Health Technology Assessment in India (HTAIn)

Economic Evaluation of Percutaneous Coronary Interventions (PCI) against Optimal Medical Therapy (OMT) for Management of Patients with Single Vessel Coronary Artery Disease (SV-CAD) without Left Main Coronary Artery (LMCA) Involvement

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ABBREVIATIONS

CAD	Coronary Artery Disease
MVD	Multiple Vessel Disease
SV-CAD	Single Vessel Diseases
PCI	Percutaneous Coronary Intervention
CABG	Coronary Artery Bypass Graft
OMT	Optimal Medical Therapy
LMCA	Left Main Coronary Artery
DES	Drug Eluting Stents
BMS	Bare Metal Stents
PTCA	Percutaneous transluminal coronary angioplasty
RCT	Randomized Controlled Trial
MASS	Medicine Angioplasty, or Surgery Study
PmLAD	Proximal or middle left anterior descending artery
CTO	chronic total coronary occlusion
SAQ	Seattle angina questionnaire
DFS	Disease Free Stage
MI	Myocardial Infarction
LAD	Left Anterior Descending Artery
LY	Life Years
QALY	Quality Adjusted Life Years
CEA	Cost Effectiveness Analysis
ICER	Incremental Cost Effectiveness Analysis
NHB	Net Health Benefits
NMB	Net Monetary Benefits

Contents

1. Introduction:

1.1 Background:

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality around the globe, according to WHO, an estimated 17.9 million people died from CVDs in 2016, representing 31% of all global deaths. Of these deaths, 85% are due to heart attack and stroke and over three quarters of CVD deaths take place in low- and middle-income countries.(1)

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels, out of which coronary heart disease or coronary artery disease (CAD) (disease of the blood vessels supplying to the heart muscle) are mostly involved, which usually involves single vessel and multi-vessel coronary artery disease. Single vessel disease (SV-CAD) is usually referred to as the presence of at least a ≥70% stenosis of a major coronary artery (left anterior descending, left circumflex, or right coronary arteries) or one of their respective major branches (diagonal, obtuse marginal, posterior descending, or posterior left ventricular arteries) .

Single vessel disease is often associated with a higher burden of comorbidities, left ventricular dysfunction, and cardiovascular risk. The goal in the management of single vessel is usually to reduce angina and heart failure symptoms and a patient's subsequent risk of adverse cardiovascular events (2). All patients with CAD first require optimal medical therapy (OMT) to alleviate symptoms, avert disease progression, prevent Cardio vascular events, and decrease mortality. 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 (3). 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 multi-vessel disease.

Medical treatment: 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-angiotensin in system blockade, nitrates, calcium-channel blocker, and aggressive lipid-lowering therapy, (4) 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 (4)(3).

Percutaneous Coronary Intervention: The goal of PCI is to provide a safe, effective, less invasive alternative to coronary artery bypass graft surgery (CABG). PCI was firstly introduced in to provide a safe, effective, less invasive alternative to coronary artery bypass graft surgery (CABG)1977,(2) 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 intervention can be equally successful as CABG (5).

Over the past 30 years, there have been substantial advances in PCI technology, first with the adoption of bare metal stent (BMS) and, after that, the use of drug eluting stents (DES) to reduce the phenomenon of restenosis. Since the advent of drug-eluting stents (DES) and the evidence attesting to their superiority over bare metal stents (6).

1.2. Review of literature:

The review of literature was targeted for studies on SV-CAD without LMCA. On this certain trials were found which were based on SV-CAD. One of these, the ACME trial, prospectively randomized 212 patients with single-vessel coronary artery disease to compare the effects of percutaneous transluminal coronary angioplasty (PTCA) with those of medical therapy on angina and exercise tolerance. After 6 months of follow-up, the angioplasty group was more likely to be free of angina (64% versus 46%, p <0.01) and achieved greater improvements in exercise duration (2.1 versus 0.5 minutes). No difference was noted in the incidence of death or MI, as one might expect in a small study of low-risk patients, but the angioplasty group required more repeat revascularization procedures (7).

In the Medicine Angioplasty, or Surgery Study (MASS) trial, 214 patients with stable angina, normal ventricular function and a proximal stenosis of the left anterior descending coronary artery > 80% were randomly assigned to undergo mammary bypass surgery (n = 70), balloon angioplasty (n = 72) or medical therapy alone (n = 72) . After an average of 3 years follow-up, the primary endpoint (cardiac death, MI, or refractory angina requiring revascularization) had been reached in two patients (3%) assigned to bypass surgery, 17 assigned to angioplasty (24%), and 12 assigned to medical therapy (17%). No patient allocated to bypass surgery needed a further revascularization procedure, compared with eight and seven patients, respectively, assigned to coronary angioplasty and medical treatment (p = 0.019). Both revascularization protocols led to greater symptomatic relief and a lower incidence of ischemia on a treadmill test. No difference was observed in the incidence of death or MI among the three treatment protocols in this small study of low-risk patients (8).

A randomized trial (COURAGE trial) was conducted on 2287 CAD patients at 50 U.S. and Canadian centers between 1999 and 2004. 1149 patients were given PCI and 1138 received optimal medical therapy alone. During a follow-up period of 2.5 to 7.0 years (median, 4.6), There were 211 primary events in the PCI group and 202 events in the medical therapy group. The 4.6-year cumulative primary-event (death) rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (HR for the PCI group, 1.05). There were no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke (20.0% vs. 19.5%; HR, 1.05); hospitalization for acute coronary syndrome (12.4% vs. 11.8%; HR, 1.07); or myocardial infarction (13.2% vs. 12.3%; HR, 1.13) (9).

The Randomized Intervention Treatment of Angina (RITA-2) trial randomized 1,018 patients with CAD to either BA and medical therapy, or medical therapy alone. Approximately 60% of the patients had single-vessel disease. Death or non-fatal MI occurred in 6.3% of patients treated with BA and 3.3% of patients treated with medicines alone (p = 0.02. Of the patients in the BA group, 7.9% required bypass grafting, and 11.1% required further nonrandomized BA. In the medical group, 23% underwent a revascularization, there was a 16.5% absolute excess of grade 2 or worse angina in the medical group at 3 months, which attenuated to 7.6% after 2 years (10).

Pursnani *et al.* performed a systematic review and meta-analysis for comparing revascularization with PCI to optimal medical therapy (OMT) in patients with stable coronary artery disease. The

primary outcome was all-cause mortality, and secondary outcomes included cardiovascular death, nonfatal myocardial infarction, subsequent revascularization, and freedom from angina, 12 RCT enrolling 7182 participants, primary analyses showed that when compared with OMT, PCI was associated with no significant improvement in mortality (risk ratio [RR], 0.85; 95% CI, 0.71–1.01), cardiac death (RR, 0.71; 95% CI, 0.47–1.06), nonfatal myocardial infarction (RR, 0.93; 95% CI, 0.70–1.24), or repeat revascularization (RR, 0.93; 95% CI, 0.76–1.14). Sensitivity analysis restricted to studies in which there was >50% stent use showed attenuation in the effect size for all-cause mortality (RR, 0.93; 95% CI, 0.78–1.11) with PCI. However, for freedom from angina, there was a significant improved outcome with PCI, as compared with OMT (RR, 1.20; 95% CI, 1.06–1.37), evident at all of the follow-up time points (11).

