Comparison of Clinical Outcomes of Calcified and Non-Calcified Coronary Artery Lesion Intervention Under IVUS Guidance

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ABSTRACT

Objective: To evaluate the clinical results of intravascular ultrasound (IVUS)-guided intervention for calcified coronary artery lesions.

Study Design: Observational study.

Place and Duration of the Study: Department of Medicine, The Aga Khan University Hospital, Karachi, from January 2013 to January 2020.

Methodology: A cohort of 134 consecutive patients who underwent intravascular ultrasonography-guided assessment of coronary arteries were included. Patients were divided into two groups: those with coronary artery calcification (CAC, n=77) and those without (non-CAC, n=57). The two groups were compared for their clinical characteristics, management, in-hospital events, follow-up, and major adverse cardiovascular events (MACEs).

Results: The mean follow-up duration was 40.3 ± 30.1 months. Most of the patients were male (n=97, 72.3%), and the mean age was 63.1 ± 12.9 years. In the CAC group, age was the most common risk factor, followed by dyslipidaemia (n=68, 88%), hypertension (n=64, 83%), and Diabetes mellitus (n=44, 57%). CAC group patients were more commonly presented with acute coronary syndrome (n=59, 76.6%), had prior PCI (n=40, 52%), had more LM disease (n=34, 44%, p=0.005), and a significant number of prior stent-ISR (n=27, 35%, p=0.024). Those who had CAC had higher MACE.

Conclusion: Patients with CAC had more co-morbidities and commonly presented with acute coronary syndrome. MACEs frequency was recorded higher in the CAC group although the results were not statistically significant.

Key Words: *Coronary artery calcification, Intravascular imaging, Coronary artery disease, Target vessel revascularisation, Percutaneous coronary intervention*.

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INTRODUCTION

Coronary artery calcification (CAC) corresponds with the amount and degree of plaque burden, as well as its composition, and is related to major adverse cardiac events.[1] Pathological evolution of coronary artery calcification shows that it begins as microcalcifications and progresses into larger calcium fragments, which eventually lead to sheet-like deposits up to 3mm or more, concurrently with the progression of plaque.[2,3]

To assess the coronary calcium burden, different modalities have been used, including electron beam computed tomography (EBCT), coronary angiogram, intravascular ultrasound (IVUS), and optic coherence tomography (OCT).

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The sensitivity of IVUS for detecting coronary calcium varies from 64% in micro-calcification to 90% in the detection of dense coherent calcification, while its specificity is 100%.[4] Along with CAC's diagnostic and prognostic values, the calcium content in a lesion also determines the intervention strategies to be adopted for revascularisation.[5]

Patients with a higher calcium burden are more likely to develop anginal symptoms and major adverse cardiovascular events. Percutaneous coronary intervention (PCI) of a calcified lesion sometimes has suboptimal results in terms of stent mal-apposition and suboptimal stent expansion, higher complication rates like stent fracture and coronary dissection, and poor long-term clinical prognosis than in non-calcified lesion.[6-8]

There is a higher prevalence of coronary artery disease among the South-Asian population. Most of the studies on IVUS utilisation in calcified lesions had been conducted on the European/North American population. There was scarce data on the use of IVUS in calcified coronary artery intervention, especially in low-middle-income countries like Pakistan. The objective of this study was to evaluate the clinical results of intravascular ultrasound (IVUS)-guided intervention for calcified coronary artery lesions.

METHODOLOGY

Before conducting the study, an approval was taken from the Ethical Review Committee (ERC), Department of Medicine, at The Aga Khan University Hospital, Pakistan. The patients included in the study were 134 who underwent IVUS imaging at the time of their coronary angiography during a period from January 2013 to March 2020. These patients were then categorised into non-CAC and CAC groups based on the absence or presence of calcification in at least more than a quadrant on IVUS assessment, respectively. Using the Health Information Management Service, the data were obtained from the patient's medical records on a pre-designed proforma. Age, gender, comorbidities, mode of initial presentation to the hospital, procedural information, data related to IVUS, coronary angiography and percutaneous coronary intervention (PCI), discharge medicines, and in-hospital and follow-up events were all included as variables. Informed consent and the last follow-up details were obtained by examining medical records and conducting telephone interviews.

Those above 18 years of age, who were lost to follow-up, who could not be contacted *via* phone calls or e-mails, and all those patients with lower than one quadrant calcification on IVUS were excluded.

