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The Comparison of Clinical Outcomes of Percutaneous Coronary Intervention with Drug Eluting Stent versus Coronary Artery Bypass Grafting for Unprotected Left Main Disease

PROJECT REPORT

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DECLARATION

I, **Dr Anand M,** hereby declare that the project in this book, titled **"The Comparison of Clinical Outcomes of Percutaneous Coronary Intervention with Drug Eluting Stent versus Coronary Artery Bypass Grafting for Unprotected Left Main Disease"** was undertaken by me under the supervision of the Faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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TITLE

“The Comparison of Clinical Outcomes of Percutaneous Coronary Intervention with Drug Eluting Stent versus Coronary Artery Bypass Grafting for Unprotected Left Main Disease”

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Abbreviations

ACS	-	Acute coronary syndrome
BMS	-	Bare metal stent
CABG	-	Coronary artery bypass grafting
CAD	-	Coronary artery disease
CASS	-	Coronary artery Surgery Study
CI	-	Confidence Interval
COPD	-	Chronic obstructive pulmonary disease
COR	-	Class of Recommendation
CVA	-	Cerebrovascular accident
DES	-	Drug eluting stent
DM	-	Diabetes mellitus
EF	-	Ejection fraction
FFR	-	Fractional Flow reserve
IABP	-	Intra-aortic Balloon pump
IHD	-	Ischemic Heart disease

ISR	-	In stent restenosis
IVUS	-	Intravascular ultrasound
LAD	-	Left anterior descending artery
LIMA	-	Left internal mammary artery
LMCA	-	Left main coronary artery
LMS	-	Left main stem
LOE	-	Level of evidence
LV EF	-	Left ventricular ejection Fraction
MACCE	-	Major adverse cardiac and cerebrovascular events
NSTEMI	-	Non-ST elevation Myocardial infarction
NYHA	-	New York Heart Association
OR	-	Odds ratio
PCI	-	Percutaneous coronary interventions
POBA	-	Plain old balloon angioplasty
PTCA	-	Percutaneous transluminal coronary angioplasty
RCA	-	Right coronary artery

RCT - Randomised control trial

SIHD - Stable ischemic heart disease

STEMI - ST elevation Myocardial infarction

ST - Stent thrombosis

STS - Society of Thoracic Surgeons

SYNTAX - Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery

TLR - Target lesion revascularisation

TVR - Target vessel revascularisation

UA - Unstable Angina

ULMCA - Unprotected Left main coronary artery

Introduction

Introduction

Left main coronary artery (LMCA) disease or in short left main disease is defined as involvement of 50% or more diameter stenosis of left main coronary artery (LMCA). Among the various anatomic lesions involved in coronary artery disease (CAD), patients with significant left main coronary artery (LMCA) disease have the highest risk and is associated with poor clinical outcomes when compared with patients without left main involvement. This is because the LMCA supplies around 75% of the left ventricular (LV) mass in patients with right dominant circulation and nearly 100% of the left ventricular mass in patients with left dominant circulation. Hence, severe left main disease will jeopardise the blood flow to a large considerable portion of the myocardium, placing the patient at high risk for life-threatening events of myocardial infarction, cardiac arrest, left ventricular dysfunction and arrhythmias[9].

Before the advent of percutaneous coronary intervention, there were many clinical trials which demonstrated a significant survival benefit of coronary artery bypass grafting (CABG) over medical therapy. Patients who were kept on medical therapy had poor prognosis with nearly 50% mortality in 3 years[15,16]. Hence, CABG became the standard of treatment for significant LMCA disease for a long time[10] and it is still Class I recommendation endorsed by both American and European societies. During this era, percutaneous coronary intervention (PCI) for left main disease was performed only on a limited basis especially in surgically ineligible patients or high risk surgical patients. However, with the remarkable advancements in medical device technology especially in stent design and newer drug eluting stents with biodegradable polymer, safer procedural techniques, more safer antithrombotic agents, and significant improvement in medical therapy during the last two decades, PCI with stenting for LMCA disease

has become feasible and shows favourable clinical outcomes[11]. The newer drug-eluting stents (DES) have a low risk of angiographic and clinical restenosis. The increased use of these newer drug eluting stents in patients with left main intervention have shown favourable results in case series and registries. This has led to multiple randomised control trials comparing outcomes of patients with left main disease undergoing revascularisation with CABG verses PCI. Most of these trials showed non-inferiority of PCI when compared to CABG in left main disease.

Based on these trials and registry data, the American and European societal guidelines have made amendments to the existing guidelines for revascularisation for left main disease. ACC/AHA guidelines provide Class IIa recommendation for PCI for left main disease with low SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score of < 23, ostial or shaft left main CAD with STS predicted risk of mortality score ≥ 5% and Class IIb for PCI for left main disease with low to intermediate SYNTAX score of < 33, bifurcation left main CAD with STS predicted risk of mortality score ≥ 2%[12]. ESC guidelines provide Class I recommendation for Left main disease with a SYNTAX score 22, Class IIa recommendation for Left main disease with a SYNTAX score 23–32 and Class III recommendation for Left main disease with a SYNTAX score >32[4]. However, both the societal guidelines recommend CABG as Class I recommendation for all groups of SYNTAX score.

As a result of these changes in recommendation, revascularisation for LMCA disease have changed substantially with more patients undergoing percutaneous intervention. However, long term outcomes of the patients undergoing PCI for left main disease have still not been systematically evaluated. In this study we planned to study retrospectively the outcomes of stenting for unprotected left main disease with coronary artery bypass grafting.

Review of Literature

Review of Literature

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium; it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of one or more epicardial coronary arteries.

Patients with coronary artery disease fall into two large groups: a) patients with chronic coronary artery disease (CAD) who most commonly present with stable angina and b) patients with acute coronary syndromes (ACSs). These include patients with acute myocardial infarction with ST-segment elevation (STEMI) on their presenting electrocardiogram and those with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). The latter include patients with non-ST-segment elevation myocardial infarction (NSTEMI) who by definition have evidence of myocyte necrosis and those with unstable angina (UA), who do not.[1]

Obesity, insulin resistance and Type 2 Diabetes mellitus, smoking, dyslipidaemia, hypertension and sedentary life style are the common risk factors for coronary artery disease. These trends are occurring in the general context of population growth and as well as the increase in the average age of the world's population. As a result, the prevalence of risk factors for CAD and the prevalence of CAD itself are both increasing rapidly, so that in analyses of the global burden of disease, there is a shift from communicable to non-communicable diseases.

Population subgroups that appear to be particularly affected are men in South Asian countries, especially India and the Middle East.

Management of coronary artery disease is a multifaceted approach consisting of medical management and revascularisation of coronary arteries. Medical management includes control of risk factors, anti-ischemic medications like beta-blockers, nitrates and calcium channel blockers, antiplatelet agents like aspirin and clopidogrel and lipid lowering agents like statins. If the patient remains symptomatic on medical management or has high risk features such as left ventricular dysfunction, symptoms at low work load, strongly positive exercise stress test or presentation as ACS, then the patient should be considered for invasive coronary angiography with the intent of revascularisation.[1]

The revascularisation can be either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and depends on multiple factors such as complexity of the coronary artery disease, patient comorbid conditions and predicted surgical mortality[4]. Numerous models have been developed for risk stratification, focussing on anatomical complexity or clinical risk, and have demonstrated their value during decision-making.

SYNTAX Score and STS Score

Complex anatomy of the coronary artery disease is usually assessed by the SYNTAX (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) score which was initially described in the SYNTAX trial [5]. The SYNTAX score is an angiographic grading tool to determine the complexity of coronary artery disease. The SYNTAX score is the sum of the points assigned

to each individual lesion identified in the coronary tree with >50% diameter narrowing in vessels >1.5mm diameter. The coronary tree is divided into 16 segments according to the AHA classification. Each segment is given a score of 1 or 2 based on the presence of disease and this score is then weighted based on a chart, with values ranging from 3.5 for the proximal left anterior descending artery (LAD) to 5.0 for left main, and 0.5 for smaller branches. Further characterization of the lesions adds points such as bifurcation or trifurcation lesion, total occlusion, Aorto-ostial involvement, calcifications, tortuosity of vessel, right or left dominant system, thrombus containing lesion or not and length of the lesion. The value of SYNTAX score ranges from 0 – 83 with higher values representing more complex lesions.

The SYNTAX score was found to be an independent predictor of long-term major adverse cardiac and cerebrovascular event (MACCE) in patients treated with PCI but not CABG.[6,7]

The Society of Thoracic Surgeons (STS) score is a risk-prediction model, validated in patients undergoing cardiac surgery, with a specific model for CABG surgery and combined CABG and valve surgery[8]. It can be used to predict in-hospital or 30-day mortality (whichever occurs last) and in-hospital morbidity. Based on the STS score, patients are risk stratified as low risk (<4%), intermediate risk (4-8%) and high risk(>8%).

Left Main disease:

Significant unprotected left main coronary artery (ULMCA) disease occurs in 5–7% of patients undergoing coronary angiography[13,14] and patients with

ULMCA disease treated medically have a 3-year mortality rate of 50%[15,16]. Several studies have shown a significant benefit following the treatment of left main (LM) stenosis with coronary artery bypass grafting (CABG) compared with medical treatment[17,18]. CABG has been the gold standard therapy for Left main disease with Class I recommendation endorsed by both ESC and AHA/ACC Guidelines. for a long time. Advances in the field of percutaneous intervention techniques, stent technology, newer antithrombotic and antiplatelets agents and background medical therapy have made percutaneous coronary intervention (PCI) for LM disease feasible and favourable outcomes when compared to CABG in specific subgroup of patients.

