induce parathyroid gland hyperplasia that does not regress despite the renal transplant. Although tertiary HPT is usually caused by hyperplasia of all four glands, in some cases the disorder can be caused by adenomas of one or more parathyroid glands [83, 84]. Serum levels of minerals and hormones involved in the metabolism and remodeling of bone have been associated with subclinical cardiovascular disease and cardiovascular morbidity and mortality as well as all-cause death both in the general population and in patients with CKD. Onufrak et al. [85] showed an association between serum levels of phosphorus and thickness of the carotid intima-media layer in the general population. Adeney et al. [86] demonstrated that patients with moderate kidney dysfunction with higher serum phosphate levels, albeit still in the normal range, had more extensive vascular and valvular calcification than those with lower phosphate levels. High-normal serum phosphate levels were associated with a greater incidence of cardiovascular morbidity and mortality and/or all cause death in several population studies [87–90] Similarly, associations have been reported between PTH levels and subclinical and clinical cardiovascular disease [91, 92] all-cause death [93], heart failure [94, 95] and even vascular dementia [96] in the general population. FGF-23 levels have been associated with cardiac events [97–99] and ischemic stroke [100, 101], in subjects with normal renal function. Older studies reported an association between serum calcium levels and risk of myocardial infarction [102], cardiovascular and non-cardiovascular death in the community [103, 104] as well as valvular calcification [105].

In the quest for a potential mechanism of action to explain these findings, associations have been reported between traditional cardiovascular risk factors and higher serum levels of phosphorus [88] FGF-23 [106, 107] and calcium [102, 108]. In animal experiments, PTH has been shown to be independently able to induce

extensive cardiovascular calcifications [109, 110]. Therefore, it should come as no surprise that patients affected by PHPT tend to suffer a higher than expected incidence of cardiovascular events compared to the general population [111, 112]. This is likely due to a combination of endothelial dysfunction [113], systemic hypertension [114, 115], left ventricular hypertrophy and dysfunction [116–118], cardiac arrhythmias and cardiac calcification. Calcium deposition is particularly frequent on the cardiac valves and in the myocardium of patients with PHPT [119, 120]. However, there does not appear to be an increased prevalence and severity of CAC especially in patients with mild hypercalcemia [121–123]. Surgical treatment for PHPT caused by adenomas restores endothelial and coronary microvascular dysfunction [124, 125]. Additionally, halted progression of cardiac and valvular calcification was reported both at one year and after 3.5 years from surgical intervention [126, 127]. Although a significant correlation between LVH and valvular calcification has been reported [119], as well as between LVH and myocardial calcifications [126], data on the effectiveness of parathyroidectomy in reversing structural and functional left ventricular changes are inconclusive [128].

An extensive body of literature documented an association between abnormalities of mineral metabolism and adverse events in ESRD [129]. For patients with moderate CKD, PTH levels have been associated with all-cause death but not cardiovascular events [130]. An association has been reported between FGF-23 and development of congestive heart failure but not atherosclerotic events in one study [131], and both types of events in another [132]. In a prospective cohort study, FGF-23 was not predictive of cardiovascular events or death in patients with CKD stage 3, while low VitD3 and elevated PTH levels were [133]. Finally, a recent meta-analysis concluded that the association between FGF-23 levels and cardiovascular outcomes may be non-causal, and therefore FGF-23 may be a bystander rather than a causative factor [134]. The inconsistent epidemiological evidence surrounding FGF-23 may be due to the heterogeneity of studies included in the analyses as well as the small number of subjects and events in some of the studies. Nonetheless, there is an undoubtful connection between the extensive vascular and valvular calcification of patients with advanced CKD and untoward outcomes [3, 21, 29, 135–137]. As described in the section dedicated to CKD, multiple trials directed at slowing the progression of calcification have been conducted. The compounds used to slow progression tested so far include: calcium-based and non calcium-based phosphate binders such as sevelamer, lanthanum and magnesium; molecules capable of stimulating the calcium sensing receptor (calcimimetics) such as cinacalcet and etelcalcetide to reduce the release of PTH from the parathyroid glands; and direct inhibitors of the formation of crystals of hydroxyapatite. Numerous publications have demonstrated the ability of non-calcium-based phosphate binders to slow the progression of cardiovascular calcification, and one meta-analysis showed that these compounds may also reduce mortality [64]. A randomized clinical trial compared the effectiveness of cinacalcet plus low dose VitD3 versus liberal doses of VitD3 to control SHPT in patients receiving hemodialysis [138]. The primary study results showed a borderline effectiveness of the calcimimetic to slow cardiovascular calcification progression. However, in the per-protocol analyses cinacalcet and low

