PREVALENCE OF MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACEs) POST ANGIOPLASTY – HUSM EXPERIENCE

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LIST OF ABBREVIATIONS

ACC	: American College of Cardiology
ACE	: Angiotensin converting enzyme
ACME	: Angioplasty Compared to Medicine
ACS	: Acute coronary syndrome
AHA	: American Heart Association
AIRE	: Acute Infarction Ramipril Efficacy Study
ARB	: Angiotensin receptor blocker
ARMYDA	: Atorvastatin for Reduction of Myocardial Damage during Angioplasty
AST	: Aspartate transaminase
ASTEROID	: A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden
BP	: Blood pressure
CABG	: Coronary artery bypass grafting
CAD	: Coronary artery disease
CAMELOT	: The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis
CAPRIE	: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
CK-MB	: Creatinine kinase-myocardial band
CI	: Confidence interval
CLARITY	: Clopidogrel as Adjunctive Therapy
CURE	: Clopidogrel in Unstable Angina to prevent Recurrent ischaemic Event

CREDO	: Clopidogrel for the Reduction of Events During Observation
DBP	: Diastolic blood pressure
eGFR	: estimated GFR
ECG	: Electrocardiography
EPISTENT	: Evaluation of Platelet IIb/IIIa Inhibitor for Stenting
ERACI II	: Argentine Randomized Study Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Patients With Multiple-Vessel Disease
ESSENCE	: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group
FBS	: Fasting blood sugar
FRISC II	: Fast Revascularisation During Instability in Coronary Artery Disease
GISSI-3	: Gruppo Italiano per lo Studio della Supravvivenza nell'Infarto Miocardico-3
HDL-C	: High density lipoprotein – cholesterol
HUSM	: Hospital Universiti Sains Malaysia
ISIS-4	: International Study of Infarct Survival-4
LAD	: Left anterior descending artery
LDH	: Lactate dehydrogenase
LCx	: Left circumflex artery
LMS	: Left main stem
LMWH	: Low molecular weight heparin
MI	: Myocardial infarction

MIRACL	: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
NCEP ATPIII	: National Cholesterol Education Program Adult Treatment Panel III
NHLBI	: National Heart, Lung and Brain Institute
NSTEMI	: Non-ST elevation myocardial infarction
PTCA	: Percutaneous transluminal coronary angioplasty
PCI	: Percutaneous coronary intervention
PROVE-IT	: Pravastatin or Atorvastatin Evaluation and Infection Therapy
OR	: Odds ratio
RCA	: Right coronary artery
RCT	: Randomised control trial
REVERSAL	: Reversal of Atherosclerosis with Aggressive Lipid Lowering
SAVE	: Survival and Ventricular Enlargement Study
SBP	: Systolic blood pressure
SD	: Standard deviation
SEM	: Standard error of mean
TIMI	: Thrombolysis In Myocardial Infarction
UA	: Unstable angina
UFH	: Unfractionated heparin
VALIANT	: Valsartan in Acute Myocardial Infarction Trial
WHO	: World Health Organisation

Abstrak

Latarbelakang: Intervensi koronari secara kutanus (PCI) telah dijalankan di kebanyakan pusat kardiologi di serata dunia untuk merawat sakit jantung. Walaubagaimanapun, pesakit-pesakit yang menjalani rawatan ini juga tidak terlepas dari komplikasi akibat prosedur ini.

Tujuan: Objektif utama kajian ini adalah untuk menentukan kadar kejadian komplikasi koronari (MACEs) selepas prosedur angioplasti di Hospital Universiti Sains Malaysia (HUSM). Objektif kedua adalah untuk menentukan demografi dan data angiografi di kalangan pesakit yang telah menjalani PCI. Juga, hubungan komplikasi prosedur angiografi dengan pembolehubah tak bersandar akan dikaji. Kawalan factor-faktor risiko termasuk kawalan kencing manis dan kolesterol selepas enam bulan dianalisakan dalam kajian ini.

Kaedah: Sejumlah 240 pesakit yang menjalani rawatan koronari angioplasty dengan 'stent placement' terlibat dalam kajian kohort prospektif ini.

Keputusan: Sejumlah 21 pesakit (8.9 %) telah mengalami MACEs selepas PCI. 5 pesakit telah gagal dihubungi dalam kajian ini. Terdapat 2 pembolehubah dalam ujian Chi-square yang menunjukkan hubungan dengan MACEs. Ini termasuk 'two vessel residual disease' ($p< 0.001$) dan penglibatan 'right coronary artery disease (RCA)' ($p=0.004$). Analisis multivariasi telah mengekalkan hubungan 2 pembolehubah tersebut iaitu 'two vessel

residual disease' (p=0.052, OR 2.55, 95 % Cl 0.99-6.58) dan 'right coronary artery disease (RCA)' (p=0.026, OR 5.53, 95 % Cl 1.22-24.96). Analisa multivariasi juga telah menunjukkan hubungan di antara HbA1C yang tinggi dengan MACEs (p=0.011, OR 1.93, 95 % Cl 1.16-3.20).