Why Left main disease is important

The LMCA is responsible for supplying ≥ 75% of the left ventricular (LV) cardiac mass in patients with right dominant type or balanced type and 100% in the case of left dominant type, and as a result, severe LMCA disease will reduce flow to a large portion of the myocardium, placing the patient at high risk for life-threatening events of LV dysfunction and arrhythmias.[9]

Left main disease is defined as 50% or more diameter stenosis of LMCA.
LMCA disease is defined as unprotected under the following circumstances:-

- "Unprotected" means that no perfusion distal to the left main stenosis is supplied by either a patent bypass graft or a collateral vessel.

Outcomes of Left main disease with CABG

Coronary artery bypass surgery is a well-established technique with excellent proven results for the treatment of coronary artery disease.

In 1975 Cohen and Gorlin[19] first reported that CABG resulted in a significant improvement in 10-year survival compared with medical therapy in patients with significant LMS stenosis, an observation confirmed in 3 randomized trials[20] and numerous observational studies over the next 2 decades. However during this period both the medical therapy and surgical techniques were outdated (e.g., aspirin, statins, and internal mammary artery [IMA] grafts were not widely used).

In the largest prospective study of LM stenosis, in which 1,484 patients in the CASS (Coronary Artery Surgery Study) registry were followed for up to 16 years, the overall median survival for CABG patients was 13.3 years versus 6.6 years for medical therapy[21].

Taggart et al.[22] in 2008 reported on a series of studies which showed in-hospital mortality rate of 2 - 3% for CABG for LM stenosis. There were only a few studies in this series which reported long term outcomes with CABG. There were two studies in this series which showed 2 year mortality rate of 5-6%.

In their review of the Cleveland Clinic experience of CABG for patients with LM stenosis, Sabik et al[23] report a 20-year follow-up of all patients operated on between 1971 and 1998. They have shown that for the 3803 patients with LM stenosis, 30-day survival is 97.6%, with 93.6% at 1 year and 83% at 5 years and 64% at 10 years. Rates of freedom from repeat revascularisation are 99.7% at 30 days, 98.9% at 1 year, 89% at 5 years, 76% at 10 years and 61% at 20 years. These studies represent the benchmark against which other treatments of the LM stem must be compared.

Early Experience with Angioplasty for LM disease

The third patient treated by Andreas Gruntzig back in 1979 had LMS balloon angioplasty. The technical result was satisfactory but the patient unfortunately died suddenly 4 months post-procedure.[24] In the 1980s, the limitations of 'plain old balloon angioplasty' (POBA) in the treatment of LMS disease became apparent. After the first series of 129 patients, reported by Hartzler and O'Keefe in 1989[25], showed a 10% in-hospital mortality and 64% 3-year mortality, the practice was quickly abandoned due to poor outcomes and better surgical results.

Interest in percutaneous treatment was only revived with the introduction of bare metal stents (BMS) and the advent of newer anti-platelet therapies aimed at reducing in-stent restenosis (ISR) and thrombosis.

In the 1990s, promising LM stent results were published though most stemmed from single centres. Silvestri et al. reported a 1-year survival of 89 % in a high-risk subgroup of patients,[26] while Park et al. reported a 91 % 3-year survival rate in a multicentre study.[27] The Unprotected Left Main Trunk Intervention Multi-Centre Assessment (ULTIMA) registry evaluated the procedural and clinical outcomes after unprotected LMS percutaneous coronary intervention (PCI) was undertaken in 25 centres.[28] This showed an overall 24 % 1-year mortality with a better outcome in low-risk groups and only a 3.4 % mortality rate at 1 year.

Early experience with drug eluting Stents for left main disease intervention

The development of drug eluting stent (DES) made percutaneous intervention for left main disease more feasible with better outcomes when compared with bare metal stents. This was due to the significant reduction in stent restenosis and target lesion revascularisation with DES when compared to BMS. In a systematic review and meta-analysis of 1278 patients, Biondi-Zoccai et al.[29]have shown that treating ULMCA lesions with drug-eluting stents is associated with a 5.5% (3.3–7.7%) risk of death, a 16.5% (11.7–21.3%) MACE rate, and a TLR rate of 6.5% (3.7–9.2%). Distal LM disease is a predictor of MACE and TLR; however, it is the presence of high-risk features that predicts death. The review also shows that most series have reported low rates of stent thrombosis (ST) (0–2%).

Various single-centre studies showed high procedural success rates, low procedural complication rates, and encouraging long-term outcome with an 11.5–20.3% major adverse cardiac event (MACE) rate at 2- to 3-year follow-up. These results were confirmed by the FRIEND [30]registry results which showed a major adverse cardiac and cerebrovascular event (MACCE) rate of 10.6% at 450 days.

Drug-eluting stent in LMCA PCI has been evaluated in several observational single- and multicentre registries showing a good efficacy and safety profile. Moreover, several observational, non-randomized registries have shown no difference in the occurrence of MACCE between patients treated with DES compared with the ones treated with CABG in this subset of patients up to 5 years of clinical follow-up.

Drug Eluting Stents vs CABG for left main disease

The 'Revascularization for Unprotected LM Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty vs. Surgical Revascularization' (MAIN-COMPARE)[31] Registry was the first large multicentre non-randomized study comparing long-term outcome following PCI with stenting vs. CABG for ULMCA disease. This registry involved 2240 patients with ULMCA stenosis who underwent stenting (DES = 784; BMS = 318) or CABG (n = 1138). Patients in the PCI cohort were less likely to have diabetes, or multivessel coronary artery disease; however, after adjustment with propensity scoring model, in the matched cohort, no significant difference was observed between the two revascularization strategies in terms of risk of death and risk of the composite outcome of death, MI, and cerebrovascular events (CVE). The rate of target vessel revascularization (TVR) was significantly higher in the group that received stents than in the group that underwent CABG. Comparisons of the group that received bare-metal stents with the group that underwent CABG and of the group that received drug-eluting stents with the group that underwent CABG produced similar results. The follow-up at 5 years confirmed those results.[32]

Consistently with this finding, Chieffo et al. showed in a nonrandomized comparison from a single-centre no difference between PCI with DES implantation and CABG in the occurrence of cardiac death, whereas CABG was correlated with lower TVR and no difference was detected in the occurrence of MACCE at 5-year clinical follow-up.

Data from Randomised control trials

Four RCTs have specifically looked at the cohort of patients with left main disease which have shown similar results.

The Study of Unprotected Left Main Stenting versus Bypass Surgery (LEMANS) was the first RCT and enrolled 105 patients with significant LMS disease (defined as >50 % stenosis angiographically).[33] The primary endpoint was the change in left ventricular ejection fraction (LVEF) at 12 months, while the secondary endpoint was a major adverse cardiac and cerebrovascular event (MACCE) at 30 days and 1 year. 105 patients were enrolled in the study with 52 patients undergoing PTCA and 53 patients undergoing CABG. There was a statistically significant improvement in LVEF with patients treated with PCI versus CABG. MACCE was equivalent at 1 year between the two groups. The study did have a number of limitations, including a small sample size, high use of BMS and a lower than contemporary use of left internal mammary artery (LIMA) grafts.10 year results of the LEMANS study was similar with no difference in MACCE between the two groups.

The Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX)[35] trial remains to this day the largest RCT to date to compare PCI to CABG in LMS disease. The LMS subset consisted of 705 patients randomised to receiving either the first-generation TAXUS DES or CABG. Major adverse cardiac and cerebrovascular event rates at 1 year in LM patients were similar for CABG and PCI (13.7% vs. 15.8%). At 1 year, stroke was significantly higher in the CABG arm (2.7% vs. 0.3%; P = 0.009), whereas repeat revascularization was significantly higher in the PCI arm (6.5% vs. 11.8% p = 0.02); there was no observed difference between groups for other end points. When patients were scored for anatomic complexity, those with higher baseline SYNTAX scores had

significantly worse outcomes with PCI than did patients with low or intermediate SYNTAX scores; outcomes for patients with CABG did not correlate with baseline SYNTAX score. Stratification into tertiles of syntax score (0–22, 23–32 and >32) revealed equivalent MACCE in the lower two tertiles, but a clear superiority of CABG in the highest tertile. The 5-year follow-up results were published in 2014.[34]The results bear a similar trend to the 1-year follow-up with similar outcomes across the whole cohort (36.9 % PCI versus 31 % CABG; P=0.12) but with a statistically greater benefit of CABG in the highest risk group based on lesion complexity.

The Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease (PreCOMBAT)[36] trial was a non-inferiority trial randomising 600 patients with LM disease to either a first-generation Cypher DES or CABG. The primary endpoint was MACCE at 1 year. Event rates at 2 years were also compared. MACCE was similar between the two groups at 1 year and 2 years. Target vessel revascularisation was significantly more in the PCI group at 2 years. The results were consistent at 5 year follow up.

Boudriot et al. studied a smaller sample group of 201 patients and unlike the previous studies, PCI failed to achieve non-inferiority of MACE at 1 year. Excess MACE was driven by target vessel revascularisation. Unusually for this type of comparison, stroke was not included as a clinical endpoint, which may well have contributed to the end result.

Overall, the four RCTs showed similar results. Total MACCE rate was similar between the 2 groups. Stroke was more common with CABG, and repeat

revascularization was more common with PCI. Subsequently, several meta-analyses have confirmed these findings.

