Clinical Profile and Major Adverse Cardiovascular Outcomes in Patients who Underwent Coronary Revascularization for Left Main Coronary Artery Disease and Left Main Equivalent Coronary Artery Disease in a Tertiary Hospital

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ABSTRACT

BACKGROUND: Percutaneous coronary intervention (PCI) for left main (LMCA) coronary artery disease (CAD) was found to be non-inferior and had similar major adverse cardiovascular events (MACE) to coronary artery bypass grafting (CABG). In the local setting, the clinical profile and MACE of patients who underwent either revascularization are, however, unknown.

OBJECTIVES: To determine the clinical profile and in-hospital MACE of patients who underwent revascularization (PCI or CABG) for LMCA and left main equivalent CAD.

METHODS: This is a prospective descriptive study. Clinical profile and in-hospital, 30-days and 90-days post revascularization MACE were determined.

RESULTS: Thirty-seven (37) adults were included. Most were males, diabetics, dyslipidemics, smokers, with previous cardiovascular events and premature CAD. Hypertension was significantly prevalent in the CABG group (PCI=62.50% vs CABG=90.48%, p=0.04). Patients who underwent CABG mostly presented with stable angina (p=0.0453). The majority of the PCI (68.75%) was done as an emergent/urgent procedure, with clear indications for PCI (i.e. STEMI). In-hospital all-cause mortality was significantly higher in the PCI group (PCI=50% vs CABG=0%, p<<0.05).

CONCLUSION: Patients with LMCA and left main equivalent CAD were mostly males and had traditional CAD risk factors. In-hospital mortality was significantly higher among the PCI group; however, those who underwent PCI were unstable and unlikely to be good surgical candidates for CABG.

Keywords: *coronary artery disease; left main coronary artery disease; percutaneous coronary intervention; coronary artery bypass grafting; major adverse cardiovascular outcome*

INTRODUCTION

Ischemic heart disease is a global burden. In the Philippines, cardiovascular diseases ranked among the top 10 leading causes of morbidity and were the leading cause of mortality in 2009. Coronary artery disease is commonly due to obstruction of the coronary arteries, usually the epicardial arteries, by atheromatous plaque.[7]

Dating back to the early 1970s, coronary artery bypass surgery has been a well-established technique, with excellent proven results. A recent review by Taggart et al published in 2008 reported on a series of studies, all of which had in-hospital mortality of between 2 and 3% after CABG for left main coronary artery stenosis, and although there was less data on long-term follow-up, those studies reported on long-term outcomes had results showing 5–6% mortality at 5 years. [2]

Percutaneous revascularization of left main coronary artery (LMCA) disease has remained controversial, since LMCA balloon angioplasty was first performed by Andreas Gruentzig in 1978.[3] The American College of Cardiology/American Heart Association (ACC/AHA) continued to support their recommendation that CABG is the preferred revascularization for patients with left main coronary artery disease, given that the high incidence of late coronary stenosis in patients who underwent PCI with bare-metal stents.[4] However, interest in percutaneous LMCA revascularization, particularly unprotected left main, has been renewed following the evolution of percutaneous catheter-based therapies to include both

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the bare-metal stent and, more recently, drug-eluting stent (DES) platforms in conjunction with advances in periprocedural and postprocedural adjunctive pharmacotherapies.[3]

The 'Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty vs. Surgical Revascularization' (MAIN-COMPARE) Registry was the first large multicenter, non-randomized study comparing long-term outcome following PCI with stenting vs. CABG for unprotected left main coronary artery (ULMCA) disease. This registry involved 2240 patients with ULMCA stenosis who underwent stenting (DES=784; BMS=318) or CABG (n= 1138). Patients in the PCI cohort were less likely to have diabetes or multivessel coronary artery disease; however, no significant difference was observed between the two revascularization strategies in terms of risk of death and risk of the composite outcome of death, myocardial infarction, and cerebrovascular events (CVE after adjustment with propensity scoring model). Encouraging results were recently reported from the *Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery* (SYNTAX) trial for patients stratified according to the presence of ULMCA disease. Percutaneous coronary intervention with DES implantation resulted in equivalent 3-year overall major adverse cardiovascular and cerebrovascular events (MACCE) compared with CABG (22.3% CABG vs. 26.8% PCI, *p=0.20*). Safety outcomes overall (death/ CVE/MI) were similar between the groups (14.3% CABG vs. 13% PCI, *p=NS*). Subgroup analysis using non-inferiority as the primary endpoint in terms of 12-month rate of MACE, among the ULMCA subgroup, the PCI group met non-inferiority (13.7 vs. 15.8%, *p=0.44*).[6]

Results from this study could provide local data on the clinical profile of patients who underwent revascularization of left main coronary artery and left main "equivalent" coronary artery disease (i.e. ≥ 70 percent reduction in luminal diameter of the left anterior descending and left circumflex vessels before any major branches) and major adverse cardiovascular/cerebrovascular in-hospital outcomes of patients who underwent PCI and/or CABG for left main artery disease and left main equivalent coronary artery disease and could influence decisions on selecting patients who would benefit well from either of the revascularization strategies.

