Perspectives in the Treatment of Cardiovascular Disease:

From Prognostic Parameters to Therapeutic Modalities

Surya Dharma

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To my great father and mother

To my brother and my dear sister

To my family. . . . . ,

My dear wife Sukhwin

My son Galvin

My daughters Ishika, Divya Yvonne and Ishani

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General introduction and outline of the thesis

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INTRODUCTION

Over the last decade, a tremendous progress has been made in cardiovascular medicine [1,2]. The progress includes the treatment of coronary artery disease (CAD) and peripheral artery disease. In CAD, several advances have been made in the management of patients with acute myocardial infarction (AMI) such as: 1) the importance of networking in the treatment of AMI; 2) perspectives on how to improve the results of primary percutaneous coronary intervention (PCI) procedures including: (i) the administration of a glycoprotein IIb/IIIa inhibitor (GPI); (ii) strategies for "fighting" the coronary thrombus during primary PCI; (iii) choice of vascular access site (radial versus femoral artery approach) for primary PCI; (iv) choice of stents (drug eluting versus bare metal stent) for patients with acute ST-segment elevation myocardial infarction (STEMI); and 3) the use of intra-aortic balloon pump (IABP) in acute coronary syndrome (ACS) patients.

Another important perspective related to patients with AMI is the utilization of simple, inexpensive but accurate biomarkers with prognostic value such as plasma uric acid concentration and leukocyte count, which are particularly useful in a rural area when other established markers are not available.

ACUTE MYOCARDIAL INFARCTION

Coronary artery disease is the leading cause of death worldwide [3,4]. Before the era of reperfusion therapy, AMI is the most common cause of mortality in ischemic heart disease with a 30-day mortality rate between 30 and 50% [5,6], of whom 50% died in the first 2 hours after onset of symptoms [7]. However, the introduction of intensive coronary care unit (ICCU) resulted in a significant reduction in ACS mortality [8] and it has further decreased to less than 15% after the introduction of fibrinolytic therapy [9], aspirin [10,11] and ACE inhibitors [12,13]. Recently, primary PCI as part of the mechanical revascularization therapy, has become the preferred option in the treatment of acute STEMI patients with its fast and efficient re-establishment of coronary blood flow that resulted in a further reduction of mortality to an average of around 5-15% at 12 months [14-18]. In AMI patients, time between onset of chest pain and reperfusion therapy is of paramount importance for both primary PCI and fibrinolytic therapy in improving survival rates [19].

In Indonesia, the cardiovascular mortality rate is increasing over the years and reached almost 30% in 2004 compared to only 5% in 1975 [20]. Recent data from National Health Survey of Indonesia, performed by the Ministry of Health, Republic of Indonesia, showed that cerebro-cardiovascular disease is the leading cause of death in Indonesia [21]. Furthermore, a 13 years cohort study in three districts in Jakarta province showed that CAD is the leading cause of mortality in Jakarta, the capital city of Indonesia [22]. An effort should be made to decrease the mortality.

Over the years, the presentation of an AMI patient has changed, and the incidence of non ST-segment elevation ACS (non STE-ACS) has increased to account for 60% of all PCIs performed annually in the US [23]. Based on our local registry, the non STE-ACS accounts for 70% of all ACS admissions in the emergency department (ED) of our hospital [24].

Despite the introduction of the ICCU and acute reperfusion therapy for the treatment of

acute STEMI, there is still a need to optimize and improve other therapeutic modalities in order to decrease the mortality rate. These strategies include: (i) optimization of the treatment in an acute phase of an AMI (pre-hospital setting); (ii) improvement of the protocols in the receiving centers; and (iii) improvement of antithrombotic strategies to refine primary PCI results (in-hospital setting).

Acute reperfusion treatment

"Time is muscle'' has remained a fundamental principle in cardiology for more than 30 years: the primary goal of therapy for acute STEMI is timely reperfusion with either fibrinolytic therapy or primary PCI [19].

Randomized controlled trials (RCT) have shown the superiority of primary PCI over fibrinolytic therapy by reducing the incidence of major adverse cardiac events (MACE) (8% versus 14%, p<0.0001). Overall, there is about 40% reduction in ischemic events with primary PCI compared to fibrinolytic therapy [6]. However, the real life AMI characteristics and situations may differ from those in RCTs, and old trials compared primary PCI with stand-alone fibrinolytic therapy. Nowadays, fibrinolytic therapy is followed by an invasive procedure. Furthermore, offering an easy, rapid and direct access to primary PCI is often difficult, due to differences in geographic location, logistics performance and equipment of emergency medical services among each region [25].

In the real world practice in Indonesia, it is difficult to perform primary PCI in all patients with a door-to-balloon (DTB) time of <90 minutes. Even in the US, the data from the National Cardiovascular Data Registry (NCDR) showed that only 57.9% of patients receive primary PCI with a DTB time of <90 minutes [26], and data from the National Registry of Myocardial Infarction (NRMI) ¾ showed that only 4.2% of the patients had primary PCI with a DTB time of <90 minutes [27]. Moreover, the GRACE registry showed that the mean DTB time and pre-hospital delay were 75 and 120 minutes, respectively, in the year 2000-2001, but in recent years (2005-2006) these delays are prolonged to 80 and 133 minutes, respectively [28]. Finally, recent data from the European registry showed that the time from first medical contact-to-balloon inflation varied between 69 and 177 minutes [29]. These real world data show that it is difficult to achieve an appropriate DTB time as recommended by the ESC and AHA guidelines [30,31].

Primary PCI that was recommended by the guidelines cannot be performed in all STEMI patients in Jakarta. Even in a city with well-organized cardiovascular emergency network, not all STEMI patients receive timely primary PCI due to several limitations. Time delay is central for the decision what reperfusion therapy to be chosen, whether bringing the patient to the treatment (primary PCI in a major center) or bringing the treatment to the patient (intravenous fibrinolytic therapy in the pre-hospital setting).Therefore, it may be wise to combine the two strategies of acute reperfusion therapy, by giving fibrinolytic therapy as soon as possible in the pre-hospital setting and immediately referring the patient to a PCI-capable hospital for either immediate or elective coronary angiography within 3-24 hours. This strategy is known as a pharmaco-invasive approach and is widely adopted worldwide [25].

The Jakarta Acute Coronary Syndrome (JAC) registry in 2008-2009 revealed that the proportion of STEMI patients who did not receive acute reperfusion therapy was 59% and a

majority of them (52%) was referred from other hospitals. Furthermore, the time from onset of infarction to hospital admission was >12 hours in ≈80% of the cases [24]. A proper network organization plays an important and central role to optimize the treatment of a patient with AMI [25,32]. Therefore, since 2011, the Jakarta Cardiovascular Care Unit Network System has been introduced in Jakarta as a system of care for AMI patients using a pharmaco-invasive approach. This network was introduced by the ED team of National Cardiovascular Center Harapan Kita, Jakarta, Indonesia in close collaboration with other local health care providers [24].

PRE-HOSPITAL CARE OF AMI PATIENTS

The main goal of the pre-hospital care of an AMI patient is to make an early diagnosis of AMI, with the purpose to provide rapid reperfusion therapy, thus minimizing the time delay from diagnosis to reperfusion [33,34]. Time delay has been associated with increased infarct size and mortality [35]. We observed that time delays were related to problems in daily management of AMI patients in Jakarta such as:

- Patient delay: lack of awareness of cardiac symptoms, fear of hospital and financial problems.
- System delay: diagnosis delay by general practitioners, diagnosis delay in the primary hospital, transportation delay, lack of collaboration between specialists in referral centers, receiving centers and ambulance organization.

A well-organized system of care for AMI patients should minimize time delays, but depends on a close and intensive collaboration between the primary hospital, regional/local ambulance services, community hospital without PCI facilities and regional PCI-capable hospitals. The Jakarta Cardiovascular Care Unit Network system was built to improve the system of care of AMI patients in Jakarta, Indonesia, serving about 11 million people with 15,000 people/km^2 [24]. It is a multidisciplinary team approach, harmonizing the activities of all hospitals in Jakarta that will give the best cardiovascular services to the community by providing two reperfusion therapy options (primary PCI or fibrinolytic therapy) depending on the time to reach the catheterization laboratory. Importantly, the effectiveness of the system should always be monitored by recording simple quality indicators in on-going registries.

The effectiveness of the network system was analyzed by recording the performance indicators in STEMI patients, such as the numbers of patients receiving primary PCI or fibrinolytic therapy, door-to-reperfusion time, and proportion of patients who presented late [32,36].

The performance indicators demonstrated that after the introduction of the network in 2011, the awareness of AMI has increased, shown by the higher proportion of STEMI patients referred from community hospitals, compared to 2008-2010 (61.2% vs. 56.2%, p<0.001). After the application of the network, the number of patients undergoing primary PCI has increased as well (83.1% vs. 73.3%, p=0.005). However, the proportion of patients who reached the target door-to-balloon time (<90 minutes), as recommended by the guidelines [30,31], did not improve between the two periods. Likewise the proportion of patients who presented late (>12 hours) did not improve between the two periods (53.1% vs. 51.2%, p=0.466). Therefore, in-

hospital mortality has not been changed. Indeed, it is known that late presentation of an AMI is associated with a larger final infarct size, even after primary PCI [37].

Based on these performance indicators, efforts should be made to improve the AMI system of care in Jakarta, including improvement of pre-hospital and in-hospital protocols. In pre-hospital care, the triage chart form and ambulance communication chart form should be improved and discussed extensively among those involved in these services. Pre-hospital 12-lead electrocardiogram recording plays an important role in a system of care for STEMI patients [38-40]. The electrocardiogram should be transmitted immediately to the ED of National Cardiovascular Center Harapan Kita, which is the host of the network (heart line) that is staffed 24 hours per day for 7 days per week (including catheterization laboratory service). The electrocardiogram transmission system needs to be improved, from a faximile system to an internet-based transmission, to be used in the ambulance for making a more rapid and earlier diagnosis of an AMI. The fibrinolytic therapy should be used strictly and should be performed in a pre-hospital setting if the time between first medical contact and reperfusion therapy exceeds 120 minutes. All members of the emergency medical staff, including staff members of primary hospitals and ambulance services should have intensive training in protocols about where and when to transfer the AMI patient. Dual antiplatelet treatment (aspirin and clopidogrel) should be given immediately in the pre-hospital setting. The routine use of early (in-ambulance) GPI administration is not included in the protocol. The recent ESC 2012 guidelines on treatment of STEMI patients has qualified routine GPI for primary PCI as a class IIb recommendation [30].

IN-HOSPITAL CARE OF AMI PATIENTS

Important perspectives in optimizing the care for acute STEMI patients in the in-hospital setting of PCI centers are:

- Strategies to optimize primary PCI
- Improving the door-to-reperfusion time in a PCI center
- Optimizing antithrombotic therapy (the role of GPI)
- Use of intra-aortic balloon pump
- Vascular access site for primary PCI
- Selection of stents (drug eluting or bare metal stent) following primary PCI
- Finding prognostic markers to be used in daily clinical practice

Strategies to optimize primary PCI

Primary PCI has become the preferred option in the treatment of patients with acute STEMI due to its rapid and effective re-establishment of epicardial coronary flow [41]. However, distal embolization of atherothrombotic material during primary PCI has become an important issue and it is a common cause of peri-procedural complications. Distal embolization can mechanically plug the microvasculature, may promote local in situ platelet adhesion and thrombosis, and may provoke microvascular spasm and local inflammatory reactions [42,43]. In brief, distal embolization by thrombotic debris may result in occlusion of the microvascular bed resulting in suboptimal reperfusion [43] and impaired prognosis due to increased infarct

size, reduced ventricular function and a fivefold increase in 5-year mortality rate [44-46]. Moreover, a large thrombus burden in the infarct-related artery (IRA) had higher incidence of stent thrombosis than a small thrombus burden [47].

Therefore, one of the strategies to optimize primary PCI is an appropriate and aggressive management of thrombus to prevent distal embolization by thrombotic debris. Recently, the available strategies are: (i) the administration of GPI; (ii) adjunctive use of mechanical devices (thrombus aspiration and embolic protection devices); and (iii) dedicated stent for thrombus entrapment.

Based on recent evidence, the administration of GPI is associated with improved clinical outcomes [48-52], while thrombus aspiration represents an useful adjunct to pharmacotherapy in preventing distal embolization, thereby decreasing microvascular damage and achieving better myocardial perfusion [53-60].

Improving the door-to-reperfusion time in a PCI center

The results of the JAC registry showed that one of the performance indicators, the door-to-balloon time, had not improved in our hospital in 2011 compared to 2008-2010. The 2012 ESC guidelines on management of STEMI patients has strengthened the importance of shortening the time delay in PCI-capable hospitals, the goal should be to achieve a door-to-balloon delay ≤60 minutes between presentation in the hospital and primary PCI (defined as wire passage into the culprit artery) [30]. In our hospital, several attempts have been made to reduce treatment delay and to shorten the door-to-reperfusion time. First, a mini catheterization laboratory was built in the emergency unit. Second, all administration purposes related to primary PCI take place in the emergency unit only (one stop AMI service). This fast track AMI service has started in October 2012 and completely adopted since April 2013. We eagerly await the results of the performance indicators before and after application of the service.

Optimizing antithrombotic therapy (the role of GPI)

Glycoprotein IIb/IIIa inhibitors are effective and potent intravenous platelet aggregation inhibitors that have been studied in the wide spectrum of patients with ACS especially in the setting of PCI with highly thrombotic lesions. Abciximab, a monoclonal antibody, eptifibatide and tirofiban, the latter two being small molecules, are the available GPI agents [49-52]. As to their use for primary PCI, these three agents have the same position (class IIa recommendation) in the 2011 ACCF/AHA/SCAI guidelines for PCI [61]. In Indonesia, eptifibatide is the only available GPI.

Early administration of GPI has been considered to overcome the delay for receiving mechanical reperfusion [62]. Furthermore, GPI administration is one of the strategies to prevent distal embolization of coronary thrombus during primary PCI [48]. However, studies on the timing of GPI administration before primary PCI have revealed conflicting results [63-70]. It is postulated that the concept of “the earlier the better” for GPI administered before primary PCI might be true in patients who present very early, especially <2 hours from onset, since no firm fibrin cloth has been formed then yet. The benefit of GPI in “very early” onset of an infarction was shown in the On-TIME 2 study [63] and in a study by Hassan et al. [64].

Meanwhile, the 2012 ESC guideline on the management of STEMI patients has qualified the routine use of GPI as an adjunct to primary PCI as a class IIb recommendation [30], and the 2011 ACCF/AHA/SCAII PCI guidelines as a class III recommendation [61].

Use of intra-aortic balloon pump

Intra-aortic balloon pump (IABP) was introduced nearly five decades ago [71], as a simple but effective device to increase coronary perfusion, reduce afterload and reduce myocardial work [72,73]. Since then, it has become the most widely used form of mechanical circulatory support for patients with AMI, whose clinical course is complicated by cardiogenic shock. However, the real utilization rate of IABP application in STEMI patients complicated by cardiogenic shock is still low (20-39%) [74,75] and the results from the recently published IABP-SHOCK II trial [76] showed that the use of IABP in AMI patients with cardiogenic shock did not improve survival compared to medical therapy. The guidelines that recommend IABP [30,61] are strongly challenged by the results of the IABP-SHOCK II trial.

The indications for IABP insertion are not limited to AMI patients who present with cardiogenic shock (7.2% population) [77,78], but also to other ACS patients with refractory ventricular failure, high-risk patients who need cardiac support during or after general surgery, patients with refractory unstable angina [79], patients with refractory malignant arrhythmia despite optimal medical treatment [80], patients who need support during revascularization procedures [81,82] and patients who are awaiting a heart transplant [83]. Most of the IABP trials included patients with cardiogenic shock complicating an AMI due to the high mortality of such patients (42-48%) [74,84,85]. It should be noted that in the real world practice, the use of IABP is not restricted to AMI patients with cardiogenic shock. Randomized studies are needed to assess the efficacy of IABP treatment in ACS patients without cardiogenic shock.

Vascular access site for primary PCI

An important perspective in primary PCI is the choice of access site between trans-femoral approach (TFA) and trans-radial approach (TRA). This has been linked with the aggresive use of antithrombotic and antiplatelet treatment in STEMI patients that often provoke access site bleeding, as shown with TFA [86,87]. Furthermore, vascular access site complications have been shown to be associated with worse outcomes [88,89]. Several studies have shown that the TRA for primary PCI in patients with STEMI is associated with less bleeding, less major vascular complications, and lower cardiac mortality rate compared with TFA [90-92].

