"CLINICAL AND ANGIOGRAPHIC PROFILE, AND MANAGEMENT TRENDS IN PATIENTS PRESENTING WITH CORONARY CHRONIC TOTAL OCCLUSIONs IN A TERTIARY CARE CENTRE IN SOUTH INDIA"

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In partial fulfillment of

DM - Branch II CARDIOLOGY

Examination to be held in August 2014

C E R T I F I C A T E

This is to certify that the dissertation entitled

"CLINICAL AND ANGIOGRAPHIC PROFILE, AND MANAGEMENT TRENDS IN PATIENTS PRESENTING WITH CORONARY CHRONIC TOTAL OCCLUSIONs IN A TERTIARY CARE CENTRE IN SOUTH INDIA"

is a bonafide work done by

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Christian Medical College, Vellore, Tamil Nadu

in partial fulfillment of the University rules and regulations
for award of
DM - Branch II CARDIOLOGY

under my guidance and supervision during the academic year 2011-14

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ABSTRACT

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AIM AND OBJECTIVES

The purpose of this study was to delineate the clinical profile and angiographic characteristics of consecutive patients diagnosed with chronic coronary total occlusions in a tertiary care hospital in India and observing the "real world" management trends for such patients.

MATERIAL AND METHODS

This single centre prospective non-randomized observational study enrolled 66 consecutive patients diagnosed with CTO. The clinical and angiographic characteristics of these patients (including calculation of SYNTAX score for each patient and a unique technical difficulty rating for each CTO lesion) and the management decisions subsequently undertaken in them were studied. Continuous variables were expressed using mean ± S.D. or median with ranges, categorical variables as frequencies and percentages. Categorical variables were analysed with Chi square test /Fisher's exact test and continuous variables with unpaired students *t* test with p values less than 0.05 considered statistically significant.

RESULTS

Out of the 66 patients with CTO enrolled, 89% were males with mean age 59 years, 85% were symptomatic having angina NYHA class II or more. 55 % of the patients had systemic hypertension, 39% had diabetes mellitus, and only 17% had LVEF < 40%. More than half of patients had CTO whose duration couldn't be discerned, with these patients predominantly undergoing CABG subsequently and also having the majority of unsuccessful PCI. About

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CONTENTS

ABSTRACT

CLINICAL AND ANGIOGRAPHIC PROFILE, AND MANAGEMENT TRENDS IN PATIENTS PRESENTING WITH CORONARY CHRONIC TOTAL OCCLUSIONs IN A TERTIARY CARE CENTRE IN SOUTH INDIA

Keywords- Chronic total occlusion, Coronary artery disease, SYNTAX score, Universal Technical difficulty score

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RESULTS :

Out of the 66 patients with CTO enrolled, 89% were males with mean age 59 years, 85% were symptomatic having angina NYHA class II or more. 55 % of the patients had systemic hypertension, 39% had diabetes mellitus, and only 17% had LVEF < 40%. More than half of patients had CTO whose duration couldn't be discerned, with these patients predominantly undergoing CABG subsequently and also having the majority of unsuccessful PCI. About half of the patients enrolled had no history of prior ACS or MI, three months or earlier before presentation. Multivessel CAD was present in more than 90% CTO patients with around 80% of patients having a SYNTAX score of 23 or above. Median SYNTAX scores were highest in patients who had CABG and least with PCI group (p value 0.04) pointing towards management trends conforming to international guidelines. RCA was the most commonly involved CTO vessel in 49% patients and the majority of patients with RCA CTO had unsuccessful PCI. Patients having CAD risk factors like diabetes and hypertension, and angiographic characteristics like bridging collaterals, blunt stump, and longer length hand technical difficulty rating of A2B0 were found to have the maximum failure with PCI. The success rate of PCI at our centre was 76% comparable to international standards. The six month follow up of CTO patients showed improvement in NYHA class of symptoms in all three treatment allocation groups with the revascularization cohort having maximum benefit.

CONCLUSIONS:

This study brings forth the clinical and angiographic data in contemporary practice in India and real world management trends with regard to coronary CTOs in addition to delineating probable factors associated with success of revascularization of this complex subset of coronary lesions, also showing a probable benefit of revascularization in these patients at a six month follow up.

INTRODUCTION

Coronary heart disease (CHD) is said to occur when the arteries of the heart , that normally provide blood and oxygen to the heart are narrowed or even completely blocked (1). CHD is the leading cause of death in India and also worldwide; it was earlier thought to affect developed countries with high per capita income primarily, but has now become the leading cause of disability and death in low and middle-income groups in developing countries, which include India. The disease is growing at rates that are much higher in these countries compared to high per-capita income countries. The disease affects predominantly younger patients in these low to middle per capita income countries, and thereby has a greater economic impact in such countries (1). There is a paucity of data on CHD in these countries including India; the available studies which report on the prevalence of cardiovascular disease point towards CHD as the largest contributor to the burden of cardiovascular disease burden. In India, with an approximate population of 1.03 billion people at the beginning of the twenty first century, about 29.8 million people were estimated to be suffering from CHD, a 3% overall prevalence in the general population (2).

Chronic Total occlusion (CTO) represents an enigma to interventional cardiologists due to the technical challenges involved, with procedural success rates considerably lower than those achieved in non-occluded arteries despite advancement in recanalization technique. There is scant data available about clinical presentation and characteristics of patients with CTOs, and about the preferred way to manage patients identified with CTO during diagnostic coronary angiography, particularly in the current era of advanced imaging techniques, recanalization and drug eluting stents. We planned to collect and analyze current data with respect to clinical and angiographic profile as well as to document the management trends being undertaken in patients diagnosed with CTO on coronary angiogram presenting to Christian Medical College, Vellore.

AIMS AND OBJECTIVES OF THE STUDY

1. To determine the clinical profile of patients identified with coronary chronic total occlusions
2. To study the angiographic profile of patients with CTO, quantifying the extent of coronary artery disease by calculation SYNTAX score and assessing technical difficulty of CTO lesions with a unique scoring system.
3. To study the management trends undertaken in patients with CTO presenting to Christian Medical College, Vellore.

REVIEW OF LITERATURE

DEFINITION :

CTO have been defined on the basis of expert consensus published by Stone (3) as significant vessel narrowing due to atherosclerotic process and intraluminal obstruction that results in either complete cessation of antegrade blood flow noted on coronary angiography (TIMI {Thrombolysis in Myocardial Infarction} grade 0 flow), also termed as “true” total occlusions, or with minimal antegrade contrast penetration through the lesion without distal vessel opacification (TIMI grade 1 flow) , which has been commonly termed as “functional” total occlusion.

The duration of coronary occlusion is difficult to pinpoint if serial angiograms are not done or available, and instead must be estimated from clinical data related to timing of event that caused the occlusion, eg. acute myocardial infarction, acute coronary syndrome with NSTEMI/unstable angina or abrupt change in the pattern of anginal chest pain with ECG changes consistent with the site of the occlusion. In a sizeable number of patients it is difficult to determine the duration of CTO with confidence. Also, the temporal criterion which was used to define a CTO had varied widely in prior reports, but the consensus is that a total occlusion of duration >3 months is “chronic.”(3) Those lesions in which no chronological sequence can be obtained from either historical evidence or ECG, are termed “chronic total occlusion of unknown duration”(3).

PREVALENCE :

Without screening the entire population (including asymptomatic individuals), the true prevalence of CTO in the general population will not be known because many patients are minimally symptomatic or asymptomatic and may never undergo diagnostic coronary arteriography. Thus, all data available comes from the details of patients undergoing for diagnostic coronary arteriography for clinical indications.

Among patients with known or suspected CHD who underwent coronary angiography during 1992, one or more CTO, was documented in about one third of cases, 46% of which were suitable for PCI (4). In a registry analysis of 8004 consecutive patients undergoing diagnostic coronary angiography in a single institution during 1990-2000, after excluding patients with prior CABG or recent myocardial infarction (MI), CTO was found in 24% of all the patients and in 52% of patients with CHD. The vessel involved by the CTO was the left anterior descending artery (LAD) in 28%, the left circumflex (LCx) in 35% and the right coronary artery (RCA) in 65% (5).

The 1999 NHLBI Dynamic Registry of patients conducted in four waves (1997 to 2004) found a decrease in patients treated for CTO from 9.6% in wave one to 5.7% in wave four. This registry also highlighted the variation in success rates for CTO treatment with a range from 71.4% to 79% compared to other lesions (96% - 97%) with percutaneous coronary intervention (PCI) (6).

The National Cardiovascular Registry of the American College of Cardiology analysed the results of almost a million patients who underwent PCI at 139 US hospitals from January 1998 through September 2000 and found that PCI was attempted for CTO in 12% of all PCIs done (7). In this registry, CTOs were most commonly found in the RCA territory and least common in the LCx ; there was increased prevalence with advancing age tending to increase with advancing age with the LAD CTOs showing the best correlation with age . Despite presenting more often with CTO, the proportion of older patients on whom CTO recanalization was attempted was significantly less (7).

In a recent prospective Canadian registry(8) conducted at three centres during 2008-2009 enrolling more than 14000 patients who underwent non-emergent coronary angiogram , at least one CTO was present in 2,630 patients i.e. a prevalence of 18.2 % overall. In post CABG patients the prevalence of CTO was 54% (58 % of these patients had multiple CTOs)

and in patients who underwent primary PCI for acute S-T segment elevation myocardial infarction (STEMI) , 10% had a CTO in the non-culprit vessel (8).

Among patients who suffer acute MI, a significant proportion develop CTO in the infarct related vessel, the frequency of which depends on how the revascularization was carried out i.e. primary angioplasty thrombolysis or none at all, as well as the time interval to patency assessment (9). In patients with STEMI managed without revascularization therapy, a completely occluded infarct-related artery was found in 87% of patients within 4 hours, 65% within 12 to 24 hours, 53% at 15 days, and 45% at one month (10,11). Among patients who underwent thrombolysis, 30% of them had a CTO at 3-6 months post- MI and those who underwent primary balloon angioplasty or stenting a CTO in the infarct related artery was found in 5 to 10% of the patients at 6-7 months follow up (3).

ANATOMY AND HISTOLOGY OF CTO :

The major limitations of CTO PCI are the inability to cross the lesion with a wire or dilate the lesion, as well as the high incidence of restenosis and reocclusion in these lesions. Therefore to innovate new techniques and revascularization therapies it is essential to understand the anatomy and histopathology of a CTO.

Srivatsa and colleagues (12) have elegantly described the histopathology of CTOs in detail. CTOs originate from thrombotic occlusions followed by thrombus organization and tissue aging. Interestingly almost 50% of all CTOs originate from lesions that are < 99% stenotic when initially observed and diagnosed on histopathology, but are seen as total occlusions on coronary angiograms with TIMI 0 flow. Also, there is very little or no relationship between the extent of histopathological endoluminal stenosis and with either lesion age or plaque composition.

The characteristic atherosclerotic plaque of CTO is composed of intra-cellular and extra-cellular lipids, calcium, extracellular matrix and smooth muscle cells. The pathological

features which are hallmark of a CTO on histopathology are 1) inflammation, 2) extent of calcification and 3) neovascularization.

The CTO can be classified on histopathology as –

1. Soft plaque- This is composed of cholesterol rich cells with foam cells, loosely held fibrous cells and loose neovascular channels. These plaques are more common in CTOs typically less than 1 year old. These plaques may allow relatively easier passage of the wire through the various tissue planes within the plaque or through the various neovascular channels that exist within.
2. Hard plaque- Here the plaque has a dense fibrotic milieu and is often composed of dense fibrotic tissue with paucity of vascularity and the age of CTO most often is > 1 year old. These are the lesions which are toughest to cross technically and are prone to guide wire tip induced dissections because of sub-intimal tracking. The extent of calcification increases as the lesion ages and thus progressively becomes harder to cross with a guide wire during PCI.

Inflammation is a hallmark of an active atherosclerotic lesion and this holds true for a CTO as well. The inflammatory cells involve predominantly the intima irrespective of the age of CTO but also affect the media and the adventitia of the vessel. CTO lesions and the involved vessel wall undergo negative remodelling as the lesion ages although plaque hemorrhage associated with inflammation may also lead to positive remodelling (3,13).

Neovascularization in atherosclerotic plaque in the CTO is extensive and progresses from the adventitia to the intima as the lesion ages with lesions > 1 year having equal or more neovascular channels than the adventitia. The origin of these neovascular channels has been demonstrated to be the vasa vasorum in the adventitia; these microchannels may recanalize the lumen of the artery distal to the occlusion identified on the CAG as a CTO with a leading

edge. The stimuli for such angiogenesis may arise from the thrombus laden plaque. In this regard there should be a distinction made with regard to the ipsilateral epicardial bridging collaterals and true microvascular collaterals; the latter may be useful for antegrade wire advancement as opposed to the former (3,14).

The proximal end of a chronic total occlusion consists of a ***proximal fibrous cap*** which makes the entry of the coronary guidewire into the CTO potentially difficult. A similar ***distal fibrous cap*** which is usually thinner exists which makes exit of the guidewire into the true lumen distal to the CTO potentially challenging after passage through the entire length of the CTO. A totally occluded segment can undergo spontaneous recanalization by lysis of the clot, advent of new microvascular channels passing through the thrombus, dilation and expansion of adventitial vasa vasorum (bridging collaterals) or through all of these mechanisms combined. Coronary microvasculature having a mean diameter of less than 0.0007 inch is invisible on coronary angiography. ***Functional occlusions*** are differentiated angiographically from true total occlusions by the presence of forward flow, which may coexist with retrograde filling from the distal part of the vessel. While tackling the lesions which have subtotal stenosis that show no collateralls carries a risk of an acute MI resulting from abrupt closure of the feeding vessel, whereas attempting to revascularise a recanalized segment doesnot. It is generally simple to negotiate through a subtotal occlusion with a coronary guidewire, but it may be laborious or impossible, even with sophisticated and dedicated CTO hardware, to negotiate through a recanalized segment. This is because the recanalized segment may consist of plentiful tortuous microvessels embedded in densely fibrous tissue or be simulated by copious vasa vasorum (15).

PATHOPHYSIOLOGY AND ROLE OF COLLATERALS

ROLE OF COLLATERALS IN PRESERVING MYOCARDIAL FUNCTION :

The presence of a well-established collateral circulation when an acute occlusion of a coronary artery occurs avoids cell death of the myocardium subtended. The extent and performance of collaterals depends on the age and the extent of occlusion i.e. collaterals are common in longstanding CHD with subtotal stenosis of vessels, but are rare in younger patients with less extensive CHD, suffering from coronary occlusion due to acute thrombosis from rupture of a non stenotic plaque.

ROLE OF COLLATERALS IN ISCHEMIA :

If a CTO has a well-developed collateral network, it is functionally equivalent to a 90 % stenosis. The collaterals sustain the functional integrity of the subtended myocardium with ischemic symptoms arising at times of increased myocardial oxygen demand such as hypertension or tachycardia in the form of exertional angina but these patients are unlikely to experience an episode of unstable angina i.e. acute occlusion with ensuing MI (15).

CLINICAL PRESENTATION :

There has been a paucity on data on the profile of patients with CTOs in the past , but recently several studies have dealt with this issue. In the recent multisite Canadian CTO registry (8) the mean age of patients with CTO was around 66 years with a majority being male (81%) . Review of several earlier databases with regard to symptom status of patients with CTO brings forth the fact that the majority of patients were symptomatic and only minority (11 to 15%) undergoing PCI for CTO were asymptomatic. Also only 9% to 18% of the patients presented with unstable angina due to CTO (3,16,17). The multisite Canadian registry the first of its kind to report on the clinical status of unselected consecutive patients

diagnosed with CTO on CAG has also reinforced these data. About 74% patients with stable coronary artery disease who underwent CAG in this report were symptomatic, even though if it is difficult to attribute the symptoms to CTO in muti-vessel disease. In line with earlier data only 5% of the patient had no symptoms (8). A history of prior MI was reported in 42% to 68% of patients with a CTO on CAG. Earlier studies have demonstrated stress-induced ischemia in patients with CTO, especially in the absence of a history of prior MI. He et al (18) demonstrated reversible perfusion defects using stress myocardial single-photon emission CT (SPECT) in 83% of the seventy one patients without history of prior myocardial infarction with single vessel disease; and CTO of a single coronary artery and also similarly Aboul Enein et al (19) demonstrated severe and extensive perfusion defects on stress in fifty six patients with no history of prior MI and a single vessel CTO. The employment of adenosine SPECT imaging is perhaps more sensitive than exercise-induced stress imaging for evaluation of perfusion defects in patients with CTO (3).

In the Canadian Multisite CTO registry (8) only 40% had a history of prior MI and 12% had history of heart failure. Also more than 50% of the patients had normal left ventricular function with a minority i.e. 17% having significantly reduced LVEF. Patients with CTO had greater prevalence of comorbidities and coexisting heart failure (12%), peripheral artery disease (8%), cerebrovascular disease (9%). In the group of patients diagnosed with CTO, 34% of patients were diabetics, 75% of patients had hypertension requiring treatment and 82% patients were found to have dyslipidemia .The electrocardiograms were analysed in the registry in 93% of the patients. Right bundle branch block was found in 7% and left bundle branch block in 6%, 5% of the patients were found to be in atrial fibrillation. When the presence of significant Q waves in the was correlated with territory of CTO, 32% of patients had Q waves in the RCA territory, 26% in the LCx and 13% in the LAD territory (8). Patients were analysed according to the treatment strategy to

which they were allocated. Patients referred to CABG compared to those put on medical management had less likelihood of prior MI, prior coronary intervention, renal insufficiency; left main coronary artery trunk involvement in 22% in the CABG patients compared to 5% in medically managed patients and 4% in the PCI Patients (8). When the patients with CTO referred to PCI were compared to the ones managed medically , the PCI group were younger (63± 0.8 yrs vs 67±0.3), had lesser diabetics (20% vs 34%) , lesser number of patients with renal insufficiency (4% vs 12%), with history of prior MI (25% vs 44%) and lesser complex anatomy by coronary index (35% vs 59%). When the CTO PCI group was compared to the CABG group , the PCI group had significantly lower patients with significant left main trunk involvement (4% vs 22%) and three- vessel CHD (31% vs 53%) (8) .Overall the medically managed patients were older , had higher prevalence of high risk findings like renal insufficiency, prior PCI and prior MI (8).

ANGIOGRAPHIC PROFILE OF CTOs :

The artery with CTO was the left anterior descending artery (LAD) in 28%, the left circumflex (LCx) in 35% and the right coronary artery (RCA) in 65% in a large study by Christofferson (5).

In the 1999 NHLBI Dynamic Registry had approximately 20% of patients who had RCA CTO , 18% with LAD CTO and the least had LCx CTO (6).

