Economic Evaluation of Percutaneous Coronary Intervention as compared to Coronary Artery Bypass Grafting in Left Main Coronary Artery Disease

HTAIn Secretariat

Department of Health Research
Ministry of Health and Family Welfare
Government of India
New Delhi, 110001

CONTENTS

ABBREVIATIONS

CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
DALY	Disability-Adjusted Life Year
DHR	Department of Health Research
EQ5D	EuroQoL-Five Dimension
GOI	Government of India
HRQoL	Health Related- Quality of Life
HTAIn	Health Technology Assessment in India
ICER	Incremental Cost-Effectiveness Ratio
INR	Indian National Rupees
LMCAD	Left Main Coronary Artery Disease
LMICs	Low and Middle Income Countries
LY	Life Years
OMT	Optimal Medical Therapy
PCI	Percutaneous Coronary Intervention
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomized Control Trials
US$	United States Dollar

LIST OF FIGURES

LIST OF TABLES

Introduction

Cardiovascular diseases (CVDs) are one of the leading causes of mortality in India.[1] Among CVDs, coronary artery disease (CAD) is the major cause of cardiovascular mortality and morbidity globally, causing approximately 7 million deaths annually.[1,2]. World Health Organization (WHO) and Global Burden of Disease study declare increased prevalence of coronary heart disease in India, where it has increased from 1% to 9%-10% in urban populations and <1% to 4%-6% in rural populations in past several years.[3]

Population growth, aging, and a stable age-adjusted mortality rate has contributed to the increased prevalence in India and other low and middle income countries (LMICs). Moreover, the mortality rate due to CVDs in India is higher than the global average. Early age onset is one major contributing factor to the high CVD mortality in India. Statistics suggest around 23% of CVD deaths occur before the age of 70 years in western countries, whereas this number is as high as 52% in India.[1] Also, the comorbid conditions like diabetes, hypertension, renal failure etc. further contributes to the increased mortality. For e.g. in Indians, the mortality rate is 11% for non-diabetic patients and 21.4% for diabetic patients.[4]

Epidemiological transition from predominantly infectious disease conditions to non-communicable diseases has also contributed to the above facts. In addition, individuals from lower socioeconomic backgrounds frequently do not receive optimal therapy, leading to poorer outcomes. Hence, there is an immense need of development of strategies such as the formulation and effective implementation of evidence based policy, reinforcement of health systems, and

emphasis on prevention, early detection, and treatment of coronary artery and other cardiovascular diseases.[1]

Coronary Artery Disease (CAD) refers to the pathological narrowing of arteries that supply blood to heart muscles. Individuals with coronary artery disease have different phenotypic variations, which include variations in the number of affected vessels, location of lesions, and degree of vascular stenosis. Among these anatomic phenotype variants, blockage of Left Major (LM) coronary artery and Triple Vessel Disease (TVD), which refers to the blockage of left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) are more complex. Left main coronary artery disease (LMCAD) accounts for 3% to 10% of patients undergoing coronary angiography. It is the highest-risk lesion subset, and correlates with worse prognosis following heart attack, compared with non-LMCAD.[5]

At present, Coronary Artery Bypass Graft surgery (CABG) and Percutaneous Coronary Intervention (PCI) are commonly available treatment options for Left Main coronary artery Disease.[6] Although CABG is considered as a gold standard treatment for left main coronary artery disease (CAD), PCI has also gained attention in recent years as an alternative approach for the treatment of these coronary artery diseases.[7] However, the best approach for the treatment of stable patients of these complex coronary artery diseases is still a subject of debate.

Contradicting results of recent randomized control trial studies have brought up the question of which is the optimal strategy in revascularization of patients with left main coronary artery disease (LMCAD). On one hand, the EXCEL trial[8] of 1901 patients, who were randomly assigned for CABG and PCI, suggest that the rate of composite outcome of death, stroke, or

myocardial infarction at 5 years is almost similar in both PCI and CABG and found PCI to be non-inferior than CABG. This trial reports that average number of stents used in LMCAD is 2.4, which have economic implications as well. NOBLE trial[9] on the other hand, reported that PCI was associated with an inferior clinical outcome when compared to CABG at 5 years" Many of the trials also use contemporary treatment approach and obsolete stent technology for e.g. in case of revascularization with PCI, further questioning the use of the extrapolation of such results in future studies. Thorough evaluation is thus required for assessing suitability of stenting versus grafting and overall surgical risk before recommendation to patients. Moreover, various national registries like CREATE, Kerala ACS, DEMAT-11 and SPREAD-12 etc. have also reported low use of evidence-based treatment for management of coronary artery disease in the country in past few years.[10–12] Hence, in the present study we have evaluated the economic and health outcomes of CABG vs PCI for left main coronary artery disease over the lifetime of a patient in Indian healthcare settings.

Aim

To conduct a full economic evaluation of Percutaneous Coronary Intervention in patients with stable Left Major Coronary Artery Disease as compared to Coronary Artery Bypass Graft in Indian healthcare setting.

Objectives

1. To ascertain the Incremental Cost-Effectiveness Ratio (ICER) of Percutaneous Coronary Intervention as compared to Coronary Artery Bypass Graft for patients with stable Left Major Coronary Artery Disease in Indian healthcare setting.
2. To ascertain the cost of treatment (over lifetime) in Percutaneous Coronary Intervention and Coronary Artery Bypass Graft for patients with stable Left Major Coronary Artery Disease in Indian healthcare setting.
3. To ascertain Health Related Quality of Life in Percutaneous Coronary Intervention and Coronary Artery Bypass Graft for patients with stable Left major Coronary Artery Disease in Indian healthcare setting.

PICOT:

Population: Patients diagnosed with Left Main Coronary Artery Disease.

Intervention: Percutaneous Coronary Intervention (PCI)

Comparator: Coronary Artery Bypass Grafting (CABG)

Outcome:

- Overall cost of the treatment in intervention group and comparator group.
- Life Years gained with PCI in comparison to CABG among LMCAD patients.
- Quality Adjusted Life Years gained in intervention and comparison group.
- Incremental Cost-Effectiveness Ratio (ICER) of PCI as compared to CABG in patients with LMCAD

Time horizon

- One Year
- Five Year
- Ten Year
- Twenty Year (corresponding to the lifetime horizon)

As, average age of patient in India, reporting for PCI or CABG for LMCAD is 58 years; we run the Markov trace for twenty years and reported costs and overall health gains for each interval of one year, five year, ten years and twenty years' time horizon for the comparison. Incremental Cost-Effectiveness Ration (ICER) also was computed for all these time points.

