Health Technology Assessment in India (HTAIn)

Economic Evaluation of Different Treatment Modalities for Management of Patients with Multivessel Coronary Artery Disease (MV-CAD)

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ABBREVIATIONS

CAD	Coronary Artery Disease
MV-CAD	Multiple Vessel Coronary Artery Disease
SV-CAD	Single Vessel Coronary Artery Disease
DVD	Double Vessel Disease
TVD	Triple Vessel Disease
PCI	Percutaneous Coronary Intervention
CABG	Coronary Artery Bypass Graft
OMT MT	Optimal Medical Therapy Medical Treatment
LMCA	Left Main Coronary Artery
MACEs	Major Adverse Cardiac Events
DES	Drug Eluting Stents
BMS	Bare Metal Stents
RCT	Randomized Controlled Trial
MASS(Trial)	Medicine Angioplasty, or Surgery Study
ISCHEMIA(Trial)	International Study of Comparative Health Effectiveness With Medical and Invasive Approaches
BEST (Trial)	Beta-Blocker Evaluation of Survival Trial
CARDia (Trial)	Coronary Artery Revascularization in Diabetes
FREEDOM (Trial)	Future Revascularization Evaluation in Patients with Diabetes Mellitus
SYNTAX (Trial)	SYNergy Between PCI With TAXUS and Cardiac Surgery
BARI (Trial)	Bypass Angioplasty Revascularization Investigation
COURAGE (Trial)	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
SIHD	Severe Ischemic Heart Disease
IR	Incomplete Revascularization
CR	Complete Revascularization
CTO	Chronic Total coronary Occlusion
SAQ	Seattle Angina Questionnaire
DFS	Disease Free Stage

MI	Myocardial Infarction
LY	Life Years
QALY	Quality Adjusted Life Years
CEA	Cost Effectiveness Analysis
ICER	Incremental Cost Effectiveness Ratio
GDP	Gross Domestic Product (per capita per person)
BPPI	Bureau of Pharma PSUs of India
INR	Indian National Rupee
NHB	Net Health Benefits
NMB	Net Monetary Benefits

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INTRODUCTION

Cardiovascular diseases (CVDs) are the number one cause of global deaths, taking an estimated 17.9 million lives every year. CVDs are a group of disorders of the heart and blood vessels and incorporate coronary heart disease, cerebrovascular disease, rheumatic coronary disease and different conditions. Four out of 5 CVD deaths are due to heart attacks and strokes, and 33% of these deaths occur rashly in individuals under 70 years of age (1).

Over the most recent three decades, the predominance of coronary artery diseases (CADs) has increased from 1.1% to about 7.5% in the urban population and from 2.1% to 3.7% in the rural population. Coronary artery diseases tends to occur at a younger age in Indians with half of cardiovascular (CV) mortality occurring in people aged less than 50 years (2). In addition, case fatality attributable to CVD in low-income countries, including India, appears to be much higher than in middle and high-income countries. The World Health Organization (WHO) has estimated that, with the present weight of CVD, India would lose $237 billion from the loss of productivity and spending on health care over a 10-year time frame (2005–2015) (3).

Multivessel coronary artery disease (MV-CAD) or Multivessel Disease (MVD) is characterised by the presence of ≥50 % diameter stenosis of at least 2 epicardial coronary arteries. The presence of MVD shows poorer prognosis and a significantly higher mortality than single-vessel disease (4). Multivessel coronary artery disease (MVD) is frequently observed in both stable and unstable patients; the prevalence of the condition ranges from 30% to 60%. The risk of death increments as progressively major epicardial coronary arteries become involved (5).

Treatment Modalities:

The goals of treatment are to reduce the risk of death, ischemic events, and to improve quality of life. Currently, all patients with established CAD undergo either guideline based conservative therapy/medical therapy or invasive therapy/revascularisation.

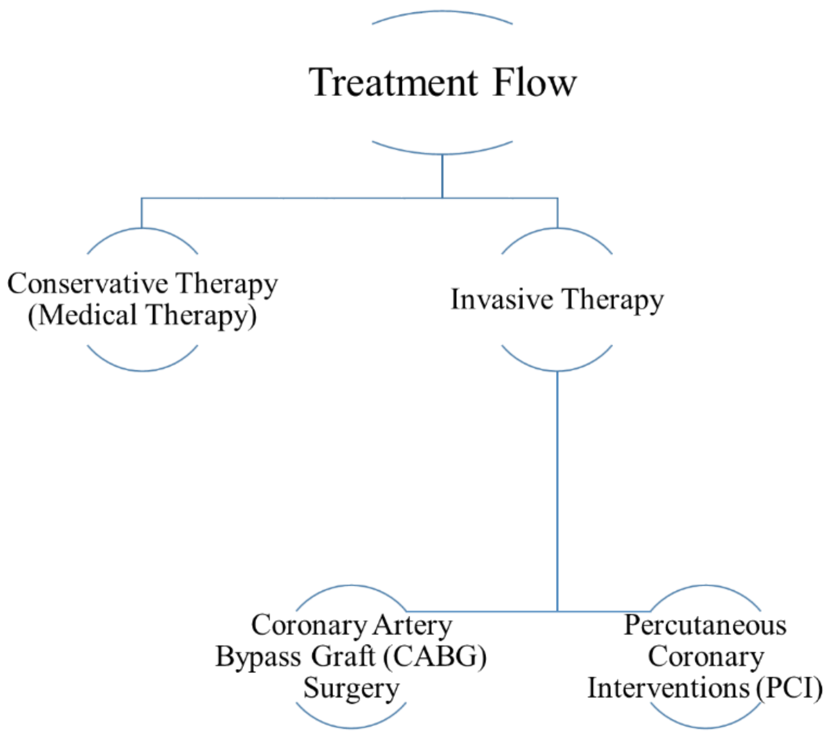

Figure 1: Treatment flow followed for patients with MV-CAD

Optimal medical therapy (OMT): All patients with CAD first require optimal medical therapy (OMT) to alleviate symptoms, avert disease progression, prevent cardio vascular events, and decrease mortality. Optimal medical therapy (OMT) for the patients with coronary artery disease used as a primary treatment modality aims to stabilize vulnerable plaque, prevents progression of atherosclerosis, and avert thrombosis. OMT included antiplatelet medication, β-blocker, Renin-angiotens in system blockade, nitrates, calcium-channel blocker, and aggressive lipid-lowering therapy, (6) all of which have been proven to reduce the risk of adverse cardiovascular events. Mechanisms of action of these agents are complex and include inhibition of interrelated processes of lipid deposition, endothelial dysfunction, inflammation, platelet aggregation, plaque destabilization, and thrombosis (6)(7).

Revascularization is indicated in patients who remain symptomatic despite OMT, for this the patient may either undergo percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery along with optimal medical therapy (OMT) or in some cases only OMT (7).

Percutaneous coronary intervention (PCI) is generally preferred in patients with single or low risk two vessel disease while coronary artery bypass graft surgery is recommended in patients with complex two vessel disease, three vessel disease or multivessel disease PCI was firstly introduced in to provide a safe, effective, less invasive alternative to coronary artery bypass graft surgery (CABG),(8) Over the years, technological advances in equipment and devices have improved safety as well as short and long term outcomes. This has greatly expanded the indications for the technique and allowed more arteries to be accessible to effective treatment with better patient outcomes. In addition, developments in adjuvant pharmacotherapy have further improved outcomes of percutaneous procedures. The results of many large trials have shown that percutaneous coronary intervention can be equally successful as CABG (9).

Coronary artery bypass graft surgery (CABG): During CABG, a healthy artery or vein from the body is connected, or grafted, to the blocked coronary artery. The grafted artery or vein bypasses (that is, goes around) the blocked portion of the coronary artery. This creates a new passage, and oxygen-rich blood is routed around the blockage to the heart muscle. This surgery may lower the risk of serious complications for people who have obstructive coronary artery disease, a type of ischemic heart disease. CABG may also be used in an emergency, such as a severe heart attack. The goal in the treatment of multi-vessel disease is to reduce angina and heart failure symptoms. In MVD, revascularisation can be accomplished by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (4). Coronary revascularization is associated with some perioperative or peri procedural complications and risks of major adverse cardiac events (MACEs). Therefore, the chosen revascularization strategy must be appropriate.

REVIEW OF LITERATURE

PCI is generally preferred in patients with single or low risk two vessel disease while coronary artery bypass graft surgery is recommended in patients with complex two vessel disease, three vessel disease and in some cases of isolated left main vessel disease (9)(10).

When introduced, the PCI was envisioned to be a procedure that would defer the need for CABG until severe multivessel coronary disease was present. Over the years, technological advances in equipment and devices have improved safety as well as short and long term outcomes. This has significantly extended the indications for the technique and allowed more arteries to be accessible to effective treatment with better patient outcomes. Furthermore, advancements in adjuvant pharmacotherapy have additionally improved the results of percutaneous procedures. The results of many large trials have shown that percutaneous intervention can be equally successful when compared to the generally utilized CABG for patients with multivessel coronary artery disease (10).

Over the years many trials have been conducted to compare the effectiveness of both the therapies and the effectiveness in the treatment of MVD (11).Since the advent of drug-eluting stents (DES) and the evidence attesting to their superiority over bare metal stents (BMS)(12), several trials investigating PCI outcomes in comparison to CABG have been conducted. The BEST trial investigators undertook an RCT to demonstrate non-inferiority of eluting stents in respect to CABG. The trial had a sample population of 800 patients and demonstrated an occurrence of a composite of death due to myocardial infarction (MI) or target-vessel revascularization at 2 years, of 11.0% in the patients in the PCI group and of 7.9% in those in the CABG group with a still significant difference at longer follow-up [median, 4.6 years (15.3% of the patients in the PCI group and in 10.6% of those in the CABG group) (13).

Another trial (SYNTAX) tested non-inferiority of PCI versus CABG in 1,800 patients. Non-inferiority criteria were not met as rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (17.8%, *vs.* 12.4% for CABG). This was thought to be due to an increased rate of repeat revascularization (13.5% *vs.* 5.9%) in the PCI group (14)(15). One trial focussed on a subgroup of diabetic patients – CARDia trial – demonstrating the superiority of CABG with combined rates of mortality, MI, stroke and repeated revascularization of 11.3% in the CABG group and 19.3% in the PCI group at 1 year (16). These findings were confirmed by FREEDOM trial in a sample of 1,900 patients with complex MVD and diabetes, demonstrating comparatively worse 5-year rates of a composite outcome, including death from any cause, nonfatal MI, or nonfatal stroke, in the PCI group (26.6% *vs.* 18.7% in the CABG group). Despite the incidence of stroke being higher in CABG cohort, death and MI were significantly higher in the PCI group, leading to the conclusion that diabetic population would best benefit from CABG rather than PCI (17).