In the National Cardiovascular Registry of the American College of Cardiology, CTOs were most commonly prevalent in the right coronary artery and least common in the circumflex artery. There was a correlation with age with CTOs tending to increase with advancing age, LAD CTO show the best correlation with age (7).

The Canadian multisite registry was the first of its kind of prospective study with analysed the angiographic profile of patients. CTO were most commonly seen in the RCA (>

50%), and least commonly in the LCx. A CTO lesion whose duration could not be determined was found in 54% of patients and this was a predictor of procedural failure and major adverse cardiovascular events in this registry. Patients with absence of ACS in the prior six weeks of the coronary angiogram amounted to 54% and bridging collaterals were found in 24% (8,20).

CLINICAL RELEVANCE AND RATIONALE FOR CTO REVASCULARIZATION

Patients with chronic total occlusion, as discussed earlier, typically have well developed collaterals to the distal vessel on coronary arteriography. During conditions with increased demand these collaterals may be insufficient to maintain adequate blood supply, thus leading to anginal symptoms. These patients rarely present with an acute coronary syndrome. A CTO is clinically distinct from an acute occlusion due to an ACS or sub-acute occlusion with a delayed presentation after an ACS (15).

The complexities involving a patient diagnosed with CTO necessitates that the further treatment be strategy be tailored to the individual .The initial strategy as with any patient with chronic stable angina begins with initiating and optimization of anti-anginal and medical treatment. If despite this the patient continues to have symptomatic angina or have large burden of ischemia revascularization should be attempted. The decision on which mode of revasularization to select (PCI or CABG) is difficult at times. In patients who have a CTO in addition to left main /and or multi vessel CHD the treatment strategy of CABG is straightforward but if there is only an isolated symptomatic CTO decision regarding further strategy is challenging. Medical treatment may not benefit the patient completely and CABG may be considered too invasive for the particular patient and thus PCI is increasingly gaining recognition as a viable treatment strategy for CTOs. Currently, there is a great deal of interest in PCI as a revascularization strategy for CTOs, primarily because of the marked

improvements observed in the acute and long-term results now achievable. However, a large number of patients with CTOs are still being managed medically or referred CABG rather than PCI due to various reasons as discussed below (21,22).

Despite the huge interest in the utilization of PCI in dealing with total occlusions there have been no direct comparisons in the form of randomized controlled trials where attempted recananalizations were compared to a medical strategy. A metanalysis of observational studies by Joyal etal (23) has provided insights to the usefulness of revascularization as strategy in dealing with these complex lesions. The ACC/AHA guidelines (24) published in 2011 have advocated quantifying the burden of coronary artery disease in patients with the help of SYNTAX score or Society of Thoracic surgeons score , which also helps formulating the revascularization strategy for the patient.

PCI is generally indicated if :

1. If the vessel occluded is responsible for the symptoms of the patient or in certain cases of silent ischemia when the ischemic burden is large.
2. The territory subtended by the CTO is viable
3. The chances of successful revascularization is moderate to high (> 60%) , with a expected rate of major cardiovascular outcome of death < 1% and MI < 5% **(25)**.

ACC/AHA guidelines gives a ***class IIa*** recommendation for the revascularization with PCI of CTOs i.e ,

- PCI of a CTO in patients with appropriate clinical indications and suitable anatomy is reasonable when performed by operators with appropriate expertise. ***Class IIa (Level of Evidence: B)*** (24)

CABG as management strategy for CTOs :

In patients with multivessel CAD the risk –benefit analysis of bypass surgery compared to PCI should be considered. Generally CABG is preferred strategy if –

1. Presence of left main artery disease.
2. Complex multi vessel CAD especially in patients with Diabetes Mellitus, severe left ventricular systolic dysfunction, and/or renal insuffiency.
3. A proximal LAD which is completely occluded.
4. More than one CTO in whom the anticipated success rate with PCI may be low.

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial has shown that patients with multivessel CAD, there was no major differences in the rates of death and myocardial infarction between the patients treated with PCI and bypass surgery but the patients with PCI were found to have more Target vessel revascularization procedures on follow up in particular the patients with complex coronary anatomies. It also important to note that presence of CTO is major contributor to a high SYNTAX score as delineated in the table given below (26). In the trials conducted a decade ago presence of a CTO was the most common indication for referral for bypass surgery.

The BARI trial enrolled 12,350 patients, randomized into two treatment arms of PCI and CABG. In this large trial the presence of one or more CTO was the most common reason for exclusion or ineligibility for PCI(25,27). Similarly in a study conducted by Rastan et al(22) patients with CTOs and high SYNTAX scores were more common in CABG registry patients compared to those randomized to PCI. In this study compared to the patients who were enrolled in the PCI arm, the patients who were referred for CABG had more complex CAD (SYNTAX score 34 vs 26, p =0.003) with significantly more chronic coronary vessel occlusion (70.8% vs. 22.5%, p= 0.04).

Table 1 : THE LESION ADVERSE CHARACTERISTIC SCORING OF SYNTAX TRIAL (26,28)

Diameter reduction*		
- Total occlusion		x5
- Significant lesion (50-99%)		x2
Total occlusion (TO)		
- Age >3months or unknown		+1
- Blunt stump		+1
- Bridging		+1
- First segment visible beyond TO		+1/ per non-visible segment
- Side branch (SB)	- Yes, SB <1.5mm**	+1
	- Yes, both SB < & ≥ 1.5mm	+1
Trifurcations		
- 1 diseased segment		+3
- 2 diseased segments		+4
- 3 diseased segments		+5
- 4 diseased segments		+6
Bifurcations		
- Type A, B, C		+1
- Type D, E, F, G		+2
- Angulation <70°		+1
Aorto ostial stenosis		+1
Severe tortuosity		+2
Length > 20mm		+1
Heavy calcification		+2
Thrombus		+1
"Diffuse disease"/small vessels		+1/ per segment number

x: multiplication
+: addition

* In the SYNTAX algorithm there is no question for % luminal diameter reduction. The lesions are considered as significant (50-99% luminal diameter reduction) or occlusive.

** If all the side branches are 1.5mm in diameter, no points are added since the lesion is considered as a bifurcation and it will be scored as such.

A meta analysis of 13 observational studies including 7,288 patients between 1979 and 2006 conducted by Joyal et a al (23) was the first of its kind comparing successful CTO recanalization to a strategy of medical management as a result of attempted but failed recanalization. This analysis showed 1) a decrease in all cause mortality of 44% in the group with successful recanalization { 14.3% vs 17.5% , odds ratio (OR) 0.56 , 95% confidence interval} , 2). a significant reduction in recurrent angina by 55% during follow up compared with patients undergoing unsuccessful PCI (OR of 0.45; 95%

confidence interval) and 3) a 78% reduction in patients referred for subsequent CABG. This study showed a neutral impact of successful recanalization on myocardial infarctions during follow up (OR of 0.74) or major adverse cardiovascular events (MACE) (OR of 0.81).

The lack of benefit of PCI in prolonging life or reducing MI is well known and the COURAGE and OAT follow up trials (29,30) have clearly shown this, but these trials have not addressed CTO specifically although in the COURAGE substudy (31) benefit of revascularization in moderate to severe ischemia documented with the use of myocardial perfusion single photon emission computed tomography had shown event reduction in CAD , and since the population of CTOs have a large ischemia burden they therefore are likely to benefit from revascularization. The MI rates are not reduced as MI/ACS are caused usually by a rupture of a non-occlusive coronary plaque and thus CTO revascularization would unlikely be of benefit in reducing MI rates.

However CTO revascularization may improve the left ventricular function in a viable territory subtended by the CTO as shown in two studies utilizing cardiac MRI. Kirschbaum etal have shown that there was a significant improvement in the left ventricular end-diastolic and systolic dimensions as well as the fractional shortening and an improvement in the left ventricular function indices upto three years post successful PCI (32–34). Valenti etal (35) in an updated cohort of more than 300 patients with successful PCI with drug eluting stents had shown a significant improvement in cardiac survival at 2 years of 91.6% compared 87.4% in whom the attempt was unsuccessful. The above meta-analysis also delineated certain high risk characteristics of CTO leading to failed recanalization. Two studies showed that calcified CTOs frequently remained uncrossable and was a poor prognostic marker suggesting a high coronary disease burden

(36,37). The patients with failed recanalization were also sicker with shorter life expectancy and had more comorbidities like renal failure.(23)

There is also a correlation between the site of CTO and the subsequent survival benefit as shown by Safley et al (38) but this is the only study which has reported such a corelation. They showed that revascularization of the LAD CTO improved survival of patients as compared to revascularization of RCA or LCx.

SUCCESS OF REVASCULARIZATION WITH PCI OF CTOs

Despite the benefits of revascularization of CTOs as enumerated, the PCI attempt rates to CTOs compared to other coronary lesions are far lower. Revascularization of CTO with PCI accounts to around 10% of the total procedures performed, maximum being 20% at selected specialized CTO centers. The presence of CTO was one of the major angiographic exclusions in clinical trials of PCI versus CABG for multivessel CAD and usually led to referral to CABG (25).

In the Canadian multisite registry (8) the practice trends of the management and referral pattern was analysed. In this registry 64% of the patients were managed medically , and CABG was performed in 26% of the patients. In patients who underwent surgical revascularization the CTO was grafted in 88% of the patients. Percutaneous intervention was performed in 30% out of which 10% had PCI to the CTO vessel. Thus 30% of the patients had successful revascularization of the CTO vessel either by PCI or surgery. The earlier registry of PCI had found that CTO group represented 12% to 15.6% of the overall PCI patient population group (6,7). Analysis of the study of Anderson et al (7) from the NHLBI dynamic registry has shown that the PCI attempt rate among the CTO patients diagnosed on coronary angiogram ranged from 11.7% in 2005 to 13.6% in 2004.

The operator volume and the skill also determines the decision of revascularization with PCI in CTO s and has resulted in wide disparity in PCI attempts (21). In the single center review from Mayo clinic (39) procedure success of PCI in the present era with balloon angioplasty to CTO was 51% between 1979 and 1989 , 72% in the early stent era 73% in the bare metal stent era and 70% in the drug eluting stent era. Not only did the success of PCI improve the in-hospital mortality, major adverse cardiovascular events and target vessel revascularization declined by more than 50% compared to the present era.

In the Canadian multicenter registry there was wide variation in success of PCI ranging 1% to 16% in the patients of CTO in all centers compared to CTO specialized and high volume centres. In this study the success rate of CTO PCI was 70% which was consistent with earlier observational retrospective studies namely such as Mid America Heart Institute study of 2007 patients with a PCI success of 74.4% (40), the British Columbia Cardiac Registry of almost fifteen hundred patients with 76.7% success (3) and the TOAST- GISE with a success rate of 77.5% (16) . More recent studies conducted at CTO specialized centers have reported success rates in excess of 80%(8) . Thompson et al (41) showed that high volume CTO operators had a 75.2% success rate to 58.9% in low volume centers whereas in the J-CTO registry by Morino etal (42,43) a guidewire crossing rate of 88% was reported in patients with CTOs.

The increasing use of coronary microcatheters like Corsair microcatheter have also contributed to the improved rates of revascularization of CTOs. In a study by Joseph et al (44) the use of corsair microcatheters have shown to increase successful revascularization rates with decreased complications especially in the hands of non - CTO specialists. There was successful recanalization in 86% of patients in the Corsair- assisted PCI compared to the 27% success with significant complications in the pre- Corsair period attempts to PCI which was mainly due to aggressive attempts at antegrade recanalization.

LIMITATIONS OF CTO PCI

CTO PCI success rates of 70% as discussed earlier are far below the 97% angiographic success rates of non-CTO PCIs (45). The CTO is the most challenging lesion in interventional cardiology due to high atherosclerotic burden, inability of vessel course visualization and the often longer length of these lesions. Inability to obtain successful guide wire crossing is the most common reason of failure of CTO PCI. Failure of balloon delivery and stents into the tough fibrotic and calcific lesions is the next level of obstacle in these procedures (46).

PCI for CTO is also associated with longer procedure and fluoroscopic times (almost twice as for non CTO lesions) and a significant utilization of catherization laboratory resources, this may result also in inefficient use of personnel and physician time which decrease the flow of patients in and out of the catherization laboratory (21). Also, as compared to non-CTO PCIs disproportionately greater use of PCI equipment such as guiding catheters, lesion crossing specialized catheters, coronary guidewires and stents is required . It may difficult in some centres for physicians to justify the disproportionate utilization of resources when compared to CABG or medical treatment especially when the rates of success of PCI in these patients are less.

ADVERSE EFFECTS AND COMPLICATIONS OF PCI UNIQUE TO CTOS

Several drawbacks and complications are often seen in and are unique to CTO PCIs as compared to other lesion subsets which further reduce the interest in revascularization of such lesions by many operators.

Firstly, a major drawback of CTO PCI is the increased radiation exposure due the long fluoroscopy times and increased use of contrast agents. The increased rates of coronary dissections due to aggressive manipulation of coronary guidewires which may occur and

may not be visualized on fluoroscopy. Many of these dissections may result in vessel wall perforations and cardiac tamponade. If the antegrade circulation is collateral dependent, damage to these collaterals can compromise the myocardial bed subtended and lead to ischemia and increased peri-procedural infarction. An experienced Japanese CTO center has reported the in-hospital complication rates of 0.5%, myocardial infarction in 3% , emergency CABG in 0.2% tamponade in 0.6% (47).

SCORING SYSTEMS FOR PREDICTING PROCEDURAL SUCCESS FOR CTOs

UNIVERSAL CLASSIFICATON

The universal classification of CTO proposed by Jayasinghe et al (48) proposed a novel and simple classification for predicting the technical difficulty in attempting PCI of CTOs. This classification was based partly on studies done earlier delineating the several angiographic predictors of successful PCI such as lesion length, presence of bridging collaterals , transluminal coronary calcification etc (36,49,50). The classification is based on the technical difficulty of revascularization and classified as Grade A and Grade B which is the risk of adverse outcomes post PCI. The higher the A ranking the greater the technical difficulty whereas the higher "B" ranking is associated with increased risk in attempting to revascularize the artery. Thus each CTO is finally classified as –

Grade "AB" classification overview

1. A0 B0 – suggests increased chances of reopening, with low risk of complications;
2. A1 B0 – Lower chances of reopening, but the risk of complications is low;
3. A2 B0 – Technically difficult lesion to cross and revacularize, but with low risk of complications;
4. A0 B1 – High probability of reopening, but at the cost of high risk of complications;
5. A1 B1 – Lower probability of reopening, with high risk;
6. A2 B1 – Technically the hardest lesions to revascularise, with high risk.

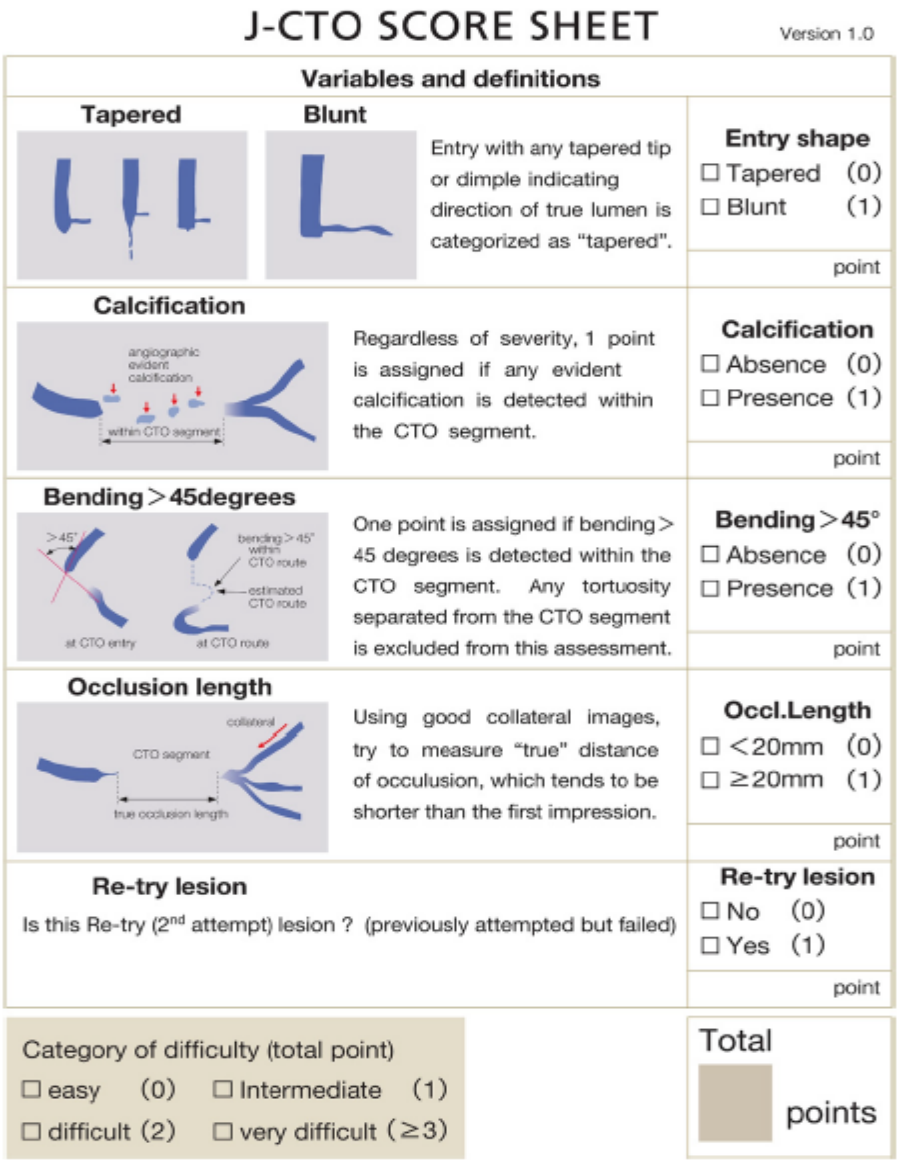
Table 2. Technical difficulty score categories by Jayasinghe etal (48)

A0-higher possibility of technical success & crossing lesion	A1- Lower possibility of technical success & crossing lesion	A2-Least possibility of technical success & crossing lesion
• A stem of patent vessel longer than 10 mm; • No branching vessels originating within 5 mm of the occlusion • Tapering configuration or a visible track • No evidence of calcification on fluoroscopy	• A stem of patent vessel shorter than 10 mm proximal to the occlusion; • Presence of branching vessels originating within 5 mm of the occlusion • Blunt configuration of the leading edge with no visible track • Evidence of some calcification on fluoroscopy	• Ostial total occlusion • Total occlusion precisely at a bifurcation point • Significant calcification on fluoroscopy • Long lesion as evidenced by retrograde filling of the distal segment.

