

An Observational Study of Patients with Significant Coronary Artery Disease after Acute Coronary Syndrome on Medical Management

Kallol Dasbaksi¹, Enakshi Saha², Suranjan Haldar³, Mohammad Zahid Hossain⁴, Minhajuddin Khurram⁵, Diptimoy Mukhopaddhay⁶

ABSTRACT

Introduction: Surgery is accepted as a traditional and standard treatment of significant coronary artery stenosis with history of an episode of acute coronary syndrome. This study involves prognostically important descriptors to identify the factors leading to functional improvement on medical management in these patients who were at potential risk of major cardiovascular and cerebrovascular events (MACCE). This ongoing study attempted to find out whether the improvement of functional status are due to antianginal effect or more than that reversely remodelling coronary atherosclerosis.

Material and methods: Between 1st January 2016 and 31st July 2017, the detailed investigations of 29 such patients were obtained, who were on waiting list for CABG after being referred from cardiology department, many with history of AMI. The improvement or deterioration of their functional status while on treatment with guideline directed optimal medical therapy (OMT) with atorvastatin (40 to 80 mg), aspirin (75mg) and clopidogrel (75mg), metoprolol succinate (12.5 to 50mg) with amlodipine (2.5 to 20mg), ramipril (1.25 to 10mg) or telmesartan (20 to 80mg) for hypertension and heart failure prescribed at the discretion of the physician along with medications for diabetes and hypothyroidism, were analysed.

Results: The first year follow-up was for the 29 patients recruited over 6 months. 17 patients with CCSA class III and 1 with II had a baseline SYNTAX score of 29±6.2, while 11 with class II had 20.3±3.2. The functional class improved with OMT medications was noted to be improving after 3 to 4 weeks and by 12 months 62% were in class I. Duke Activity Status Index (DASI), improved from 19.3±3 to 23±2 at 6 months and to 30.8±2 by 1 year in 18 patients. The associated peripheral vascular disease symptoms also improved Mortality was 6.7%.

Conclusion: In clinically stabilized patients with severe CAD, after ACS, with or without myocardial infarction, conservative management with OMT, has been observed to improve cardiac function with reduced odds of mortality and improved quality of life with lifestyle modification, some dietary and physical restriction.

Keywords: Acute Coronary Syndrome (ACS), Duke Activity Status Index (DASI), Significant Obstructive Coronary Artery Disease (CAD), Left Main Obstructive Coronary Artery Disease (LMCAD)

worldwide. Globally 7.2 million deaths are caused by IHD each year.¹ A 2016 study revealed premature mortality in terms of years of life lost because coronary artery disease (CAD) in India increased by 59%, from 23.2 million (1990) and projected to involve 37 million by 2020.² Epidemiological studies showed a sizeable burden of CAD in rural (3-5%) and urban (7-10%) populations. A conservative estimate also indicates that there could be 30 million CAD patients in India of which 14 million are in urban and 16 million in rural areas.³ The estimation of age-standardized CVD death rate of 272 per 100 000 population in India is higher than the global average of 235 per 100 000 population. Some aspects of the obstructive coronary artery disease (CAD) epidemic in India are of particular causes of concern, including its accelerated buildup of early atherosclerosis in the population, and the high case fatality rate due to some genetic, nutritional and metabolic diseases like diabetes.⁴ Extensive use of tobacco including indigenous tobacco (Bidi, Jarda, Gutkha) in variety of forms is an established etiology of Buerger's disease or thromboangiitis obliterans^{2,3,4,5} affecting the medium caliber arteries of extremities and other organs⁶ and is also an etiology for CAD in the Indian subcontinent.^{3,4} In such patients with tobacco intake or smoking of Indian cigar (bidi), the left anterior descending artery (LAD) diameters are often observed by us as 0.5 to 1 mm in diameter in such non diabetic patients during coronary artery bypass surgery (CABG) with poor long term prognosis. The average diameter of LAD is usually 1.5 to 1.75 mm in average Indian middle class male patients in their forties to sixties, with history of smoking cigarettes, are often found in our hospital during CABG except in those with diabetes. However, it was

¹Associate Professor, Department of Cardiothoracic Surgery,

²Associate Professor, Department of Anaesthesiology, ³Assistant Professor, Department of Cardiothoracic Surgery, ⁴Assistant Professor, Department of Cardiothoracic Surgery, ⁵Senior Resident, Department of Cardiothoracic Surgery, ⁶Senior Resident, Department of Cardiothoracic Surgery, Medical College, Kolkata, India

Corresponding author: Dr. Enakshi Saha, Associate Professor, Department of Anaesthesiology, Medical College, Kolkata, India

How to cite this article: Kallol Dasbaksi, Enakshi Saha, Suranjan Haldar, Mohammad Zahid Hossain, Minhajuddin Khurram, Diptimoy Mukhopaddhay. An observational study of patients with significant coronary artery disease after acute coronary syndrome on medical management. International Journal of Contemporary Medical Research 2020;7(5):E1-E10.

DOI: <http://dx.doi.org/10.21276/ijcmr.2020.7.5.30>



INTRODUCTION

Measuring the global burden of disease and epidemiological transitions by multiple studies have revealed that Ischemic heart disease (IHD) is the leading cause of death and disability

just observation shared by several other cardiac surgeons in India, but no literature review is available. A contemporary Indian study reported the diameter in adult males in proximal LAD as 1.69 ± 0.37 mm in Indians which are smaller than 1.89 ± 0.37 mm in England.⁷ Among the CAD population, triple vessel disease (TVD) is more common (55%) than double vessel disease (DVD) (24%) and single vessel disease (24%) combined in another Indian report.⁸