The advantage of TRA in ACS patients was shown by the pivotal RIVAL study, which demonstrated significantly lower vascular access site complications in patients treated with TRA than in patients treated with TFA, in both STEMI and non STE-ACS (1.4% vs. 3.7%, $p<0.0001$). In patients with STEMI, TRA, as compared to TFA, was associated with improved outcome: death, MI, stroke or non-CABG-related major bleeding within 30 days (3.1% vs. 5.2%; hazard ratio=0.60; $p=0.026$) and reduced mortality alone (1.3% vs. 3.2%; hazard ratio=0.39; $p=0.006$) [93].

A sub-analysis of the HORIZONS-AMI study has strengthen the advantage of TRA compared to TFA, by showing reduced major bleeding and improved event-free survival at one year for

patients who underwent primary PCI with TRA [94]. The RIFLE-STEACS study demonstrated that primary PCI and rescue PCI with TRA reduced 30-day cardiac mortality compared to TFA (5.2% vs. 9.2%, p=0.02). The TRA was associated with a significantly lower rate of access site-related bleeding (2.6% vs. 6.8%, p=0.002) [91]. Finally, the recent STEMI-RADIAL trial showed that PCI with TRA compared to TFA was associated with a significantly lower incidence of 30-days major bleeding and access site complications (1.4% vs. 7.2%, p=0.0001) and a signifcanty improved composite end-point of death, myocardial infarction, stroke and major bleeding (4.6% vs. 11%, p=0.0028). Furthermore, TRA was associated with shorter ICCU stay and lower contrast volume than TFA (p=0.0016 and p<0.01, respectively) [92].

Other reported advantages of TRA include earlier patient mobilization, reduced procedural and hospital costs [95-99], and equal operator radiation exposure compared to TFA [100].

We need more studies that compare TRA with TFA in the real world primary PCI procedures, particularly with respect to TRA's benefit on mortality rate. A global consensus regarding access site for primary PCI is needed to give the best cardiovascular services to the community, based on recent evidence. Now, the use of TRA in primary PCI is supported by the recent 2012 ESC guidelines on the management of STEMI patients which qualifies TRA for primary PCI, if performed by an experienced radial operator, with a class IIa recommendation (level of evidence: B) [30].

Spasm prophylaxis in TRA

The most common complication related to TRA is radial artery spasm (RAS), which can lead to serious complications and is commonly associated with procedural failure [101,102]. Therefore, a spasmolytic cocktail is needed to prevent RAS during a coronary procedure with TRA [103]. The most common cocktail used to prevent RAS are nitroglycerin and a calcium-channel blocker [104,105]. However, there is uncertainty whether dual agent therapy (calcium-channel blocker plus nitroglycerine) might have an advantage over single agent therapy (nitroglycerin alone) in preventing RAS.

Importantly, we believe that the incidence of RAS is inversely related to the operator's experience. The more experienced the operator, the less manipulation, the shorter and the smoother the procedure will be; the patient will feel more comfortable, thus will have less spasm [101,106-108].

The TRA technique requires a specific set of skills, and is associated with a significant learning curve. With appropriate training, similar success rates with the TRA and TFA may be achieved even in complex cases. Although published data suggest that 100-200 cases are necessary to become proficient in the TRA technique, expertise with TRA begins to plateau at around 1000 procedures. The learning curve is highly individual and more experienced operators may become proficient sooner. Therefore, a learning curve is essential and primary PCI using TRA should be performed only by skilled high-volume radial operators in elective settings, expected to perform primary PCI via the radial artery with high success rate [109].

Selection of stents between drug-eluting stent (DES) and bare metal stent (BMS) in STEMI patients undergoing primary PCI

The introduction of the first generation DES in 2002 has revolutionized the strategy of PCI worldwide by significantly reducing restenosis rate and target lesion revascularization rate compared to BMS [110]. However, DES is associated with an increased risk of stent thrombosis, particularly very late after stent implantation and after withdrawal of antiplatelet therapy [111-118]. Moreover, concerns have been raised with regard to the safety of DES in patients with AMI [119], and several studies have shown conflicting results. Data from a registry has suggested that implantation of DES during primary PCI was associated with an increased risk of stent thrombosis and associated with high morbidity and mortality rate [120]. Furthermore, a recent meta-analysis showed that the safety of the first generation DES was unfavorable due to very late stent thrombosis cases [121], possibly due to its association with late acquired stent malapposition [122]. But in other studies in STEMI patients treated with primary PCI, first generation DES were shown to be superior to BMS in terms of safety and efficacy [123-125]. Therefore, the second generation DES (everolimus and zotarolimus) have been developed to overcome the disadvantages related to the first generation DES. Several trials have shown an improvement of clinical outcomes in patients who received a second generation DES, after medium to long-term follow up [126-128]. The use of second generation DES has increased and these stents are now widely used for off-label indications [129] including in primary PCI of acute STEMI patients.

A recent meta-analysis showed that the everolimus-eluting stent was associated with a significant reduction in both early (30 days) definite stent thrombosis (relative risk=0.28; $p<0.0001$) and early definite/ probable stent thrombosis (relative risk=0.54; $p=0.005$) compared with pooled paclitaxel, sirolimus and zotarolimus eluting stents [130]. Although promising, the efficacy and safety of the second generation DES in primary PCI needs to be investigated further. Now, the 2012 ESC guideline on management of STEMI patients has qualified the use of DES in STEMI patients as a class IIa indication [30].

Another important perspective of acute AMI patient care is how to optimize the acute result of primary PCI, regardless of the stent type. It is postulated that stenting in a patient with acute STEMI with a highly thrombotic lesion may result in stent undersizing or incomplete stent apposition, which is known to be the predictor of stent thrombosis [131], probably due to the masking effect of thrombus in the vessel. Therefore, during primary PCI, it is reasonable to administer GPI and to perform manual thrombus aspiration, as recommended by the 2011 ACCF/AHA/SCAI PCI guidelines [61] and the 2012 ESC guidelines on management of STEMI patients [30] (class IIa indication). Finally, to evaluate the acute and long-term results of stent implantation in detail, intravascular ultrasound is an useful tool to analyze stent deployment, late stent malapposition and vessel remodeling [132-138].

Finding prognostic markers to be used in daily clinical practice

Risk stratification should be applied in all ACS patients to help the physician to identify high-risk patients and to decide the treatment strategy. Despite the use of established prognostic markers such as cardiac troponins, C-reactive protein, interleukin-6, natriuretic peptides, and

many others [139,140], there is a need to find a simple, inexpensive and accurate prognostic marker that can be used in remote areas without facilities to measure the well-established markers. It has been investigated whether serum uric acid concentration can be used as an independent predictor of MACE in patients with CAD, or only as an indirect marker of adverse event due to the association of uric acid with other cardiovascular risk factors [141-145]. The role of uric acid in ACS and its prognostic value in STEMI patients are uncertain.

Another simple marker with interesting perspectives is the blood leukocyte count. Inflammation plays an important role in the initiation and progression of atherosclerosis, including acute plaque rupture that causes acute thrombosis, which is manifested as an ACS [146-148]. The leukocyte is one of the inflammatory components [149], and the leukocyte can be measured in daily clinical practice in almost all laboratories worldwide. The prognostic value of the leukocyte count in cardiovascular disease was demonstrated in several trials, and showed conflicting results [150-156]. More studies are needed to find out whether serum uric acid concentration and blood leukocyte count have prognostic values in ACS patients.

OBJECTIVE AND OUTLINE OF THIS THESIS

This thesis describes some prognostic parameters and therapeutic modalities in the treatment of cardiovascular disease and the aim was: 1a) to assess the characteristics of ACS patients based on local ACS registry data (JAC registry); 1b) to evaluate the implementation of a treatment protocol for acute STEMI patients (the Jakarta Cardiovascular Care Unit Network System) in clinical practice based on the performance indicators; 2) to evaluate, review and describe several recent modalities and strategies to optimize primary PCI results; 3) to evaluate the safety and efficacy of IABP support from a real world ACS registry; 4) to evaluate the use of trans-radial approach for coronary procedures; and 5) to evaluate the prognostic relevance of simple biomarkers in ACS patients.

Chapter 2 is focused on the system of care for AMI patients. **Chapter 2.1** describes the characteristics of acute STEMI patients based on the JAC registry. This information should give insight for finding and building an appropriate AMI system of care in Jakarta, Indonesia. A model of an AMI system of care in Jakarta was introduced. **Chapter 2.2** studies the quality of care and performance indicators of the Jakarta Cardiovascular Care Unit Network System (based on data from the JAC registry), which is a cardiovascular care system that aims to optimize pre-hospital and in-hospital protocols for patients with acute STEMI.

Chapter 3 describes several strategies to improve the result of primary PCI. **Chapter 3.1** provides an updated review on how to prevent distal embolization of atherothrombotic material during primary PCI based on most recent data including the evolving role of GPI (agent selection, timing and route of administration), application of manual and mechanical thrombus aspiration, use of protection devices and use of stents specially designed for thrombus entrapment. Chapter 3.1 closes with a number of technical suggestions while performing the thrombus aspiration, and provides a practical clinical algorithm to prevent distal

embolization during primary PCI. **Chapter 3.2** evaluates the immediate and short-term results of early eptifibatide initiation (eptifibatide bolus administered ≤30 minutes after ED admission) compared to late initiation (>30 minutes after ED admission) in acute STEMI patients undergoing primary PCI. As primary end-point we have chosen the IRA patency before PCI, defined as the presence of TIMI 2 or 3 flow before angioplasty (angiographic criteria), and as secondary end-points we have chosen creatine kinase-MB level, left ventricular ejection fraction, in-hospital bleeding and 30-day mortality. **Chapter 3.3** briefly describes the safety and efficacy of a second generation DES (everolimus) in acute STEMI patients undergoing primary PCI after 30-days follow up. Eptifibatide infusion was routinely given in all patients before primary PCI. In **Chapter 3.4** we compare the outcomes between TRA and TFA in acute STEMI patients who underwent primary PCI. All operators were well experienced in performing TFA before adopting the TRA as a preferred access for primary PCI. Short-term (30 days) and long-term (one year) mortality and MACE rates were the primary end-points. Secondary end-points were vascular access site complications and bleeding events.

Chapter 4 is focused on the use of assist device (IABP) in patients with ACS. **Chapter 4.1** studies the outcome of patients receiving IABP treatment in our ACS series of patients from a real world local registry including patients with and without cardiogenic shock. Patients who survive and who did not survive were compared at 30 days.

Chapter 5 describes issues related to TRA for coronary procedures. **Chapter 5.1** describes the choice of a spasmolytic cocktail for the TRA between diltiazem plus nitroglycerin and nitroglycerin alone. Clinical RAS was the primary end-point.

Chapter 6 evaluates two prognostic markers in patients with ACS. **Chapter 6.1** investigates the prognostic importance of serum uric acid concentration in acute STEMI patients who received fibrinolytic therapy and **Chapter 6.2** describes the prognostic importance of blood leukocyte count in acute non-STEMI patients.

Finally, in **Chapter 7**, a general summary, conclusions and future perspectives are presented.

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System of care for acute myocardial infarction

Acute myocardial infarction system of care in the third world

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Abstract

Background

We studied the characteristics of ST-elevation myocardial infarction (STEMI) patients from a local acute coronary syndrome (ACS) registry in order to find and build an appropriate acute myocardial infarction (AMI) system of care in Jakarta, Indonesia.

Methods

Data were collected from the Jakarta Acute Coronary Syndrome (JAC) registry 2008-2009, which contained 2103 ACS patients, including 654 acute STEMI patients admitted to the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia.

Results

The proportion of patients who did not receive reperfusion therapy was 59% in all STEMI patients and the majority of them (52%) came from inter-hospital referral. The time from onset of infarction to hospital admission was more than 12 h in almost 80% of the cases and 60% had an anterior wall MI. In-hospital mortality was significantly higher in patients who did not receive reperfusion therapy compared with patients receiving acute reperfusion therapy, either with primary percutaneous coronary intervention (PPCI) or fibrinolytic therapy (13.3% vs. 5.3% vs. 6.2%, $p<0.001$).

Conclusion

The Jakarta Cardiovascular Care Unit Network System was built to improve the care of AMI patients in Jakarta. This network will harmonise the activities of all hospitals in Jakarta and will provide the best cardiovascular services to the community by giving two reperfusion therapy options (PPCI or pharmaco-invasive strategy) depending on the time needed for the patient to reach the cath-lab.

Keywords: ST-elevation myocardial infarction, system of care, pharmaco-invasive strategy.

Introduction

Tremendous progress has been made in the management of patients with ST-elevation myocardial infarction (STEMI) over the last 20 years [1,2]. Primary percutaneous coronary intervention (PPCI) is the preferred option for treating STEMI patients. Offering an easy, direct and fast access to this procedure is still difficult due to geographic and structural differences in medical services [3], especially in developing countries. Therefore, each community should find their own system of care of acute myocardial infarction (AMI) based on their AMI characteristic and emergency medical services availabilty.

The cardiovascular mortality rate in Indonesia is increasing over the years, reaching almost 30% in 2004 compared with only 5% in 1975 [4]. Recently, data from the National Health Survey of Indonesia, which was performed by the Ministry of Health, Republic of Indonesia, showed that cerebro-cardiovascular disease is the leading cause of death in Indonesia [5]. A 13-years cohort study in three districts in the Jakarta province showed that coronary artery disease is the leading cause of mortality in Jakarta, the capital city of Indonesia [6].

Jakarta is a big metropolitan city with its unique multicultural atmosphere. About 11 million people live in Jakarta with 15,000 people/km^2 of density [7]. Recently, traffic congestion has become a serious problem in the community and it is the most common cause of time delay for giving acute reperfusion therapy [8].

Efforts should be made to decrease the cardiovascular disease burden by improving primary and secondary health care. The data from the local ACS registry are very important. They will provide feedback and generate new ideas on how to improve the system of care of ACS and find the most appropriate AMI care system in Jakarta. This article will review the system of care of STEMI patients in the real-world situation in Jakarta, Indonesia, based on a local ACS registry.

Patients and Methods

Data were derived from the Jakarta Acute Coronary Syndrome (JAC) Registry database (single-centre registry) from the year 2008-2009, which contained 2103 ACS patients, including 654 acute STEMI patients who were admitted to the National Cardiovascular Center Harapan Kita (NCCHK), Jakarta, Indonesia. The NCCHK acts as a national referral hospital with 24-h cardiovascular services including PPCI capabilities. For PPCI cases, the interventional cardiologist will arive at the cath-lab in less then 30 min after the first call, whereas cath-lab nurses and radiology staff are available 24 h a day in the hospital. The numbers of PCI cases and operator volume were according to the ACC/AHA guideline recommendations.

For all patients, the initial diagnosis was made based on the history of typical chest pain and the finding of ST-segment elevation on the initial ECG. Time to hospital admission was defined as the time between the onset of chest pain and admission to the emergency department (ED) of NCCHK. All information on demographic characteristics, medical history including physical examination and treatment options were collected from a standardised ACS registry form.

Acute adjunctive therapy was given in the ED using the doses recommended by the ESC and ACC/AHA guidelines.

Statistical Methods

Continuous data are presented as mean ± standard deviation or median (range) if the distribution is abnormal. Categorical variables are presented as number and percentages. Chi-square test is used to evaluate differences between two variables. A p-value of <0.05 was considered statistically significant. All statistical analysis was performed using a statistical package (SPSS 13.0 version).

Results

There were 9634 patients admitted to the ED in the year 2009, and ACS was diagnosed in 3402 patients (35%). A valid and complete database was observed and 2103 patients were eligible for analysis (Figure 1).

The mean age of the ACS patients was 57.6 ±10.2 years, of which 77.7% were male and Javanese was the most common race affected (31.5%). Hypertension was the most common risk factor (66%). Most of patients came to the ED by themselves. The characteristics of STEMI patients are listed in Table 1.

STEMI patients without reperfusion therapy

A sub-analysis was performed in STEMI patients not receiving reperfusion therapy. The most common source of referral for these patients was inter-hospital referral (52%), and almost 80% of them reached our hospital with the onset of infarction already more than 12 h (Table 2).

In-hospital mortality was significantly higher among patients who did not receive reperfusion therapy compared with patients who received acute reperfusion therapy, either by PPCI or fibrinolytic therapy (13.3% vs. 5.3% vs. 6.2%; p<0.001) (Figure 2).

Changes in in-hospital mortality

In 2007, the ACS mortality was 6.6% and decreased to 4.1% in 2009, probably due to the more invasive approach in the moderate-to high-risk ACS patient. The Ministry of Health of Indonesia greatly contributes by making a PCI package free of charge for poor people, and this effort has increased the number of PCIs in the hospital (2005 elective PCIs and 276 primary PCIs) in the year of 2010.

Discussion

Improvement in the system of care of AMI is one of the major efforts to decrease the mortality among ACS patients. The JAC registry data showed that Jakarta should build its own AMI system of care, especially for STEMI patients. This is because most STEMI patients (59%) did not receive reperfusion therapy and almost 80% of the patients presented very late (>12 h). It was shown that the patients not receiving reperfusion therapy had an almost two and a half fold increase of in-hospital mortality compared with patients who did receive reperfusion therapy (Figure 2).