B0-grade denotes a relatively low risk of adverse outcomes
Absence of bridging collateral vessels; **Absence of an aneurysmal appearance at the point of occlusion or in close proximity;** **Presence of good distal vasculature as seen by retrograde filling via collaterals from other arteries.**

Morino et al (42,43) proposed another simple integer score, the "J-CTO score and prediction rule". This is another simple scoring system which also gives the physician an approximate idea of the time to cross the CTO as this score has been shown to predict guidewire crossing time. This score thus predicted the technical difficulty of the planned PCI and the procedural time a physician is likely to encounter prior to attempting revascularization.

Figure1



As shown in the scoring sheet the rule classified the patients into 4 groups :

1. Easy (score of 0)
2. Intermediate (score of 1)
3. difficult (score of 2)
4. very difficult (score ≥of 3)

The J-CTO score (43) predicts 'procedural difficulty' and the 'time efficiency' of attempting revascularization of a CTO. Both may correlate but are not identical, as a PCI

procedure for a difficult CTO lesion may ultimately may have a successful outcome depending on the operator skill and specialized CTO revascularization devices but these procedures may be time consuming. Thus the patients in the designated "Easy" group had a 97.8% procedural success rate with approximately 90% lesions taking < 30 min of crossing time whereas the "Very difficult" had a success of of 73.3% with only 15% of the lesions crossed in < 30 min and almost 40% requiring 60 minutes or more for successful coronary guidewire cross (43).

TECHINQUES OF CTO PCI AND ADVANCES IN THE CURRENT ERA :

Choosing an approach is the initial step in revascularization of CTO by PCI. The techniques are broadly characterized as either antegrade or retrograde, with several successfully employed variations having been described. The antegrade approach may be performed in a similar way to standard PCI where the lesion is wired, dilated, and stented with routine equipment. A proper guiding catheter selection is critical to ensure a successful outcome as in any PCI. Guiding catheter support is of paramount in CTO PCI where the ability to pass wires and equipment with repeated pushing through long tortuous or occluded segments is essential for success. Larger guiding catheters i.e. 7 French or 8 French lumen are frequently employed due their increased stiffness and ability to handle adjunctive equipment (i.e., intravascular ultrasound). Guiding catheters used for CTOs arising from the left coronary tree are usually the Amplatz or Extra Backup, and either traditional or modified Amplatz for those in the right coronary artery. The Amplatz guides are particularly are useful as they provide excellent support even when seated in the coronary sinus non-coaxial with the proximal vessel, thus lowering the chances of dissection. For difficult lesions, additional guide support can be achieved through the use of an anchor balloon, typically a small over-

the-wire (OTW) balloon placed in a small side branch and inflated to low pressure to provide counterforce for firm engagement of the guide catheter.(51)

The guidewire design has undergone a significant improvement and has provided have improved success rate in revascularization in CTOs. It is reasonable to attempt CTO PCI with standard workhorse wires and select progressively stiffer wires as necessary to re-enter the distal true lumen. Several coronary wires are available and offer choices in hydrophilicity and varying tip stiffness and are particularly useful in attempting CTO PCI. Non- hydrophilic wires (Miracle Bros/ Confianza, Abbott Vascular Inc, Abbott Park, IL) offer better tactile response when attempting to penetrate the CTO and are favoured when blunt dissecting through a fibrocalcific cap or organized thrombotic core. Hydrophilic wires (Fielder/Whisper, Abbott Vascular Inc) are preferred when navigating micro channels or tortuous segments where increased tip lubricity is helpful in overcoming frictional forces. The addition of an OTW balloon or a supporting catheter offers reinforcement when attempting to penetrate demanding lesions. By providing a fulcrum for the wire, these devices, when advanced close to the lesion, increase the buckling load on the wire tip, thus allowing for maximum penetrating force.

The introduction of microcatheters has also helped to improve manoeuvrability by reducing friction along the length of the wire and permitting guidewire exchanges without loss of progress through the lesion and are increased preferred to angioplasty balloons for this purpose, and also because of reduced wire bias and optimal wire torque response. Catheters currently approved for use and with widespread popularity in the CTO community are primarily marketed as neurovascular devices, and include the Transit (Cordis Corp, Warren, NJ), Tracker (Boston Scientific, Natick, MA), and the Finecross (Terumo Medical Corp, Somerset, NJ) catheters. An adaptation of the standard support catheter, the Tornus (Abbott

Vascular Inc) is a braided stainless steel catheter with a tapered threaded tip that allows the catheter to be advanced through a lesion while torquing to provide additional penetrating force. Commonly used guidewires and devices for CTO PCI are listed in Table 3 below:

Table3 Types of PCI Hardware available for CTO PCIs

Guidewires	Tip Load (g)	Utility
Fielder, FC, XT	1	Excellent for antegrade microchannel and retrograde collateral tracking
Miracle Bros	3, 4.5, 6, 9, 12	Variable penetrating power with excellent tactile feedback
Confianza	9, 12	Excellent penetrating force with great tip steering against resistance
Confianza Pro	9, 12	Improved torqueability associated with hydrophilic coating
Pilot 50, 150, 200	1, 5, 3, 4.5	Hydrophilic with a nitinol shaping wire
Choice PT,PT Graphix	3.2, 3.0	Hydrophilic and good support for device tracking
Runthrough	1	Soft tip with nitinol core and hydrophilic coating
Persuader	3, 6, 9	Variable power for penetration
Whisper LS, MS	1, 3	Excellent tracking in tortuous vessels
Support Catheters	**Crossing Profile (F)**	**Length (cm)**
Finecross	Tapered 1.8–2.6	130, 150
Progreat	Tapered 2.4–2.9	110, 130
Tracker	Tapered 1.9–2.4	150
Transit	Tapered 2.5–2.8	100–170
Tornus	2.1, 2.6	135
Corsair	Tapered 1.3–2.8	135–150

SUBINTIMAL TRACKING AND RE-ENTRY TECHNIQUES :

Subintimal space entry is a common occurrence during attempted in CTO PCIs and several novel techniques are employed in these cases. Muhammad et al(52) in a study have shown subintimal wire tracking occurred in 45% of cases. A previous attempt at CTO PCI was more common (42% vs. 7%, $p \leq 0.05$) in those cases where subintimal tracking was present. Also these cases were associated with a significantly longer final mean stent length (71 vs. 50 mm), procedure time (122 vs. 69 min), fluoroscopy time (47 vs. 22 min), and contrast

dose (300 vs. 199 mL, $P \leq 0.05$ for all). There was one perforation in the subintimal group which was successfully treated with stent placement.

The use of subintimal guidewire left behind which is left behind as a marker to help guide passing of a second coronary wire into the true lumen and is termed as " parallel wire method"(53).

A novel modification of the support catheter concept by BridgePoint Medical Systems (Minneapolis, MN) has produced a complete CTO PCI crossing system particularly applicable to an antegrade approach. The system is comprised of 3 elements: the CrossBoss CTO catheter, the Stingray CTO orienting balloon catheter, and the Stingray reentry guidewire with a tapered tip. The CTO catheter has a highly torqueable coiled wire shaft and an atraumatic 1-mm rounded tip that tracks in advance of a guidewire via the facilitated antegrade steering spin technique. Now depending on whether the crossing catheter remains within the true lumen during penetration of the lesion, the CrossBoss may be removed, leaving a guidewire in place to allow either balloon angioplasty and stenting or implementation of the second element, the Stingray re-entry balloon catheter. To facilitate re-entry into the true lumen, the Stingray balloon is advanced within the subintimal space adjacent to or just past the distal cap and inflated, which provides a fulcrum with orthogonal orientation of 2 exit holes within the balloon. Then, using a proprietary re-entry guidewire, the distal true lumen is entered via the abluminal exit hole (54,55).

USE OF COLLATERALS IN REVASCULARIZATION :

The contralateral collaterals when present offer a variety of advantages in dealing with PCI of CTOs. During an antegrade attempt of revascularization contrast injection

through collateral vessels (via an additional diagnostic catheter) will help delineating the distal true lumen and provides a target for distal guidewire manipulation.

Retrograde approach to CTOs is an adaptation of the technique first described by Kahn and Hartzler (56). It is generally used after the failure of the intial antegrade attempt at revascularization as it requires considerable technical skill and specialized hardware. It uses the collateral vessels in an attempt to cross the occluded segment through an intial penetration of the distal fibrous cap.

There are both epicardial and endomyocardial (septal perforator) collateral channels which exist and the latter are preferred for revascularization with retrograde PCI. These endomyocardial collaterals are generally less tortuous and more elastic, thus facilitating guidewire passage and also reduce the risk of perforation during guidewire manipulation. The septal collaterals can also be dilated to allow easy passage of balloons and even stents when required. Epicardial collaterals are less ideal given as they are very fragile, thin-walled vessels that can be perforated by balloon dilation or aggressive wire manipulation. Navigation of collateral vessels is typically approached with the assistance of one of the many commercially available microcatheters. These are as follows -

- Small outer diameter over the wire (OTG) microcatheters e.g. Finecross catheter. It is an end-hole catheter with a tapered profile available in length 130- 150cm , also allowing selective contrast injection of candidate collaterals vessels.
- Corsair microcatheter (Asahi Intecc Co Ltd, Aichi, Japan) - It is specially designed for retrograde collateral navigation and acts as a septal channel dilator with a flexible, gradually tapering tip. It has a braided tungsten core, with an outer diameter of 2.6F and has a 20-cm screw-head tip comprised of a tungsten wire helix that allows the operator to progress through septal or epicardial channels by rotation in either direction. The catheter should not be over rotated to more than 180 degrees in either

direction. This catheter is designed to maximize flexibility and its tip is made from a polyamide and tungsten powder mixture whereas the hydrophilic coating reduces the frictional forces. Corsair has greater fluoroscopic tip visibility and also allows antegrade contrast injection for distal lumen visualization **(44,57)**.

- Tornus microcather (Asahi Intecc) – This is also a braided wire mesh OTW microcatheter which has a left handed thread and is helpful for channel preparation and crossing the resistant occlusion. The Tornus is advanced with only counterclockwise rotation and removed using counterclockwise rotation. There should always be coronary wire within its lumen during manipulation and should not be over rotated to prevent kinking of the catheter. This catheter doesnot allow for antegrade contrast injections as the contrast escapes through the wire braid and does not reach the tip.

DEDICATED CTO DEVICES :

In recent times several new devices designs specifically for revascularization of CTOs have been launched. The RVT CTO Guidewire Device (ReVascular Therapeutics, Sunnyvale, CA) which is a 0.014 inch gudewire system that is composed of a rotating wire tip which is placed in a hollow outer shaft which can be engaged to facilitate wire passage through difficult lesions. The rotating tip has also audio and video feedback of the load condition on the tip of wire. A first in man study of this device in consecutive cohort of patients undergoing CTO PCI has reported an overall success rate of 62.5% with no major adverse effects at 30 day follow up **(58)**.

The **CROSSER** (Flow Cardia, Sunnyvale, CA) is another dedicated CTO device has gained the Food and Drug Administration's approval of the CROSSER in 2008. This is a 6F-compatible monorail catheter and with irrigation outlets placed within a vibrating stainless

steel tip. When the device is activated at the site of occlusion, the device is advanced in front of the guidewire while the blunt tip vibrates at 20 kHz and delivers saline irrigation for cooling. The high-frequency motion of the catheter tip is designed to fragment the fibrous tissue along the length of the CTO with potentially lower risk of perforation. This device was used in 125 consecutive patients with failed CTO PCI attempt using conventional techniques reported a success rate of crossing the lesion in 60.8% of cases with an average fluoroscopy time of 12.4 minutes **(**59**)**.

MATERIALS AND METHODS

STUDY DESIGN :

This was a prospective observational study of patients of coronary artery disease (CAD) diagnosed with CTOs on coronary angiogram. The detailed clinical profile of these patients was studied with respect to coronary risk factors and other parameters. The angiographic data was analysed delineating CTO territory also including the number, location and angiographic severity of additional coronary lesions (defined as stenosis of 50% or more), vessel tortuosity, CTO location at the site of a significant bifurcation, calcification, lesion length of the occlusion and the extent of CAD was expressed as the SYNTAX score(26). The management decisions undertaken in the patients i.e. either medical management or revascularization (percutaneous coronary intervention or coronary artery artery bypass surgery) diagnosed with CTO were noted.

SETTING :

The study was conducted in the Department of Cardiology, Christian Medical College, Vellore between December 2012 to November 2013. The study enrolled 66 consecutive patients who underwent a coronary angiogram (CAG) in CMCH Vellore or had undergone CAG elsewhere and were diagnosed with CTO in one or more vessel. A detailed clinical history, meticulous clinical examination and coronary risk factor analysis was done for each patient diagnosed with CTO. The coronary angiograms were analyzed for lesions with >50% extent or complete occlusions. An attempt was made to study the detailed angiographic profile of patients with CTOs, the burden and complexity of CAD was quantified on the basis of SYNTAX score(28) and CTOs were also classified according to the universal classification(48). The management decision subsequently taken for these patients i.e. were

they managed medically or revascularization was attempted with PCI or referred for CABG was noted and an attempt was made to correlate the management of the patient with the extent of CAD, complexity of CTO with the help of SYNTAX score and universal classification of CTOs.

INCLUSION CRITERIA :

- All patients with coronary artery disease (> 50% stenosis on coronary angiogram, visual assessment by a single investigator) with CTO in one or more vessel were enrolled in the study.

A CTO was defined on the basis of expert consensus published by Stone (3) as significant vessel narrowing due to atherosclerotic process and intraluminal obstruction that results in either complete cessation of antegrade blood flow noted on coronary angiography (TIMI {Thrombolysis in Myocardial Infarction} grade 0 flow) which was known or assumed to be of more than three months verified on coronary angiography or history of prior acute coronary syndrome (ACS) ≥ 3 months of presentation to us.

A CTO with no prior history of ACS and unknown duration was classified as "CTO of duration unknown."(3)

An ACS was defined as hospitalization for ST segment elevation myocardial infarction or unstable angina and/or rest angina pain or chest pain with minimal activity or of worsening intensity and /or electrocardiographic changes consistent with ischemia and/or cardiac biomarker rise.

EXCLUSION CRITERIA :

- All patients with prior CABG.
- Patients who have history of Acute coronary syndrome (ACS) within last three months.

CLINICAL PROFILE :

The clinical profile of all the patients was studied with a detailed clinical history and clinical examination. The demographic profile of the patients was also noted.

The symptom status e.g.) class of angina, dyspnoea, palpitations and fatigue was noted and classified according to the New York Heath Association (60) , history of syncope were also noted.

The presence or absence of prior ACS either on basis of history or evidence on electrocardiogram, prior history of CAD, conventional CAD risk factors i.e. smoking status (past or current), Diabetes mellitus (HbA1c >6.5 g%), systemic hypertension, chronic kidney disease, peripheral artery disease, were assessed in each patient .

The clinical and biochemical parameters like body mass index and estimated GFR (calculated by abbreviated MDRD calculator) which was divided into two groups with 60ml/min/m2 as a cut off. The fasting total cholesterol, serum LDL, HDL and triglycerides were obtained for each patient.

A 12 lead electrocardiogram (ECG) was obtained for every patient and all ECGs were interpreted for evidence of prior myocardial infarction (MI) in accordance with the electrocardiographic definition of MI (61), which are as follows:

- Any Q wave present in any lead (V2 to V3 > 0.02 s) or QS complex present in leads V2 and V3;

- When a Q wave ≥ 0.03 s and 0.1 ≥ mV deep or if in any leads I, II, aVL, aVF, or V4 to V6 a QS complex was present in any 2 leads of a contiguous lead grouping (I, aVL,V6; V4 to V6; II, III, and aVF);
- Or, if any R wave ≥ 0.04 s in V1to V2 and R/S ≥ 1 with a concordant positive T wave provided no conduction defect was present.

2D ECHO was obtained for every patient and the left ventricular function was assessed as ejection fraction (LVEF) by modified Simpsons method and was classified by as follows (62):

- LVEF ≥ 40% group encompassing mildly reduced to normal LVEF
- LVEF < 40% - group of patients with moderate to severe LV systolic dysfunction

ANGIOGRAPHIC PROFILE :

Presence of significant CAD was on coronary arteriography defined as stenosis in any vessel of > 50% and CTOs were identified as per the definition discussed above. The vessels with CAD, CTOs were noted with respect to various characteristics namely –

1. Location and number of CTO vessels
2. Duration- chronic or unknown
3. Type of stump- Leading edge or blunt
4. Length of lesion
5. Presence or absence of bridging collaterals
6. Presence or absence of side branches
7. If any trifurcation present at the lesion with number of diseased segments
8. Presence of thrombotic lesion
9. Presence of calcification
10. Lesion angulation

The above lesions were defined in reference to the one used in calculation of the SYNTAX score(28) and subsequently the SYNTAX score was calculated for each patient. The SYNTAX score was correlated with the extent and complexity of coronary artery disease and retrospectively with the management decision undertaken for the patient.

The SYNTAX score is calculated by a computer program consisting of sequential and interactive self-guided questions. All the definitions mentioned below were used to describe the various lesions while assessment of the coronary angiograms and calculation of the SYNTAX score (28)

Dominance: a) Right dominance: When the posterior descending coronary artery (PDA) the arises from the right coronary system.

b) Left dominance: the PDA is a branch of the left coronary artery.

Total occlusion: When there was no antegrade blood flow beyond occlusion point i.e. TIMI zero flow

Bridging collaterals: Small microchannels running in parallel to the vessel and forming a bridge between the proximal vessel to the distal vessel which is responsible for the ipsilateral collateral formation.

Trifurcation: When the proximal artery divides into one main vessel and two side branches, i.e there is a junction of three branches,

Bifurcation: The branching point of the main vessel and a side branch with the branch being ≥1.5 mm. Bifurcation lesions are classified according to the that suggested by Medina et al (63) and may involve 1 segment (types A, B and E), 2 segments (types C, F and G) or 3 segments (type D).

Aorto ostial: When a lesion is located immediately at the origin of the coronary vessels from the aorta

Severe tortuosity: Depending on the bends of coronary vessel , if one bend of the vessel ≥ 90°, or ≥3 bends of 45° to 90° proximal to the diseased segment.

Length >20mm: The length of the vessel at the region of the stenosis that has ≥ 50% reduction in luminal diameter is estimated in the angiographic view where the lesion appears to be the longest. (If there is a bifurcation lesion at least one of the branches has a lesion length of >20mm).

Heavy calcification: When multiple persisting opacifications visible of the coronary wall in more than one view surrounding the whole lumen of the coronary artery at the site of the lesion.

Thrombus: Spherical, irregular or ovoid intraluminal filling defect or a radioluscent lesion is surrounded on three sides by contrast medium seen present distal or within the coronary stenosis in multiple views or embolization is visible of intraluminal material downstream.