However, the benefit of CABG over PCI becomes more evident according to increasing anatomic complexities (i.e., SYNTAX Score > 32) the rate of adverse events significantly increased in patients with PCI with high complexity of LMCA and concomitant CAD, whereas the rate was nearly similar in patients with lower anatomic complexity (i.e., SYNTAX Score ≤ 32). In particular, the relative clinical benefits of CABG over PCI may become prominent over time; in this regard, the 5- or 10-year follow-up results of several important studies have become available, and the overall findings were consistent.

The limitations of these trials were that they were done with first generation stents. Hence with the increased use of second generation DES which has better stent design, intravascular imaging and newer antithrombotic agents the MACCE events with PCI may come down. In CABG, off-pump surgery has been increasingly used, use of arterial conduits have increased and the perioperative care has become more organized. However, none of the available RCTs of DES versus CABG were adequately powered and included contemporary devices with newer-generation DES.

Meta-analysis

A meta-analysis of first-generation DES versus CABG was published in 2013 by Athapan et al[38]. The MACE rates did not differ between the PCI and CABG group up to 5 years. However PCI was associated with a lower rate of stroke and higher rate of target vessel revascularisation (TVR) as noted in previous studies.

Influence of lesion location and complexity on PCI

In an analysis of the Drug-Eluting Stent For Left Main Coronary Artery Disease (DELTA) registry comparing ostial/mid-shaft lesion versus distal lesions, Naganuma et al. demonstrated a higher rate of TLR with distal lesions.[40]Various reports suggest that treatment of bifurcation lesions with one-stent approach was more favourable than treatment with a two-stent approach[39]. The TLR rate is relatively low (< 5%) with a one-stent approach resulting nearly equivalent to results obtained with DES for ostial or mid-ULMCA lesions. There is little consensus on the optimal two-stent strategy (i.e. crush, culotte, or T-stenting) to approach a distal ULMCA lesion mostly driven by the preference of the operator but so far never investigated in a randomized comparison.

Intravascular Ultrasound

Stent sizing and apposition is very important for LMCA interventions in order to prevent complications such as stent thrombosis and restenosis. The use of intravascular ultrasound (IVUS)-guided PCI in this context may be beneficial but has never been formally investigated in an RCT. Data from registries are available which suggest better outcomes with the use of intravascular imaging.

Park et al. compared the use of IVUS-guided treatment of LMS lesions with conventional angiography in the MAIN-COMPARE registry.[41] In 201 matched pairs of the overall population, there was a tendency of lower risk of 3-year mortality with IVUS guidance compared with angiography guidance (6.0% versus 13.6%, log-rank p = 0.063) which was statistically significant in the group receiving drug eluting stents.

Stent type

A meta-analysis by Pandya et al. which comprised 44 studies, showed that Left main stenting with DES were associated with a better outcome than BMS.[42] The Intracoronary Stenting and Angiographic Results: Drug- Eluting Stents for Unprotected Coronary Left Main Lesions (ISAR LEFT MAIN) trials have compared different types of DES. The ISAR LEFT MAIN study compared the two first-generation DES (Cypher sirolimus-eluting stent [SES] and Taxus paclitaxel-eluting stent [PES]) and showed similar outcomes with both types of stents.[43] MACE rate at 1 year was was 13.6% in the PES and 15.8% in the SES group (p = 0.44).The ISAR-LEFT MAIN 2 study compared second-generation zotarolimus-eluting stent (ZES) and everolimus-eluting stent (EES) and once again showed similar clinical and angiographic outcomes at 1 year.[44] At 1 year, MACE was 17.5% in the ZES group and 14.3% in the EES group (p = 0.25). Thus, the types of DES from a similar generation do not seem to influence outcome.

Guidelines

Both the European and American societies have issued guidelines on revascularisation of patient with LM disease (Table 1, Table 2).

CABG maintains a Class I indication across all anatomical subgroups. The European Society of Cardiology (ESC)[4] guidelines have given Class I recommendation in patients with a low SYNTAX score (<23) and 2A for an intermediate score (23 – 32). By contrast, the AHA/ACC [12]guidelines give only Class IIa recommendation for low SYNTAX scores and a Class IIb

recommendaion for intermediate scores. Both societies are in agreement about the superiority of CABG for patients with a high SYNTAX score.

Table 1
AHA/ ACC Guidelines for PCI – 2011

ULMCA

	Class Of Recommendation (COR)	**LOE**
CABG	I	B
PCI	IIa—For SIHD when *both* of the following are present: ● Anatomic conditions associated with a low risk of PCI procedural complications and a high likelihood of good long-term outcome (eg, a low SYNTAX score of ≤ 22, ostial or trunk left main CAD) ● Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (eg, STS-predicted risk of operative mortality _5%) IIa—For UA/NSTEMI if not a CABG candidate IIa—For STEMI when distal coronary flow is TIMI flow grade _3 and PCI can be performed more rapidly and safely than CABG	B B C
	IIb—For SIHD when *both* of the following are present: ● Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and an intermediate to high likelihood of good long-term outcome (eg, low-intermediate SYNTAX score of ≥ 33, bifurcation left main CAD) ● Clinical characteristics that predict an increased risk of adverse surgical outcomes (eg, moderate-severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted risk of operative mortality > 2%)	B
	III: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B

TABLE 2
ESC GUIDELINES – 2014

	CABG		PCI	
	COR	**LOE**	**COR**	**LOE**
Left main disease with a SYNTAX score 22.	I	B	I	B
Left main disease with a SYNTAX score 23–32	I	B	IIa	B
Left main disease with a SYNTAX score >32.	I	B	III	B

Future Trials

The Class I recommendation of CABG in high Syntax scores is unlikely to be challenged in RCTs. However, the role of PCI in less-severe disease with low to intermediate SNTAX score needs to be firmly established. There are two trials which are underway which specifically look into this specific subgroup.

EXCEL is a multicentre study specifically looking at the treatment of patients with a low or intermediate SYNTAX score (<32). Use of the second generation Xience (Everolimus eluting Stent) DES will make the results more relevant to current practice. The primary endpoint is the composite of death, MI and stroke at a mean of 3-year follow-up. TVR is included in the secondary endpoint. The use of IVUS guidance to perform PCI is strongly recommended both pre- and post-treatment.

The Nordic-Baltic-British Left Main Revascularization Study (NOBLE) trial is also a multicentre trial comparing the contemporary Biomatrix stent versus CABG. Though the SYNTAX score is not being used for patient selection, the

inclusion criteria will yield a population not dissimilar to that of EXCEL trial. In addition to the LMS lesions, there should be ≤3 additional non-complex lesions elsewhere to qualify for participation. The primary endpoint is MACE at 2 years. The results of these two trials may have an impact on treatment guidelines for left main disease with low and intermediate SYNTAX scores.

The Future

The role of newer antiplatelet agents like prasugrel and ticagrelor in the treatment of left main percutaneous interventions is not evaluated in the RCTs. Whether increased use of these newer antiplatelet agents leads to decreased MACCE in left main intervention needs to be assessed. The influence of diabetes mellitus on the outcome of left main percutaneous interventions is not clear. The subgroup analysis of SYNTAX study showed higher MACCE rates in the PCI arm compared with the CABG arm in diabetic patients. However, it has to be evaluated in further trials.

There is a lack of systematic collection of data from the developing nations which are underrepresented in these trials. There is a paucity of data from the Indian subcontinent on the outcomes of patients treated either with percutaneous coronary intervention or CABG for left main coronary artery disease. Hence this study is planned in SCTIMST as it is a tertiary centre handling considerable number of left main disease patients

Aim of the study

Aim of the study

To compare the clinical outcomes of patients who underwent Left main coronary artery stenting versus coronary artery bypass surgery in patients with left main coronary artery disease.

Materials and Methods

Materials and methods

Study design

It is a single center retrospective observational study conducted in SCTIMST, Trivandrum. The study was approved by the institutional ethics committee.

Selection of Patients and Data Collection

All consecutive patients with coronary artery disease involving the left main coronary artery who underwent coronary angiogram between 1/1/2010 and 31/12/2014 were evaluated. In this cohort of patients, those who underwent revascularisation with either a coronary artery bypass grafting or left main coronary artery (LMCA) stenting were assessed and included in the study if the patients met the inclusion and exclusion criteria (criteria is provided below). Patients in the PCI group were identified from the hospital electronic medical records system using key search words such as “LMCA”, “PTCA to LMCA”, “PCI to LMCA”, “LMCA stenting” , “Left main disease” and “LMCA PTCA” in the hospital discharge summary, outpatient department summary and angiogram report data. Patients in the CABG group were identified from the hospital electronic medical records system using key search words such as “LMCA”, “Left main disease” in the hospital discharge summary, outpatient department summary and surgical report data. The data of the patients were collected from the hospital record files using a structured proforma. The coronary angiogram of

every patient in the study was evaluated by the principal investigator and the lesion characteristics assessed and SYNTAX score was calculated. The SYNTAX score was calculated online from the portal *http://www.syntaxscore.com/calculator/syntaxscore/frameset.htm*. STS score was also calculated online with the available data from the portal *http://riskcalc.sts.org/stswebriskcalc/#/calculate*. Follow up of these patients were obtained from the hospital medical record files. If the patient did not have follow up in the last 12 months, they were contacted over phone and follow up data obtained. Follow up duration was calculated as number of days from procedure to MACCE (Major Adverse Cardiovascular or Cerebrovascular events) or till the last date of follow up in those patients who did not have any MACCE event. For those lost to follow up, time from procedure to last follow up and status at that time were entered.

Inclusion criteria:

- Age > 18 years
- The patient must have significant de novo unprotected left main coronary artery (ULMCA) stenosis (>50% by visual estimation) with or without any additional target lesions (>70% by visual estimation) who underwent either a Coronary artery bypass grafting or left main coronary artery (LMCA) stenting from 1/1/2010 to 31/12/2014. “Unprotected” in this context means that no perfusion distal to the left main stenosis is supplied by either a patent bypass graft or a collateral vessel.