Perspective

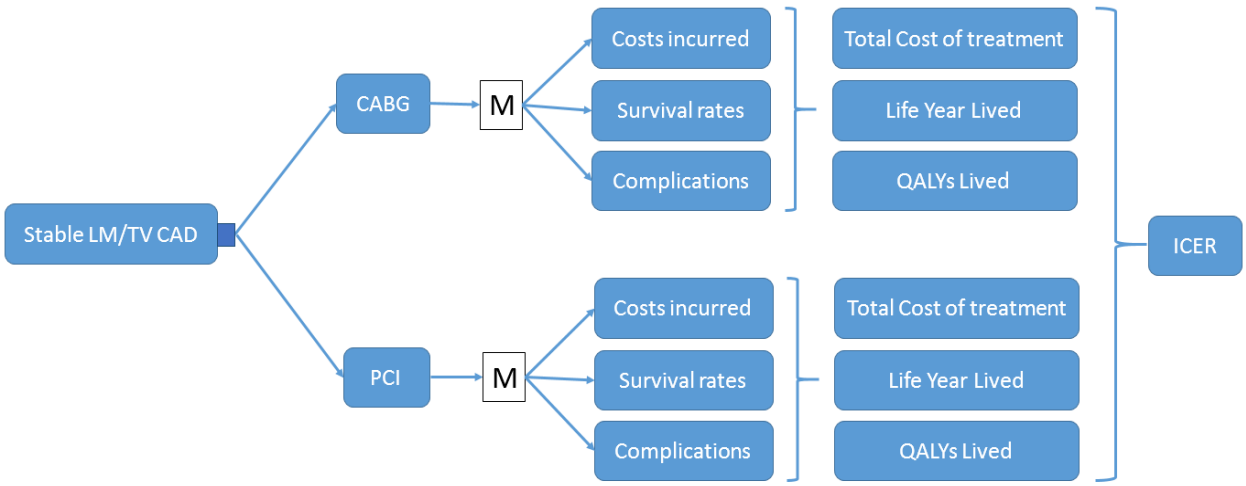
- Abridged Societal Perspective

  (Including health system's cost as well as patient's out of pocket expenditure)

Methodology:

This study is a model based estimation of incremental costs and QALYs gained in CABG group and percutaneous coronary intervention group in LMCAD patients. We used two separate Markov models to estimate the overall costs and health outcome for the comparison. Data pertaining to the costs, clinical effectiveness and Quality of Life was taken from the secondary literature. No primary data collection was done for the inputs parameters of this study. All future costs and clinical outcomes were discounted at the annual rate of 3 percent in accordance to the HTAIn Manual. Two scenario were run separately for patients of stable LM with or without TVD were in first (intervention) scenario, all patients were initially re-vascularised with PCI and its subsequent health outcome were estimated using dynamic transition model. This dynamic transition model included all the initial and subsequent costs and health outcome giving results in terms of total cost and quality adjusted life years gained. A broad conceptual framework for this economic evaluation is given below in figure 1.

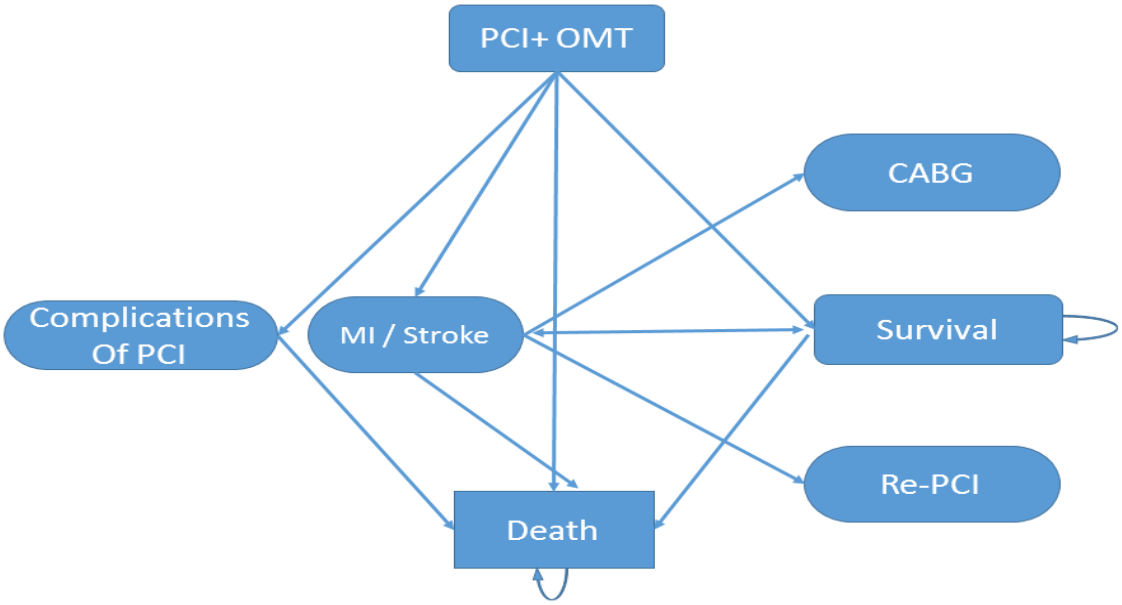
Figure 1. Conceptual framework for the economic evaluation for PCI versus CABG



Estimation of Costs and Health Outcomes in Scenario I (PCI+OMT)

A dynamic transition model was built using the course of disease and stages/events in the life history after PCI as reported in the literature for the patient of stable LM CAD. This model covered both the peri-procedural and post procedural events and stages after PCI. Peri-procedural complications and events as reported in the literature by most of the trials on LM CAD are Myocardial Infarction, Stroke, Access Site Infection, and Peri-Procedural Death. In the subsequent years, post procedural events like post-procedural Myocardial Infarction, Stroke, need for repeat revascularization through PCI or CABG as reported in the literature was used during the analysis. As suggested by literature and clinical opinion, follow up drugs and their cost was also considered in the evaluation. Drugs included in the follow up period after PCI were Aspirin, Atorvastatin, Atenolol, Clopidogrel, Enalapril , Nitrates, and Amlodipine. Their cost was taken from the Jan Aushadhi Rate List. Markov model with its health states/events used in PCI state is as shown in figure 2.