Diffuse disease/small vessels: If more than 75% of the length of the segment has a vessel diameter of 2mm, irrespective of the presence or absence of a lesion.

CTOs were also classified on the basis of Universal classification of CTO (48) into five categories as discussed earlier and the complexity of the lesion was correlated with the management decision undertaken.

TREATMENT ALLOCATION AND TRENDS

The patients diagnosed with CTOs were either managed medically, referred for CABG or underwent PCI at our centre, the treatment decision being taken by the treating physician.

The patients were subsequently classified into three groups of medical management (absence of revascularization) , PCI and CABG, and the clinical , angiographic variables in the three arms was studied. The patients who underwent PCI to CTOs were further subdivided into two

groups depending on whether the PCI was successful or not accordance to the following criteria.

PCI Success - Percentage residual diameter stenosis < 50% on visual assessment on coronary arteriography, with successful recanalization of the artery and TIMI II/ III flow.

Patients were followed up at six months post treatment allocation and NYHA symptom class was assessed and noted.

Statistical analysis:

Assuming a prevalence of coronary CTO of 18% (8), a sample size of 60 was calculated at 95 % confidence interval with precision of 10%. Analysis of data was done with StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP. All continuous variables were described as mean with standard deviation or median with ranges. Categorical variables were presented with frequencies and percentages. Chi square test /Fisher's exact test was used to find relation between two categorical variables (PCI lesion with other variables). SYNTAX score among treatment groups was compared using Kruskal Wallis test and post hoc test was done Mann Whitney U test. A p value of less than 0.05 was considered significant

OBSERVATIONS AND RESULTS

This study prospectively enrolled 66 patients with CTOs in patients with coronary artery disease between December 2012 to November 2013 diagnosed on coronary angiogram. The clinical profile of patients was studied for all the 66 patients as shown below (Table 4). The mean age of CTO patients was 58±9.3 with 89% being male. Out of 66 patients, almost 85% had history of angina chest pain (NYHA class I- III) and only 15% were pain free. 55% of the patients were hypertensives and 39% patients were found to be diabetics. The mean eGFR was 64 ± 14.4 ml/min/m2 in the CTO patients. There were 50% of patients who had history of acute coronary syndrome more than three months prior to presentation. Almost 53% of the CTO patients were either current or past smokers.

Table 4 : Baseline clinical characteristics of patients with CTOs

Variables	Value
AGE (yrs)	58 ± 9
Males	59 (89)
Diabetes Mellitus	26 (39)
Hypertension	36 (55)
eGFR (ml/min/1.73m2)	64.4 ± 14.4
Dyslipidemia	21 (32)
History of prior ACS	33 (50)
Peripheral vascular disease	3 (4)

Prior CHF		3 (4)
History of CVA		1 (2)
Current / past smoker		34 (53)
CTO of unknown duration		37 (56)
LVEF	≥ 40 %	55 (83)
	< 40 %	11 (17)

*Values are mean± Standard deviation or number (percentage)

There were only 4% patients having symptoms or history of suggestive of congestive heart failure with only 17% patients having moderate left ventricular dysfunction with LVEF < 40% with more than half (83%) of the patients with CTOs having mild or normal LVEF (LVEF≥40%). Only a single patient had history of prior CVA and only 4% of patients having peripheral arterial disease.

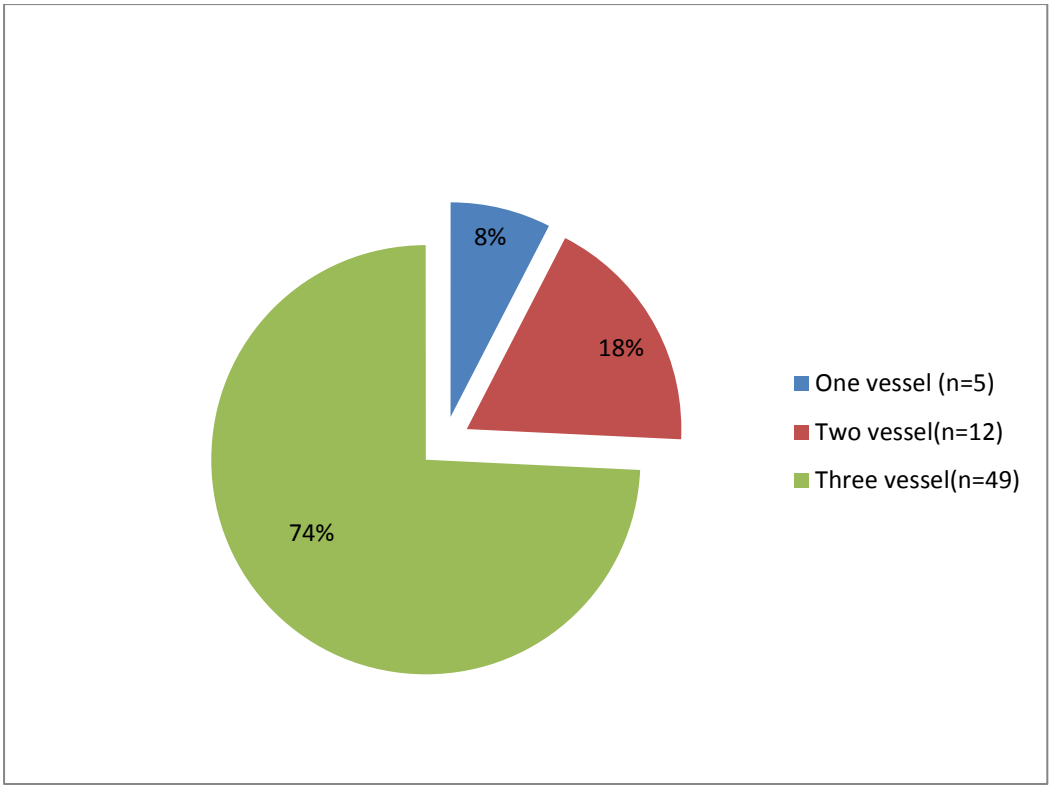


Figure 2 : Pie chart showing the distribution of number of coronary vessels involved in the entire study group (n=66)

The coronary anatomy as assessed on the coronary angiogram showed that most of the patients with CTOs had multi-vessel coronary artery disease with 74% having triple vessel and 18% having double vessel CAD with only 8% with single vessel coronary artery disease respectively (figure 2). Of the 66 patients 56% of the patients had occlusion of unknown duration with no documented history of prior myocardial infarction or acute coronary syndrome.

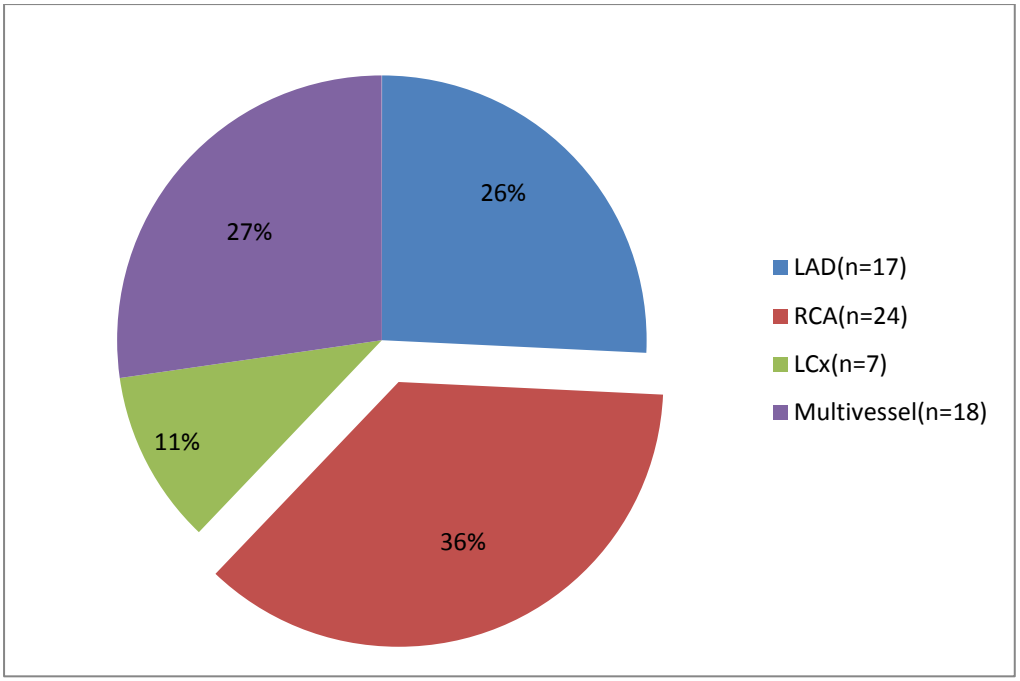


Figure 3: Distribution of CTO vessels (patients n=66)

There were a total of 36% patients who were diagnosed with solitary right coronary artery (RCA) CTO, with 26% of the patients having CTO in the left anterior descending artery (LAD) with LCx present in only 11% of the patients. Complete total occlusion in more than one territory was present in 27% of the patients (figure 3).

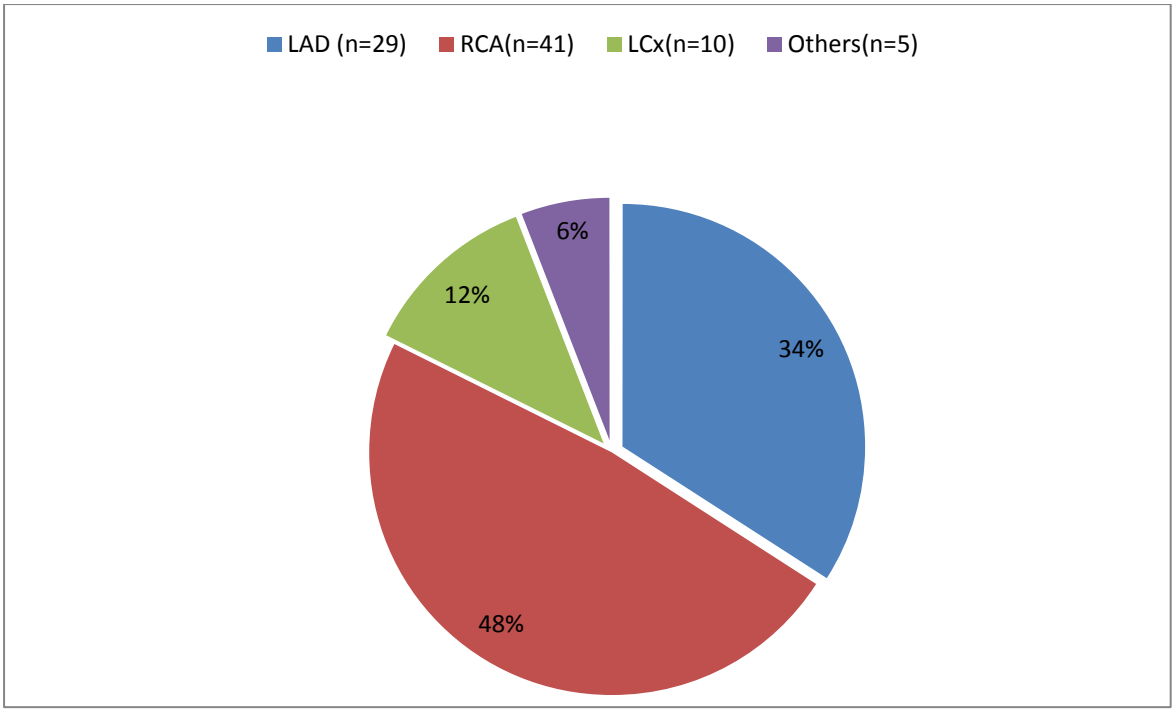


Figure 4 : The distribution of CTO vessel involved (vessels n=84)

There were in all eighty four CTO lesions in the total number of patients enrolled into the study. The RCA was most common artery with 48% of CTO lesions, LAD was next with 34% whereas LCx was involved only 6%, other artery territories like diagonal or Ramus Intermedius present in 6% patients (refer figure 4).

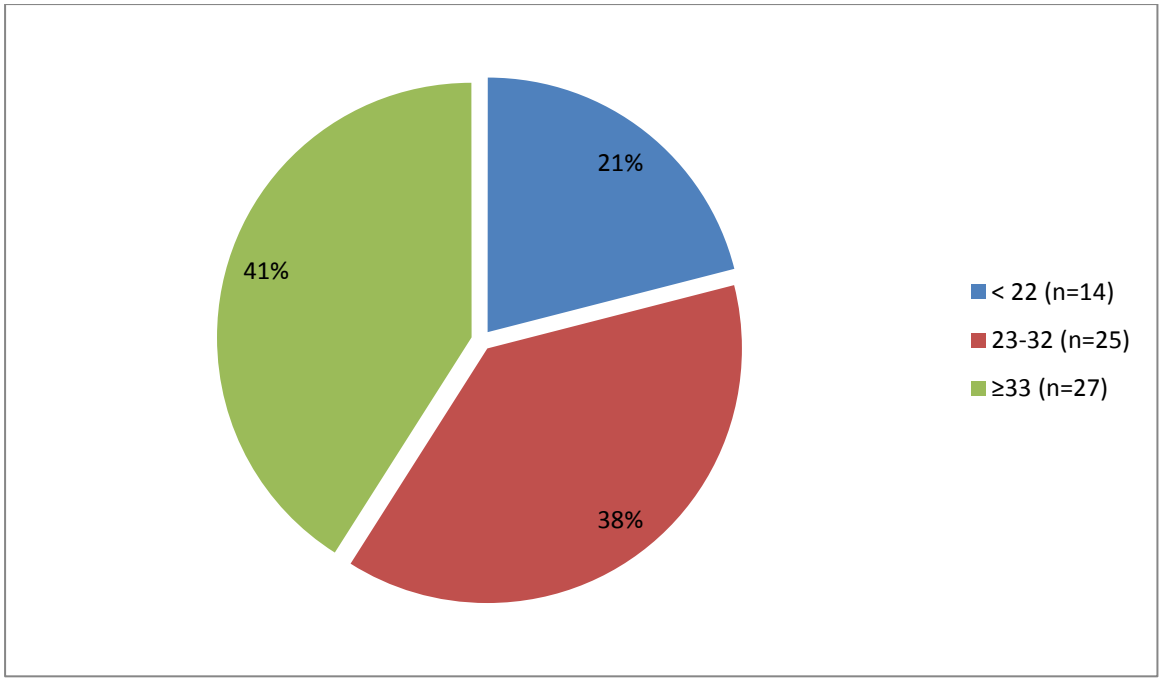


Figure 5: Distribution of SYNTAX score in CTO patients (n=66)

The SYNTAX score was calculated for all the patients with coronary CTOs, and classified into three groups of <22, 23-32 and ≥33 as shown in figure 5. The majority of patients enrolled with CTOs had a SYNTAX score of 23 or above with 38% in the 23-32 group and 41% in the ≥ 33 group, with only 21% having a SYNTAX score less than 22.

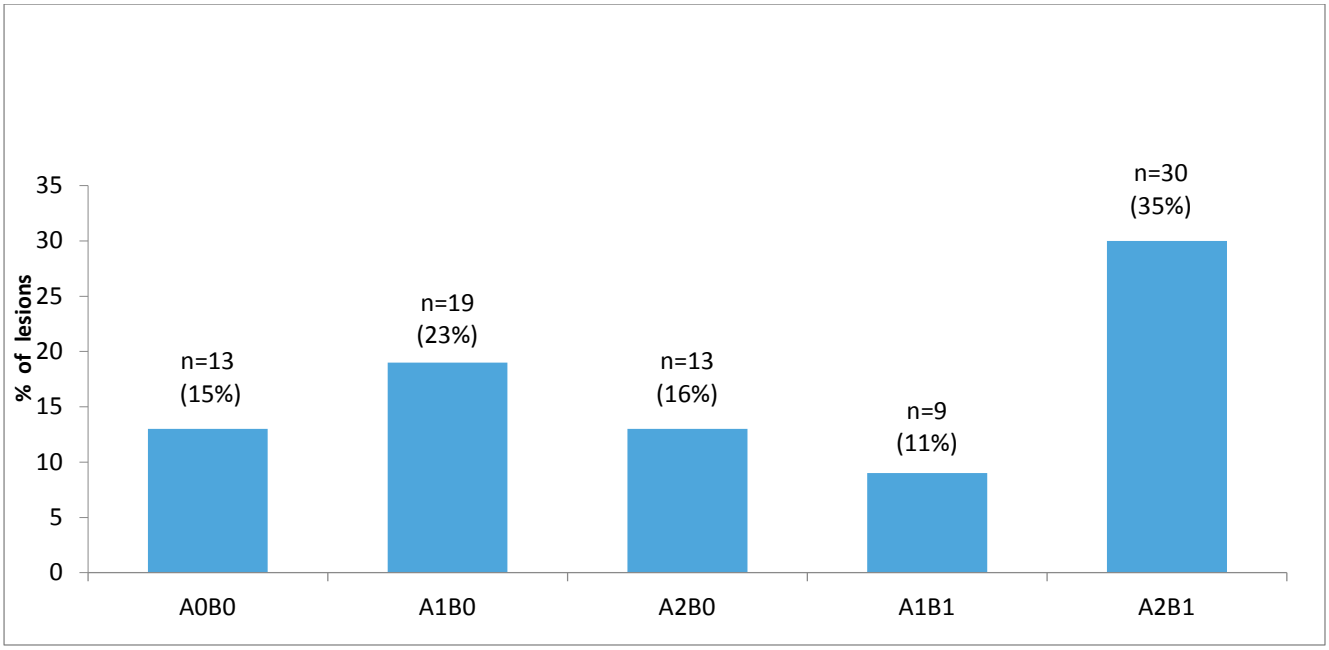


Figure 6: Distribution of the Technical difficulty rating in the CTO lesions (n=84)

Each CTO lesion was classified according to Universal classification of CTOs (48) as shown in figure 6, the majority of lesions belonged to the A2B1 group (35%) which is supposed to be technically the most challenging followed the A1B0 group which had 22% lesions.

The management decision undertaken for a particular patient was studied and the patients were allocated into medical management, PCI group or referred for CABG. The group of PCI patients were further divided into successful or failed groups as shown in figure 6.