OBJECTIVES

Primary Objectives. The study aimed to determine the clinical profile in terms of:

1. Mean age
2. Sex
3. Comorbidities (hypertension, diabetes, dyslipidemia, smoking/smoking history, family history of premature coronary artery disease)
4. Functional capacity (New York Heart Classification and/or Canadian Cardiovascular Society grading for angina)
5. LV systolic function (Ejection Fraction on echocardiogram)
6. Number of coronary arteries with significant disease

The study also aimed to determine in-hospital all-cause mortality, post-procedure acute coronary syndrome and stroke among patients who underwent percutaneous coronary intervention (PCI) and those who underwent coronary artery bypass graft (CABG) for left main and left main equivalent coronary artery disease.

Secondary Objectives. The study also aimed to determine all-cause mortality, acute coronary syndrome, stroke, in patients who underwent PCI and those who underwent CABG after 30 days and three months

METHODOLOGY

Study setting, design, and study population. The study was conducted in a tertiary hospital and teaching institution.

The study population included competent adult (age 19 years old and above) patients who were determined to have left main coronary artery disease, and/or proximal left anterior descending and proximal left circumflex artery disease on coronary angiography and who underwent revascularization with PCI and/or CABG. For those patients who underwent revascularization with PCI of isolated right coronary artery disease, clinical profiles were only described and were not followed up for major cardiovascular outcomes.

The study was a prospective, descriptive type of study, where major adverse cardiovascular outcomes, defined as all-cause mortality, post-procedure acute coronary syndrome, or stroke were determined at the following time intervals: during hospital admission, at 30-day and third month follow up. Subjects were identified and recruited by either one of the investigators using the cardiac catheterization laboratory database for those patients who underwent PCI and the Integrated Surgical Information System (ISIS) database for those patients who underwent coronary artery bypass graft (CABG). No bias was observed in the recruitment process, whether under charity/service patients or pay-patients. The recruitment process was done by another investigator if the primary investigator was directly involved in the care of the patient, with the primary investigator made unaware of the patient's recruitment and/or inclusion in the study. Patients were recruited from January 2017 – September 2017, using convenient sampling. The selection of a revascularization procedure was solely based on the discretion of the respective interventional cardiologist/attending physicians of the patients included in the study.

Approval from the hospital research ethics review board was obtained and granted, and patients included in the study were only enrolled after completion of consent forms. At the start of the study, clinical profiles, which include age, sex, comorbidities such as hypertension, diabetes mellitus, previous history of cardiovascular

events, family history of premature coronary artery disease), baseline functional capacity as defined by New York Heart Association (NYHA) Classification and/or Canadian Cardiovascular Society (CCS) classification for those with a report of angina, present smoking or history of smoking, dyslipidemia, echocardiographic documentation of left ventricular systolic function, and coronary angiography results (where angiogram films were adjudicated by at least three interventional cardiologists - one consultant and two fellows-in-training) of the included subjects were described during the hospital stay. The recruited patients were involved in the study for a total of three months: initially, during admission; second, during their follow up consult 30 days after the procedure, and third, during their follow up consult 90 days or three months after the procedure. All follow-ups for major adverse cardiovascular outcomes (all-cause mortality, post-procedure ACS, and stroke) at 30 days and 90 days post-procedure were done through phone interviews. To mitigate potential biases, the investigator who recruited the patient (i.e., not directly involved in the patient's care) included in the study was also the one who did the follow-up for outcomes of MACE during admission, one month and three months post-procedure via phone interview.

Definition of Terms

Significant left main coronary artery disease is operationally defined as the presence of at least ≥ 50% stenosis in any segment of the left main coronary artery on coronary angiogram

Significant left main equivalent coronary artery disease is operationally defined as the presence of ≥ 70% stenosis at the proximal segments of left anterior descending (LAD) artery AND left circumflex (LCx) artery prior to any major branches

Significant coronary artery lesion is arbitrarily defined as the presence of at least one ≥ 70% stenosis in the left anterior descending artery (LAD), left circumflex artery (LCx), and/or right coronary artery (RCA).