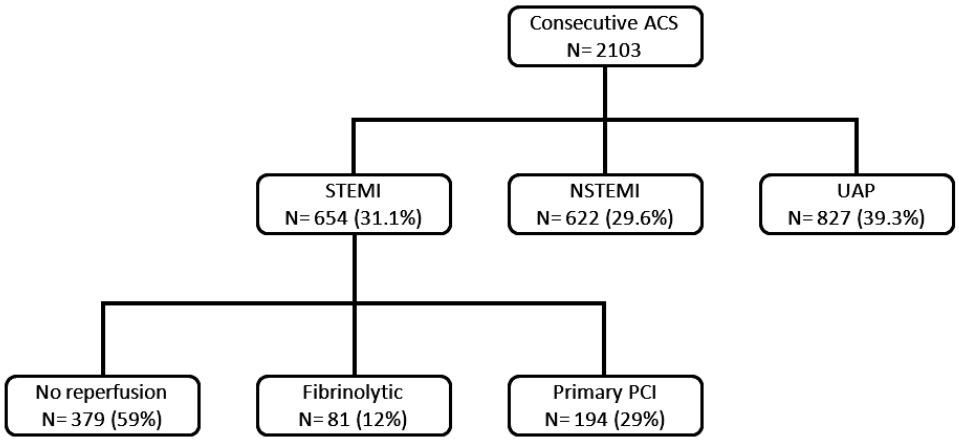

Figure 1. Patient distribution from the Jakarta Acute Coronary Syndrome registry. NSTEMI= Non ST-elevation myocardial infarction, UAP= unstable angina pectoris.

How to build the AMI system of care in Jakarta?

The Joint statement of AHA STEMI/PCI focused update recommendation has recommended (Class I) that each community should develop an appropriate STEMI system of care [9}, and the system of care of AMI is different between countries based on local health medical service availability. For example, models of STEMI systems of care include that in Vienna with its city-wide system of care [10], France with the famous SAMU-nationwide system [11], Minneapolis [12] and Mayo clinic [13] with their regional system of care. Although they have some differences in the protocol, all of the systems are using a pharmaco-invasive approach.

Before choosing which strategy could be used for the AMI system of care in Jakarta, it is important to know the problems in the real-world cardiovascular services in Jakarta, and we have observed some time delays and problems identified in daily practice, such as:

- Patient delay, such as lack of awareness of cardiac symptoms, fear of hospitals and financial problems;
- Delay in making an early diagnosis and treatment in primary hospital/clinic;
- Transportation delay due to traffic congestion;
- Lack of collaboration between hospitals and doctors;
- Lack of ambulance organisation.

To improve the system of care, a multidisciplinary approach is needed to solve the problem, and for that reason, a seminar was held on 22 July 2010, attended by the Governor of Jakarta, General Secretary of the Ministry of Health of the Republic of Indonesia, all the stakeholders, and directors of all hospitals in Jakarta. The emergency team from National Cardiovascular Center Harapan Kita Hospital introduced the idea of building a Jakarta Cardiovascular Care Unit Network System. An agreement was made, and all bodies are highly motivated to build the AMI system of care based on the consideration that is described below.

Table 1. Characteristic of STEMI patients (N=654).

Variable	**Description**
Location of STEMI	
Anterior	388 (60%)
Non-anterior	266 (40%)
Killip class, N (%)	
I	439 (70%)
II	171 (24%)
III	22 (3%)
IV	17 (3%)
Onset of infarction	
≤12 h	317 (49%)
>12 h	337 (51%)
Door-to-needle time, (minute)	38 (10-333)
Door-to-balloon time	
≤90 min	87 (44%)
>90 min	107 (55%)
Overall median (minute)	95

Door-to-needle time was presented as median (range).

Table 2. Characteristic of STEMI patients without reperfusion therapy (N=271).

Variables	Description, N (%)
Source of referral	
Walk in/ ambulance	85 (31%)
Primary physician	11 (4%)
Inter-hospital	140 (52%)
Intra-hospital	35 (13%)
Onset of infarction	
≤12 h	57 (21%)
>12 h	211 (78%)
Location of infarction	
Anterior	179 (66%)
Non-anterior	92 (34%)

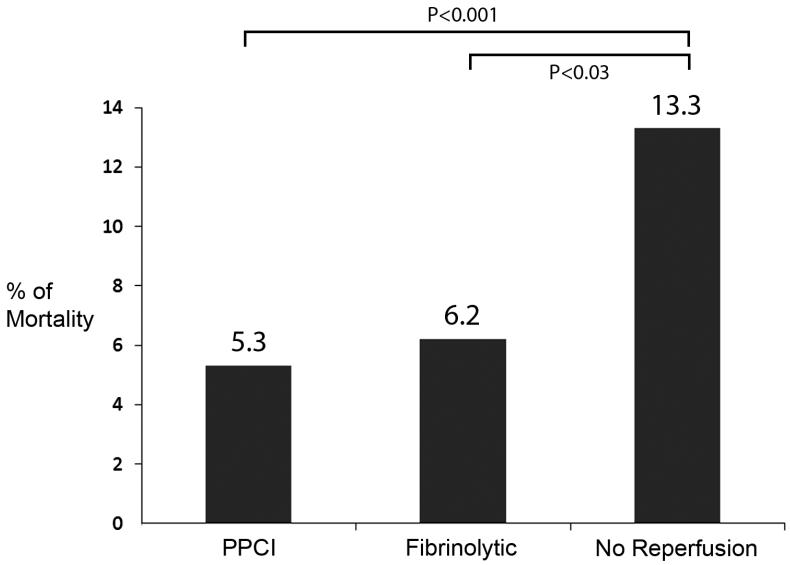

Figure 2. In-hospital mortality of STEMI patients. PPCI= primary percutaneous coronary intervention.

Considerations for choice of reperfusion therapy

Randomized controlled trials (RCTs) have shown the superiority of PPCI over fibrinolysis treatment by reducing the incidence of major adverse cardiac events (MACE) (8% vs. 14%; p<0.0001). Overall, there is about a 40% reduction in ischaemic events with PPCI compared with lytic treatment [2], but real life may be different from RCTs, and old trials have compared PPCI with stand-alone fibrinolytic treatment. Although the benefit of PPCI was seen in transfer patients in the DANAMI study [14], there was an under-use of PCI in post-fibrinolytic patients, in which the number of rescue PCIs was only 1,9%.

The benefit of fibrinolytic treatment is highest if it is done early after an infarction, as shown by Boersma et al. by the golden hour of thrombolysis. Within the first three hours after an infarction many lives could be saved reaching 60 lives-saved per 1000 treated patients if the time delay of treatment is no more than one hour [15]. Furthermore, Juliard et al. have shown that the longer the door-to-thrombolysis time, the higher the mortality will be (6.7% vs. 1.8%, p<0.05) [16].

The importance of time delay is also apparent in PPCI [17,18]. Nallamothu et al. showed that for every 10 min PCI-related time delay (defined as difference between door-to-balloon and door-to-needle time), there will be a 0.94% decrease in mortality benefit (p=0.006), and there is no benefit if the delay is more than 62 min [19]. Furthermore, Pinto et al. [20] and Betriu et al. [21] showed that multivariate adjusted odds of death were the same for fibrinolytic therapy and PCI, when the PCI-related delay was 114 min (95% CI 96-132 min; p<0.001). Time delay is very crucial and time to reperfusion is as important for PCI as it is for fibrinolysis.

In the real-world practice in Indonesia, it is difficult to do PPCI in all patients with a door-to-balloon (DTB) time less than 90 min. Data from the National Cardiovascular Data Registry (NCDR) registry showed that only 57.9% of patients achieve a DTB of <90 min [22], and data from the US National Registry of Myocardial Infarction (NRMI) ¾ analysis showed that only 4.2% patients had a DTB <90 min [23]. Data from the Global Registry of Acute Coronary Events (GRACE) registry showed the mean DTB time and pre-hospital delay were 75 and 120 min in the year 2000-2001, but in the recent years (2005-2006) it is longer (80 and 133 min, respectively) [24]. Recent data from the European registry showed that the first medical contact-to-balloon inflation time varied from 69 to 177 min [25]. All these real-world data show that it is difficult to achieve an appropriate DTB time as recommended by the ESC and AHA guidelines.

Gibson et al. [26] showed the risk of early recurrent MI following thrombolysis was higher in the non-PCI group compared with the PCI group (4.5% vs. 1.6%, p<0.001). This analysis suggested that fibrinolysis should not be used as a stand-alone procedure, and it should be followed by routine angioplasty.

To determine how early an "early" angioplasty should be in post-fibrinolytic patients, the decision should be based on the result of the fibrinolytic treatment. In case of a failed fibrinolysis, immediate rescue PCI is the best option as shown in the REACT trial [27]. For a successful fibrinolysis, routine early invasive approach within 1.6 to 15.7 h after fibrinolytic treatment showed a significantly lower ischaemic event rate compared with a selective invasive approach, as shown by CAPITAL AMI, CARESS-AMI, TRANSFER-AMI, SIAM and GRACIA-1 trials [28]. Overall comparison of pharmaco-invasive strategies including both rescue PCI and routine PCI with stand-alone fibrinolysis showed a 50% reduction in the risk of combined cardiovascular ischemic events. These data suggest that routine angioplasty should be done within the first 24 h after successful fibrinolytic treatment and immediately in failed fibrinolysis.

Reperfusion strategies for STEMI patients

The role of PCI in an early onset of infarction could be divided into primary PCI, pharmacological reperfusion in combination with PCI (pharmaco-invasive strategy) and rescue PCI after failed pharmacological reperfusion.

The pharmaco-invasive strategy is defined as giving pharmacological reperfusion (fibrinolytic agent) with an invasive strategy/PCI backup [29]. It means that all patients who receive fibrinolytic therapy should be referred to hospitals capable of performing PCI for either rescue PCI in case of failed fibrinolyic, or elective PCI within 3-24 h in successful fibrinolytic cases.

Primary PCI as recommended by guidelines can not be performed in all STEMI patients in Jakarta and neither can it work perfectly in a city with a well-organised cardiovascular emergency network system due to several limitations. Time delay is central for decision making in choosing reperfusion therapy, whether bringing the patient to the treatment (bringing the patient to PPCI) or bringing the treatment to the patient (giving an intravenous fibrinolytic agent in the pre-hospital setting) [3]. A wise approach, therefore, may be combining the two strategies, by giving fibrinolytic therapy as soon as possible in the pre-hospital setting and

immediately referring the patient to a hospital capable of performing PCI for either immediate or elective coronary angiography within 3-24 h. Nowadays, the pharmaco-invasive strategy is widely adopted throughout the world. In Jakarta, the pharmaco-invasive strategy looks feasible and can be applied for an AMI system of care.

Therapeutic strategies for AMI in Jakarta

Some initiatives that should be undertaken are:

1. Pre-hospital setting:
   a. Automated External Defibrillators (AED) and Basic Life Support (BLS) should be introduced in the community. This needs collaboration between the Indonesian Heart Association, the Indonesian Heart Foundation and the Government of Jakarta;
   b. Pre-hospital ECG activation is needed for an early accurate diagnosis;
   c. A patient transfer protocol and destination protocol should be designed.
2. In-hospital setting: the mission of the strategy is to reduce time delays for reperfusion therapy and increase the use of reperfusion therapy in STEMI patients.
3. Post-discharge state: a secondary prevention program is needed.

A suggested model for an AMI system of care in Jakarta is shown in Figure 3.

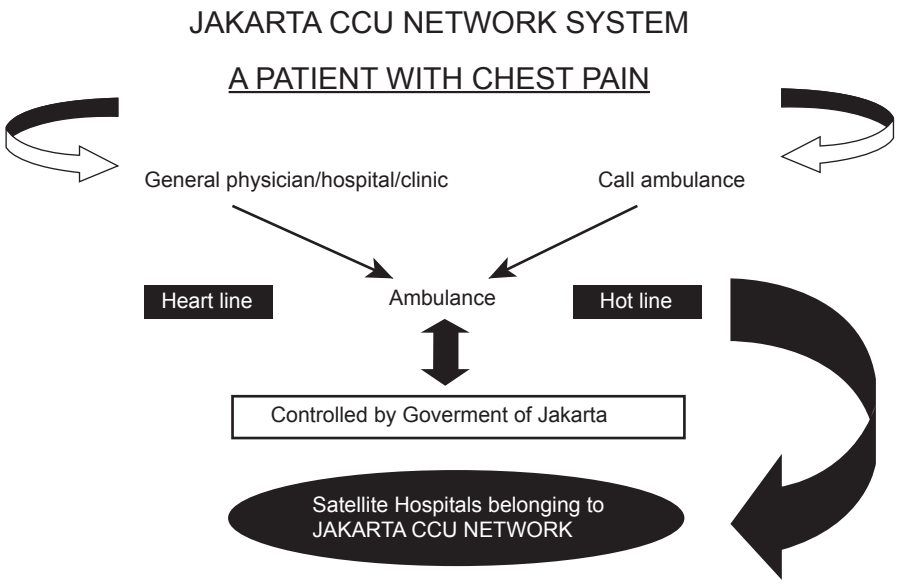

Figure 3. Suggested model of AMI system of care in Jakarta (Jakarta Cardiovascular Care Unit Network System). CCU= cardiovascular care unit.

A patient with chest pain will either come to the primary hospital/primary physician, clinic and/or call an ambulance through the hotline. Twelve-lead ECG recording will be transmitted immediately to be evaluated by the cardiologist on duty (through the heart line) and the diagnosis is made followed by choice of reperfusion therapy. Primary PCI is preferred if:

1. Estimated door-to-balloon time is less than 90 min,
2. Fibrinolytic therapy is contraindicated.

If not, fibrinolytic therapy will be given (streptokinase 1.5 million unit or ateplase 100 mg, intravenously) in the ED/primary hospital or during transportation. The patient will be referred to the nearest PCI-capable hospital that belongs to the Jakarta CCU Network. An evaluation will be made in the receiving center, including physical examination and 12-lead ECG. Rescue PCI will be done immediately in case of failed fibrinolytic and elective coronary angiography/ PCI within 3-24 h for successful fibrinolytic treatment.

Of note:

- The ambulance network is coordinated by the government of Jakarta;
- If possible, PPCI patients will be transferred directly to the cath-lab (bypassing the ED or PCI hospital);
- The hotline number is the direct line ambulance telephone number (118), and there are 44 ambulance units spread out in Jakarta and organised centrally;
- ECG transmission will be by internet service;
- The heart line is the receiving center telephone number in the National Cardiovascular Center Harapan Kita Hospital and is manned 24 h a day.

Study Limitation

The data were collected from a single-center registry and the coverage of ACS patients for analysis was 62% from all ACS admissions. However, since our hospital is the only national cardiac referral hospital in Jakarta and daily experience matches the characteristics of STEMI patients as reported above, the reported data should be representative for all ACS patients admitted to the ED.

Conclusions

Analysis of the JAC registry showed a proportion of patients currently not receiving reperfusion therapy of 59% of all STEMI patients; the majority of them (52%) were from inter-hospital referrals. The time from onset of infarction to hospital admission was more than 12 h in almost 80% cases.

Network organisation is central to optimising patient care at the acute stage of an MI and there is a strong need to build a well-organised cardiovascular care unit network system in Jakarta. This involves a multidisciplinary approach that should give an appropriate diagnosis and initial treatment with rapid and safe transport to a PCI-capable hospital.

A pharmaco-invasive strategy looks feasible in which fibrinolytic therapy will be given in pre-hospital setting if the expected time to transfer for PCI is delayed, followed by coronary angiography/angioplasty.

A multidisciplinary team approach is the best way to design a network, harmonising

the activities of all hospitals in Jakarta that will give the best cardiovascular services to the community by providing two reperfusion therapy options (PPCI or pharmaco-invasive strategy) depending on the time needed for the patient to reach the cath-lab. And last, but not least, the effectiveness of the system should be monitored by recording simple quality indicators in ongoing registries.

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Temporal trends of system of care for STEMI: Insights from the Jakarta Cardiovascular Care Unit Network System

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Submitted

Abstract

Background

Guideline implementation programs are of paramount importance in optimizing acute ST-elevation myocardial infarction (STEMI) care. Assessment of performance indicators from a local STEMI network will provide knowledge of how to improve the system of care.