A very small number of patients with CAD requiring percutaneous coronary artery intervention (PCI) or coronary artery bypass surgery (CABG) from the low income group could afford the costly diagnostic tests and therapy in private setups and depended on government or charitable institutions with facility of very limited beds.⁴ After the medical facilities in West Bengal, India, became completely free of cost of medicines and disposables, investigations and various implants, from 2016, the number of cases of ST elevated myocardial infarction (STEMI) receiving reperfusion therapy increased and the median symptom-to-door time of 300 minutes for Indian patients reported previously⁴ decreased. Mechanical complications of acute myocardial infarction (AMI) also decreased, as observed by our personal experience.⁹ and also world wide.¹⁰ The number of referred cases of CAD and those with triple vessel disease (TVD) or left main coronary artery disease (LMCAD) increased in our hospital due to increased number of coronary angiography (CAG). The policy of social subsidy also led to increased numbers of thoracic and cardio vascular surgery including more valve surgery^{11,12} and heart transplantations (HT) in government medical colleges of West Bengal. The 1st case of HT was thus successfully done in our hospital in Medical College, Kolkata, in November, 2018 and is being regularly carried out. However, due to policy of free treatment, there was an increase in number of patients from the lower socio economic class of both rural and urban areas. The case loads increased exponentially for both PCI and CABG. The waiting list for cardiac surgery also increased from a few weeks to 2 months before 2016 and now ranged from 6 months to 1 year which is commensurable to the huge population of India in comparison to the West where the waiting list is less¹³ but even much less than 2 to 3 years in Brazil.¹⁴ During waiting period for CABG, the patients received guideline directed optimal medical therapy (OMT) comprising aspirin (75 mg) and clopidogrel (75 mg) as dual anti platelet therapy (DAPT), statins (atorvastatin 40 to 80 mg), betablockers as metoprolol succinate (25 to 50 mg) with and without ACE receptor inhibitor (ARI) as ramipril (2.5 to 5 mg) or ACE receptor blocker (ARB) telmesartan (40 to 80 mg), with and without antihypertensive medicines amlodipine (2.5, 5 or 10 mg), at physician's discretion, from the hospital pharmacy regularly. The disbursing of free medicines ensured a regular follow-up. Generally, wait-listed patients for CABG are called over phone according to the waiting list or earlier who deteriorated despite medicines. However preferences were made for earlier CABG to cases of acute coronary syndrome (ACS) with severe angina or in stent stenosis or any CAD with ACS not responding to conservative

management. But it was also observed that after a few weeks, certain number of such wait listed patients refused CABG when contacted as their disabilities improved with OMT over 6 to 8 weeks. Such patients went on increasing over the weeks and were followed up over a year and the data of 29 such patients were compiled as they regularly visited the OPD to get the medicines. The follow up is still being continued. Present study attempted to find out whether the improvement of functional status are due to antianginal effect or more than that reversely remodelling coronary atherosclerosis.

MATERIAL AND METHODS

Between 1st January 2016 and 31st July 2017, among the patients of ischemic heart disease (IHD), who were referred from our cardiology OPD for CABG already on OMT, 29 patients with history of ACS did not give their consent for surgery and were followed up. They were gradually recruited in this study over a period of 5 to 6 months. Their disability status were reviewed, indication for and risks without CABG were explained to them and were regularly followed over 1 year. There were more patients at the beginning of the study, but those who did not respond to OMT were revascularized. By shared decision making (SDM) during counselling with patients, written consent for refusal of CABG was obtained from all the 29 patients and conservative management was continued with regular follow-up.

The purposes of this study are: (1) to review the natural history of patients with CAD including LMCAD with history of ACS on OMT with DAPT, Statins, betablockers with and without ARI or ARBs and antihypertensive medicines (2) to determine the prognostic significance of different degrees of CADs inclusive of LMCADs on OMT, and (3) to determine if prognostically important descriptors of functional class can be identified and used to characterize high and low risk patients and predict variables for long and short term survival.

The patients were examined clinically for their symptoms, CCSA and NYHA classes, disability status, blood pressure and pulse rates and other haematological, biochemical parameters, echocardiography. The figures were all documented for changes. CAGs were reviewed and verified for stenoses, lumen sizes, run off, length of stenosed segments, retrograde flow in cases of chronic total occlusion (CTO) etc. The synergy between PCI with TAXUS and cardiac surgery (SYNTAX) score were calculated to document the ischemic burden and operative risk (Table 1). The Canadian Cardiovascular society angina class (CCSA) and NYHA functional classification of heart failure and for general functional capacity and Duke activity status index (DASI) scores were calculated. All patients had history of ACS and some also had of AMI. The changes in echocardiography, NYHA, CCSA and DASI (Table 2 and 3) status were noted. The measurements were done after 2, 6 and 12 months of enlistment and compiled for any improvement or decline, survival and death due to major adverse cardiovascular and cerebrovascular events (MACCE).

Exclusion criteria

Several other patients who were not operated, included stable IHD patients with non occluded left anterior descending (LAD) artery with double vessel disease (DVD) with left circumflex (LCX) or right coronary artery (RCA) obstructive disease, or TVD with <50% LAD, LCX and RCA obstructive disease or recent total occlusion (TO) of LAD (Figure 1,D and H, 100% TO of LAD was stented) or 99% ostial LMCAD with patent left LCX and LAD, with large area of myocardium at risk, (Figure. 1, A, showing 99% LAD block with B, normal RCA) and 99% ostial LAD block (Figure 1,C) had CABG. Patients with extensive akinetic thin myocardium in echocardiography or dobutamine stress echocardiography (DSE) or extensive myocardial infarction in cardiac magnetic resonance imaging (CMRI) or diffuse coronary artery disease with no graftable artery were also excluded. Patients with dilated ischemic cardiomyopathy (DCM) were also excluded, some of which were then considered for heart transplantation.

All the data were processed in Microsoft XL, tabulation done, and statistical averages, standard deviations and relevant proportion were calculated. Continuous variables are expressed as mean value \pm SD. Differences in continuous variables were assessed with 1-way analysis of variance or the unpaired t test; the χ^2 test was used for categorical variables. No further statistical tests could be done due to small numbers of these cases.

Since it was a retrospective study and no individual patient identifiers were used, the patients consent was waived off by the Institutional Ethical committee, but written consent for the study was obtained from all the patients for publication.