PCI-related Myocardial infarction is arbitrarily defined by the elevation of cTn values (to >5 times the 99th percentile of the URL) in patients who underwent PCI, with normal baseline values (≤99th percentile of the URL) or a rise in cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (1) symptoms suggestive of myocardial ischemia, (2) new ischemic changes on the ECG, (3) angiographic findings consistent with a procedural complication, or (4) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.[11]

CABG-related Myocardial infarction is arbitrarily defined by an elevation of cardiac biomarker values (to >10 times the 99th percentile of the URL) in patients who underwent CABG, with normal baseline cTn values (≤99th percentile of the URL). Also, either (1) new pathologic Q waves or new LBBB, (2) angiographically documented new graft or new native coronary artery occlusion, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required. [11]

Stroke: Sudden onset of focal neurological deficit lasting more than 24 hours due to an underlying vascular pathology. [8]

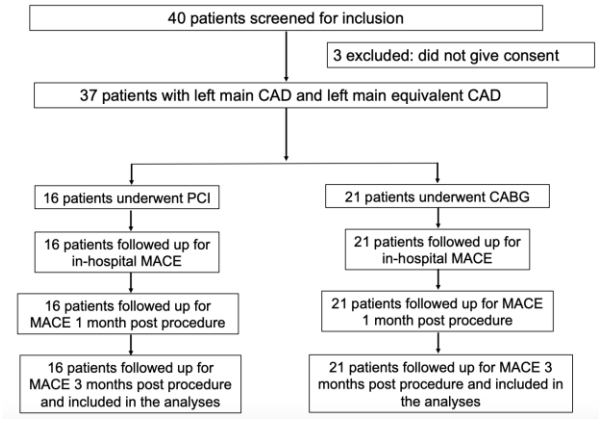

Figure 1. Flow diagram of the number of patients recruited, followed-up and included in the analysis

Statistical Analysis

Descriptive analysis was done using tables, frequency, percentages, and mean values to summarize the data collected. For baseline characteristics or event rates of outcomes, absolute numbers and percentages were utilized. Proportions and frequencies were reported for qualitative variables. For quantitative variables, a *t*-test of two independent samples was used to determine if there is a significant difference. For categorical variables, the Z-test was used. A p-value of < 0.05 was considered statistically significant. Any missing data for any patient included were obtained by reviewing the patient's chart thoroughly and/or elicited from the physicians directly involved in the patient's care. The follow-up rate was adequate, as there were no patients enrolled who were lost to follow-up.

RESULTS

Baseline Characteristics. A total of 40 patients were screened for inclusion (19 for PCI group, 21 for CABG group), and three patients from the PCI arm were excluded due to no consent given. Thirty-seven patients with a mean age of 60 years old were included in the study, with 16 patients for the PCI group and 21 patients for the CABG group (*Figure 1*). *Table 1* summarizes the baseline characteristics of the study patients stratified according to the type of revascularization they underwent (PCI or CABG). Most patients were males, with 10 patients (62.5%) in the PCI arm and 20 patients (95.24%) in the CABG group. Comorbidities such as type 2 diabetes, dyslipidemia, smoking or smoking history, family history of premature CAD, and previous history of CV events were similar in both groups, except for hypertension (62.5% PCI, 90.48% CABG, *p=0.04*).

Likewise, the majority of patients reported or were initially assessed to be in NYHA functional class II, while only in