1.3 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 single vessel diseases. 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 in SV-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 best treatment modality, in terms of cost effectiveness, available for the management of patients with single-vessel coronary artery disease (SV-CAD) without the involvement of left main coronary artery (LMCA)?

Aim

- To conduct a full economic evaluation to see which treatment modality between percutaneous coronary interventions (PCI) with optimal medical therapy (OMT) and OMT alone is the better alternative for managing patients with SV-CAD.

Objectives

- To estimate the incremental cost for the management of patient with SV-CAD without LMCA involvement through PCI + OMT as compared to OMT alone.
- To estimate incremental health benefits for the management of patient with SV-CAD without LMCA involvement through PCI + OMT as compared to OMT alone.
- To estimate Incremental Cost-Effectiveness Ratio for the management of patient with SV-CAD without LMCA involvement through PCI + OMT as compared to OMT alone.

2. Methodology:

2.1 PICO:

- **Study Population:** Adult Patients suffering from SV-CAD without LMCA involvement
- **Interventions:** Percutaneous Coronary Intervention with Optimal Medical Therapy (PCI + OMT)
- **Comparators:** Optimal Medical Therapy (OMT) alone
- **Outcome:** Life Years (LYs) and Quality Adjusted Life Years (QALYs)
- **Time Horizon**: Life time horizon

2.2 Literature Review:

- **Search strategy:** A Targeted Literature Search has been done for the relevant articles in different Electronic databases.
- **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.
- **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', 'Revascularization', 'Angioplasty', 'Left Anterior Descending Artery', 'Single vessel diseases', 'left circumflex', 'Right Coronary artery'. A range of search filters like article type, date range searched; availability of full text articles. The electronic databases were last searched on 15 May 2020 and search was restricted only to published English language articles.
- **Study selection:** The results of the searches conducted using different databases were further selected on the basis of Inclusion and Exclusion criteria. Studies were selected for

inclusion/exclusion through a two-stage process as illustrated in PRISMA flowchart (Fig 1). The inclusion and exclusion criteria opted for the study selection was as follows:

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

1. Population: Adult General Population, Diabetic population with associated SV-CAD
2. Interventions: Articles reporting about the PCI with OMT were selected.
3. Comparator: Articles reporting about the OMT only were selected.
4. Outcomes: Studies reported about the clinical outcomes of PCI with OMT were selected.
5. Study designs: Systematic Reviews, Randomized control trial (RCTs), Economic Evaluations and Observational studies comparing the PCI vs OMT in patients with single vessel disease.

- **Study Exclusion Criteria:** Study were excluded which were found irrelevant in relation to Research question of the study.

1. Literature review, narrative review, reports, case reports and case studies are excluded.
2. Heart diseases apart from SV-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.

2.3 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 was extracted by two reviewers and finalized by the third reviewer.

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

Electronic database Search Results: A sum total of 964 records identified through different electronic database searching and 816 of which were screened after duplicates removal. After applying pre-specified inclusion/exclusion criteria, 725 articles were found inappropriate and hence excluded after titles and abstracts screening. Rest of the articles (n=64) were selected for full text read and 26 of which were further screened and excluded as not found fit for further

inclusions. Thirty-Eight (n=38) studies were finally selected for data extraction and thirty one (n=31) out of which were excluded due to inappropriate/insufficient data, patients with CTO, patients with diseases other than diabetes and hypertension. We finally included 7 articles (refer to table 1 & figure 1). The major findings of the finalized trials are summarized in table 2. As most trials focused on eliciting results for patients enrolled in the COURAGE trial which specifically looked at SV-CAD patients as a specific subset apart from the main study population, most of the parameters are used from that study. The systematic review that we found also had outcomes relying on the COURAGE trial for SV-CAD findings (17). So findings of the COURAGE trial have been incorporated with inputs from the systematic review incorporated wherever necessary.

Table 1: search results from different database:

Databases	**Search strategy Used**	**Filters used**	**Identified articles**
PubMed	((((Optimal medical therapy) OR OMT)) AND (((Percutaneous coronary intervention) OR PCI) OR Angioplasty)) AND ((((coronary artery disease) OR (((Single vessel disease) OR ((((left anterior descending) OR left circumflex) OR Right coronary artery)))))	**Filters:** Full text, Clinical Trial, Controlled Clinical Trial, Evaluation Study, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Review, Systematic Reviews, English language	562
Cochrane library	(optimal medical therapy OR OMT) AND ("percutaneous coronary intervention OR PCI OR Angioplasty) AND (coronary artery disease OR single vessel diseases OR left anterior descending OR left circumflex OR Right coronary artery)	Filters:Trials	129

Embase	(“optimal medical therapy” OR OMT) AND ("percutaneous coronary intervention” OR PCI OR Angioplasty) AND (“coronary artery disease” OR “single vessel diseases” OR “left anterior descending” OR “left circumflex” OR “Right coronary artery”)	No filters	86
Scopus	(“optimal medical therapy” OR OMT) AND ("percutaneous coronary intervention” OR PCI OR Angioplasty) AND (“coronary artery disease” OR “single vessel diseases” OR “left anterior descending” OR “left circumflex” OR “Right coronary artery”)	Filters: English language	187

