CALCIFIC CORONARY LESIONS

Anupama V Hegde, Asha Moorthy, Abhinay Tibdewal,
Jain T. Kallarakkal, Maddury Jyotsna

INTRODUCTION:

Calcified coronary lesions pose significant challenge to interventional cardiologists. Coronary artery calcification (CAC) results in reduced vascular compliance, abnormal vascular responses and impaired myocardial perfusion [1].

Heavy calcification is a risk factor for failure of traditional balloon angioplasty, associated with major adverse cardiac events after stenting in acute coronary syndrome and decreased success rate for chronic total occlusions. Severe luminal narrowing in heavily calcified vessels may lead to failure of passage of balloons and stents. Fibro calcific lesions are difficult to dilate and may lead to incomplete stent expansion, thus resulting in increased the risk of restenosis as well as stent thrombosis [2, 3].

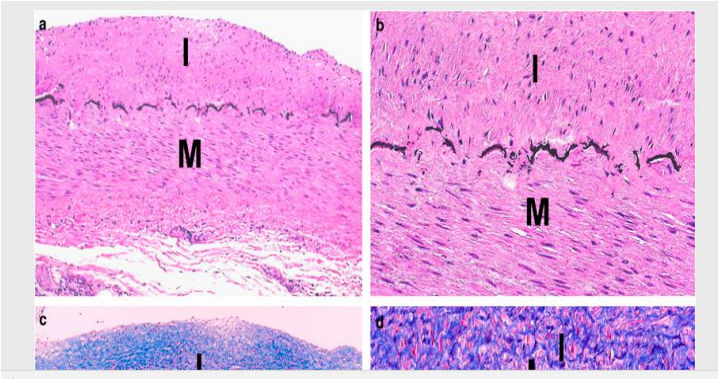
Attempts to dilate these lesions with high pressure balloon inflation increase the risk of extensive dissection and perforation. Techniques to modify moderate to heavily calcified lesions like atherectomy and use of scoring and cutting balloon can improve outcomes in these patients [4, 5].

Pathophysiology

The calcium regulatory mechanisms which control bone formation also control CAC. Alkaline phosphatase which is responsible for early calcium deposition has marker for vascular calcification [6, 7].

Two types of CAC are recognized- atherosclerotic and medial artery calcification [6].Inflammatory mediators and increased lipid content in the atherosclerotic plaques induce osteogenic modification of Vascular smooth muscle cells (VSMC) [8].CAC in media is associated with advanced age, diabetes mellitus and chronic kidney disease (CKD) [6] (Fig 1).

Fig 1: Medial Calcification



Previously medial calcification was thought to be a benign process and now it is found to increase vascular stiffness, thus associated with adverse coronary outcomes [3, 9].Extent of CAC is correlates with plaque burden. Micro calcifications in fibrous caps can cause cavitation-induced plaque rupture [10] (Fig 2).

Fig 2: Micrographs showing the three major epicardial coronary arteries from patients the who died of a sudden cardiac ischemic death.
a).Demonstrates severe atheromatous lesions, calcium deposits of luminal atherosclerotic plaques with hemorrhage, Nhyaline material in the tunic media(H&E,200X). b).photomicrograph of a coronary plaque (H&E,Stain) showing intraplaque hemorrhage with the necrotic core with a form of calcification that result in irregular nodules of calcium(H&E,200X). c).Indicates a prevalently fibrous plaque characterized by a necrotic core associated with a thick fibrous and this photograph of coronary plaques demonstrates multiple necrotic cores (H&E,400X). d).Shows occasionally lymhoplasmacyte-rich infiltrates and fibro proliferative tissue together with areas of free cholesterol crystals(H&E,400X).

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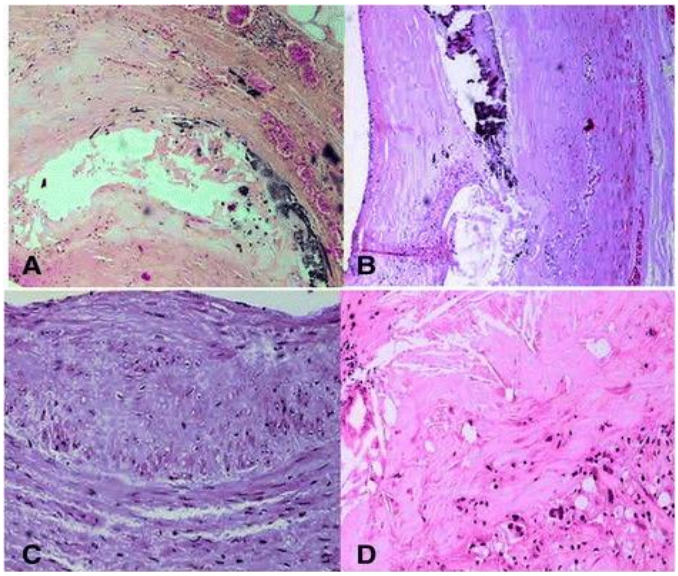
Anupama V Hegde[1], Asha Moorthy[2], Abhinay Tibdewal[3], Jain T. Kallarakkal [4], Maddury Jyotsna[5]
[1]Asst.Professor, Department of cardiology, M.S. Ramaiah Medical College and Hospitals
[2]Professor& HOD of Cardiology,Sri Ramachandra University & Saveetha Medical College,Chennai(Retd)
[3]DM Resident, M.S. Ramaiah Medical College and Hospitals
[4]Interventional Cardiologist, St Mary's Hospital, Thodupuzha, Kerala
5 Professor & HOU-IV, Department of cardiology, NIMS, India
Corresponding author:Anupama V Hegde
Email: anupamadnb@rediffmail.com



Calcific nodules can cause plaque rupture and lead to thrombus formation. Recurrent plaque rupture and haemorrhage with subsequent healing can cause extensive fibro calcific narrowing of the coronary lumen, as seen in patients with chronic stable angina and sudden cardiac death (SCD).

Atherosclerotic calcification begins as early as the second decade of life, just after fatty streak formation. With refined microscopic methods, the lesions of younger adults have revealed small aggregates of crystalline calcium among the lipid particles of lipid cores. Calcific deposits are found more frequently and in greater amounts in elderly individuals and more advanced lesions [11].

Calcium phosphate (hydroxyapatite, Ca3[−PO4]2 −×Ca [OH]2), which contains 40% calcium by weight, precipitates in diseased coronary arteries by a mechanism similar to that found in active bone formation and remodeling. Electron microscopic evidence supports the theory by which hydroxyapatite, the predominant crystalline form in calcium deposits, is formed primarily in vesicles that pinch off from arterial wall cells, analogous to the way matrix vesicles pinch off from chondrocytes in developing bone [12].

A very close spatial association between cholesterol deposits and hydroxyapatite has also been demonstrated. Fitzpatrick et al used in situ hybridization to identify mRNA of matrix proteins associated with mineralization in coronary artery specimens. Using undecalcified sections of post-mortem coronary arteries, they found mineralization to be diffuse, rather than solely confined to the intima, and present in all atherosclerotic plaques[13].