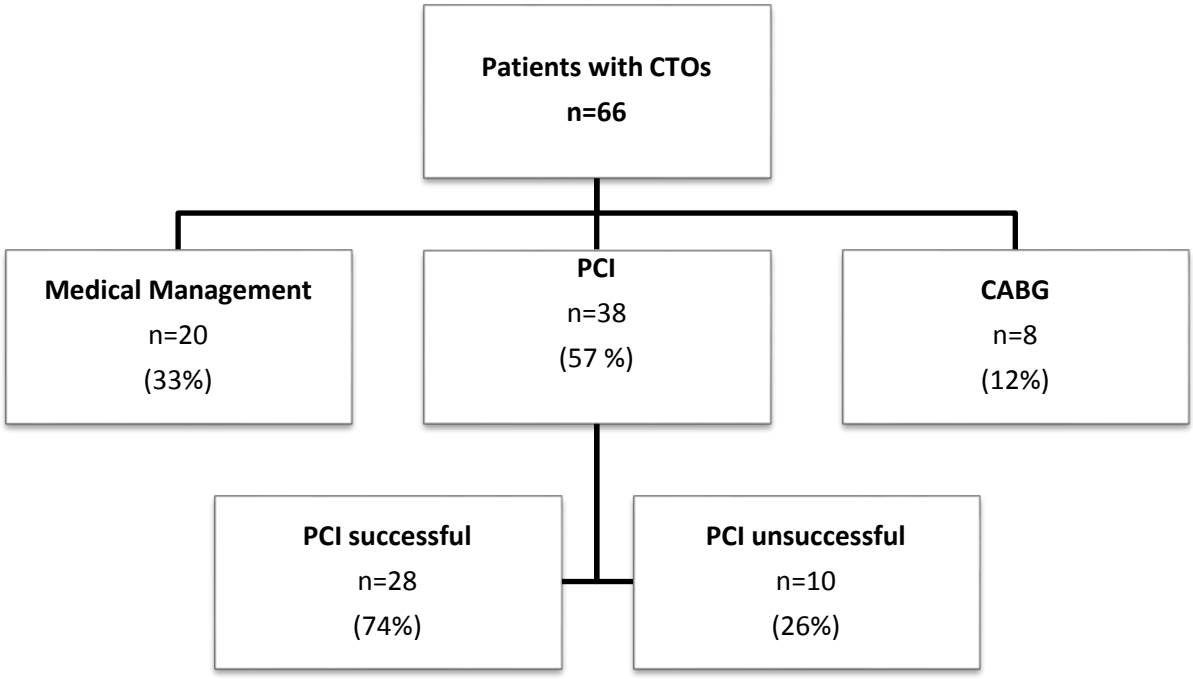


Figure 7: Treatment allocation and PCI outcomes in patients with CTOs

Out of the 66 patients with CTOs, 33% were continued on medical management, 57% underwent PCI to CTO and 26% patients were referred for CABG. The patients who were taken up for PCI , who had a successful revascularization were 74%.

Table 5: Baseline characteristics of patients according to treatment allocation

		Medical (n=20)	PCI (n=38)	CABG (n=8)	p-value
AGE(yrs)		59 ± 8	59 ± 11	57 ± 7	0.8
Males		18 (90)	35 (92)	6 (75)	0.3
Diabetes Mellitus		8 (40)	14 (37)	4 (50)	0.8
Hypertension		12 (60)	19 (50)	5 (63)	0.7
eGFR	<60 ml/min/1.73m2	8 (40)	11 (29)	4 (50)	0.4
	≥60 ml/min/1.73m2	12 (60)	27 (71)	4 (50)	
Dyslipidemia on medication		9 (45)	9 (24)	3 (38)	0.2
Triglycerides		134 ± 56	156 ± 82	109 ± 53	0.2
LDL		92 ± 39	89 ± 41	70 ± 20	0.3
HDL		39 ± 9	38 ± 9	35 ± 6	0.7
Prior ACS		8 (40)	19 (50)	2 (25)	0.4
CTO of unknown duration		12 (60)	19 (50)	6 (75)	0.4
PAD		1 (5)	1 (3)	1 (12)	0.4
Prior CHF		1 (5)	2 (5)	0 (0)	0.8
Prior CVA		0 (0)	1 (3)	0 (0)	0.6
Smoking (current/ past)		14 (70)	19 (50)	1 (12)	**0.02**
SYNTAX SCORE					**0.04**
Median		26.5	22.6	30.5	
Range		9-51.5	7.6-42.5	12-34.5	

LVEF				
<40 %	4 (20)	5 (13)	2 (25)	0.6
≥40 %	16 (80)	33 (86)	6 (75)	
CORONARY ANATOMY				
One vessel	1 (5)	4 (11)	0 (0)	
Two vessel	1 (5)	8 (21)	3 (38)	
Three vessel	18 (90)	26 (68)	5 (62)	
CTO vessel				
LAD	3 (16)	12 (34)	2 (25)	
RCA	9 (47)	13 (35)	2 (25)	
LCx	2 (11)	5 (13)	0 (0)	
Multivessel CTO	5 (26)	9 (18)	4 (50)	

*Values are mean± Standard deviation or number (percentage)

The mean age of patients in the three arms of treatment was almost similar with patients who underwent CABG being slightly younger. Majority of patients were males but the CABG arm had 25% female patients also. The patients who had dyslipidemia amounted to 25% in the PCI arm which was lesser than the other two group of patients although difference was not statistically significant. Patients who were past or current smokers were only around 12% in the CABG group whereas as 70% of the patients in the medical therapy group were past or present smokers, **this difference was statistically significant (p =0.02)** .

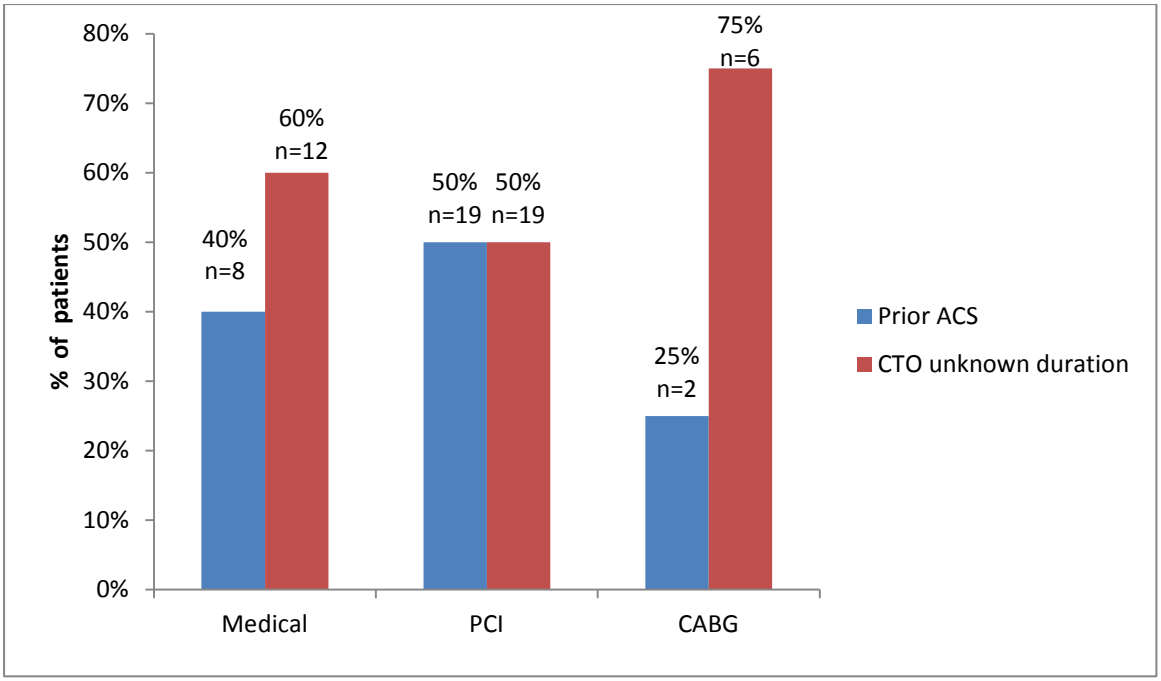
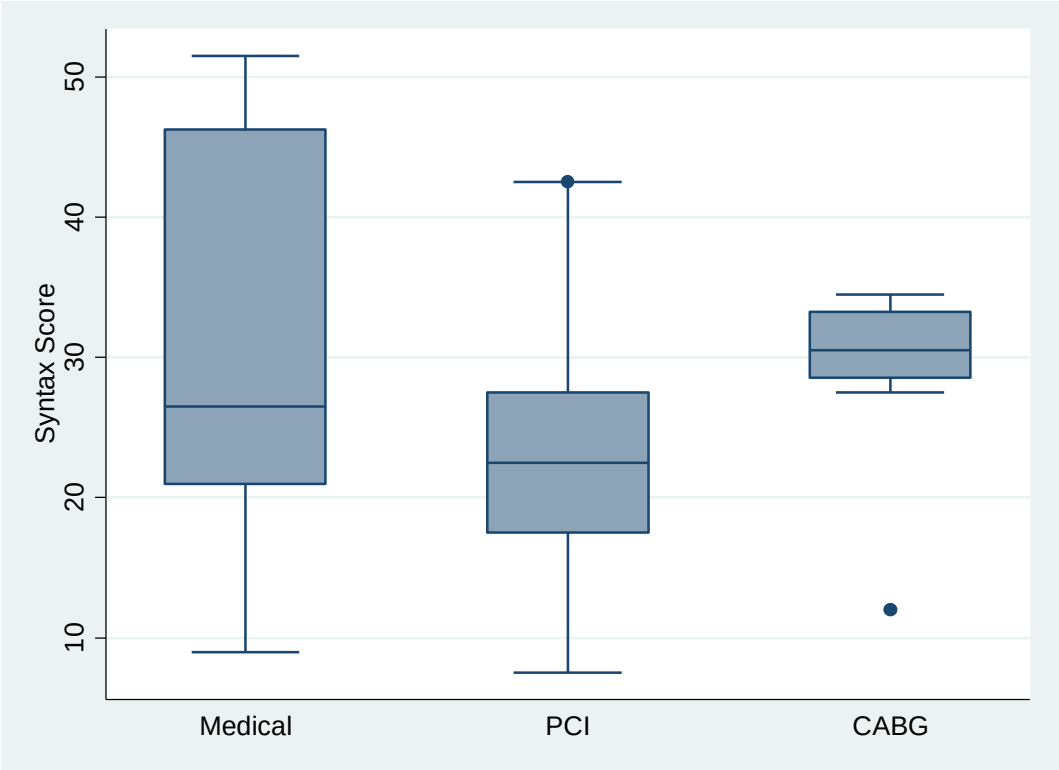


Figure 8: Prevalence of prior ACS and CTO of unknown duration in different treatment allocation groups

As seen in figure 8 occlusions of unknown duration were present in 75% of the patients in CABG group, 60% in the medical group and 50% in the PCI group. The CABG group also had lesser patients (25%) with prior MI/ ACS compared to the other two groups.

The median values of the SYNTAX score of patients in the three treatment arm showed a significant difference (p =0.04) with the median SYNTAX score being lowest in the PCI group followed by the medical management group and was the highest in the CABG group.



(single outlier values in PCI and CABG group are represented by dots)

Figure 9: Box and Whisker diagram showing distribution of SYNTAX scores in patients in different treatment allocation groups.

The distribution of SYNTAX score in figure 9 shows that medical group of patients had a wider dispersion with majority of patients within 50-75th percentile whereas patients who underwent CABG had narrower dispersion and most of patients lying within the 25th-75th percentile.

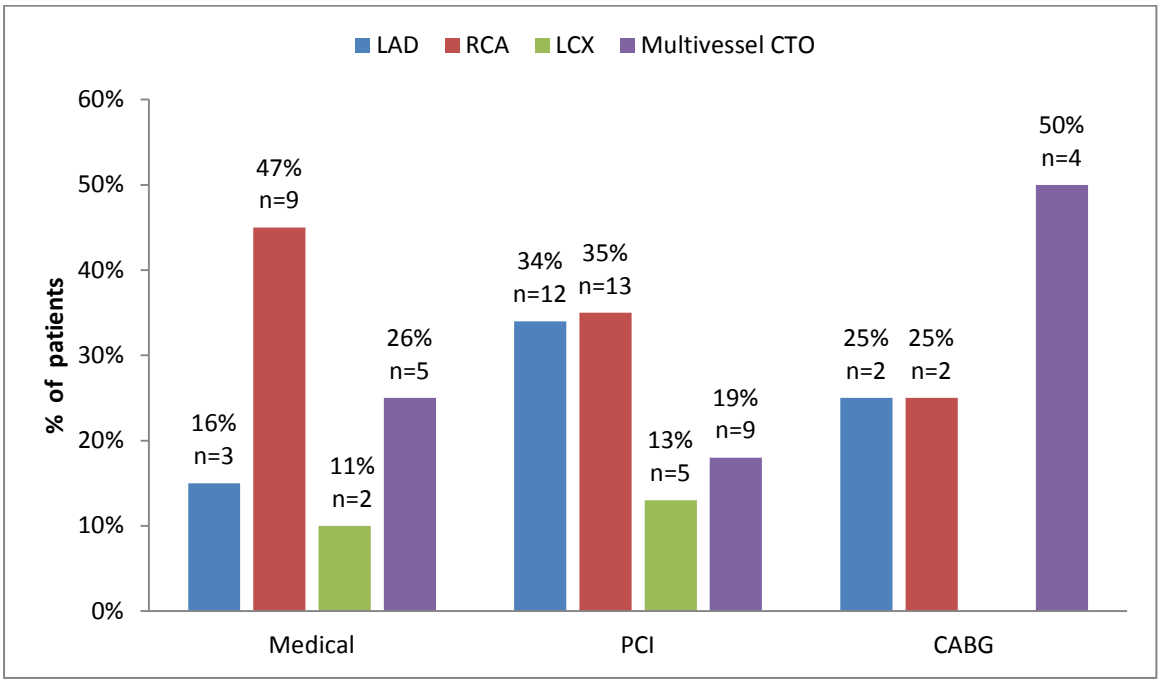


Figure 10: Distribution of CTO vessels in different treatment allocation groups

The distribution of CTOs according to the arterial territory (figure 10) showed that the RCA was most comon vessel involved in the medical group (47%), RCA and LAD were present in 35% and 34% patients respectively in the PCI group where as in the CABG group the number of patients with more than one CTO was 50%.

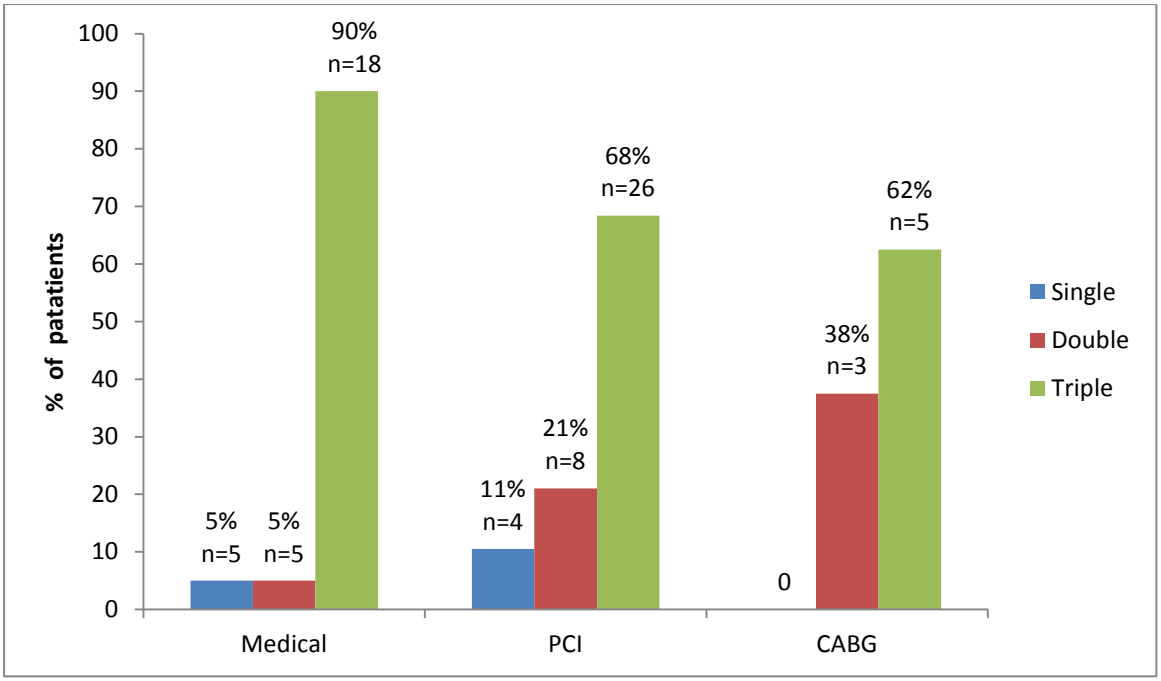


Figure 11: Number of vessels involved in patients in different treatment allocation groups

The majority of patients with CTOs in all three groups had triple vessel coronary disease, with 90% patients in the medical group having triple vessel CAD, 62% in the CABG group and 68% in the PCI group (figure 11). CTO patients with single vessel disease were minority (only 9 patients) and PCI was the mode of revascularization (if attempted) in them.

Table 6:

Comparison of clinical characteristics of CTO patients based on PCI outcomes (n=38)

Variables	Patients PCI Attempted		
	Success (n=29)	Failure (n=9)	P-value
AGE (yrs)	59 ± 12	58 ± 11	0.8
Male	28 (97)	8 (89)	0.3
Diabetes Mellitus	9 (31)	5 (56)	0.3
HbA1c	6.1 ± 0.8	6.8 ± 1.7	0.09
Hypertension	14 (48)	6 (68)	0.3
eGFR (≥60 ml/min/1.73m2)	63.9 ± 13	68 ± 21	0.4
Unknown CTO duration	13 (45)	5 (56)	0.5
current/ past smoker	17 (59)	2 (22)	0.1
LVEF≥ 40%	24 (83)	9 (100)	0.1

*Values are mean± Standard deviation or number (percentage)

The patients who underwent PCI for CTO lesions were 38 in number and the total lesions attempted amounted to 46. The patients and lesions in the PCI group were divided into success and failure groups as shown in Table 6 and Table 7.

The mean age of patients was similar in both the groups. As seen earlier majority of the patients in these two groups were males, especially predominant in the successful group (97%). The majority of patients with CTOs in both success and failed PCI groups were in the group with mild or normal LVEF, accounting for 82% in the success group and all the patients in failed PCI group. The patients who had CTO of unknown duration had greater failure with PCI (56% patients vs 45% in the PCI success group).