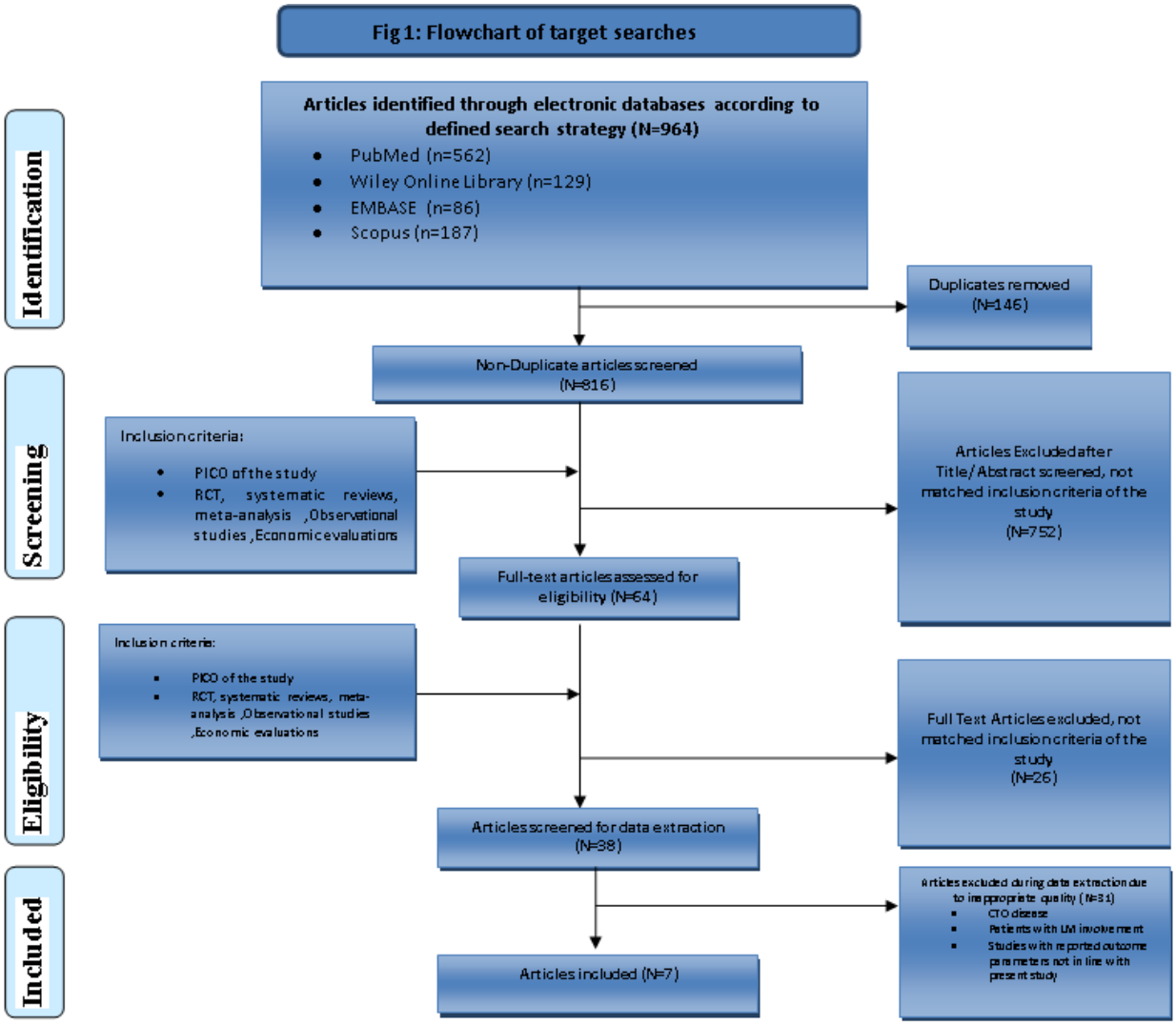

Figure 1: Flow chart of the searches at different databases

Table2: Major findings of studies finalized for data extraction.

Author - Year of Study	Study type	Disease studied	Treatment Strategies studied	Results
Boden *et al.*2007(3)	RCT	Stable Coronary Disease	PCI vs OMT	There were no significant differences between the PCI group and the medical-therapy group in the composite of death, MI, and stroke.

Weintraub *et al*.2008(12)	RCT (angina specific health status of COURAGE trial)	Stable Coronary Disease	PCI vs OMT	At baseline, 22% of the patients were free of angina. At 3 months, 53% in the PCI and 42% in the OMT were angina-free (P<0.001). Patients with more severe angina had a greater benefit from PCI. By 36 months, there was no significant difference in health status between the treatment groups.
Weintraub *et al*.2008(13)	Cost-Effectiveness analysis	Stable Coronary Disease	PCI vs OMT	Added cost of PCI was $10,000, without significant gain in life-years or QALY-years. ICER varied from just over $168,000 to just under $300,000 per life-year or OALY gained with PCI. The costs per patient for a significant improvement in quality of life $124,233, respectively.
Zhang *et al*.2011(14)	Cost effectiveness analysis	Stable Coronary Disease	PCI vs OMT	Improvement in angina severity was significantly greater for PCI patients in the lowest and middle tertiles. The number of patients needed to treat was much larger for the highest tertile. The added in-trial cost of PCI ranged from $7,300 to $13,000. ICER ranged from $80,000 to $330,000 for the lowest and middle tertiles and from $520,000 to $3,000,000 for the highest tertile for 1 additional patient to achieve significant clinical improvement in health status.
Sedlis *et al*.2015(15)	Follow-up of COURAGE study	Stable Coronary Disease	PCI vs OMT	A total of 561 deaths (180 during the follow-up period in the original trial and 381 during the extended follow-up period) occurred: 284 deaths (25%) in the PCI group and 277 (24%) in the medical-therapy group (adjusted hazard ratio, 1.03; 95% confidence interval, 0.83 to 1.21; P = 0.76).

Mancini *et al*.2018(16)	Pooled-analysis	Patients with stable CAD and T2DM	OMT+ vs PCI+OMT vs CABG+OMT	PCI + OMT significantly reduced the need for subsequent revascularization compared to OMT, (HR 0.66, CI: 0.57 to 0.76, p< 0.0001). Overall, the 5-year risk of the composite outcome for PCI + OMT and OMT were not different (HR: 1.12; 95% CI: 0.95 to 1.31 The CCS Class improved at 1 year according to randomized treatment strategy as follows: OMT, 0.9 ± 1.3; PCI þ OMT, 1.3 ± 1.3; CABG + OMT, 1.6 ± 1.3 (p<0.0001 for trend).
Pursnani *et al*.2012(17)	Systematic Review and Meta-Analysis	CAD	PCI vs OMT	The all-cause mortality point estimate at the longest follow-up duration notably did favor the PCI group (risk ratio [RR], 0.85; 95% CI, 0.71–1.01), Effect measures at the ≤1 year (RR, 1.34; 95% CI, 0.87–2.08) and 1 to 5 years (RR, 0.97; 95% CI, 0.56–1.69),secondary outcome-cardiac death (RR, 0.71; 95% CI, 0.47–1.06), nonfatal myocardial infarction (RR, 0.93; 95% CI, 0.70–1.24), or repeat revascularization (RR, 0.93; 95% CI, 0.76–1.14), with consistent results over all follow-up time points.

3. Model overview:

The study involved a comparison of costs and consequences for the treatment of SV-CAD patients using either form of therapy – **PCI + OMT** or **OMT alone** – and analyzing them over a lifetime horizon. For this purpose, a basic conceptual framework was generated as a foundation for a hybrid markov model with essentially three health states – Disease Free State (DFS), Alive and Death (refer to figures 2 & 3). As we were looking at both the peri-procedural phase of treatment (immediate 1 month after therapy administration) and the long term follow up phase; the peri-procedural phase simulation was built into the main model as a nested mini-model with a cycle length of 1 month. As such the overall cycle length was 1 year (Alive to Death phase) where the patients were entering at the state of DFS (completing 1 month of peri-procedural phase as well as those continuing from the previous cycle). 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 – both in the peri-procedural and follow up phases were modelled. In the peri-procedural phase, the primary events modelled were peri-procedural non-fatal MI, peri-procedural stroke. Apart from these the patient either transitions to the DFS or Death states. Starting from DFS the follow up phase starts, where the patients follow the respective treatment regimens (modelled to a lifetime horizon). Again, in this phase we modelled the respective health events of spontaneous MI, stroke and hospitalization for other acute coronary syndromes (like unstable angina). The patients have these events and revert back to the DFS state from where they proceed to the Alive state and then move on to the absorbing state of Death.

Due to a lack of individual data specific to death due to these events, a pooled average death available from literature for the DFS state was used to calculate total number of deaths of the patients dying from the DFS stage.