Osteopontin is a phosphorylated glycoprotein, regulated by local cytokines, with known involvement in the formation and calcification of bone. Giachelli and associates[14], using immunochemistry and in situ hybridization, demonstrated that medial smooth muscle cells in uninjured arteries contain very low levels of osteopontin and mRNA.They also showed that basic fibroblast growth factor, transforming growth factor-β, and angiotensin II, all proteins implicated in the arterial injury response, elevated osteopontin expression in confluent vascular smooth muscle cells in vitro.

Recent advances have identified microRNAs (miRs) as key regulators of CAC by directing the complex genetic reprogramming of smooth muscle cells (VSM) and the functional responses of other related cell types relevant for vascular calcification [15].

The transcription factor, osterix, was identified as a miR-125b target, and inhibition of miR-125 was associated with increased Runx2 and osterixexpression, as well as increased alkaline phosphatase activity and SMC calcification. Other studies found that miRsthat targeted Runx2, including miR-133 and miR-204, were down-regulated in murine aorta SMC, leading to calcificationin vitro [16,17].

Members of the bone morphogenetic protein (BMP) superfamily also are known regulators of calcification, and BMP2 and BMP4 are recognized as osteogenic differentiation factors identified in calcified atherosclerotic vessels.

Epidemiology and risk factors

The prevalence of CAC is age and gender-dependent,occurring in over 90% of men and 67% of women olderthan 70 years of age.

Additionally, people who havehigher body mass index, higher blood pressure, abnormal lipids (higher low density lipoprotein or triglycerides, lower high density lipoprotein, or use of lipid-lowering medication), glucose disorders (impaired fasting glucose, untreated or treated diabetes mellitus), a familial history of CAC,chronic kidney disease (CKD), higher fibrinogen level andhigher C-reactive protein level are more susceptible to CAC [18] (table1).

Table 1:High risk factors intimal calcification vs medial calcification

Risk factor	Intimal calcification	Medial calcification
Advanced age	Yes	Yes
Diabetes mellitus	Yes	Yes
Hypertension	Yes	Yes
Male	Yes	No
Cigarette Smoking	Yes	No
Renal etiology		
Dysfunction(↓GFR)	No	Yes
Hypercalcemia	No	Yes
Hyperphosphatemla	Yes	Yes
PTH abnormalities	No	No
Duration of Dialysis	No	Yes

Curtsey of good men et al

GFR=glomerular filtration rate; PTH=Parathyroid hormone.

Calcium intake showed no significant adverse or beneficial effect on vascularcalcification and cardiovascular endpoints. In a cross-sectional analysis of 720 individuals with type 2 diabetes, there was no significant association between dietary calcium intake or calcium supplements with calcified plaque or mortality risk. Rather, calcium supplement use was modestly associated with reduced all-cause mortality in women.

Detection of Coronary artery calcification.

Various modalities have been used to detect coronary calcification with different extent of diagnostic capability. Coronary artery calcification is potentially detectable in vivo by the following methods: plain film roentgenography, coronary arteriography, fluoroscopy, including digital subtraction fluoroscopy, cinefluorography, conventional, helical, and electron beam computed tomography, intravascular ultrasound, magnetic resonance imaging, and transthoracic and transesophageal echocardiography. In current practice, fluoroscopy and EBCT are most commonly used to detect coronary calcification noninvasively, while cinefluorography and IVUS are used by coronary interventionists to evaluate calcification in specific lesions before angioplasty.

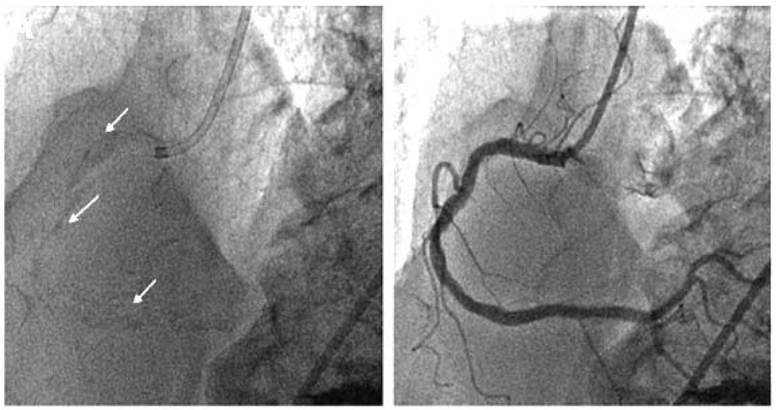
Plain chest roentgenography

Coronary calcification is not easily detected by chest X-ray. The accuracy of detection is only 42%.

Fluoroscopy and conventional coronary angiography

Fluoroscopy has been frequently used in detection of coronary calcification. Angiographic CAC is often classified into 3 groups: none/mild, moderate, andsevere. Severe calcification is most commonly defined as radioopacities seen without cardiac motion before contrast injection, usually affecting both sides of the arterial lumen and moderate calcification as radioopacities notedonly during the cardiac cycle before contrast injection (Fig3).

Fig 3: Example of severe coronary artery calcification as assessed by angiography before (A) and after (B) contrast injection. Note the presence of calcium on both sides of the coronary artery visible on the still image A (arrows)



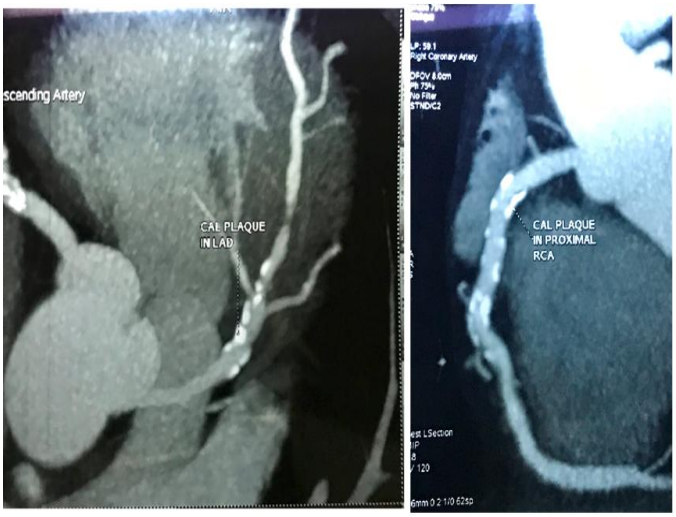
Detrano and Froelicher, summarizes seven studies examining fluoroscopic detection of coronary calcification in 2670 patients undergoing coronary arteriography [19]. Sensitivity in detecting significant stenoses (greater than 50% diameter obstructions) ranged from 40% to 79%, with specificity ranging from 52% to 95%.

Conventional computed tomography

Computed tomography is extremely sensitive in detecting coronary calcification as calcium attenuates X-ray beam. In a study evaluating CT detection of calcium as a marker of significant angiographic stenosis, sensitivities of 16% to 78% were found, depending on which vessel included the calcified plaque. Specificities

were 78% to 100% and positive predictive values 83% to 100%, suggesting that significant coronary artery disease was likely to be present when coronary calcification was seen on CT Fig 4.

Fig 4: CT scan showing the calcium in LAD and RCA



Computed tomography, fluoroscopy, and angiography were compared in a study of 47 patients with a mean age of 57 years. The CT scans showed calcification in 62% of vessels with significant lesions on angiography, whereas fluoroscopy showed calcium in only 35%. In a group without angina, coronary calcification was found by CT in only 4%, and no patient had significant stenosis on coronary arteriography. In this study CT detected calcification in all patients in whom fluoroscopy showed calcification and in all patients in whom angiography showed stenosis. Overall, CT showed calcification in 50% more vessels than did fluoroscopy.