RESULTS

Physiologic evidence of ischemia of the patients was often less when reviewed in Cardiothoracic surgery OPD. This may be due to the fact that during the intervening 7 to 10

days before referral, they continued to receive medicines in Cardiology. Median follow-up was 12 to 18 months, depending on gradual recruitment for the 29 patients. There were 23 males and 6 females with a median age of 58 ± 10.2 years, range 48 to 73 years. The number and percentage of patients with NYHA and CCSA class III status was 17 (58.6%) and with class II, 12(41.3%). 18 patients had a baseline SYNTAX score of 29 ± 6.2 , range 25 to 38, while 11 had 20.3 ± 3 , range 18 to 25. LMCA lesion >50% was present in 11(37.9%). Proximal LAD lesion >70% was present in 23(79.3%) patients and >70% stenosis of LCX and RCA in 19 (65.5%) and 21 (72.4%) patients respectively (Table 1). Total cholesterol (189 ± 14) mg/dl, LDL (133 ± 23) triglycerides (198 ± 90) mg/dl was noted at the beginning which decreased gradually over 2 and 6 months and finally after 12 months the results were 127(8), 79(3), 138(4) respectively. CRP, (normal levels are below 3.0 mg/L) was usually have been found to have decreased by the time of first visit to our OPD. It was 4.8 mg in 3 patients which gradually became lower over 6 to 12 months. Diabetes mellitus was present in total 15/29 patients. 7/29 had HbA1C <8 and 8 (27.7%) had HbA1C > 8.1 \pm 2 which decreased after 12 months to values <7.5 and was unchanged in only 2 patients at 10 months, who died (Table 2).

The patients with LMCAD above 50% was present in 11 patients out of which 2 patients with 70% lesion, both females, recovered from NSTEMI but expired after 8 months on OMT, both being 68 and 73 year. RCA was patent in both of them, but they could not improve much beyond DASI score of 19.3 ± 3 . There was also diffuse disease in LAD in both of them. Cause of death was intractable cardiac failure. The functional class improved with OMT after 6 to 8 weeks. Out of 29 patients with history of unstable angina 7 had no AMI while 22 had history of MI with 14 (48.2%) STEMI and 8 (27.5%) NSTEMI (Table 1). Most patients reported improvement in functional quality of life after OMT. DASI score of 23 ± 2 was found in 16 (44.2%) and 19.3 ± 3 in 13

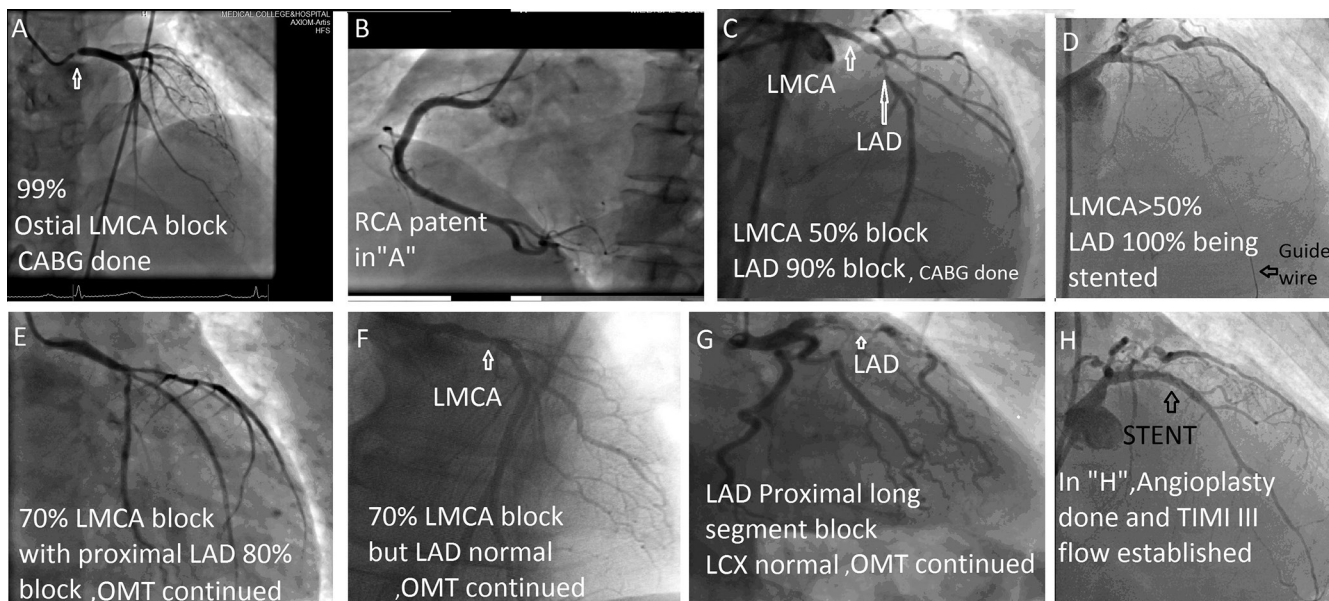


Figure-1: Angiographic frames of several cases. A,B,C,D,H were excluded from study while E,F,G were included (vide exclusion criteria)

Baseline characteristics		
Variable		Summary Statistics
Demographics		(N 29)
Age, mean (±sd) (years)		58 (10.2)
Male, n,(%)		23 (79.3)
Female n,(%)		6 (20.6)
Unstable angina, n(%)		29
MI, (%)		22/29(75.8)
STEMI ± Thrombolysis		8/29(27.5%)
NSTEMI		14/29(48.2%)
UA	LMCA-3, Non LMCA TVD/DVD-4	7 /29(24.1%)
NYHA & CCSA class I n(%)		0
NYHA & CCSA class II n(%)		12, (41.3)
NYHA & CCSA class III n(%)		17(58.6)
NYHA & CCSA class IV n(%)		0
Comorbidity, n (%)		
Hypertension, n,mm/Hg,(sd)		21, 146/96 (12.2)
COPD, n(%)		8 (27.5)
CKD stage 2 eGFR 60-89ml/min		5 (17.2%)
DM n,(%)		15,(51.7%)
Perpheral vascular disease n, (%)		5(17.2)
CAG		
LMCA	(>50%) n,(%)	7/29,(24.1%)
NSTEMI	n, %	5,(17.2%)
LMCA	(>70%)n,(%)	4/29,(13.7%)
NSTEMI	n,%	2/29(06.8%)
LMCA with UA, >50%,2,>70% 1,		3/29(10.3%)
LAD proximal ± LMCA	(>70%),n(%)	23/29(79.3)
Left circumflex,	(>70%)n,(%)	19/29(65.5)
Right coronary artery,	(>70%) n(%)	21/29,(72.4)
Non LMCA MI	STEMI	8(27.5%)
Non LMCA MI	NSTEMI	7(24.1%)
SYNTAX score (±sd),	29±6.2,n(%)	18(62.0)
SYNTAX score (±sd),	20±3.2,n(%)	11 (37.9)
DASI score,19±3, n (%) a		16(55.1)
DASI score 23± 2 score, n(%) b		13(44.8)
DASI score 30.8±2 c		0
CCSA= Canadian Cardiovascular Society angina		
DASI = Duke Activity Status Index, Predictor Variables for Long and short Term Survival For a,b,c, vide result		