Table 1. Clinical Profile of Included Patients

Characteristics	PCI	CABG	p-value
Total	16	21	0.2450
Age	61.19 ± 11.76	59.95 ± 8.54	0.7132
Sex			
Male	10 (62.50%)	20 (95.24%)	0.0118
Female	6 (37.50%)	1 (4.76%)	0.0118
Comorbidities			
Hypertension	10 (62.50%)	19 (90.48%)	0.0406
Diabetes Mellitus	8 (50.00%)	11 (52.38%)	0.8859
Dyslipidemia	9 (56.25%)	11 (52.38%)	0.8150
Smoker/Smoking History	8 (50.00%)	13 (61.90%)	0.4690
Family History of Premature CAD	10 (62.50%)	12 (57.14%)	0.7423
Previous History of Cardiovascular Events	6 (37.50%)	10 (47.62%)	0.5382
Baseline Functional Capacity			
NYHA I	3 (18.75%)	0 (0.00%)	0.0385
NYHA II	6 (37.50%)	8 (38.10%)	0.9705
NYHA III	3 (18.75%)	3 (14.29%)	0.7151
NYHA IV	1 (6.25%)	0 (0.00%)	0.2455
CCS Grade I	1 (6.25%)	1 (4.76%)	0.8428
CCS Grade II	2 (12.50%)	9 (42.86%)	0.0453
CCS Grade III	0 (0.00%)	0 (0.00%)	-
CCS Grade IV	0 (0.00%)	0 (0.00%)	-
Systolic Function on Echo			
EF ≥ 40%	10 (62.50%)	19 (90.48%)	0.0406
EF < 40%	6 (37.50%)	2 (9.52%)	0.0406
Coronary Angiography			
Left Main Coronary Artery	13 (81.25%)	10 (47.62%)	0.0366
Left Anterior Descending Artery	15 (93.75%)	21(100.00%)	0.2455
Left Circumflex Artery	10 (62.50%)	21(100.00%)	0.0022
Right Coronal Artery	7 (43.75%)	17 (64.86%)	0.0189
Timing of Intervention			
Emergent/Urgent	11 (68.75%)	2 (9.52%)	0.0002
STEMI	8 (72.73%)	0 (0.00%)	0.0518
Unstable angina high risk	0 (0.00%)	1 (50.00%)	0.0146
NSTEMI high risk	2 (18.18%)	1 (50.00%)	0.3259
Cardiogenic shock	1 (9.10%)	0 (0.00%)	0.6572
Elective	5 (31.25%)	19 (90.48%)	0.0002

* Emergent: operationally defined as revascularization (PCI or CABG) done within ≤ 48 hours the patient's hospital admission and coronary angiogram was done

** Urgent: operationally defined as revascularization (PCI or CABG) done within ≤ 7 days the patient's hospital admission and coronary angiogram was done

*** Elective: revascularization done beyond 7 days the coronary angiogram was done

PCI group did report or were assessed to be in NYHA functional class I (3,37.5%, *p=0.0385*). Also notable is the number of patients who reported angina as presenting symptom, with majority of them underwent CABG and were assessed to be in CCS Class II (2, 12.5% vs 9, 42.86%, *p=0.0453*). Overall systolic function in terms of ejection fraction based on echocardiography during hospitalization revealed generally preserved EF of ≥ 40% on both groups.

Patients who underwent coronary angiography before revascularization either by PCI or CABG were shown to have significantly diseased (≥ 70% stenosis at its ostium to proximal segment) left anterior descending (LAD) arteries, though the difference between the two groups was not statistically significant. On the other hand, left main coronary artery disease (LMCA) (≥ 50% stenosis in any segment) was higher (81.25%) in the PCI group while significant disease involvement (≥ 70% stenosis at its ostium to proximal segment) of the left circumflex artery (LCx) (100%, *p=0.0022*) and right coronary artery (64.87%, *p=0.0189*) were observed in the CABG group. In the PCI group, 16 patients (81.25%) had significantly diseased LMCA while three patients (18.75%) had left main equivalent CAD, with at least ostio-proximal segments of LAD and LCx assessed to have significant stenoses. Also, noteworthy to highlight was that three patients who had LMCA disease had concomitant coronary dissections, two of whom had involvement of LAD and one patient with significantly diseased LAD, LCx, and RCA. In the CABG group, 10 patients (47.62%) had LMCA disease while the remaining 11 patients (52.35%) were left main equivalent CAD. Among the 10 patients with LMCA disease, most patients (9) had concomitant significant stenosis of the LAD, LCx, and RCA, with only one patient with significantly diseased LAD and LCx.

The timing of the intervention was significantly different statistically across the groups (*p<0.05*), as most patients who underwent PCI had the intervention on an emergent/urgent basis, while CABG patients had the intervention on an elective basis. The PCI was primarily done as emergent/urgent procedures as most patients presented with clear indications for PCI (8, or 50% of patients came in for STEMI and two (12.5%) patients came in for fa cardiogenic shock and one (6.25%) came in for NSTEMI with high-risk features. Urgent CABG was done on two patients: one patient for NSTEMI with high-risk features and the other one for intractable angina. Although the latter rendered a statistically significant difference (*p=0.0146*), it should be kept in mind that the choice of revascularization was decided upon by the primary attending physician/interventional cardiologist. On the other hand, the CABG group was mostly done on an elective basis, with the majority (19 patients, 90.48%) risk-assessed as "standard risk" surgery (preoperative STS score or EUROSCORE of < 5% in-hospital mortality) under the PhilHealth Z-benefit package. The remaining five (31.25%) patients who underwent PCI on an elective basis were re-admitted for staged/completion revascularization via PCI of the remaining significant left main equivalent lesions. No data

Table 2. Clinical outcomes of the included patients.