dose VitD3 were very effective at slowing progression of CAC, and valvular calcification [139]. The related outcome trial failed to show a reduction in all-cause mortality and major cardiovascular events [140], although a subanalysis showed a potential role of cinacalcet in reducing non-atherosclerotic cardiovascular events [141]. In a subanalysis of the INDEPENDENT trial, patients with ESRD who received the non-calcium based phosphate binder sevelamer along with cinacalcet showed a lower mortality rate than those receiving calcium-based binders with cinacalcet or patients receiving VitD3 with any binder [142]. These results highlighted the importance of phosphorus control while avoiding imbalances of calcium metabolism. The most recent trial directed at slowing progression of cardiovascular calcification in ESRD explored the potential of a direct inhibitor of hydroxyapatite [75]. The drug reduced further expansion of CAC by 45–75% in the intention to treat and per-protocol analyses. No outcome data are yet available related to this compound. Parathyroidectomy has a role in SHPT when medical therapy fails to control the biochemical alterations of this conditions often associated with severe bone and vascular abnormalities. In observational studies parathyroidectomy has been associated with slowing of CAC progression [143] and reduction in cardiovascular mortality [144–146]. However, no randomized controlled study has been conducted to compare medical therapy versus surgical intervention for SHPT [147], often leaving the choice of treatment to the preference of the treating physician.

Hypoparathyroidism

Sporadic idiopathic hypoparathyroidism (SIH), either due to an autoimmune disease or caused by complex genetic abnormalities, is a rare endocrinological disorder characterized by low serum levels of parathyroid hormone and calcium, and elevation in serum phosphate [148]. The disease can manifest with a variety of neuromuscular and sensory symptoms such tetany, muscle cramping, airway obstruction, laryngospasm, chronic fatiguability, peri-oral numbness and generalized paresthesia, but also seizures, parkinsonism, depression, irritability and cognitive impairment. Ectopic deposition of crystals of calcium and phosphorus has been reported to involve several tissues. Calcification of the cerebral basal ganglia has been classically associated with this disorder (Fig. 13.3) [149]. Although its true pathogenesis remains unclear, it is probably related to prolonged hypocalcemia and simultaneous hyperphosphatemia [150]. Calcification of the eyes and kidneys is also frequent and associated with cataract formation and progressive renal function decline [151]. Peripheral vascular calcification and coronary artery calcification have been reported, but with a much lower prevalence [152]. Therefore, the impact of CAC on the incidence of cardiovascular events in patients affected by hypoparathyroidism is unknown. Nonetheless, other types of cardiovascular complications have been reported such as supraventricular and ventricular cardiac arrhythmias, the latter probably secondary to prolonged QT, and left ventricular systolic dysfunction.