All the patients who underwent coronary angiogram with IVUS were reviewed by the primary cardiology team and all the clinical, demographic, and prior cardiac procedural details were obtained. Patients were transferred to the Catheterisation-laboratory after taking informed permission for the procedure, where they underwent a coronary angiography followed by IVUS. IVUS (greyscale) imaging assessment was performed using a 20 MHz, 2.9 French Eagle Eye® Platinum RX digital IVUS catheter (Philips Volcano San Diego, CA, USA) and after that, all the data were collected. The interventional cardiologist and radiographers interpreted the IVUS images, and all the data were transferred to DVD-ROM for its offline interpretation. During the time of this study, this entire procedure was carried out by a group of specialists/experts, consisting of an interventional cardiologist, interventional training fellows, and a Catheterisation-laboratory radiographer. Complete data was then reviewed with a certified standard software. The value of external elastic membrane (EEM) and minimum luminal area (MLA) were assessed proximal, at and distal to the lesion. EEM minus lumen CSA was used to estimate plaque and media cross-sectional area (CSA). At the MLA, a cross-sectional analysis was performed.

Patients undergoing PCI were all pre-medicated with dual antiplatelets. Unfractionated heparin was used during PCI to achieve therapeutic activated clotting time, and the procedure was carried out in accordance with standard PCI guidelines.

The mean period of follow-up was 40.3 ± 30.1 months. The clinical events at the follow-up were recorded by evaluating the patient's hospital medical records, hospital admission, clinic visits, and telephone interviews with each patient or one of their immediate family members if he/she was deceased or unreachable. Cardiovascular mortality, all-cause mortality, life-threatening arrhythmias, myocardial infarction (MI), target vessel revascularisation (TVR), and hospitalisations secondary to heart failure and stroke, were all the observed events. MI was described as typical anginal symptoms, increased serum troponin level with or without ischemic ECG abnormalities. Life-threatening arrhythmias included any evidence of ventricular tachycardia or ventricular fibrillation on the patient's ECG or device interrogation. TVR was defined by PCI or bypass grafting of restenosis of previously performed IVUS-guided PCI.

STATA software was used for the data analysis (version 14.2; StataCorp). The quantitative variables were allocated a mean and standard deviation, whereas the qualitative variables were given frequencies/percentages. The Chi-square test or Fisher's exact test was used for the comparison of qualitative data, while the independent t-test was used to evaluate quantitative data, as applicable, assuming a two-sided p-value <0.05 as statistically significant.

RESULTS

A total of 134 patients who had IVUS with left heart catheterisation were included in the study and were separated into two groups: CAC (n=77) and non-CAC (n=57), based on the presence or absence of calcification assessed on IVUS, respectively. Their baseline characteristics are shown in Table I. CAC patients had more comorbidities, including hypertension, Diabetes mellitus, dyslipidaemia, and CKD, were more often smokers, more commonly present with acute coronary syndrome (unstable angina, NSTEMI, and STEMI), and had prior PCI as compared to the non-CAC group. Cardiac rhythm on presentation and discharge medications did not differ among the two groups.

The parameters for left heart catheterisation are also shown in Table I. It was observed that femoral access was the most common arterial access for the procedure (n=69, 51.5%), in which the femoral route was more common in the CAC group (n=42, 55%) while the radial was commoner in the non-CAC group (n=30, 53%). LM disease was noted in 46 (34.3%) patients, out of which the majority of the patients (n=34, 44%, p-value=0.005) were in the CAC group. On the other hand, single-vessel disease was the most common coronary artery disease (n=51, 38.1%) and included the majority of the non-CAC group (n=29, 51%).

The IVUS details and management are shown in Table II. In both groups, IVUS was performed mostly on the left anterior descending artery, but the CAC group had a greater number of LM-IVUS. Multivessel disease and in-stent restenosis were also more prevalent in the CAC group and needed revascularisation (PCI or CABG) more often. Drug-eluting stents (n=92, 68.6%) were used in the majority of patients, combined with good expansion that was observed under IVUS monitoring.

IVUS measurements (Table II) showed that there was more LM and other vessel stenosis with lower MLA and EEM values in the CAC group as compared to the non-CAC group, while the size, length, and number of stents were comparable between the two groups.

In this study, all patients' follow-up data (both in-hospital and long-term) were obtained (Table III). The mean period of follow-up was 40.3 ± 30.1 months. It was also observed that the CAC group had more in-hospital and long-term events (MACEs) as compared to the non-CAC group, although the results were not statistically significant.

Table I: Baseline clinical characteristics.