Outcomes	PCI	CABG	p-value
All-cause Mortality			
In-Hospital	8 (50.00%)	0 (0.00%)	0.0003
30 Days	0 (0.00%)	0 (0.00%)	-
3 Months	0 (0.00%)	0 (0.00%)	-
Myocardial Infarction			
In-Hospital or procedural ACS	0 (0.00%)	0 (0.00%)	-
MI at 30 Days	1 (12.50%)	0 (0.00%)	0.1163
MI 3 Months	0 (0.00%)	0 (0.00%)	-
Stroke			
In-Hospital	0 (0.00%)	0 (0.00%)	-
30 Days	0 (0.00%)	0 (0.00%)	-
3 Months	0 (0.00%)	0 (0.00%)	-

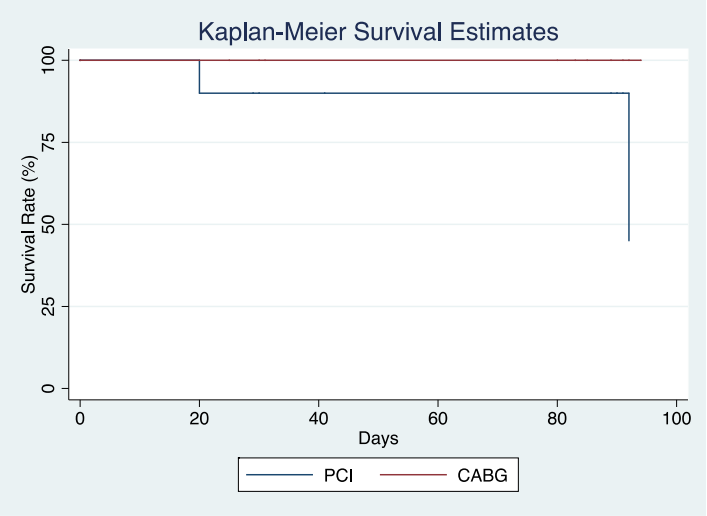

Figure 2. Kaplan –Meier Curve comparing survival rates of patients who underwent PCI versus CABG. Note: Log-rank test for equality of survivor functions *p=0.0233*

for the pre-specified variables of interest in each of the patients included were missing.

Major Adverse Cardiovascular Outcomes. *Table 2* summarizes the major adverse cardiovascular outcomes, in terms of all-cause mortality, post procedure ACS and stroke, during hospitalization, 30 days and 90 days post-revascularization. No patient was lost to follow-up during the study period.

In-hospital all-cause mortality was observed to be significantly higher (50%, *p<0.05*) in the PCI group compared to the CABG group. Five out of eight patients who died (62.50%) succumbed due to cardiogenic shock, one out of eight (12.50%) died of fatal arrhythmia and two out of eight (25.00%) died of septic shock from HAP. Expectedly, this finding can be rationalized by the fact that most patients who underwent revascularization via PCI came in with clear indications for PCI (i.e. STEMI, in cardiogenic shock) and that they were relatively unstable and "sicker" patients, as justified by the timing of intervention, whereby the majority of the PCI were done as "emergent/urgent" procedures (*p<0.05*).

On follow-up at 30-days and 90-days post-revascularization, all-cause mortality and stroke were not observed among the study population. Only one patient (12.5%) who underwent PCI for left main equivalent coronary artery disease had acute coronary syndrome (NSTEMI) a month after, though this outcome did not have an inter-group statistically significant difference (*p=0.1163*).

Figure 2 shows the Kaplan-Meier survival estimates for patients who underwent PCI versus CABG for left main coronary artery disease and left main equivalent coronary artery disease. Based on the results that eight patients who underwent PCI died, survival (i.e., freedom from death) among PCI patients is significantly less than that compared to those who underwent CABG, with log-rank test *p=0.0233*.