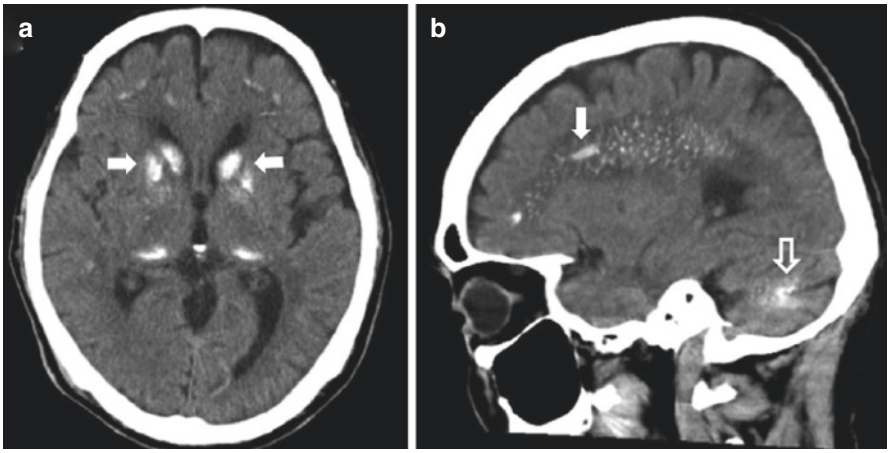

Fig. 13.3 Head computed tomography scan showing extensive calcification of the basal ganglia (horizontal arrows in section **a** and solid vertical arrow in section **b**), and cerebellum (open vertical arrow in section **b**) (reproduced with permission from Harada K [149])

A form of relative hypoparathyroidism, known as low turnover bone disease, has been described in patients with ESRD. In this condition serum levels of PTH are relatively lower than needed to induce periodic bone remodeling, and this causes progressive bone weakening and worsening cardiovascular calcification. As in the case of very high PTH levels, low levels of PTH have also been associated with increased mortality in patients undergoing hemodialysis [153, 154]. The use of high calcium concentrations in the dialysate fluid, large doses of calcium-based phosphate binders and VitD3 appear to be the most frequent mechanisms inducing suppression of pulsatile release of PTH that is necessary for its activity on bone remodeling and mineral metabolism. In a subanalysis of a randomized clinical trial in ESRD, the authors showed that the progression of CAC was more pronounced in patients with diabetes mellitus, particularly in those receiving calcium-based phosphate binders compared to those receiving a calcium free binder [155]. Confirming the significance of this observation, in a longitudinal study of over 53,500 Japanese patients receiving dialysis, the highest incidence of myocardial infarction was observed in patients with high dialysate calcium and low serum PTH levels [156].

Human Immunodeficiency Syndrome

After the introduction of highly active antiretroviral therapy (HAART) patients living with human immunodeficiency virus (PLWH) have had a significant increase in life expectancy [157, 158]. As a result, cardiovascular diseases (CVD) have become a leading cause of mortality and morbidity in PLWH [159, 160]. An intense debate has revolved around the pathophysiology of CVD development, spurred by the observation that traditional risk factors are highly prevalent in PLWH but do not

appear to justify the entire risk [161]. The consensus appears to be that a combination of traditional and non-traditional risk factors is contributory [162]. Several investigators have raised the possibility that some HAART, especially abacavir and those in the protease inhibitor family, may raise the risk of cardiovascular events [163–165]. Additionally, smoldering inflammation and a state of ongoing immune activation due to chronic HIV infection, enhanced permeability of the gastrointestinal barrier to bacteria, and co-infection with other viruses are likely sources of ongoing vascular damage [166]. As a result PLWH are believed to experience an accelerated ageing process in the context of a highly inflamed environment (*inflam-ageing of HIV*). In fact, several publications have demonstrated an increased inflammatory arterial burden in PLWH [167, 168].

Despite the increased risk, most of the tools utilized to predict atherosclerotic cardiovascular events in the general population perform poorly in PLWH [169]. Therefore, imaging of sub-clinical atherosclerosis has received mounting attention in this population for early detection of disease, enhanced risk prediction and -ultimately- improved prognosis.