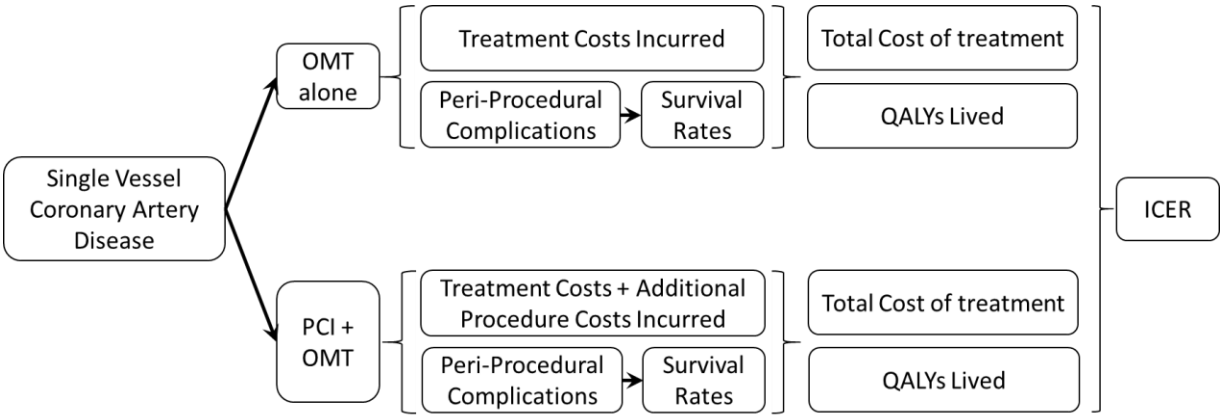

Figure 2: Conceptual Framework for the processes to be modelled and generated in treatment of patients with SV-CAD with either PCI + OMT or OMT alone

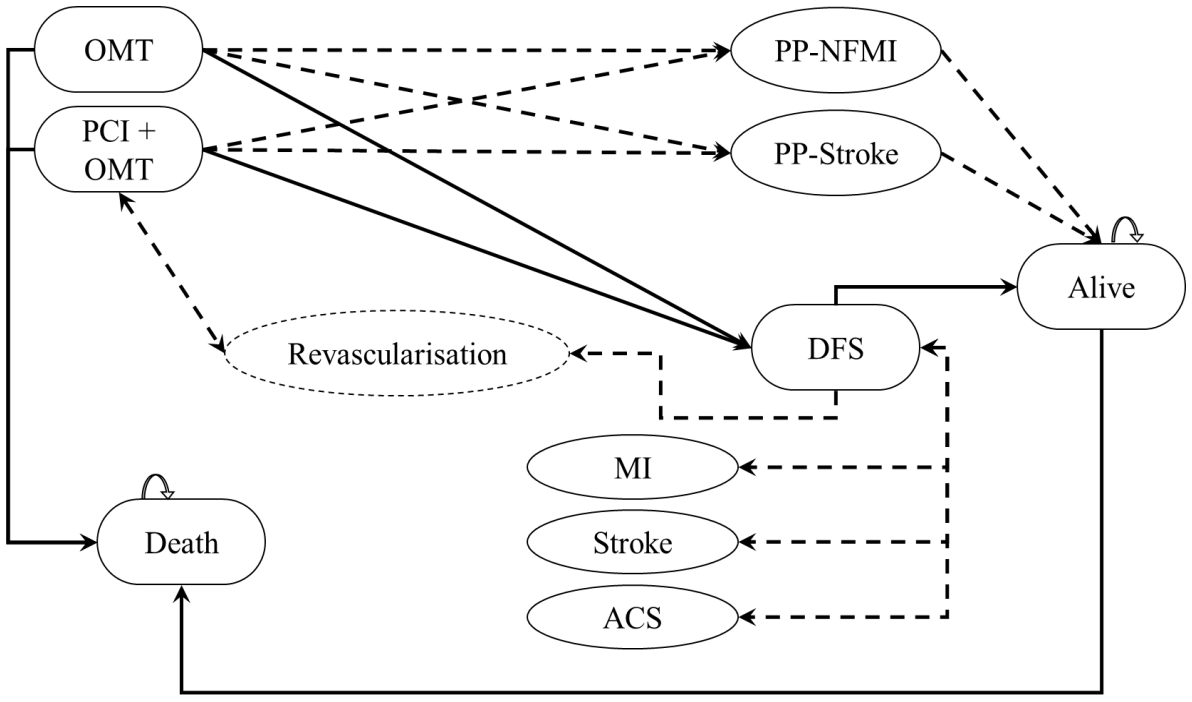

Figure 3: Illustration of the Markov model with the various transitions used in this study

Coming to the treatment protocol followed while modelling, the patients were administered the therapy in either arm and then following a 1 month peri-procedural phase the patient either moved on to the DFS or dies or had a peri-procedural event. 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 or ACS. In all these, the patients revert back to the DFS. Another event here is that of

revascularization where the patients undergo an index invasive procedure (PCI/CABG) or a repeat in case of PCI 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. From here, the patients again entered the whole cycle starting from the peri-procedural phase to the follow up phase and all the associated health stages and events.

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 Life Years (LYs) gained and Quality Adjusted Life Years (QALYs) gained for health benefits and the incremental costs of PCI + OMT over 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 to see whether the use of PCI + OMT was cost effective or not, over the use of OMT alone, for the treatment of SV-CAD in India.

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 table 3). The cost for managing patients with PCI, and subsequent revascularizations with PCI and CABG, were taken from the Pradhan Mantri Jan Arogya Yojana (PMJAY) rates for generalizability of results. Prices for drugs administered in OMT (both in the OMT alone and with PCI) were taken from local rates as per the Pradhan Mantri Jan Aushadhi Pariyojna Rates of drugs by the Government of India. 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 both the therapies were run separately to generate separate ICER values for both scenarios. Other costs pertaining to management of stroke and ACS hospitalization were taken from a target review of available literature from our country settings, again for generalizability of results. For MI the PMJAY rates were taken in conjunction with additional management costs associated with hospitalization from review of literature. All the drawn estimates were then adjusted for inflation to generate cost estimates for the current year.

Table 3: Cost of parameters form India.

Parameter	**Annual Cost per person (in INR)**		**Source**
Cost of PCI	70780		PMJAY Rates (18)
Cost of MI	53058		PMJAY Rates (18), Agrawal 2017 (19)
Cost of Stroke	79636		Kwatra 2013 (20)
Cost of ACS hospitalization	14108		Agrawal 2017 (19)
Cost of CABG	118000		PMJAY Rates (18)
Cost of Drugs in OMT			
Drug Category	**BPPI Prices (in INR)**	**Average Market Prices (in INR)**	**Source**
ACE Inhibitor	869.20	6536.93	Jan Aushadhi Rates(21)
Angiotensin Receptor Blocker	808.14	4148.43	
Statin	1424.12	16081.91	
β-Blocker	320.69	1064.69	
Calcium Channel Blocker	240.65	2092.18	

Aspirin (Antiplatelet)	327.74	654.21	
Clopidogrel (PCI specific Antiplatelet)	1184.37	5782.66	
Nitrates	319.66	619.57	
Cost of OMT alone	3471.52	25855.23	Calculated
Cost of OMT used with PCI	4655.89	31637.9	Calculated

Valuation of Health Benefits

Based on review of literature the primary endpoints identified in the management of SV-CAD were identified. These were both individual values, and as a composite value, collating death, NFMI 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. An assumption made in the model here was that as specific mortality for the peri-procedural phase was not available in case of SV-CAD patients, the cardiac mortality was used to substitute it. The basis for this was that as the mortality rates have been given as a composite for the overall follow-up period, it has been assumed that it is constant for the entire period.