Table-1: Baseline Characteristics of the stable patients 7 to 10 days after release from Cardiology

(55.1%) patients during first visit which gradually increased to 30.8±2 in 18 (62.0%) patients which indicated more improvement in functional status after 12 months. But 2 patients with persistent DASI 19.3±3 expired after 8 months [Table 2]. These 2 patients with an eventful course had lower NYHA functional severity class, but less angina due to diabetes mellitus, lower walking distance in plain road and less than 2 minute step test (2MST), lower ejection fraction, 35±4.6 vs. 42±5.4% in patients who improved. The DASI score (a) 19±3 in 16 patients improved to (b) 23± 2 in 7 patients in 2 months while 7 with 23± 2 score improved to (c) 30.8±2 that is 5 to 9 METs.

On further analysis the improvement in variables, CCSA, NYHA and DASI were associated with event-free survival. During follow-up, none of the 27 surviving including the 2 patients who died, experienced AMI or ACS. Over 12 months, 93.1% of these patients were seen to have improved and their

functional DASI score increased from 19±3% to 23±2, or roughly ≤5 METs to ≥6.5 METs. 18 (62%) patients achieved NYHA and CCSA class I status and a DASI score of 30.8± 2 (≥9 METs), a significant achievement without any change in their CAG. NYHA and CCSA class improved from class III to II in 17/29(58.6%) to 11/17(64.7%of 17) at 2 month and after further 4 months, 4 remaining in class III improved to class II. Thus the number at 6 months at class II was 11+4=15 patients as 4 from original class III improved to II (Table 2). This figure included both 11 (37.9%) LMCAD and 18 (62.0%) TVD or DVD cases without LMCAD lesions. The number of MI was 22/29(75.8%). Out of 22, 14/29(48.2%) were found to be NSTEMI (9 in LMCA and 5 in TVD or DVD group) and 8/29(27.5%) had STEMI ±thrombolysis (nil in LMCA and 8 in TVD or DVD group). It signifies, that STEMI in >70% LMCAD lesions are fatal and rarely reach hospital for streptokinase therapy within the golden hours.

Changes of baseline characteristics	7-10 days on OMT	2 months on OMT	6 months on OMT	12 months on OMT
Preoperative laboratory values				
Hematocrit, % (\pm sd)	38 (4)	40(3)	40(2)	41(2)
Creatinine, mg/dl (\pm sd)	1.04,(.5)	0.9(.4)	.9(.3)	.9(.3)
Total cholesterol, mg/dl (\pm sd)	189 (14)	130(12)	123(7)	127(8)
LDL-cholesterol mg/dl (\pm sd)	133 (23)	89(32)	83(5)	79(3)
Triglycerides mg/dl (\pm sd)	198 (90)	143(15)	134(4)	138(4)
CRP, mg/dl, (\pm sd)	4.8(3)	2.4(1)	2.3(1)	2.3(2)
Diabetes mellitus, Total 15/29,% 7/29 HbA1C <8	8(27.7)	6(20.6)<8	2*(6.8)<7.5	nil
HbA1C 8.1 \pm 2 in 8/29				
Peripheral vascular disease, n,(%)	5/29(17.2)	2/29(6)	0	0,
Cardiac morbidity, n (%) NYHA & CCSa class I n, (%)				
Abnormal LVEF %, (\pm sd)	35 (4.6)	39(4.9)	42(5.4)	45(3.4)
Disability extent				
NYHA & CCSA class I, n, %	0,	6/12(50)	6+3/11&3/6	12+3/11+3/6
NYHA & CCSA class II n, (%)	12, (41.3)	6/12(50)	8/11+3/6	5/8+4/6
NYHA & CCSA class III n, (%)	17(58.6)	6/17(35.2)	2/17(11.7)	
NYHA & CCSA from III to class II n, (%) on OMT		11/17(64.7)	4/6(66.6)	2* expired
NYHA & CCSA from III to class I, n, %	0	0	4/17(23.5%)	2/17(11.7)
NYHA & CCSA class IV n, (%)	nil			
DASI score 30.8 \pm 2		6(20.6)	14(48.2)	18(62.0)
DASI score 23 \pm 2 score, n(%)	13(44.8)	14(48.2)	13(44.8)	9(31.0)
DASI score, 19 \pm 3, n (%)	16(55.1)	9(31.0)	2*(6.8), expired after 10 months	
*Death profile of 2 patients on OMT, LVEF 34-40%, history of NSTEMI, LMCAD of 70%, but HbA1C <7.5 at 8th month				
Table-2: Changes of baseline characteristics, functional status LVEF, DASI score during treatment and follow up on Guideline directed optimal medical therapy (OMT)				

Regarding coronary angiography (CAG), out of 11 patients with LMCA disease 7 had >50% atherosclerotic lesion and 4 had >70% lesion. Out of the latter 4 patients, 2 had UA with >70% lesion and 2 had NSTEMI (later died). Out of 7 LMCA patients with >50% stenosis, 2 had UA while 5 had NSTEMI. The SYNTAX score also improved during the next 6 to 12 months.

DISCUSSION

This study was an evaluation of 1 year outcome of patients with history of ACS due to significant CAD including unprotected LMCAD who preferred to be treated with OMT. The patients had 100 percent follow up over 1 year.

Historical data from past

Mortality from cardio vascular diseases (CVD) and stroke reached epidemic proportions in the USA during 1940s and 50s due to some prevalent social belief and practice of that period regarding high calorie intake, sedentary lifestyles, smoking and obesity which was prevalent in the affluent society contrary to present generation.^{15,16} Modification of risk factors for IHD as observed in Framingham study¹⁷ which included hypertension, diabetes, smoking led to significant decrease in mortality in 1970s. Though aspirin had been suggested as a deterrent against myocardial infarction (MI) in mid nineteen fifties by Dr. Lawrence Craven, a suburban general practitioner in Glendale, California, his theory was completely ignored till Sir John Vane who won the Nobel Prize in Physiology in 1982, when aspirin was recognized for its anti platelet and thus anti thrombotic use against MI.¹⁸ Introduction of aspirin into general guidelines along with

ACEI captopril, and statins¹⁹ significantly improved cardiac function and survival with significant CAD, and it's most important of prototype, LMCA disease.