Methods and Results

Between 2008-2011, 1505 STEMI patients were enrolled. We compared the performance indicators before (n=869) and after implementation (n=636) of a local STEMI network. In 2011 (after introduction of STEMI networking) compared to 2008-2010, there were more of inter-hospital referrals for STEMI patients (61% vs. 56%, p<0.001) more primary percutaneous coronary intervention (PCI) procedures (83% vs. 73%, p=0.005), and more patients reaching door-to-needle time ≤30 minutes (84.5% vs. 80.2%, p<0.001), but numbers of patients who presented very late (>12 hours after symptom onset) were similar (53% vs. 51%, p=NS). Moreover, the numbers of patients with door-to-balloon time ≤90 minutes and in-hospital mortality rate were similar in 2011 compared to 2008-2010 (49.1% vs. 51.3%, p=NS and 8.3% vs. 6.9%, p=NS, respectively).

Conclusion

After a local network implementation for patients with STEMI, there were significantly more inter-hospital referral cases, primary PCI procedures, and patients with a door-to-needle time ≤30 minutes, compared to the period before implementation of this network. However, numbers of patients who presented very late, the targeted door-to-balloon time and in-hospital mortality rate were similar in both periods. To improve the STEMI networking based on recent guidelines, existing pre-hospital and in-hospital protocols should be improved and managed more carefully, and should be accommodated whenever possible.

Keywords: system of care, acute myocardial infarction, performance indicators.

Introduction

The recent 2012 ESC guideline on ST-segment elevation myocardial infarction (STEMI) stressed the importance of networking for the management of acute myocardial infarction (AMI) [1]. In an earlier report, we emphasized the concept of a trained health system network in order to decrease the mortality rate of STEMI patients. The mission of such a network is how to increase the use of acute reperfusion treatment in the pre-hospital and in-hospital settings, using a pharmaco-invasive strategy in Jakarta, Indonesia [2].

After the initial introduction of the network, we analyzed the effectiveness of the system to improve the network protocols using a registry that we set up in 2008 as an integral part of modern health care [3,4]. We analyzed the quality of care and performance indicators of our local acute coronary syndrome registry, to further improve the STEMI system of care in Jakarta, Indonesia.

Methods

Data was collected from the Jakarta Acute Coronary Syndrome (JAC) registry and included 1505 patients admitted with acute STEMI in emergency department of the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia (Figure 1). Initial diagnosis was made on the basis of presence of typical chest pain and ST-segment elevation (≥0.1 mV) in two or more contiguous leads on the initial ECG.

All demographic, clinical and laboratory variables were obtained from the registry. The profiles of STEMI patients were compared before the introduction of the STEMI networking (between 2008-2010) and after introduction of the network (in 2011). Reperfusion therapy was given according to the recommendations of the ESC [1] and ACCF/AHA/SCAI [5] guidelines.

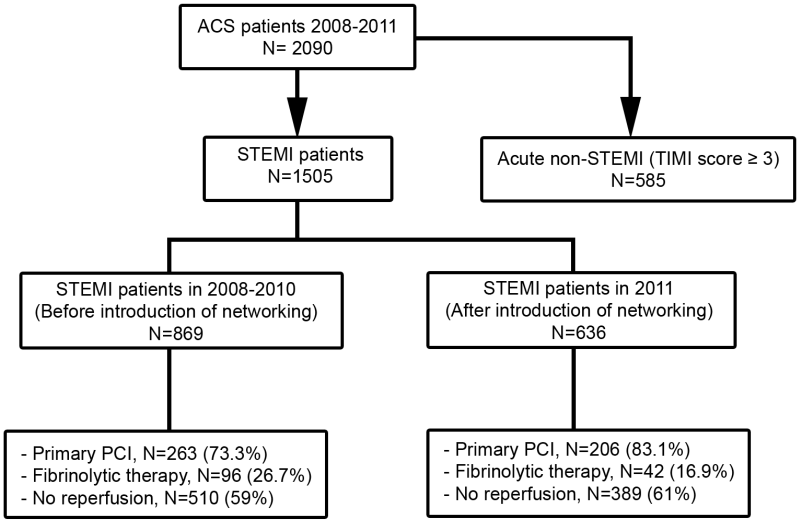

Figure 1. Patient distribution from the Jakarta Acute Coronary Syndrome registry.
ACS= acute coronary syndrome, STEMI= ST-elevation myocardial infarction, PCI= percutaneous coronary intervention, TIMI= Thrombolysis in Myocardial Infarction.

Study end-points

Study end-points are the performance indicators in two time periods: before and after the implementation of the network, such as the number of inter-hospital referral cases, number of primary PCI procedures, number of patients who presented very late (>12 hours after onset of chest pain), and the time delay between admission to the hospital and actual reperfusion (door-to-balloon time and door-to-needle time).

Statistical methods

Continuous variables are presented as mean values ± standard deviation (SD) or median (range) if not fitting a normal distribution. Categorical variables were expressed as percentages or proportions. Normally distributed variables were compared by Student's *t*-test and skewed distribution data by Mann-Whitney *U*-test. Categorical variables were tested by chi-square test. A p-value <0.05 was considered significant. All statistical analyses were performed with SPSS version 17.0.

Results

The median age of the STEMI patients was 55 years (ranging from 24 to 96 years) and most of them were male (86%). Similar with our earlier report [2], hypertension was the most common risk factor (54%) in our STEMI population. The source of referral was mostly from another hospital (58.3%) (Table 1).

Table 1. Demographic data and hospitalization information of STEMI patients (N=1505).

Variables	**Description**
Age, years	55 (24-96)
Gender	
Female	214 (14.2%)
Male	1291 (85.7%)
Source of referral	
Walk in/ambulance	502 (33.3%)
Primary physician	56 (3.7%)
Inter-hospital	878 (58.3%)
Intra-hospital	70 (4.6%)
Risk factor profile	
Raised BMI	320 (21.2%)
Carotid artery stenosis	3 (0.2%)
Family history of known CAD	368 (24.4%)
Dyslipidemia	580 (38.5%)
Hypertension	813 (54%)
Diabetes Mellitus	434 (29%)
Current smoker	698 (46.3%)

BMI= body mass index, CAD= coronary artery disease.

Table 2. STEMI profile based on network application period.

Variables	2008-2010 (before implementation of AMI networking) N=869	2011 (after implementation of AMI networking) N=636	P value
Referral status			
Walk in/ambulance	281 (32.3%)	221 (34.7%)	
Primary physician	43 (4.9%)	13 (2.0%)	
Inter-hospital	488 (56.2%)	390 (61.2%)	<0.001
Intra-hospital	57 (6.6%)	13 (2.0%)	
Onset of infarction			
≤12 hours	422 (48.8%)	299 (46.9%)	0.466
>12 hours	442 (51.2%)	338 (53.1%)	
Reperfusion strategy			
Primary PCI	263 (73.3%)	206 (83.1%)	0.005
Fibrinolytic therapy	96 (26.7%)	42 (16.9%)	

AMI= acute myocardial infarction, PCI= percutaneous coronary intervention.

Table 3. Characteristics of STEMI patients before and after implementation of Jakarta Cardiovascular Care Unit Network System.

Variables	2008-2010 (before implementation of AMI networking) N=869	2011 (after implementation of AMI networking) N=636	P value
Location of MI			
Anterior	530 (61%)	376 (59.1%)	0.464
Non anterior	339 (39%)	260 (40.9%)	
Killip class			
I	598 (69.2%)	429 (68.5%)	
II	223 (25.8%)	151 (24.1%)	0.047
III	25 (2.9%)	17 (2.7%)	
IV	18 (2.1%)	29 (4.6%)	
DTN ≤30 minutes	77 (80.2%)	120 (84.5%)	<0.001
DTB ≤90 minutes	135 (51.3%)	105 (49.1%)	0.364
In-hospital mortality	60 (6.9%)	53 (8.3%)	0.303

AMI= acute myocardial infarction, DTN= door-to-needle, DTB= door-to-balloon.

The number of inter-hospital referrals for STEMI cases has significantly increased in 2011 compared to 2008-2010 (61.2% vs. 56.2%, p<0.001), but numbers of patients with STEMI who presented very late were similar (53.1% vs. 51.2%, p=0.466). There was a significant increase of primary PCI in 2011 (83.1% vs. 73.3% p=0.005) (Table 2). For patients who received fibrinolytic therapy, the numbers of patients with a door-to-needle time ≤30 minutes was higher in 2011 than in 2008-2010 (84.5% vs. 80.2%, p<0.001). For patients who underwent primary PCI, the number of patients with a door-to-balloon time ≤90 minutes had not improved (49.1% vs. 51.3%, p= 0.364) (Table 3). In-hospital mortality had not changed between 2011 and 2008-2010 (8.3% vs. 6.9%, p=0.303).

Discussion

The Jakarta Cardiovascular Care Unit Network system was built to improve the system of care of AMI in Jakarta, Indonesia, serving about 11 million people with 15,000 people/km^2 of density [2]. The effectiveness of the system can be monitored by recording the performance indicators in STEMI patients, such as number of patients receiving acute reperfusion treatment (numbers of primary PCI and fibrinolytic therapy), time from door-to-reperfusion, and number of patients who presented very late [4,6].

After the introduction of the network, there was a growing awareness of the primary physician in the primary hospital, as is shown by the increased numbers of STEMI patients referred from another hospital.

In the receiving center, the number of patients receiving primary PCI has increased after the application of the network, which might suggest that the pre-hospital protocol to make an accurate diagnosis of AMI has improved. However, the proportion of patients who received PCI with a door-to-balloon time ≤90 minutes, as recommended by the guideline, had not improved between the two periods. It has shown earlier that when PCI-related time delay increases, the mortality benefit decreases [7-9]. Moreover, the 2012 ESC guideline [1] on management of STEMI patients has strengthen the importance of shortening the time delay for primary PCI, and recommends a door-to-balloon time <60 minutes in a PCI-capable hospital. To further improve the protocol of the receiving center, we (as the host of the network) have installed a catheterization laboratory in the emergency department that contributes to the fast track AMI service. This system might reduce the time delay related to reperfusion treatment, including administration delay. This program has started since October 2012.

The number of patients receiving fibrinolytic therapy has decreased in 2011, although more patients had reached a door-to-needle time ≤30 minutes compared to the 2008-2010 period before the network was introduced. If the estimated first medical contact-to-balloon time is >120 minutes, we like to start, in the near future, fibrinolytic therapy in the pre-hospital setting, as recommended by the guideline [1]. Local authorities have to collaborate in training all health care providers on how to perform fibrinolytic therapy according to a standard protocol.

Finally, the proportion of patients with STEMI who presented very late (>12 h) had not improved between the two periods. This might explain the similar in-hospital mortality in the two periods. As late presentation is associated with high mortality [2], we should get the

patients to the hospital that provides reperfusion therapy earlier. For that purpose we have to analyse how to improve patient delay (delay in recognizing the symptom) and system delay (under use of ECG transmission, lack of ambulance organization, etc). Pre-hospital 12-lead electrocardiogram plays an important role in a system of care for STEMI patients [10-12]. Currently, we are using a fax machine for ECG transmission but this system has several limitations, such as the unavailability of a fax machine in the ambulance. Therefore, we should transmit the ECG by a telephone- or internet-based system.

Based on the results of the performance indicators before and after network introduction, also the pre-hospital protocol should be improved. Two models of a pre-hospital triage form and an ambulance communication chart form are illustrated in Figures 2 and 3. These forms should be filled by the health care provides in the pre-hospital setting.

Prior AMI guideline implementation programs have improved the patient care and the patient's outcome [13-15]. However, the widespread dissemination of evidence-based medicine in daily practice is still lacking and a significant number of patients remain undertreated [16-20]. Therefore, the integrated STEMI care program we developed and implemented will include pre-hospital and in-hospital care. As preliminary data looks promising, we have to improve at all points of the health care system.

Study limitations

This single center registry should be combined with the registries of other receiving centers to know the real STEMI profile in Jakarta. However, our center is the cardiac referral hospital in Jakarta with the highest case load, thus characteristics of the patients in our National Cardiovascular Center Harapan Kita registry will reflect the STEMI profile in Jakarta very well.

Conclusion

For STEMI patients, the introduction of a regional AMI network has significantly increased the number of inter-hospital referral cases and the number of patients who underwent acute reperfusion procedures in the receiving center, with more patients who reached door-to-needle time ≤30 minutes. However, the proportion of patients who presented very late, the door-to-balloon time, and the in-hospital mortality have not improved. The receiving and referral center protocols have to be adapted in order to increase the quality of care of AMI patients in Jakarta.

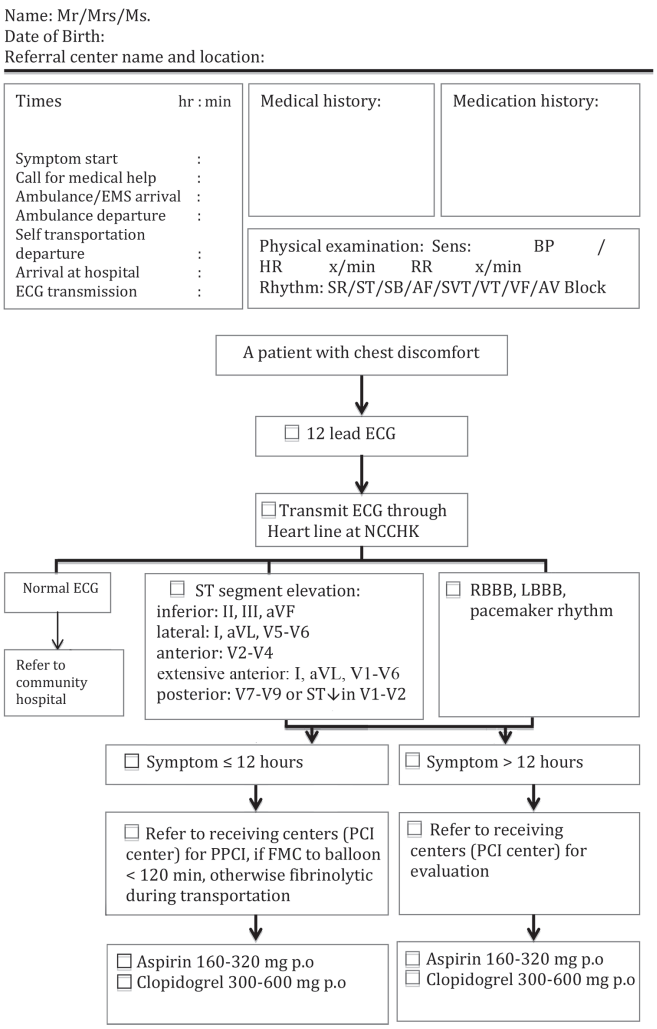

Figure 2. The pre-hospital triage of AMI patients in Jakarta Cardiovascular Care Unit Network System. An internet-based ECG transmission system (Heart line) is located in the Emergency Department of the National Cardiovascular Center Harapan Kita Hospital with 24 hours service. Diagnosis and choice of reperfusion therapy will be decided through Heart line. The choice of fibrinolytic agent is Streptokinase or Alteplase. In post-fibrinolytic patients, rescue PCI will be performed for failed fibrinolysis. After successful fibrinolytic therapy, coronary angiography will be performed within 3-24 hours.

EMS= emergency medical service, BP= blood pressure, HR= heart rate, RR= respiratory rate, SR= sinus rhythm, SB= sinus bradycardia, ST= sinus tachycardia, AF= atrial fibrillation, SVT= supra-ventricular tachycardia, VT= ventricular tachycardia, VF= ventricular fibrillation, AV= atrioventricular, NCCHK= National Cardiovascular Center Harapan Kita, RBBB= right bundle branch block, LBBB= left bundle branch block, PPCI= primary percutaneous coronary intervention, FMC= first medical contact, p.o= per os (oral).

Date: __ /__ /____ First ambulance call: ____:____ Ambulance ID:

Patient's information:

Name:
Date of birth/age:__ __ ____/ _____ years
Body weight:_____ kg
Start of symptom: ___ : ___
Diagnosis: STEMI Non-STE ACS Non cardiac
First ECG transmitted:____:____
Call Heart line: ___ : ___
Estimated duration of arrival at receiving center (PCI center): _____ minutes
Receiving center destination:

Fibrinolytic check list:
Did the patient have:

- previous intracranial hemorrhage or stroke ?	Yes/No
- ischaemic stroke in the preceding 6 months?	Yes/No
- CNS damage or neoplasms or AV malformation?	Yes/No
- recent major trauma/surgery/head injury?	Yes/No
- gastrointestinal bleeding within the past month?	Yes/No
- known bleeding disorder?	Yes/No
- aortic dissection?	Yes/No
- non compressible punctures in the past 24 hours?	Yes/No
- transient ischemic attack in the last 6 months?	Yes/No
- received oral anticoagulant therapy?	Yes/No
- systolic BP > 180 mmHg or diastolic BP > 110 mmHg?	Yes/No
- advanced liver disease?	Yes/No
- infective endocarditis?	Yes/No
- active peptic ulcer?	Yes/No
- prolonged or traumatic resuscitation?	Yes/No

If all questions are answered with NO, fibrinolytic therapy could be given. Consult to Heart line team at NCCHK before starting fibrinolytic therapy.