While conventional CT appears to have better capability than fluoroscopy to detect coronary artery calcification, its limitations are slow scan times resulting in motion artifacts, volume averaging, breathing misregistration, and inability to quantify amount of plaque.

Helical or spiral computed tomography

Helical CT has faster scan time and hence is better than conventional CT. Overlap of sections increase the rate of detection of calcium. Shemesh et al reported [20, 21] coronary calcium imaging by helical CT as having a sensitivity of 91% and a specificity of 52% when compared with angiographically significant coronary obstructive disease. Double helical CT was useful in predicting the absence of coronary artery disease in elderly women in the absence of calcification. However, other preliminary data have shown that even at these accelerated scan times, and especially with single helical CT, calcific deposits are blurred due to cardiac motion, and small calcifications may not be seen. Still, helical CT remains superior to fluoroscopy and conventional CT in detecting calcification. Double-helix CT scanners appear to be more sensitive than single-helix scanners in detection of coronary calcification because of their higher resolution and thinner slice capabilities.

Electron Beam Computed Tomography (EBCT)

Electron beam computed tomography uses an electron gun and a stationary tungsten "target" rather than a standard x-ray tube to generate x-rays, permitting very rapid scanning times. For purposes of detecting coronary calcium, EBCT images are obtained in 100 ms with a scan slice thickness of 3 mm. The scans, which are usually acquired during one or two separate breath-holding sequences, are triggered by the electrocardiographic signal at 80% of the RR interval, near the end of diastole and before atrial contraction, to minimize the effect of cardiac motion. The rapid image acquisition time virtually eliminates motion artifact related to cardiac contraction. The unopacified coronary arteries are easily identified by EBCT because the lower CT density of periarterial fat produces marked contrast to blood in the coronary arteries, while the mural calcium is evident because of its high CT density relative to blood. A screening study for coronary calcium can be completed within 10 or 15 minutes, requiring only a few seconds of scanning time. Electron beam CT scanners are more expensive than conventional or spiral CT scanners and are available in relatively fewer sites.

Tanenbaumet al [22], were the first to report use of EBCT for detecting calcific deposits in the coronary arteries. In their series 83% of the patients with significant stenosis, had calcification in at least one vessel on angiography and specify for detection of significant stenosis was 100%. Agatson et al [23] published first large series on EBCT in 1992. Five hundred eighty-four consecutive patients with a mean age of 48 years were included in this study. Patients with a history of coronary artery disease consistently had more calcium than patients of comparable age with no history of coronary artery disease (P<.0001). The authors concluded that EBCT appeared to be an excellent technique for detecting and

quantifying calcification of coronary arteries. The study A larger multicentre study [24]that looked at coronary calcification as an indicator of significant stenosis involved 431 patients with symptoms of coronary artery disease (CAD) (251 men and 180 women; mean age 56 years). In this group, sensitivity of any detectable calcification by EBCT as an indicator of significant stenosis (greater than 50% narrowing) was 92% and specificity 43%. When these CT images were reinterpreted in a blinded and standardized manner, however, specificity was only 31% 82.

In a more recent multicentre study[25]51 of 710 enrolled patients, 427 had significant angiographic disease, and coronary calcification was detected in 404, yielding a sensitivity of 95%. Of the 23 patients without calcification, 83% had single-vessel disease on angiography. Of the 283 patients without angiographically significant disease, 124 had negative EBCT studies.

The presence and amount of calcium detected on EBCT indicates the atherosclerotic burden, however fails to correlate with the region of significant stenosis. in a recent review, Rumberger et al[26]suggested that the magnitude of the calcium score can be used to a high specificity in predicting associated stenosis somewhere within the epicardial coronary system, but the extent of additionally showed that the mean total calcium score calcification at a given anatomic site may be less useful increased with age. in predicting luminal narrowing identified at angiography. Several studies have shown variability in repeated measures of coronary calcium by EBCT; therefore, use of serial EBCT scans in individual patients to track the progression or regression of calcium is problematic.

EBCT is not a very expensive modality and has low radiation exposure. Non- reproducibility of results is the major disadvantage.

Intravascular ultrasound (IVUS)

IVUS is the recent addition in the armamentarium for detection of CAC. The sonograms provide information not only about the lumen of the artery but also about the thickness and tissue characteristics of the arterial wall. Calcification is seen as a hyperechoic area with shadowing: fibrotic noncalcified plaques are seen as hyperechoic areas without shadowing. Friedrich and colleagues [27] reported on the ability of IVUS to detect the histological extent of in situ coronary calcium. Mintz et al [28] compared IVUS to angiography and found that angiography was significantly less sensitive than IVUS in detecting calcification at the site of a target lesion. This finding was confirmed by Tuzcu et al (Fig 5) (Fig 6).

Fig 5: Intimal calcium from 9 to 12º clock - Hyper Echogenic, Brighter than adventitia,

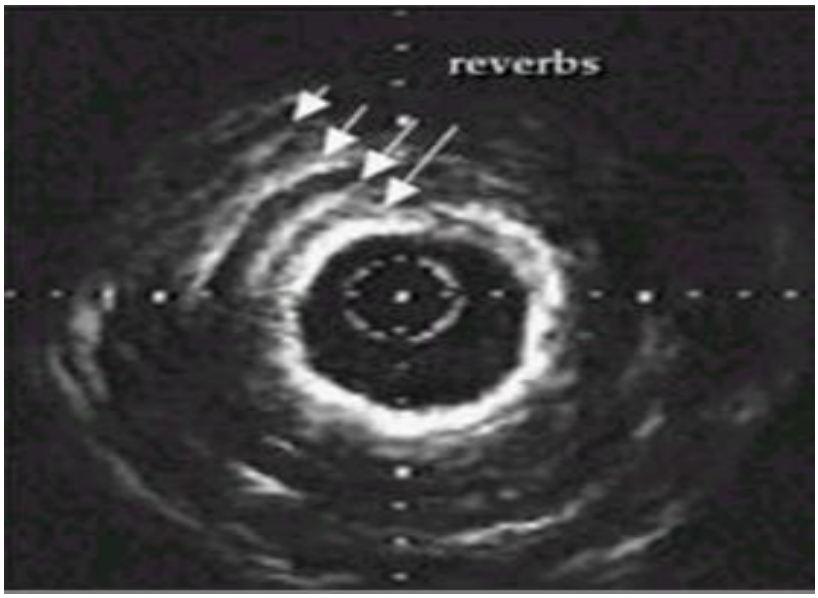
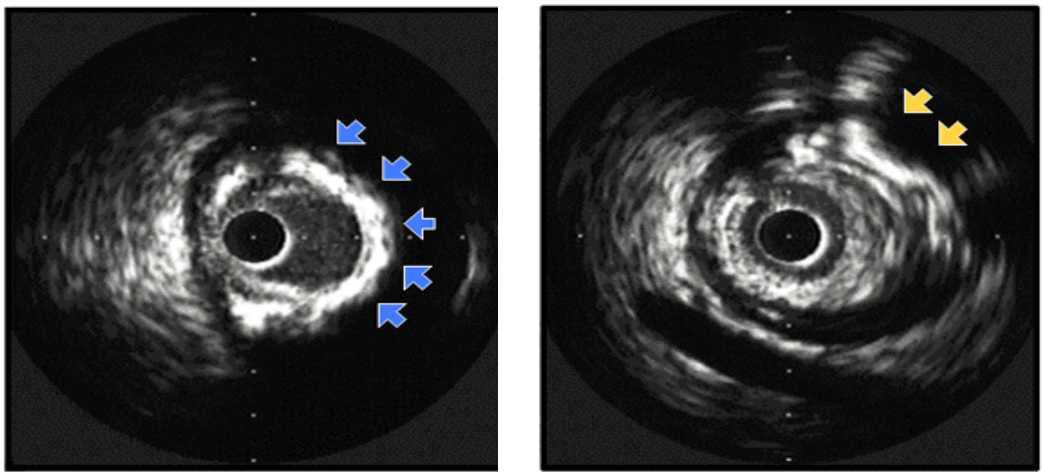