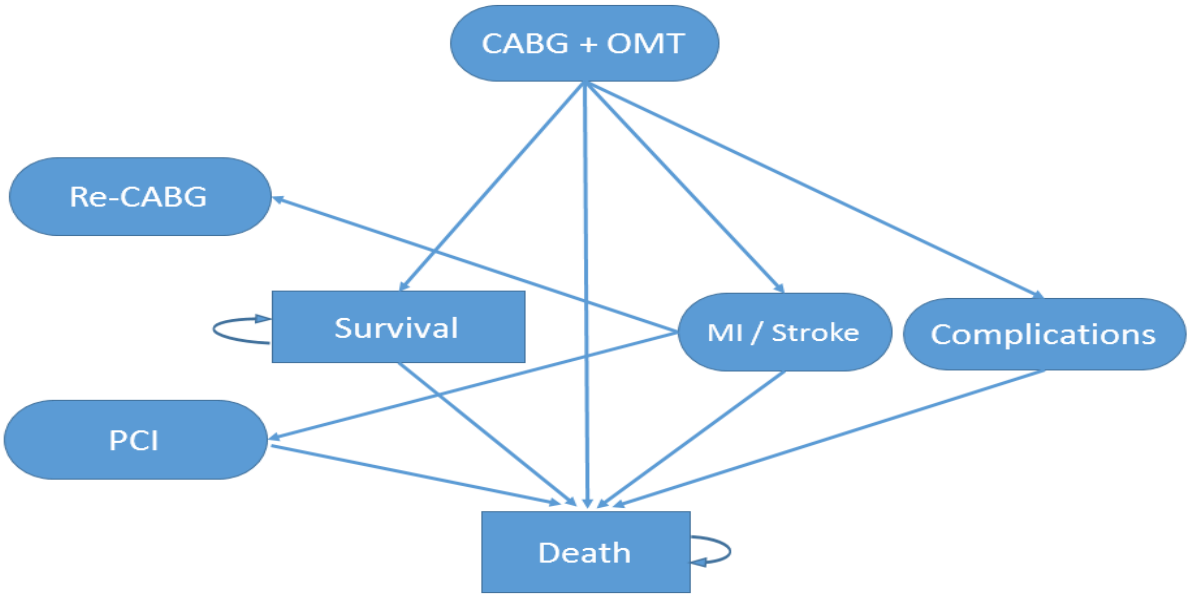
Figure 2. Markov Model used for the PCI Scenario



Estimation of Costs and Health Outcomes in Scenario II (CABG+OMT)

Similarly, a dynamic transition model was built using the course of disease and stages/events in the life history after CABG as reported in the literature for the patient of stable LM CAD. This model covered both the peri-procedural and post procedural events and stages after CABG. Peri-procedural complications and events as reported in the literature by most of the trials on LM CAD are Myocardial Infarction, Stroke, Access Site Infection, Sternum Infection and Peri-Procedural Death. In the subsequent years, post procedural events like post-procedural Myocardial Infarction, Stroke, need for repeat revascularization through PCI or CABG as reported in the literature was used during the analysis. As suggested by literature and clinical opinion, follow up drugs and their cost was also considered in the evaluation. Drugs included in the follow up period after CABG were Aspirin, Atorvastatin, Atenolol, Enalapril. Nitrates and Amlodipine. Their cost was taken from the Jan Aushadhi Rate List. Markov model with its health states/events used in CABG state is as shown in figure 3.

Figure 3. Markov Model used for the CABG Scenario



Literature review on Clinical Effectiveness

A target Literature Review (TLR) was conducted in PubMed to retrieve studies published on CABG and PCI in LMCAD patients using the following search strategy:

((((Coronary artery Bypass Surgery [Title/Abstract]) OR (CABG [Title/Abstract])) AND (Per cutaneous Intervention [Title/Abstract])) OR (PCI [Title/Abstract])) AND (Left main coronary artery Disease [Title/Abstract])

Titles and abstracts were screened and full text articles were downloaded which are eligible for the study, according to set inclusion and exclusion criteria. Only articles that are published on English are considered in the study. Published literature that include patients with Stable Left main coronary artery disease (LMCAD) only were considered for analysis. Published literature that include patients with Stable Left main coronary artery disease (LMCAD) are considered for analysis. We reviewed various articles such as Randomized Control Trails, Meta-analysis and systematic review and meta-analysis. Most important studies include NOBEL trail among unprotected left main stenosis, EXCEL trial in LMCAD patients and SYNTAX TRIAL in LMCAD.

Table 1: Summary table of literature review on clinical effectiveness

Author, Year	**Disease under study**	**Study design, (sample size)**	**Trail Name**	**Intervention and Comparator**	**Follow up period**	**Study Conclusion**
Ahmad Y et al.,	Left main coronary	systematic review and	-	PCI and CABG	10 years (Mean	This study concluded that

2020[13]	artery disease	meta-analysis (4612)			avg. follow up is 67.1 months)	long term mortality remain same in after PCI with DES compared with CABG in LMCAD patients
Park DW et al., 2020[14]	Unprotected left main coronary artery disease	Prospective, open-label, randomized trial (600)	PRECOMBAT trial	PCI and CABG	10 years	This study concluded that there was no significant difference in the occurrence of MACCE among LMCAD patients treated with PCI and CABG after 10 years follow up period.
Holm NR et	Left main coronary	Prospective, randomised,	NOBLE Trail	PCI and CABG	5 years	Mortality was similar in both

al., 2019[9]	artery disease	open-label, multi center, non-inferiority trial. (1,184)				the groups however, higher rates of non-procedural MI and repeat revascularisation was reported in PCI group. When compared to CABG at 5 years, PCI was associated with an inferior clinical outcome.
Stone G. W. et al., 2019[8]	Left main coronary artery disease.	International, open label, multi center, randomized trial. (1,905)	EXCEL Trail	PCI and CABG	5 years	Study concluded that the rate of composite outcome of death, stroke, or myocardial infarction at 5 years is similar

						in both PCI and CABG and found no significant difference.
Thuijs DJFM et al., 2019[15]	Patients with de-novo three-vessel and left main coronary artery disease.	Multicentric, Randomized Control Trail. (1,800)	SYNTAX Trial	PCI and CABG	10 years	Study concluded that there was no significant difference between first-generation paclitaxel-eluting stents and CABG in terms of all-cause mortality at 10 years.
Boudriot E et al., 2011[16]	unprotected left main coronary artery disease	multicenter, randomized trail (201)	-	PCI and CABG	1 Year	With respective to MACCE, it was concluded that PCI is inferior to

	with or without Multiple vessel disease.					CABG among unprotected LM stenosis patients. It is mainly due to higher repeat revascularization rates, however, death and MI rates are non – inferior in PCI group at lower perioperative morbidity.

