ORIGINAL ARTICLE

One-Year Outcomes of Two-Week Double-Dose Clopidogrel Treatment following Percutaneous Coronary Intervention in a State General Hospital in Malaysia

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ABSTRACT

Introduction: Previous studies reported that a two-week double-dose clopidogrel treatment following percutaneous coronary intervention has no difference in safety compared to standard therapy. This study aimed to determine the all-cause readmission rate and survival after a year of percutaneous coronary intervention (PCI) in patients who were treated with two-week double-dose clopidogrel regimen. **Methods:** This was a retrospective study on patients who underwent PCI in a state general hospital in Malaysia in 2014. Patients' one month and one-year survival status were retrieved using the hospital electronic patient management system. Patients who received a two-week course of 150mg clopidogrel and subsequently a one-year course of standard double antiplatelet therapy were included. **Results:** A total of 381 out of 563 patients who underwent PCI were included in the analysis, while those who were switched to ticagrelor and transferred to other hospitals post-PCI excluded. Patients had a mean age of 56.9 (SD 10.7), with majority male (331, 86.9%) and Malay (144, 37.8%). The PCI was mainly indicated for ST-elevated myocardial infarction (188, 49.3%), non-STEMI (114, 29.9%) and unstable angina (36, 9.4%). A total of 107 (28.1%) patients were readmitted within the one year post-PCI period. Readmissions were mainly due to ACS (55.5%) and bleeding events (2.4%). The 30-day and 1-year all-cause mortality was 33 cases and 43 cases, respectively. **Conclusion:** The low readmission and bleeding related readmission suggested that the two-week double-dose clopidogrel regimen was safe for the post PCI patients. Future randomised trial to establish the efficacy of this dosing regimen is therefore warranted.

Keywords: Antiplatelet, Percutaneous coronary intervention, Survival, Readmission

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INTRODUCTION

Coronary heart disease (CHD) is the most common cause of mortality in America, accounting for 370,000 people annually (1). All-cause mortality due to coronary heart disease in the America in year 2008 was 23.8% for all ethnicity (2). Malaysia, a multi-ethnic, developing and middle-income country accounted for a similar rate of mortality for CHD. CHD was the most common cause of deaths in Malaysia, accounted for 29,400 deaths (20.1% of all deaths) in year 2012 and 23.3% of all hospital deaths in year 2014 (3,4).

Within this context, the number of Malaysian public hospital equipped with percutaneous coronary intervention (PCI) facilities has increased over the years. Patients presenting with acute coronary syndrome in the Malaysian public hospital were given the option of undergoing PCI. Meanwhile, as PCI procedures become more common in the public hospitals, pharmacotherapy post PCI has also become increasingly important.

Dual antiplatelet therapy (DAPT), defined as the combination of aspirin and a P2Y12 receptor inhibitor such as clopidogrel, prasugrel and ticagrelor, are primarily used in patients who underwent PCI with drug eluting stents (5). DAPT provides extra benefits by reducing the risk of recurrent thrombotic events after PCI. However, it is noteworthy that patients who were treated using DAPT regimen faced a higher risk of major bleeding (6). It has been established that DAPT was able to reduce the event of stent thrombosis and recurrent myocardial infarct in comparison to conventional regimen (7,8).

The current American College of Cardiology Foundation & American Heart Association Task Force on Practice

Guidelines and the European Society of Cardiology recommended at least 12 months of DAPT after drug-eluting stent (DES) implantation post PCI (9-11). Some other studies have reported using a shorter 3 to 6 months (12) or longer 18 to 48 months (7) duration of DAPT.
To date, the optimal duration of DAPT post-DES implantation remained poorly defined. In the local setting, a total duration of 12 months DAPT post-PCI was the general practice. Nevertheless, there was a lack of local evidence on the outcome of patients after the DAPT therapy. Hence, this study was designed to study the rate of unplanned admission among patients who underwent PCI and their post-30 days and post-1 year survival.

The study was registered with the National Medical Research Register. The investigators did not collect the name, identification number or other identifier data of patients. Ethics approval was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia before the conduct of this study.