Fig.6: Types of calcium
Superficial calcium Deep calcium



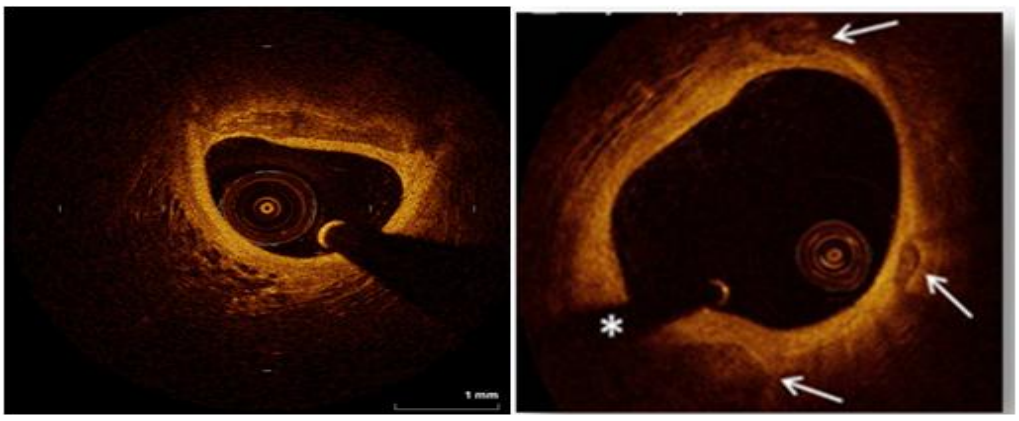
PROSPECT 29study which was a three-vessel evaluation of coronaries with radiofrequency IVUS showed that higher concentration of calcium was associated with larger atherosclerotic burden and higher cardiovascular MACE at the end of three years.

IVUS in comparison to other diagnostic modalities is invasive and presently performed during conventional coronary angiography. It is not useful as screening modality. However IVUS can detect atherosclerotic involvement in patients with normal conventional coronary angiogram. It also helps in assessing the significance of stenosis and type of atherosclerotic plaque, thus useful in selecting appropriate atherectomy devices.

Optical coherence tomography (OCT)

OCT provides higher resolution than grey-scale IVUS and detects calcium as low-intensity, low-attenuation areas with sharp borders. It has sensitivity of 95% and specificity of 97%. As light penetrates calcium OCT can measure the thickness of calcium deposition and measure the volume of calcium. Kunihiro Shimamura and colleagues [30] have shown that OCT provides pivotal information on sites of calcium, with accurate measurements of the minimum distance from the lumen, a major determinant of stent/scaffold under expansion, malapposition and eccentricity (Fig 7).

Fig 7: OCT showing the coronary



(a)Extensive calcium(b) focal calcium at 12, 4 and 6 o'clock position

Magnetic Resonance Imaging (MRI)

The role of MRI in detecting CAC is minimal. It fails to detect micro calcifications. T2-weighted spin-echo (static dark blood) images primarily as a result of the low density of mobile protons in calcified lesions. In addition, because of the sensitivity of MRI to the heterogeneous magnetic susceptibility found in calcified tissue, gradient-echo magnitude (static or dynamic bright blood) images also typically depict calcified lesions as discreet areas of reduced signal intensity.

Transthoracic and Transoesophageal Echocardiogram

Both are useful in detecting valvular calcification, however have limited role in detecting coronary calcification due to limited acoustic window.

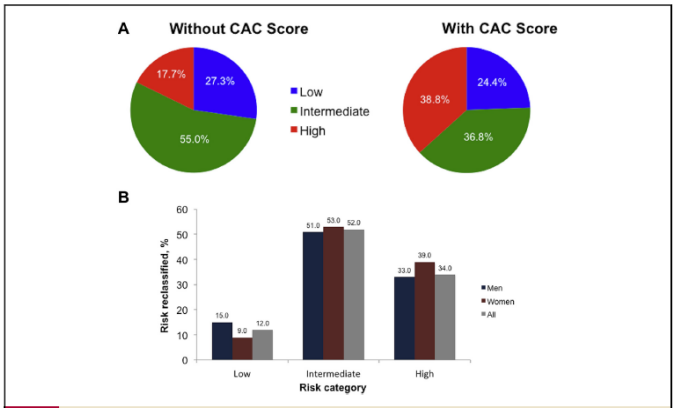
Prognosis

Large – scale observational studies have shown the significance of CT – based calcium scoring in predicting major adverse cardiac events like death and MI in patients with intermediate degree of calcification. Recent ACC/AHA guidelines has given class IIa, level of evidence B, for CAC assessment in asymptomatic patients with intermediate cardiac risk (10-20% risk of developing cardiac events over 10 years). Asymptomatic persons with CAC score of ≥ 400 hounsfield units without traditional risk factors have worst cardiovascular outcomes than those with ≥ 3 risk factors with no CT –detectable CAC [31] (Fig 8).

Fig 8: CAC data from the MESA from Rotterdam study

A) Data from MESA

B) Data from Rotterdam study



Courtesy Mahesh V Madhavan et al JACC 2014 63;1703-14

Integrating functional and anatomical information can improve predictive value of investigating modality. In a recent study that combined single-photon emission computed tomography myocardial perfusion imaging with CAC scoring, overlapping regions with both calcification and poor perfusion strongly predicted MACE [32].Dweck et al [33] employed radiolabelled F-sodium fluoride to visualize regions of active inflammation and calcification on positron emission tomography, offering the promise to detect pre-clinical CAC to facilitate earlier diagnosis, risk factor modification and/or treatment.

Philip Greenland et al[34] in their Prospective observational population-based study, of 1461 asymptomatic adults with coronary risk factors includes participants with at least 1 coronary risk factor (45 years) who underwent computed tomography (CT) examination (screened between 1990-1992, contacted yearly for up to 8.5 years after CT scan, and were assessed for CHD), concluded that high CACS can modify predicted risk obtained from Framingham Risk Score alone, especially among patients in the intermediate risk category in whom clinical decision making is most uncertain.