Literature review on Quality of Life data

Sources and Selection criteria

A targeted literature review (TLR) was performed using research articles from PubMed and Google Scholar platforms. Studies published from January 1, 2000, till present were considered. 23 articles were selected on the basis of following search terms:

((((Coronary artery Bypass Surgery [Title/Abstract]) OR (CABG [Title/Abstract])) AND (Per cutaneous Intervention [Title/Abstract])) OR (PCI [Title/Abstract])) AND (Left main coronary artery Disease [Title/Abstract]) AND ((Quality of Life [Title /Abstract]) OR (QoL[Title/Abstract]))

These literature search results were further selected on the basis of following Inclusion and Exclusion criteria. Selection was based on reported follow up time along with primary and secondary clinical endpoints. Preference was given to the recent metaanalysis and randomized control trial studies with long term outcomes.

Inclusion Criteria

Population: Published literature that include patients with Stable Left main coronary artery disease (LMCAD) were considered for analysis.

Interventions: Articles reporting on Quality of life after PCI with Drug Eluting Stents (DES) as compared to CABG were included in analysis.

Comparators: Article reporting Quality of life after CABG in patients with LMCAD were considered.

Outcomes: Health outcomes measured in either EQ-5D scores or SF-36 questionnaire along with hazard ratios were considered.

Study Design: Both randomized control trials (RCTs) and metaanalysis studies were included for comparing Percutaneous Coronary Intervention (PCI) with coronary artery bypass grafting (CABG) as an optimal strategy treatment of Left Main coronary artery disease (LM).

Exclusion Criteria

- Articles with acute coronary artery disease symptoms or studies performed on patients with triple vessel (TVD) or multi-vessel disease (MVD) or any other heart disease apart from Left Main Coronary Artery Disease i.e. non- LMCAD were excluded.
- LM patients with other comorbidities were excluded.
- Articles in languages other than English were excluded.
- Conference abstracts, letters to the editor, qualitative studies, reviews, case series, case reports, commentaries and interpretation of trials were also excluded.

Table 2: Summary table of literature review on Quality of Life data

S.No	Author/Journal/ Year	Study Design	Clinical Endpoints	Follow up period	Conclusion
1	Ahmad et al/ European Heart Journal (2020)[13]	A metanalysis of RCTs	**Primary:** All-cause mortality; **Secondary**: Cardiac death,	67.1 months weighted average	No significant difference in PCI vs CABG was obtained in

			MI, Stroke,Unplanned revascularization		all primary and secondary clinical endpoints except that PCI results in increased risk of unplanned revascularization
2	Golicki et al/ Quality of Life Research(2014)[17]	An observational longitudinal cohort study of patients with stroke.	-	1 week and 4 months post-stroke	The EQ-5D-5L index, based on the crosswalk value set, seems to be appropriately responsive in patients with stroke, 4 months after disease onset. As far as EQ-5D-5L index is scored according to crosswalk

					approach, the EQ-5D-3L index appears to be more responsive in stroke population.
3	Baron et al /JAAC(2017)EXCEL[18]	RCT of 1905 patients with LMCAD whom 1,788 participated in the QoL substudy (a prospective (QoL) substudy performed alongside the EXCEL trial)	QoLwas assessed using Seattle Angina Questionnaire, the 12-ItemShort Form Health Survey, the Rose Dyspnea Scale, the Patient Health Questionnaire-8, and the EQ-5D	1, 12 and 36 months	Both PCI and CABG result in similar QoL improvement through 36 months, although a greater early benefit is seen with PCI.
4	Lee et al/ Journal of American	Meta-analysis of	**Primary:** MI at the longest	4.5 years weighted	Patients treated with CABG had

	Cardiology(2019)[19]	RCTs for Risk of MI after CABG vs after PCI with mv or LMCAD	available follow-up in the intention-to-treat population.	average	a significantly lower risk of MI than those with PCI. The magnitude of risk reduction was similar across patients with multivessel disease or LMCAD
5	Andrade et al/ Arq Bras Cardiol. 2019[20]	Stent versus CABG: systematic review with meta-analysis of PCI using Stents versus CABG in randomized controlled trials	All case-mortality, stroke, AMI and new revascularization. Mortality was divided into early mortality, mortality at one year and late mortality		Compared with CABG, PCI using Stents showed lower 30 days mortality, higher late mortality and lower incidence of stroke. Diabetes and a high SYNTAX were

					the subgroups that influenced more adversely the results of PCI
6	Gallow et al/ The Journal of Thoracic and Cardiovascular Surgery 2020[21]	Meta-analysis study with 5 RCTs of 4595 patients	All cause Mortality, Stroke , MI, Repeat Revascularization	30 day, 1 yr , 5 year	No difference in 5-years mortality PCI is associated with a higher risk for MI and repeat revascularization compared to CABG for LM disease at 5 yr PCI was associated with lower periprocedural MI at index procedure but higher non

					periprocedural MI at 5 years. Stroke was lower in the PCI at 30-day and 1-year follow-up but no difference was observed at 5 years.

Estimation of Costs

To take the representative cost of doing PCI and CABG in India, cost parameters used in the model were taken from PMJAY Health Benefits Packages list, which are applicable to both private as well as public healthcare facilities. Costs of other complications and health events also were taken either from PMJAY Health Benefits Package list or from the published secondary literature. Cost of medicines prescribed to PCI and CABG group were also listed according to the literature and clinical expertise and then Jan Aushadhi rates were applied to find the overall follow-up cost. Any incremental cost of peri-procedural Myocardial Infarction is not added in this analysis.