Exclusion criteria:

- Patients who underwent concomitant valve surgery along with CABG
- Patients who have undergone CABG previously
- Any life threatening condition other than cardiac cause which affected outcome

Objectives

Primary end point

- Major adverse cardiovascular or cerebrovascular events (MACCE)

Secondary end point

- Individual components of the MACCE
    - Death,
    - MI
    - Stroke
    - Target vessel revascularistion

Definition of end points

- Death was defined as death from any cause.
- MI – Myocardial infarction – as per the third universal definition of MI[3]
- Stroke was defined as a focal neurological deficit lasting >24 hours which resulted in irreversible brain damage or body impairment.
- Target-vessel revascularization was defined as repeat revascularization of the treated vessel either by PCI or CABG, including any segments of the left anterior descending artery and the left circumflex artery.

Statistical analysis

Statistical analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc, Chicago, Illinois, USA, V 23.0 for Windows). Continuous data were represented as mean or median with standard deviation or range as the dispersion measure, as appropriate. Categorical data were represented as percentages. The comparison of continuous data between the two groups were performed using student t test. The comparison of categorical data between the two groups were performed using Chi square or Fisher's exact test, as appropriate. The odds ratio (OR), its standard error and 95% confidence interval were calculated for the various parameters that could have an influence on the MACCE between the two groups . Kaplan-Meier survival analysis with log rank test was used to compare event free survival between the two groups. All tests were two-tailed, and a p value <0.05 was considered statistically significant.

Results

Results

A total of 117 patients were enrolled in the study. Out of these 37 patients were in the PCI group and 80 patients were in the CABG group (Figure 1). Out of the 37 patients in the PCI group two patients were lost to follow up and in the CABG group five patients were lost to follow up.

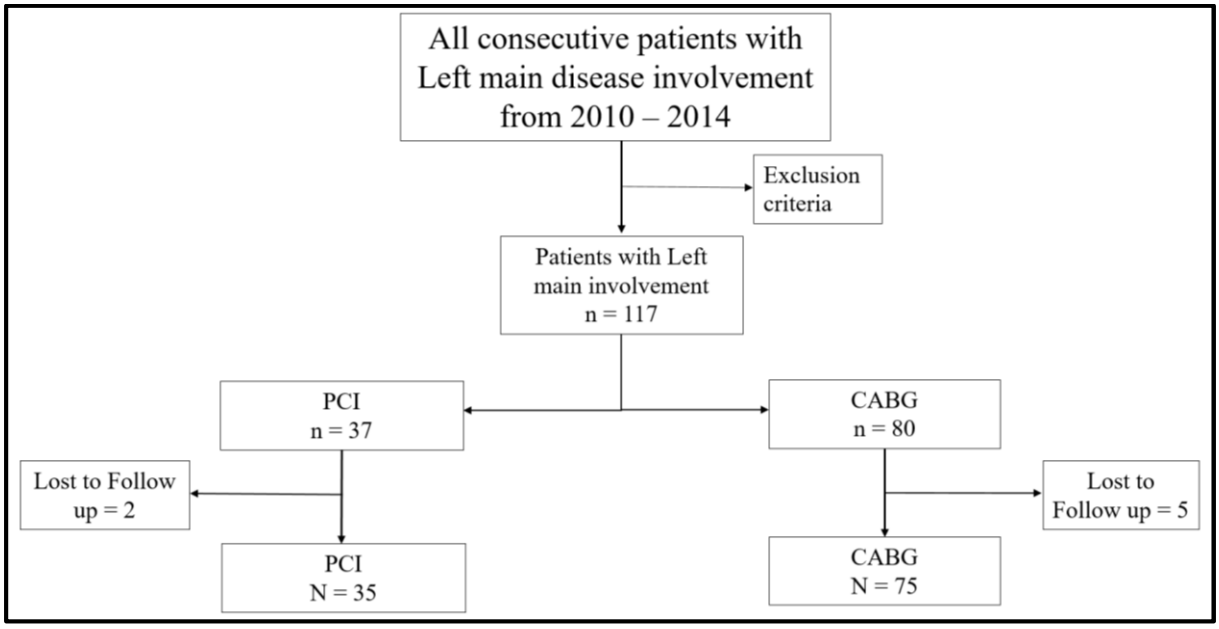


Figure 1. Flow chart of the study

Baseline characteristics

The baseline characteristics of the patients in both the groups are given in Table 3. The baseline characteristics are similar in both the groups with respect to the age, sex, smoking, hypertension, family history of CAD, dyslipidaemia, ejection fraction and NYHA Class. The average age of the patients was 58.29 in

the PCI group and 58.05 in the CABG group (p = 0.91). Patients with diabetes mellitus were more in the CABG group than in PCI group (63.75% vs 40.54%

Table 3 Baseline characteristics

	PCI (n=37)	**CABG (n=80)**	**p value**
Age - (yrs ± SD)	58.29 ± 13.69	58.05 ± 8.69	0.91
Male Sex - no (%)	27 (72.97)	67 (83.75)	0.17
DM - no (%)	15 (40.54)	51 (63.75)	0.019
HTN - no (%)	23 (62.16)	55 (68.75)	0.48
DLP - no (%)	21 (59.46)	51 (63.75)	0.66
Smoker - no (%) (Current / Past)	11 (29.73)	38 (47.50)	0.07
F/H/O CAD - no (%)	11 (29.73)	20 (25)	0.59
Crea >=1.5 - no (%)	3 (8.11)	4 (5)	0.51
NYHA			
I/II - no (%)	29 (78.37)	63 (78.75)	0.96
III/IV- no (%)	8 (21.62)	17 (21.25)	0.96
EF - % ± SD	54.62 ± 9.78	56.70% ± 11.42	0.35
<=40 - no (%)	4 (10.81)	13 (16.25)	0.44
41-50 - no (%)	6 (16.21)	8 (10)	0.34
>50 - no (%)	27 (72.97)	59 (73.75)	0.93

Table 3 Baseline characteristics Contd.,

	PCI (n=37)	**CABG (n=80)**	**p value**
Syntax – Median (Range)	23 (10 – 34)	30 (11 – 48)	
Syntax – Mean ± SD	22.12 ± 7.06	30.36 ± 6.59	<0.0001
<23 - no (%)	17 (45.96)	9 (11.25)	<0.0001
23 – 32 - no (%)	18 (48.65)	45 (56.25)	0.44
>32 - no (%)	2 (5.41)	26 (32.5)	0.0015
Previous MI - no (%)	15 (40.54)	32 (40)	0.956
Clinical Presentation			
ACS - no (%)	15 (40.54)	31 (38.75)	0.85
CSA - no (%)	22 (59.46)	49 (61.25)	0.85
STS % ± SD	2.83 ± 1.05	0.77 ± 0.01	<0.0001
STS – Median (Range)	0.8% (0.17 – 21)	0.55% (0.23 – 4.33)	
<4 - no (%)	31 (83.78)	79 (98.75)	0.0016
4-8 - no (%)	4 (10.81)	1 (1.25)	0.0179
>8 - no (%)	2 (5.41)	0 (0)	0.0367

with p value of 0.019 – statistically significant). Patients with history of smoking were numerically more in the CABG group than in PCI group but it was not statistically significant (47.5% vs 29.73% with p value of 0.07). Most of the patients in both the groups were in NYHA Class I/II with 78.37% in PCI group and 78.75% in CABG group. The mean left ventricular ejection fraction was 54.62% in PCI group and 56.7% in CABG group (p = 0.35). Patients presenting with previous myocardial infarction was 40.54% in PCI group and 40% in CABG group (p=0.96). Patients presenting with acute coronary syndrome was 40.54% in PCI group and 39% in CABG group (p=0.85).

Importantly SYNTAX score in the PCI group was lower than that in the CABG group which was statistically significant (Figure 2). Patients with low SYNTAX score (<23) were more in the PCI group than in the CABG group (45.96% vs 11.25%, p < 0.0001). Patients with high SYNTAX score (>32) were less in the PCI group than in the CABG group (5.41% vs 32.5%, p = 0.0015). The average SYNTAX score was 22 in the PCI group and 30 in the CABG group (p<0.0001). Society of thoracic Surgeons (STS) Adult cardiac surgery risk score (STS score) was higher in the PCI group when compared to CABG group. This was due to two patients in the PCI group who had very high scores.

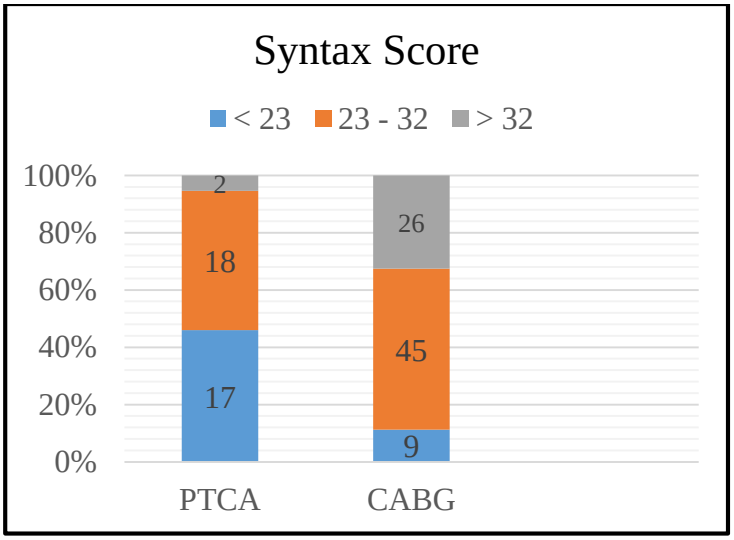


Figure 2. Bar Chart showing the distribution of SYNTAX score between the two groups.