In a pooled analysis of individual patient-level data of the SYNTAX and BEST randomized trials, Cavalcante *et al.* analyzed the outcomes of 1,166 patients in which 577 were randomized to PCI and 589 to CABG. In patients with MVD with proximal left anterior descending artery (LAD) involvement, CABG is associated with a significantly lower rate of cardiac death, MI and all-cause revascularization when compared with DES-PCI. There was no difference among the groups as far as all-cause mortality and stroke were concerned, but the combined outcome of major adverse cardiovascular and cerebrovascular events (i.e., all-cause death, MI, stroke, revascularization) favoured CABG. The authors concluded that in patients with MVD CABG was superior in terms of survival and cardiovascular events to drug-eluting stents at 5 years of follow-up (18).

Need for the study:

Overall, all the studies have been conducted in western countries and have focused on eliciting the difference in clinical outcomes for patients with left main coronary artery disease with or without triple vessel disease. The existing data specifically looking at MV-CAD is quite low and what studies do exist are dated with no conclusive response to which strategy be used in treatment of double and triple vessel diseases (DVD and TVD respectively). In addition, very little literature exists pertaining to cost-effectiveness of the therapies. This is compounded by the scarcity of studies from the South-East Asian and specifically Indian subcontinent region for clinical outcomes of OMT alone versus PCI with OMT and CABG with OMT in MV-CAD treatment. Hence, the present study is being undertaken to bridge a few of these existing gaps and lay the foundation for future economic evaluations and health technology assessments.

Research Question

- What is the most cost effective treatment modality available for the management of patients with multivessel coronary artery disease (MV-CAD)?

Aim

- To conduct a full economic evaluation to see which treatment modality - Invasive Procedures or Conservative Therapy (OMT) is the better alternative for managing patients with MV-CAD
- To conduct a full economic evaluation to see which treatment modality in invasive procedures - percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) surgery is the better alternative for managing patients with MV-CAD

Primary Objectives

- To estimate the Incremental Cost-Effectiveness Ratio (ICER) for the management of MV-CAD patients with either Invasive or Conservative Therapy
- To estimate the ICER for the management of MV-CAD patients requiring Invasive therapy with either CABG or PCI
- To estimate the Net Benefits (health as well as monetary) for the use of Invasive therapy over Conservative therapy and CABG over PCI respectively

Secondary Objective

- To estimate the ICER, Net Health Benefit & Net Monetary Benefit for the management of a diabetic MV-CAD patient with either invasive or conservative therapy
- To estimate the ICER, Net Health Benefit & Net Monetary Benefit for the management of a diabetic MV-CAD patient requiring Invasive therapy with either CABG or PCI

METHODOLOGY

PICO for the Base Case Analysis

Stage 1 – Invasive vs Conservative Therapy

- **Study Population:** Adult Patients suffering from MV-CAD
- **Interventions:** Invasive Therapy (pooled for either PCI or CABG)
- **Comparators:** Conservative Therapy (OMT alone)
- **Outcome:** Quality Adjusted Life Years (QALYs)
- **Time Horizon**: Life time horizon

Stage 2 – CABG vs PCI

- **Study Population:** Adult Patients suffering from MV-CAD requiring invasive therapy
- **Interventions:** CABG (with associated OMT)
- **Comparators:** PCI (with associated OMT)
- **Outcome:** Quality Adjusted Life Years (QALYs)
- **Time Horizon**: Life time horizon

PICO for the Sub-group Analysis – Diabetic Patients

Stage 1 – Invasive vs Conservative Therapy

- **Study Population:** Diabetic Adult Patients suffering from MV-CAD
- **Interventions:** Invasive Therapy (pooled for either PCI or CABG)
- **Comparators:** Conservative Therapy (OMT alone)
- **Outcome:** Quality Adjusted Life Years (QALYs)
- **Time Horizon**: Life time horizon

Stage 2 – CABG vs PCI

- **Study Population:** Diabetic Adult Patients suffering from MV-CAD requiring invasive therapy
- **Interventions:** CABG (with associated OMT)
- **Comparators:** PCI (with associated OMT)
- **Outcome:** Quality Adjusted Life Years (QALYs)
- **Time Horizon**: Life time horizon

Literature Review:

Search strategy: Targeted Literature review with systematic searches has been done for the relevant articles in different Electronic databases. We adhered to general guidelines for conducting a targeted review as suggested in the Cochrane RevMan Handbook for systematic reviews.(19) We only included all the meta analysis, systematic reviews, and randomized control trial designs for the review.

Databases and sources: Comprehensive searches were done to find out the relevant published articles at different electronic databases**.** We searched on PUBMED, EMBASE, SCOPUS and Cochrane Central Register of Controlled Trials (CENTRAL) searches for systematic reviews, Meta-analysis, randomized clinical trials (RCTs), observational studies and economic evaluations. Two systematic searches were carried out separately for clinical effectiveness data and economic evaluations on the aforementioned electronic databases.

Search Terms: Keeping in view the research questions, specific keywords were selected and strategies were made using conjunctions and linking words like 'AND', 'OR', 'NOT'. Articles were searched by using various combinations of keywords: 'coronary artery disease', 'percutaneous coronary intervention', 'optimal medical therapy', 'coronary artery bypass graft', 'coronary artery bypass surgery', 'revascularization', 'angioplasty', 'multi-vessel diseases', 'multivessel coronary artery disease', 'diabetes', 'quality of life', 'cost-effectiveness'. A range of search filters like article type, date range searched; availability of full text articles. The electronic databases were last searched on 10th July 2020 and search was restricted only to published English language articles.

Study inclusion criteria: Articles were selected on the basis of following criteria -

1. Population: Adult General Population, Diabetic population with associated MV-CAD with normal LV systolic function.
2. Interventions: Articles reporting about the PCI with or without OMT were selected.
3. Comparator: Articles reporting about the OMT only were selected.
4. Outcomes: Studies reported about the clinical outcomes of PCI with or without OMT were selected.

5. Study designs: Meta-analysis, Systematic Reviews, Randomized control trial (RCTs), Economic Evaluations, Patient-level pooled analysis estimates and Observational studies.

Study Exclusion Criteria: Studies were excluded which were found irrelevant in relation to research question and studies with following criteria were excluded -

1. Literature review, narrative review, reports, case reports and case studies were excluded.
2. Heart diseases apart from MV-CAD were not considered.
3. Neonatal and Infant population.
4. Patients with disease other than diabetes and hypertension in association with SV-CAD were not included.
5. Literature published in Non-English language.

Data Extraction:

Data extraction was done in to a data extraction sheet created in Microsoft Office Excel and all data were extracted the under different headings: title, author, year of publication, aim and objective, study design, study population, Patients/study inclusion criteria, models/statistical test, study outcomes, Rates, results etc. Data were extracted by two reviewers and finalized by third reviewer.

All data were extracted as per objectives of the study in different data extraction sheets under the same headings.

Using the search builder in electronic sources and by manual searching in cross references and citation indices, we retrieved the following papers eligible for the review.

Table 1: Major findings of studies finalized for data extraction for Invasive vs Conservative therapies

Author - Year of Study	Study type	Disease studied	Treatment Strategies studied	Results

Anthony *et al* 2013 (20)	BARI 2D TRIAL (RCT)	Patients with type 2 diabetes with mild or stable cardiac symptoms	Early revascularization compared with medical therapy	The occurrence of the primary outcome, 5-year mortality, was 11.7% in the revascularization group versus 12.2% in the medical therapy group ($p = 0.97$) and 11.8% in the insulin-sensitizing group versus 12.1% in the insulin-providing group ($p = 0.89$).
D.J. Maron *et al*2020 (21)	ISCHEMIA TRIAL: Main Outcomes (RCT & Network Meta-analysis)	Stable Coronary Disease	Initial Invasive or Conservative Strategy	Among patients with stable coronary disease and moderate or severe ischemia, no evidence was found that an initial invasive strategy, as compared with an initial conservative strategy, reduced the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years. The trial findings were sensitive to the definition of myocardial infarction that was used.
John A. Spertus *et al*2015 (22)	ISCHEMIA TRIAL : Health-Status Outcomes (RCT & Network Meta-analysis)	Coronary Artery Disease	Invasive vs Conservative Strategy	Patients randomly assigned to the invasive strategy had greater improvement in angina-related health status than those assigned to the conservative strategy.
Harmony R. Reynolds *et al*2018 (23)	Secondary Analysis of the ISCHEMIA trial	Coronary Disease	Invasive vs Conservative Strategy	Women were more likely to have no obstructive CAD (<50% stenosis in all vessels on CCTA) (353 of 1022

				[34.4%] vs 378 of 3353 [.3%]) men. Women in the ISCHEMIA trial had more frequent angina, independent of less extensive CAD, and less severe ischemia than men.
David J. Maron *et al* 2018 (24)	(ISCHEMIA) Trial: Rationale and Design	SIHD with moderate or severe ischemia	Cardiac catheterization and Revascularization VS OMT	ISCHEMIA will provide new scientific evidence regarding whether an invasive management strategy improves clinical outcomes when added to optimal medical therapy in patients with SIHD and moderate or severe ischemia.
Judith S. Hochman *et al*2019 (25)	Report on ISCHEMIA Trial (RCT)	SIHD with moderate or severe ischemia	Cardiac catheterization and Revascularization VS OMT	Among the 3912 of 5179 randomized participants who underwent coronary computed tomography angiography, 79.0%had multivessel CAD (n = 2679 of 3390) and 86.8%had left anterior descending (LAD) stenosis (n = 3190 of 3677) (proximal in 46.8% [n = 1749 of 3739]).
Garcia S *et al*2013 (26)	Meta-Analysis	Multivessel CAD	Complete Revascularisation vs IR	CR is achieved more commonly with CABG than PCI. Among patients with Multivessel CAD, CR may be the optimal revascularization strategy.

