Summary, Conclusions and Future Perspectives

Summary

Cardiovascular disease is the leading cause of mortality worldwide, including Indonesia. To decrease mortality rates, the system of care for acute myocardial infarction (AMI) patients had to be improved. The Jakarta Acute Coronary Syndrome (JAC) registry revealed that 59% of all ST-segment elevation myocardial infarction (STEMI) patients do not receive reperfusion therapy and ≈52% of these patients were referred from other hospitals. The time from onset of infarction to hospital admission was >12 hours in ≈80% of the cases. This thesis shows that, based on the characteristics of patients with acute coronary syndrome (ACS) derived from the JAC registry, implementation of a network using a pharmaco-invasive reperfusion strategy in Jakarta is feasible. This network focused on the care of AMI patients in the pre-hospital as well as in-hospital setting (**Chapter 2.1**).

After introduction of the network (Jakarta Cardiovascular Care Unit Network system), the implementation and effectiveness of the treatment protocol for patients with STEMI were evaluated by measuring performance indicators. **Chapter 2.2** shows that after introduction of the network in 2011, STEMI patients had more inter-hospital referrals (61% vs. 56%, p<0.001) more primary percutaneous coronary intervention (PCI) procedures (83% vs. 73%, p=0.005), and more often a door-to-needle time <30 minutes (84.5% vs. 80.2%, p<0.001) than in the period 2008-2010, but numbers of patients who presented very late (>12 hours after symptom onset) were similar (53% vs. 51%). Moreover, the numbers of patients with door-to-balloon time <90 minutes and in-hospital mortality rate were similar in 2011 and in 2008-2010 (49.1% vs. 51.3%, and 8.3% vs. 6.9%, respectively). We need further improvements of the pre-hospital protocols, particularly the electrocardiogram (ECG) transmission system, and further improvements of in-hospital protocols.

An important perspective in the treatment of acute STEMI patients is how to improve the result of acute reperfusion therapy (primary PCI), as illustrated in **Chapter 3**. It is well known that primary PCI as part of mechanical reperfusion therapy is the preferred treatment option in patients with acute STEMI. Distal embolization by atherothrombotic material that might occur during primary PCI will cause microvascular bed occlusion, leading to suboptimal reperfusion and increase in mortality rate. **Chapter 3.1** provides a review on the management of thrombus in the catheterization laboratory in the setting of primary PCI. This review discusses several strategies available for “fighting” coronary thrombus to prevent distal embolization of atherothrombotic material, based on latest evidence. The available modalities are: (i) glycoprotein IIb/IIIa inhibitors (GPIs); (ii) use of manual and mechanical thrombus aspiration catheters; (iii) use of protection devices; and (iv) use of stents specially designed for thrombus entrapment. At the end of chapter 3.1 we present a practical guide for thrombus aspiration and a practical clinical algorithm to be used during primary PCI.

The study presented in **Chapter 3.2** aims to test the “the earlier, the better concept” for GPI administration before primary PCI. We investigated the timing of eptifibatide initiation. Early intravenous administration (≤30 minutes after ED admission) was compared with late initiation

(>30 minutes) of eptifibatide administration. The pre-procedural patency of the infarct-related artery (IRA) was the primary end-point. In this population (mostly patients with acute STEMI who presented late), we failed to show an improvement in pre-procedural IRA patency in the early group, i.e., eptifibatide initiation ≤30 minutes after ED admission, as compared to late initiation of eptifibatide administration. Furthermore, the enzymatic infarct size and left ventricular ejection fraction were similar in the early group and in the late group.

The purpose of the randomized study presented in **Chapter 3.3** is to assess the efficacy and safety of a second generation drug-eluting stent (everolimus) compared to a bare metal stent in patients with acute STEMI undergoing primary PCI using routine eptifibatide infusion. After 30-days follow-up, the major adverse cardiac event (MACE) rate was similar between everolimus-eluting stent group and bare metal stent group (both 1.3%). No stent thrombosis was observed in the everolimus-eluting stent group. The achievement of final TIMI flow 2 or 3, myocardial blush grade 2 or 3 and in-hospital bleeding rate were similar in the two groups.