Subclinical Atherosclerosis in HIV

Early publications remarked on the increased carotid intima-media thickness (IMT) as an indirect marker of atherosclerosis in PLWH. Hsue et al. reported that PLWH had a thicker IMT than matched controls; HIV infection was an independent predictor of carotid IMT after adjustment for age, sex, smoking, hypertension, dyslipidemia and diabetes mellitus [170]. Additionally, a nadir CD4 count <200 cells/mL was a predictor of IMT progression in these patients. Similarly, Salmazo et al. reported that PLWH had a thicker carotid IMT than controls [171]. Furthermore, carotid plaques were detected with ultrasound imaging in 37% of PLWH and 4% of controls ($p < 0.001$). PLWH with carotid plaques had higher serum lipid levels and poorer glycemic control. Infection with HIV increased the odds of having a carotid plaque by five fold after adjustment for obesity, smoking and age. Chest computed tomography has provided valuable insight into the prevalence and development of atherosclerotic disease in PLWH. Post et al. reported a higher prevalence of non-calcified coronary artery plaques detected by means of computed tomography angiography (CTA) in PLWH compared to controls, although they did not observe an increased prevalence or extent of coronary artery calcium (CAC) [172]. On the contrary, Guaraldi et al. remarked on the utility of CAC as a marker of ageing and cardiovascular risk in PLWH [173]. Using previously validated CAC equations, they showed that as many as 40% of PLWH have a vascular age on average 15-year older than age and sex matched controls. Cardiometabolic risk factors such as elevated serum triglycerides and cholesterol lipoproteins were associated with increased vascular age in univariate analyses, although the only multivariable predictor of older vascular age was the current CD4 cell count. Additional indirect evidence of accelerated ageing and atherosclerosis accrual in PLWH was provided by the observation

that high CAC scores are associated with a lower bone mineral density of the femoral head [174].

The importance of altered cardiometabolism as a predisposing factor to the development of subclinical atherosclerosis in PLWH was addressed in several publications. Guaraldi et al. described an association of CAC with the presence of lipodystrophy in long-term users of HAART [175]. Epicardial adipose tissue (EAT) is visceral adipose tissue layered directly over the coronary arteries and is a source of adipocytokines that can stimulate the development of atherosclerosis both via paracrine and endocrine mechanisms [176]. EAT volume is increased in PLWH [177], and is associated with high CAC scores as well as lipodystrophy, serum lipoprotein levels, markers of HIV infection such as CD4 cell count and duration of HAART use [178]. The increase of EAT over time was shown to parallel progression of CAC and to be associated with male sex and CD4 cell count [179]. Finally, both EAT and CAC were shown to be predictive of incident myocardial infarction and death in an observational study of 843 PLWH followed for a median of 2.8 years [180]. Not only is CAC more abundant and prevalent in PLWH, marking the presence of more extensive atherosclerosis, but it also progresses more rapidly than in the general population [181]. Its progression is associated with age, LDL cholesterol serum level, abdominal visceral adipose tissue and CD4 cell count [182]. As noted, there are recurrent factors involved in the development and progression of CAC in PLWH, supporting the notion that traditional and non-traditional risk factors are involved. Nuclear-based molecular imaging provides a more sophisticated approach to detecting subclinical atherosclerosis and accrual of vascular calcification. ^{18}F-sodium fluoride (NaF) is a tracer used in positron emission tomography imaging with high affinity for growing microcrystals of hydroxyapatite [183]. Its primary use is for the detection of bone metastases. However, recent evidence suggests that it avidly adheres on the surface of microcrystals in the context of unstable atherosclerotic plaques [184, 185]. In a recent experiment, areas of high uptake of NaF were detected in 50% of 300 arterial territories in metabolically stable PLWH receiving long-term HAART (Fig. 13.4) [186]. Furthermore, coronary artery uptake of NaF was significantly more frequent than FDG uptake in PLWH [187]. The high prevalence of NaF uptake in PLWH contrasted with a much lower prevalence than in ambulatory patients with diabetes mellitus, considered at equally increased cardiovascular risk [188]. Using molecular imaging another interesting observation was made by Zanni et al. [189] In a proof of concept study in 12 HAART naïve patients, the author compared baseline vascular and systemic (i.e. axillary and mediastinal lymph nodes) inflammation assessed with FDG, as well as biomarkers of immune activation prior to and after initiation of HAART. Patients were treated with a combination HAART and followed for a median of 7 months before imaging and serological markers were repeated. Although systemic inflammation and markers of immune activation decreased, there was parallel increase in vascular inflammation. Therefore, based on these preliminary results, there seems to be a disconnect between the cardiovascular and systemic effects of HAART, supporting the notion that HAART may be responsible for part of the increased risk reported in PLWH.