As per Indian settings, the mean age of onset of CAD was also adjusted (51 years as opposed to 61 years in developed countries) in the model (22). 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 of 4.6 years of the reference study, for which the primary endpoints were estimated.

The transition probabilities were then generated from the available dataset (refer to table 4) 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 peri-procedural phase for 1 month. This means that the transition

probabilities of the peri-procedural phase were for a one time period of 1 month every 1 year cycle, for which separate probabilities were calculated as per follow-up phase events of the disease.

Table 4: Derived transition probabilities for the Markov Model.

Parameter	**1 year probability**	**1 month probability**	**Source**
OMT to PP MI		4.32336E-05	Boden 2007 (COURAGE Trial)(3)
OMT to PP Stroke		5.28549E-05	
OMT to Cardiac Death (PP)		0.000120344	
OMT to Cardiac Death	0.001443178		
OMT to Death	0.004059981		
PCI to PP MI		0.000174199	
PCI to PP Stroke		5.45711E-05	
PCI to Cardiac Death (PP)		0.000114288	
PCI to Cardiac Death	0.001370593		
PCI to Death	0.003710238		
DFS (PCI) to Spont MI	0.006495489		
DFS (OMT) to Spont MI	0.006937827		
DFS (PCI) to ACS Hosp	0.007776418		
DFS (OMT) to ACS Hosp	0.008536497		
DFS (PCI) to Stroke	0.001310861		

DFS (OMT) to Stroke	0.000807255		
Revascularization with PCI in PCI	0.013896723		
Revascularization with PCI in OMT	0.02080189		
Revascularization with CABG in PCI	0.004615392		
Revascularization with CABG in OMT	0.004703424		
OMT to PP MI	0.00051868		
OMT to PP Stroke	0.000634074		

The utility weights for all health states and events were taken from review of literature (refer table 5). Here, an assumption has been made that the values taken from literature hold true for our population – as local setting specific utility value sets were not available.

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

Time	Utility Weight	Source
Alive after PP (1 month) in PCI-OMT	0.92	Weintraub *et al.* 2008 (23)
Alive after 1 Year in PCI-OMT	0.93	
Alive after 2 Years in PCI-OMT	0.93	
Alive after 3 Years in PCI-OMT	0.92	
Alive after PP (1 month) in OMT alone	0.91	
Alive after 1 Year in OMT alone	0.93	

Alive after 2 Years in OMT alone	0.92	
Alive after 3 Years in OMT alone	0.9	
With MI (peri-procedural/follow-up)	0.7	Excel Trial (24)
With Stroke (peri-procedural/follow-up)	0.69	Golicki 2014 (25)

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 (26)(27).

ICER = $(C_1 – C_2) / (E_1 – E_2)$

Here, C_1 and C_2 are the costs associated to the treatment regimens of PCI + OMT and OMT alone respectively; 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 cost effectiveness here:

- 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 in treating patients with SV-CAD.

Net Benefit Analyses

Apart from generating ICER values, the net health benefit and net monetary benefits of PCI + OMT over 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." (28).

$$NHB = \text{incremental gain in QALYs} - (\text{incremental cost} / \text{CEA threshold})$$

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 (29). 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.

$$NMB = (\text{incremental gain in QALYs} \times \text{CEA threshold}) - \text{incremental cost}$$

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 (26)(27).

Sensitivity Analysis

Parameter uncertainty can lead to uncertainty in the results as the values assumed for various parameters will not be 100% accurate. The extent to which this uncertainty arises would depend on the robustness and correctness of the available data and the corresponding assumptions made during this study. For that estimation, both deterministic (one-way) and probabilistic sensitivity analyses were conducted so as to factor in the chances of parameter uncertainty and subsequent results of statistical insignificance.

For the sake of generalization of results the sensitivity will be done on the base case scenario with the BPPI prices of drugs for OMT.

4. Results:

The results are as summarized in the following tables (refer table 6, figures 4 & 5). Separate ICERs and Net Benefit values were calculated as per the prices of drugs in the Jan Aushadhi list.

Table 6: Results for the base case scenarios

Result (per patient)	With BPPI Price rates of OMT Drugs	With Average Market Price rates of OMT Drugs
Incremental QALYs (in years)	0.311	0.311
Incremental Cost (in INR)	66,286.6	75,565.5
ICER per QALY (in INR)	2,12,979.69	2,42,793.09
ICER : CEA Threshold*	1.4	1.6
NHB (in QALYs)	-0.125	-0.187
NMB (in INR)	-19,043.17	-28,322.12

*CEA Threshold = GDP per capita per person of India (INR 1,51,793.69 as of May 31st, 2020 as per World Bank)(30)

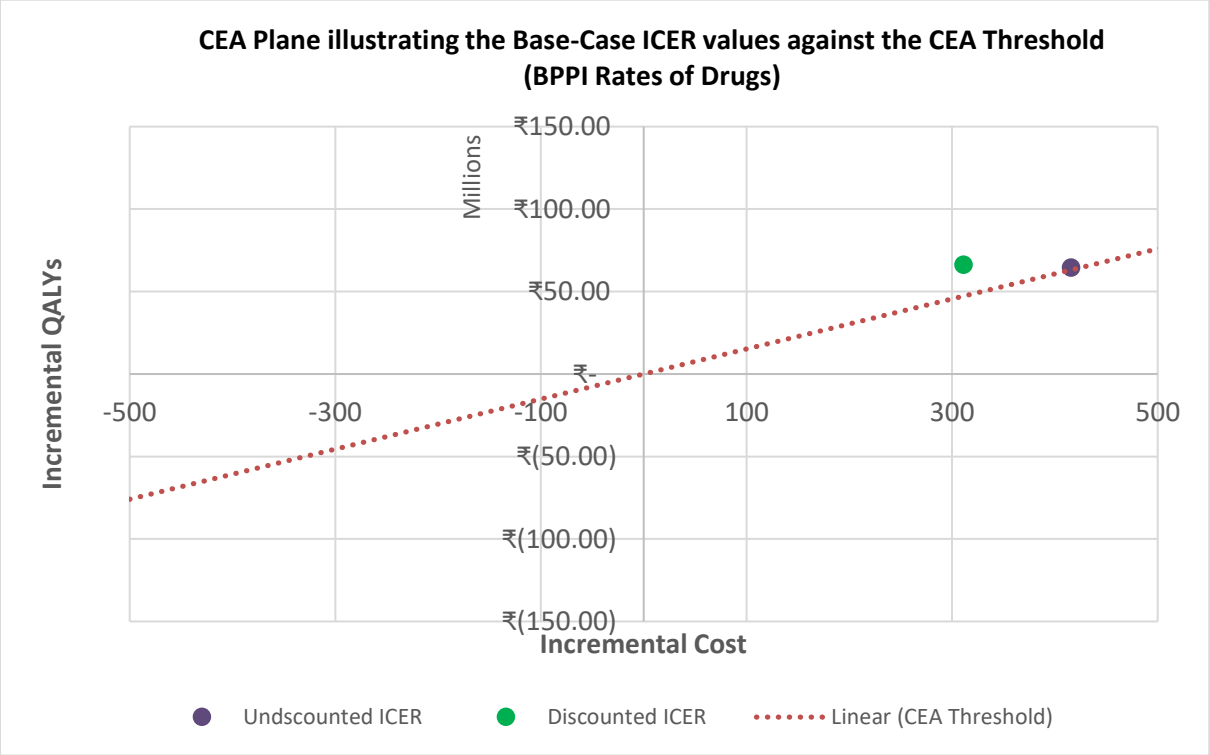

Figure 4: CEA Plane illustrating the Base-Case ICER values against the CEA Threshold (BPPI Rates of Drugs)