Estimation of changes in functional assessment by improvement of collateral flow

The change in anatomic extent and complexity of coronary artery diseases (CAD) are major factors in deciding on the best management approach to judge the progression of atherosclerosis and repair of tissue damage. The anatomic extent can be estimated by CAG and risk stratification by SYNTAX scoring system which was used in our study. It was observed that the patients who had gained most from the OMT were those who had some degree of stenosis in LAD and one or both RCA or LCX were less stenosed. Usually, in such cases, there is often established collateral flow which may improve with OMT (Figure, 1, E had significant LAD obstruction along with 50% LMCAD, the RCA was patent). Similarly, in Figure 1,F, there was 50% LMCAD but normal LAD while in 1,G, there was long segment LAD 90% obstruction but good LCX flow. But all 1E, F and G had improved due to improvement of preexisting collateral flows in addition to anti atherogenic effects of OMT. But the LMCA ostial stenosis as observed in Figure, 1, A with normal RCA, was not a candidate for OMT. There was persistent UA, with more than 60% of LV myocardium at risk, which was relieved by CABG. The evidence of change of ischemic load can be calculated by stress test or TMT. But it is laboratory orientated and requires significant waiting period for our patients who usually belong to low resource setting daily

wedge earner families. So, a much patient friendly physical activity questionnaire like DASI scoring system.^{20,21,22} (Table 3) was carried out initially and followed during subsequent OPD visits. This score could be compared with the same test data obtained earlier and the change in ischemic burden could be estimated in OPD.

DASI has been found to be a well validated measure of self-reported functional capacity assessment that can also be expressed as metabolic equivalents (METs) and has been shown to correlate with adverse outcomes in those with CAD. DASI divided by 3.5 = estimated DASI metabolic equivalents.²⁰ Lower functional capacity, assessed by DASI, below 5 MET was associated with higher ischemic burden with decreased coronary flow reserve and higher odds of MACCE during intermediate follow-up.²³

The lowest unchanged DASI score remained associated with increased 1-year mortality risk and increasing score had improved survival of 93.1% at 1 year (Table 2 and 3), after adjustment for traditional cardiac risk factors, eGFR, CRP and SYNTAX score. Though 18/29(62%) of the patients achieved CCSA class I after 1 year their DASI score was still confined to within 34, that is well within the risk of future but lower MACCE which is a limitation of medical management and indicates residual disease. In patients with LMCAD 9/11 with LMCAD (81%) patients had satisfactory recovery of functional status which is comparable to gradually increasing longevity with addition of newly invented OMT as observed in earlier studies with LMCAD^{23,24} and more recent study.²⁵ For each MET increase in exercise capacity, a 17% reduction

in mortality rate has been calculated to have resulted.²⁶ In Non LMCA patients, ischemia during household stressful activities substantially reduced during stress which were also assessed by other estimates of physical activities like 2 minute step test (2MST).²⁶ There was also improvement in claudication distance in cases of peripheral vascular disease which is comparable to finding by other groups.²⁷ These improved scores of household activities could indicate both amelioration of symptoms due to ischemia and heart failure but achievement of persistent higher functional scores to DASI score above 35 in responders indicates reduction of atherosclerotic burden also.

LMCA disease progression: assessment by OMT

Since James Herrick's original description of a LMCA stenosis in 1912, the natural outcome of this type of lesion has been thought to be poor.^{23,28} It is responsible for 84% of the blood supplied to left ventricle in case of left coronary dominant system and significant stenosis of LMCA is diagnosed in 5–7% of patients undergoing coronary angiography and histologically, the LMCA has more elastic fibres than other coronary arteries, which explains the higher restenosis rate after balloon angioplasty due to elastic recoil. LMCA has an average length of 10.8 ± 5.2 mm (range 2–23 mm) and an average diameter of 4.9 ± 0.8 mm based on 100-autopsy cases study which found that it is a relationship between the length of LMCA the and the angle between the branches in which it bifurcates. Investigators observed a larger angle of division is found in long LMCA. Atherosclerotic plaques tend to develop in low shear stress

Can you	Yes	No
1. take care of yourself (eating, dressing, bathing or using the toilet)?	2.75	0
2. walk indoors, such as around your house?	1.75	0
3. walk a block or two on level ground?	2.75	0
4. climb a flight of stairs or walk up a hill?	5.5	0
5. run a short distance?	8	0
6. do light work around the house, such as dusting or washing dishes?	2.7	0
7 do moderate work around the house, such as vacuuming, sweeping floors or carrying in groceries?	3.5	0
8. do heavy work around the house, such as scrubbing floors or lifting and moving heavy furniture?	8	0
9. do yard work, such as raking leaves, weeding or pushing a power mower?	4.5	0
10. have sexual relations?	5.25	0
11. participate in moderate recreational activities, such as golf, bowling, dancing, doubles tennis or throwing a baseball or football?	6	0
12. participate in strenuous sports, such as swimming, singles tennis, football, basketball or skiing?	7.5	0
	58.2	
Notes:		
Scoring the Duke Activity Status Index (DASI): Add the point values for all questions checked in the Yes column and		
DASI divided by 3.5 = estimated DASI metabolic equivalents. (Reprinted from Hltaky et al ²⁰)		
DASI, had poor correlations with measured exercise capacity in patients with peak oxygen uptake <5 METS		
A DASI score of 34 represents a threshold for identifying patients at risk for myocardial injury, MI, moderate-to-severe complications, and new disability, Coutinho-Myrrha et al 2014²²		
The first three CCSA classes were inversely related to the DASI. The mean (± SD) scores were as follows:		
Class I, 31.4±16.7; class II, 22.5±15.4; class III, 14.7±14.3; and class IV, 15.5±14.9 (P<0.01) Kaul PK et al (2009) ²¹		
Duke Activity Status Index (DASI) = If sum of “Yes” replies A, then VO ₂ peak = (0.43 x A) + 9.6		
VO ₂ peak = ml/kg/min ÷ 3.5 ml/kg/min = METS		
Table-3: Duke Activity Status Index (DASI), Predictor Variables for Long and short Term Survival, (Reprinted from Hltaky et al ²⁰)		