Input Parameters Used

Following input parameters were used to feed the model for the Economic Evaluation:

Table 3: Input parameters of PCI and CABG used for Economic Evaluation

INPUT PARAMETER	CABG	PCI	SOURCE
Annual Probabilities of Various Clinical Events			
Peri-procedural MI	0.05978903	0.038277697	13
Reopening for Bleeding	0.038106317	0.001687763	13
Surgery for Sternum Infection	0.005054749	0	13
Surgery for Access site complication	0.006733981	0.003372678	13
All-Cause Mortality in 1st Year	0.032810789	0.031974564	13
Cardiovascular Mortality in 1st Year	0.025285084	0.028046441	13
Non Procedural MI in 1st year	0.041146335	0.04139462	13
Repeat Vascularization 1st year	0.044975617	0.082164284	13
Stroke in 1st year	0.017452945	0.007086584	13
All-Cause Mortality in Subsequent Years	0.019024713	0.021299256	13
Cardiovascular Mortality in Subsequent Years	0.009783416	0.010053807	13
Non Procedural MI in Subsequent Years	0.010864537	0.01553577	13
Revascularization with PCI in Subsequent Years	0.003965619	0.00676505	13
Revascularization with CABG in Subsequent Year	0.015862476	0.027060199	13
Stroke in Subsequent Years	0.00671382	0.005175455	13
Cost Parameters used in the Analysis			
One time Cost of Procedure (PCI/CABG)	118000	113032*	PMJAY HBPs
Annual Cost of OMT	3693	4655	Jan Aushadhi
Discount Rate (Annual)	0.03		HTAIn Manual
Cost of MI Management	61650		22

Cost of Reopening for Bleeding	10000	PMJAY HBPs
Cost for sternum infection Management	20000	PMJAY HBPs
Cost of access site infection Management	1800	PMJAY HBPs
Cost of Stroke	80612	23
QoL Stroke	0.69	17
QoL MI	0.70	18
QoL post PCI	0.876	18
QoL post CABG	0.876	18

Estimation of ICER

QALYs and cost are calculated based on the proportion of cohort in the each respective health state. QALY of the intervention group and comparator group are calculated from the utility and life years. Incremental cost and incremental QALY is calculated from the difference between the cost and QALY of intervention and comparator. ICER is the ratio of incremental cost and incremental QALY which represents the cost-effectiveness of the intervention to gaining one QALY. Discount of 3% was incorporated in the total cost and QALY and discounted ICER was also calculated.

Results

As described in the methodology section, the analysis was done for both scenarios with four different time horizons. In the first case, when estimations were done using one year time horizon, taking data about peri-procedural and post procedural health outcomes from the meta-analysis results directly. These results are favoring the PCI as there is almost same mortality and significantly lesser cost than CABG. One year time horizon results per patient are summarized in the table below:

Table 4: Total cost of PCI versus CABG for one year time horizon

1 YEAR TIME HORIZON	PCI	CABG
Cost OMT	4506	3572
Cost CABG	0	123307
Cost PCI	122319	0
Cost MI	2552	2537
Cost Stroke	571	1407
Cost Re-opening for bleeding	18	398
Cost Surgery for Sternum Infection	0	106
Cost Surgery for access complication	6	13
Total Cost	129973	131339

When model is run for a longer period, especially for the twenty years period, results actually change. This change is primarily because of more number of repeat revascularizations required in PCI scenario. Here, the incremental QALYs lived are more in the CABG scenario and as depicted in the table below, incremental cost is negative i.e. lesser cost per patient is incurred in CABG than in PCI for the management of LMCAD in the longer run.

Table 5: Cost estimates of PCI versus CABG for a life time horizon

LIFE TIME HORIZON	PCI	CABG
Cost OMT	74837	60557
Cost CABG	52452	149844
Cost PCI	125593	7626
Cost MI	35432	11200
Cost Stroke	6707	8875
Cost Re-opening for bleeding	171	104
Cost Surgery for Sternum Infection	45	27
Cost Surgery for access complication	6	4
Total Cost	295243	238236
Discounted Cost	255295	211869

When comparing the costs and Quality Adjusted Life Years gained, over the first year; ICER of PCI versus CABG is -5,22,023, which is primarily due to more upfront cost of CABG as compared to PCI and comparatively lesser peri-procedural complications in PCI than CABG.

Table 6: ICER of PCI versus CABG over one year time horizon

Cost with PCI	129973	**Incremental Cost**	**Incremental QALYs**	**ICER**
Cost with CABG	131339			
QALYs with PCI	0.839	-1366	0.002617	**-5,22,023**
QALYs with CABG	0.837			

In the five years' time horizon, PCI yields less health outcome in terms of QALYs lived and has the incremental cost of INR 9464. As shown in the table below, PCI spends incremental cost of 283196 INR per Quality Adjusted Life Year lost as compared to CABG. Hence, at five years' time horizon, CABG dominates over PCI.

Table 7: ICER of PCI versus CABG over five year time horizon

Cost with PCI	160083	**Incremental Cost**	**Incremental QALYs**	**ICER**
Cost with CABG	150619			
QALYs with PCI	3.857	9464	-0.033419	**-2,83,196**
QALYs with CABG	3.891			

At ten years' time horizon, there is incremental cost of 26742 INR with PCI over CABG and QALYs lived with CABG are more over PCI. Here, PCI spends incremental cost of 249373 INR per Quality Adjusted Life Year lost. Hence, at ten year also, CABG dominates as PCI is not a cost-effective strategy as compared to CABG over ten years' time horizon.

Table 8: ICER of PCI versus CABG over ten year time horizon

Cost with PCI	202948	**Incremental Cost**	**Incremental QALYs**	**ICER**
Cost with CABG	176206			
QALYs with PCI	6.827	26742	-0.107237	**-2,49,373**
QALYs with CABG	6.934			

At 20 years, the incremental cost in in PCI as compared to CABG is 43426 and QALY lost in PCI scenario as compared to CABG is 0.2486. By calculating ICER, PCI spends incremental 174674 INR per QALY lost as compared to CABG. So, at twenty years' time horizon, which also corresponds to the life time horizon, PCI is the cost-ineffective strategy as compared to CABG as depicted in the table below.