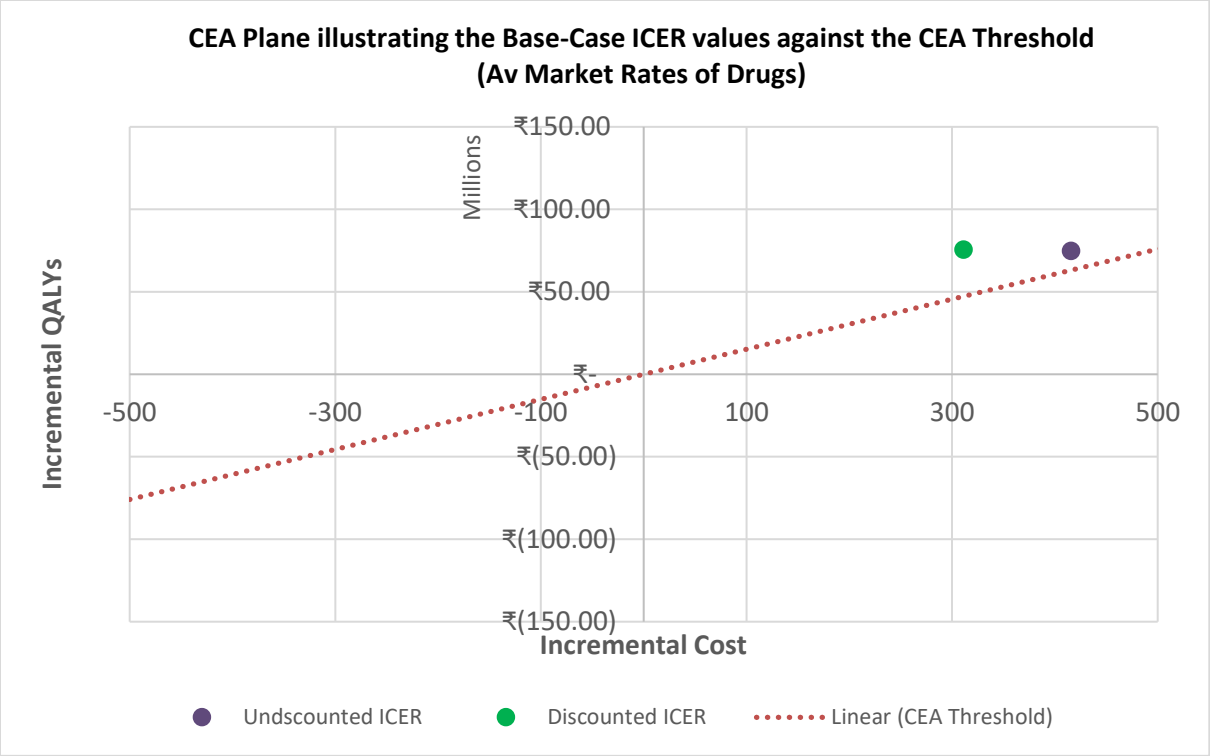

Figure 5: CEA Plane illustrating the Base-Case ICER values against the CEA Threshold (Average Market Prices of Drugs).

In terms of NHB also there is an overall loss of health benefits if we spend in providing treatment with PCI + OMT as opposed to simply treating patients with OMT alone. There is also a net monetary loss if an investment is made in PCI rather than OMT as per our findings (refer table 6).

As parameter uncertainty is also bound to occur, both deterministic (or one-way) sensitivity analysis (OWSA) and a probabilistic sensitivity analysis (PSA) were done. The results of these are as illustrated below (refer figure 6, 7 & 8). As per the OWSA results the parameter most likely to influence results was the rate or revascularization in the PCI arm followed by hospitalization for ACS in OMT and PCI + OMT arms respectively. The next 7 parameters are listed in the diagram in descending order of their tendency to have an effect on the ICER values (refer figure 6).