Whady Hueb *et al*2007 (27)	RCT: Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS II)	Multivessel CAD	MT ALONE vs PCI or CABG combined with MT	All 3 treatment regimens yielded comparable, relatively low rates of death. MT was associated with an incidence of long-term events and rate of additional revascularization similar to those for PCI. CABG was superior to MT in terms of the primary end points, reaching a significant 44% reduction in primary end points at the 5-year follow-up of patients with stable multivessel coronary artery disease.
J. Iqbal *et al*2015 (28)	Systematic Review : Insights From the SYNTAX Trial at 5-Year Follow-Up	Complex Coronary Artery Disease	MT ALONE vs PCI or CABG combined with MT	The treatment effect with OMT (36% relative reduction in mortality over 5-year) was greater than the treatment effect of revascularization strategy (26% elative reduction in mortality with CABG versus PCI over 5-year). On stratified analysis, all the components of OMT were important for reducing adverse outcomes irrespective of revascularization strategy.
EG Lima *et al*2013 (29)	(MASS II) RCT	Stable multi-vessel CAD in patients with diabetes	3 therapeutic strategies, medical treatment without revascularization (MT), surgery (CABG), and angioplasty (PCI)	Among patients with stable multivessel CAD and preserved left ventricular ejection fraction, the 3 therapeutic regimens had high rates of overall and cardiac-related

			in patients with multi-vessel and stable coronary artery Disease.	deaths among diabetic compared with nondiabetic patients. Moreover, better outcomes were observed in diabetic patients undergoing CABG compared to MT in relation to overall and cardiac mortality in a 10-year follow-up.
Mancini *et al*2016 (30)	Patient level pooled analysis	Patients With Type 2 Diabetes and Coronary Disease	OMT with or without PCI or CABG	During a median 4.5-year follow-up, CABG + OMT was superior to PCI + OMT for the primary endpoint (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.59 to 0.85; p = 0.0002), death (HR: 0.76; 95% CI: 0.60 to 0.96; p= 0.024), and MI (HR: 0.50; 95% CI: 0.38 to 0.67; p = 0.0001), but not stroke (HR: 1.54; 95% CI: 0.96 to 2.48; p=0.074). CABG+OMT was also superior to OMT alone for prevention of the primary endpoint (HR: 0.79; 95% CI: 0.64 to 0.97; p= 0.022) and MI (HR: 0.55; 95% CI: 0.41 to 0.74; p = 0.0001), and was superior to PCI+OMT for the primary endpoint in patients with 3-vessel CAD (HR: 0.72; 95% CI: 0.58 to 0.89; p = 0.002) and normal LVEF (HR: 0.71;95% CI: 0.58 to 0.87; p = 0.0012). There were no

				significant differences in OMT versus PCI + OMT.
Whady Hueb *et al*2004 (31)	MASS II trial (RCT)	Multivessel CAD	CABG vs PCI vs MT alone	The one-year survival rates were 96.0% for CABG, 95.6% for PCI, and 98.5% for MT. The rates for one-year survival free of Q-wave MI were 98% for CABG, 92% for PCI, and 97% for MT. In addition, CABG was superior to MT for eliminating anginal symptoms.
S. Verma *et al*2013 (32)	Meta-analysis of RCTs	Patients With Diabetes and Coronary Disease	CABG vs PCI	The eight trials included 7468 participants, of whom 3612 had diabetes. At mean or median 5-year (or longest) follow-up, individuals with diabetes allocated to CABG had lower all-cause mortality than did those allocated to PCI (RR 0·67, 95% CI 0·52–0·86; p=0·002; I^2=25%; 3131 patients, eight trials). Treatment effects in individuals without diabetes showed no mortality benefit (1·03, 0·77–1·37; p=0·78; I^2=46%; 3790 patients, five trials; p interaction=0.03).

Table 2: Major findings of studies finalized for data extraction for CABG vs PCI

Author - Year of Study	Study type	Disease studied	Treatment Strategies studied	Results
Whady Hueb et al2007 (27)	RCT: Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS II)	Multivessel CAD	MT Alone vs PCI or CABG combined with MT	All 3 treatment regimens yielded comparable, relatively low rates of death. MT was associated with an incidence of long-term events and rate of additional revascularization similar to those for PCI. CABG was superior to MT in terms of the primary end points, reaching a significant 44% reduction in primary end points at the 5-year follow-up of patients with stable multivessel coronary artery disease.
Elizabeth A. Magnuson *et al* 2013 (33)	Cost Effectiveness Analysis: Results from FREEDOM trial	MVD patients with diabetes	PCI vs CABG	Despite higher initial costs, CABG is a highly cost-effective revascularization strategy compared with DES-PCI for patients with diabetes and multivessel CAD.
Z Fanari *et al* 2015 (34)	Meta Analysis	MVD	PCI with stents vs CABG	In patients with multi-vessel CAD, PCI with DES is associated with no significant difference in death or MI at 1 or 2 years. However at 5 years, PCI is associated with higher incidence of death and MI.

Patrick W. Serruys *et al* 2009 (14)	SYNTAX trial (RCT)	Severe CAD	PCI vs CABG	Rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group. At 12 months, the rates of death and myocardial infarction were similar between the two groups; stroke was significantly more likely to occur with CABG
J. Iqbal *et a* l2015 (28)	Systematic Review : Insights From the SYNTAX Trial at 5-Year Follow-Up	Complex Coronary Artery Disease	MT Alone vs PCI or CABG combined with MT	The treatment effect with OMT (36% relative reduction in mortality over 5-year) was greater than the treatment effect of revascularization strategy (26% elative reduction in mortality with CABG versus PCI over 5-year). On stratified analysis, all the components of OMT were important for reducing adverse outcomes irrespective of revascularization strategy.
EG Lima et al2013 (29)	(MASS II) RCT	stable multi-vessel CAD in patients with diabetes	3 therapeutic strategies, medical treatment without revascularization (MT), surgery (CABG), and angioplasty (PCI) in patients with multi-vessel and stable coronary artery Disease.	Among patients with stable multivessel CAD and preserved left ventricular ejection fraction, the 3 therapeutic regimens had high rates of overall and cardiac-related deaths among diabetic compared with nondiabetic patients. Moreover, better outcomes were observed in diabetic patients undergoing CABG compared to MT in

				relation to overall and cardiac mortality in a 10-year follow-up.
Mancini et al2016 (30)	Patient level pooled analysis	Patients With Type 2 Diabetes and Coronary Disease	OMT with or without PCI or CABG	During a median 4.5-year follow-up, CABG + OMT was superior to PCI + OMT for the primary endpoint (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.59 to 0.85; p = 0.0002), death (HR: 0.76; 95% CI: 0.60 to 0.96; p= 0.024), and MI (HR: 0.50; 95% CI: 0.38 to 0.67; p = 0.0001), but not stroke (HR: 1.54; 95% CI: 0.96 to 2.48; p=0.074). CABG+OMT was also superior to OMT alone for prevention of the primary endpoint (HR: 0.79; 95% CI: 0.64 to 0.97; p= 0.022) and MI (HR: 0.55; 95% CI: 0.41 to 0.74; p = 0.0001), and was superior to PCI þ OMT for the primary endpoint in patients with 3-vessel CAD (HR: 0.72; 95% CI: 0.58 to 0.89; p = 0.002) and normal LVEF (HR: 0.71;95% CI: 0.58 to 0.87; p = 0.0012). There were no significant differences in OMT versus PCI + OMT.

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The large and globally conducted ISCHEMIA trial was also considered eligible for data extraction because they had also taken Indian patients into consideration. The goal of the trial was to evaluate routine invasive therapy compared with optimal medical therapy among patients with stable ischemic heart disease and moderate to severe myocardial ischemia on non-invasive stress testing (24). COURAGE and BARI 2D, the two largest prior trials comparing coronary revascularization vs. medical therapy in SIHD patients, found that among patients selected on the basis of coronary anatomy after cardiac catheterization, an initial management strategy of coronary revascularization (PCI, PCI or CABG, respectively) did not significantly reduce the primary endpoints of death or MI (COURAGE), or death (BARI 2D) compared with OMT alone (10)(20). The ISCHEMIA Trial was designed to compare outcomes with an initial invasive vs a conservative treatment strategy for managing SIHD patients with moderate or severe ischemia on stress testing. ISCHEMIA is an NHLBI-supported trial where all 5179 randomized participants received secondary prevention that includes lifestyle advice and pharmacologic interventions referred to as optimal medical therapy (OMT). Another reason for considering this trial was the inclusion of all types of CADs. Additionally, they had also performed a network meta-analysis to collate results from all prior trials (till date) related to CADs and different treatment regimens(35).

For our study purpose, where we have considered OMT, PCI and CABG for comparison, the datasets from ISCHEMIA study primarily rely on MASS-II findings for comparing OMT, PCI and CABG specifically for MV-CAD. Hence, data's have been extracted from both ISCHEMIA and the MASS-II trial. The other trials had focused on PCI and CABG, while OMT was not a major comparative concern. Some studies like Iqbal *et al* have compared PCI & CABG with or without OMT but not much data was available to help with our current study. Hence the long term follow up data of MASS-II trial and key parameter variances from the ISCHEMIA study have been incorporated in the study for analysis.

MODEL OVERVIEW:

The study involved a comparison of costs and consequences for the treatment of MV-CAD patients in 2 stages:

- Stage 1 – All patients with Conservative Therapy (OMT) or Invasive Therapy (PCI or CABG)
- Stage 2 – Invasive therapy patients with either PCI or CABG

The stages are purely for model purposes based on the treatment flow followed while treating patients. The analysis was over a lifetime horizon. A basic conceptual framework was generated as a foundation for a hybrid Markov model with essentially two health states –Alive and Death (refer to figure4). As we were looking at the long term follow up phase; the overall cycle length was 1 year (Alive to Death phase). The transition probabilities for all states were generated using the aforementioned extensive review of literature. Apart from the heath states, certain health events were considered as most of the disease transitions take place for a limited time reverting to either the Alive or Death state. Also, seeing that the disease consequences are more morbidity driven, the major health events of follow up phases were modelled. The primary events modelled were peri-procedural stroke and apart from these the patient either transitions to the Alive or Death states. In follow up phase the patients follow the respective treatment regimens (modelled to a lifetime horizon). Again, in this phase we modelled the respective health events of MI and stroke. The patients have these events and revert back to the alive state and then move on to the absorbing state of Death.

The periprocedural phase – immediately after the invasive procedure (PCI and CABG) has been modelled and adjusted for in the first year of treatment at the start as a zero cycle for patients in the invasive therapy arms. Apart from the stroke and MI modelled separately this phase also included major bleeding, infections, atrial arrhythmia and vascular site complications. Coming to the treatment protocol followed while modelling, the patients were administered the therapy in different arms. All the alive patients from here moved to the alive stage from where the patient either moves to the death stage directly or had an event – MI or stroke. Another event here is that of revascularization where the patients undergo an index invasive procedure (PCI/CABG) or a repeat in case of PCI and CABG arm of treatment (repeat PCI/CABG). The patient usually move into this transition event in case the original therapy administered to them is not showing favorable results (based on ejection fraction and any remaining stenosis). From here, the patients again entered the whole cycle to the follow up phase and all the associated health stages and events.