areas. The part of LMCA with the lowest shear stress are the lateral walls of the bifurcation, opposite to the carina. The carina is a high shear stress area, so it is frequently free of disease.²⁹ A three-year mortality rate of 50% has been reported for the patients with significant LMCA stenosis treated medically.^{24,29} Other investigators reasoned that higher mortality in these patients was observed if there was associated risk factors of MI with lower LVEF, higher LVEDP greater than 15 mm Hg and higher arterio-venous oxygen difference found during coronary angiography²⁴ and without these risk factors, survival was higher.²⁴ All the depicted risk factors are very much pertinent to this day but the invasive tests have been replaced by various imaging modalities like echocardiography and cardiac magnetic resonance imaging (CMRI) derived LVEF and pulmonary artery pressure, left atrial pressure, and LVEDP for assessing myocardial ischemia and residual functioning muscle mass which has great impact on survival. The present day improved survival was due to better management of those risk factors of heart failure and atherosclerosis with improved OMT which is discussed later. Those who did not respond to OMT were revascularized if found fit. Ischemic load can be estimated by myocardial perfusion scan. CAG, creatinine clearance, diabetes mellitus and MI are used for SNTAX score to decide about various modes of invasive or conservative management. Persistence of higher LVEDP > 12 mm Hg, on exertion is indicative of subendocardial ischemia and endothelial dysfunction resulting in angina or shortness of breath which can be assessed clinically by functional assay by stress echocardiography^{25,26} and managed accordingly, with CABG and management of any ischemic MR. For more sick patients, DASI scores which are more practical, subjective, is cheap alternative methods to TMT^{20,30,31} and have been found to be useful for follow-up of functional changes. Improvement in NYHA and CCSA class from III to II and further to I over 2 to 6 month periods were noted in 100% of the non LMCAD patients and in 80% of patients with LMCAD on OMT. It was observed that CAD above 70% in LAD failed to improve function and needed CABG (Figure 1 C) but 50% to 70% LMCAD with normal LAD lesion (Figure 1E and F) led to adequate functional recovery. In this study, it was also noted in other patients that 100% chronic total occlusion (CTO) of LAD with or without retrograde flow were rarely symptomatic if LCX and RCA were uninvolved and were mostly managed with OMT. The long segment LMCAD of 99% in one asymptomatic patient (not included in this study, Figure 1 G) did improve significantly on OMT. But in case of acute occlusion of LADs, revascularization by PCI (not included in this study, Figure 1D & H) is necessary. The protective effect of a well-developed coronary collateral circulation, (Figure 1 E, F and G) which translates into relevant improvements in all-cause and cardiac mortality in the acute and chronic phases of coronary artery disease, as well as into a reduction of future adverse cardiovascular events can not be excluded.³² But OMT must have improved to sustain these collaterals in 93.2% of our patients as responders and prevented further

atherosclerotic occlusion. In 2 non responders in our study, OMT must have been inadequate and CABG was necessary which was refused. Our findings are agreeable to those observed during framing of the 1999 ACC/AHA Guidelines for CABG. It was observed that due to introduction of statins, beta blockers, aspirin, the reported significant improvement in median survival in >50% LMCAD in medically treated patients increased to 6.6 years³⁰ which means a substantial increase in longevity from the earlier 3 years, as observed during 1970s.²⁴ Still OMT has limited choice to allow for return to previous strenuous activities for those with history of UA.

Mending the diseased myocardium and atherosclerosis

Although CABG could improve the blood flow to ischemic tissue they are ineffective in preventing the atherosclerotic progression. Genesis of atherosclerosis reportedly involves the immunological reaction between the STAT and JAK families, Janus activated kinases (JAKs) and other tyrosine kinases can activate STATs or signal transducer and activator of transcription gene.³³ The STAT proteins are localized in the cytoplasm, can translocate into the nucleus to bind DNA, and dually function in signal transduction and transcriptional regulation. These proteins have been shown to participate in diverse cellular processes, including differentiations of pluripotent stem cells maintenance, lipid metabolism, neuron function, carcinogenesis, inflammation, and immunity. STAT3 contributes to a balance between autophagy and hypertrophy in response to angiotensin II by promoting cardiac fibrosis after MI. It also promotes differentiation of cardiomyocytes by myocardial regeneration in residual living tissue.³⁴ Disrupted aberrant JAK-STAT signaling may lead to a variety of diseases including various form of cancers³⁵, disorders affecting the immune system, atherosclerosis.³⁶ There is endothelial cell dysfunction, macrophage polarization, inflammation, and immunomodulation during atherosclerosis. Cytokines like interleukin (IL)-6 is a multifunctional cytokine that activates not only JAK1, JAK2 but also activates by phosphorylation STAT 1 and STAT3 enhancing atherosclerosis by genetic alteration. Statins inhibit this phosphorylation and thus atherosclerosis progression is inhibited.³⁶ IL-6 was also studied to result by JAK-STAT signaling cascades in potentiation of hypertension and tissue injury.³⁷ IL6 was also inhibited by ACE inhibitors which attenuated angiotensin II-induced renal fibrosis and dysfunction by Inhibition of STAT3 activation.³⁸ So, both statins and ACEIs resulted in reverse remodeling of vascular endothelium by limiting atherosclerosis side by side hypertension, renal preservation and reverse remodeling of failing myocardium^{36,39} which is reflected in better survival of patients with hypertension and heart failure.³⁰ Regression of coronary atherosclerotic plaque volume has also been reported to have taken place.^{40,41} Statins are reported to be effective as vascular endothelial growth factor, a key cytokine in the regulation of neovascularization, in augmenting endothelial progenitor cell (EPC) differentiation⁴² for angiogenesis. OMT and

other life style modification, weighed in favour to induce vascular reverse remodeling of atherosclerotic process and myocardium.