Time of fibrinolytic started: ___ : ___
Fibrinolytic agent: Streptokinase/Alteplase

Figure 3. The communication form and fibrinolytic check list for the emergency medical service/ambulance staff.

STEMI= ST-segment elevation myocardial infarction, non STE ACS= non-ST elevation acute coronary syndrome, CNS= central nervous system, AV= arteriovenous, BP= blood pressure, NCCHK= National Cardiovascular Center Harapan Kita.

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Strategies to improve the result of primary percutaneous coronary intervention procedure

Thrombus management in the catheterization laboratory in the setting of primary percutaneous coronary intervention: what is the current evidence?

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Abstract

Primary percutaneous coronary intervention (PCI) has become the preferred option in the treatment of acute ST-elevation myocardial infarction (STEMI) due to its rapid and effective re-establishment of epicardial coronary flow. Distal embolization of coronary thrombus may occur in 15% of the primary PCI population, and is a common cause of periprocedural complications. It may result in occlusion of the microvascular bed, resulting in suboptimal reperfusion and impaired prognosis due to increased infarct size, reduced ventricular function, and a fivefold increase in 5-year mortality. Several strategies used for the prevention of distal embolization are the evolving role of intravenous glycoprotein IIb/IIIa inhibitors (GPIs), use of adjunctive mechanical devices (manual or mechanical thrombus aspiration catheters and proximal/distal protection devices), and specifically designed stents for thrombus entrapment. Based on recent evidence, the administration of GPIs is associated with improvement in clinical outcomes and manual thrombus aspiration is an attractive concept, easy to use, and may improve the 1-year clinical outcome for STEMI patients undergoing primary PCI.

INTRODUCTION

Recently, primary percutaneous coronary intervention (PCI) has become the preferred option in the treatment of acute ST-elevation myocardial infarction (STEMI) due to its rapid and effective re-establishment of epicardial coronary flow [1-3]. Randomized controlled trials have shown the superiority of primary PCI with an overall 40% reduction of major adverse cardiovascular events (MACE) compared to fibrinolytic treatment [4].

One of the technical issues that arises in primary PCI is how to prevent embolization of atherothrombotic material, that occurs in 15% of the primary PCI population [5], and is a common cause of periprocedural complications. Once embolization occurs, distal emboli can: (1) mechanically 'plug' the microvasculature, leading to continued ischemic necrosis of the myocardium; (2) promote local in situ platelet adhesion and thrombosis, causing impairment of tissue reperfusion and a higher chance of the so called "no-reflow phenomenon"; and (3) may also provoke microvascular spasm and local inflammatory reactions that may further complicate recovery due to more extensive myocardial necrosis (Figure 1) [6,7].

Indeed, distal embolization of thrombus may result in occlusion of the microvascular bed, resulting in suboptimal reperfusion [7] and impaired prognosis due to increased infarct size, reduced ventricular function and a fivefold increase in 5-year mortality [8-11].

Furthermore, STEMI patients with a large thrombus burden suffer from a higher incidence of infarct related artery stent thrombosis compared to patients with a small thrombus burden (8.2% vs. 1.3%, $p<0.001$) [12]. Therefore, an appropriate and aggresive management of the thrombus is needed for the prevention of distal embolization and to achieve a better acute reperfusion result as well as better long-term result.

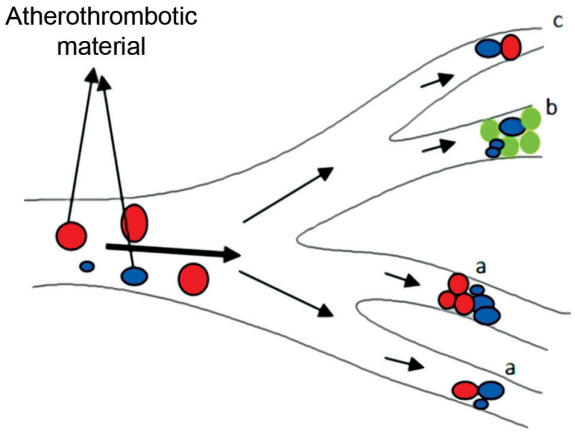

Figure 1. The hypothesis of distal embolization (an illustration). Distal embolization of atherothrombotic material (red and blue circles) can 'plug' the microvasculature (a), promote local platelet adhesion (b), and cause spasm (c) that can lead to serious impairment of tissue reperfusion and the no reflow phenomenon. Arrows indicate the distal embolization of thrombotic material into the microvasculature.

ACUTE REPERFUSION PARAMETERS

Acute reperfusion parameters during primary PCI are important tools for immediate evaluation of the success of reperfusion treatment. The most commonly used parameters are the thrombolysis in myocardial infarction (TIMI) flow, myocardial blush grade (MBG) and ST segment resolution on ECG after the procedure [13].

The TIMI flow grading assesses flow in the large epicardial coronary vessels, but myocardial perfusion takes place at the microvascular level, while MBG assesses contrast filling in distal microvessels as a measure of myocardial perfusion (Figure 1) [13,14]. Myocardial perfusion after primary PCI is the strongest predictor of mortality independent of infarct related artery re-opening as shown by Stone and colleagues [15]. Patients with MBG 0 or 1 have a higher mortality compared to patients with MBG 2 and 3 (18.3% vs. 13.2% vs. 6.8%, p=0.004). A successful primary PCI is indicated by achieving TIMI 3 flow [16] (better epicardial artery flow), MBG 3 [17], and complete ST segment resolution [18] (better microvascular perfusion) after the index procedure and is associated with lower mortality.

MANAGEMENT STRATEGIES PREVENTING DISTAL EMBOLIZATION OF CORONARY THROMBUS

Currently, there are several strategies available for 'fighting' distal embolization of coronary thrombus including:

a. Pharmacologic approaches to dissolve the thrombus (with a special role for glycoprotein IIb/IIIa inhibitors (GPIs))
b. Use of adjunctive mechanical devices (thrombus aspiration and embolic protection devices)
c. Dedicated stent for thrombus entrapment (e.g., MGuard stent)

ROLE OF GLYCOPROTEIN IIB/IIIA INHIBITORS

GPIs are effective and potent intravenous platelet aggregation inhibitors that have been studied in the wide spectrum of acute coronary syndrome especially in the setting of PCI with highly thrombotic lesions; abciximab (large molecule), eptifibatide and tirofiban (small molecule) are the available GPI agents [19-23]. An important issue is which GPI agents should be used and when in our daily clinical practice.

Small molecule versus large molecule GPI

A meta-analysis that was performed by De Luca et al. [24] showed that patients receiving abciximab in the setting of primary PCI had lower 30 day mortality compared to the control group of patients not receiving abciximab (2.4% vs. 3.4%, p=0.047), and this beneficial effect was even seen at 6 and 12 months follow-up (4.4% vs. 6.2%, p=0.01).

Benefits from small molecule administration (tirofiban and eptifibatide) as compared with abciximab among patients who underwent primary PCI were studied in a meta-analysis involving 2197 patients, and showed no significant difference in clinical outcomes between the two groups in terms of death, final TIMI flow grade, and ST segment resolution [25]. A larger report analysing the role of eptifibatide and abciximab was derived from the SCAAR

registry involving 11,479 patients who underwent primary PCI and found non-inferiority of the two treatments when compared to each other [26]. Another meta-analysis comparing tirofiban and eptifibatide (n=4653) to abciximab (n=2696) was performed by Ottani et al; this analysis also documented non-inferiority of small molecules compared to abciximab in STEMI patients treated with primary PCI [27].

The statement from the 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) PCI guideline executive summary mentions that "In patients undergoing primary PCI treated with UFH (unfractionated heparin), it is reasonable to administer a GPIIb/IIIa Inhibitor (abciximab, double bolus eptifibatide or high bolus dose tirofiban), whether or not patients were pretreated with clopidogrel" as class IIa indication [28]. This statement has clearly put the same position for all three GPIs.

Timing of GPI administration

The proper time of administering GPIs has been studied recently (early vs. delayed administration) and showed conflicting results [29,30]. Theoretically, the faster the GPI being given, the more rapid platelet aggregation inhibition would be expected.

A meta analysis by De Luca et al. [31], which involved seven randomized trials on early GPI administration in primary PCI, showed that early abciximab group patients (n=357) had significantly lower mortality (p=0.02), more patients had post-procedural TIMI 3 flow (p=0.04), MBG 3 (p=0.03), and complete ST segment resolution (p<0.0001) with less embolization (p=0.02), compared to the late abciximab group (n=365).

Results from the Leiden MISSION study (n=179) was in favour of early in-ambulance abciximab administration and this was associated with a smaller infarct size, improved left ventricular function and a lower risk of heart failure during clinical follow-up compared to in-hospital abciximab administration [32]. The ON-TIME 2 study (n=984) by van't Hof et al. has further emphasized the routine (early) pre-hospital initiation of high-bolus dose tirofiban to improved ST segment resolution and clinical outcome after primary PCI, without increasing the bleeding risk [33].

However, another study, the recently published MISTRAL trial (n=256), failed to demonstrate a clinical benefit of early in-ambulance administration of abciximab in STEMI patients [34]. It is postulated that especially very early (<2 hours of onset of complaints) GPI administration may be of benefit for primary PCI patients, which would make sense since no firm cloth has been formed yet.

Guideline statement on the timing of GPI administration

Because of the conflicting results, the 2011 ACCF/AHA/SCAI PCI guideline executive summary has indicated GPI administration as class III indication for routine pre-catheterization laboratory (e.g., ambulance or emergency room) as part of an upstream strategy for patients with STEMI undergoing PCI [28], while the recent 2012 European Society of Cardiology (ESC) guideline on STEMI has indicated it as class IIb [35]. Larger randomized trials are needed to analyse further the proper timing of GPIs.

Intracoronary vs intravenous GPI administration

A higher local GPI concentration by intracoronary administration might disrupt platelet cross-linking, thus augmenting thrombus disaggregation [36,37], and is associated with improved clinical outcome in acute coronary syndrome patients undergoing PCI [38]. The recently published INFUSE-AMI trial [39] showed that infarct size at 30 days was significantly reduced by bolus intracoronary abciximab delivered to the infarct lesion site compared to the no abciximab group (p=0.03).

A meta-analysis involving small to moderate scale trials has shown beneficial clinical effects of intracoronary versus intravenous GPI administration [40]; however, another medium scale randomized study (CICERO trial) [41] showed no improvement in myocardial reperfusion as assessed by ST segment resolution in the intracoronary group compared to intravenous GPI administration during primary PCI (64% vs. 62%, p=0.562), with similar incidence of 30 days MACE (5.5% vs. 6.1%, p=0.786).

These unsolved issues with regard to the route of GPI administration need to be confirmed further by larger randomized trials; meanwhile, the recent guideline on PCI has indicated class IIb indication for intracoronary abciximab administration in primary PCI [28].

ADJUNCTIVE MECHANICAL DEVICES: THROMBUS ASPIRATION CATHETER (MECHANICAL VERSUS MANUAL THROMBUS ASPIRATION)

There are two approaches available for thrombus aspiration [42]:

a. Mechanical thrombus aspiration, for example, Angiojet, X-Sizer, Rinspirator catheters, etc.
b. Manual thrombus aspiration, for example, Thrombuster II, Export, Diver catheters, etc (Figure 2).

The use of thrombus aspiration catheters has been widely adopted in almost all primary PCI procedures due to the result from the TAPAS trial [43]. From TAPAS, we learned that manual thrombus aspiration is applicable in a large majority of STEMI patients and results in a better reperfusion parameter shown by a lower proportion of patients achieving MBG 0 or 1 compared to conventional PCI group (17.1% vs. 26.3%, p<0.001). Moreover, 1 year mortality was significantly lower in the thrombus aspiration group compared to conventional PCI without aspiration (3.6% vs. 6.7%, p=0.02) [44]. On the other hand, the use of mechanical thrombus aspiration has failed to show a clinical benefit compared to the manual aspiration catheter as shown by a pooled analysis of individual patient data from 11 STEMI trials involving 2686 patients [45]. We are eagerly awaiting the results of the TOTAL trial [46] (n=4000) and TASTE trial [47] (n=5000) as they are the largest randomized studies comparing routine aspiration thrombectomy followed by PCI versus conventional PCI in STEMI patients undergoing primary PCI that are currently ongoing.

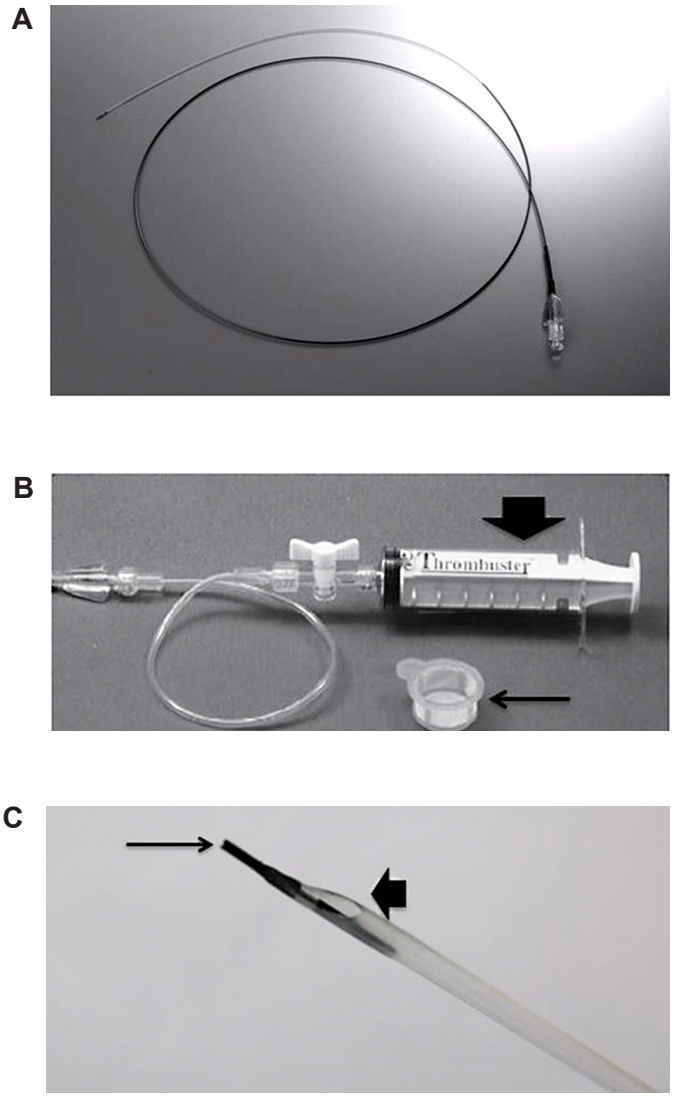

Figure 2. Picture of a 6F manual thrombus aspiration catheter (A). Manual thrombosuction device, the syringe (arrow head) and filter (small arrow) (B). The tip of thrombus aspiration catheter. Small arrow indicates the guidewire lumen and arrow head indicates lumen for aspiration of thrombus (C).

Larger lumen vs smaller lumen of thrombus aspiration catheter

It has been postulated that larger lumen catheters will retrieve more thrombus particles compared to smaller lumen catheters. However, a sub-analysis of the TAPAS trial has shown that there was no significant difference in MBG or electrocardiographic outcome between the Diver catheter (internal lumen 0.062 inches) compared to the Export catheter (internal lumen 0.041 inches); size distribution of retrieved thrombotic particles was similar per device, indicating that a larger internal lumen diameter does not automatically result in retrieval of larger thrombotic particles [48].

Thrombectomy plus GPI

Burzotta et al. have shown the advantage of GPI administration in combination with thrombus aspiration from a pooled analysis of trials on thrombectomy in acute myocardial infarction based on individual patient data by showing that patients receiving GPI plus thrombectomy had lower mortality compared to thrombectomy alone, GPI alone, or neither GPI/thrombectomy (3.3% vs. 4.8% vs. 5.0% vs. 7.4%, p=0.02) [45].

Embolic protection devices

Other percutaneous strategies that have been developed in attempts to reduce embolization are the use of distal or proximal protection devices with thrombus aspiration. The use of distal protection devices in the EMERALD [49] and PROMISE [50] trials showed no benefit in terms of fast ST segment resolution, final infarct size or the incidence of MACE in 6 months. Furthermore, a meta-analysis of randomized trials showed that distal protection devices did not reduce the risk of no-reflow compared to standard PCI in STEMI patients [51]. The use of a proximal protection device (Proxis) in the PREPARE [52] study improved microvascular flow as reflected by improved immediate complete ST segment resolution; however, the study was underpowered to detect clinical benefit.