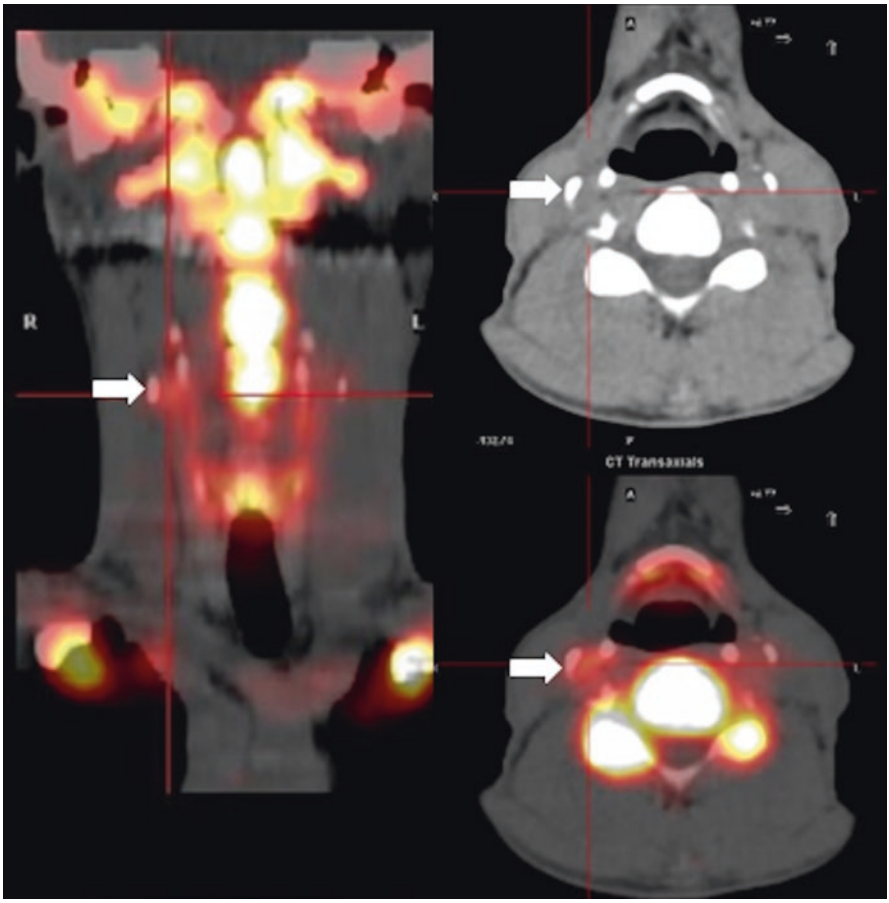

Fig. 13.4 Positron emission tomography/computed tomography merged images on the carotid arteries of a patient living with HIV. The crosshair and white arrows point at an area along the right carotid artery where a calcified lesion shows a high uptake of ^{18}F-sodium-fluoride. (reproduced with permission from Raggi P [186]. under the Creative Commons Attribution 4.0 International License; http://creativecommons.org/licenses/by/4.0/)

Pseudoxanthoma Elasticum

This autosomal recessive disease affects 1:100.000 to 1:25.000 live births and it is due to a defect in the ATP binding cassette-6 (*ABCC6*) gene [190, 191]. The hallmark of the disease is a yellowish discoloration and loss of elasticity of the skin, especially in the neck, nape and axillary areas, visual impairment and vascular calcification [192]. The actual pathophysiology of calcification is unclear, but the defective *ABCC6* gene is likely associated with a low level of the naturally occurring inhibitor of calcification pyrophosphate [193]. Other inhibitors of systemic calcification, such as MGA and fetuin-A, as also seen in patients with CKD [194], may