Therapies for CAC Medical therapy

Various studies have evaluated medical therapy in CAC. St. Francis heart study[35]included >1000 patients with calcium score of > 80th percentile for age and gender – matched cohort who were randomized to 20mg atorvastatin or placebo. There was significant reduction in low- density lipoprotein in atorvastatin arm with no change in CAC score. Calcium-channel blockers, hormonal therapies, phosphate binders and medicinal supplements have shown some benefit in small scale studies [36,37].No studies have investigated whether modulating the receptor activator of nuclearfactor-kappaB or proliferator-activated receptor gamma pathways influence CAC in humans (Table 2).

Table 2: Therapies for CAC medical therapy

First author (ref no)	year	n	design	Intervention	Outcomes
Motro and Shemesh	2001	201	RCT	NifedipinevsHCTZ/amiloride	Nifedipine was associated with significantly reduced coronary calcium progression at 3 years in hypertensive patients.
Chertow et al	2002	200	RCT	Sevelamer vs calcium-based phosphate binder	Sevelamer was associated with significantly lower CAC score progression in hemodialysis patient at 52 weeks
Arad et al	2005	1005	RCT	Atorvastatin vs vitamin C vs Vitamin E vs placebo	Treatment arms did not have significant effect on CAC progression
Houslay et al	2006	102	RCT	Atorvastatin vs placebo	Statins had no significant effect on CAC progression
Manson et al	2007	1064	RCT	Esterogen vs placebo	Women treated with esterogen had significantly lower calcified plaque burden
Maahs et al	2007	478	CS	ACEI/ARBs vs other antihypertensives	Diabetes with albuminuria had significant reduction in CAC progression with ACEI/ARB treatment
Quinibi et al	2008	203	RCT	Calcium acetate/atorvastatin vs sevelamer/atorvastatin	Calcium acetate and sevelamer group had comparable rates of CAC progression at 1 year
Budoff et al	2009	65	RCT	AGE/ vitamin B12 and B6/ folic acid/L-arginine vs placebo	Treatment group experienced significantly lower rates of CAC progression at 1 year
Zeb et al	2012	65	RCT	AGE/CoQ10 vs placebo	AGE/CoQ10 was associated with significantly lower rates of CAC progression at 1 year
AGE-aged garlic extract, RCT-randomized control trial, CS- case series					

Studies targeting medical therapy for coronary artery calcification

PERCUTANEOUS CORONARY INTERVENTION

The major problem encounter during the PCI of the calcific coronary lesions are

1. Difficulty in stunt delivery
2. Stent under expantation
3. Stent dislodgement.

So imaging is advisable in these circumstances

Special interventional procedures required in the presence of significant calcium in the artery or different from the route angioplasty such as very high pressure balloon dilatations, rotablation etc.

BALLOON ANGIOPLASTY AND STENTING

CAC reduces the rate of success of balloon angioplasty and stenting and increase complications. Non-compliant fibro calcific lesions need high pressure balloon dilatation resulting in increased risk of coronary dissection and thrombus formation. Moreover, the force applied by the balloon over the vessel wall may not be uniform due to differential deposition of calcium across the vessel wall resulting in further vessel dissection and acute closure of the distal vessel. MI, restenosis and MACE. Severely calcified vessel may not allow the balloon to cross the lesion leading to procedure failure. Angiographic measures of procedural success, such as acute gain and diameter stenosis, are often worse in calcified lesions [38, 39, 40]. Calcified lesions are also associated with particulate embolization, resulting in increased rates of peri-procedural myonecrois.

Stent implantation improves luminal size, acute and long-term outcomes compared to balloon angioplasty alone with drug- eluting stents (DES) being better than bare metal stents (BMS). However stent under-deployment, scaffold malapposition and asymmetric expansion are common in severely calcified lesions [61].Some studies have reported similar incidence of restenosis and revascularization in both calcified and non-calcified lesions. Conversely few studies have reported higher rate of stent restenosis in DES and requirement of repeat revascularization in severely calcified lesions compared to non-calcified lesions. Potential risk factors for restenosis and repeat revascularization include stent under-expansion, damage of DES polymer coats by calcified lesions, or adjunctive use of other devices (e.g., rotational atherectomy [RA]), that might directly promote neo-intimal hyperplasia [40,62].

Percutaneous coronary intervention using devices to improve coronary lumen

It is necessary for contemporary interventionists to be well versed in techniques of modifying moderate to heavily calcified lesions. Techniques of debulking include percutaneous trans luminal rotational atherectomy (PTRA), orbital atherectomy (OA), scoring balloon (SBA) and cutting balloon atherectomy (CBA), and laser excimer coronary atherectomy(ELCA).

Percutaneous transluminal rotational atherectomy (PTRA)

High-speed rotational atherectomy, as a mechanism of ablating atheromatous plaque by slowly advancing a spinning, diamond-coated burr was introduced by David Auth in 1980s and approved by FDA in 1993. The procedure utilizes the principle of "differential cutting", in which atherectomy device preferentially ablates inelastic tissue composed of fibrotic or calcific tissue and is safely deflected from more elastic tissue (Fig 10) (Fig 11).

Fig 10: Different Rota Burr sizes

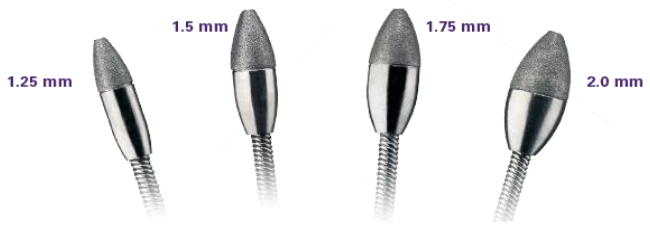
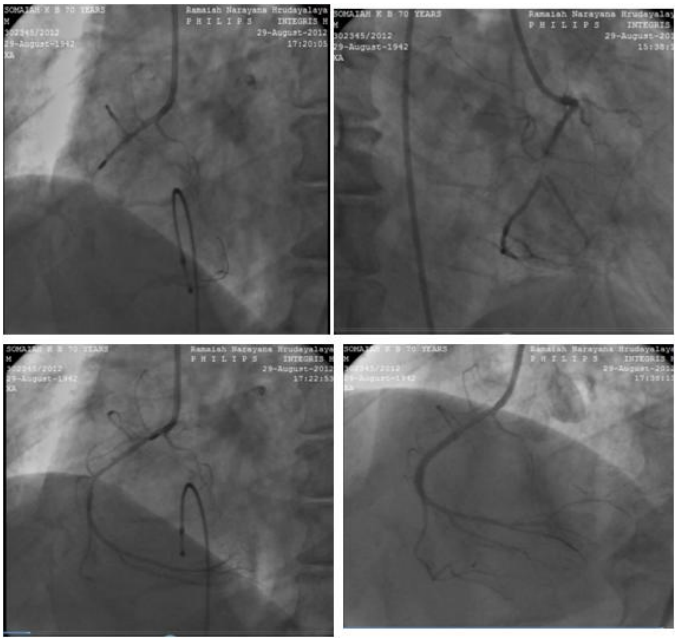


Fig 11:PCI in calcific coronary lesions
a) Calcific coronary lesion in RCAb)Rota ablation with 1.5 BURR c) Post Rota ablation d) Post stenting



In a pilot randomized study, involving 64 patients, Guerin and colleagues [47]compared percutaneous transluminal angioplasty (PTA) with PTRA. They found that there was no significant increase in Q-wave MI, numerically significant non-Q-wave- MI in PTRA group and no significant difference in success rate.