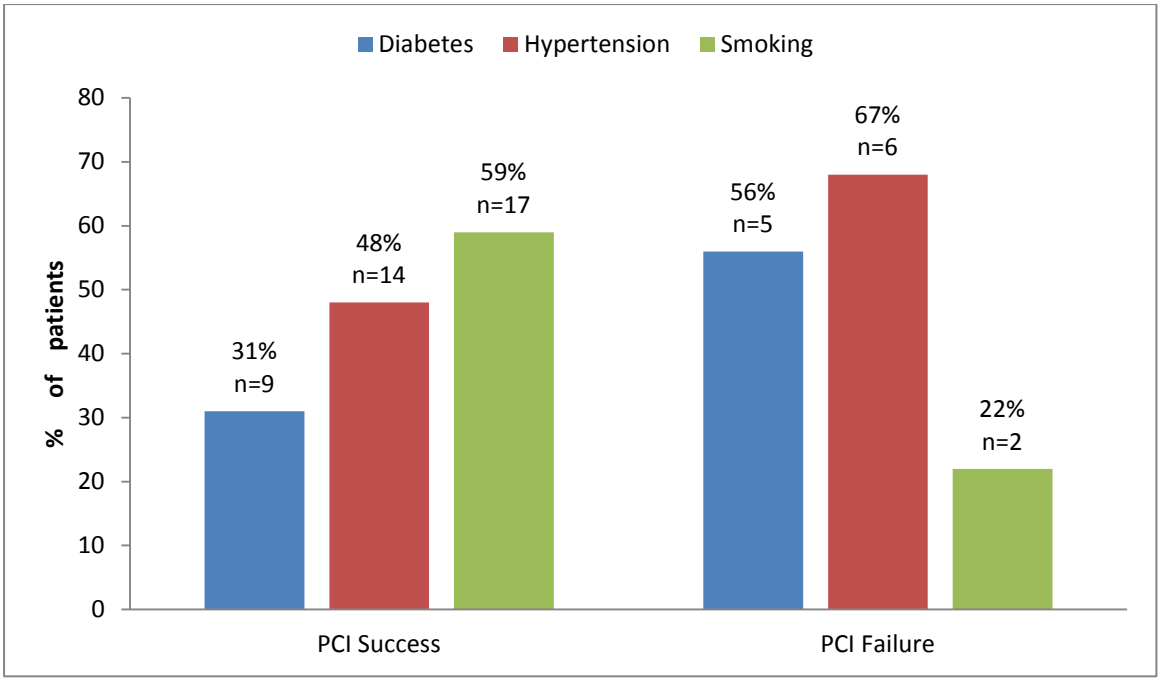


Figure 12. Comparison of clinical characteristics in CTO patients (n=38) undergoing PCI with successful and unsuccessful outcomes

As shown below in the Table 6 and figure 12 , the patients with diabetes , hypertension and were more predominant with lesser number of smokers in the failed PCI group compared to the patients who underwent successful revascularization with PCI but these were not statistically significant.

Table 7:

Comparison of angiographic characteristics of CTO lesions in successful and unsuccessful PCI outcomes (n=46)

Variables	PCI		
	Success (n=33)	Failure (n=13)	p-value
CTO vessel			
LAD RCA LCx Others	15 (45) 13 (39) 4 (12) 1 (3)	1 (8) 10 (77) 1 (8) 1 (8)	0.07
Bifurcation CTO	6 (18)	3 (23)	0.7
Blunt stump	8 (2)	4 (31)	0.6
CTO length (>20mm)	13 (39)	5 (38)	0.9
Bridging collaterals	8 (25)	6 (46)	0.2
Calcification	7 (21)	1 (8)	0.3
Presence of side branches	16 (48)	5 (38)	0.6
Use of Miracle series coronary wire	25 (75)	9 (68)	0.7
Use of microcatheters	6 (20)	2 (20)	0.8
Technical Difficulty score			
A0B0	8 (24)	2 (15)	0.7
A1B0	9 (27)	4 (31)	
A2B0	4 (13)	1 (8)	
A1B1	5 (15)	1 (8)	
A2B1	7 (21)	5 (38)	

* Values are number (percentage)

Revascularization with PCI was attempted in 46 lesions and the distribution ,salient angiographic features and the hardware use and effect on revascularization are shown below in Table 4. These were further subdivided into those who had successful revascularization and those who had failed PCI.

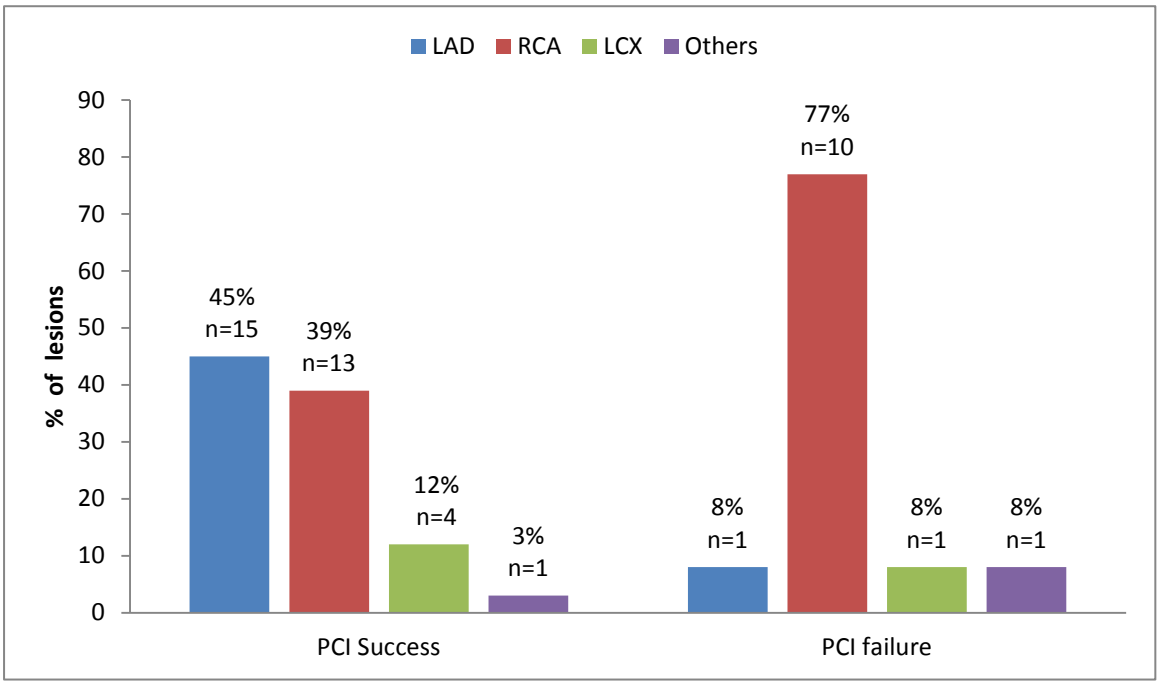


Figure 13: Distribution of vessels involved by CTO lesions in patients with successful and unsuccessful PCI outcomes

As show in Table 7 and figure 13, LAD was most common CTO artery that was successfully revascularized with PCI closely followed by RCA with 39% of lesions. In the lesions in which the PCI attempt failed the RCA was most common arterial territory with 76% of the lesions, this difference was not statistically significant with a p value of 0.07.

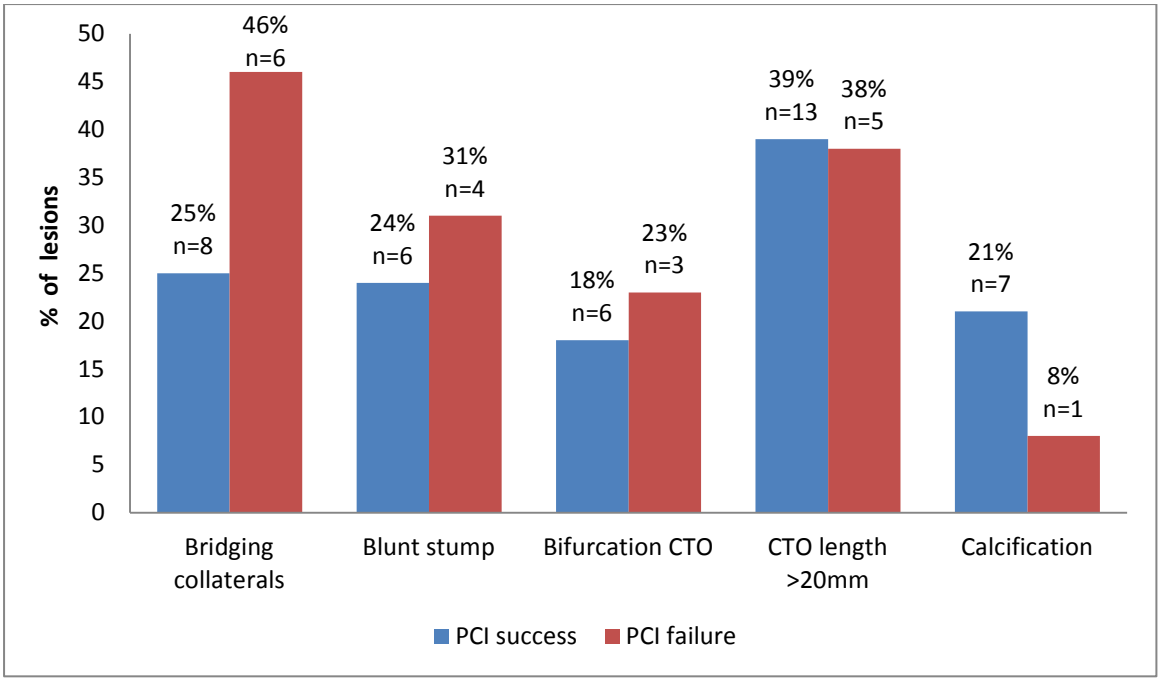


Figure 14: Comparison of Angiographic characteristics of CTO lesions in patients with successful and unsuccessful PCI outcomes

The patients who had successful revascularization in the study had fewer bridging collaterals, with fewer lesions with blunt stump and lesser number of bifurcation lesions. The CTO length >20mm was present equally in both success and failed groups. The lesions successfully revascularized were more calcified in our study , none of the above results though were statistically significant (figure 14).

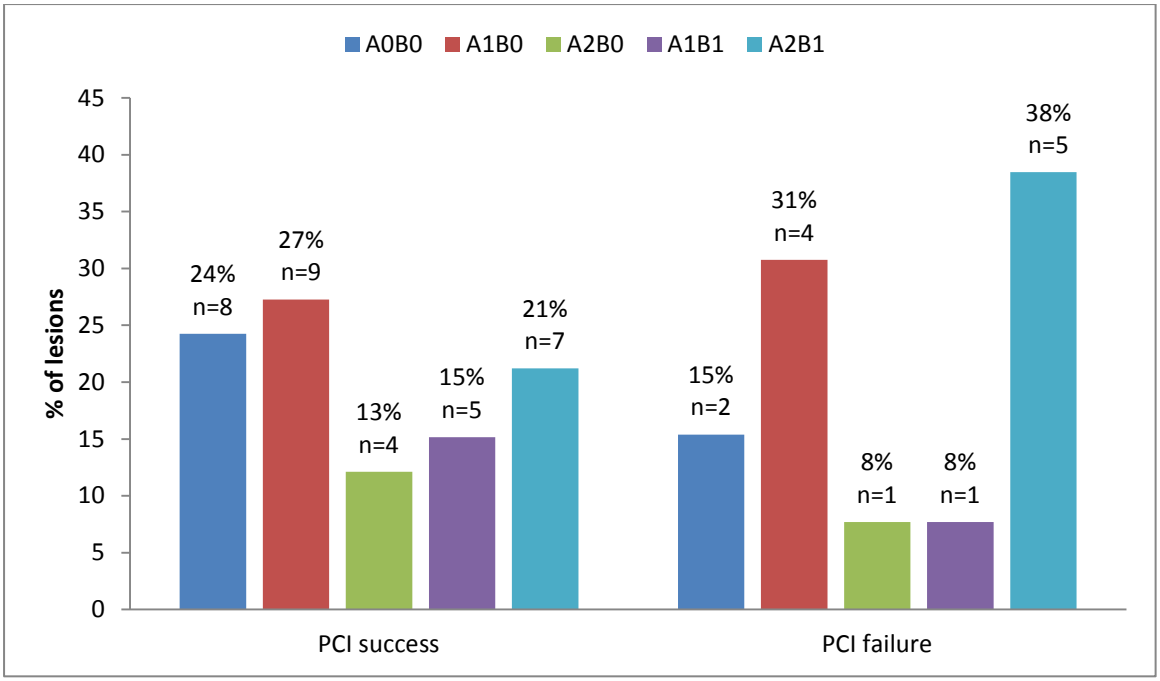


Figure 15: Distribution of Technical difficulty score in CTO lesions (n=46) in patients with successful and unsuccessful PCI outcomes

The CTO lesions were scored for technical difficulty for all the 46 lesions in the PCI group and the distribution shown in Table 3 and figure 15. The analysis shows that the lesions who had failed PCI had 38% in the A2B1 group but 21% of these technically challenging lesions were successfully revascularized at our centre. In this centre the A0B0 and A1B0 group accounted for almost 50 % of the successful PCI group (Figure 15).

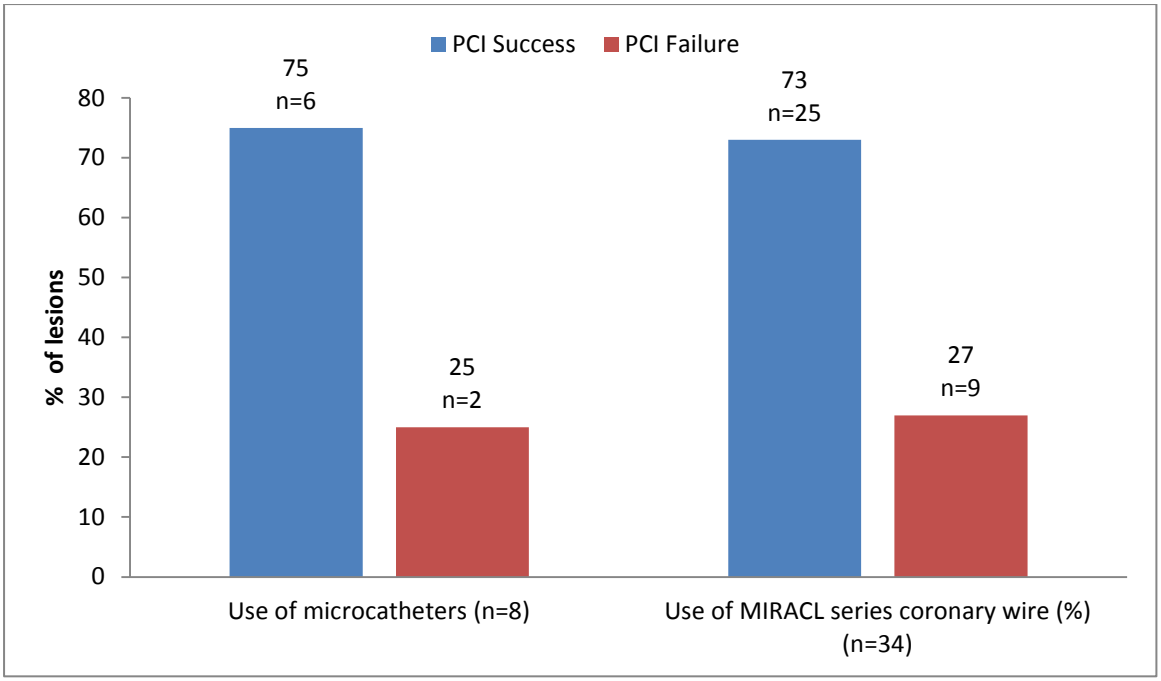


Figure 16: Comparison of dedicated CTO PCI hardware in patients with successful and unsuccessful PCI outcomes

The hardware utilized was analysed and it was found that use of microcatheters enhanced the PCI success in the CTO lesions to 75%. The use of MIRACL series of coronary wires in the CTO lesions for PCI also had a 73% success as shown in figure 16.

Table 8.Comparison of NYHA symptom class distribution at baseline and 6 month follow up in different treatment allocation groups.

	NYHA I	NYHA II	NYHA III
Medical (n=8)			
Baseline	0	7 (88)	1 (12)
Follow up	5 (63)	3 (37)	0
PCI (n=34)			
Baseline	2 (6)	26 (77)	6 (17)
Follow up	31 (91)	3 (9)	0
CABG (n=7)			
Baseline	0	7 (100)	0
Follow up	7 (100)	0	0

*Values are number (percentage)

Patients were followed at six months from initial presentation and were assessed clinically on the basis of NYHA symptom class. There were 49 patients who were assessed after six months with 17 patients on whom no clinical data could be obtained and were considered as lost to follow up.

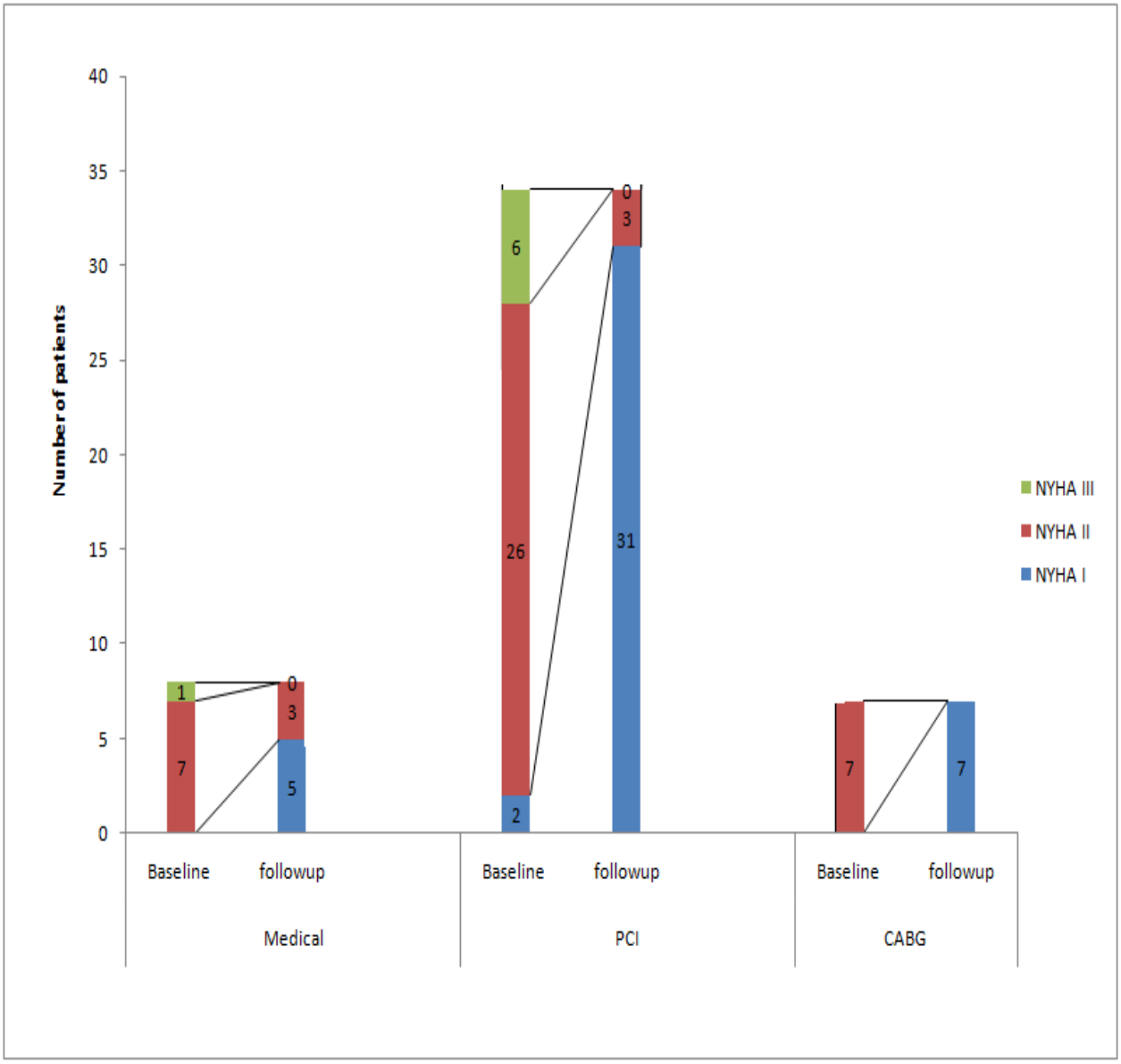


Figure 16: Comparison of NYHA symptom class distribution at baseline and 6 month follow up in different treatment allocation groups

As seen in Table 8 and figure 16, there was there was improvement in NYHA symptom class in patients in all three treatment allocation groups. The patients with revascularization (PCI or CABG) having the maximum benefit with 100% of CABG patients being in NYHA class I and only 9% of patients in the PCI group still having NYHA II symptoms at six months. Those on medical treatment also showed improvement with 63% being in NYHA class I but this group still had 37% patients with NYHA II symptoms at follow up.