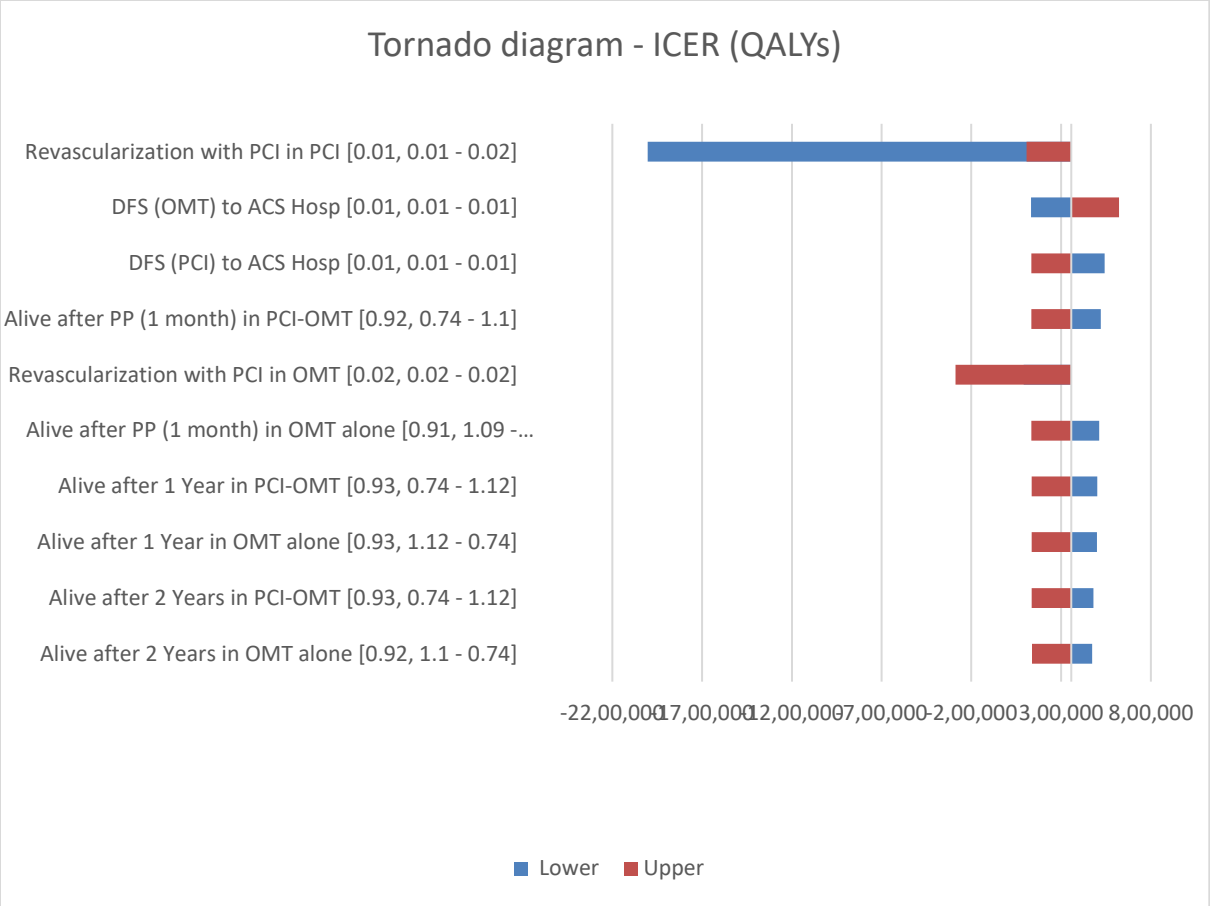

Figure 6: Tornado diagram illustrating the top 10 parameters likely to influence the ICER values based on changes in independent values of the parameters

Coming to the results of the PSA the cost-effectiveness cloud and the cost-effectiveness acceptability curve are as follows (refer figures 7 & 8). Overall, only 48% of the total generated ICER iterations from the PSA fall in the cost-effective range as per our cost-effectiveness threshold (kept at one times the current GDP per capita per person of India). Almost 40% iterations show that the PCI + OMT therapy is dominated by OMT alone therapy while the rest require further evaluation as these values lie in the north east quadrant of the CE Cloud graph (refer figure 7). This further goes to show that the use of PCI + OMT is not something that can be recommended easily over OMT alone therapy, specifically for SV-CAD. Also, as seen with the CEAC (refer figure 8), even at a high willing-to-pay (WTP) threshold of INR 8,00,000, the use of PCI will have a maximum of 60% chances of being cost-effective.

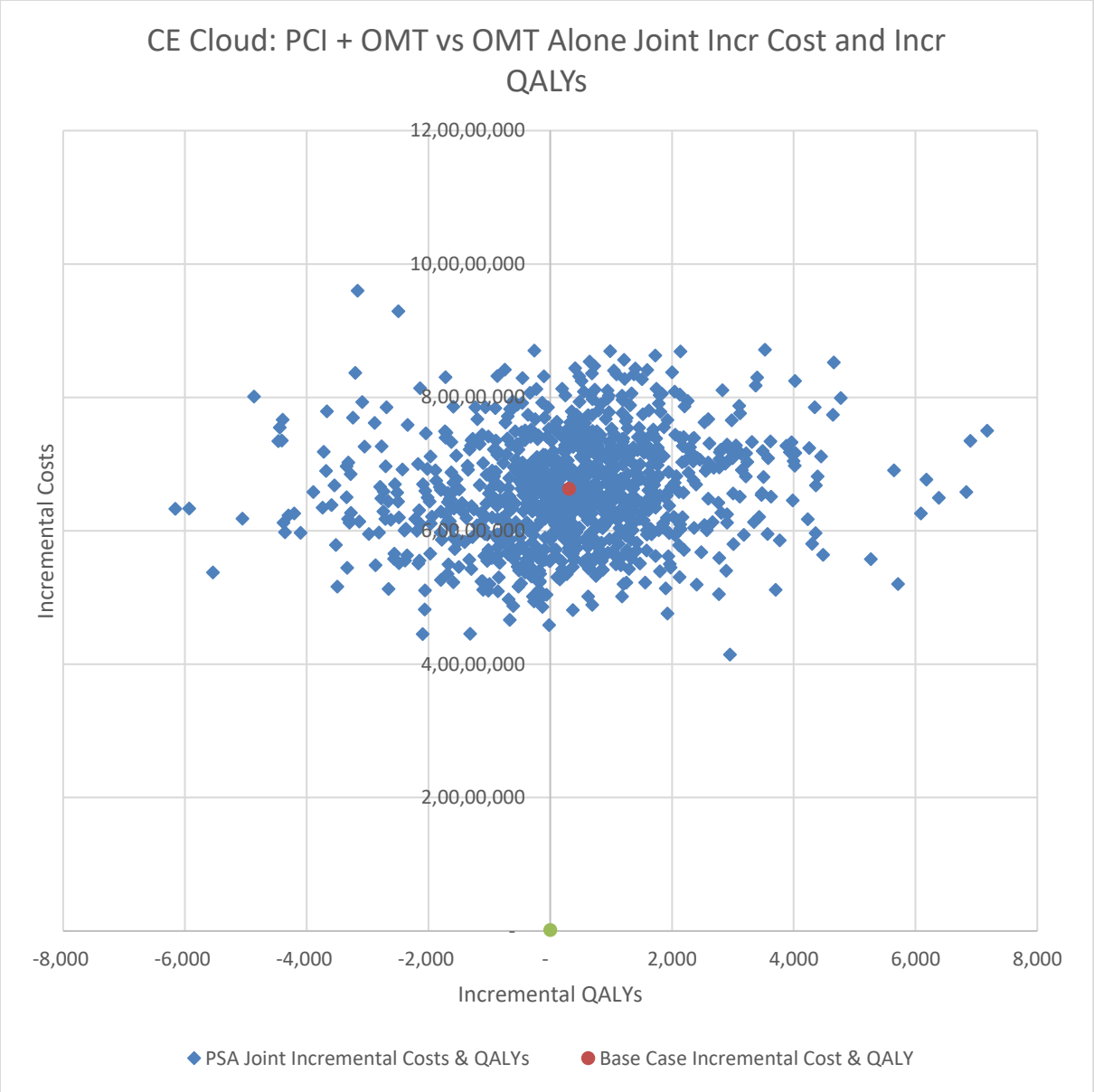

Figure 7: CE Cloud showing the spread of ICERs from the PSA simulations around the Base Case ICER value