	Total (n=134)	CAC group (n=77)	Non-CAC group (n=57)	p-value[a]
Male(%)	97(72.4%)	55(71.4%)	42(73.7%)	0.773
Age[b]	63.1± 12.9	65.8±11.43	59.47±13.95	0.004
Hypertension	104(77%)	64(83%)	40(70%)	0.076
Diabetes mellitus	73(54%)	44(57%)	29(51%)	0.471
Dyslipidaemia	111(83%)	68(88%)	43(75%)	0.051
Smoking				
Current	13(10%)	5(6%)	8(14%)	0.309
Former	40(30%)	25(33%)	15(26%)	
CKD	13(10%)	9(11%)	4(7%)	0.366
Presentation				
Stable angina	39(29%)	18(23%)	21(37%)	
Unstable angina	13(10%)	10(13%)	3(5%)	
NSTEMI	50(37%)	34(44%)	16(28%)	0.068
STEMI	31(23%)	15(19%)	16(28%)	
Pre-op	1(0.75%)	0	1(1.75%)	
Prior PCI				
Prior Stenting	58(43%)	40(52%)	18(32%)	0.019
Prior LM PCI	2(1.5%)	2(1.5%)	0	0.220
Other vessel prior PCI				
PCI to LAD	28(21%)	19(25%)	9(16%)	
PCI to LCX-OM	4(3%)	3(3%)	1(2%)	
PCI to RCA	4(3%)	2(3%)	2(4%)	
PCI to LAD and LCX	9(7%)	8(10%)	1(2%)	0.111
PCI to LAD and RCA	6(4%)	4(5%)	2(4%)	
Prior Triple vessel PCI	2(1.5%)	2(1.5%)	0	
Prior PCI to diagonal	1(0.75%)	1(1%)	0	
Prior CABG	8(6%)	4(5%)	4(7%)	0.660
Pre-procedural arrest	6(5%)	2(3%)	4(7%)	0.221
Cardiac rhythm on presentation				
Sinus rhythm	122(91%)	69(90%)	53(93%)	
Atrial fibrillation	8(6%)	6(7%)	2(4%)	0.527
Ventricular tachycardia	2(1.5%)	1(1.3%)	1(2%)	
Cardiogenic shock	9(7%)	3(4%)	6(11%)	0.130
Discharge medications				
Aspirin	125(97%)	71(97%)	54(96%)	0.489
Clopidogrel	113(88%)	62(85%)	51(91%)	0.294
Ticagrelor	12(9%)	9(12%)	3(5%)	0.177
Statins	128(99.2%)	64(88%)	53(95%)	0.77
Beta-blockers	115(89.1%)	73(100%)	55(98%)	0.252
ACE/ARBs	62(48.0%)	66(90%)	49(88%)	0.598
Diuretics	62(48%)	36(49%)	26(46%)	0.745
Anti-anginal	32(24%)	17(23%)	15(27%)	0.648
Anti-coagulants	19(15%)	10(14%)	9(16%)	0.706
Arterial access				
Femoral	69(52%)	42(55%)	27(47%)	0.411
Radial	65(48%)	35(45%)	30(53%)	0.411
Coronary angiogram details				
LM disease (only)	46(34%)	34(44%)	12(21%)	0.005
Other diseased vessel				
SVCAD	51(38%)	22(29%)	29(51%)	SVCAD
2VCAD	21(16%)	14(18%)	7(12%)	2VCAD
3VCAD	23(17%)	14(18%)	9(16%)	3VCAD
LM+SVCAD	5(4%)	3(4%)	2(4%)	LM+SVCAD
LM+2VCAD	10(7%)	10(13%)	0	LM+2VCAD
LM+3VCAD	17(13%)	11(14%)	6(10%)	LM+3VCAD
LM+3VCAD+Graft disease	4(3%)	2(3%)	2(4%)	LM+3VCAD+ Graft disease

[a] Pearson's Chi-square. [b] Independent t-test. CKD: Chronic kidney disease, NSTEMI: Non-ST elevation myocardial infarction, STEMI: ST-elevation myocardial infarction, PCI: Percutaneous coronary intervention, LM: Left main coronary artery, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, CABG: Coronary artery bypass graft.

Table II: Details of IVUS and subsequent management.