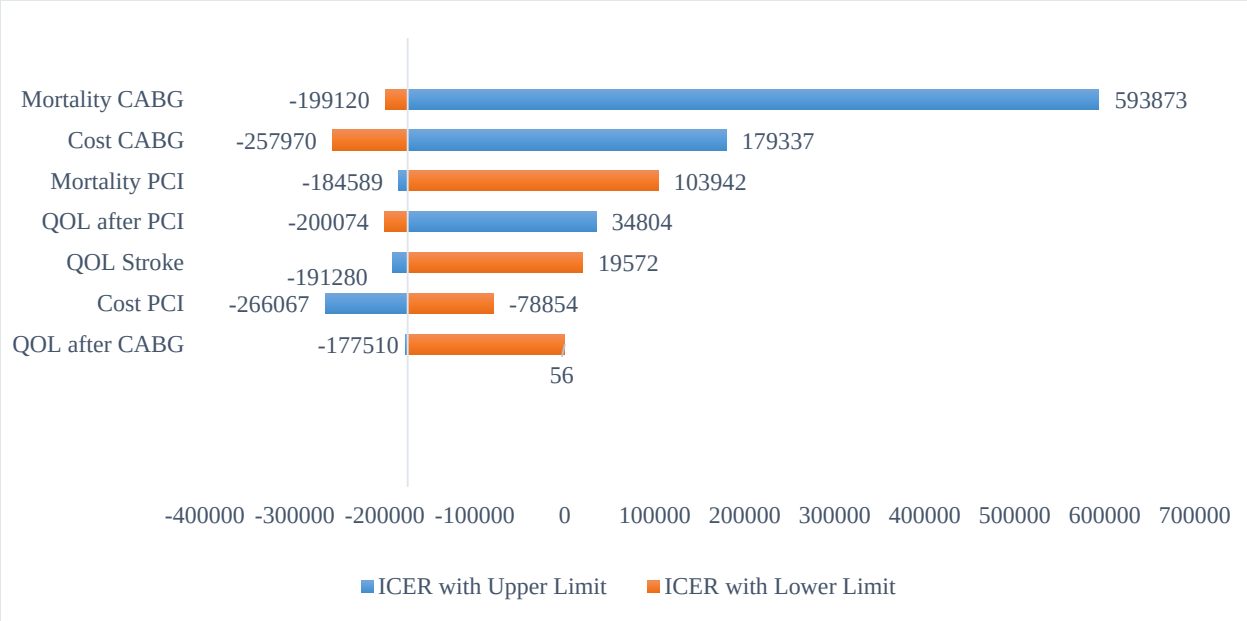
Table 9: ICER of PCI versus CABG over twenty year time horizon

Cost with PCI	255295	**Incremental Cost**	**Incremental QALYs**	**ICER**
Cost with CABG	211869			
QALYs with PCI	10.927	43426	-0.248610	-1,74,674
QALYs with CABG	11.176			

One Way Sensitivity Analysis

In such model based economic evaluations, there is always a degree of uncertainty due to various factors such as patient heterogeneity, methodological structural model and parameter uncertainties which would influence cost-effectiveness outcome. We have tried to address the variation in the input parameters from some different country by doing One Way Sensitivity Analysis. This OWSA was conducted by varying key parameters by twenty percent of their base value; except for mortality of PCI and CABG follow-up, which was varied to the upper and lower bound of studies included in the meta-analysis. This sensitivity analysis was done for lifetime horizon (twenty year) scenario of this economic model.

Figure 4. One Way Sensitivity Analysis results for lifetime horizon



Probabilistic Sensitivity Analysis

We also did a probabilistic sensitivity analysis to address the uncertainty in the input parameters by looking into joint effect of this variance on cost-effectiveness results. With help of Visual Basics, we ran 1000 monte carlo simulations in MS Excel. Every time, random set of parameters based on their upper and lower bound were fed into the model to generate the incremental cost and incremental quality adjusted life years, which were then plotted on a graph against base case results. Out of these simulations, 420 results fall into North-West quadrant, which means to be dominated i.e. not cost effective due to higher incremental cost but lesser quality adjusted life-years lived. Out of 1000, 14 results fall in South-East quadrant signifying less cost and more quality adjusted life years lived with PCI, proving it to be cost effective than CABG. Rest 566 simulation results fall in either North-East or South-West quadrant, which further needs comparison with cost-effectiveness threshold of the region. Out of these 566 simulations, when compared with cost-effectiveness threshold for India (which is one times per capita GDP i.e. 1,50,000) only 285 simulations fall in cost-effective category.

Based on the results of this probabilistic sensitivity analysis, considering effect joint variation in input parameters of the model; CABG is cost-effective than PCI in 715 simulations out of 1000. It conveys that PSA results favor CABG in 71.5% of cases and PCI is favored only in 28.5% of cases when compared to CABG in LMCAD.

Figure 5. Results of 1000 PSA iterations of Incremental Cost (INR) and QALYs with PCI as compared to CABG