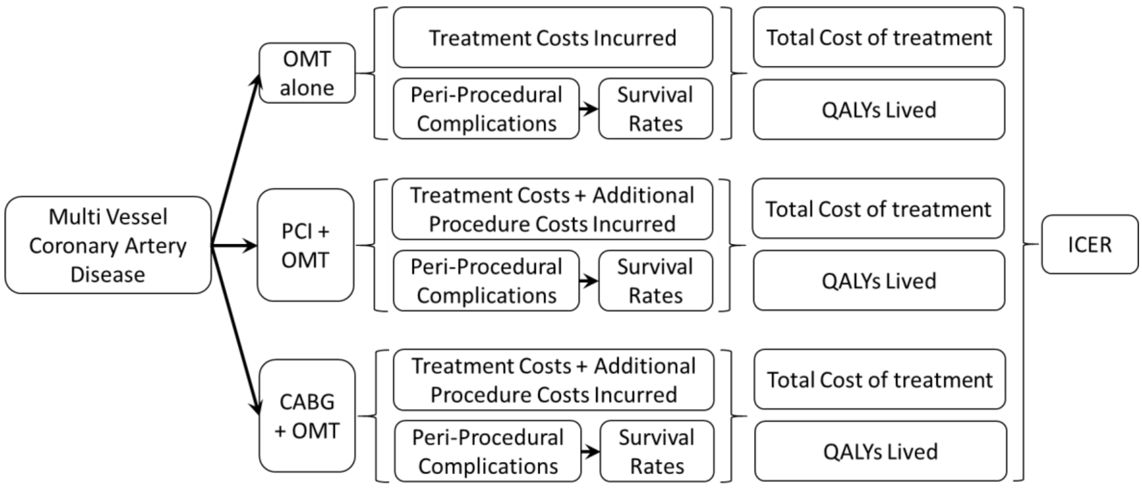

Figure 2: Conceptual framework of the treatment modalities of Multi-vessel coronary artery diseases

This analysis has been run based on the earlier mentioned treatment flow. The flowchart of the comparative groups formed are as illustrated below.

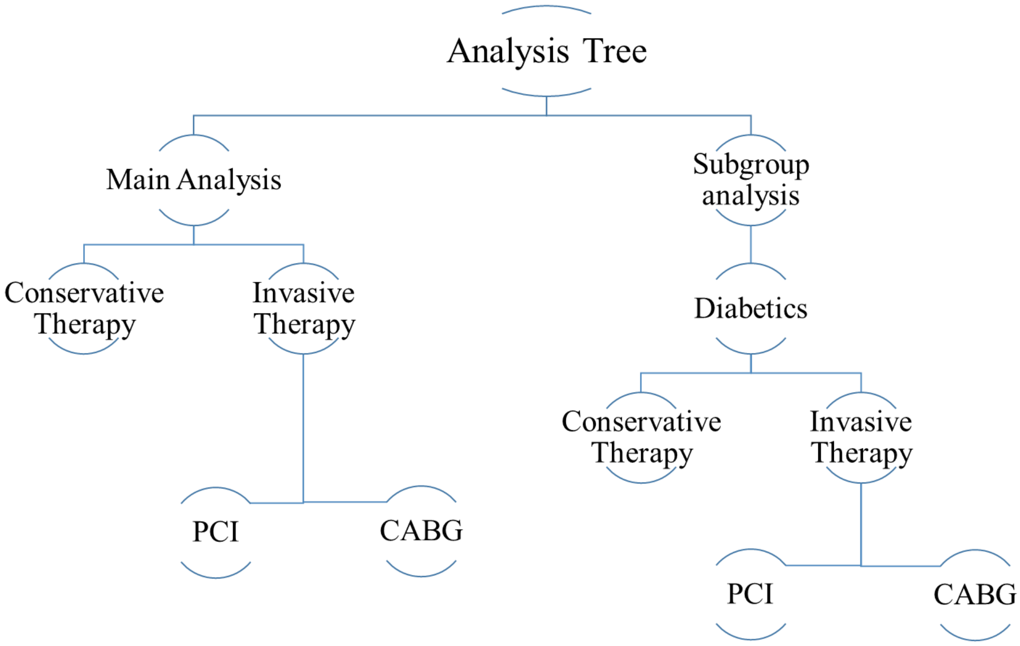

Figure 3: Analysis tree of the various treatment groups compared

The analysis was conducted using an abridged societal perspective, i.e., it included both the health system costs as well as the out-of-pocket expenditures borne by the patients for treatment. The productivity losses were not accounted for due to lack of data about it. The model used transition probabilities (generated on the basis of review of literature) and outcomes were generated in terms of Quality Adjusted Life Years (QALYs) gained for health benefits and the incremental costs of PCI + OMT over CABG + OMT and OMT alone. Subsequent to this, an Incremental Cost Effectiveness Ratios (ICERs) was also computed against the QALYs gained. The ICER was then compared with the GDP per annum per person in India in the following comparing scenarios.

- Comparing Invasive Therapy (PCI/CABG pooled together) vs Conservative Therapy (OMT alone) in general population
- Comparing CABG vs PCI in general population undergoing invasive therapy
- Comparing the above two scenarios specifically for diabetic population as a subgroup

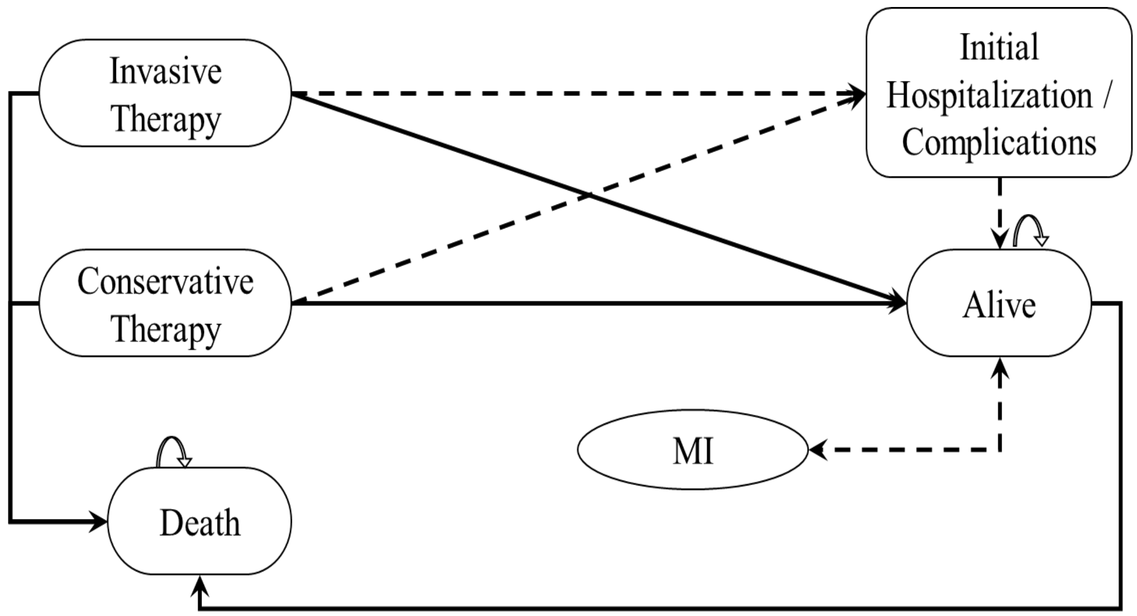

Figure 4: Markov Model for stage 1 comparing Invasive and Conservative therapies

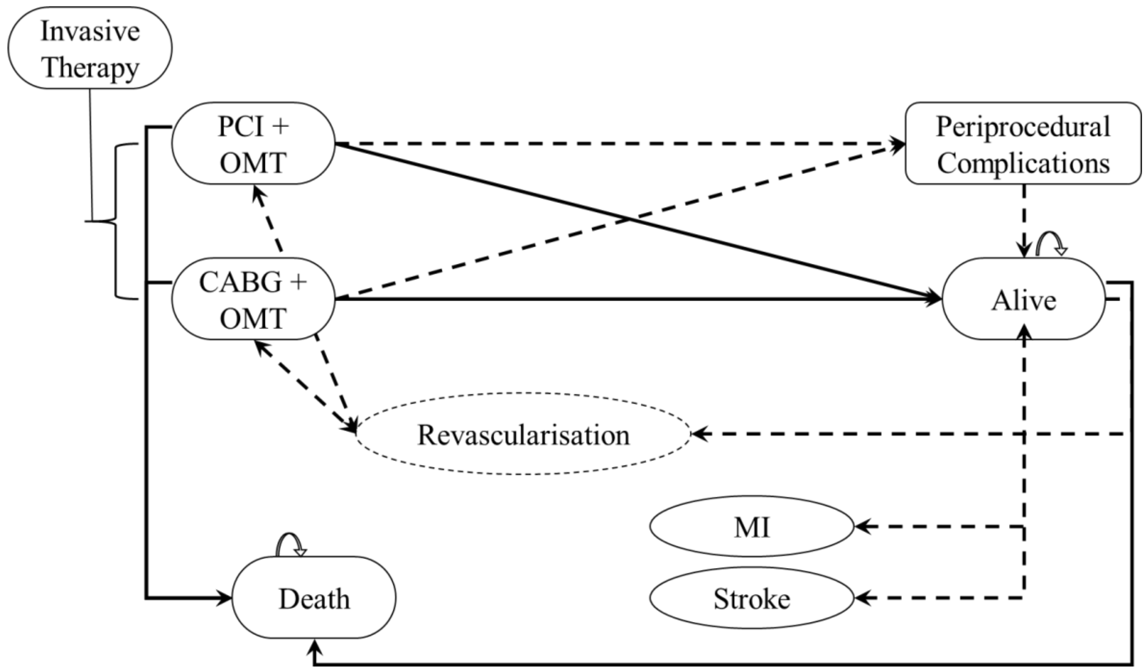

Figure 5: Markov models for Stage 2 comparing CABG vs PCI

Estimation of Costs

All the required costs were taken from review of literature and were of an abridged societal perspective (both health system costs and out-of-pocket expenses born by the patient except their productivity and wage losses). For the purpose of our model the costs were taken from Indian settings (refer to table3). The cost for managing patients with PCI+OMT, CABG+OMT and subsequent revascularizations with PCI and CABG, were taken from the Pradhan Mantri Jan Arogya Yojana (PMJAY) rates for generalizability of results (36). Prices for drugs administered in OMT (both in the OMT alone and with PCI and CABG) were taken from local rates as per the Pradhan Mantri Jan Aushadhi Pariyojana Rates of drugs by the Government of India. The prices of anti-diabetic drugs has also been taken from the same. All medication costs were computed on the basis of standard treatment protocols for management of CAD patients and diabetics. In case of diabetic MV-CAD patients, as the patients have been considered to be pre-diagnosed patients, the cost for diagnosis of diabetes or any other diagnostic procedures associated with it have not been considered. The costs have been calculated based on two scenarios of OMT medicine prices:

- Prices as per Bureau of Pharma Public Sector Undertakings of India (BPPI)
- Prices as per the Average of the Market Prices of the top 3 leading brands in India

Based on these two rates, the cost trace for all therapies were run separately to generate separate ICER values for all scenarios. Other costs pertaining to management of stroke and MI were taken from a target review of available literature from our country settings, again for generalizability of results. All the drawn estimates were then adjusted for inflation to generate cost estimates for the current year.