The number of patients undergoing PCI has increased with successive years indicating the acceptance of PCI as a treatment modality for left main diseases and increasing expertise in the field of left main interventions in the study centre (Figure 3).

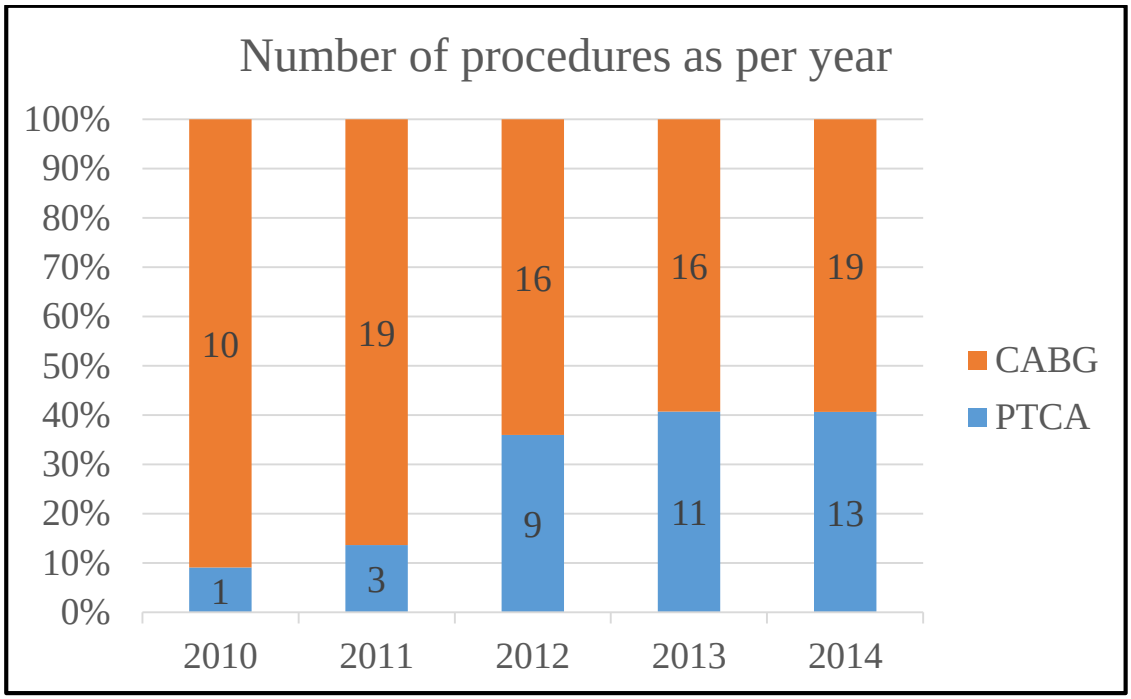


Figure 3. Bar chart showing PCI for left main disease with successive years.

The indications for patients undergoing PTCA for left main disease were as follows – emergency PTCA with unavailability of CABG slot was in 15 patients, patient's preference was in 9 patients and high risk CABG in the rest 13 patients (Table 4).

Table 4 – Indications for PTCA

Indication for PTCA	**No. (%)**
Emergency	15 (40.54%)
Patient's preference	9 (24.32%)
High risk CABG	13 (35.14%)

Angiographic Characteristics

The baseline characteristics have shown that SYNTAX score was less in the PCI group when compared to CABG group which was statistically significant. Analysis of the left main lesion with regards to the location as ostial, mid and distal lesion shows that CABG group had more distal lesion when compared to PCI group which was statistically significant (51.35% vs. 75% with p value = 0.01) (Table 5). Number of patients with involvement of left main ± single vessel disease was more in the PCI group when compared to the CABG group (29.73% vs. 10% with p value = 0.007). Number of patients with involvement of left main + triple vessel disease (3VD) was less in the PCI group when compared to the CABG group (35.13% vs. 57.5% with p value = 0.03). Involvement of the right coronary system was seen in 25 (65.57%) of patients in PCI group verses 67(83.75%) of the patients in the CABG group which was statistically significant (p = 0.03).

Table 5 – Angiographic Characteristics

	PCI (n = 37)	**CABG (n = 80)**	**p value**
Dominance			
Right – no (%)	34(91.89)	68(85)	0.3
Left – no (%)	1(2.7)	4(5)	0.57
Codominant – no (%)	2(5.4)	8(10)	0.41
LMCA			
Ostial – no (%)	10 (27.03)	14 (17.5)	0.24
Mid – no (%)	7 (18.91)	6 (7.5)	0.04
Distal – no (%)	19 (51.35)	60 (75)	0.01
LMCA ± 1VD – no (%)	11(29.73)	8(10)	0.007
LMCA + 2VD – no (%)	13(35.13)	26(32.5)	0.78
LMCA + 3VD – no (%)	13(35.13)	46(57.5)	0.03
RCA involvement – no (%)	25(65.57)	67(83.75)	0.03

Procedural Characteristics

Table 6 - Procedural Characteristics of PCI group

Procedural Characteristics - PCI (n = 37)	
No. of Stents per patient - Mean ± SD	2.22 ± 1.1
Stent length per patient (mm) - Mean ± SD	42.03 ± 24.31
Stent length of Lt system per patient (mm) - Mean ± SD	31.89 ± 16.99
RCA stent length per patient (mm) – Mean (Range)	10.14 (0 – 69)
Imaging guidance (IVUS) – no (%)	13 (35.13)
IABP support – no (%)	6 (16.21)
PCI locations	
Ostial – no (%)	10 (27.03)
Mid – no (%)	7 (18.92)
Distal – no (%)	19 (51.35)
Other Coronary PCI (RCA) – no (%)	11 (29.73)
Distal Bifurcation – no (%)	19 (51.35)
Provisional Stenting – no (%)	15 (78.94)
Bifurcation Stenting– no (%)	4 (21.05)
Coronary Angiogram on follow up – no (%)	8 (21.62%)
DAPT on 30 months follow up – no (%)	34 (94.44%)

Procedural characteristics of the PCI group is shown in the table 6. The average number of stents per patient was 2.22. PCI was done using imaging guidance of intravascular ultrasound in only 13 patients (35%). Distal LMCA bifurcation lesion was present in 19 patients. Of these 19 patients, 15 patients underwent provisional single stent strategy while 4 patients underwent dedicated bifurcation stenting. PCI to RCA was done in 11 patients (29.73%). Coronary angiogram was done in only eight patients (21.62%) on follow up. On follow up 34 patients (94.44%) were on dual antiplatelet therapy with a mean follow up period of 30 months.

Table 7 - Procedural Characteristics of CABG group

Procedural Characteristics - CABG (n = 80)	
No of grafts/ patient (mean ± SD)	3.975 ± 1.006
LIMA – no (%)	79 (98.75)
Associated Procedure – no (%)	4 (5)
Off pump – no (%)	7 (8.75)
Other Arterial grafts	Nil

As shown in table 7, the number of grafts per patient is four. LIMA was used in 79 patients (98.75%). The number of off pump CABG is very low with seven patients (8.75%) undergoing off pump surgery. Other than left internal mammary artery no other arterial graft was used as per the institutional policy.

Follow up:

Follow up data is completely available in 35 patients in the PCI group and 75 patients in the CABG group. The mean follow up duration was 30.7 months in the PCI group and 37.48 months in the CABG group (p=0.07). On follow up, eight patients (21.62%) in the PCI group had coronary angiogram while no patients in the CABG group had coronary angiogram. On follow up 34 patients (94.44%) were on dual antiplatelet therapy. At 30 months follow up there were a total of five events (13.51%) in the PCI group and five events (6.25%) in the CABG group (p=0.24).

30 days outcome:

Table 8

Endpoint	PCI (n=37)	CABG (n=80)	Odds Ratio	95% CI	p Value
MACCE – no (%)	1 (2.7%)	4 (5%)	0.54	0.06 – 5.01	0.59
MI – no (%)	0	0			
Death – no (%)	1 (2.7%)	2 (2.5%)	1.08	0.09 - 12.30	0.95
CVA – no (%)	0	2 (2.5%)	0.43	0.02 - 9.17	0.59
Composite of death, MI and CVA – no (%)	1 (2.7%)	4 (5%)	0.54	0.06 – 5.01	0.59
TVR – no (%)	0	0			
Hospital Stay – days (mean ± SD)	4.03 ± 2.51	6.83 ± 2.2			<0.0001

The MACCE rate at 30 days was four (5%) in the CABG group and one (2.7%) in the PCI group (OR = 0.54 with p value = 0.59). Out of the four events in the CABG group, 2 patients (2.5%) had died and 2 patients (2.5%) had CVA. In the PCI group there was one death (2.7%) in the immediate post procedural period.

There was no significant difference in the total MACCE rate between the two groups at 30 days. The composite endpoint of death, MI and CVA also showed no significant difference between the two groups (2.7% in PCI vs 5% in CABG with OR = 0.54 with 95% CI = 0.06 – 5.01 with p value = 0.59). The only statistical difference between the two groups was length of hospital stay which was 4.03 days in the PCI group and 6.83 days in the CABG group (p value < 0.0001).