MATERIALS AND METHODS

This was a retrospective study conducted at public funded state general hospital in Ipoh. Patients included in this study were patients who underwent PCI and given two weeks of clopidogrel (150mg once daily) followed by 75 mg once daily clopidogrel for a year combined with acetylsalicylic acid 100 – 150 mg once daily as part of their double antiplatelet. All patients on clopidogrel during study period were given Apo-Clopidogrel® Apotex Inc. Patients who were switched to other antiplatelet therapy, in hospital death and those who were transferred out to other hospitals post PCI were excluded from the readmission analysis (Figure 1). List of patients that underwent PCI in year 2014 was obtained from the PCI registry of Interventional Cardiac Laboratory in the hospital. Data of patients who underwent PCI from January 2014 until December 2014 were collected. In the study centre, PCI procedures include both stent and ballon angioplasty, but only stented patients were included in this study. Information that were captured included patients' demographics (age, gender, ethnicity, co-morbidities, smoking status, ejection fraction), indication for PCI and type of stent used. Patients' one month and one-year survival status were retrieved using the hospital electronic patient management system. For patients who defaulted follow-up at the hospital, their one-year survival status was retrieved from the National Registration Department. Reasons of exclusion were patients transferred to other hospitals for follow-ups, allergies to clopidogrel or acetylsalicylate and in-hospital deaths (Figure 1). The cause of admission was decided based on the diagnosis written in the discharge summary. If multiple diagnosis was recorded in the discharge summary, case note was traced and the diagnosis was decided by discussion with cardiologist.

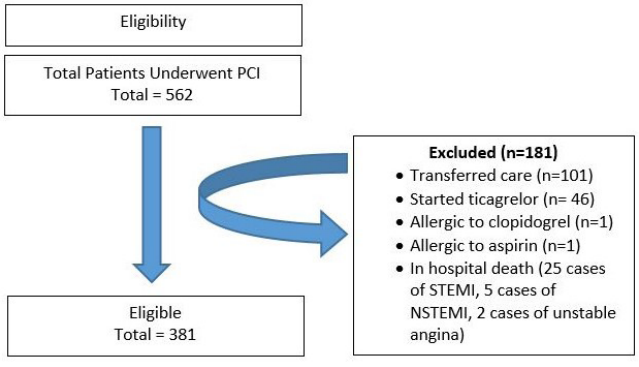

Figure 1: Recruitment of patients

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) for Windows (version 20.0; IBM, New York, America). The baseline demographic characteristics of patients and reason for one year unplanned readmissions were reported as frequencies and percentages. Multiple logistic regression was performed to determine the sociodemographic predictors of higher readmission among patients, presented with odds ratio and 95% confidence interval. The statistical significance level was set at 5%. We employed a conservative estimation of sample size, with an estimated readmission prevalence of 15% (Hannan et al. 2011), and the confidence interval and margin of error fixed at 95% and 5%. The minimal sample size required was 195 (2004, Raosoft Inc, Seattle, Washington, America).

RESULTS

Total patients that underwent PCI were 563 in year 2014, where 381 (67.7%) patients were included for readmission analysis. The average age of the patients in the study was 56.9 ± 10.7 years. Majority of the patients were male (331/381; 86.1%) and the ethnicity distribution of patients were as follow: Malay 37.8% (144/381), Indian 34.6% (132/381) and Chinese 27.6% (105/381). Majority of the patients (280/381; 73.7%) had at least one concurrent disease. Smokers accounted for 32.3% (123/381) of patients. The most common concurrent chronic disease among these patients were hypertension (266; 69.8%) followed by diabetes mellitus among 53.5% (204/381) of patients. ST elevation MI (STEMI) was the most common reason of PCI among the patients (Table I).

A total of 107 (28.1%) patients had 156 unplanned readmissions one year post-PCI, of which patients' admission within 30 days were 9.4% (36/381). The unplanned readmissions were attributed to cardiac, non-cardiac and bleeding related causes. Cardiac readmission was the highest (98/156; 62.8%) among the unplanned admissions. Among the patients that were admitted for cardiac cause, acute coronary syndrome was most common, accounting for 80 out of 98 admissions. There was a total of 37.2% (58/156) non-

Table 1: Baseline Demographic Characteristic of Patients that Underwent PCI

Baseline Characteristics	No Admission (N=274)	Readmission (N=107)	Total (N=381)	p value
Age (year)	56.0 (10.7)	59.2 (10.4)	56.9 (10.7)	0.008
Gender, Male	238 (86.9)	93 (86.9)	331 (86.9)	0.568
Ethnicity				
Malay	106 (38.7)	38 (35.5)	144 (37.8)	
Chinese	70 (25.5)	35 (32.7)	105 (27.6)	0.370
Indian	98 (35.8)	34 (31.8)	132 (34.6)	
Present with Comorbidities,	185 (67.5)	95 (88.8)	280 (73.7)	<0.001
Comorbidities List[a]				
Hypertension			266 (69.8)	
Diabetes			204 (53.5)	
Hyperlipidemia			83 (21.8)	
Ischemic heart diseases			58 (15.2)	
Chronic pulmonary disease			51 (13.4)	
Thyroid disorders			46 (12.1)	
Renal Disease			25 (6.6)	
Congestive heart failure			21 (5.5)	
Cerebrovascular disease			11 (2.9)	
Rheumatic disease			11 (2.9)	
Peptic ulcer disease related			11 (2.9)	
Atrial Fibrillation			7 (1.8)	
Benign prostate hyperplasia			4 (1.0)	
Gout			4 (1.0)	
Others			9 (2.4)	
Smokers	93 (33.9)	30 (28.0)	123 (32.3)	0.268
Reason for PCI				
ST Elevated MI (STEMI)	144 (52.6)	44 (41.1)	188 (49.3)	
Non-ST Elevated MI (NSTEMI)	84 (30.7)	30 (28.0)	114 (29.9)	0.004
Unstable Angina (UA)	17 (6.2)	19 (17.8)	36 (9.4)	
Others	29 (10.6)	14 (13.1)	43 (11.3)	
Stent Type				
Drug Eluting	201 (73.3)	80 (74.8)	281 (73.8)	0.538
Bare Metal	58 (21.2)	24 (22.4)	82 (21.5)	
Combination	15 (5.5)	3 (2.8)	18 (4.7)	