Pesakit yang ada kencing manis dan LDL-Kolesterol (LDL-C) sebelum prosedur koronari angioplasti mempunyai perkembangan yang baik dari segi kawalan metabolik iaitu pengurangan dalam HbA1C (p=0.002) dan LDL-C (p<0.001). 55.7% pesakit yang mempunyai hiperlipidaemia telah mencapai LDL-C < 2.6mmol/l.

Kesimpulan Kesimpulannya, keputusan kajian ini telah menunjukkan kadar MACEs di kalangan pesakit yang telah menjalani PCI adalah tidak tinggi di HUSM. 'Residual two vessel disease', penglibatan 'RCA' dan HbA1C yang tinggi menunjukkan hubungan erat dengan kadar kejadian MACEs selepas PCI. Kumpulan pesakit ini mungkin mendapat manfaat jika menjalani kajian reangiografi lebih awal, terapi revaskularisasi secara berperingkat dan kawalan factor-faktor risiko metabolik yang lebih agresif.

Abstract

Background: Percutaneous coronary intervention (PCI) has been done in most cardiology centres worldwide for relief of angina. However, the procedure is also associated with intra and post procedural complications.

Objectives: The primary objective of this study was to determine the prevalence of major adverse cardiovascular events (MACEs) in patients undergoing PCI in our cardiology unit in Hospital Universiti Sains Malaysia (HUSM). The second objective was to have a baseline demographic and angiographic data of the patients who had undergone PCI as well as comparison of association between independent variables with MACEs. Risk factor control in terms of diabetic and lipid control was also analysed during clinic follow-up.

Methods: A total of 240 patients who underwent coronary angioplasty with stent placements were recruited into this prospective cohort study.

Results: 21 patients (8.9 %) had MACEs post PCI. 5 patients had drop out from the study during follow-up. 2 variables were significantly associated with MACEs post PCI using Chi-Square test including two vessel residual disease ($p<0.001$) and right coronary artery disease(RCA) involvement ($p=0.004$). Multivariate analysis maintained the association of the 2 variables including two vessel residual disease ($p=0.052$, adjusted OR 2.55 95% CI 0.99-6.58) and RCA involvement ($p=0.026$, adjusted OR 5.53 95% CI 1.22-24.96).

Multivariate analysis also identified higher HbA1C had significant association with MACEs (p=0.011, adjusted OR 1.93, 95% CI 1.16-3.20).

Patients who were diabetics or had high LDL-Cholesterol (LDL-C) prior to coronary angioplasty had significant improvement in metabolic risk control including reduction in HbA1C (p=0.002) and LDL-C (p<0.001). Furthermore, 55.7% of our hyperlipidaemic patients managed to achieve targeted LDL-C of <2.6mmol/l.

Conclusion: This study has shown that the prevalence of MACEs in patients undergoing PCI was not high in HUSM. Residual two vessel disease, RCA involvement and higher HbA1C were highly predictive of increased risk for MACEs post PCI. This group of patients may benefit from earlier reangiographic studies, staged revascularization therapies and more aggressive control of metabolic risk factors.

Chapter 1

1.0 Introduction

In Malaysia, cardiovascular disease remains an important cause of death. It accounts for 20-25% of all deaths in government hospitals from 2000 to 2005. Acute coronary syndrome accounts for the majority of these deaths (Kementerian Kesihatan Malaysia 2000-2005). There has been much progress made in the management of coronary heart disease, especially in revascularization of occluded coronary blood vessels.

Patients with acute coronary syndrome undergo percutaneous transluminal coronary angioplasty (PTCA) to improve survival in STEMI and to alleviate symptoms of angina in unstable angina or NSTEMI.

In the Angioplasty Compared to Medicine (ACME) trial, 212 patients with stable angina and single-vessel coronary artery disease were randomly assigned to treatment with PTCA or medical therapy. Although the initial success rate of PTCA was only 80%, patients who underwent the procedure had a greater improvement in exercise performance and required less antianginal medication. These patients were also more likely to be free of angina than the patients treated medically (Parisi et al, 1992).

Bucher et al (2000) did a meta-analysis of randomized controlled trials conducted worldwide between 1979 and 1998 on patients with coronary artery disease and noted that patients treated with angioplasty had less angina as compared with medical treatment.

Most patients with unstable angina can be treated successfully with aggressive medical therapy. However, coronary angiography and revascularization have a role in patients with refractory angina. Peyter et al (1985) did a study on 60 patients with unstable angina that was refractory to treatment and noted improved cardiac functional status after successful coronary angioplasty. This was demonstrated by absence of ischemia during thallium isotope studies in 80% of the study patients.