Table 3: Cost parameters from India.

Cost Parameter	**Annual Cost per person (in INR) as per BPPI prices**(37)	**Annual Cost per person (in INR) as per Average Market prices**
Cost of OMT alone (BPPI)	3,472	25,855
Cost of OMT used with PCI (BPPI)	4,656	31,638
Cost of MT used with CABG (BPPI)	2,750	22,814
Cost of anti-diabetic drugs (insulin, etc.) (BPPI)	2,150	4,521
Procedural Costs (36)	**Annual Cost per person (in INR)**	
Cost of PCI	40,600	

Cost of single stent (drug-eluting)	31,800
Cost of CABG	1,18,000
Cost of managing MI	53,058
Cost of managing Stroke	79,636
Cost of Hospitalization	14,108

Valuation of Health Benefits

Based on review of literature the primary endpoints identified in the management of MV-CAD were identified. These were both individual values, and as a composite value, collating death, and Stroke. In case of the deaths, specific mortality incurred due to cardiac causes was taken separately from the death due to any other cause.

As per Indian settings, the mean age of onset of MV-CAD was also adjusted (51 years as opposed to 60+ years in developed countries) in the model. Again, an assumption has been made that the probabilities generated with available data remain constant for the remainder of lifetime of the patient – even after the actual follow up period which was 5 years in the case of the general population and 10 years when comparing the general population to diabetics and non-diabetics. The transition probabilities were then generated from the available dataset (refer to table4)for both double vessel and triple vessel disease and were generated keeping in mind the cycle length of the main model as 1 year, and a separate set for the nested model for diabetic and non-diabetic population with same cycle length.

Table 4: Derived transition probabilities for the Markov Model.

Probabilities for Initial Hospitalization/Periprocedural Events		
Parameter	**Invasive**	**Conservative**
Complications like MI	0.043	0.026
Death	0.056	0.033
	PCI	**CABG**
MI	0.027	0.024
Stroke	0.001	0.01
Other Complications	0.069	0.364

Death	0.018	0.014
Probabilities for Follow-Up events		
	Invasive	**Conservative**
MI	0.020389	0.023519
Cardiac Death	0.028001	0.032461
Death from other causes	0.017839	0.016463
	PCI	**CABG**
MI	0.0138	0.0063
Stroke	0.0040	0.0057
Repeat Revascularization	0.0408	0.0198
Cardiac Death	0.0134	0.0100
Death from other causes	0.0215	0.0180
Probabilities for Diabetic Patients in Initial treatment therapies		
	Invasive	**Conservative**
MI	0.1	0.116
Cardiac Death	0.026	0.028
Death from other causes	0.132	0.135
Probabilities for Diabetic Patients in Invasive Methods		
Periprocedural Probabilities		
	PCI	**CABG**
MI	0.013	0.016
Stroke	0.016	0.002
Other Complications	0.619	0.09
Death	0.016	0.007
Follow Up		
MI	0.027417	0.011928
Stroke	0.004788	0.010148
Repeat Revascularization	0.016856	0.006578
Death	0.031493	0.021173

The utility weights for all health states and events were taken from review of literature (refer to table 5).

Table 5: Utility weights for the various health states and events in the model.

Time	Utility Weight
Quality weight at 1yr for OMT	0.846
Quality weight at 3yr for OMT	0.849
Quality weight at 1yr for PCI	0.855
Quality weight at 3yr for PCI	0.858
Quality weight at 1yr for CABG	0.856
Quality weight at 3yr for CABG	0.859
Quality weight for MI	0.69
Quality weight for Stroke	0.7
Quality weight for diabetics	0.75
Quality weight for non-diabetics	0.767

Statistical analysis

Cost-effectiveness

Cost Effectiveness Analysis is essentially to generate an Incremental Cost Effectiveness Ratio (ICER) which when compared with the GDP per capita of a country tells us whether the therapy is cost effective or not. For this the difference in the costs for the therapy regimens being analyzed and the difference of the associated health benefits of the same are needed (38)(39).

$$\mathbf{ICER = (C_1 - C_2) / (E_1 - E_2)}$$

Here, C_1 and C_2 are the costs associated to the treatment different regimen; similarly E_1 and E_2 are the associated health benefits for the respective regimens. From the available literature sources all the health benefit data and costs were input in to the mathematical model to run a virtual simulation of the patients undergoing their respective therapies over a lifetime horizon.

On the available two sets of prices of medications in OMT, two scenarios have been analyzed for costs whereas only the first has been used for cost-effectiveness as the base case:

- OMT prices as per Bureau of Pharma Public Sector Undertakings of India (BPPI)
- OMT prices as per the Average of the Market Prices of the top 3 leading brands in India

Total Costs and consequences have then been calculated by summing up all costs incurred and health benefits gained respectively, by the patients over the course of their lifetime (capped at 70 years based on the average life expectancy in India of 69.2 years).

Both undiscounted as well as discounted values, for costs and consequences, have been generated (discounting against a discount factor of 3%). Based on the cost of drugs, separate ICERs have been generated for both sets of drug prices. These ICERs were then compared with the GDP per capita of India to see whether PCI + OMT is a cost effective strategy, or not, as compared to OMT alone and CABG + OMT in treating patients with MV-CAD.

Net Benefit Analyses

Apart from generating ICER values, the net health benefit and net monetary benefits of PCI + OMT over CABG+OMT and OMT alone were also calculated.

Net health benefit (NHB) is a summary statistic that represents the impact on population health of introducing a new intervention. As per the York Health Economics Consortium "Net health benefit assumes that 'lost health' can be estimated as an 'opportunity cost' to represent the health that is foregone elsewhere as a result of moving funds to pay for a new intervention." (40).

NHB = incremental gain in QALYs – (incremental cost / CEA threshold)

A positive NHB means that the overall population health will increase as a result of the new intervention whereas a negative NHB means that the health benefits of the new intervention are not sufficient to outweigh the health losses that arise from the healthcare that ceases to be funded in order to fund the new treatment.

"Net monetary benefit (NMB) is a summary statistic that represents the value of an intervention in monetary terms when a willingness to pay threshold for a unit of benefit (for example a measure of health outcome or QALY) is known" as per the York Health Economics Consortium (41). The use of NMB scales both health outcomes and use of resources to costs, with the result that comparisons without the use of ratios (such as in ICERs) can be made.

NMB = (incremental gain in QALYs x CEA threshold) – incremental cost

A positive value indicates that the intervention is cost-effective compared to the alternative at the given willingness-to-pay threshold. A negative value indicates that the intervention is not cost-effective at the given willing-to-pay threshold. For analysis, the willing-to-pay threshold is usually kept equal to the CEA threshold to generate these net benefit results.

Discounting

All the estimations of costs and outcomes were discounted at a rate of 3% per annum so as to give an estimate in accordance with the present time. This is because the costs were incurred in the present while the associated outcomes would be achieved in the future (time variable up to death of patient). So, as per review of literature, a discounting rate of 3% was chosen for discounting health costs and effects for generalization of results (38)(39).

RESULTS

The results are as summarized in the following tables as per the scenarios described before.

Table 6: Summary of results for MV-CAD patients:

Category (MV-CAD patients)		BPPI Price of drugs			
		ICER (in INR)	ICER:GDP	NHB (in QALYs)	NMB (in INR)
Stage 1	*Invasive vs Conservative*	12,97,907.37	8.55	-0.698	-1,05,970.17
Stage 2	*CABG vs PCI*	-70,250.59	-0.46	0.906	1,37,464.71

ICER = Incremental Cost-Effectiveness Ratio, GDP = Gross Domestic Product (per capita per person), NHB = Net Health Benefit, NMB = Net Monetary Benefit, QALY = Quality Adjusted Life Year, INR = Indian National Rupee, BPPI = Bureau of Pharma Public Sector Undertakings of India, *CEA Threshold = GDP per capita per person of India (INR 1,51,793.69 as of May 31st, 2020 as per World Bank)

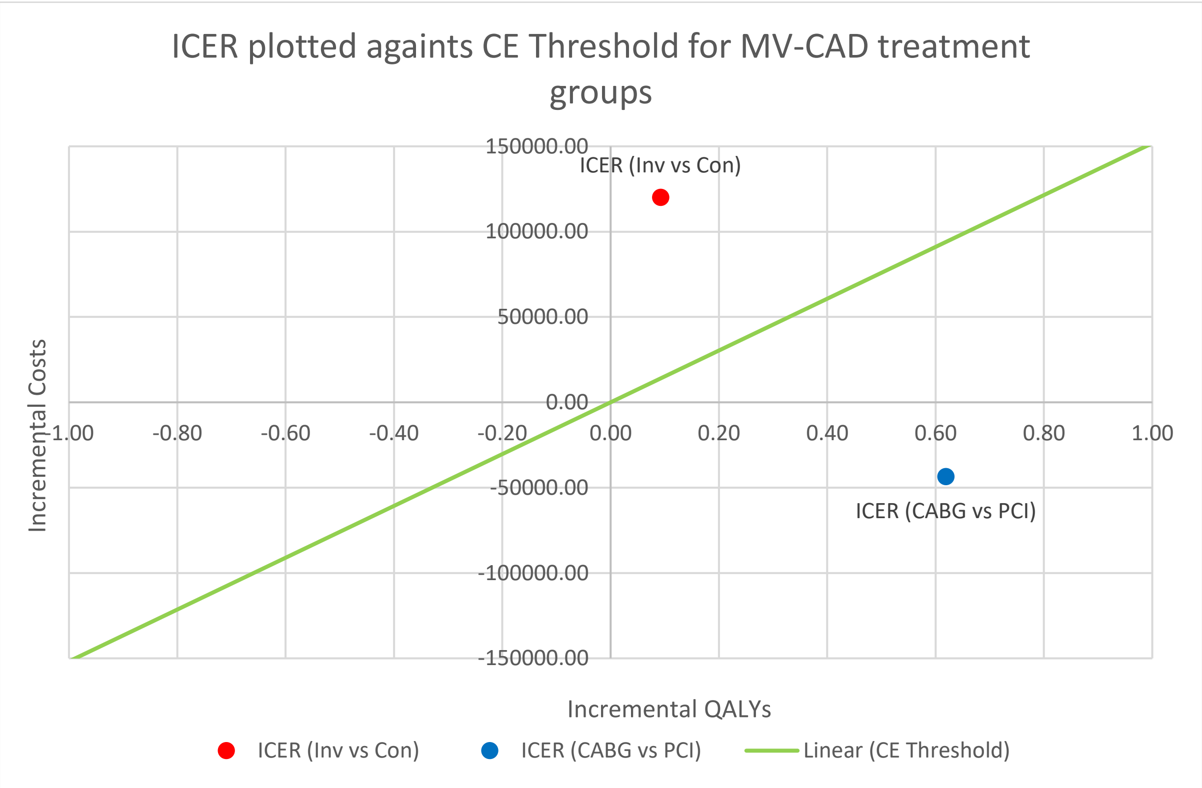

Figure 6: ICERs against CE threshold for Invasive vs Conservative Therapy and CABG vs PCI respectively in MV-CAD patients

As per our findings, when treating either MV-CAD, the between invasive and conservative (OMT) therapies, the invasive therapy is highly cost-ineffective with negative net health and monetary benefits. Regarding the patients that do undergo invasive therapy, CABG proves to dominate PCI with a positive net health benefit along with being cost effective.