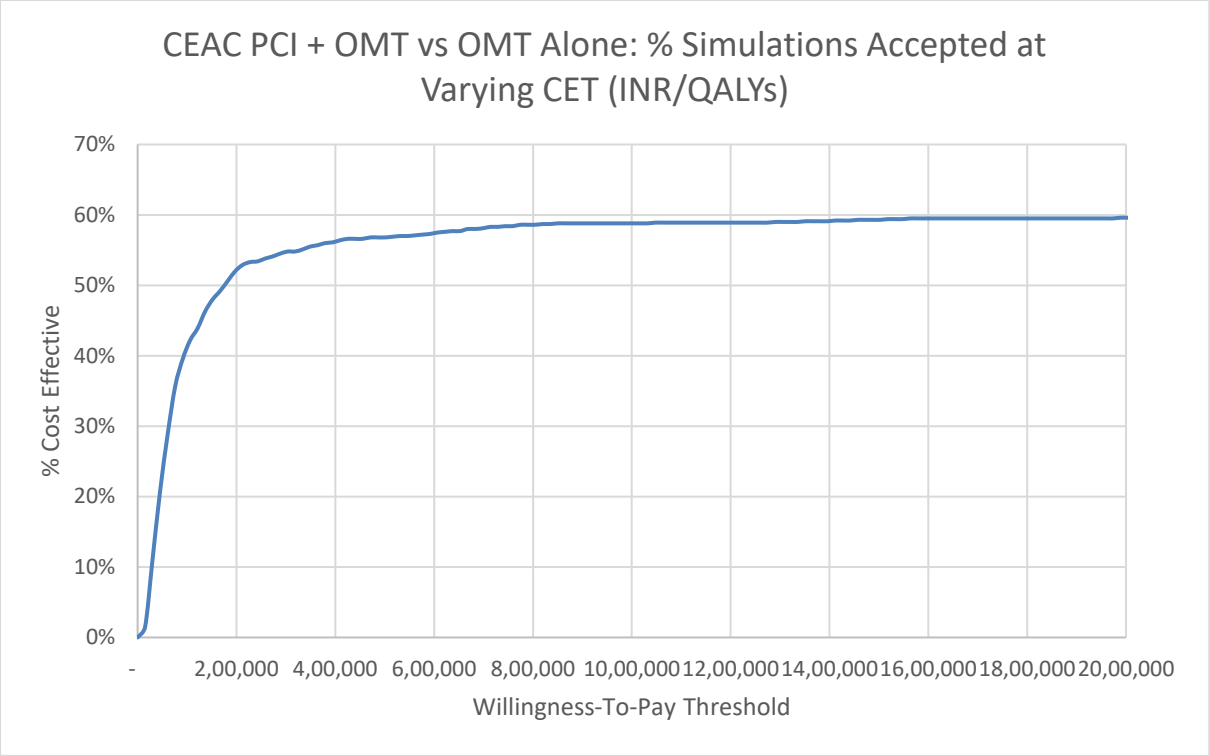

Figure 8: CEAC illustrating the relationship between the WTP threshold and the percent chances of the therapy (PCI + OMT in this case) being cost-effective

To sum up, as per our findings, the ICER is higher than the CEA threshold which means that using PCI + OMT to treat SV-CAD, as against those treated with OMT alone, is not a cost-effective strategy in India.

Discussion:

In this economic evaluation of PCI with OMT vs. OMT only patient with single vessel coronary artery disease, used a comprehensive, state transition model, concluded that the strategy of PCI with OMT was not found be cost-effective then the OMT alone. The primary results from COURAGE trail demonstrated that initial management strategy in patients with stable coronary artery disease, PCI did not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy, there was no significant difference between the PCI and medical therapy groups in death or myocardial infarction (3). The results from a meta-analysis of 12 included RCTs showed that in patients with stable coronary artery disease, PCI, as compared with OMT did not reduce the risk of mortality, cardiovascular death, nonfatal myocardial infarction, or revascularization, however PCI provided a greater angina relief compared with OMT alone (11).

The present study focused on the effectiveness of clinical outcome with involvement of single vessel coronary artery disease, it has been found that there is not much difference in PCI+OMT and OMT alone, however, in a Long-term survival analysis of patients with stable ischemic heart disease was showed that the number of coronary arteries diseased predicted survival (HR, 1.25; 95% CI, 1.09–1.43), Percutaneous coronary intervention did not offer a survival advantage over optimal medical therapy (HR, 0.95; 95% CI, 0.77–1.16) and there was no interaction between therapeutic strategy and number of coronary arteries diseased or severity of ischemia. In fully adjusted models, the number of coronary arteries diseased was not associated with increased mortality (31).

However in this study the quality of life was found a marked improvement over a period of time in both the groups but in PCI group, showed better quality of life as compare to the medical therapy group. the finding from other studies also supports these findings (12) (32), the results from another study was observed variability in Seattle Angina Questionnaire scores 1 year after randomization. Adding PCI conferred a greater mean improvement in Seattle Angina Questionnaire scores that were not affected by patient characteristics. The proportion of patients free of angina or having very good/excellent physical limitation or quality of life at 1 year was 57%, 58%, 66% with PCI+OMT and 50%, 55%, 59% with OMT alone group, respectively. However, other characteristics, such as baseline symptoms, age, diabetes mellitus, and the magnitude of

myocardium subtended by narrowed coronary arteries were as, or more, important than revascularization in predicting symptoms (32).

The present economic analysis study showed that the cost of PCI plus optimal medical therapy was more expensive than cost of optimal medical therapy alone, almost entirely because of the initial cost of the PCI procedure as there is not much difference in the OMT drugs used to given to the patients underwent for the PCI procedure. The results from a study supports the cost difference between the interventions, as a cost analysis study from France analyzed the cost of all interventions for stable coronary artery disease, which was found Euro 1567 with OMT, Euro 5908 with PCI-BMS, Euro 6623 with PCI-DES and Euro 16,612 with CABG (33).

In this study the cost effectiveness of PCI with OMT was not found cost effective then OMT alone intervention for the treatment of patients with single vessel coronary artery. The cost-effectiveness of revascularization compared with medical therapy for coronary artery disease has been studied previously. Of the previous full economic analyses comparing medical therapy to invasive therapy with stenting, most were randomized trials. The Trial of Invasive versus Medical Therapy in the Elderly (TIME) patents with involvement of 1, 2 and multi-vessel coronary arteries suggested that PCI was cost-effective then the OMT,(34) while the analysis from the COURAGE trial did not find the addition of PCI to optimal medical therapy to be a cost-effective initial Management strategy for symptomatic, chronic coronary artery disease.(23) The Bypass Angioplasty Revascularization 2 Diabetes (BARI2D) study, included only diabetic patients and concluded that PCI was not cost-effective (35).

Limitations

In the literature review very less studies was found which compares the PCI with OMT or without OMT and OMT alone, that was more challenging task to find out those articles which were only focused on patient with single vessel coronary artery diseases comparing the PCI with OMT or without OMT and OMT alone so data were extracted from the COURAGE trial, in which they reported their data according to number of arteries involved. Most of included articles in the present studies were related to the COURAGE trial in different year publication with different

objectives and post hoc analysis of the main courage, however most of the data were extracted from the main COURAGE trial.

Assumptions

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 4.6 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.
- Sub-groups like patients with diabetes have not been viewed separately due to a lack of data. The values have been assumed to be at a pooled level of general population (with or without comorbidities). As such, individual effect of certain comorbidities has not been analyzed separately.
- 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 evident from results of our study, PCI is not a cost-effective strategy for management of SV-CAD as compared to OMT. Even in terms of net benefits, investing in PCI results in a negative net health benefit for the patient meaning that OMT would have been the better option of treatment both clinically and cost-effectiveness wise.

Considering that just for a gain of 0.3 QALYs the incremental cost per patient is INR 66292, PCI does not seem to be an effective strategy for treatment. Thus, this study recommends that in cases of SV-CAD, the mainstay treatment be centred around the use of OMT therapy alone.

PCI may be considered as the second line of treatment in cases requiring revascularization as per clinical experts' opinion.

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