ACC/AHA Guidelines 2006 noted that many patients with chronic stable angina or unstable angina who do not respond adequately to medical therapy often have significant coronary artery stenosis that are suitable for revascularization with PCI. The committee also supported utilizing stenting as the primary therapy following unstable angina and NSTEMI based on studies such as FRISC II and TACTICS TIMI 18. These trials have favored the invasive approach over medical therapy (ACC/AHA Guidelines, 2006).

In patients who had undergone successful PTCA, major adverse cardiovascular events (MACES) have been noted. Factors associated with MACES include advanced age, female sex, diabetes, prior myocardial infarction, multivessel disease, left main or equivalent coronary disease, pre-existing left ventricular impairment and impaired renal function (ACC/AHA Guidelines, 2006).

Another important factor for MACE occurrence is restenosis of the stented vessel. Restenosis occurs in about 30% of patients in whom a narrowed artery has been dilated (Leimgruber et al, 1986). A study conducted in Zurich in 1987 by Gruentzig et al

involving 169 undergoing PTCA noted 30% of patients developing restenosis during the first 6 months.

The NHLBI Dynamic Registry of Coronary Interventions was initiated in 1997 to assess the practice of percutaneous coronary intervention (PCI) in the United States. In 2002, the expert panel examined angina rates at 1-year follow-up in Registry patients and factors predictive of recurrence of symptoms. The study noted that approximately 25% of patients receiving PCI are angina-free at 1 year. Female gender and other subgroups with risk factors had more angina symptoms. The registry committee concluded that evaluations of patients post PCI using self-reported activity and quality of life limitations to evaluate angina as a key follow-up outcome was recommended (Richard Holubkov et al, 2002).

In HUSM, coronary angiograms with angioplasty have been done since October 2002 in the cardiology unit. My study aims to follow-up the patients who underwent coronary angioplasty with regards to MACEs. This would help in determining the outcome of our patients and also whether the risk factors are adequately controlled.

1.1 Thrombus formation

1.1.1 Physiology of thrombus formation.

Accumulation of lipid-laden macrophages and smooth muscle cells also known as foam cells occur within atherosclerotic plaques. The oxidized low-density lipoprotein cholesterol (LDL-C) found in foam cells is cytotoxic, procoagulant and chemotactic. As the atherosclerotic plaque grows, macrophage proteases and neutrophil elastases produced within the plaque cause thinning of the fibromuscular cap that covers the lipid core. The increasing plaque instability coupled with blood-flow shearing effect and circumferential wall stress lead to plaque fissuring or rupture in the cap producing a rich substrate for thrombus formation.

1.2 Definition and Pathogenesis of Acute Coronary Syndrome.

ACS consists of unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) and ST elevation myocardial infarction (STEMI). It is a clinical spectrum depending upon the degree and acuteness of coronary occlusion.

a)Unstable angina

In majority of unstable angina cases, there is disruption of atherosclerotic plaque. Though this is non-occlusive, it usually results in reduced myocardial perfusion with resultant haemodynamic deficit.

Intense focal spasm which occurs in Printzmetal's angina causes dynamic obstruction by intense focal spasm of a segment of an epicardial coronary artery. This spasm is caused

by hypercontractility of vascular smooth muscle and/or endothelial dysfunction. Unstable angina can also be caused by severe narrowing without any spasm or thrombus. This usually occurs in some patients with progressive atherosclerosis or with restenosis after a percutaneous coronary intervention.

Infection leading to arterial inflammation can also lead to unstable angina via arterial narrowing, plaque destabilization, rupture and thrombogenesis. Activated macrophages and T-lymphocytes at the plaque shoulder can cause metalloproteinases expression leading to disruption of the plaque. This will subsequently cause unstable angina.

Patients with underlying coronary atherosclerotic disease have compromised myocardial perfusion. Thus, certain precipitating conditions will lead to development of unstable angina and/or NSTEMI in these individuals. These conditions include increased myocardial oxygen requirements such as in fever and thyrotoxicosis, reduced coronary blood flow due to hypotension, and reduced myocardial oxygen delivery such as in anaemia or hypoxaemia (Braunwald E, 1998).

In stable angina, there is a fixed coronary stenosis leading to reduced blood flow and development of a slow and progressive plaque growth. This process allows for the occasional development of collateral flow in stable angina (Malaysian Clinical Practice Guidelines on UA/NSTEMI, 2002).

b) NSTEMI

In NSTEMI, disruption of atherosclerotic plaques causes microembolism of platelet aggregates and components of the disrupted plaque. This process causes microinfarction and lead to release of myocardial markers.

c) STEMI

STEMI involves myocardial muscle necrosis due to inadequate blood supply following acute total coronary occlusion. This is usually caused by an atherosclerotic plaque rupture, fissuring or ulceration with superimposed thrombosis and coronary vasospasm. STEMI can also occur from non-atherosclerotic arterial diseases such as coronary embolism, coronary vasospasm and vasculitis (Fallon et al, 1996).