The results of the subgroup analysis are illustrated below. Overall, invasive therapy does have a QALY gain over conservative OMT but when comparing amongst themselves, CABG had a better gain n QALYs for diabetics than non-diabetics.

Table 7: Summary of results for Diabetic MV-CAD patients:

Category (Diabetic MV-CAD patients)		BPPI Price of drugs			
		ICER (in INR)	ICER:GDP	NHB (in QALYs)	NMB (in INR)
Stage 1	*Invasive vs Conservative*	7,77,458.76	5.12	-0.611	-92,730.82
Stage 2	*CABG vs PCI*	-34,856.08	-0.23	1.01	1,53,329.18

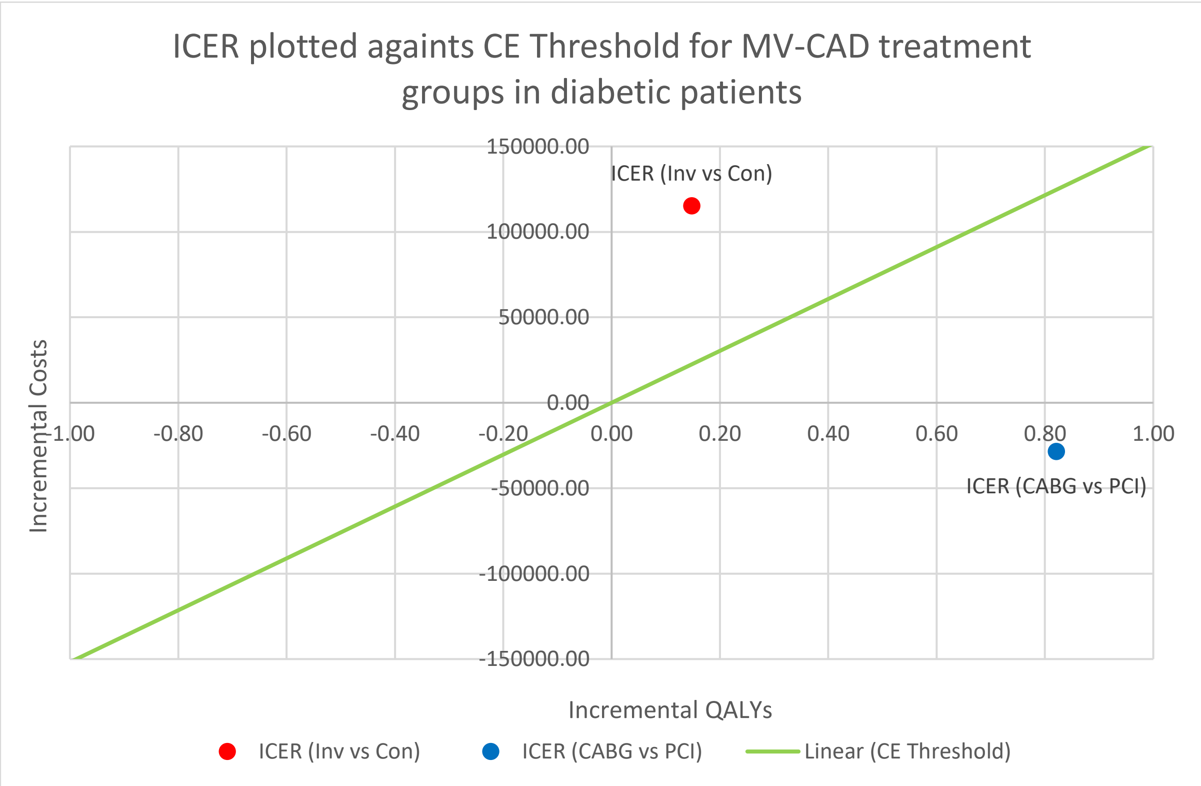

Figure 7: ICERs against CE threshold for Invasive vs Conservative Therapy and CABG vs PCI respectively in Diabetic MV-CAD patients

The PSA results for the same are also illustrated in the following figures. In case of invasive vs conservative therapy, even at a really high willing-to-pay threshold of almost INR 60,00,000 the invasive therapy can only have a 50% probability of being cost-effective. In case the patient does need to go for invasive therapy, CABG is the dominant therapy to choose from among the two (i.e. PCI and CABG). In diabetics the trends seen were almost similar to that seen in the general population.

Hence our results can be said to be quite robust in the sense that the PSA results are mostly in line with the findings of the study.

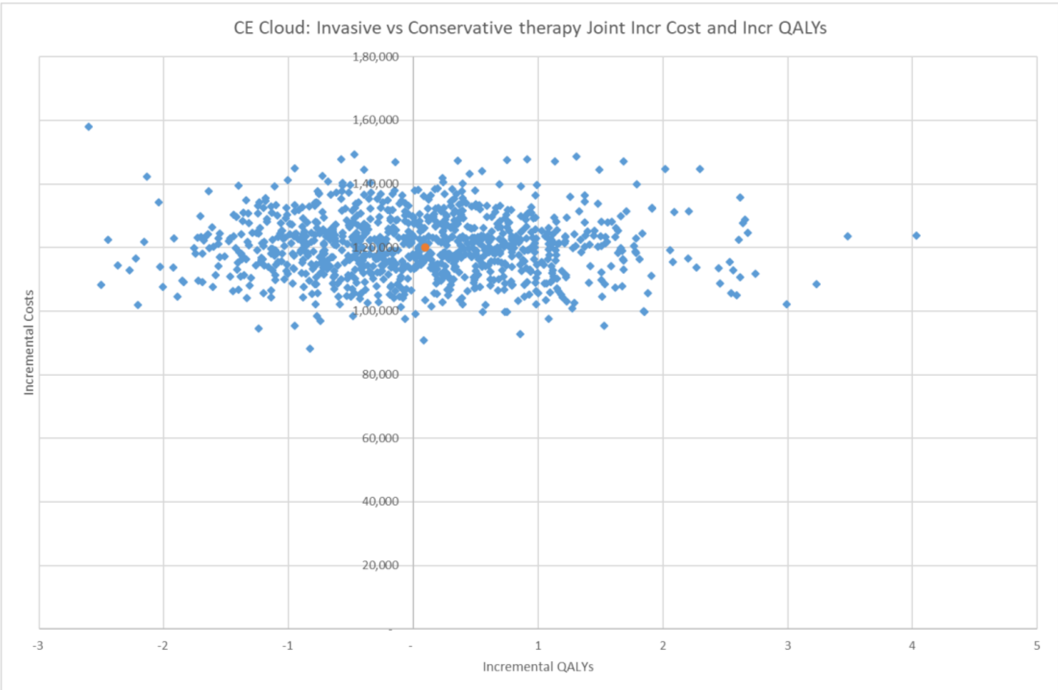

Figure 8: CE cloud for ICERs in MV-CAD patients treated by Invasive vs Conservative Therapy

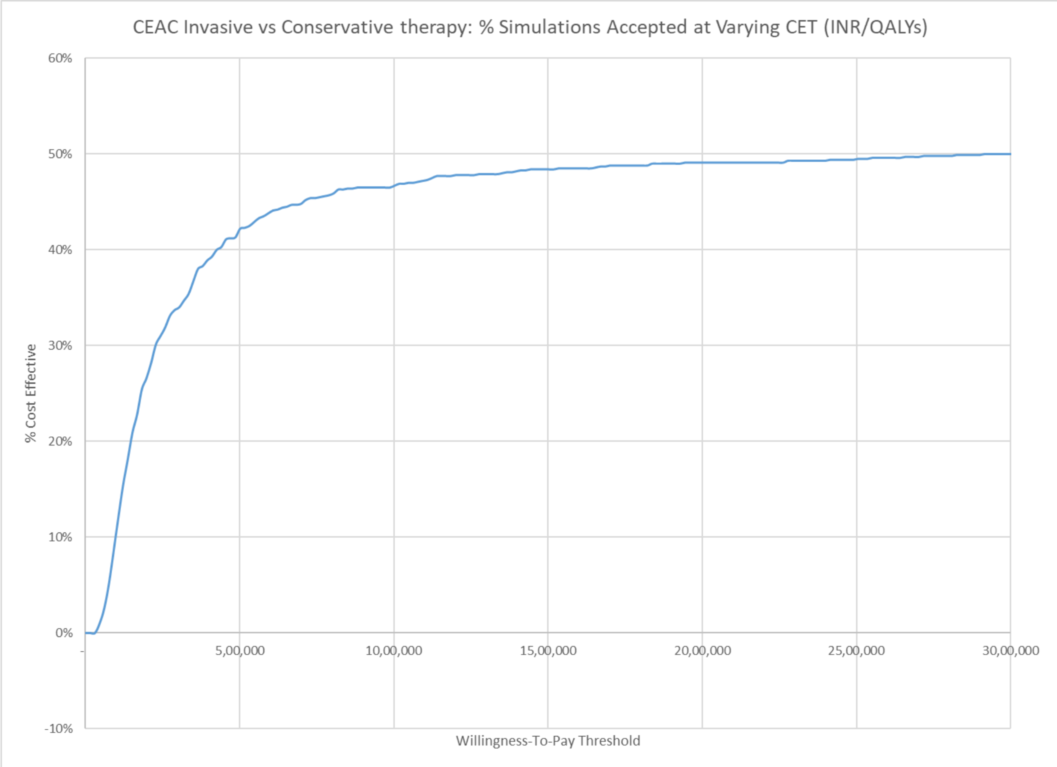

Figure 9: Cost-Effectiveness Acceptability Curve for MV-CAD patients treated by Invasive vs Conservative Therapy