Angiographic analysis at 6 months demonstrated no significant difference in restenosis between the two groups.

Excimer Laser, Rotational atherectomy and Balloon Angioplasty Comparison (ERBAC) study[48] revealed that despite similar luminal gain and procedural success in both groups, there was non-significant increase in restenosis in PTRA group (57%vs 47%, p=0.14) and significant increase in TVR in PTRA and laser groups compared to PTA (46%vs 37%, p= 0.04).

The Comparison of Balloon versus Rotatiomal Atherectomy (COBRA) [49] concluded that the need for stent implantation for inadequate PTRA or PTA lumen gain for bailout was higher in PTA alone group (9.6%vs2.0%).

The Angioplasty versus Rotational atherectomy for the Treatment of Diffuse In-stent Restenosis Trial (ARTIST) [50] demonstrated attend towards more periprocedural complications in PTRA group (composite of death, MI, CABG, PTCA, tamponade and puncture site complications: 14%vs 8%, p=0.09), at 6 months' event-free survival was worse in PTRA group (79.6vs91.1%. p=0.0019). PTA alone demonstrated better efficacy.

The Rotational Atherectomy prior to TAXUS Stent Treatment for Complex Native Coronary Artery Disease (ROTAXUS)[51] concluded that in-spite of better immediate procedural success in PTRA group, 9 months angiographic study revealed no significant difference in diameter stenosis or restenosis in both the groups, though in-stent late-luminal loss favored PTA alone group and hence PTA with default PTRA should remain default strategy prior to stent deployment.

Precations to be taken during Rotablation in calcific coronary lesions- usually the size of bur is determined by the size of artery but in seriously calcific coronary lesion better to take a smaller sized bur when there is significant calcium. Exception is if 1.5 of bur of rota is not able to cross the lesion then if we down size the bur to 1.25 then it may cross the lesion but it gets stuck after crossing the lesion and taking out the bur may difficult. So it's better to over size than under sizing. Preclinical studies suggest that slow flow is less frequently observed with low-speed than high-speed RA because of less platelet aggregation with low-speed RA. Latest study Sakakura et al showed there is no reduction in the incidence of slow flow following low-speed RA as compared with high-speed RA (51 A).

Orbital Atherectomy

The Diamondback 360°coronary orbital atherectomy device (OAS) was recently approved by FDA. Based on the principles of differential sanding and centrifugal force, the system consists of an eccentrically mounted, diamond-coated "crown"that orbits over a guide-wire. A thin layer of plaque is "sanded"off with each pass of the device and elastic tissue flexes away from the crown. The elliptical orbit of the device allows the micro debris to disperse as opposed to rota burr. The particle size generated by the orbital atherectomy is about 2 microns which is much smaller than from rotablation (5 microns).

Fig 12: Orbiter Device

ORBIT trial [52] revealedreductions in diameter stenosis from 85.6% to 40% with use of OAS alone.ORBIT II [53] enrolled443 patients with severely calcified lesions to assess safety as well as efficacy of OAS. 3.4% demonstrated significant dissection, 1.8% had perforation, 0.9% had slow/no reflow and 1.8% developed abrupt closure. Primary efficacy end-point (stent delivery with residual stenosis <50% and freedom from 30-day MACE) was appreciated by 88.9% of patients and primary safety end-point of freedom from 30-day mace was seen in80.6% of the patients.

Scoring balloon angioplasty (SBA)

SBA, refers to inflation of a balloon catheter with one or more metallic edges coming in contact with vessel wall on balloon dilatation. The leading metallic edge is designed to cut or score the plaque, causing a cleavage plane that theoretically enhances more controlled lumen dilation than routine balloon angioplasty.

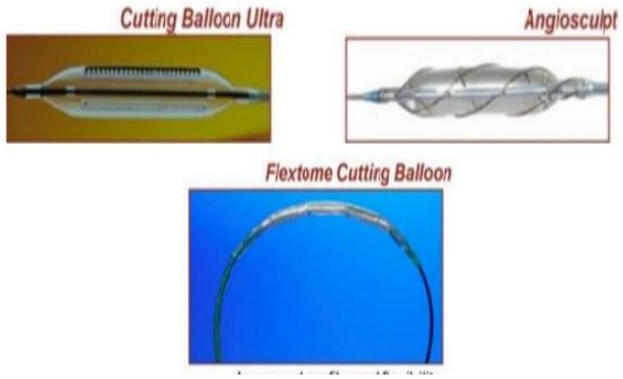
Cutting balloon angioplasty (CBA)

CBA was developed by Barath et al in early 1990s [54].The balloon material covers three or four

longitudinally placed microsurgical blades that angle outward toward the vessel wall when inflated and become parallel to vessel wall when deflated. These edges are sharp and meant to penetrate the vessel wall in controlled manner. On inflation the blades are deployed at 60 degrees from the balloon and create controlled cuts in the plaque on contact with the vessel wall.

The Flex-tome balloon system and the Angio-sculpt balloon catheter are currently available cutting balloons (Fig 13).

Fig 13: Devices for cutting balloon angioplasty.



Hara and colleagues[55], in their study which compared PTA with CBA revealed that 67% lumen expansion was due to vessel area expansion and 33% due to plaque shift in PTCA group as against 45% due vessel stretch and 55% due to plaque compression in CBA group.

Several registries and randomized trials have demonstrated reasonable success and less bail-out stenting with CBA. A meta- analysis of 4 randomized trial of cutting balloon atherectomy versus balloon angioplasty (pre- stent era) in calcified and noncalcified lesions showed that there was no difference in restenosis rate in either group but higher rate of perforation and MI was noted in CBA group[60].

Excimer Laser Atherectomy (ELCA)

ELCA was approved by FDA in 1992 for human use. The application of laser energy to the vessel wall results in photochemical, photomechanical and photothermal interactions that produce gas vapour and acoustic shock waves within the tissue that ultimately cause debulking effect. ELCA is used in uncross able chronic total occlusions, balloon-resistant calcified lesions and under-expanded stent lesions.

The multi-centre Amsterdam- Rotterdam (AMRO) trial [56]revealed higher degree of late luminal loss and non-significant but higher restenosis in ELCA group compared to PTA at 6-month angiographic follow-up.

ERBAC trial showed that 18.5% of the lesions could not be crossed by ECLA and required crossover to PTA.

Coronary Artery Bypass Graft (CABG)

Calcified vessels pose a technical challenge to operating surgeons. Severely calcified lesions are associated with atheroembolic episodes and incomplete revascularization, thus, causing higher MACE in high risk patients. Patients with CAC are prone to develop saphenous vein calcification resulting in early and late graft failure [57, 58].

ACUITY trial (Acute Catheterization and Urgent Intervention Triage strategy) [59]showed that CAC was independently associated with death, MI and MACE at the end of one year in patients undergoing CABG.