Dedicated stent for thrombus entrapment (MGuard stent)

Another alternative strategy to reduce embolization of atherothrombotic material is thrombus entrapment, blocking embolic material at its source. The MGuard stent has the capability to trap embolic material at source. It is a proprietary metal stent covered with an ultra thin, micron level flexible mesh sleeve fabricated by circular knitting. During deployment of the stent, the flexible mesh freely expands over the stent struts, and the pores open in parallel with the stent, sandwiching embolic and pro-thrombotic material between the flexible mesh and the intima. The MAGICAL trial [52] showed a promising result with 90% of patients reaching TIMI 3 flow with 0% and 1.7% major adverse cerebro-cardiovascular events at 30 days and 6 months, respectively. Although this short term result looks promising, it needs a longer follow up to observe the restenosis and stent thrombosis rate, and randomized studies are needed to address definitively the benefit of this specially designed stent.

Guideline statement on adjunctive therapeutic devices

Based on recent evidence, the 2011 ACCF/AHA/SCAI PCI guideline executive summary has mentioned that "adjunctive therapeutic devices with aspiration thrombectomy is reasonable for patients undergoing primary PCI", as class IIa indication [28]. The similar statement was also mentioned in the 2012 ESC guideline on STEMI [35].

WHAT TO DO WHEN ASPIRATION FAILS

A report from a small case series has reported that in patients with massive residual intracoronary thrombus after repeated aspiration, local fibrinolysis with small doses of tenecteplase may improve angiographic and clinical outcomes in this difficult setting of patients with acute myocardial infarction, without systemic effects [53]. Larger randomized studies are needed to confirm the role of intracoronary fibrinolytic therapy when thrombus aspiration fails to improve reperfusion in STEMI patients undergoing primary PCI.

HOW TO DO IMPROVED THROMBUS ASPIRATION DURING PRIMARY PCI

Some technical considerations during manual thrombus aspiration based on our clinical experience are: (1) aspirate with a simple catheter to minimize micro/macro embolization (using, for example, Thrombuster II, Export catheter or equivalent); (2) start aspiration before crossing the lesion; (3) perform gentle & progressive crossing; (4) apply permanent negative pressure during aspiration; (5) perform a sufficient number of passes; (6) aspirate the whole catheter system after aspiration before making an angiogram evaluation (to minimize embolization of thrombotic material that was left in the inner lumen of the guiding catheter while retrieving the aspiration catheter) and; (7) if aspiration stops suddenly, the device should be removed (while maintaining negative pressure) to check whether there is a large thrombus obstructing the lumen.

Thrombus aspiration can be done several times depending on immediate reperfusion parameter evaluation. Direct stenting of the culprit lesion is advised when feasible and the true vessel diameter can be adequately estimated. Balloon predilation could be considered in selected cases. A suggested model for a clinical algorithm during primary PCI is shown in Figure 3.

Other important considerations are the onset of the infarction and age of the thrombus, vessel anatomy (tortuosity, calcification, tight lesion distal to the thrombus, small size vessel), the site of the occlusion (proximal or distal), and guiding catheter support.

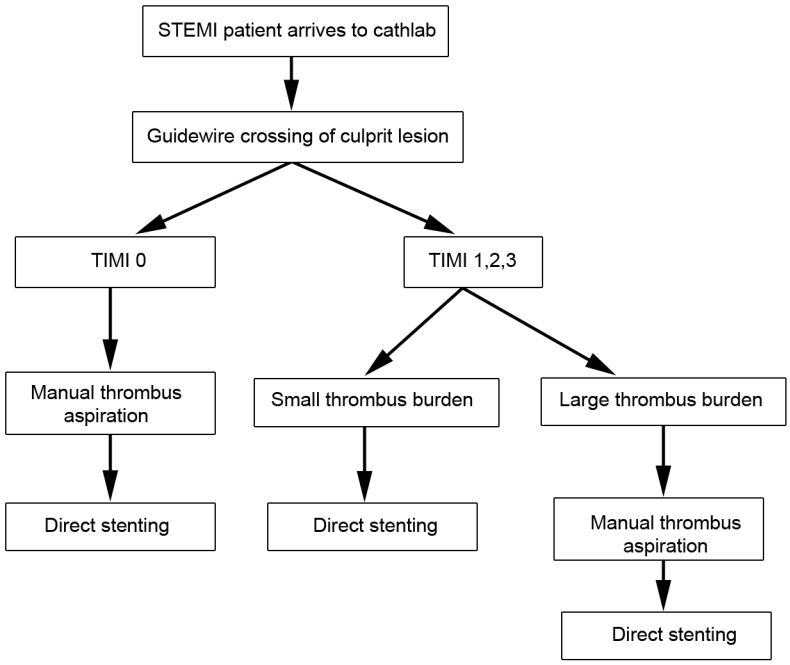

Figure 3. A Suggested clinical algorithm during Primary PCI.
STEMI= ST-elevation myocardial infarction, TIMI= Thrombolysis in Myocardial Infarction.

CONCLUSION

Distal embolization is a relatively common phenomenon in primary PCI patients presenting with STEMI, and is associated with poor myocardial perfusion and adverse clinical outcomes. Pharmacological strategies with the use of GPIs as an adjunct to primary PCI have been demonstrated to be associated with improvements in outcomes, particularly in high-risk patients. While embolic protection devices and MGuard stents are theoretically attractive, randomized data assessing their clinical efficacy are limited. Selective manual thrombus aspiration is an attractive concept that is easy, fast, and may improve 1 year clinical outcome.

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Early versus late initiation of intravenous eptifibatide in patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Submitted

Abstract

Aims

The timing of eptifibatide initiation for acute ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PCI) remains unclear. Therefore we compared the outcome of early versus late eptifibatide initiation in STEMI patients undergoing primary PCI.

Methods

Acute STEMI patients who underwent primary PCI (n=324) were enrolled in this retrospective study; 164 patients received eptifibatide bolus ≤30 min after admission (early group) and 160 patients received eptifibatide bolus >30 min (late group). The primary end-point was pre-procedural infarct-related artery (IRA) patency. Secondary end-points were CK-MB level, left ventricular ejection fraction (LVEF), in-hospital bleeding and 30-day mortality.

Results

Most of patients in the early group (90%) and late group (89%) were late presenters (>2 h after symptom onset). The two groups had similar pre-procedural TIMI 2-3 flow of the IRA (26% vs. 24%, p=NS), similar CK-MB levels (339 U/L vs. 281 U/L, p=NS), and similar LVEF (52% vs. 50%, p=NS). The 30-day mortality tended to be lower in the early group than in the late group (2% vs. 7%, p=NS). Compared to the late group, the early group was associated with shorter door-to-device time (p<0.001) and shorter procedural time (p=0.004), without increased bleeding risk (13% vs. 18%, p=NS).

Conclusion

Early intravenous eptifibatide administration before primary PCI did not improve pre-procedural IRA patency, CK-MB level and LVEF compared with late initiation. However, the early group was associated with shorter door-to-device time and shorter procedural time, tended to have lower 30-day mortality, and no increased bleeding risk, compared with the late group.

Keywords: eptifibatide, timing of administration, primary PCI.

Introduction

Primary percutaneous coronary intervention (PCI) has become the treatment of choice for the treatment of acute ST-elevation myocardial infarction (STEMI) [1-3]. However, based on real world practice, application of timely primary PCI with the recommended door-to-balloon time remains difficult [4]. Furthermore, during primary PCI, embolization of atherothrombotic material might occur [5] which is the most common cause of peri-procedural complications [6].

Early administration of glycoprotein IIb/IIIa inhibitor (GPI) has been considered to overcome the delay for receiving mechanical reperfusion [7], and GPI administration is also one of the strategies to prevent distal embolization of coronary thrombus during primary PCI [8]. It is hypothesized that the earlier the GPI is given in the acute phase of an infarction, the earlier platelet aggregation inhibition is achieved, leading to earlier contribution to opening of the infarct-related artery (IRA). It is known that IRA patency before primary PCI is related to improved left ventricular function [9] and survival [10].

Until now, the appropriate timing of eptifibatide initiation for acute STEMI patients undergoing primary PCI remains unclear. Therefore, we conducted a study to compare the immediate and short-term outcome of acute STEMI patients undergoing primary PCI, who received early eptifibatide infusion (≤30 min after admission) and late eptifibatide infusion (>30 min after admission).

Patients and Methods

This study was designed as a retrospective observational study, enrolling 350 acute STEMI patients (≤12 h after onset of symptoms) who underwent primary PCI in National Cardiovascular Center Harapan Kita, Jakarta, Indonesia from the period of April 2011 to October 2012. Three hundred and twenty four patients were eligible for analysis and divided into two groups. The early group (n=164) received intravenous eptifibatide infusion ≤30 minutes after admission to the emergency department (ED), and the late group (n=160) received eptifibatide infusion >30 minutes after ED admission.

On admission to the ED, all patients received a single intravenous bolus eptifibatide infusion of 180 µg/kg before primary PCI, followed by a continuous infusion of 2.0 µg/kg/min up to 12-18 hours. Patients who received bail-out intracoronary eptifibatide administration (n=20), incomplete clinical variables (n=4) and lost to follow-up (n=2) were excluded.

Primary PCI procedure

Primary PCI was performed according to the local protocol: standard views were recorded for diagnostic coronary angiography prior to the PCI procedure, and the thrombolysis in myocardial infarction (TIMI) flow of the IRA was assessed before primary PCI. After a guide-wire has crossed the culprit lesion, manual thrombus aspiration was performed when feasible. The decisions as to predilatation or direct stenting and stent choices between drug-eluting or bare metal stent were left to the operator's discretion. Stenting only the IRA was mandatory. Final angiography was performed in a standard view to assess final TIMI flow of the IRA.

Antiplatelet and anticoagulant regimen

All patients were pre-treated with 160-320 mg acetylsalicylic acid and 600 mg clopidogrel orally, followed by daily administration of 75 mg clopidogrel planned for at least one year after discharge and 80-100 mg acetylsalicylic acid indefinitely. Before the primary PCI procedure, all patients received an intravenous bolus of unfractionated heparin (50-60 IU/kg). None of the patients received fibrinolytic agents.

Definitions

Acute STEMI was diagnosed by persistent chest pain of more than 20 minutes, not relieved by sublingual nitrate and an ECG with ST-segment elevation in two or more contiguous leads (≥2 mm in precordial leads, ≥1 mm in limb leads).

Patients of the "early" group received intravenous eptifibatide within 30 min after admission, calculated from the time of ED admission to first bolus dose of eptifibatide, whereas patients of the "late" group received eptifibatide after the first 30 min.

TIMI flow was graded as follows: TIMI flow grade 0: absent antegrade flow; TIMI flow grade 1: partial contrast penetration beyond an occlusion with incomplete distal filling; TIMI flow grade 2: patent epicardial artery with opacification of the entire distal artery (however, contrast filling and/or washout is delayed); TIMI flow grade 3: patent epicardial artery with normal flow [11].

Creatine kinase-MB (CK-MB) level in plasma was measured by immunological UV assay (Roche Hitachi 912) after arrival in ED and repeated after 8 h.

Left ventricular ejection fraction (LVEF) was measured with two-dimensional echocardiography using the modified Simpson's rule [12], performed one day after primary PCI.

In-hospital bleeding criteria were defined according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria [13] and described as: (1) Severe or life-threatening bleeding: Intracranial bleeding or bleeding that causes substantial hemodynamic compromise requiring treatment; (2) Moderate bleeding: Bleeding which needs blood transfusion; and (3) Minor bleeding: Other bleeding, neither requiring transfusion nor causing hemodynamic compromise.

Death was defined as death from all cause within 30-days follow-up. Procedural time was calculated from time of injection of local anesthetics to guide catheter removal. Door-to-device time was calculated from ED admission to the introduction of first device, being a thrombus aspiration catheter or a balloon catheter into the IRA.

Procedural success was defined as completion of primary PCI without associated in major clinical complications (e.g., stroke, death or coronary artery perforation) [14].

Study end-points

The primary end-point of the study was pre-procedural TIMI flow 2 or 3. Secondary end-points were CK-MB level, LVEF, the rate of in-hospital bleeding, and 30-day mortality. Length of stay, procedural time and door-to-device time were also assessed. Two blinded independent interventional cardiologists verified the TIMI flow in each patient. One month clinical follow-up was judged by an independent clinical event committee that was blinded to group allocation of the patients.

Statistical analysis

For normally distributed continuous variables, data were expressed as mean ± standard deviation. If not normally distributed, data were expressed as median (range). Percentages were used to expressed categorical variables. Chi-square tests were used to compare categorical variables. Student's *t*-test or Mann-Whitney *U*-test were used to compare numerical variables between the two groups. We also compared the profile of patients who achieved pre-procedural TIMI flow 2-3 in the total cohort.

Assuming a 33% difference in pre-procedural coronary artery patency (TIMI flow 2 or 3) between the two groups, 95% probability (2-sided) and 80% study power, a minimum of 77 patients was needed per group. Pre-procedural TIMI flow 2 or 3 was estimated to be 52% in the early group and 19% in the late group [9]. We also compared the profiles of patients with pre-procedural TIMI flow 2-3 and with pre-procedural TIMI flow 0-1 in the total cohort.

A P value of <0.05 was considered statistically significant. All statistical analysis were performed with a statistical package (SPSS 17.0 version).

Results

Clinical, angiographic and procedural characteristics

Most of the patients in the early group (90%) and late group (89%) were late presenters (>2 h after onset of symptoms). All characteristics were well-balanced between the two groups (Table 1). However, in the late group there were more patients with dyslipidemia than in the early group (54% vs. 38%, p=0.006).

The median door-to-eptifibatide initiation time was 30 min in all patients. The median (interquartile range) door-to-eptifibatide time in the early and late group were 25 (15-30) min and 66 (46-105) min, respectively (p<0.001). Compared to the late group, the early group had significantly shorter median door-to-device time (79 vs. 98 min, p<0.001) and shorter median procedural time (35 vs. 40 min, p=0.004). Other angiographic and procedural variables were similar between the two groups (Table 2).

Study end-points

The early and late group did not differ with respect to pre-procedural TIMI 2 or 3 flow (26% vs. 24%, p=NS) (Figure 1), CK-MB levels (339 U/L vs. 281 U/L, p=NS), and LVEF (52% vs. 50%, p=NS) (Table 3). The 30-day mortality tended to be lower in the early group compared to the late group (2% vs. 7%, p=NS). In-hospital bleeding rate did not differ either (13% vs. 18%, p=NS), which was predominantly mild bleeding.

Characteristics of patients with pre-procedural TIMI flow 2/3

In the total cohort, the clinical characteristics between patients with initial TIMI flow 2-3 and patients with initial TIMI flow 0-1 were similar (Table 4). However, CK-MB levels were significantly lower in patients with pre-procedural TIMI flow 2-3 than in those with TIMI flow 1-2 (p<0.001).

Table 1. Baseline characteristics.

	Early group (N=164)	Late group (N=160)	P Value
Demographic characteristics			
Age, years	54 ± 9	56 ± 8	NS
Male gender	141 (86%)	136 (85%)	NS
Body mass index, kg/m^2	25 (15-36)	25 (18-35)	NS
Risk Factors			
Hypertension	89 (54%)	89 (56%)	NS
Dyslipidemia	63 (38%)	86 (54%)	0.006
Diabetes Mellitus	41 (25%)	48 (30%)	NS
Smoker	113 (69%)	103 (64%)	NS
Location of MI			
Anterior wall	83 (51%)	82 (51%)	NS
Onset of infarction			
≤ 2 hours	17 (10%)	18 (11%)	NS
2-6 hours	92 (56%)	87 (54%)	NS
6-12 hours	55 (33%)	55 (34%)	NS
Vital sign			
Systolic BP, mmHg	130 (62-208)	132 (61-217)	NS
Diastolic BP, mmHg	78 (38-121)	81 (44-152)	NS
Heart Rate, bpm	75 (16-146)	75 (31-160)	NS
Risk stratification			
Killip Class > 1	43 (26%)	32 (20%)	NS
TIMI Risk Score* ≥4	80 (49%)	81 (51%)	NS
Laboratorium parameter at admission			
Hemoglobin, mg/dL	14 ± 1.7	15 ± 8.4	NS
Creatinin, mg/dL	1.1 ± 0.4	1.2 ±1.0	NS
Blood Glucose, mg/dL	145 (85-559)	158 (68-597)	NS
Leukocyte count, /μL	12,725 (6070-22,000)	12,005 (1623-39,650)	NS
Length of stay, days	5 (1-28)	5 (2-38)	NS

MI= myocardial infarction, BP= blood pressure, bpm= beat per minute, *TIMI= thrombolysis in myocardial infarction risk variables, NS= not significant.

Discussion

The main findings from this study are: 1) Early intravenous administration of eptifibatide before primary PCI did not improve pre-procedural IRA patency, CK-MB level, and LVEF, compared to late administration; 2) The early group was associated with shorter door-to-device time and shorter procedural time; and 3) 30-day mortality tended to be lower in the early group than in the late group (2% vs. 7%, p=NS), without increasing the bleeding risk.