12 months outcome:

Table 9

Endpoint	PCI (n=37)	CABG (n=80)	Odds Ratio	95% CI	p Value
MACCE – no (%)	3 (8.11)	5 (6.25)	1.29	0.29 - 5.72	0.73
MI – no (%)	1 (2.70)	0	6.44	0.26 - 161.83	0.26
Death – no (%)	2 (5.41)	3 (3.75)	1.44	0.23 - 8.99	0.69
CVA – no (%)	0	2 (2.5%)	0.43	0.02 - 9.17	0.59
Composite of death, MI and CVA – no (%)	2 (5.41)	5 (6.25)	0.87	0.16 - 4.67	0.87
TVR – no (%)	2 (5.41)	0	10.73	0.50 - 229.15	0.13

The MACCE rate at 12 months was five (6.25%) in the CABG group and three (8.11%) in the PCI group (OR = 1.29 with 95% CI of 0.29 - 5.72 with p value = 0.73). Out of the five events in the CABG group, 3 patients (3.75%) had died and 2 patients (2.5%) had CVA. In the PCI group there was two death (5.41%), one patient (2.7%) had MI and two patients (5.41%) had target vessel revascularisation.

There was no significant difference in the total MACCE rate between the two groups at 12 months. The composite endpoint of death, MI and CVA also showed no significant difference between the two groups (5.41% in PCI vs 6.25% in CABG with OR = 0.87 with 95% CI = 0.16 – 4.67 with p value = 0.87). There were two target vessel revascularisation in the PCI group and nil in the CABG group (OR = 10.73, 95% CI = 0.5 – 229.15, p value = 0.13).

30 months outcome:

Table 10

Endpoint	**PCI (n=37)**	**CABG (n=80)**	**OR**	**95% CI**	**p value**
MACCE – no (%)	5 (13.51)	5 (6.25)	2.16	0.59 - 7.93	0.24
MI – no (%)	1 (2.70)	0	6.44	0.26 - 161.8	0.26
Death – no (%)	3 (8.11)	3 (3.75)	2.16	0.42 - 11.22	0.36
CVA – no (%)	0	2 (2.5%)	0.43	0.02 - 9.17	0.59
Composite of death, MI and CVA- no (%)	3 (8.11)	5 (6.25)	1.29	0.29 - 5.71	0.73
TVR – no (%)	3 (8.11)	0	15.03	0.76 - 298.4	0.08
Mean Follow up – months (mean ± SD)	30.7±14.7	37.48 ± 19.68			0.07

The MACCE rate at 30 months was five (6.25%) in the CABG group and five (13.51%) in the PCI group (OR = 2.16 with 95% CI of 0.59 - 7.93 with p value = 0.24). Out of the five events in the CABG group, 3 patients (3.75%) had died and 2 patients (2.5%) had CVA. In the PCI group there were three deaths (8.11%), one

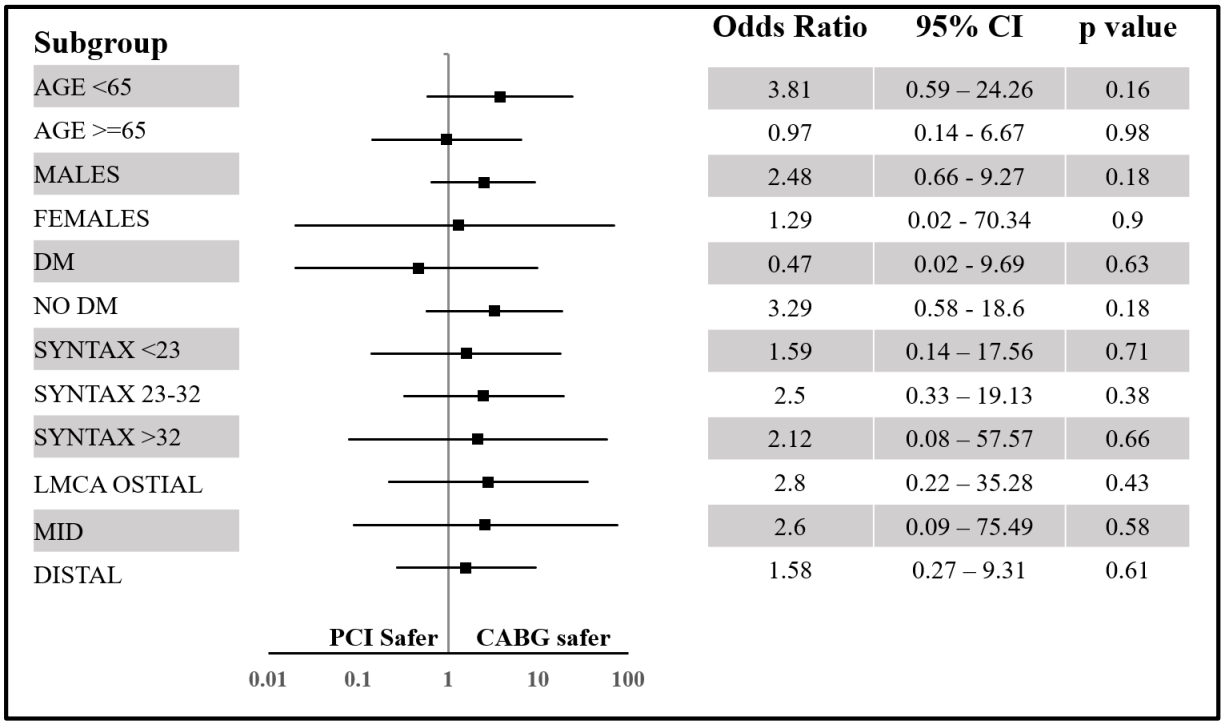
patient (2.7%) had MI and three patients (8.11%) had target vessel revascularisation. The composite endpoint of death, MI and CVA also showed no significant difference between the two groups (8.11% in PCI vs 6.25% in CABG with OR = 1.29 with 95% CI = 0.29 – 5.71 with p value = 0.73). There were three target vessel revascularisation in the PCI group and nil in the CABG group (OR = 15.03, 95% CI = 0.76 – 298.4, p value = 0.08). The mean follow up was 30.7 months in the PCI group and 37.48 months in the CABG group. Overall there was no significant difference in the total MACCE rate between the two groups at 30 months with an increased trend towards target vessel revascularisation in the PCI group when compared to CABG group.

Subgroup analysis for MACCE rates:

Multiple subgroup analysis was made for any interaction between the PCI and CABG group for the MACCE rates at 30 months follow up. As shown in figure 4, there was no significant interaction based on the subgroup for the MACCE rates between the two groups. As seen in the figure there is a trend towards better CABG in the subgroups of patients who are males, not having diabetes mellitus and ejection fraction > 50%. This trend may be due to small number of patients in both the groups and small number of total events.

Subgroup analysis for TVR:

Multiple subgroup analysis was also performed to rule any interaction between the PCI and CABG group for the target vessel revascularisation at 30 months follow up. As shown in Table 11, there was no significant interaction based on the subgroup for TVR between the two groups.



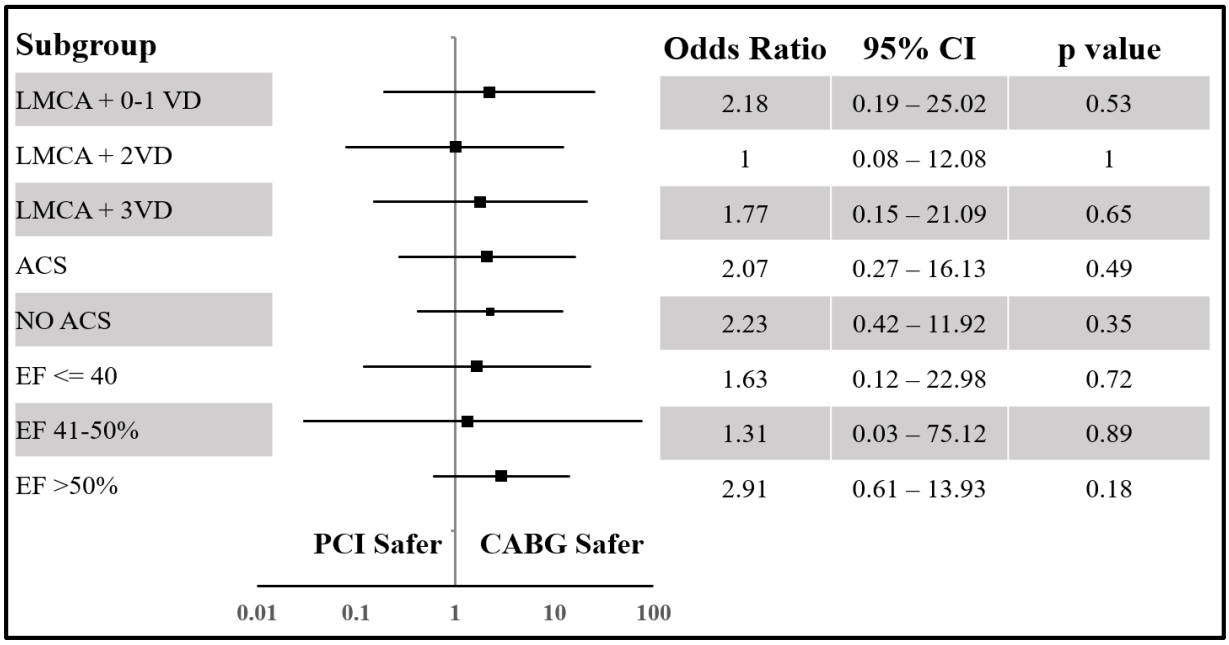


Figure 4. Forrest plot showing subgroup analysis for MACCE at 30 months.