DISCUSSION

Randomized trials comparing PCI using DES with CABG in patients with unprotected LMCA disease provide limited evidence and thus remain controversial. A randomized trial by Boudriot et al failed to prove the non-inferiority of PCI using sirolimus-eluting stents compared with CABG with regards to major adverse cardiac events in patients with unprotected LMCA disease.[13] In contrast, the Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stents in Patients with Left Main Coronary Artery diseases (PRECOMBAT) trial by Park et al showed non-inferiority of PCI compared with CABG with respect to major adverse cardiac or cerebrovascular events.[14] Several experts, however, commented that results from these randomized trials should be interpreted with caution especially when applying it to daily clinical practice because patients with relatively low risks for the outcomes measured were selected and enrolled. As such, the importance of a large-scale observational study reflecting a real-world comparison between PCI and CABG could not be overemphasized.

In our present study, albeit a small population, a total of 37 patients with left main coronary artery disease and left main equivalent coronary artery disease were treated medically according to local guidelines and followed up during hospitalization, 30 days and 90 days post revascularization. Baseline characteristics in the study population were similar across the groups, except for hypertension which was statistically significantly higher among patients who underwent CABG. Functional capacity in terms of New York Heart Association functional class showed similar class (FC II) across the two groups,

however, more patients reported and/or were complaining of chest pain during ordinary activities (CCS II) especially in the CABG group. Overall left ventricular systolic function (LVEF) measured by 2D echocardiogram showed that the majority of patients (62.5% in PCI, 90.48% in CABG) have generally preserved EF of ~ 40%. This is in contrast to a local study by Ines et al where patients who underwent multi-vessel PCI have generally reduced EF (<40%).[15] In the same study by Ines et al, the LAD was the most commonly encountered coronary artery with significant lesion[15], which was also observed in our study. The remaining parameters for clinical profiles of the patients involved were similar to those previously described in other studies done in institutions locally and abroad.

As mentioned, the timing of the intervention was significantly different statistically across groups, as half (50%) of those patients who underwent PCI have clear cut indications for such (i.e., primary PCI for STEMI). In-hospital mortality rate was higher in the PCI group. Conversely, survival rate of patients who underwent PCI were significantly lower compared to those who underwent CABG as shown by the Kaplan-Meier survival curve. However, it should be emphasized, and the authors acknowledge the fact that the high mortality rate in the PCI group might be caused by the inclusion of more unstable patients at admission, while those who underwent CABG were thought to have very low surgical mortality at the outset. Furthermore, limitations in our hospital logistics and patients' financial capabilities for emergency CABG or "double-set up" for those patients who were found to have significant LMCA or left main equivalent CAD may have influenced interventional cardiologists' decision to proceed with PCI for such subset of patients.

Limitations of the study

It should be noted that revascularization strategy choice (PCI or CABG) for the patients included in the study were solely based on the interventional cardiologist/attending physician's discretion after considering the patient's overall clinical status and prognosis at presentation. Also, the relatively low sample size may not completely reflect the real-world comparison. The low turn-out of patients included in this prospective study were mainly due to a decrease in the number of patients coming in during the study period. In terms of major adverse cardiovascular outcomes post revascularization, the follow ups in this study were only done 1-month and 3-months after, which could also not be reflective on the true, long term clinical outcomes. An attempt to do subgroup analysis of clinical profile variables and its possible association with clinical outcomes was done, however, it was not feasible as there were no events (all-cause mortality, ACS, stroke) observed in the CABG group.

Given these limitations, we recommend that objective review of coronary anatomy and lesions through SYNTAX scoring should be done, and that a dedicated multidisciplinary or "heart team" should be established to guide decisions on which revascularization strategy would be best for every patient presenting with left main and left main equivalent coronary artery disease. Likewise, establishment of readily available and affordable "double set up" for those patients requiring emergent/urgent CABG could not be overemphasized. A larger, multicenter approach and longer duration of study could be done to address the limitation on the number of patients included in the observation.

CONCLUSION

Similar to available literature, this prospective descriptive study showed that most patients found to have left main and left main equivalent coronary artery disease have the traditional CAD risk factors (i.e. male sex, diabetes mellitus, dyslipidemia, smoking) and had previous cardiovascular events. Hypertension was found to be more prevalent in those who underwent CABG. In-hospital mortality was significantly higher among those who underwent PCI; however, those who underwent PCI were relatively more unstable and were unlikely to be good surgical candidates for CABG. Decisions to which revascularization strategy be done to patients with left main and left main equivalent coronary artery disease must be based on the patient's overall clinical status on presentation, thus management should highly be individualized.

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