DISCUSSION

There are few studies worldwide and in India which have analysed the clinical characteristics of CTOs and the management trends of patients with CTOs in the current era of interventional cardiology. This study was a prospective observational study conducted with the aim to provide data on patients diagnosed with coronary CTOs at our centre with systematic and detailed analysis of their clinical and angiographic profile. The treatment options selected in these patients were also studied to determine current trends in the management of these complex lesions.

CLINICAL CHARACTERISTICS

Our study, conducted at a high volume tertiary care centre in South India, is one of few which provide details of these complex coronary lesions in our country. The demographic profile of patients of CTO in our study showed mean age of patients was lower as compared to data from the west (8,42,45), which showed a mean age of patients around 66 years, although the gender predominance and smoking status (almost 50% in our study were smokers) was in concordance with the same studies. All patients with CTOs enrolled into our study had at least NYHA class II or more symptoms with angina as the predominant symptom, this is in agreement with previous data which also had only 11-15% patients who were asymptomatic (3,16,17) with the Canadian registry (8) of CTOs published in 2012 having just 5% in the same category. In our study it was seen that CTO patients had high prevalence of CAD risk factors (39% had diabetes mellitus, 55% had systemic hypertension, 36% had moderate renal dysfunction whereas only 4.5 % patients had congestive heart failure). Majority of patients with CTOs had either normal or mildly reduced LVEF ($\geq$ 40%) and only about half of the CTO patients had history of prior ACS with the rest having CTO of unknown duration in our study; these trends are similar to data from prior studies including the recent Canadian and J-CTO registries (8,42) in which 40-68% of patients had

history of prior MI with greater prevalence of coronary risk factors in patients with CTO. This strongly points towards a potential benefit of revascularization either in these patients with either PCI or CABG, as majority of CTO patients are symptomatic and half of them do not have a history of MI or ACS in the past. Although in multivessel coronary artery disease in which CTOs were most often present (refer figure 3), it may be difficult to attribute the symptoms to the presence of CTO.

When CTO patients were studied according to treatment allocation, it was noted that patients who underwent CABG or received medical therapy had more comorbidities as these groups had more diabetics, hypertensives and more patients with moderate chronic kidney dysfunction (eGFR < 60ml/min/m2) and dyslipidemia, compared to those patients who underwent PCI (Table 5). This data is on expected lines as patients having multiple comobidities and risk factors are likely to sicker and undergo medical management or surgery if complex coronary anatomy and/or accompanying diabetes or CKD is present, compared to those undergoing PCI. This data is also concordant with findings of the Canadian registry of CTOs (8) and a recent study by Abbott (45) which have also showed a similar trend.

Patients who had successful PCI to CTOs in our study had fewer diabetics amongst them (31% in success vs 56% in failed PCI) and these had better overall glycemic control (HbA1c of 6.1 vs 6.8); there were fewer hypertensives as well (48% vs 68%). The patients with CTO of unknown duration were fewer in the successful PCI group (44% vs 56%) as shown in Table 6. These differences show that successful revascularization of CTOs with PCI may be influenced by clinical risk factors; but it is important to note that these differences were not statistically significant and such trends have have not been shown in other large studies except for the presence of occlusions of unknown duration which have been shown by the Canadian registry (8) and Barlis et al (20) to be a risk factor for PCI failure and referral for CABG .

ANGIOGRAPHIC CHARACTERISTICS

The CTO vessel distribution in the whole group of patients showed that the RCA was vessel most frequently involved, with RCA CTOs, being present in 49% of patients. This is largely in concordance with all the previous data on CTOs in large number of studies(5–7) and the recent CTO registries from Canada and Japan (8,42). Majority of patients with CTOs had multivessel CAD and thus this was the group which dominated when the three arms of treatment (medical, PCI and CABG) were studied. We observed that in our centre, LAD was the common CTO vessel found in the PCI success arm whereas RCA was most common vessel in the PCI failure group; a similar trend was also shown in the study by Morino in Japan(43).

The coronary burden determined in the study population group by the calculation of the SYNTAX score showed that majority of patients (79%) in our study had a SYNTAX score of 23 or above, reinforcing the fact that coronary CTOs are associated with complex multivessel coronary artery disease as seen in other CTO registries (8,42,45) although the use of SYNTAX score specifically in the subset of patients with CTO to estimate the extent of coronary burden has not been used earlier. It was interesting to note that the SYNTAX score in patients in the medical arm had wider dispersion (refer figure 9) probably due to increased prevalence of complex coronary anatomy not amenable to revascularization with either PCI or CABG like diffuse small calibre vessels etc. Thus at our centre patients with patients with higher SYNTAX scores either received revascularization with CABG or were continued on medical management with the patients in PCI group having a lower overall SYNTAX score and thus less complex anatomy. This data is in accordance with well estabilished guidelines for revascularization with PCI or CABG (24). Also, in our study we tried to analyse the technical difficulty in revascularization of CTO lesions and the risk involved in recanalizing such lesions. Each lesion was scored according to a novel CTO scoring system given by

Jayasinghe etal (48) (also refer Table 2) which showed that majority of the of lesions (35%) were scored as the technically most challenging, this probably is the reason why PCI was attempted less commonly in the past. Even in our study more than 40% of CTO patients underwent CABG or received medical therapy. Furthermore comparison of the technical difficulty scores with regards to success of PCI shows that there greater number of lesions with A2B1 in the PCI failure group and more than 50% lesions in the PCI success group were either A0B0 or A1B0 which are supposed to have highest probability of technical success and associated with lower risk (figure 15).

Further when comparing the distribution of certain angiographic characteristics of CTOs in the PCI group, the presence of bridging collaterals, absence of a lesion edge (or blunt stump), presence of bifurcation at CTO lesion were more common in the lesions which had successful revascularization with PCI (Figure14). Earlier data from CTO registries and Canadian and Japanese data support our findings and the trends observed in our hospital (6,8,25,42,43,45).

The use of microcatheters at our centre greatly enhanced the chances of success in CTO PCI with 75% of lesions being successfully revascularized with use of the same. This trend is in agreement with earlier study from our own centre by Joseph et al (44) and also data available from high volume centres internationally. Also the use of MIRACL series coronary guidewire was associated with high chances of lesion revascularization with over 70% CTO lesions in which these wires were used, were successful (21).

Out of the 66 CTO patients, 69% of patients underwent revascularization of CTOs (PCI or CABG) with PCI being successful in 74% of the patients, which is at par with current international data which state a success of PCI at high volume centres of 75-80% (3,41) but still lower than those reported by the Japanese who have reported 88% successful guidewire crossing (43) in CTO lesions. Also, when there is indirect evidence of myocardial viability as

evidenced by the presence of angina symptoms or preserved LV function, CTO PCI provides symptomatic relief. Thus, with the advent of newer techniques and hardware for PCI, CTO PCI is associated with high success rates.

As seen in Table 8 and figure 16, there was there was improvement in NYHA symptom class in patients in all three treatment allocation groups with patients undergoing revascularization (PCI or CABG) having the maximum benefit. The patients with CTOs who are predominantly symptomatic at presentation when followed up at six months show a trend towards a benefit of revascularization in relation to NYHA symptom class when compared to medical therapy , with all CABG patients in NYHA class I, and only 9% of patients in the PCI group still having NYHA II symptoms at six month follow up, although these results were not significantly different probably due to the relatively small sample size.

STUDY LIMITATIONS

1. The major limitation was lack of randomization of patients into three treatment allocation arms for patients with CTOs.
2. This was a single center, non-blinded study and hence the findings may not necessarily be representative of the entire region.
3. Observer bias which may have affected assessment of coronary angiograms, calculation of SYNTAX score etc.
4. There was a lack objective documentation of myocardial viability with imaging and the incorporation of this data into treatment decision making for CTO patients.
5. The management decision for patients was entirely dependent on the treating physician which may have lacked uniformity.
6. The sample size was small. A larger multi-centre study would be needed to accurately delineate prevalence, characteristics and predictors for success of revascularization for patients with CTOs.

CONCLUSIONS

1. This study provides a status report of the clinical and angiographic profile, and management trends of patients with CTOs in the current era of interventional cardiology from a high volume centre in South India
2. The majority of patients in the study were symptomatic (89% with angina) with either normal or mildly decreased LVEF (≥40%).
3. CTOs are found in patients with high prevalence of CAD risk factors like diabetes mellitus, systemic hypertension and smoking.
4. CTOs are found in patients with predominantly multivessel (double or triple vessel) CAD and majority have SYNTAX scores of 23 and above suggesting high CAD burden in these patients.
5. More than half of patients were classified as having CTO of unknown duration (no prior history of ACS or MI).
6. Almost half of patients with CTO had RCA as the culprit CTO vessel followed by LAD. Interestingly RCA was the most common CTO vessel in the unsuccessful PCI group.
7. Certain angiographic variables like bridging collaterals, blunt stump, longer length of lesion and higher technical difficulty score may predict failure in revascularization of CTOs with PCI but a randomized study with larger numbers is required to answer this question in detail with statistical certainty.
8. The higher the technical difficulty score, the higher the procedural risks and lower the chances of successful revascularization.

9. A high rate of successful revascularization of CTOs with PCI was achieved but this was still lower than those documented recently (>90%) from centres specializing in CTO recanalization.
10. Revascularization seemed to improve the symptom status assessed by NYHA class in the patients with CTO who were followed up at 6 months.

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APPENDIX-I

CLINICAL & ANGIOGRAPHIC PROFILE, & MANAGEMENT TRENDS IN PATIENTS PRESENING WITH CORONARY CHRONIC TOTAL OCCLUSIONs IN A TERTIARY CARE CENTRE IN SOUTH INDIA

PROFORMA

Name of Patient-

Age- Sex- Hospital No.-
Address-

Tel no. Weight- Height- BMI-

Date of Admission- Date of Discharge- Date of Procedure-

Presenting Complaints

Chest Pain- Y/N CCS Angina Class- NYHA Class-
Dyspnoea- Y/N

Syncope- Y/N Asymptomatic- Others-

Past Illness/Comorbidities

Prior CAD- Y/N Prior ACS- Y/N Diabetes- Hypertension-
CKD- PAD- H/O CHF- Prior PCI/CABG
CVA- Dyslipidemia-

Addictions-

Smoking- Past/ Current/ Never Alcoholism-
Others-

General Examination

B.P.- HR RR- Edema- CHF- JVP-

Systemic examination

CVS LV S3 RS P/A

Investigations

Hb	TLC/DL	Sr.Creatinine	Urea	Sr.Eectrolytes	LipidProfile	HBA1c

ECG

Rhythm q waves duration (secs)- (mm) Territory- No of Leads-

ST Elevation (mm)- ST Depression (mm)- R/S ratio V1- Others-
Post Procedure-

ECHO

LVEF	LVID d/s	RWMA	IVSd/LVPwd	Other

VIABILITY STUDIES

SPECT REST/STRESS-EXERCISE OR PHARMACOLOGICAL
AREA OF VIABLE MYOCARDIUM
OTHERS- CT/MRI/PET

CAG

Access-

Dominance Right/Left	LMCA	LAD	RCA	LCx	
2.CTO Artery			3.Total Occlusion-		
4. Site , If at bifurcation or not ,			5.Aneurysmal segment at or near occlusion s		
6.Blunt Stump/Leading Edge					
8.Collaterals -			9. First segment visualized by Contrast-		
10.Side Branch-			11. Trifurcation/Bifurcation-		
12. Angulation- 13.Aorto Ostial Lesion-			Medina Class		
14.Severe Tortuosity-			15. Length 20 mm		
16. Heavy Calcification-			17. Thrombus-		

TIMI Flow- LAD- RCA- LCX-

SYNTAX Score **PCI Vs CABG**

Technical difficulty Score

Treatment and Management Undertaken

- **Medical Management**
- **PCI**

Radial/ Femoral Access		
Antegrade/ Retro		
Success		
Attempt /Staged		
Vessels Stented-		
GC/Wire/ Hardwa		
No of Stents Stent Size- Deployed at(atm)		
TIMI Flow-		

- **CABG Referral Grafts Used**

Complications

- **Access site:- Bleeding/ Hematoma/ Pseudoaneurysm/ AV Fistula**
- **Lesion :- Dissection/ Perforation/ Pericardial Effusion**

Follow Up

Symptoms Status-

Compliance to Treatment-

Follow up Duration-

ECG- ECHO- CAG if Done-

APPENDIX II

INFORMATION SHEET

CLINICAL AND ANGIOGRAPHIC PROFILE, AND MANAGEMENT TRENDS IN PATIENTS PRESENING WITH CORONARY CHRONIC TOTAL OCCLUSIONs IN A TERTIARY CARE CENTRE IN SOUTH INDIA

INTRODUCTION : The heart is made of muscle, and has three arteries which supply oxygenated blood for its nutrition, which are known as coronary arteries. Atherosclerosis is a disease of these arteries which leads to obstructive lesions in the vessels which can occlude the vessel to varying degrees. If the coronary artery is totally occluded it is known as a total occlusion which can be diagnosed by doing a test called coronary angiogram (CAG).

PROCEDURE DETAILS : This is a study being performed in this hospital in which all patients with total occlusions diagnosed on a coronary angiogram in one or more coronary arteries are being enrolled and their clinical data such as age, previous history of heart attack, whether diabetic or not, smoking habbits, alcohol consumption etc will be noted. ECG, treadmill test and Echocardiographic parameters or any other invetigation relevant to this study done in CMCH or elsewhere for the same will be noted down in this study by the doctor.

A coronary angiogram is performed in a cardiac catherization laboratory under local anesthesia and is done in most of the cases through the radial artery (artery felt at the wrist joint) in CMCH Vellore. During the coronary angiogram if a total occlusion in the coronary arteries is observed by the doctor , your clinical data i.e age, previous history of heart attack, whether you are a diabetic or not, smoking habbits, alcohol consumption etc will be noted. Also the angiogram details will be noted such as the number of lesions in the vessels, the severity, percentage occlusion etc. Finally the treating doctor will take a decision regarding your illness and whether you in his view need to continue medicines or should undergo angioplasty to one of your vessels or should be referred for coronary artery bypass surgery.

If you have history of having a heart attack in the past 3 months or have history or ECG suggestive of same or if you had a CABG surgery in the past you then clinical data will not be included in this study as these are the exclusion criteria of this study.