be defective or reduced. The resulting imbalance between inhibitors of calcification and serum phosphate and calcium levels leads to the creation of an environment favouring the development of systemic calcification. Crystals of amorphous calcification (calcium, hydrogen and phosphate), as well as true hydroxyapatite are found in the context of disrupted elastic fibers in the mid dermis, and in the intima and media of small to mid-size arteries (Fig. 13.5). Calcifications can also be found amid disrupted collagen fibers in the myocardium and pericardium of affected patients. The typical eye lesions are known as angioid streaks of the fundus; despite looking like proliferating vessels they are due to disruption of the Bruch's membrane by fibrocalcific deposits. Eventually the retina is invaded by proliferating neovessels that can lead to severe macular damage and blindness [195]. The most frequent cardiovascular manifestations of pseudoxanthoma elasticum (PXE) are claudication of the upper and lower extremities and transient ischemic attacks and stroke [196, 197], while the risk of myocardial infarction does not appear to be significantly increased above that of the general population. However, an increased risk of ischemic heart disease and vascular calcification has been reported in heterozygous carriers of ABBC6 mutations [198]. Aortic aneurysms, stenosis of the radial and carotid arteries have also been reported, along with asymptomatic calcification of kidneys, spleen, pancreas, breast, testicles and liver. Progressive loss of kidney

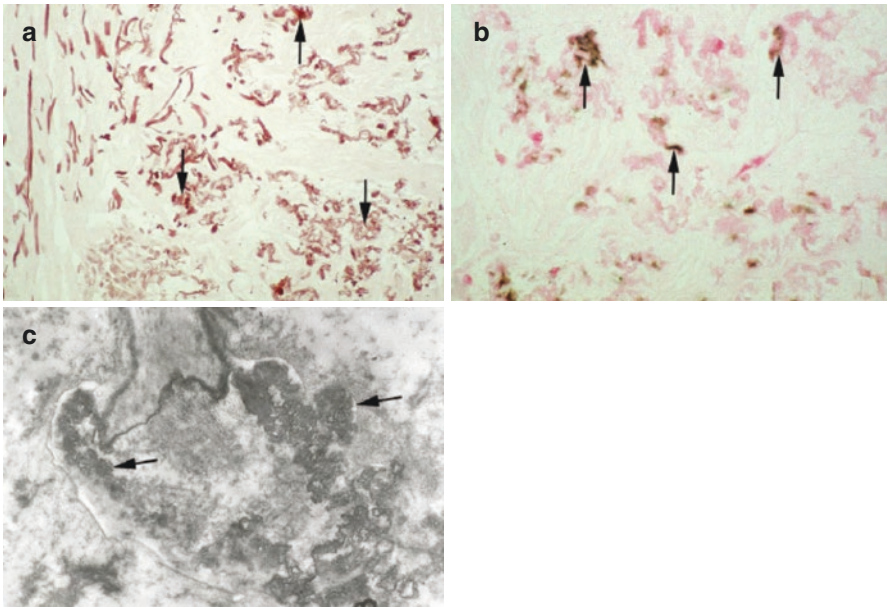

Fig. 13.5 Histological findings in a patient with pseudoxantoma elasticum, showing disrupted (**a**) and calcified (**b**) elastic fibers in the dermis; (**c**) the electronmicroscopy image shows high resolution details of the calcified elastic fibers. (reproduced with permission from Germain DP [191] under the Creative Commons Attribution 4.0 International License; http://creativecommons.org/licenses/by/4.0/)

function has been reported as well as frequent gastrointestinal bleeding. Eventually, increased peripheral resistance and pulse pressure due to medial calcification may also induce brain damage and cognitive impairment leading to another highly undesirable cardiovascular complication [199, 200].

A recent trial demonstrated that slowing of peripheral arterial calcification in PXE can be obtained with etidronate, a bisphosphonate with a mechanism of action similar to that of pyrophosphate normally used for the treatment of osteoporosis [201]. Other potentially effective new therapies are the newly developed direct inhibitors of hydroxyapatite crystals formation [202]. These derivatives of the naturally occurring inhibitor of vascular calcification, myo-inositol hexakisphosphate, have been shown to inhibit inception and growth of cardiovascular calcification in animal experiments independent of the underlying pathophysiologic mechanism [203]. These drugs hold great promise for the treatment of systemic calcification not only in rare diseases, but for patients with advanced CKD [75] and the general population as well.

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