CONCLUSIONS

CAC poses a challenge to both treating interventional cardiologists and surgeons. Severe calcification of coronaries is associated with higher procedural failure rates and MACE. Improved diagnostic modalities andadjunctive devices that help in debulking, plaque modification and lumen preparation prior to stenting improve procedural success. Use of DES has improved outcomes of PCI in patients with CAC. Deeper understanding of pathophysiology of CAC and its association with advanced atherosclerosis is necessary. Improvement in early diagnosis of CAC and treatment armamentarium can improve prognosis in these patients.

REFERENCES

1. Wang L, Jerosch-Herold M, Jacobs DR Jr., et al. Coronary artery calcification and myocardial perfusion in asymptomatic adults: the MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2006; 48:1018–26.

2. Genereux P, Madhawan MV, Mintz GS et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: pooled analysis from Horizons –AMI and ACUITY trials. J Am Coll Cardiol 2014.

3. Hsu JT, Kyo E, Chu CM et al. Impact of calcification length ratio on the intervention for chronic total occlusions. Int J Cardiol 150:135-141, 2011 .

4. Virmani R, Farb A, Burke AP, Coronary angioplasty from the perspective of atherosclerotic plaque: morphologic predictors of immediate success and restenosis. Am Heart J 127: 163-179. 1994.

5. Krishnaswamy A. Factors associated with stent thrombosis causing ST-segment elevation myocardial infarction. American Heart association Scientific Sessions 2013.

6. Demer LL, Tintut Y. Vascular calcification: pathobiology of a multifaceted disease. Circulation 2008; 117:2938–48.

7. Johnson RC, Leopold JA, Loscalzo J. Vascular calcification: pathobiologicalmechanisms and clinical implications. Circ Res 2006; 99: 1044–59.

8. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. Arterioscler Thromb Vasc Biol 2004; 24:1161–70.

9. Sangiorgi G, Rumberger JA, Severson A, et al. Arterial calcification andnot lumen stenosis is highly correlated with atherosclerotic plaque burdenin humans: a histologic study of 723 coronary artery segments usingnondecalcifying methodology. J Am Coll Cardiol 1998; 31:126–33.

10. Kelly-Arnold A, Maldonado N, Laudier D, et al. Revised microcalcification hypothesis for fibrous cap rupture in human coronaryarteries. Proc Natl Acad Sci U S A 2013; 110:10741–6.

11. Stary HC. Composition and classification of human atherosclerotic lesions. Virchows Arch A PatholAnatHistopathol.. 1992;421:277-290. Cross Ref Pub Med.

12. Bostrom K, Watson KE, Horn S, Wortham C, Herman IM, Demer LL. Bone morphogenetic protein expression in human atherosclerotic lesions. J Clin Invest. 1993; 91:1800-1809.

13. Fitzpatrick LA, Severson A, Edwards WD, Ingram RT. Diffuse calcification in human coronary arteries: association of osteopontin with atherosclerosis. J Clin Invest. 1994; 94:1597-1604.

14. Giachelli CM, Bae N, Almeida M, Denhardt DT, Alpers CE, Schwartz SM. Osteopontin is elevated during neointima formation in rat arteries and is a novel component of human atherosclerotic plaques. J Clin Invest. 1993;92:1686-1696.

15. Leopald J.MicroRNAs regulates vascular medial calcification. Cells 2014;3:963-980.

16. Goettsch C, Rauner M, Pacyna N, et al. MiR-125 regulates calcification of vascular smooth muscle cells. Am J Pathol 2011.

17. Liao XB, Zhang ZY, Yuan K, et al. MiR-133a modulates osteogenic differentiation of vascular smooth muscle cells. Endocrinology 2013;154:3344-3352.

18. Wong ND, Kouwabunnat D,Vo AN et al. Coronary calcium atherosclerosis by ultrafast computed tomography in asymptomatic men and women; relation to age and risk factors. AmHeart J 1994; 127:422-30.

19. Detrano R, Wong N, French WJ, Georgiou D, Young EK, Brezden O, Brundage B. Prevalence of coronary calcific deposits in 1,000 high risk, asymptomatic individuals. Eur Heart J. 1993; 13:P1065. Abstract.

20. Shemesh J, Apter S, Rozenman J, Lusky A, Rath S, Itzchak Y, Motro M. Calcification of coronary arteries: detection and quantification with double-helix CT. Radiology.. 1995;197:779-783.PubMed.

21. Shemesh J, Tenenbaum A, Fisman EZ, Apter S, Rath S, Rozenman J, Itzchak Y, Motro M. Absence of coronary calcification on double-helical CT scans: predictor of angiographically normal coronary

arteries in elderly women. Radiology.. 1996;199:665-668.PubMed.

22. Tanenbaum SR, Kondos GT, Veselik KE, Prendergast MR, Brundage BH, Chomka EV. Detection of calcific deposits in coronary arteries by ultrafast computed tomography and correlation with angiography. Am J Cardiol. 1989;63:870-872.CrossRefPubMed.

23. Agatston AS, Janowitz WH. Coronary calcification: detection by ultrafast computed tomography. In: Stanford W, Rumberger JA, eds. Ultrafast Computed Tomography in Cardiac Imaging: Principles and Practice. Mt Kisco, NY: Futura; 1992:77-95.

24. Breen JB, Sheedy PF II, Schwartz RS, Stanson AW, Kaufmann RB, Moll PP, Rumberger JA. Coronary artery calcification detected with ultrafast CT as an indication of coronary artery disease. Radiology.. 1992;185:435-439.PubMed.

25. Georgiou D, Budoff M, Kennedy J, Bleiweis MS, Wolfkiel C, Brody AS, Stanford W, Shields P, Brundage BH. The value of ultrafast CT coronary calcification in predicting significant coronary artery disease compared to angiography: a multicenter study. Circulation. 1993;88(suppl I):I-639. Abstract.

26. Rumberger JA, Sheedy PF, Breen JF, Fitzpatrick LA, Schwartz RS. Electron beam computed tomogram Cphy and coronary artery disease: scanning for coronary artery calcification. Mayo Clin Proc. 1996;71:369-377.CrossRefPubMed.

27. Friedrich GJ, Moes NY, Muhlberger VA, Gabl C, Mikuz G, Hausmann D, Fitzgerald PJ, Yock PG. Detection of intralesional calcium by intracoronary ultrasound depends on the histologic pattern. Am Heart J.. 1994;128:435-441.CrossRefPubMed.

28. Mintz GS, Douek P, Pichard AD, et al. Target lesion calcification in coronary artery disease; an intravascular ultrasound study. J Am Coll Cardiol 1992;20:1149-56 .

29. Xu Y, Mintz GS, Tam A, et al. Prevalence, distribution, predictors and outcomes of patients with calcified nodules in native vessel coronary arteries: a 3-vessel intravascular ultrasound analysis fronm Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT). Circulation 2012;126:37-46 .

30. Kunihiro Shimamura, MD; Giulio Guagliumi, MD, Optical Coherence Tomography for Online Guidance of Complex Coronary Interventions. Circ J 2016;80:2063-72.

31. Greenland P, LaBree L, Azen SP,et al. Coronary artery calcium score combined with Framingham Score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-15.

32. Ghadri JR, Fiechter M, Fuchs TA et al. Registry for the Evaluation of the PROgnostic value of a novel integrated imaging approach combining Single Photon Emission Computed Tomograhy with coronary calcification imaging (REPROSPECT). Eur Heart J Cardiovasc Imaging 2013;14:374-80.