[a] Multiple comorbidities may present in one particular patient

cardiac related reasons. Over the one year, 9 (2.4%) patients were admitted for bleeding (Table II).

Univariate and multivariate logistics regression analysis was performed. Patients with co-morbidities had 2.4 times higher odds of unplanned readmission compared to patients without co-morbidities (OR: 2.46; 95% CI: 1.15-5.26). Patients presenting with unstable angina had 3.1 times higher odds of unplanned readmission compared to patients presenting with STEMI or NSTEMI (OR: 3.16, 95% CI: 1.47-6.78) (Table III).

During the study period, there was 32 in-hospital mortality (25 cases of STEMI, 5 cases of NSTEMI, 2 cases of unstable angina) and one out-of-hospital mortality within 30 days. Subsequently, 10 mortalities happened within the next 5 months (3 cases of cardiogenic shock, 2 cases of stroke, 1 case of ACS, 1 case of STEMI), accounting for total mortality cases of 43 within a year. The cause of death could not be determined for the other three cases because there was no record of admission in the hospital system.

DISCUSSION

This study evaluated the readmission and survival outcome among post-PCI patients treated with 2 weeks

Table II: Reason for One Year Unplanned Readmissions among Patients that Underwent PCI

Reasons for Unplanned Admission	Admission, n
Cardiac Related Admission	
Acute Coronary Syndrome	80
Heart failure	12
Cardiac syncope	2
Post infarct angina	2
Chostocondritis	2
Non-Cardiac Admission	
Infection	
Diabetic foot ulcer	3
Dengue	3
Urosepsis	2
Hospital acquired pneumonia	2
Community acquired pneumonia	2
Nosocomial Infection	2
Forehead abscess	1
Acute gastroenteritis	1
Renal abcess	1
Adverse Drug Related	
Sinus Bradycardia secondary to BB	2
Anaphylaxis shock secondary to ACEI	1
Other Non-Cardiac Conditions	
Gastroesophageal reflux disease (GERD)	7
Hypertension emergency	4
CKD or ESRF with fluid overload	3
Hypoglycaemia	2
Uncontrolled diabetes	2
Sensorineural Hearing Loss	2
Hepatitis	1
Vertebra stenosis	1
Hyperkalaemia	1
Gouty arthirits	1
Advance diabetic retinopathy	1
Bleeding Related	
Upper gastrointestinal bleeding	7
Anaemia haemorrhoids bleed	1
Bleeding from distal tooth	1
Stroke	4
TOTAL ADMISSIONS	**156**

double dose of clopidogrel in a local tertiary hospital. One-year all-cause unplanned readmission happened in 1 out of 3 patients that underwent PCI, while 43 patients died within one-year post-PCI. This study provided an alternative dosing of clopidogrel among patients who underwent PCI, which demonstrated low bleeding risk and low readmission outcome.

While the current clinical practice guideline

Table III: Results of Logistic Regression Analysis (Predictors of readmission post-PCI)

Variable	Univariate	Multivariate
	Crude OR (95% CI)	Adjusted OR (95% CI)
Age (years)	1.03 (1.01, 1.05)	
Gender		
Male	0.99 (0.51,1.93)	
Female	1.00	
Ethnicity		
Indian	0.97 (0.57, 1.66)	
Chinese	1.40 (0.81, 2.42)	
Malay	1.00	
Smoking Status		
Smoker	0.76 (0.46, 1.24)	
Non-Smoker	1.00	
Presence of Co-Morbids		
Yes	3.81 (1.99, 7.31)	2.46 (1.15, 5.26)
None	1.00	1.00
Diabetic		
Diabetic	1.26 (0.81, 1.97)	
Non-Diabetic	1.00	
Hypertensive		
Hypertensive	3.05 (1.84, 5.06)	1.91 (1.05, 3.45)
Non-Hypertensive	1.00	
Reason for Initial PCI		
NSTEMI	1.17 (0.68, 1.99)	1.07 (0.61, 1.85)
UA	3.66 (1.75, 7.64)	3.16 (1.47, 6.78)
Others	1.58 (0.77, 3.25)	1.34 (0.64, 2.82)
STEMI	1.00	1.00
PCI Findings		
Two Vessel Disease	1.55 (0.94, 2.58)	
Three Vessel Disease	1.44 (0.79, 2.63)	
Single Vessel Disease	1.00	