	Total (n=134)	CAC group (n=77)	Non-CAC group (n=57)	p-value[a]
IVUS details				
Pre PCI IVUS done	99(74%)	60(78%)	39(68%)	0.216
Post PCI IVUS done	102(76%)	60(78%)	42(74%)	0.569
Prior stent well expanded at the index procedure	27(47%)	17(29.8%)	10(17.54%)	0.022
ISR in prior stent	36(63%)	27(35%)	9(16%)	0.024
New stent well-expanded	82(84%)	45(46%)	37(38%)	0.586
IVUS of LM	46(34%)	33(43%)	13(22%)	0.016
Other target vessel IVUS				
IVUS of LAD	94(70%)	50(65%)	44(77%)	
IVUS of LCX	8(6%)	5(6%)	3(5%)	0.084
IVUS of RCA	12(9%)	6(8%)	6(10%)	
IVUS of Ramus	1(0.75%)	1(1%)	0	
IVUS of Graft	2(1.49%)	0	2(4%)	
IVUS guided PCI				
Stenting	100(75%)	55(71%)	45(79%)	
POBA	18(13%)	13(16%)	5(9%)	0.405
Rota Ablation	8(6%)	8(10%)	0	
Management				
PCI to LM only	2(1.5%)	2(3%)	0	
PCI to LM to LAD	12(9%)	8(10%)	4(7%)	
PCI to LM to LCX	2(1.5%)	1(1.3%)	1(2%)	
PCI to LAD	60(45%)	29(38%)	31(54%)	
PCI to LCX	9(7%)	6(8%)	3(5%)	
PCI to RCA	10(7%)	7(9%)	3(5%)	
Multi-vessel PCI	18(14%)	12(14%)	6(10%)	0.029
PCI to Diagonal	2(1.49%)	1(1%)	1(2%)	
PCI to Ramus	1(0.75%)	1(1%)	0	
Graft PCI	2(2%)	0	2(4%)	
CABG	8(6%)	8(10%)	0	
Medical management	6(5%)	0	6(11%)	
IVUS measurements				
EEM of LM (mm^2)	4.54	4.48	4.68	0.285
MLA of LM (mm^2)	6.05	5.80	6.96	0.306
LM % stenosis	55.1	57.5	48	0.2395
EEM of Target vessel other than LM (mm^2)	3.98	3.96	4.01	0.713
MLA of Target vessel other than LM (mm^2)	4.24	4.21	4.29	0.876
Other Target vessel % stenosis (mm^2)	77.8	78.6	76.7	0.527
No. of stents used	1.62	1.51	1.78	0.162
Size of stent (mm)	3.18	3.15	3.22	0.517
Length of the stent (mm)	24.3	23.8	25.0	0.510

[a] *Pearson's Chi-square, IVUS: Intravascular ultrasound, PCI: Percutaneous coronary intervention, ISR: In-stent restenosis, LM: Left main coronary artery, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, CABG: Coronary artery bypass graft, POBA: Percutaneous old balloon angioplasty.*

Table III: Follow-up events.

	Total (n=134)	CAC group (n=77)	Non-CAC group (n=57)	p-value[a]
In-hospital events				
Total events in the same admission	28(21%)	18(23%)	10(17.5%)	
Cardiac death	3(2%)	2(2.6%)	1(2%)	
Stroke	1(0.75%)	1(1.3%)	0	
Bleeding	6(4.5%)	4(5%)	2(3.5%)	
CIN	5(3.7%)	2(2.6%)	3(5%)	0.780
All-cause mortality	2(1.5%)	2(2.6%)	0	
Arrhythmias	9(7%)	5(6.5%)	4(7%)	
Access site haematoma	1(0.75%)	1(1.3%)	0	
Heart Failure	1(0.75%)	1(1.3%)	0	
Long-term events				
Total events on follow-up	25(18.6%)	17(22%)	8(14%)	
PCI to non-target vessel	6(4.4%)	3(4%)	3(5%)	
PCI to target vessel (TVR)	1(0.75%)	1(1.3%)	0	
CABG (TVR)	2(1.5%)	1(1.3%)	1(1.75%)	
Bleeding	2(1.5%)	2(2.6%)	0	
Life-threatening Arrhythmias	3 (2.2%)	3(3.9%)	0	0.219
All-cause mortality	1(0.75%)	1(1.3%)	0	
Heart failure/pulmonary oedema	3(2.2%)	2(2.6%)	1(1.75%)	
Cardiovascular death (fatal MI)	3(2.2%)	2(2.6%)	1(1.75%)	
Non-fatal MI	3(2.2%)	1(1.3%)	2(3.5%)	
Stroke	1(0.75%)	1(1.3%)	0	

[a] *Pearson's Chi-square, TVR: Target vessel revascularisation.*

DISCUSSION

This is Pakistan's first major and detailed IVUS research, including a prolonged duration of follow-up and a comparison between patients with and without CAC. This study demonstrated that there was a trend towards worse in-hospital as well as long-term outcomes in the calcified coronary artery PCI group which was statistically non-significant. Similarly, coronary artery calcification in this study population was more commonly found in elder patients with more comorbidities, and they had a more acute mode of presentation as well. It was also observed that CAC patients had more LM and multivessel disease along with a higher prevalence of in-stent restenosis.