Table 11 – Subgroup analysis for TVR

	PCI No/Total no (%)	CABG No/Total no (%)	OR	CI	p value
AGE < 65	2/24 (8.33)	0/61 (0)	12.55	0.59 – 271	0.11
AGE ≥ 65	1/13 (7.69)	0/19 (0)	4.33	0.16 - 114	0.38
MALES	3/27 (11.11)	0/67 (0)	17.18	0.86 – 343.8	0.06
FEMALES	0/10 (0)	0/13 (0)	1.29	0.02 - 70.34	0.9
DM	0/15 (0)	0/51 (0)	3.32	0.06 – 174.5	0.55
NO DM	3/22 (13.63)	0/29 (0)	9.18	0.45 – 186.8	0.15
SYNTAX <23	1/17 (5.88)	0/9 (0)	1.63	0.06 – 44.01	0.71
SYNTAX 23-32	2/18 (11.11)	0/45 (0)	12.29	0.56 – 268.6	0.11
SYNTAX >32	0/2 (0)	0/26 (0)	10.6	0.17 – 658.4	0.26
LMCA OSTIAL	1/10 (10)	0/14 (0)	4.14	0.15 – 112.1	0.39
MID	1/7 (14.28)	0/6 (0)	2.6	0.09 – 75.49	0.58
DISTAL	1/19 (5.26)	0/60 (0)	9.31	0.36 – 237.9	0.18
LMCA + 0-1 VD	1/11 (9.09)	0/8 (0)	2.22	0.08 – 61.41	0.64
LMCA + 2VD	1/13 (7.69)	0/26 (0)	5.89	0.22 – 154.5	0.29
LMCA + 3VD	1/13 (7.69)	0/46 (0)	10.33	0.2 – 268.5	0.16
ACS	0/15 (0)	0/31 (0)	2.03	0.04 – 107.3	0.73
NO ACS	3/22 (13.63)	0/49 (0)	15.4	0.76 – 310.8	0.07
EF ≤ 40	0/4 (0)	0/13 (0)	3.00	0.05 – 174.3	0.59
EF 41-50%	0/6 (0)	0/8 (0)	1.31	0.03 – 75.12	0.89
EF >50%	3/27 (11.11)	0/59 (0)	15.15	0.76 – 303.5	0.08

Predictors of MACCE:

The various parameters were analysed for the predication of MACCE at 30 months follow up in the entire LMCA cohort, the PCI group and the CABG group. However no parameter was significantly associated with the MACCE in the entire cohort, PCI group or CABG group (Table 12, 13, 14). It may be due to small number of patients in the entire cohort and fewer event rates in both the CABG and PCI group.

Event free Survival

When comparing the major adverse cardiovascular and cerebrovascular events at 30 months between the two groups there is no significant difference in the event rate. This is shown in the Kaplan Meier curve in the figure 5. As seen in the figure, most of the MACCE occurs within the first 30 days in the CABG group while most of the events in the PCI group occur after the first 30 days. In the CABG group after first 30 days there is minimal events implying that CABG may be favourable to PCI in the long term.

Table 12 – Entire Cohort

	OR	CI	p value
AGE < 65	0.38	0.10 – 1.39	0.14
MALES	5.22	0.29 – 92.37	0.25
DM	0.33	0.08 – 1.34	0.12
SYNTAX <23	2.33	0.61 – 8.89	0.21
SYNTAX 23-32	0.57	0.15 – 2.13	0.41
SYNTAX >32	0.79	0.16 – 3.96	0.78
LMCA OSTIAL	1.66	0.39 – 6.91	0.5
MID	0.91	0.11 – 7.81	0.91
DISTAL	0.7	0.19 – 2.64	0.64
LMCA + 0-1 VD	3.45	0.89 – 13.63	0.07
LMCA + 2VD	0.86	0.21 – 3.49	0.83
LMCA + 3VD	0.42	0.11 – 1.71	0.23
ACS	1.03	0.28 – 3.84	0.96
EF ≤ 40	2.52	0.59 – 10.71	0.15
EF 41-50%	0.34	0.02 – 6.12	0.46
EF >50%	0.84	0.21 – 3.46	0.81

Table 13 – PCI Group

	OR	95 % CI	p value
AGE < 65	0.21	0.03 to 1.34	0.09
MALES	4.2	0.21 to 82.78	0.34
DM	0.10	0.01 to 2.01	0.13
SYNTAX <23	1.76	0.26 to 11.83	0.56
SYNTAX 23-32	0.79	0.11 to 4.71	0.71
SYNTAX >32	1.29	0.05 to 30.62	0.87
LMCA OSTIAL	1.8	0.26 to 12.41	0.55
MID	1.07	0.10 to 11.13	0.95
DISTAL	0.63	0.09 – 4.23	0.64
LMCA + 0-1 VD	3.45	0.51 to 24.25	0.19
LMCA + 2VD	0.46	0.05 to 4.57	0.51
LMCA + 3VD	0.46	0.05 to 4.57	0.51
ACS	0.98	0.14 to 6.57	0.98
EF ≤ 40	2.06	0.18 to 23.3	0.56
EF 41-50%	0.44	0.02 to 8.98	0.59
EF >50%	1.48	0.15 to 14.90	0.74

Table 14 – CABG Group

	OR	95% CI	p value
AGE < 65	4.82	0.74 - 30.99	0.09
MALES	2.2	0.12 - 42.18	0.6
DM	0.85	0.14 - 5.41	0.86
SYNTAX <23	1.97	0.19 - 19.64	0.56
SYNTAX 23-32	0.52	0.08 - 3.27	0.49
SYNTAX >32	1.39	0.22 - 8.8	0.73
LMCA OSTIAL	1.14	0.12 - 11.02	0.91
MID	1.04	0.05 - 21.01	0.98
DISTAL	1.33	0.14 - 12.64	0.8
LMCA + 0-1 VD	2.25	0.22 - 22.66	0.49
LMCA + 2VD	1.38	0.22 - 8.80	0.73
LMCA + 3VD	0.49	0.08 - 3.11	0.45
ACS	1.05	0.17 - 6.66	0.96
EF ≤ 40	3.44	0.52 - 22.63	0.2
EF 41-50%	0.77	0.04 - 15.28	0.87
EF >50%	0.51	0.08 - 3.42	0.54

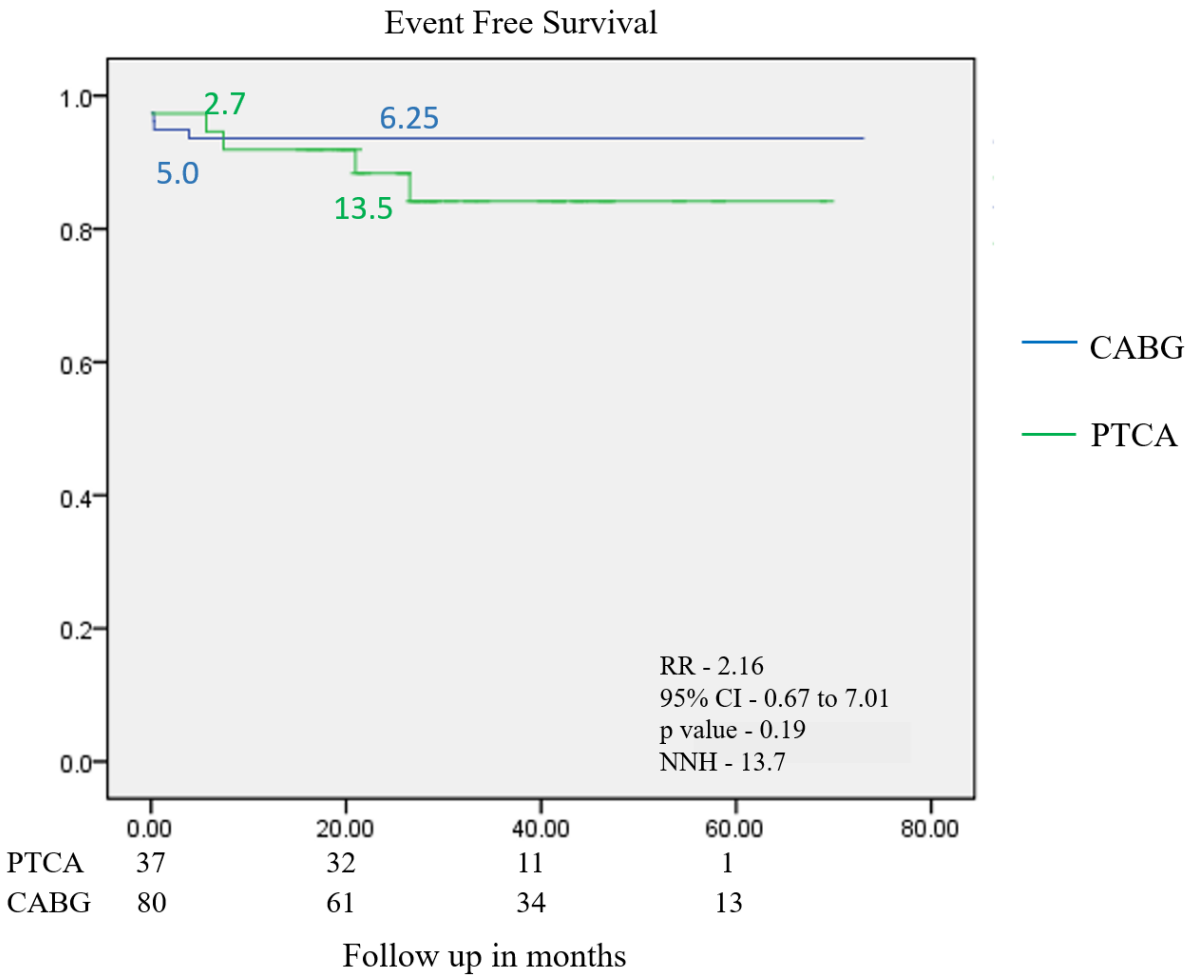


Figure 5. Kaplan Meier curve showing event free survival on long term follow up

Discussion

Discussion

This study compared the clinical outcomes of patients with left main disease who underwent percutaneous coronary intervention with CABG. The study shows that outcomes of patients undergoing PCI is similar to CABG with respect to the major adverse cardiac and cerebrovascular events (MACCE).