1.3 Diagnosis of Acute Coronary Syndrome.

Most patients with acute coronary syndrome usually present with chest pain. The chest pain or discomfort is usually central, retrosternal in the left chest and may radiate to the jaw or down the upper limb. The nature of the pain varies from crushing, pressing or burning in nature. The severity of the pain also varies hence it is difficult to differentiate the diagnosis of STEMI, NSTEMI and unstable angina based on symptoms. Furthermore, some of the patients especially in women, diabetics and the elderly may present with atypical symptoms such as shortness of breath, epigastric discomfort and nausea.

The objective of physical examination in acute coronary syndrome is to identify precipitating factors and complications. Evidence of hypotension, left ventricular or biventricular failure carries a poorer prognosis.

a) Unstable angina/ NSTEMI

Electrocardiography is helpful in supporting the diagnosis and provides prognostic information (Cannon et al, 1997). ECG features to diagnose UA/NSTEMI include:

1) ST segment depression > 0.05mV
2) T-wave inversion > 0.2mV in the precordial leads

Serum biochemical cardiac markers are important indicators of myocardial necrosis. As UA does not involve myocardial necrosis, the serum cardiac markers are not elevated. NSTEMI is differentiated from UA by the presence of elevated serum cardiac markers.

b) STEMI

ECG features in STEMI are:

1) New onset ST-segment elevation of:
    - $\geq$ 0.1 mV in 2 contiguous limb leads, or V4 to V6 and/or
    - $\geq$0.2 mV in 2 contiguous precordial leads V1 to V3
2) presumed new left bundle branch block

Diagnosis of STEMI is also made based on the rise in serum cardiac markers (Malaysian Clinical Practice Guidelines on Management of Acute ST Segment Elevation Myocardial Infarction, 2007).

These cardiac biomarkers include cardiac troponins, creatinine kinase-myocardial band (CK-MB), creatinine kinase, myoglobin and fatty acid binding proteins. Cardiac troponins and CK-MB are the most specific cardiac biomarkers. They are raised after 3-8 hours after onset of NSTEMI or STEMI. CK-MB rises early and fall early, thus it is useful for diagnosis of re-infarction. Troponins are not useful for diagnosing re-infarction as it remains elevated up to 14 days. Myoglobin is not cardiac specific but it has high sensitivity and is detected as early as 2 hours after onset of chest pain (Mair et al, 1995 and Zimmerman et al, 1999). AST and LDH levels are not sensitive or specific for NSTEMI or STEMI with frequent false positive elevations. It is recommended that serum cardiac biomarkers be measured at periodic intervals, at hospital admission and repeated at 12-24 hours later.

In patients with ongoing chest pain and high index suspicion of acute coronary syndrome, repeated 12 lead ECG tracings at close intervals at least 15 minutes may show evolving changes.

1.4 Management of Acute Coronary Syndrome

Antithrombotic therapy is essential to improve mortality in acute coronary syndrome. The most effective therapy is combination of aspirin, clopidogrel, unfractionated heparin

(UFH) or low molecular weight heparin (LMWH) and a platelet glycoprotein IIb/IIIa receptor antagonist.

a) Antiplatelet agents

Antiplatelet therapy consists of acetylsalicyclic acid (ASA), an cyclo-oxygenase inhibitor and clopidogrel and ticlopidine, both adenosine diphosphate receptor (ADP) antagonists.

ASA acts by inhibiting cyclooxygenase-1 within platelets, hence preventing the formation of thromboxane A2 which inhibits platelet aggregation. Additionally, ASA may also reduce plaque rupture and its sequalae (Ridker et al, 1997). Antiplatelet Trialists Collaboration (1994), a collaborative overview of randomized trials of antiplatelet therapy noted significant reduction of death, myocardial infarction and stroke in various categories of patients by 25 %.

ADP antagonists blocks adenosine diphosphate receptor resulting in inhibition of platelet aggregation. CAPRIE steering committee (1996) reported relative risk reduction in incidence of ischaemia, MI or vascular death by 8.7% in favour of clopidogrel when patients were randomized to receive either ASA 325mg/day or clopidogrel 75mg/day). CURE trial showed significant reduction in incidence of cardiovascular death, nonfatal MI or stroke by 9.3% in patients who were given clopidogrel (300mg immediately followed by 75mg/day) within 24 hours after the onset of ACS (Yusuf et al, 2001).