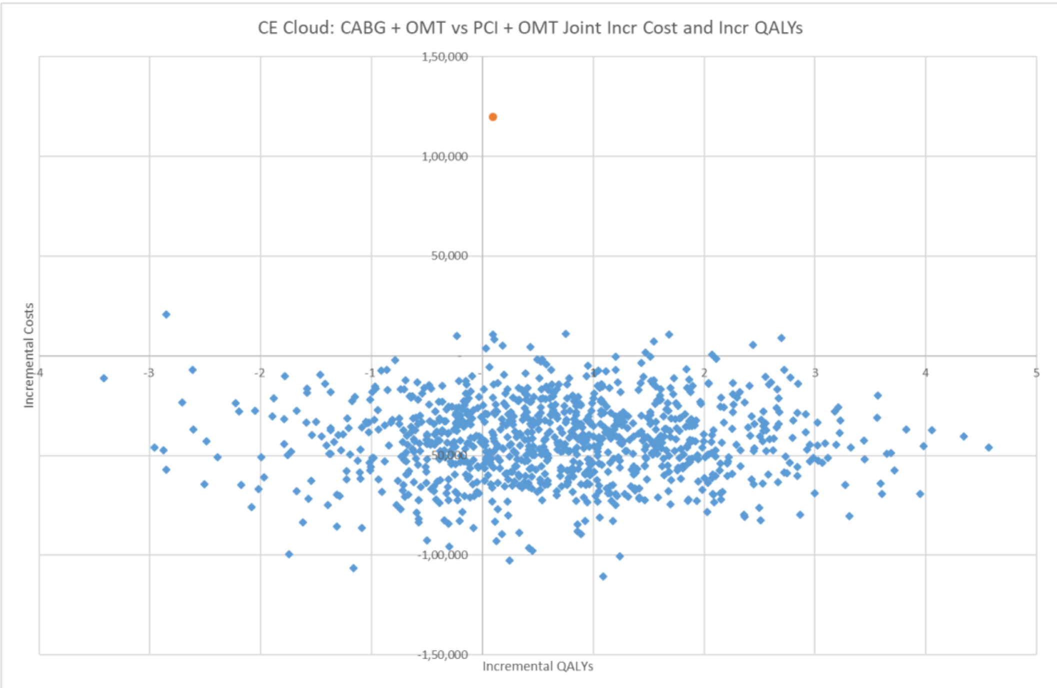

Figure 10: CE cloud for ICERs in MV-CAD patients undergoing invasive therapy with CABG vs PCI

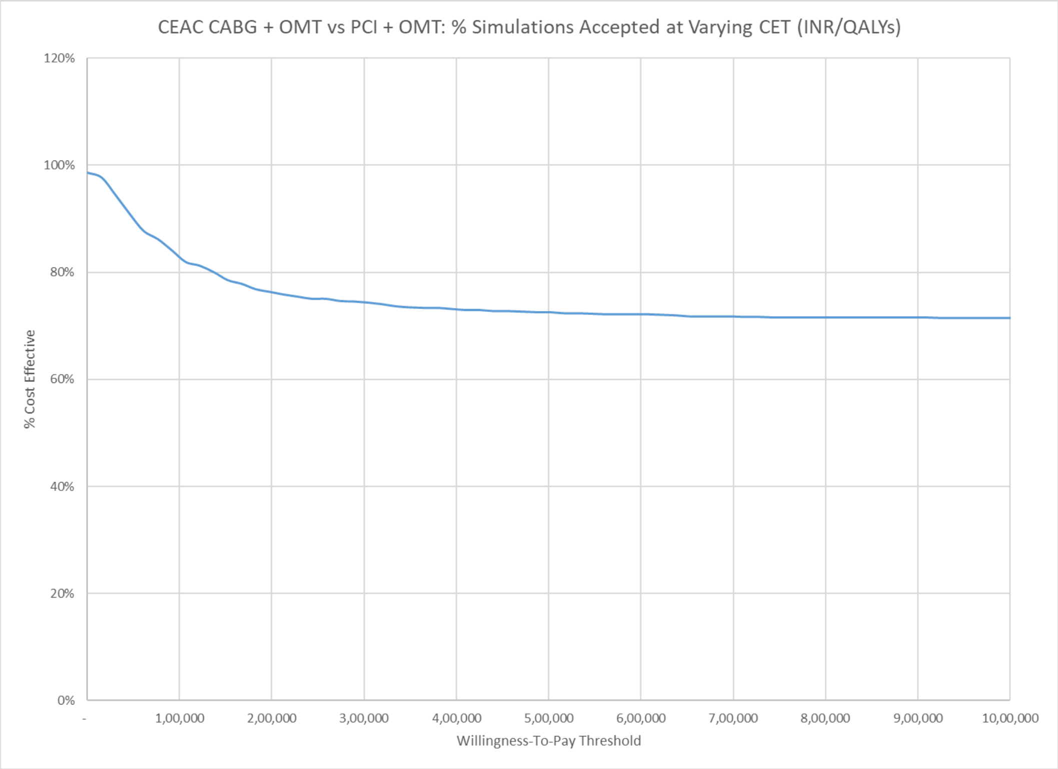

Figure 11: Cost-Effectiveness Acceptability Curve for MV-CAD patients undergoing invasive therapy with CABG vs PCI

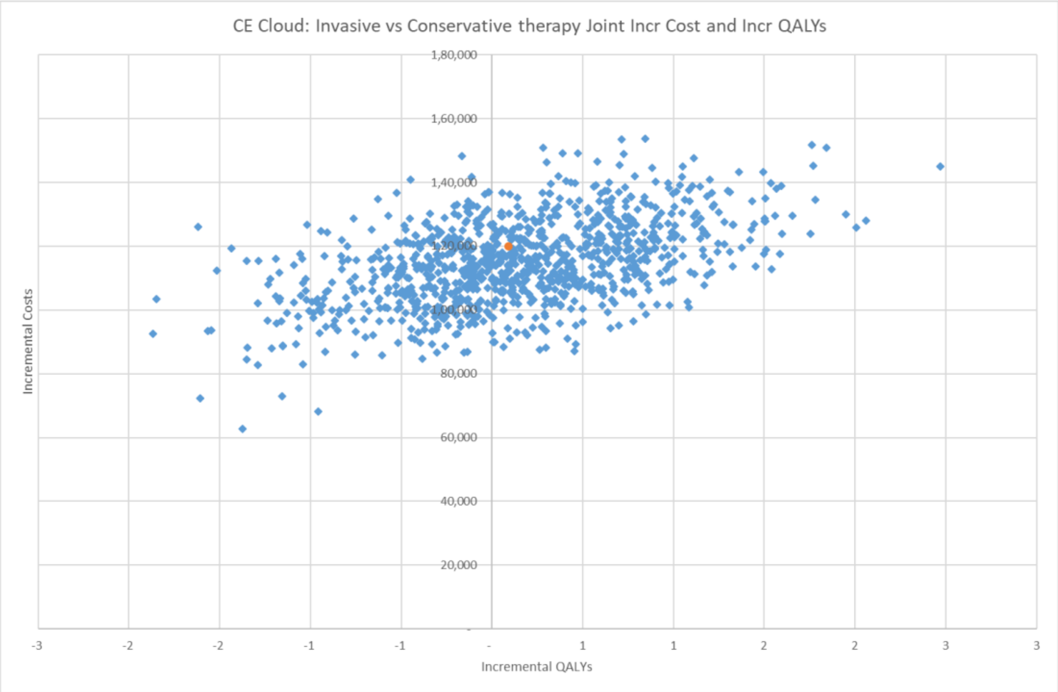

Figure 12: CE cloud for ICERs in Diabetic MV-CAD patients treated by Invasive vs Conservative Therapy

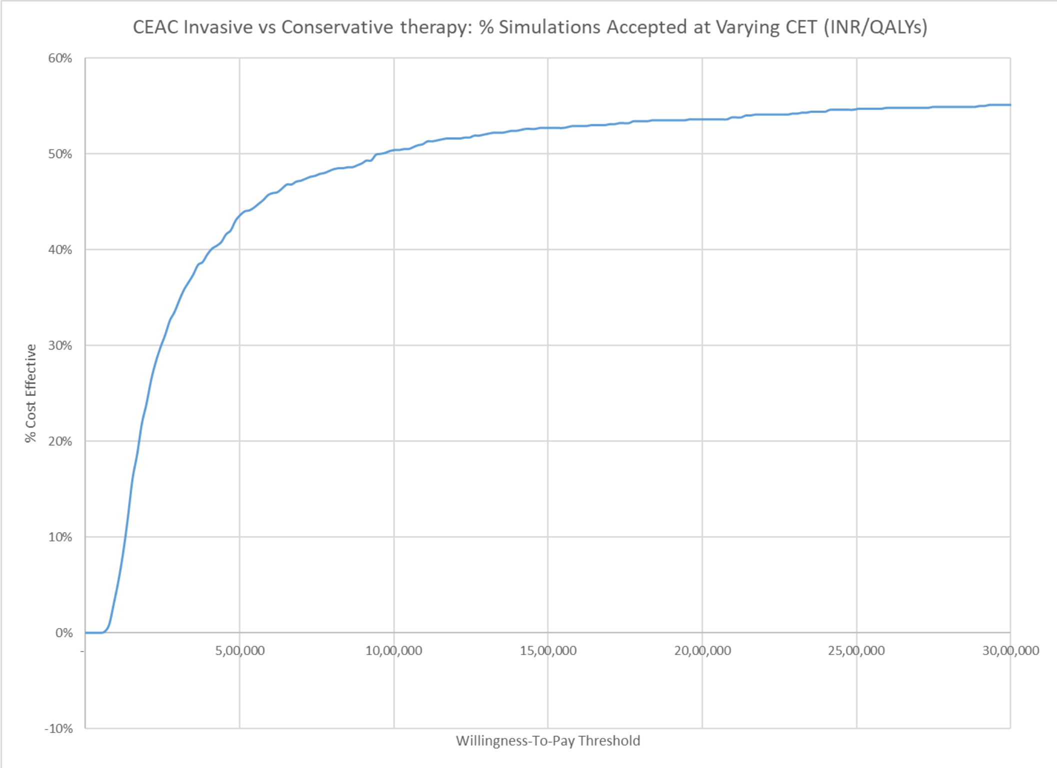

Figure 13: Cost-Effectiveness Acceptability Curve for Diabetic MV-CAD patients treated by Invasive vs Conservative Therapy