The timing of GPI administration before primary PCI has been analysed in several studies and showed conflicting results [9,15-18]. A meta-analysis by De Luca et al. [19]

Table 2. Angiographic and procedure related characteristics.

	Early group (N=164)	Late group (N=160)	P Value
Access site			
Trans radial approach	58 (35%)	42 (26%)	NS
Procedure during primary PCI			
Use of IABP	4 (2%)	4 (2%)	NS
Thrombus aspiration	98 (60%)	95 (59%)	NS
Direct stenting	48 (29%)	33 (21%)	NS
Predilation before stenting	116 (71%)	127 (79%)	NS
DES implantation	55 (33%)	57 (36%)	NS
Infarct related coronary artery			
LM	0 (0)	1 (0.6%)	NS
LAD	84 (51%)	92 (57%)	NS
LCX	8 (5%)	5 (3%)	NS
RCA	69 (42%)	56 (35%)	NS
Number of diseased vessels			
Single vessel	62 (38%)	55 (34%)	NS
Multi vessel	102 (62%)	105 (66%)	
Door-to-device time, min	79 (29-248)	98 (24-366)	<0.001
Initial TIMI flow grade			
0/1	122 (74%)	122 (76%)	
2	19 (12%)	17 (11%)	NS
3	23 (14%)	21 (13%)	
Final TIMI flow grade			
0/1	4 (2%)	1 (1%)	
2	12 (7%)	13 (8%)	NS
3	148 (90%)	146 (91%)	
Procedural time, min	35 (12-94)	40 (16-163)	0.004
Procedural success	164 (100%)	160 (100%)	NS

PCI= percutaneous coronary intervention, IABP= intra-aortic balloon pump, DES= drug-eluting stent, LM= left main artery, LAD= left anterior descending artery, LCX= left circumflex artery, RCA= right coronary artery, TIMI= thrombolysis in myocardial infarction, NS= not significant.

has shown a better outcome for patients who received early abciximab initiation than for patients with late initiation of abciximab administration. However, the MISTRAL study found that very early abciximab administration in the ambulance failed to demonstrate a clinical benefit as compared to abciximab administration after admission to the ED [16]. The largest randomized study comparing early and late GPI initiation, the ON-TIME 2 study [15], has further emphasized the clinical benefit of routine early pre-hospital initiation with high bolus dose tirofiban without increasing the bleeding risk, as compared to late tirofiban initiation.

For eptifibatide, some small to moderate scale studies [17,18,20,21] have shown an

Table 3. End-points of the study.

	Early group (N=164)	Late group (N=160)	P Value
Primary end-point			
Pre-procedural TIMI flow 2/3	42 (26%)	38 (24%)	NS
Secondary end-points			
Baseline CK-MB, U/L	43 (6-499)	48 (9-894)	NS
CK-MB after 8 h, U/L	339 (12-1672)	281 (15-2400)	NS
LVEF, %	52 (17-76)	50 (14-80)	NS
In hospital bleeding*			
Severe	0 (0)	0 (0)	NS
Moderate	5 (3%)	3 (2%)	NS
Mild	17 (10%)	26 (16%)	NS
Mortality within the first 30-days	4 (2%)	11 (7%)	NS

*GUSTO bleeding criteria, TIMI= thrombolysis in myocardial infarction, CK-MB= creatine kinase-MB, LVEF= left ventricular ejection fraction, MACE= major adverse cardiac event, NS= not significant.

improvement of pre-procedural epicardial flow, which was not reflected in our study.

Two conditions might explain the negative results of our study. First, most of the patients in the early (90%) and late group (89%) arrived at the ED relatively late (>2 h after onset of symptoms), a finding that agrees well with one of our previous reports [4]. It is postulated that the concept of “the earlier the better” for GPI used before primary PCI might be true only in patients who were admitted to the ED within 2 hours after onset of symptoms, probably related to the integrity of the thrombus. Hassan et al. [9] and van’t Hof et al. [15] have shown the beneficial effect of pre-hospital GPI initiation.

Second, in our study, we used a single bolus of eptifibatide. The guideline advocates a double bolus of eptifibatide with a class IIa indication [22]. However, our population had a smaller body weight compared to a western population, shown by a median BMI of 25 kg/m^2 in both groups (Table 1). Lower body weight is associated with increased bleeding risk [23]. To minimize the bleeding risk in our population, we used a single bolus of eptifibatide, but whether a single bolus dose is less effective than a double bolus dose in our population, deserves further investigation.

The classification used to define “early” and “late” GPI initiation in STEMI patients undergoing primary PCI differs among the studies. The description “early” was given to GPI administration in ED [18], or in-ambulance [9,15,16], whereas GPI administration was “late” if given in the cath-lab [9,18] or in a coronary care unit [10]. In our study, we defined “early” when patients received an intravenous bolus of eptifibatide within the first 30 min after ED admission. Moreover, in our study population, 30 min is the median value for the door-to-first bolus dose of eptifibatide time. To date, clear and standard criteria of timing of GPI administration in acute STEMI patients are lacking; this is the first study that takes 30 min as the cut-off time to

Table 4. Baseline characteristics based on pre-procedural TIMI flow.

	Pre-procedural TIMI flow 2/3 (N=80)	Pre-procedural TIMI flow 0/1 (N=244)	P Value
Age, years	55 (33-77)	55 (30-79)	NS
Male	67 (84%)	210 (86%)	NS
BMI, kg/m^2	25 (18-36)	25 (15-36)	NS
Onset of MI, h	5 (0.5-11)	5 (0.5-12)	NS
Early eptifibatide	42 (52%)	122 (50%)	NS
Risk Factors			
Hypertension	41 (51%)	137 (56%)	NS
Dyslipidemia	36 (45%)	113 (46%)	NS
Diabetes Mellitus	22 (27%)	67 (27%)	NS
Smoker	59 (74%)	157 (64%)	NS
Killip class >1	21 (26%)	54 (22%)	NS
LVEF, %	53 (14-80)	50 (20-79)	NS
CK-MB after 8 h, U/L	186 (12-994)	349 (15-2400)	<0.001
Length of stay, days	4 (2-38)	5 (1-38)	NS
Mortality within the first 30 days	4 (5%)	11 (4%)	NS

BMI= body mass index, MI= myocardial infarction, LVEF= left ventricular ejection fraction, CK-MB= creatine kinase-MB, NS= not significant.

differentiate between early and late eptifibatide initiation.

Eptifibatide, one of the approved GP IIb/IIIa inhibitors, is a small heptapeptide that is highly selective and rapidly dissociates from its receptor after cessation of therapy [24]. In Indonesia, eptifibatide is the only available GPI and since several studies have shown the non-inferiority of eptifibatide compared to abciximab [25-28], intravenous eptifibatide administered in the ED has been used as a routine protocol in our institution for STEMI patients undergoing primary PCI since 2011.

In our study,the door-to-device time and the procedural time were shorter in the early group, which might reflect an increased awareness of the ED staff to react and activate the cath-lab more promptly. It was shown that early activation of the cath-lab is associated with a reduced door-to-balloon time [29]. Door-to-device time has been shown to be associated with mortality [30]. Although not significant, our study showed a tendency of lower mortality in the early group. Further studies are needed to investigate whether the early group has lower risk of peri-procedural complications leading to a smoother and faster completion of the procedure compared to the late group. Furthermore, both groups had similar LVEF, probably due to similar infarct sizes in both groups. This is in contrast with the results of Hassan et al. who found a benefit of pre-hospital abciximab administration on infarct size and LVEF compared with in-hospital abciximab administration [9]. Another important finding from the current study is that the bleeding risk was not increased in the early group compared to late

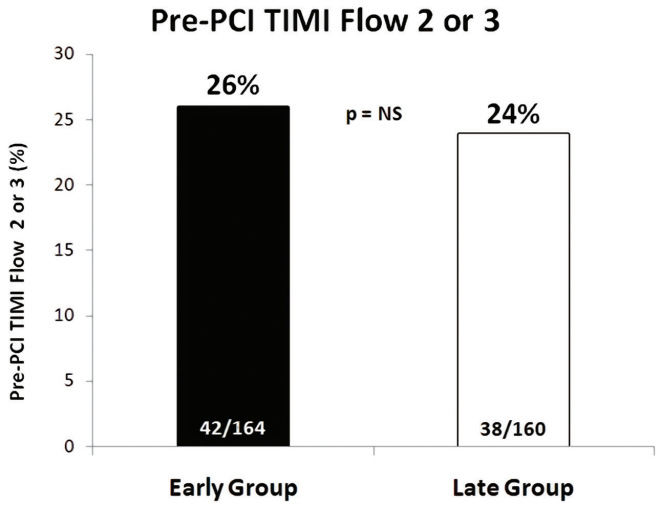

Figure 1. Primary end-point: Pre-PCI TIMI flow 2 or 3 by treatment group.
PCI= percutaneous coronary intervention, TIMI= thrombolysis in myocardial infarction, NS= not significant.

group, suggesting a good safety profile of early eptifibatide administration. But this favourable safety profile did not lead to any significant clinical benefit.

In a sub-analysis of patients with pre-procedural TIMI flow 2/3 (Table 4), we found that patients with initial TIMI flow 2/3 before primary PCI had significantly smaller CK-MB levels than patients with initial TIMI flow 0/1. This data adds to the importance of IRA patency before primary PCI, as shown by Hassan et al [9]. Although our study failed to find any clinical benefit in patients with pre-procedural TIMI flow 2-3, LVEF tended to be higher in patients with initial TIMI flow 2-3 than in patients with initial TIMI flow 0-1 (53% vs. 50%, p=NS).

Finally, network organization is essential to optimize patient care at the acute stage of an acute myocardial infarction [31]. Thus, the benefit of intravenous administration of antiplatelet agents might be seen best in the first hour after onset of an infarction (golden hours), and it might be initiated immediately after the first medical contact. Larger multicenter randomized trials are needed to observe the proper timing of eptifibatide initiation in a real world early STEMI population that is arriving at the ED relatively late. Until then, the recent 2012 ESC guideline has indicated the routine use of GPI as an adjunct to primary PCI as a class IIb recommendation [22], and the 2011 ACCF/AHA/SCAI PCI guideline as a class III recommendation [32].

Limitations

Several limitations should be addressed. First, this is a non-randomized study, in which we included almost all consecutive patients undergoing primary PCI reflecting a true real world practice. Second, we did not evaluate the myocardial blush grade, TIMI frame count and

ST segment resolution after primary PCI. However, pre-procedural TIMI flow was assessed in all patients to assess epicardial flow and microvascular perfusion, both immediately before and after primary PCI. Finally, we administered a single bolus of eptifibatide due to a lower body weight of our population than generally present in western studies.

Conclusion

From this study, which mostly enrolled late STEMI presenters, early intravenous initiation of eptifibatide before primary PCI did not improve pre-procedural IRA patency, CK-MB level and LVEF, compared to late administration of eptifibatide. However, the early group was associated with shorter door-to-device time and shorter procedural time, and tended to have a lower 30-day mortality, without having an increased bleeding risk. Larger randomized trials are needed to evaluate the proper timing of eptifibatide initiation before primary PCI, particularly in STEMI patients admitted to the ED relatively late.

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A randomized comparison between everolimus-eluting stent and cobalt chromium stent in patients with acute ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention using routine intravenous eptifibatide: the X-MAN (Xience versus Multi-Link stent in Acute myocardial infarctioN) trial, a pilot study

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Abstract

Objective

To determine the efficacy and safety of an everolimus-eluting stent (EES/Xience) compared with a Cobalt Chromium stent (CoCr/Multilink-Vision) in patients with acute ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) with routine administration of eptifibatide infusion.

Methods

This is a prospective, single center, randomized trial comparing EES (n=75) and CoCr stent (n=75) implantation in patients with acute STEMI undergoing primary PCI. Intravenous eptifibatide administration was mandatory by protocol in this pilot study. The primary efficacy end-point was major adverse cardiac events (MACE) at 30 days, defined as the composite of death, reinfarction and target vessel revascularization. Secondary safety end-points were stent thrombosis at 30 days and in-hospital bleeding event. Acute reperfusion parameters were also assessed.

Results

One-month MACE rate did not differ between EES and CoCr group (1.3% vs 1.3%, p=1.0). No stent thrombosis cases were observed in the EES group. The groups did not differ with respect to in-hospital bleeding events (5% vs. 9%, p=0.37), achievement of final TIMI flow 2 or 3 (p=0.21), achievement of myocardial blush grade 2 or 3 (p=0.45), CK-MB level at 8-12 h after stenting (p=0.29), and left ventricular ejection fraction (p=0.21).

Conclusion

This pilot study demonstrates that after one-month follow-up, the use of EES is as safe and effective as the use of CoCr stents in patients with acute STEMI undergoing primary PCI with routine administration of intravenous eptifibatide.

Keywords: Everolimus, Cobalt Chromium, eptifibatide, STEMI, primary PCI, stent.

Introduction

Currently, primary percutaneous coronary intervention (PCI) as part of mechanical revascularization therapy has become a preferred option in the treatment of acute ST-elevation myocardial infarction (STEMI) patients with its fast and efficient re-establishment of coronary blood flow resulting in a reduction of mortality of 5-15% at 12 months compared to fibrinolytic therapy [1-5]. One of the unresolved issues in the setting of primary PCI is the stent choice between drug-eluting stent (DES) and bare metal stent (BMS).

We hypothesized that in STEMI patients undergoing primary PCI with routine administration of eptifibatide, implantation of an everolimus-eluting stent (EES) is as safe and effective as implantation of a bare metal stent in 30-days follow-up. Until now, there are no randomized studies specifically investigating the role of EES and cobalt chromium stent in acute STEMI patients undergoing primary PCI with routine administration of eptifibatide. The present X-MAN study was performed to compare the efficacy and safety of EES (Xience stent) and BMS (Cobalt Chromium-Multi Link/Vision stent) in acute STEMI patients (≤12 hours of symptom onset) undergoing primary PCI, in whom routine intravenous eptifibatide was mandatory by protocol.

Patients and Methods

The X-MAN study was designed as a single-center, prospective, randomized pilot study, performed at the emergency department and catheterization laboratory of National Cardiovascular Center Harapan Kita, Jakarta, Indonesia, in the period of February 2011 to November 2012. All eligible patients were randomized into two groups of stents: (1) the EES group consisting of patients who received Xience V or Xience Prime (Abbott Vascular, Santa Clara, CA, USA) and (2) the cobalt chromium (CoCr) group (cobalt chromium stent/Multi Link or Vision stents; Abbott Vascular). Patients were randomized in the emergency department before primary PCI. Only a single type of stent was allowed in each patient. The study protocol was approved by the local ethical committee. All patients provided written informed consent before randomization. The trial was performed according to the declaration of Helsinki.

Inclusion criteria were: presence of acute myocardial infarction with ≤12 hours of symptom onset (chest pain of more than 20 minutes, not relieved by sublingual nitrates), ST-segment elevation in two or more contiguous leads (≥2 mm in precordial leads, ≥1 mm in limb leads), and planned for primary PCI with stent implantation.

Patients with left main disease, previous PCI, history of fibrinolytic treatment, past coronary artery bypass surgery, cardiogenic shock, renal failure, recent major bleeding, known hemorrhagic diathesis, and end-stage chronic diseases were excluded. From 410 patients who underwent primary PCI in the period of February 2011 to November 2012, a total of 150 patients were recruited who fulfilled the inclusion criteria.

Primary PCI was performed according to the standard techniques. Stenting, if feasible, was performed only in the infarct-related coronary artery (IRA). Technical considerations, such as direct stenting or balloon predilation, were left to the operator`s discretion (see Table 2).

Manual thrombus aspiration protocol

Manual thrombus aspiration was recommended. After the guide wire has crossed the lesion, thrombus aspiration was routinely performed in a totally occluded culprit vessel (Thrombolysis in Myocardial Infarction [TIMI] flow of 0). If pre-procedural TIMI flow 1 to 3 was observed, the aspiration judgement was based on the presence or absence of a large thrombus burden. If a large thrombus burden was visualized, manual thrombectomy was performed. Direct stenting was advised if a lesion with a small thrombus burden was present [6]. The most commonly used thrombus aspiration catheter was a 6F Thrombuster II (Kaneka, Japan).

Administration of GPI (Eptifibatide)

After arrival in the emergency department, patients received intravenous eptifibatide using a weight adjusted dose (a single intravenous bolus of 180 µg/kg followed by a continous infusion of 2.0 µg/kg/min up to 12-18 hours) as soon as primary PCI had been planned. Additional intracoronary eptifibatide was given at the operator's discretion.