Recently, the choice of an access site for a primary PCI procedure, trans-radial approach (TRA) vs. trans-femoral approach (TFA) has become an important issue in the field of interventional cardiology, since choice of access site has been linked with the aggressive antithrombotic and antiplatelet treatment in STEMI patients, that oven provoke access site bleeding. Bleeding from the access site itself has been associated with an increased risk of death and ischemic events. **Chapter 3.4** demonstrates that changing the access for primary PCI from the femoral to the radial artery was associated with a significant reduction of 30-day mortality and MACE rates (by ≈50% for both). At one year, the mortality and MACE rates were also in favor of TRA compared to TFA (reduced by about 40-50% for both). TRA was associated with a significantly lower rate of access site complications (0.9% vs. 8.2%, $p<0.0001$) and a lower rate of major bleeding (1.1% vs. 4.3%, $p<0.001$) than TFA.

In ≈50 years of use, the intra-aortic balloon pump (IABP) has become the most common method of mechanical cardiac assistance in acute cardiology, particularly in ACS patients. However, real world data regarding IABP application in ACS patients is relatively scarce. In **Chapter 4.1** we analyzed the characteristics of ACS patients who received IABP support. The survivors had higher proportion of non-cardiogenic shock ($p<0.001$), more IABP usage as backup for a revascularization procedure ($p=0.002$), fewer history of resuscitation ($p=0.043$) and fewer usage of mechanical ventilator support ($p<0.001$) than the non-survivors.
At 30 days follow-up, non-ST elevation (STE) ACS patients had lower mortality than STEMI patients ($p<0.001$) and non-STE ACS patients without cardiogenic shock showed the lowest mortality compared to other profiles of ACS patients ($p<0.001$). We also found that heart rates ≥100 beats per minute prior to IABP insertion was the strongest predictor of 30-days mortality (hazard ratio=5.69; $p=0.011$).

During trans-radial catheterization, a spasmolytic cocktail is needed to prevent radial artery spasm (RAS), which may lead to serious complications. Spasm itself is a predictor of procedural

failure. Nitroglycerin and calcium channel blocker are the most common vasodilator cocktail used during TRA. Whether the combination of the two drugs might have an advantage in preventing radial spasm over a single agent, is as yet uncertain. The results of the study described in **Chapter 5.1** showed that the incidence of RAS did not differ significantly between patients who received combination therapy (diltiazem plus nitroglycerin) and patients who received nitroglycerin alone (5% vs. 7%).

Chapter 6.1 evaluates whether serum uric acid level can be used as a prognostic marker in patients with acute STEMI who had fibrinolytic treatment. This prospective observational study has two important results. First, in STEMI patients with the lowest quartile of serum uric acid level (<4.8 mg/dL) and with the highest quartile (>7.3 mg/dL), the MACE rates were 8% and 20%, respectively (p=0.006). Second, the measurement of serum uric acid concentration in this study provides prognostic information of in-hospital MACE (hazard ratio=3.10; p<0.024) independently of, and better than other well-established parameters, such as age, prior AMI, history of hypertension or diabetes mellitus, resting heart rate, anterior STEMI and time delay to reperfusion therapy.

In **Chapter 6.2**, in acute non-STEMI patients, we found that a blood leukocyte count on admission >11,000/μL was an independent predictor of in-hospital MACE (hazard ratio=3.028; p<0.001). Thus, non-STEMI patients with high blood leukocyte count on admission should be treated aggressively to improve the outcome of these patients.

The quality of pre-clinical and clinical care for patients with an acute myocardial infarction in Jakarta depends on a well-organized care system that is specifically devoted to rapid diagnosis, rapid referral to a PCI-capable hospital, and rapid reperfusion therapy. Such a system, the Jakarta Cardiovascular Care Unit Network system, is assessed in this thesis for its functionality by using a registry in which quality indicators and performance measures allow qualification of the current care for patients with an acute myocardial infarction. This registry, named Jakarta Acute Coronary Syndrome (JAC) registry, allows the cardiologists and other health care professionals to determine: (1) the efficacy and safety of the care, (2) the features that need improvement, and (3) the requirements to improve these features, with the only purpose to increase the quality of pre-clinical and clinical care for patients with an acute myocardial infarction in Jakarta.