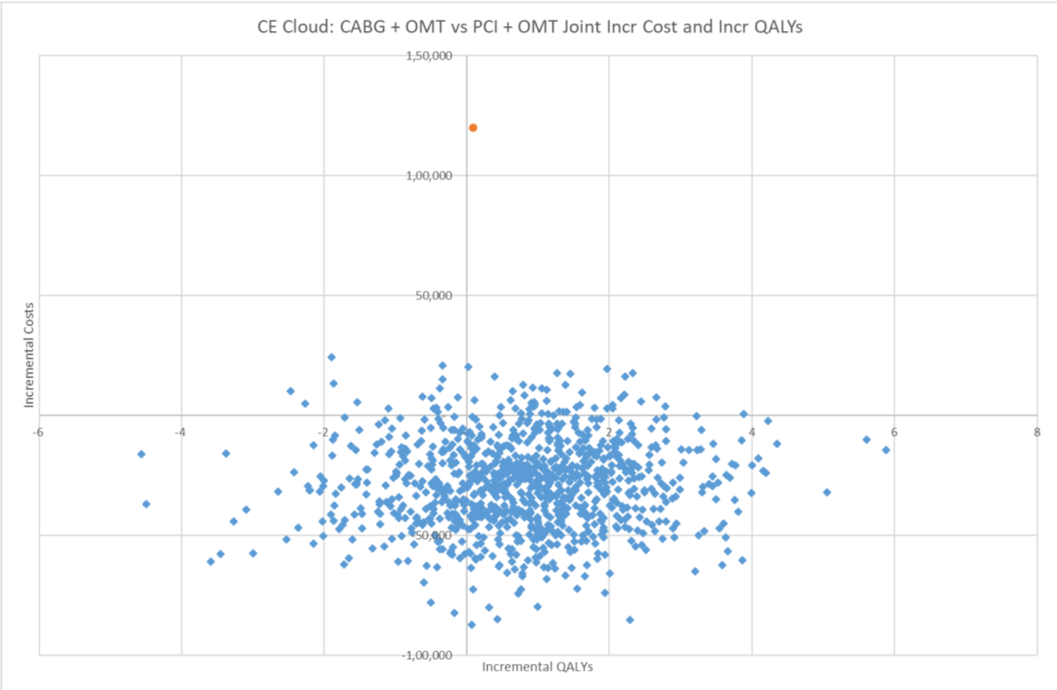

Figure 14: CE cloud for ICERs in Diabetic MV-CAD patients undergoing invasive therapy with CABG vs PCI

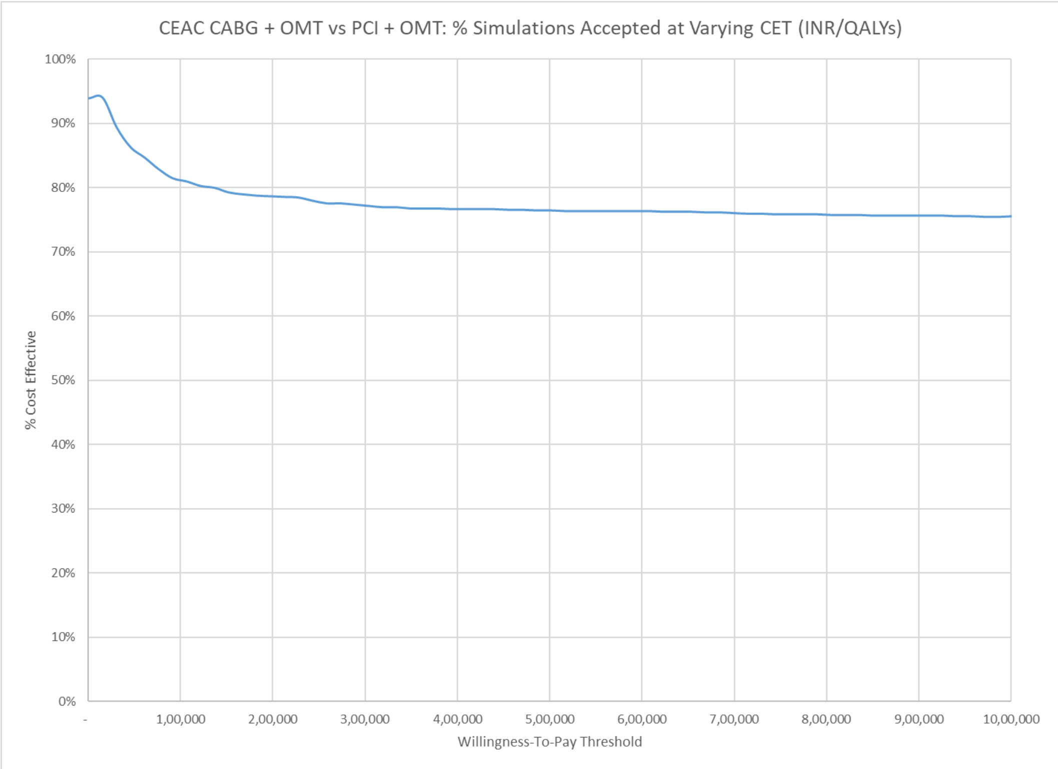

Figure 15: Cost-Effectiveness Acceptability Curve for Diabetic MV-CAD patients undergoing invasive therapy with CABG vs PCI

To summarize, the results are as follows:

- Initially, between invasive and conservative therapies, the invasive therapies are not cost-effective.
- In case patient undergoes invasive therapy, CABG + OMT is cost effective and a cost saving strategy in comparison to PCI + OMT, specifically for multivessel disease. This might be associated to the fact that while the price of the procedure for PCI might be lesser than that for CABG, the overall price of therapy goes up due to the price of stents implanted – depending on number of vessels involved – and the additional drugs required in PCI therapy – clopidogrel and more nitrates as compared to CABG.
- Also in comparing CABG over PCI, it is clear that the simulations project CABG to be the dominant therapy over PCI.
- Even the net monetary and health benefits associated with the use of CABG are good.
- The results in the diabetics sub-group mirrored the results for general population with an overall lesser QALYs lived than the general population.

Hence, it would be advisable to keep the mainstay treatment of MV-CAD patients as OMT alone first and then if the patient does require invasive therapies, CABG should be considered as the treatment of choice rather than PCI for patients.

DISCUSSION:

In the current study, the results demonstrated that conservative therapy can be used as initial management strategy for patients with MV-CAD. However, Revascularization becomes necessary with increasing complexities. In this economic evaluation of PCI vs CABG patient with multivessel vessel coronary artery disease, used a comprehensive, state transition model, concluded that the strategy of CABG was found be dominant over the PCI and seems to be better choice of treatment because of higher QoL gained and lower cost. The primary results from MASS 2 trial demonstrated that no significant difference between the CABG, PCI, and MT groups with regard to cardiac death or acute MI during one-year follow-up. However, angina requiring new revascularization was higher in the PCI group compared with the other treatments. The CABG-treated patients had better symptomatic relief than patients who underwent the PCI or MT strategy.(27) The results from a meta-analysis of 8 RCTs by Verma *et al* show that allocation to CABG versus PCI in patients with diabetes and multivessel disease is associated with a large (about a third) RR reduction in all-cause mortality at a mean or median 5-year (or longest) follow-up (p=0.002), with no difference noted at 1-year follow-up. Importantly, the mortality benefit of CABG was quantitatively much the same in trials that used either BMS or DES with no difference noted between PCI strategies, and was only present in patients with diabetes, with a statistically significant subgroup effect for the comparison with diabetes versus without diabetes. Despite the overall mortality benefit noted, CABG was associated with a higher rate of stroke than was PCI, particularly at 1-year follow-up (27).

All the studies done so far have mainly contributed to literature with primary focus on two treatment regimens, i.e. PCI and CABG with or without OMT. The international ischemia trial failed to show that routine invasive therapy was associated with a reduction in major adverse ischemic events compared with optimal medical therapy among stable patients with moderate ischemia. Although the overall interpretation of this trial was negative, there were mixed findings with evidence for both harm and benefit. This signals that: 1) invasive therapy for stable ischemic heart disease patients needs to be carefully considered in the context of angina burden and background medical therapy, and 2) likelihood that optimal coronary revascularization can be achieved with low procedural complications (35). On the other hand, the largest randomized trial performed at a single institution, MASS-II, compared the relative efficacy of three current therapeutic strategies for patients with symptomatic multivessel CAD. The trial showed no difference in cardiac death or acute MI among patients in the CABG, PCI, or MT group. However, it did show a significantly greater need for additional revascularization procedures in patients who underwent PCI (31).

The present study focused on the effectiveness of clinical outcome with involvement of multivessel coronary artery disease, it has been found that there is not much difference in PCI+OMT and OMT alone, however, when PCI is compared with CABG, it was found be dominant and cost effective over the PCI. The same treatment modalities were compared across the two subgroups: the diabetics and non-diabetics group. It was observed that the ICER values were pretty high in the non- diabetics group. The probable reason for higher QALYs and cost in the non-diabetics group was the higher mortality rates in the diabetics group.

Limitations and Assumptions:

In the literature review very less studies was found which compares the PCI with CABG along with OMT, that was more challenging task to find out those articles which were only focused on patient with multi vessel coronary artery diseases comparing the PCI and CABG with or without OMT and OMT alone so majority of data were extracted from the MASS-II trial and ISCHEMIA trial. Most of included articles in the present studies were related to the ISCHEMIA and MASS-II trial in different year publication with different objectives; however, most of the data were extracted from the main MASS-II and ISCHEMIA trial.

Certain assumptions have been made while running the simulations in the mathematical model. These have been listed below:

- The cycle length has been set at 1 year for the model assuming that the frequency of events is once per year for the patients.
- The clinical outcomes have been assumed to hold true for the population of India as India specific data on required transition states was not available. As such, the rates of progression of the disease have been assumed to be true for our study setting.
- The outcome values taken from literature are values over a 1, 5 and 10 year follow-up period. While imputing and running these in the model it has been assumed that these remain constant for the rest of the life of the patient; as the model has been extrapolated to a lifetime horizon.
- The model was run till the patient cohort reached the age of 70. This was done keeping the life expectancy of our population in mind, i.e., 69.2 years.

- In terms of utility values for each health state and event also, in the absence of a country specific value set, the values taken from literature have been assumed to hold true for our study population. These values are from developed countries where the socio-demographics and disease burden and progression might differ from our population.
- Cost for PCI and CABG has been directly taken from the PMJAY coverage rates. These cover all the expenses incurred in the health systems and have been taken so as to have generalizable results.
- While running the model, as outcome values for revascularization were of a pooled nature (PCI and CABG combined) and independent data for each of the two was not available (except the number undergoing the process); the same outcome parametric values have been used for both processes.
- The prices of drugs used in OMT have been taken as that of the ideal therapy. Patient level medication doses might vary to some extent for which the sensitivity was tested.

CONCLUSION

As is evident from results of our study, invasive therapy is not a cost-effective strategy to start treatment of MV-CAD patients. Conservative therapy of OMT should thus be the initial therapy to start treating patients. If the patient does require invasive therapy for one or the other reason, CABG should be the preferred therapy over PCI due to it being cost-effective as well as cost saving over PCI.

Based on this study, our recommendation would be to keep the conservative therapy regimen of OMT alone as the mainstay treatment with CABG being the preferred invasive therapy for cases showing unfavourable or worsening prognosis with OMT alone. PCI might be considered but owing to its higher costs attributable to the number of stents to be implanted, it is not recommended by this study (as the health gains are not that prominent as compared to CABG so as to justify investing in that higher cost).

In the case of diabetics, our recommendation remains the same that the mainstay treatment be focussed around OMT alone and the patients be moved to CABG on the discretion of physician and the patient's response to OMT therapy.

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