The degree of CAC directly correlated with atherosclerosis and the prevalence of CAC increased with age and multiple comorbidities which was supported by the previous studies.[9] Calcified vessels with LM and/or multivessel disease were the subject of a heart team approach and those with low surgical risk and good targets underwent bypass grafts and the rest surgically-turned-down-patients underwent complex PCI. Interventional cardiologists always face difficulty in dealing with calcified coronary artery lesions due to their more acute clinical presentation and associated procedural complications, as PCI of calcified lesions is associated with unfavourable ischemic events, such as definite stent-thrombosis and unplanned ischemia-driven target vessel revascularisation during one year of PCI when compared to patients with no or mild calcification in the coronary arteries.[10,11] To overcome this challenge, many interventionists used intravascular imaging (IVI), predominantly IVUS and optical coherence tomography(OCT), to assess the anatomy of coronary arteries, the status of calcification, stent opposition, stent expansion, and associated intravascular complications like coronary artery dissection.[12-14]

Even though stent under-expansion rates in prior stents were lower in the calcified group, the prevalence of ISR was still higher in the calcified group. This could be explained by a higher prevalence of comorbid conditions in the calcified group.

IVUS-guided assessment had shown that angiographically significant coronary artery disease (CAD) correlates with calcium status in coronary arteries.[1,2,4] Similarly, in this study, the LM disease and multivessel CAD were more prevalent in patients with calcified coronary arteries as compared to patients with no calcification. Previous studies from upper to upper-middle-income nations also observed similar findings.[5,15]

PCI of calcified lesions without the use of intravascular imaging resulted in poor short- and long-term outcomes.[10,11]

Several studies had shown that using intravascular imaging reduces MACE and improves the prognosis of calcified lesion PCI.[16-18] This study also established that using IVUS in the CAC group resulted in a statistically insignificant difference in MACE in both groups. The target vessel/lesion failure was 2.24% (n=3), which was quite low when compared to the SIPS trial[19] in which TVR was 17%. Jeremias *et al.* found restenosis rate at 6 months was 33.3%.[20] However, further large, multi-centre, randomised trials are needed in this area. These findings will assist in boosting trust in the use of IVUS and improve clinical outcomes, particularly in patients with coronary artery calcification.

Some limitations of this study must be considered; firstly, it was a retrospective, single-centre, observational study. Secondly, the number of included patients was relatively smaller as compared to the burden of disease in the South Asian population. Thirdly, coronary angiography and revascularisation were only performed on symptomatic individuals after the initial procedure. Fourth, during the initial procedure, the decision to use IVUS was determined by the interventional cardiologist's preference for pre-PCI assessment of CAD lesion and/or post-PCI analysis of stent expansion, or for excluding coronary artery dissection. Finally, no additional IVUS data were collected, such as total plaque burden, quantification of plaque content and calcium, or post-PCI measures.

CONCLUSION

Acute coronary syndrome was more frequently found in patients with CAC, who also had higher comorbidities. MACEs were observed at higher rates in the CAC group. Thus, even if the results are not statistically significant, it can be stated that PCI of CAC lesions under IVUS guidance leads to appropriate management and improves both short- and long-term clinical outcomes.

ETHICAL APPROVAL:
Before conducting the study, an approval was taken from the Ethical Review Committee (ERC), Department of Medicine at The Aga Khan University Hospital, Pakistan.

PATIENTS' CONSENT:
Informed consent and the last follow-up details were obtained by examining medical records and conducting telephone interviews.

COMPETING INTEREST:
The authors did not declare any conflict of interest.

AUTHORS' CONTRIBUTION:
MNR: Conceived the idea and design of the manuscript, and contributed in data collection, interpretation, and proofreading.
AN: Wrote the final manuscript, collected the data, and analysed the results.
IU: Wrote the abstract and initial synopsis, collected the data.
GA: Collected, analysed, formatted the data and tables.
AF: Analysed the data, contributed in proofreading and grammatical corrections of the manuscript.
MAK: Contributed to data analysis tools and the manuscript's final version as a research specialist.

All authors read and approved the final version of the manuscript to be published.

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