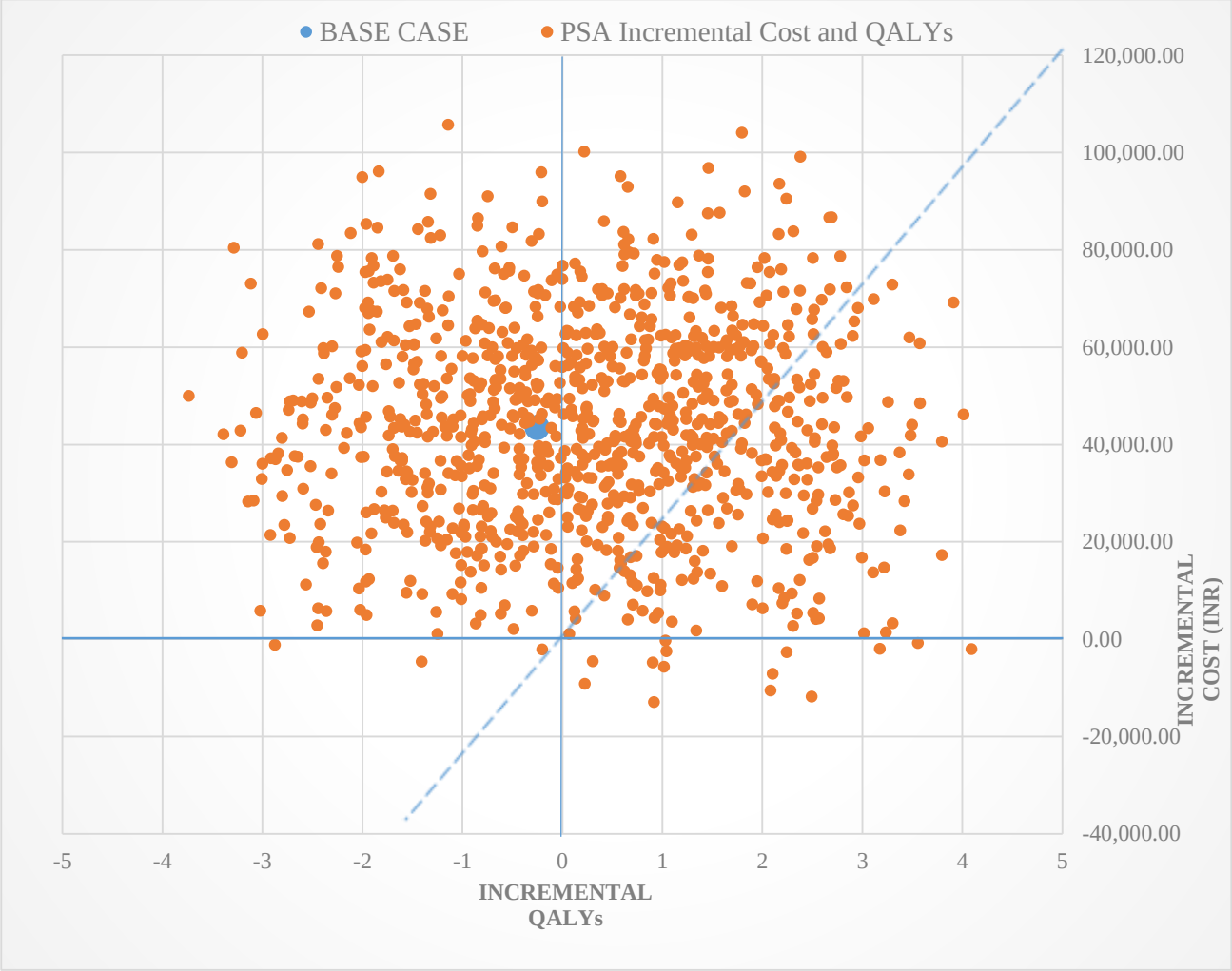
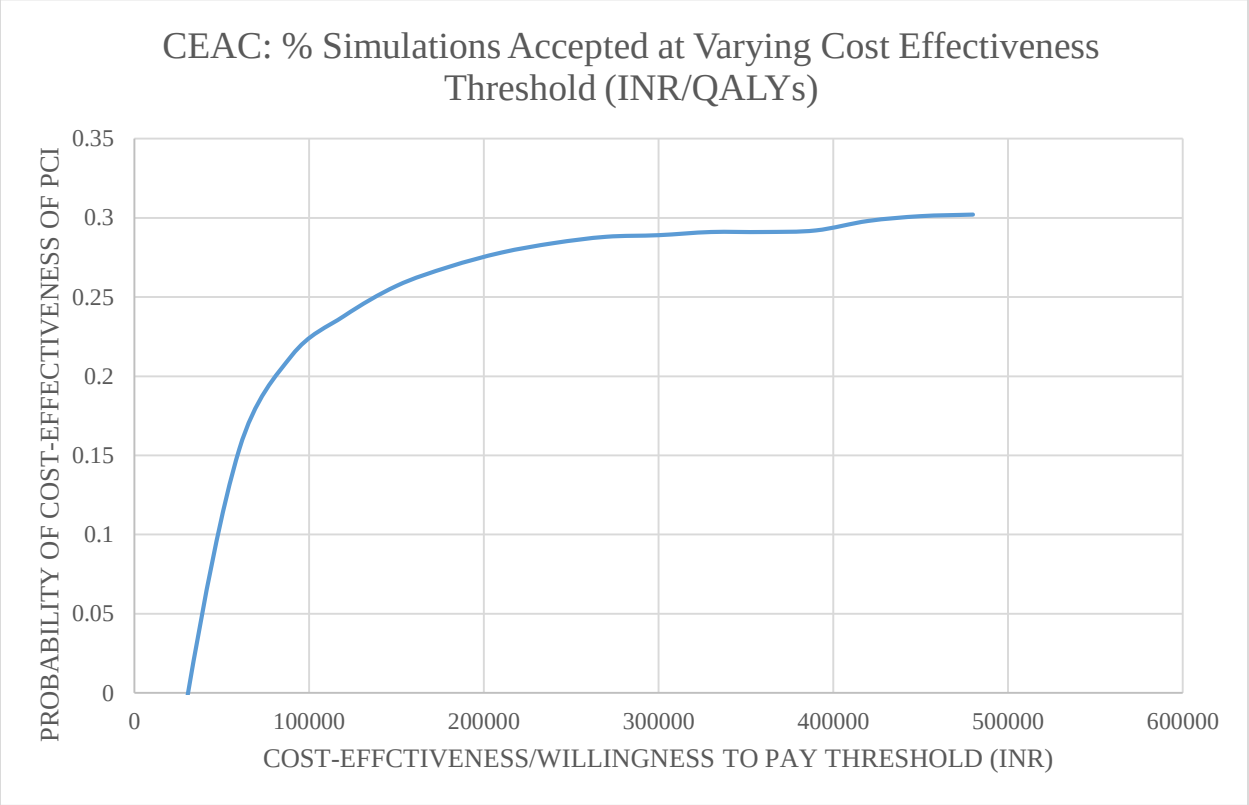


Figure 6 shows the cost effectiveness acceptability curve explaining the relationship of cost-effectiveness threshold with results of probabilistic sensitivity analysis. This shows that probability of interventions to be cost-effective at threshold of one times per capita GDP is around 28% and it goes only up to 30% even at threshold as high as three times per capita GDP of India.

Figure 6. Cost-effectiveness acceptability curve of PCI as compared to CABG based on PSA



Conclusion & Recommendations

As evident from results of our study, upfront cost of CABG is more in the first year as compared to PCI with and there is not much difference in the clinical outcomes of the these interventions. However, in the subsequent years, i.e. 5 years horizon, 10 years horizon and lifetime (twenty years' time) horizon; CABG is more clinically effective and also cost-effective as compared to PCI. Although, there is only a marginal difference in the health outcome of CABG over PCI in management of stable LM CAD patients in terms of QALYs gained, the overall cost of CABG is significantly less as compared to PCI due to difference in the need of repeat revascularization subsequently.

Thus, this study recommends that in cases of Left Main Coronary Artery Disease, the mainstay treatment should be centered on Coronary Artery Bypass Graft. PCI may be considered as the second line of treatment in cases requiring revascularization as per clinical experts' opinion.