Pleiotropic effects of statins

Some mechanisms having been discussed in previous paragraphs. Pleiotropic effects also include improvement of endothelial dysfunction, increased nitric oxide bioavailability to endothelial cells, reduction of oxidation of LDL particles by down regulating adhesion molecules and chemoattractants, which thus behaves as antioxidant. Other actions include inhibition of inflammatory responses and stabilization of atherosclerotic plaques by alteration in the lipid cores as lasting cardiovascular protective effects substantially unrelated to their cholesterol-lowering action.⁴² It has also been reported to have antihypertensive action.⁴³ The “healed” plaques are discretely smaller, have better structure and is less prone to rupture thus reducing further odds of MACCE. Even so, the occurrence of cardiovascular events despite optimized treatment in a significant proportion of patients receiving statins, the so-called “residual risk”, suggests that the anti atherosclerotic effect is just only one facet of halting atheroma progression⁴⁰, the other measures like control of diabetes, hypothyroidism, hypertension, cardiac failure, food and life style modification should also be taken in unison.

Stable ischemic heart disease (SIHD) in general population

It is not known how many patients with SIHD are there in population with or without significant LMCA disease unless they all have CAG or computerized tomographic coronary angiography. The contemporary large multicentric RCTs assessing clinical outcomes from medical versus revascularization therapy like ISCHEMIA Trial in such SIHD patients had their results published in 2019 and very recently updated in April, 2020. This trial showed that in patients with SIHD that evaluated routine revascularization added to optimal medical therapy (OMT), as compared with OMT alone, did not show a reduction in death or myocardial infarction (MI) with early revascularization.^{44,45} The similarity with this study with ours is that, all the patients had severe CAD in ISCHEMIA trial. But there was exclusion of patients with LMCA diseases. But, the patients in our study with stable angina at present had significant obstructive LMCA disease. But the OMT even in this sick population increased both functional status and cardiac function as judged by serial echocardiography and had definite survival benefit, which however was less in those in LMCAD patients with 6.9% mortality (Table 2). Most patients in our study who could not walk more than 30 to 50 meters at the early stage after referral after ACS, at the end of 10 to 12 months could walk more than 1 km to get of medicines from OPD, even in those with significant LMCA, which could not be explained by our present knowledge. The study is still ongoing.

CONCLUSION

The safety of deferred revascularization in patients with

stable LMCAD disease is less well known. It has already been established that the prognosis of patients with ACS who have no critical narrowing of a coronary artery seems to be better than that of patients with ACS who have CAD substantial enough to warrant PCI⁴⁶ or CABG. But even in these subsets of high risk patients who were stabilized from ACS, and refused CABG for significant stenosis which were not amenable to PCI, combination of life style modifications and modern guideline directed OMT with statins, ACEI or ARBs, DAPT, betablockers and control of metabolic diseases has shown to have worked in unison and resulted in significant recovery of cardiac function as observed in our study group. All these factors must have acted by controlling progression of atherosclerosis and neutralizing the risk factors of hypertension, diabetes, cardiac and renal failure. But the “residual risk” of odds of MACCE must be explained to each patient and statutory warning to avoid binge drinking, binge eating and prompt treatment for any intercurrent infection which may result again in unstable angina or infarction, must be followed along with life style modification.

REFERENCES

1. Lopez AD, Mathers CD. Measuring the global burden of disease and epidemiological transitions: 2002-2030. *Ann Trop Med Parasitol.* 2006;100:481-499.
2. Prabhakaran D, Jeemon P, Roy A, Cardiovascular Diseases in India Current Epidemiology and Future Directions, *Circulation*, 2016;133:1605–1620
3. Kaul U, Bhatia V. Perspective on coronary interventions & cardiac surgeries in India. *Indian J Med Res.* 2010;132:543–548.
4. Ramaraj R, Alpert JS, Indian Poverty and Cardiovascular Disease, *Am J Cardiol.* 2008; 102:102-6.
5. Cacione DG, Macedo CR, do Carmo Novaes F, Baptista-Silva JCC. Pharmacological treatment for Buerger's disease. *Cochrane Database of Systematic Reviews* 2020, Issue 5. Art. No.: CD011033.
6. Olin JW, Shih A. Thromboangiitis obliterans (Buerger's disease). *Curr Opin Rheumatol.* 2006;18:18-24.
7. Harten P, et al., Multiple organ manifestations in thromboangiitis obliterans (Buerger's disease). A case report. *Anigology.* 1996;47:419-25.
8. Raut BK et al, Coronary artery dimensions in normal Indians, *Indian Heart Journal*, 2017; 69: 512–514513
9. Dasbaksi K et al, Outcome analysis after surgical management of ventricular septal defect complicating acute myocardial infarction, *International J contemporary Med Research*, 2019;6: L1-9
10. Puerto E et al, Temporal Trends in Mechanical Complications of Acute Myocardial Infarction in the Elderly, *Journal of the American College of Cardiology*, 2018,72(9).
11. Zahid Hossain, Suranjan Haldar, Minhajuddin Khurram, Kallol Dasbaksi,Prakash Sanki, Plaban Mukherjee, Enakshi Saha, “Concomitant Tricuspid Annuloplasty in Functional Tricuspid Regurgitation: De Vega Suture Annuloplasty versus Ring Annuloplasty Along With Mitral Valve Replacement - A Comparative Study”, *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 2020;19:35-42.