recommended ticagrelor over clopidogrel among stented patients (19), the use of ticagrelor was restricted in the local public hospital, as medications for patients admitted in the public hospitals were fully subsidised by the federal government. Specifically, ticagrelor costed 6.7 times higher than clopidogrel. In the local hospital, all patients would be started on clopidogrel post-PCI, while switching to ticagrelor happened only when patients readmitted for stent thrombosis or recurrent acute coronary syndrome.

The evidence supporting this practice has been documented in a few papers. Mehta et al. reported that a 7-day double-dose clopidogrel regimen was associated with a reduction in cardiovascular events and stent thrombosis compared with the standard dose (20). Two systematic reviews reported a higher clopidogrel maintenance dose (150mg) can reduce major adverse cardiac events compared to standard 75mg clopidogrel, without significant increase in bleeding risk (13,21). Additionally, double dose clopidogrel overcomes the diminished clopidogrel response among the Asian population due to genetic polymorphism (22,23). A recent local study demonstrated the benefits of double dose clopidogrel therapy in achieving a minimum clopidogrel plasma concentration for a therapeutic effect (24). In congruence with the previous studies, our findings reported a low readmission of the 2 weeks double dose clopidogrel. Given the high risk of stent thrombosis and non-responders to clopidogrel among the local population, with the current economic constraint of the public facilities, this regimen may serve as a practical alternative for post-PCI patients in the local setting with minimal adverse outcome.

It is imperative to note that the 30 days readmission rate was the most commonly used parameter to measure post PCI patients' outcome in most studies. In this study, the 30 days readmission rate was notably low (9.4%). This was comparable to larger studies conducted in the United States from year 1998 – 2008 (14) and year 2007 – 2010 (15), where the readmission rates ranged from 8.0% to 9.4%. In contrary, another study involving multiple sites reported a higher readmission rate of 11 – 15% (16). Nevertheless, with the presence of several hospitals in the study district, readmission of patients to other hospitals cannot be ruled out, which may result in a low readmission rate.

In our study, the presence of comorbidities, hypertension and unstable angina were the factors associated with higher readmission within 1-year post PCI. In consistence with other studies, the most common reason associated with readmission were cardiac related. In Massachusetts, predictors of 30 days readmission among 25,358 patients who underwent PCI included history of heart failure, advanced age, emergency PCI and diabetes (17). While in a single centre study at the Mayo Clinic, female patients, low education, patients with unstable angina, stroke events and chronic diseases were associated with higher readmission (14). Hence, in order to reduce the events of readmission, elderly patients with comorbidities and those from a lower social class should be monitored more closely and given detailed counselling post-PCI.

Despite the widely reported bleeding side effects of clopidogrel, the incidence of bleeding requiring admission was low (2.4%) in this study. Notably, one patient completed only 10 months of clopidogrel due to recurrent upper gastrointestinal bleeding. Meanwhile, one event of lethal subarachnoid bleeding occurred at day fifteenth post PCI. In the Efficient trial (18), patients were started on double dose clopidogrel for one month, resulted in a bleeding incidence of 8.3% (4/47). Our findings suggested that the shorter duration of double dose clopidogrel adopted in this study could be the reason of fewer major bleeding events.

One of the limitation of this study was due to its retrospective nature, with considerably large pool of missing data causing one-third of post-PCI patients not taken into account. This was a single centred study and therefore the results cannot be generalized to other hospitals, but only illustrate the findings in a tertiary cardiac hospital. However, it offered valuable insight regarding the adverse events, readmission and mortality among post-PCI patients in the local setting. In addition, the current outcome of the two weeks high

dose clopidogrel regimen may provide preliminary results and act as a guidance for other cardiac hospital and adapted among post-PCI patients in the near future. In order to confirm the findings of this study, future randomized control studies comparing 2 to 4 weeks of double dose clopidogrel and ticagrelor in ACS patients undergoing PCI is warranted.

CONCLUSION

This study suggests that the two-week double-dose clopidogrel treatment following percutaneous coronary intervention was safe, with low bleeding adverse events and low readmission. Nevertheless, a large-scale randomized control trial is needed to verify the findings.

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