Limitations and Assumptions

Since we considered an abridged societal perspective for this economic evaluation, we did not account for productivity loses for PCI and CABG. There could be significant difference in the productivity loss in these two management options because of significant difference in hospital stay. This analysis uses the clinical effectiveness parameters form studies/trials which are not India specific, so there could be some variation in the health outcomes of PCI or CABG. This analysis uses utility weights from outside India and these utility weights may not truly represent preferences of Indian patients. This economic evaluation does not includes the subgroup analysis for diabetic and other sub-groups due to lack of powered data which could give generalizable results. While estimating the health outcomes for extended periods, we assumed that

effectiveness parameters in subsequent years will remain same; which may not be the case in the real world. Also, 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, which will not be in reality. 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 package rates. These cover all the expenses incurred in the health systems and have been taken so as to have generalizable results.

REFERENCE

1. Prabhakaran D, Jeemon P. Global Burden of Cardiovascular Disease Cardiovascular Diseases in India. 2016:1605-1620. doi:10.1161/CIRCULATIONAHA.114.008729
2. Mishra S, Ray S, Dalal JJ, et al. Management standards for stable coronary artery disease in India. *Indian Heart J*. 2016;68:S31-S49. doi:10.1016/j.ihj.2016.11.320
3. Gupta R, Mohan I, Narula J. Trends in Coronary Heart Disease Epidemiology in India. *Ann Glob Heal*. 2016;82(2):307-315. doi:10.1016/j.aogh.2016.04.002
4. Ardeshna DR, Bob-manuel T, Nanda A, et al. Asian-Indians : a review of coronary artery disease in this understudied cohort in the United States. 2018;6(7):4-10. doi:10.21037/atm.2017.10.18
5. Huang L, Zhang L, Li T, Liu Y, Wang Y, Liu B. Human Plasma Metabolomics Implicates Modified 9-cis-Retinoic Acid in the Phenotype of Left Main Artery Lesions in Acute ST-Segment Elevated Myocardial Infarction. *Sci Rep*. 2018;(July):1-11. doi:10.1038/s41598-018-30219-w
6. Manzil AS, Rajan JS, Radhakrishnan V. Clinical Outcomes in Patients Undergoing Triple-Vessel Angioplasty for Symptomatic Coronary Artery Disease. 2015;(October):746-752.
7. Duggal B, Subramanian J, Duggal M, et al. Survival outcomes post percutaneous coronary intervention : Why the hype about stent type ? Lessons from a healthcare system in India. 2018:1-14.
8. Article O. for Left Main Coronary Disease. 2019:1-11. doi:10.1056/NEJMoa1909406
9. Spence MS, Erglis A, Menown IBA, et al. Articles Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis : updated 5-year outcomes from the randomised ,. 2019;6736(19):1-9. doi:10.1016/S0140-

6736(19)32972-1

10. Manuscript A. NIH Public Access. 2015;168(5):690-697. doi:10.1016/j.ahj.2014.07.029.Rationale

11. Mohanan PP, Mathew R, Harikrishnan S, et al. Presentation , management , and outcomes of 25 748 acute coronary syndrome admissions in Kerala , India : results from the Kerala ACS Registry. 2013:121-129. doi:10.1093/eurheartj/ehs219

12. Pagidipati NJ, Huffman MD, Jeemon P, Gupta R, Negi P. Association between Gender , Process of Care Measures , and Outcomes in ACS in India : Results from the Detection and Management of Coronary Heart Disease (DEMAT) Registry. 2013;8(4):1-7. doi:10.1371/journal.pone.0062061

13. Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs . coronary artery bypass grafting for left main coronary artery disease : a meta-analysis of randomized controlled trials. 2020:1-8. doi:10.1093/eurheartj/ehaa135

14. Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease. 2020:1-10. doi:10.1161/CIRCULATIONAHA.120.046039

15. Thuijs DJFM, Kappetein AP, Serruys PW, et al. Articles Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease : 10-year follow-up of the multicentre randomised controlled SYNTAX trial. 2019;6736(19):1-10. doi:10.1016/S0140-6736(19)31997-X

16. Boudriot E, Thiele H, Walther T, Liebetrau C. Randomized Comparison of Percutaneous Coronary Intervention With Sirolimus-Eluting Stents Versus Coronary Artery Bypass Grafting in Unprotected Left Main Stem Stenosis. *JAC*. 2011;57(5):538-545.

doi:10.1016/j.jacc.2010.09.038

17. Adam B, Karlin A, Pickard MFJAS. Comparing responsiveness of the EQ-5D-5L , EQ-5D-3L and EQ VAS in stroke patients Comparing responsiveness of the EQ-5D-5L , EQ-5D-3L and EQ VAS in stroke patients. 2014;(November). doi:10.1007/s11136-014-0873-7

18. Puskas JD, Ben-yehuda O, Es G Van, Taggart DP. Quality-of-Life After Everolimus-Eluting Stents or Bypass Surgery for Left-Main Disease. 2017;70(25). doi:10.1016/j.jacc.2017.10.036

19. Lee PH, Park H, Lee JS, Lee S, Lee CW. Meta-Analysis Comparing the Risk of Myocardial Infarction Following Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention in Patients With Multivessel or Left Main Coronary Artery Disease. *Am J Cardiol*. 2019;124(6):842-850. doi:10.1016/j.amjcard.2019.06.009

20. José P, Andrade N De, Luiz J, et al. Original Article Stent versus Coronary Artery Bypass Surgery in Multi-Vessel and Left Main Coronary Artery Disease : A Meta-Analysis of Randomized Trials with Subgroups Evaluation. 2018:511-523. doi:10.5935/abc.20190027

21. Perrin N, Bortolussi G, Guariento A. PCI vs. CABG for left main coronary artery disease: a meta-analysis. *J Thorac Cardiovasc Surg*. 2020. doi:10.1016/j.jtcvs.2020.04.010

22. Agrawal A, Gandhe MB, Gandhe S, Agrawal N. Study of length of stay and average cost of treatment in Medicine Intensive Care Unit at tertiary care center. 2017:24-29. doi:10.4103/2394-2010.199329

23. Kwatra G, Kaur P, Toor G, et al. Cost of stroke from a tertiary center in northwest India. 2013;61(1). doi:10.4103/0028-3886.125270