12. Suranjan Haldar, Mohammad Zahid Hossain, Kallol Dasbaksi, Minhajuddin Khurram, Diptimoy Mukhopadhyay, Plaban Mukherjee. Analysis of surgical resection and prognostic factors of primary chest wall chondrosarcomas. *International Journal of Contemporary Medical Research*, 2020;7:C1-C5.
13. McHugh F, Lindsay GM, Hanlon P, et al. Nurse led shared care for patients on the waiting list for coronary artery bypass surgery: a randomised controlled trial. *Heart*. 2001;86:317-323.
14. Haddad N et al Consequences of the Prolonged Waiting Time for Patients Candidates for Heart Surgery, *Arq Bras. Cardiol.*, 2002; 78:459-65
15. Endo A. A historical perspective on the discovery of statins. *Proc Jpn Acad Ser B Phys Biol Sci*. 2010;86:484-493.
16. Dinsa GD, Goryakin Y, Fumagalli E, Suhreke M. Obesity and socioeconomic status in developing countries: a systematic review. *Obes Rev*. 2012;13:1067-1079.
17. Kannel WB, Gordon T, Schwartz MJ. Systolic versus diastolic blood pressure and risk of coronary heart disease. The Framingham study. *Am J Cardiol*. 1971;27:335-46.
18. Miner J, Hoffhines A. The discovery of aspirin's antithrombotic effects. *Tex Heart Inst J* 2007; 34: 179-86.
19. Kirklin JW et al, Guidelines and indications for coronary artery bypass graft surgery: A report of the American College of Cardiology/American Heart Association task force on assessment of diagnostic and therapeutic cardiovascular procedures (subcommittee on coronary artery bypass graft surgery), *Journal of the American College of Cardiology*, 1991; 17: 543-589
20. Hlatky MA et al A Brief Self -Administered Questionnaire to Determine Functional Capacity (The Duke Activity Status Index), *Am J Cardio*, 1989;64:651-654
21. Kaul P, Naylor CD, Armstrong PW, Mark DB, Theroux P, Dagenais GR. Assessment of activity status and survival according to the Canadian Cardiovascular Society angina classification. *Can J Cardiol*. 2009;25:e225-e231.
22. Coutinho-Myrrha MA et al, Duke Activity Status Index for cardiovascular diseases: validation of the Portuguese translation. *Arq Bras Cardiol*. 2014;102:383-390.
23. Ramadan et al, Management of Left Main Coronary Artery Disease, *J Am Heart Assoc*. 2018;7:e008151.
24. Conley MJ, Ely RL, Kisslo J, Lee KL, McNeer JF, Rosati RA. The prognostic spectrum of left main stenosis. *Circulation*. 1978;57:947-952.
25. Patel MR et al, ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease, *J Am Coll Cardiol*. 2017; 69: 2212-2241
26. Eileen Handberg et al, Impaired Coronary Vascular Reactivity and Functional Capacity in Women: Results From the NHLBI Women's Ischemia Syndrome Evaluation (WISE) Study Author links open overlay panel, *Journal of the American College of Cardiology*, 2006;3:S44-S49
27. Senthong V, Wu Y, Hazen SL, Tang WH. Predicting long-term prognosis in stable peripheral artery disease with baseline functional capacity estimated by the Duke Activity Status Index. *Am Heart J*. 2017;184:17-25.
28. Hillis LD et al as writing committee, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *Circulation*. 2011;124:e652-e735
29. Lucian M. Predescu et al, Current treatment of left main coronary artery disease, *Cor et Vasa*, 2016; 58: e328-e339
30. Eagle KA et al, ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery: Executive Summary and Recommendations, A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery), *Circulation*. 1999;100:1464-1480,
31. Duceppe E et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery [published correction appears in *Can J Cardiol*. 2017 Dec;33(12):1735]. *Can J Cardiol*. 2017;33:17-32.
32. Stoller M, Seiler C, Salient Features of the Coronary Collateral Circulation and Its Clinical Relevance, *Swiss Med Wkly*. 2015; 145:w14154.
33. Chen Q, Lv J, Yang W, Xu B, Wang Z, Yu Z, Wu J, Yang Y, Han Y. Targeted inhibition of STAT3 as a potential treatment strategy for atherosclerosis. *Theranostics*, 2019; 9:6424-6442.
34. Nakao S, Tsukamoto T, Ueyama T, Kawamura T. STAT3 for Cardiac Regenerative Medicine: Involvement in Stem Cell Biology, Pathophysiology, and Bioengineering. *Int J Mol Sci*. 2020;21:1937.
35. Pencik J, Pham HT, Schmoeller J, et al. JAK-STAT signaling in cancer: From cytokines to non-coding genome. *Cytokine*. 2016;87:26-36.
36. Jougasaki M, Ichiki T, Takenoshita Y, Setoguchi M. Statins suppress interleukin-6-induced monocyte chemo-attractant protein-1 by inhibiting Janus kinase/signal transducers and activators of transcription pathways in human vascular endothelial cells. *Br J Pharmacol*. 2010;159:1294-1303.
37. Satou R, Gonzalez-Villalobos RA. JAK-STAT and the renin-angiotensin system: The role of the JAK-STAT pathway in blood pressure and intrarenal renin-angiotensin system regulation. *JAKSTAT*. 2012;1:250-256.
38. Zheng, C., Huang, L., Luo, W. et al. Inhibition of STAT3 in tubular epithelial cells prevents kidney fibrosis and nephropathy in STZ-induced diabetic mice. *Cell Death Dis* 2019;10:848.
39. Zouein FA, Zgheib C, Hamza S, et al. Role of STAT3 in angiotensin II-induced hypertension and cardiac remodeling revealed by mice lacking STAT3 serine 727 phosphorylation. *Hypertens Res*. 2013;36:496-503.
40. Bittencourt MS, Cerci RJ. Statin effects on atherosclerotic plaques: regression or healing?. *BMC Med*. 2015;13:260.
41. Gamou T, Sakata K, Tada H, et al. Effect of Reverse Vessel Remodeling on Regression of Coronary Atherosclerosis in Patients Treated With Aggressive Lipid- and Blood Pressure-Lowering Therapy- Insight

- From MILLION Study. *Circ J.* 2017;81:1490-1495.
42. Jean Davignon, Beneficial Cardiovascular Pleiotropic Effects of Statins, *Circulation*, 2004; 23: 39-43.
 43. Pasquale Strazzullo, Sally M. Kerry, Antonio Barbato, Marco Versiero, Lanfranco D'Elia, Francesco P. Cappuccio, Do Statins Reduce Blood Pressure? A Meta-Analysis of Randomized, Controlled Trials, *Hypertension*. 2007;49:792-798.
 44. Judith S. et al, for the ISCHEMIA Research Group, Baseline Characteristics and Risk Profiles of Participants in the ISCHEMIA Randomized Clinical Trial, *JAMA Cardiol.* 2019;4:273-286.
 45. Harmony R. Reynolds, Judith S. Hochman, International Study of Comparative Health Effectiveness With Medical and Invasive Approaches – ISCHEMIA, Presented by Dr. Harmony R. Reynolds at the American College of Cardiology Virtual Annual Scientific Session Together With World Congress of Cardiology (ACC 2020/WCC), March 29, 2020. Summary Reviewer: Deepak L. Bhatt, Trial Sponsor: National Heart, Lung, and Blood Institute, date published:03/30/2020, Date Updated: 04/09/2020
 46. von Korn H, Graefe V, Ohlow MA, et al. Acute coronary syndrome without significant stenosis on angiography: characteristics and prognosis. *Tex Heart Inst J.* 2008;35:406-412

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 30-03-2020; **Accepted:** 15-04-2020; **Published:** 31-05-2020