Conclusions

1. The Jakarta Cardiovascular Care Unit Network System was built to improve the care of AMI patients in Jakarta.
2. In order to increase the quality of care for AMI patients in Jakarta, the protocols in the receiving and referral centers have to be improved and an ECG transmission system has to be implemented.
3. Selective manual thrombus aspiration is an attractive concept, easy to use, and may improve the 1-year clinical outcome.

4. Large randomized trials are needed to evaluate the proper timing of eptifibatide initiation before primary PCI, preferably in patients with STEMI who presented <2 hours after symptom onset.
5. Among the cohort of STEMI patients undergoing primary PCI, the use of an everolimus-eluting stent with routine administration of intravenous eptifibatide is as safe and effective as bare metal stents after 1-month follow-up.
6. A complete transition from femoral artery access to a radial artery access is safe and effective for STEMI patients undergoing primary PCI, with favorable effects on short-term and long-term outcomes.
7. IABP appears to be safe and tended to be favorable in ACS patients without cardiogenic shock, particularly in patients presenting with non-STE ACS.
8. Diltiazem plus nitroglycerin showed no significant advantage compared to nitroglycerin alone, as a vasodilator cocktail to prevent RAS in patients undergoing trans-radial coronary procedures if performed by experienced radial operators.
9. In STEMI patients who received fibrinolytic treatment, serum uric acid concentration is an independent predictor of in-hospital MACE. This simple, inexpensive and accurate prognostic marker might be useful for risk stratification in developing countries that are primarily using a fibrinolytic agent as reperfusion therapy.
10. In non-STEMI patients, the blood leukocyte count on admission is an independent predictor of in-hospital MACE. Thus, an aggressive treatment is indicated in acute non-STEMI patients with a leukocyte count >11,000/μL.

Future perspectives

System of care for patients with acute myocardial infarction

In the acute phase of an acute myocardial infarction, a rapid diagnosis and early reperfusion therapy will minimize infarct size and prevent major complications. A well-organized network for the care of acute myocardial infarction patients enables a standardized guideline-based treatment in order to improve the quality of dedicated care. Professional collaboration between the primary physician, ambulance service, primary hospitals, and PCI-capable hospitals is essential to develop appropriate local and regional treatment protocols for acute myocardial infarction patients. Evaluations based on an ongoing registry will lead to new ideas on how to improve the network.

Primary percutaneous coronary intervention

Primary PCI remains the preferred option for the treatment of patients with acute ST-segment elevation myocardial infarction. Several strategies are available to optimize the result of primary PCI that deserve further investigation in the future such as: (i) timing and route of glycoprotein IIb/IIIa inhibitors administration which are still controversial; (ii) use of thrombus aspiration catheters in a large cohort of patients; (iii) choice of stents between bare metal and drug-eluting stents or a dedicated stent for thrombus entrapment; (iv) choice of access site between radial and femoral artery approach, which so far is in favor of the radial artery approach; and (v) use of an intra-aortic balloon pump, particularly in patients without cardiogenic shock. All

evidence will lead to global consensus about the best practice of cardiovascular medicine for the community.

Trans-radial approach for cardiovascular intervention

In current cardiology practice, the radial artery approach emerged as an effective alternative to the femoral artery approach for cardiovascular interventions like percutaneous coronary intervention and carotid artery angioplasty. The trans-radial approach requires a specific set of skills and its successful application is associated with a learning curve. In the future, the trans-radial approach is expected to be adopted in most catheterization laboratories in the world as the default strategy in a wide variety of patient groups.

Biomarkers in acute coronary syndrome

Biomarkers play an important role in the diagnosis and risk stratification of acute coronary syndrome patients. The ideal biomarkers that offer (1) early detection of myocardial necrosis, (2) risk stratification, (3) monitoring of disease progression, and (4) selection of therapy, remain to be elucidated. We need simple, inexpensive and accurate biomarkers that could be used when other established markers are not available.

The best practice of cardiovascular medicine is based on current evidence, incorporating data from clinical trials to be put into global consensus documents or guidelines. The care of patients with acute myocardial infarction will continue to improve, provided by the emerging therapeutic modalities and may lead to improvements of clinical outcomes of the patients.