33. Dweck MR, Chow MW, Joshi NV et al. Coronary arterial 18 F sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol 2012;59:1539-48.

34. Phillip G, LaBree L, Stanley P Azen et al. Coronary Artery Calcium Score Combined With Framingham Score for Risk prediction in Asymptomatic Individuals. JAMA 2004;291:210-215.

35. Arad Y, Spadaro LA, Roth M et al. Treatment of Asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C and vitamin E; the St. Francis Heart Study, randomized clinical trial. J Am Coll Cardiol 2006;46: 166- 72.

36. Motro M, Shemesh J. Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. Hypertension2001;37:1410-3.

37. Manson JE, Allison MA, Rossouw JE et al. Esterogen therapy and coronary artery calcification.N Eng J Med 2007; 356:2591-602.

38. Tan SK, Sulke N, Taub N, Sowton E. Clinical and lesion morphologic determinants of coronary

angioplasty success and complications;current experience. J Am Coll Cardiol1995;25:855-65.

39. Hoffmann R, Mintz GS, Popma JJ et al. Treatment of calcified coronary lesions with Palmtz-Schatz stents. An intravascular ultrasound study. Eur Heart J 1998;19:1224-31 .

40. Kawaguchi R, Tsurugaya H, Hoshizaki et al. Impact of lesion calcification on clinical and angiographic outcomes after sirolimus eluting stent implantation in real-world patients : Cardiovasc Revasc Med2008;9:2-8.

41. Chertow GM, Burke SK, Raggi P, for the Treat to Goal working group.Sevelmer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int2002;62:245-52.

42. Houslay ES, Cowell SJ, Prescott RJ et al. Progressive coronary artery calcification despite intensive lipid-lowering treatment;a randomized control trial. Heart 2006;92:1207-12.

43. Maahs DM, Snell- Burgeon JK, Kinney GL et al. ACEI/ARB treatment in type 1 diabetes patients with albuminuria associated with lower odds of progression of coronary artery calcification. J Diabetes Complications 2007;21:273-9.

44. Quinibi W, Moustafa M, Muenz LR et al. A 1-year randomized trial of calcium acetate versus Sevelamer on progression of coronary artery disease in hemodialysis patients with comparable lipid control; the Calcium Acetate Renagel Evaluation-2 (CARE-2) study . Am J Kidney Dis 2008;51:952-65.

45. Budoff MJ, Ahmadi N, Gul KM et al. Aged garlic extract supplemented with B vitamins, folic acidand L-arginine retards the progression of subclinical atherosclerosis; a randomized clinical trial. Prev Med 2009;49:101-7.

46. Zeb I, Ahmadi N, Nasir K et al. Aged garlic extract and coenzyme Q10 have favourable effect on inflammatory markers and coronary atherosclerosis progression; a randomized clinical trial. J cardiovasc Dis Res 2012; 3:185-90.

47. Guerin Y, Spaulding C, Desnos N et al;rotational atherectomy with adjunctive balloon angioplasty versus conventional percutaneous transluminal coronary angioplasty in type B2 lesions; results of a randomized study Am Heart J 1996;131:879-883.

48. Reifart N, Vandormael M, Krajcar M, et al. Randomized comparison of angioplasty of complex coronay lesions at a single centre. Excimer laser rotational atherectomy and balloon angioplasty comparison (ERBAC) study. Circulation 1997;96:91-98.

49. Dietz U, Rupprehct HJ, Ekinci O, et al. Angiographic analysis of immediate and long-term results of PTCR versus PTCA in complex lesions (COBRA). Catheter Cardiovasc Interv 2001;53: 358-67.

50. Vom Dahl J, Dietz U, Haager PK, et al; Rotational atherectomy does not reduce recurrent in-stent restenosis;Results of Angioplasty versus Rotational Atherectomy for Treatment of diffuse In-stent restenosis Trial (ARTIST) Circulation 2002;105:583-588.

51. Abdel –Wahab M, Richardt G, Joachim Buttner H et al. High-speed Rotational Atherectomy before Paclitaxel –eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Atherectomy Prior to Taxus Stent Treatment for Complex Native Coronary Artery Disease) trial. JACC Cardiovasc Interv 2013;6:10-19.

51 A.Kenichi Sakakura MD, Hiroshi Funayama MD, Yousuke Taniguchi MD,Yoshimasa Tsurumaki MD, Kei Yamamoto MD, Mitsunari Matsumoto MD, Hiroshi Wada MD, Shin-ichi Momomura MD, Hideo Fujita MD The incidence of slow flow after rotational atherectomy of calcified coronary arteries: A randomized study of low speed versus high speed Catheterization and Cardiovascular Interventions Volume 89, Issue 5, April 2017, Pages 832–840.

52. Parikh K, Chandra P, Choksi N et al. Safety and feasibility of Orbital atherectomy for the treatment of calcified coronary lesions: the ORBIT I trial. Catheter Cardiovasc Interv 2013; 81:1134-1139.

53. Chambers JW, Feldman RL, Himmelstein SI, et al. Pivotal trial to evaluate the safety and efficacy of the orbital atherectomy system in treating de novo, severely calcified coronary lesions (ORBIT II). JACC Cardiovasc Interv 2014;7:510-518.

54. Barath P, Fishbin MC, Vari S et al. Cutting balloon – a novel approach to percutaneous angioplasty. Am J Cardiology 1991;68:1249-1252.

55. Hara H, Nakamura M, Asahara T et al. Intravascular ultrasonic comparisons of mechanisms of vasodilatation of cutting balloon angioplasty versus conventional balloon angioplasty Am J Cardiol 2002;89:1253-1256.

56. Appelmann YE, Piek JJ, Strikwerda S, et al: Randomized trial of excimer laser angioplasty versus balloon angioplasty for treatment of obstructive coronary artery disease. Lancet 1996;347:79-84.

57. Osswald B, Blackstone E, Tochtermann U et al. Does the completeness of revascularization affect early survival after coronary artery bypass grafting in elderly patients? Eur J Cardiothorac Surg 2001;20:120-6.

58. Nakayama Y, Sakata R, Ura M et al. Coronary artery bypass grafting in dialysis patients. Ann Thrac Surg 1999;68:1257-61.

59. Ertelt K, Genereux P, Mintz GS, et al. Impact of the severity of coronary artery calcification on clinical events in patients undergoing coronary artery bypass grafting (from the Acute Catheterization and Urgent Intervention Triage Strategy Trial) Am J Cardiol 2013; 112:1730-7.

60. Bittl JA, Chew DP, Topol E et al, Meta- analysis of randomized trials of percutaneous transluminal coronary angioplasty versus atherectomy, cutting balloon atherectomy or laser angioplasty. J Am Coll Cadiol 2004;43:936-42.

61. Mosseri M, Satler LF, Pichard AD et al. Impact of vessel calcification on outcomes after coronary stenting. Cardiovasc Revasc Med 2005;6:147-53.

62. Kuriyama N, Kobayashi Y, Yamaguchi M, Shibata Y. Usefulness of rotational atherectomy in preventing polymer damage of everolimus-eluting stent in calcified coronary artery. J Am Coll Cardiol Intv 2011;4:588-9