The baseline characteristics show that the patients undergoing CABG had higher incidence of diabetes mellitus when compared to PCI group (64% vs. 41%, p = 0.02). In our study, there were more smokers in the CABG group than in PCI group but it was not statistically significant (48% vs. 30%, p = 0.07). MAIN-COMPARE[31] registry data also showed higher incidence of diabetes mellitus in the CABG group when compared to PCI group (35% vs. 30%, p = 0.01). MAIN-COMPARE registry data also showed higher incidence of dyslipidaemia and current smokers in the CABG group when compared to PCI group. ASAN registry[45] also showed similar baseline characteristics with patients in the CABG group had more diabetes mellitus, hypertension and dyslipidaemia. This is one of the limitations of observational study as patients with more risk factors have undergone CABG as per the existing guidelines or consensus opinion at the time of intervention.

Angiographic data:

The SYNTAX score in the PCI group was less when compared to CABG group (22.12 vs. 30.36, p < 0.0001) in our study. This is similar to the finding in

SYNTAX registry where PCI patients had less SYNTAX score when compared to CABG group (32 vs. 36). This discrepancy again shows that more complex anatomic lesions have undergone CABG as per the existing guidelines. These variables could have tilted the outcomes in favour of PCI. The angiographic characteristics show that distal lesions were common in CABG group than in PCI group (75% vs. 51% p = 0.01) while ostial and shaft lesions were less in CABG group than in PCI group (25% vs. 46%, p = 0.02). This characteristic is similar to the findings in MAIN-COMPARE registry and ASAN registry. In MAIN-COMPARE registry, CABG group had more distal lesions than PCI group (54% vs. 49%, p = 0.04).

Our data showed LMCA ± single vessel disease was more common in PCI group when compared to CABG group (30% vs. 10%, p = 0.007) and LMCA + triple vessel disease was more common in CABG group when compared to PCI group (58% vs. 35%, p = 0.03). This was in accordance with the findings in MAIN-COMPARE registry and ASAN registry. In MAIN-COMPARE registry, left main involvement only was 25% in PCI group vs. 6% in CABG group and involvement of Left main + triple vessel disease was 25% in PCI group vs. 57% in CABG group (p < 0.0001). ASAN registry also showed similar angiographic characteristics. In our study, right coronary involvement was significantly higher in the CABG group when compared to PCI group (84% vs. 66%, p = 0.03). The MAIN-COMPARE registry showed RCA involvement of 36% in PCI group and 71% in CABG group with p < 0.0001. The ASAN registry showed similar data for RCA involvement.

However, the two major randomised trials – the SYNTAX trial[35] and the PRECOMBAT trial[36] did not show any baseline difference in the angiographic characteristics of the two groups. This shows the importance of conducting randomised control trials in this cohort of left main disease patients. As our study is an observational study the difference in these baseline clinical and angiographic characteristics is bound to happen due to physician preference and treatment according to the existing guidelines and data. The outcomes in our study could have been affected by the differences in these baseline and angiographic characteristics.

Procedural Characteristics:

Procedural characteristics in our study show that only thirteen patients (35%) in the PCI group underwent IVUS guided intervention. In comparison, PRECOMBAT trial had 91% of the PCI group had IVUS guidance and MAIN-COMPARE registry had 77.5% of the PCI group had IVUS guidance. Nineteen patients underwent distal bifurcation intervention, out of which 15 patients (78%) underwent single stent strategy while 4 patients underwent dedicated bifurcation strategy. The PRECOMBAT trial had single stent strategy in 46% of the patients and the MAIN-COMPARE registry had 60% of the patients with single stent strategy. Thus higher number of patients in our study underwent single stent strategy for left main bifurcation lesions. The follow up angiography in our series was present in only eight patients (21.62%) of the PCI group which is very low when compared to PRECOMBAT trial where 75% in PCI group underwent follow up angiography.

In the CABG group, the use of left internal thoracic artery or left internal mammary artery (LIMA) for grafting the left anterior descending artery was very high with 79 patients (98.75%) had the LIMA graft. In PRECOMBAT trial, 94% had LIMA grafted and in SYNTAX trial 95% had LIMA used. The use of off-pump surgery in our setting was low with only seven patients (8.75%) undergoing this procedure. This was very low when compared to PRECOMBAT trial (64%) and the SYNTAX trial (15%).

MACCE:

The MACCE events at 12 months in our study were similar between the two groups with 8.11% in the PCI group and 6.25% in the CABG group (Odds ratio – 1.29, 95% Confidence interval = 0.29 – 5.72, p = 0.73). The composite endpoint of death, MI and CVA did not differ between the two groups with 5.41% in the PCI group and 6.25% in the CABG group (OR – 0.87, 95% CI = 0.16 – 4.76, p = 0.87). The target vessel revascularisation (TVR) events were more in the PCI group when compared to CABG group but it was not statistically significant (5.41% vs. 0, OR – 10.73, 95% CI = 0.5 – 229.15, p = 0.13). The cerebrovascular events (CVA) were more in the CABG group when compared to PCI group but it was not statistically significant (2.25% vs. 0, OR – 0.43, 95% CI = 0.02 – 9.17, p = 0.59). The MACCE at 30 months were similar between the two groups which has been already shown.

The MACCE rate at 12 months was lower in our study when compared to the other trials. SYNTAX substudy had 15.8% in the PCI group and 13.7% in the

CABG group, p = 0.44. The PRECOMBAT trial had 8.7% in the PCI group and 6.7% in the CABG group which is very similar to our data. In both the SYNTAX trial and the PRECOMBAT trial, the rate of target vessel revascularisation (TVR) was significantly more in the PCI group than in CABG. TVR was 9% in PCI group and 4.2% in CABG group with OR = 2.18 (p = 0.02) in the PRECOMBAT trial. TVR were 6.7% in CABG vs. 12% in PCI with OR = 5.3 p = 0.02 in the SYNTAX substudy. The MAIN-COMPARE registry also showed similar MACCE events between the two groups with more TVR in the PCI group when compared to the CABG group which was statistically significant.

The rate of CVA was significantly higher in the CABG group than in PCI group in the SYNTAX substudy and ASAN registry. However, the PRECOMBAT trial and MAIN-COMPARE registry did not show increased risk of CVA with CABG group. The findings of our study were consistent with these trials with MACCE rate similar between the two groups, trend towards increased target vessel revascularisation (TVR) for the PCI group and increased CVA events with the CABG group which was not statistically significant.

The total event rate was lower in our study as compared to SYNTAX substudy and the MAIN-COMPARE registry. This may be due to small number of patients in the total cohort. This may be also due to lower SYNTAX score in the PCI group, more cases of bifurcation stenting having undergone single stent strategy, inclusion of patients who have undergone PCI with drug eluting stents only and better compliance to dual antiplatelet therapy. The lower rate of follow up angiography in the PCI group could have underdiagnosed in stent restenosis of left main disease and thereby reducing angiographically driven TVR. The total event rate in the CABG group was also lower which may be due to increased use

of left internal mammary artery for left main grafting and lower surgical risk population as reflected by the lower mean STS score (0.55%) in the CABG group.

As the total event rate was lower in our study and total number of patients in both the groups were small, subgroup analysis of the various parameters for MACCE or TVR which could have affected the outcomes between the PCI group and CABG group did not attain any statistical significance. Similarly, no parameter was significantly associated with the MACCE in the entire cohort, PCI group or CABG group. Our study was underpowered to find out the statistical significance for the various subgroup analysis and individual components of the MACCE rate.

Kaplan Meier curve of event free survival (Figure 5) shows that most of the events in CABG occur during the first 30 days with the curve becoming nearly flat after 12 months. On the other hand most of the events in PCI occur after the first 30 days. This is shown in the figure as divergence of the two curves at 30 months. Presently the MACCE at 30 months follow up is not statistically significant between the two groups. Once the long term follow up of these patients becomes available, the comparison of PTCA with CABG may achieve statistical significance.

Limitations of the study

Limitations of the study

Our study was a single centre, retrospective observational study. The study had the drawbacks of an observational study with strong likelihood of bias and confounding of variables.

The total number of patients in the entire cohort was small with only around 30 months of follow up and the total MACCE were also less.

The entire cohort had heterogeneous coronary artery disease with number of vessel involvement varying from only left main disease to left main + triple vessel disease.

The follow up coronary angiography was available in only eight patients (21.2%) of those who underwent left main disease PCI which could have underdiagnosed the rate of instent restenosis and thereby leading to lesser target vessel revascularisation.

The type of drug eluting stent varied widely from first generation to second generation and biocompatible polymer to biodegradable polymer.

Conclusion

Conclusion

For patients with unprotected LMCA disease, percutaneous coronary intervention with stenting is non-inferior to CABG with regards to total major adverse cardiac and cerebrovascular events.

Target vessel revascularization was numerically higher among patients who underwent PCI than among those who underwent CABG but it did not attain statistical significance.

However, longer follow up is required to determine whether PCI is non-inferior to CABG in revascularisation of these patients with left main disease.

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