In case of any query please contact –
Cardiology I office
CMCH, Vellore.
0416-2282698

APPENDIX III

CONSENT FORM

CLINICAL AND ANGIOGRAPHIC PROFILE, AND MANAGEMENT TRENDS IN PATIENTS PRESENING WITH CORONARY CHRONIC TOTAL OCCLUSIONs IN A TERTIARY CARE CENTRE IN SOUTH INDIA

Study Number: IRB/8108

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

(v) I agree to take part in the above study.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

APPENDIX IV

ABBREVIATIONS AND GLOSSARY

ACS- Acute coronary syndrome

CTO- Chronic total occlusion

CABG- Coronary artery bypass surgery

CHD- Coronary heart disease

CAD- Coronary artery disease

ECG- electrocardiogram

MACE- major adverse cardiovascular events

MI- Myocardial infarction

NYHA- New York Heart Association

NSTEMI- Non ST elevation MI

PCI- Percutaneous coronary intervention

LAD- Left anterior descending artery

LCX- Left circumflex artery

LVEF- Left ventricular ejection fraction

RCA- Right coronary artery

RI- Ramus intermedius

S.D.- standard deviation

TIMI- Thrombolysis in Myocardial Infarction

GLOSSARY FOR MASTERCHART

Clinical Variables (Diabetes, Hypertension etc)

1= Present 2- Absent

Chest Pain

0- No chest pain

1- NYHA class I 2- NYHA II

3- NYHA class III 4- NYHA class IV

CTO duration

1= > 3 months duration 2= duration unknown

ECG evidence of prior MI

1- Yes 2-No

Smoking status

1- Past 2- current 3- Never

CTO Artery Territory

0- LAD 1- RCA

3- LCx 4- LAD,RCA

5- LAD,LCx 6– RCA, LCx

7- RI, RCA 8- LAD, RI

Technical Difficulty score

0- A0B0 1- A1B0

2- A2BO 3 -A2B1

4- A1B1 5-A2B1

Arteries invoved (Left main, LAD, RCA, LCx, Others)

0- No 1- Yes

CTO bifurcation lesion

0- No 1- Yes

CTO stump

0—blunt stump 1– Leading edge

CTO Side branches

0-None 1- Present

Bridging collaterals

0-None 1- Present

CTO Angulation

0- None 1- <70 degrees, 2- > 70 degrees

CTO tortuosity

0- None 1- Present

CTO length

0- <20mm 1- > 20mm

CTO Heavy calcification

0- None 1– Present

CTO Thrombotic lesion

0- No 1- Yes

Management recommendation

0- Medical 1- PCI 3- CABG

MIRACL Coronary wire used

0- Used 1- Not used

PCI success

0- Yes 1- No

Follow up

1- NYHA I 3- NYHA III

2- NYHA II 4- No follow up

S.No.	hosp_no	age	Sex	Bmi_rec	chtpain	Dysp	Synco	CTOdur	hba1c	DM	HTN	CKD	PAD	CHF	CVA	DL	smk	eGFR	TLC	Trg	HDL	LDL	ECG	LVEF	LM	LAD	RCA	LCx	Other	CTOart	TD1
1	365142f	66	1	24.16	4	0	2	2	5.0	2	1	2	2	2	2	2	3	83.00	123	129	36	67	2	58.0	0	1	0	1	0	0	2
2	375539f	64	1	23.88	2	0	2	2	6.4	2	2	2	2	2	2	2	2	52.00	188	136	38	114	2	30.2	0	1	0	0	0	0	2
3	047781f	63	2	32.00	2	2	2	2	7.3	2	2	2	2	2	2	2	2	68.00	174	124	47	109	2	56.3	0	1	1	1	0	3	5
4	287740f	57	1	23.94	4	2	2	1	5.5	2	1	2	2	2	2	1	2	78.50	157	95	59	84	1	40.0	0	1	1	1	0	4	2
5	299531f	61	2	26.91	1	2	2	2	6.9	1	1	1	1	2	2	2	3	44.00	113	145	38	55	1	44.6	0	1	0	1	0	0	1
6	303337f	54	1	25.68	3	3	2	2	5.3	2	1	2	2	2	2	2	2	56.00	92	98	38	35	2	59.0	1	1	1	1	0	1	4
7	310259f	50	2	20.82	2	0	2	2	6.6	2	2	2	2	2	2	1	3	87.00	192	220	39	106	1	56.0	0	1	0	1	0	0	5
8	276238f	57	1	23.88	2	2	2	2	6.8	2	1	2	2	2	2	1	3	47.00	124	126	41	70	1	38.0	0	1	1	0	0	5	5
9	393064f	62	2	26.66	2	2	2	2	5.5	1	1	2	2	2	2	1	3	67.43	124	62	35	80	1	55.0	1	1	1	0	0	5	5
10	293557f	60	1	24.60	3	0	2	2	7.0	2	2	2	2	2	2	2	3	58.00	190	111	28	139	2	38.0	0	1	1	1	0	5	1
11	382862f	56	1	21.71	2	2	2	2	5.7	2	1	2	2	2	2	2	3	52.67	130	100	36	73	1	44.6	0	1	1	0	0	1	5
12	402095f	56	1	19.53	4	2	2	2	5.8	1	2	2	2	2	2	2	1	45.46	152	237	26	78	2	35.0	0	1	1	1	0	1	2
13	376805f	65	1	21.97	2	2	2	1	6.7	1	2	2	2	2	2	2	2	73.94	88	96	38	51	1	43.0	0	1	1	1	0	1	1
14	381512f	68	1	21.50	2	0	2	1	6.5	1	1	2	2	2	2	2	1	66.00	114	61	50	49	2	55.3	0	1	0	1	0	4	0
15	157235f	39	1	23.88	2	0	2	2	5.4	2	1	2	2	2	2	1	2	84.00	143	131	31	92	1	59.0	0	1	1	1	0	1	5
16	288022f	60	1	18.80	4	2	2	2	7.0	1	2	2	2	2	2	2	2	65.64	180	107	40	118	1	34.0	1	1	1	1	0	5	4
17	223853F	53	1	23.00	2	0	2	1	5.2	2	2	2	2	2	2	2	1	62.00	136	57	24	88	1	56.0	1	1	1	0	0	5	1
18	369348f	43	1	25.39	2	0	2	2	5.5	2	1	2	2	2	2	2	1	84.00	143	84	32	98	2	57.3	0	1	1	1	0	1	5
19	286967f	62	1	32.87	2	2	2	1	6.4	2	1	2	2	2	2	2	3	77.00	129	116	52	54	1	46.8	0	1	1	1	0	7	2
20	595237d	64	1	29.20	2	2	2	1	6.9	2	1	1	2	2	2	1	2	43.64	87	102	30	41	1	42.0	0	1	1	1	1	8	5
21	349729F	64	1	25.10	4	0	0	2	-	2	2	2	1	2	2	1	2	53.00	209	187	42	138	2	57.7	0	1	1	1	0	1	5
22	370339f	67	1	19.36	2	0	2	2	9.1	1	1	2	2	2	2	1	2	66.00	173	163	35	107	1	53.3	1	0	1	1	1	1	5
23	401351d	51	1	27.18	2	0	2	2	8.2	1	1	2	2	2	2	1	3	65.00	124	71	32	71	1	62.0	0	1	1	1	0	7	5
24	332660f	54	1	26.45	2	2	1	1	6.9	1	2	2	2	2	2	1	1	45.00	229	283	51	128	1	40.7	0	0	1	1	1	1	5
25	312588f	60	1	22.15	2	2	2	1	7.4	1	2	2	2	2	2	2	3	54.00	110	80	43	49	1	30.0	0	0	1	1	0	1	5
26	298978d	57	2	26.00	2	2	2	2	5.6	2	2	2	2	1	2	2	3	64.00	254	164	41	183	1	43.0	0	1	1	0	0	0	2
27	288253f	70	1	23.18	2	0	2	2	6.5	1	1	2	2	2	2	2	3	64.00	97	80	32	46	2	55.5	0	1	1	1	0	5	2
28	299893f	43	1	22.50	2	2	1	1	7.6	2	1	2	2	2	2	2	3	77.65	117	106	37	63	1	44.8	0	1	1	0	0	5	4
29	814120c	53	1	23.90	4	2	2	1	6.6	1	2	2	2	2	2	2	1	67.00	125	66	26	62	1	35.0	0	1	1	1	0	3	5
30	273193f	67	1	24.91	2	2	2	2	4.8	2	1	2	2	2	2	2	3	59.00	125	123	44	58	2	58.6	0	0	1	1	0	7	0
31	283727f	42	1	19.10	3	3	2	2	5.2	2	2	2	2	2	2	2	1	81.00	105	68	39	51	1	59.0	0	1	1	0	0	5	1
32	410021f	63	1	21.88	2	2	2	2	6.6	2	2	2	2	2	2	2	1	52.00	151	112	51	82	1	43.0	0	1	1	0	0	0	1
33	232571f	50	1	22.80	2	2	2	2	5.5	2	1	2	2	2	2	1	1	75.00	130	89	39	68	1	46.4	0	1	0	1	0	0	5

34	361674d	57	1	28.00	2	2	2	2	7.3	1	2	2	2	2	2	2	3	72.00	189	98	41	126	2	58.0	0	1	0	0	0	0	0
35	293369F	63	1	23.40	2	0	2	2	5.4	2	2	2	2	2	2	2	2	65.60	138	106	34	80	1	57.0	0	1	1	1	0	1	5
36	244115f	62	1	20.70	2	0	2	1	5.5	2	2	2	2	2	2	2	3	79.00	241	216	39	152	1	42.0	0	0	1	1	0	7	5
37	633826d	62	1	22.89	2	2	2	1	6.0	1	1	2	2	1	2	1	1	49.64	121	110	30	75	1	34.9	0	1	1	0	0	1	0
38	399276f	36	1	26.09	2	0	2	1	5.7	2	1	2	2	2	2	2	3	81.00	152	212	43	67	1	55.0	0	0	1	1	0	1	0
39	294989f	72	1	28.40	2	2	2	2	6.0	2	2	2	2	2	2	2	1	67.00	171	206	19	18	2	57.9	0	1	0	1	0	0	1
40	337789f	58	1	27.00	2	2	2	2	7.4	1	1	2	2	2	2	1	1	47.00	289	260	33	211	1	43.0	0	1	1	1	0	1	1
41	336762f	58	1	16.49	2	2	2	1	5.4	2	2	2	2	2	2	2	2	73.85	108	91	33	56	1	42.0	0	1	0	0	1	9	4
42	399955f	84	1	27.34	2	0	0	1	5.5	2	1	2	1	2	2	1	3	33.00	233	199	39	148	1	43.0	0	1	1	1	0	5	5
43	253713f	60	1	25.00	2	0	2	2	5.7	1	2	2	2	2	2	2	3	72.00	135	233	40	68	2	55.0	0	1	0	1	0	0	1
44	408100f	54	1	21.08	2	2	1	1	6.7	2	1	2	2	2	2	1	1	48.00	180	179	30	120	2	60.7	0	0	1	1	0	1	4
45	664429d	70	1	32.42	3	0	2	2	5.4	2	1	2	2	2	2	2	3	78.00	184	118	32	124	2	57.0	0	0	1	1	0	1	2
46	3055914f	72	1	22.59	3	3	2	1	6.5	2	1	2	2	2	2	2	3	63.97	101	130	36	45	2	57.4	0	0	1	1	0	3	4
47	325203f	52	1	24.01	2	0	2	1	6.5	1	1	2	2	2	2	1	1	55.64	136	107	38	81	1	59.6	0	1	0	0	1	0	1
48	217668f	54	2	19.90	4	2	2	1	5.7	2	2	2	2	2	2	2	3	83.00	122	103	33	77	1	43.0	0	1	1	1	0	0	2
49	470033b	54	1	24.00	2	2	2	2	5.9	2	2	2	2	2	2	2	1	65.00	115	103	46	53	2	57.1	0	1	1	0	0	1	4
50	380103f	72	1	21.93	2	0	1	1	7.9	1	1	2	2	2	2	2	2	40.66	152	237	26	78	1	38.5	0	1	0	0	0	0	1
51	398764f	50	1	29.00	2	0	2	1	6.4	1	1	2	2	2	2	2	2	63.00	125	133	28	74	1	44.0	0	1	1	1	0	0	2
52	048534f	52	1	24.61	2	0	2	2	6.3	2	1	2	2	2	2	1	3	75.00	201	186	55	113	2	55.0	0	1	0	1	0	4	0
53	352818f	57	1	21.71	4	2	2	1	6.6	1	2	2	2	2	2	1	1	53.00	143	134	34	83	1	43.0	0	0	1	0	0	1	5
54	197808f	59	1	21.50	2	0	2	1	5.5	2	2	2	2	2	2	2	2	45.90	140	103	39	81	1	37.0	0	1	1	0	0	5	2
55	377417F	51	1	24.30	2	0	2	2	5.9	2	2	2	2	2	2	2	2	67.00	177	162	42	105	2	58.0	0	1	0	0	0	0	0
56	373911f	59	1	23.73	2	2	2	2	10.2	1	1	2	2	2	2	2	3	63.00	271	459	46	61	2	57.8	0	1	1	1	0	1	1
57	418388f	49	1	24.80	3	0	2	2	7.5	1	1	2	2	2	2	2	3	76.00	125	76	21	87	1	52.0	0	1	1	0	0	1	4
58	344829f	60	1	23.44	3	2	2	1	4.8	2	2	2	2	2	2	2	3	112.00	177	111	43	111	1	44.7	1	1	1	1	0	1	5
59	296427f	73	1	24.17	4	0	2	1	6.2	1	1	2	2	2	2	2	1	35.00	136	250	32	56	1	57.7	0	1	1	0	0	1	1
60	259157f	35	1	23.45	4	0	2	1	-	2	2	2	2	2	2	1	3	79.30	240	265	40	163	2	55.0	0	1	0	0	0	0	5
61	302987f	69	2	21.46	2	0	2	2	5.8	2	1	2	2	2	1	2	3	61.25	277	120	66	185	2	57.0	0	1	1	0	1	0	0
62	441816c	67	1	28.90	2	2	2	1	6.6	1	1	2	2	2	2	1	3	53.00	138	138	51	61	1	55.0	0	0	1	0	1	1	5
63	181081f	65	1	18.40	2	2	2	2	8.0	1	1	2	2	2	2	2	3	64.00	100	136	30	52	1	57.0	0	0	1	0	1	1	5
64	290981f	75	1	14.87	3	0	2	1	6.4	2	2	2	2	1	2	2	3	63.00	137	84	33	81	1	27.2	0	1	1	1	0	7	1
65	277217f	58	1	23.05	2	2	2	2	5.5	2	2	2	2	2	2	2	1	69.42	187	340	40	106	2	56.0	0	1	1	1	0	3	1
66	340723f	58	1	22.30	2	2	2	1	6.2	1	1	2	2	2	2	1	3	79.00	131	138	39	71	1	43.0	0	1	1	1	0	7	5

hosp_no	TD2	bifur1	bifur2	stump	stump2	Bridg1	Bridg 2	side2	Medina	Medina2	Ang	Ang2	Ost	Ost2	Tort	Tort	Len	Len2	calcif	calcif2	throm	throm2	SYNTAX	Mange	PCI-Suc1	Sucess2	wire	Fol-up
365142f	NA	0	NA	0	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	29.5	0	NA	NA		4
375539f	NA	1	0	1	NA	0	0	NA	2	NA	2	NA	0	NA	0	NA	1	NA	0	NA	0	NA	25.5	0	NA	NA		4
047781f	6	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	42.5	1	NA	NA		1
287740f	NA	1	NA	0	NA	0	0	NA	2	NA	2	NA	0	NA	0	NA	0	NA	0	NA	0	NA	21	0	NA	NA		4
299531f	NA	1	NA	1	NA	0	0	NA	3	NA	2	NA	0	NA	0	NA	1	NA	0	NA	0	NA	27.5	2	NA	NA		1
303337f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	51	0	NA	NA		2
310259f	NA	1	NA	1	NA	1	0	NA	4	NA	2	NA	0	NA	0	NA	1	NA	1	NA	0	NA	29.5	2	NA	NA		1
276238f	5	0	0	0	1	0	0	1	0	0	2	0	0	1	0	0	0	1	0	0	0	0	33.5	2	NA	NA		1
393064f	5	1	0	0	1	0	0	0	3	0	0	0	0	0	0	0	1	1	1	1	0	0	46.5	0	NA	NA		4
293557f	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	1	NA	0	NA	0	NA	34.5	0	NA	NA		4
382862f	6	0	NA	1	NA	1	0	NA	0	NA	0	NA	0	NA	1	0	0	1	0	0	0	0	33	2	NA	NA		1
402095f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	21	0	NA	NA		4
376805f	NA	0	0	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	47	0	NA	NA		1
381512f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	12	0	NA	NA		4
157235f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	21	0	NA	NA		4
288022f	4	0	0	0	0	0	1	0	0	0	0	2	0	0	0	0	0	1	1	0	0	0	51.5	0	NA	NA		1
223853F	0	1	0	1	1	0	0	2	3	0	0	2	0	0	0	0	1	0	0	0	0	0	29.5	2	NA	NA		1
369348f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	24	0	NA	NA		4
286967f	2	0	1	1	1	0	0	3	0	3	2	2	0	0	0	0	0	0	0	0	0	0	46	0	NA	NA		4
595237d	5	0	0	0	1	0	0	3	0	0	0	0	0	0	0	0	0	0	1	0	0	0	25	0	NA	NA		4
349729F	NA	0	NA	0	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	20	0	NA	NA		4
370339f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	30	0	NA	NA		2
401351d	0	0	0	0	1	1	0	3	0	0	0	0	0	0	0	0	1	0	0	0	0	0	34.5	2	NA	NA		1
332660f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	11	0	NA	NA		1
312588f	NA	0	NA	0	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	12	2	NA	NA		4
298978d	6	1	NA	1	NA	0	0	NA	2	NA	2	NA	0	NA	0	NA	0	NA	0	NA	0	NA	27.5	0	NA	NA		1
288253f	1	0	0	1	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	31.5	2	NA	NA		1
299893f	1	0	0	1	1	0	1	2	0	0	0	0	0	0	0	0	1	0	0	0	0	0	31.5	1	0	0	0	1
814120c	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	31.5	1	0	NA	0	3
273193f	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	17.5	1	0	0	0	1
283727f	0	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	17.5	1	0	0	0	1
410021f	6	0	0	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	1	NA	0	NA	37.5	1	0	NA	0	4
232571f	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	1	NA	0	NA	31.5	1	0	NA	0	1

361674d	6	1	NA	1	NA	0	0	NA	4	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	18.5	1	0	NA	1	1
293369F	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	26	1	0	NA	1	1
244115f	2	1	1	1	1	0	0	2	0	2	0	2	0	0	0	0	0	0	0	0	0	0	26.5	1	0	1	0	2
633826d	NA	0	0	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	21	1	0	NA	0	4
399276f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	13	1	0	NA	1	1
294989f	6	1	NA	1	NA	0	0	NA	2	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	14.5	1	0	NA	0	1
337789f	6	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	20	1	0	NA	0	4
336762f	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	26.5	1	0	1	0	1
399955f	5	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	1	1	1	0	0	34.5	1	0	0	1	1
253713f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	1	NA	0	NA	18.5	1	0	NA	0	1
408100f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	9	0	0	NA	1	2
664429d	NA	0	NA	0	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	15	1	0	NA	0	1
3055914f	NA	0	0	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	7.5	1	0	NA	0	1
325203f	NA	1	0	1	NA	0	0	NA	3	NA	2	NA	0	NA	0	NA	0	NA	0	NA	0	NA	24.5	1	0	NA	0	1
217668f	NA	0	0	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	25.5	1	0	NA	0	1
470033b	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	8	1	0	NA	0	1
380103f	NA	1	NA	1	NA	0	0	NA	2	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	21.5	1	0	NA	1	1
398764f	6	1	NA	1	NA	0	0	NA	3	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	27.5	1	0	NA	0	1
048534f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	23	1	0	NA	0	1
352818f	NA	0	NA	1	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	11	1	0	NA	0	1
197808f	5	0	0	1	1	0	1	0	0	0	2	0	0	0	0	0	0	1	1	1	0	0	38.5	1	0	1	0	3
377417F	6	1	NA	1	NA	0	0	NA	3	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	21.5	1	0	NA	0	1
373911f	NA	0	NA	0	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	19	1	1	NA	1	1
418388f	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	24	1	1	NA	0	1
344829f	NA	0	0	1	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	31	1	1	NA	0	1
296427f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	22	1	1	NA	1	1
259157f	NA	1	NA	1	NA	1	0	NA	2	NA	2	NA	0	NA	0	NA	1	NA	0	NA	0	NA	23.5	1	1	NA	1	1
302987f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	25.5	1	1	NA	0	1
441816c	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	1	NA	0	NA	1	NA	0	NA	0	NA	8	1	1	NA	1	1
181081f	6	0	NA	0	NA	1	0	NA	0	NA	0	NA	0	NA	0	NA	1	NA	0	NA	0	NA	17	1	1	NA	0	1
290981f	1	1	0	1	1	0	0	2	2	0	2	2	0	0	0	0	0	0	0	0	0	0	29	1	1	0	0	1
277217f	NA	0	NA	1	NA	0	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0	NA	22	1	1	NA		4
340723f	5	0	1	0	1	1	0	2	0	4	0	2	1	0	0	0	1	1	0	0	0	0	46.5	0	NA	NA	0	1