Antiplatelet and anticoagulant regimen

All patients were pre-treated with 160-320 mg acetylsalicylic acid and 600 mg clopidogrel orally before primary PCI, followed by daily administration of 75 mg clopidogrel planned for at least 1 year after discharge and 80-100 mg acetylsalicylic acid indefinitely. Before PCI, all patients received an intravenous bolus of unfractionated heparin (50-60 IU/kg).

Microvascular perfusion evaluation

Diagnostic modalities that were used to evaluate microvascular perfusion were the angiographic measurement of coronary flow and tissue perfusion (TIMI flow and myocardial blush grading) in all patients following primary PCI, applying the following definitions:

- TIMI flow grading: TIMI flow grade 0: absent antegrade flow; TIMI flow grade 1: partial contrast penetration beyond an occlusion with incomplete distal filling; TIMI flow grade 2: patent epicardial artery with opacification of the entire distal artery also contrast filling or washout is delayed; TIMI flow grade 3: patent epicardial artery with normal flow [7].
- Myocardial blush grading (MBG): MBG 0: failure of dye to enter the microvasculature; MBG 1: dye slowly enters but fails to exit the microvasculature; MBG 2: delayed entry and exit of dye from the microvasculature; MBG 3: normal entry and exit of dye from the microvasculature [8].

Cardiac markers

Creatine kinase-MB (CK-MB) level in plasma was measured by immunoinhibition assay (Roche Hitachi 912, Germany) after arrival in emergency department and 8-12 hours after stent implantation. Serum troponin T concentration was measured with the cTnT assay from Roche Diagnostics (Mannheim, Germany). The lowest cTnT value to be measured reliably with this assay is 0,03 µg/L which is the lowest cTnT concentration that can be measured reproducibly with the between-run coefficient of variation of 10%.

Echocardiography evaluation

Left ventricular ejection fraction (LVEF) was calculated using Simpson's method from a two-dimensional trans-thoracic echocardiography evaluation [9], performed at the second day of admission by dedicated personnel who were blinded to the treatment allocation.

Study end-points

The primary end-point (efficacy end-point) of this pilot study was the MACE rate at one-month follow-up, defined as the composite of all-cause death, reinfarction and clinically-indicated target vessel revascularization (TVR). Secondary end-points (safety end-points) were stent thrombosis rate at 30-days and in-hospital bleeding event. Acute reperfusion parameters (TIMI flow and MBG), CK-MB level at 8-12 h after stenting, and LVEF were also assessed.

Two independent interventional cardiologists blinded to the treatment assignment of the patients, verified the assessment of TIMI flow and MBG. One month clinical follow-up was judged by an independent clinical event committee, blinded to the allocated stent type.

Definitions

Death was defined as all-cause death during 1-month follow-up. Re-infarction during follow-up was defined as a troponin T rise >0.03 μg/L with symptoms, or a second rise of troponin T >25% after recent MI in the presence of symptoms or the development of new Q waves on ECG [10,11]. We defined TVR as a re-intervention driven by any lesion located in the IRA and included coronary artery bypass surgery involving the IRA [12]. Stent thrombosis criteria were according to the Academic Research Consortium classification [13].

In-hospital bleeding criteria were according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria [14] and described as: 1) Severe or life-threatening bleeding: Intracranial bleeding or bleeding that causes substantial hemodynamic compromise requiring treatment; 2) Moderate bleeding: Bleeding that needs blood transfusion; 3) Minor bleeding: Other bleeding, neither requiring transfusion nor causing hemodynamic compromise.

Door-to-device time was defined as the time from patient arrival at the emergency department to the introduction of the first device, either a thrombus aspiration catheter or a balloon catheter into the IRA.

Procedural success was defined as completion of the planned procedure without associated in cath-lab major clinical complications (e.g., stroke, death or coronary artery perforation) [15]. The flow-chart of the study is presented in Figure 1.

Statistical methods

Data were expressed as mean ± standard deviation for normally distributed continous variables. If data was distributed not normally, data was expressed as median and interquartile range. Continous variables were compared with Student's *t*-test or Mann-Whitney *U*-test. Chi-square test or Fisher`s exact test were used to compare categorical variables. Cox proportional hazards models were used to examine the association of stent type with the risk of clinical events (MACE).

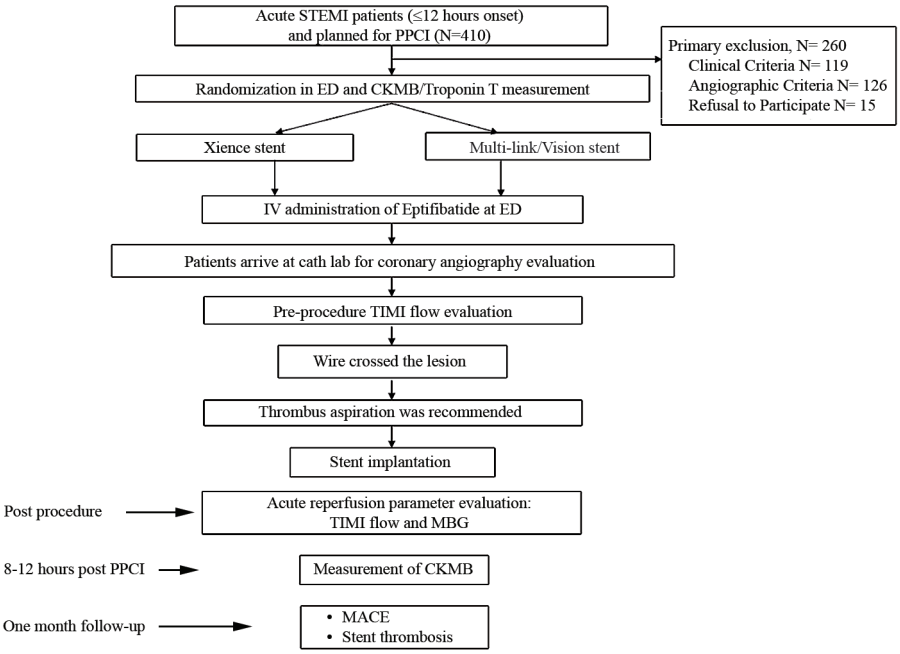

Figure 1. Flow chart of the study.
STEMI= ST-segment elevation myocardial infarction, CK-MB= creatine kinase-MB, PPCI= primary percutaneous coronary intervention, ED= emergency department, TIMI= thrombolysis in myocardial infarction, MBG= myocardial blush grade, MACE= major adverse cardiac event.

As data regarding the use of EES in patients with eptifibatide treatment is lacking, we decided to enroll 150 patients (75 patients for each arm) in this pilot study before recruiting a larger population. Thus, study equivalence is not being tested.

A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using a statistical package (SPSS version 17.0, SPSS Inc. Chicago, IL, USA).

Results

Baseline characteristics. Table 1 shows the baseline clinical characteristics of the patients in the two study groups. Most patients (85%) were male. The study groups were well-balanced in terms of baseline clinical characteristics and risk factors. Table 2 shows angiographic characteristics and procedural results. The two groups had similar anatomical and procedural characteristics. Thrombus aspiration was performed in 59% of the patients. PCI only on IRA was performed in the majority of the patients (93%). Procedural success was obtained in all patients (100%).

Study end-points. During 1-month follow-up, MACE rates did not differ between the EES and the CoCr group (1.3% vs. 1.3%, p=1.0) (Table 3). A single case with probable stent thrombosis was observed in the CoCr group and none in the EES group. In-hospital bleeding event rates were similar in the EES and CoCr groups (5% vs. 9%, p=0.37) (Table 4).

Table 1. Baseline characteristics.

	EES group (N=75)	CoCr group (N=75)	P Value
Demographic characteristics			
Age, years	56 ± 9.6	54 ± 9.5	0.16
Male	67 (89%)	61 (81%)	0.17
BMI, kg/m^2	24 (23-27)	25 (23-27)	0.9
Risk Factors			
Hypertension	37 (49%)	37 (51%)	1.0
Diabetes mellitus	22 (29%)	17 (23%)	0.35
Dyslipidemia	36 (48%)	37 (49%)	0.87
Smoking	46 (61%)	48 (64%)	0.86
Family history of CAD	20 (27%)	20 (27%)	1.0
Location of infarction			
Anterior wall	37 (49%)	39 (52%)	0.74
Onset of infarction			
≤ 2 hours	6 (8%)	3 (4%)	0.49
2-6 hours	44 (59%)	51 (68%)	0.24
> 6 hours	25 (33%)	21 (28%)	0.48
Risk stratification			
Killip class I	63 (84%)	62 (83%)	0.83
Door-to-reperfusion time			
Door-to-device time, minutes	86 (70-114)	90 (70-106)	0.82
Door-to-device time ≤90 minutes	41 (55%)	35 (47%)	0.33
Laboratory parameter			
Creatinin, mg/dL	1.0 (0.9-1.2)	1.0 (0.8-1.2)	0.4
Glucose, mg/dL	146 (123-207)	146 (122-195)	0.97
Hemoglobin, g/dL	14 ± 1.4	14 ± 1.6	0.49
Medication at discharge			
ACE Inhibitor or ARB	62 (83%)	61 (81%)	0.83
Clopidogrel	74 (99%)	75 (100%)	1.0
Acetylsalicylic acid	74 (99%)	74 (97%)	1.0
Beta-blocker	58 (77%)	52 (69%)	0.27
Statin	74 (99%)	71 (95%)	0.37
Medication at 1 month			
Acetylsalicylic acid	74 (99%)	75 (99%)	1.0
Clopidogrel	75 (100%)	75 (100%)	1.0

EES= everolimus-eluting stent, CoCr= cobalt chromium, BMI= body mass index, CAD= coronary artery disease, LVEF= left ventricular ejection fraction, ACE= angiotensin converting enzyme, ARB= angiotensin receptor blocker.

Table 2. Procedural and angiographical characteristics.

	EES group (N=75)	CoCr group (N=75)	P Value
Access site			
Trans radial approach	36 (48%)	39 (52%)	0.62
Procedural related variables			
Thrombus aspiration	38 (51%)	50 (67%)	0.06
Direct stenting	31 (41%)	25 (33%)	0.31
Predilation before stenting	45 (60%)	50 (67%)	0.39
IRA only PCI	68 (91%)	72 (96%)	0.19
Maximal inflation pressure, atm	13.6 ± 2.9	13.5 ± 3.2	0.85
Number of stents at target lesion	1.1 ± 0.3	1.0 ± 0.2	0.35
Total stent length, mm	23 (18-28)	23 (18-28)	0.38
Lesion characteristics			
Total occlusion	44 (59%)	51 (68%)	0.24
Bifurcation	31 (41%)	26 (35%)	0.4
Reference vessel diameter, mm	3.1 ± 0.4	3.2 ± 0.4	0.62
Initial TIMI flow grade			
0/1	42 (56%)	49 (65%)	0.24
2	6 (8%)	4 (5%)	0.51
3	17 (23%)	14 (19%)	0.54
Final TIMI flow grade			
0/1	1 (1.3%)	5 (7%)	0.21
2	15 (20%)	18 (24%)	0.55
3	59 (79%)	52 (69%)	0.19
IRA			
LAD	42 (56%)	41 (55%)	0.87
LCX	5 (7%)	2 (3%)	0.44
RCA	28 (37%)	32 (43%)	0.5
Number of diseased vessels			
Single vessel	30 (40%)	29 (39%)	0.87
Multi vessel	45 (60%)	46 (61%)	
Procedural success	75 (100%)	75 (100%)	1.0

IRA= infarct-related artery, PCI= percutaneous coronary intervention, TIMI= thrombolysis in myocardial infarction, LM= left main, LAD= left anterior descending artery, LCX= left circumflex artery, RCA= right coronary artery.

Acute reperfusion parameters. The EES and CoCr stent groups showed no significant differences in the achievement of final TIMI flow 2 or 3 (99% and 93%, p=0.21) and MBG 2 or 3 (72% and 77%, p=0.45) (Table 4).

Table 3. Primary end-point.

	EES (N=75)	CoCr (N=75)	HR (95% CI)	P Value
Primary end-point				
Death/re-MI/TVR at 30-days	1 (1.3%)	1 (1.3%)	0.9 (0.06-15.8)	1.0

MI= myocardial infarction, TVR= target vessel revascularization, HR= hazard ratio, CI= confidence interval.

Table 4. Secondary end-points.

	EES (N=75)	CoCr (N=75)	P Value
Secondary end-point			
Stent thrombosis at 30-days			
Definite	0	0	1.0
Probable	0	1 (1.3%)	
Possible	0	0	
In-hospital bleeding*			
Severe	0	0	0.37
Moderate	0	3 (4%)	
Mild	4 (5%)	4 (5%)	
Other end-points			
Post procedural TIMI flow grade 2/3	74 (99%)	70 (93%)	0.21
Myocardial blush grade 2/3	54 (72%)	58 (77%)	0.45

*GUSTO bleeding criteria, TIMI= thrombolysis in myocardial infarction.

CK-MB level and left ventricular function. CK-MB level in serum obtained 8-12 h after primary PCI did not differ between EES and CoCr stent group (p=0.29). Echocardiographic findings revealed a non-significant difference in LVEF between the groups (53% vs. 50%, p=0.21) (Table 5).

Discussion

The most important finding of this study is that the short-term (30 days) efficacy and safety of EES in acute STEMI patients (≤12 hours of onset) undergoing primary PCI with routine administration of intravenous eptifibatide are as good as the short-term efficacy and safety of the CoCr stent. These results contribute to the knowledge of efficacy and safety of DES in acute STEMI patients treated by primary PCI.

Table 5. CK-MB and LVEF.

	EES (N=75)	CoCr (N=75)	P Value
CK-MB, U/L			
At baseline	44 (26-110)	44 (31-80)	0.95
After 8-12 h	281 (168-475)	358 (160-536)	0.29
LVEF, %	53 (45-61)	50 (45-58)	0.21

Values are expressed as median (interquartile range). CK-MB= creatine kinase-MB, LVEF= left ventricular ejection fraction.

Drug-eluting stent in acute STEMI

The use of first generation DES in the setting of primary PCI for acute STEMI remained controversial due to an increased risk of late stent thrombosis [16], possibly related to delayed culprit vessel healing after DES implantation [17] and late acquired stent malapposition [18,19]. Second generation DES have been developed to overcome the disadvantages related to first generation DES. Since several trials have shown an improvement of clinical outcomes during mid to long-term follow-up in patients who received second generation DES [20-22], the use of DES have been widely used for off-label indications [23]. In acute STEMI, the use of EES has been investigated in several trials which showed favourable results compared with first generation DES [24,25] or BMS [26].

The ESC 2012 guidelines on the management of STEMI has qualified the use of DES for STEMI patients as class IIa recommendation [27]. However, data regarding efficacy and safety of second generation DES after primary PCI is still relatively scarce.

Our study showed that the use of EES after primary PCI is safe and does not increase the risk of MACE during 30-days follow-up. Furthermore, we did not find any stent thrombosis case in the EES group. Concordant with this result, a recent meta-analysis showed that EES was associated with a significant reduction in early (30 days) definite stent thrombosis (relative risk=0.28; $p<0.0001$) and early definite/ probable stent thrombosis (relative risk=0.54; $p=0.005$) compared with pooled paclitaxel, sirolimus and zotarolimus-eluting stents [28].

Optimizing acute reperfusion treatment

Acute reperfusion parameters (TIMI flow and MBG) during primary PCI are important tools for immediate evaluation of a successful reperfusion treatment [29]. The use of routine GPI administration in combination with manual thrombus aspiration during primary PCI resulted in the achievement of final TIMI flow 2/3 and MBG grade 2/3 in 96% and 74% of the study population, respectively. These results strengthen the findings from Burzotta and colleagues who used the combination of GPI and thrombus aspiration during primary PCI and showed that the combination was associated with a lower mortality rate than GPI alone and thrombus aspiration alone [30].

Administration of GPI and manual thrombus aspiration during primary PCI are recommended by the 2011 ACCF/AHA/SCAI guideline for PCI [31] and the 2012 ESC guideline on management of STEMI patients [27] (class IIa). However, routine pre-catheterization use of GPI has been indicated as a class IIb recommendation. In the EXAMINATION trial [26], GPI (predominantly abciximab) was used in 52% of the study population, whereas in our study, eptifibatide was administered to all patients of the study population. Moreover, in our study, the similar MACE rate in the EES and CoCr groups can be explained by equal success to achieve reperfusion (final TIMI flow and MBG), which leads to similar CK-MB rises (p=0.29) and similar LVEF (p=0.21). The choice to use CK-MB level at 8-12 h after stenting was based on the fact that in patients with reperfused infarcts, serial CK-MB values in serum peak after 8.7 h and 12.6 h after onset of chest pain in patients with early and late reperfusion respectively [32].

Several reasons may explain the low MACE rate and the absence of stent thrombosis associated with EES in our study. Firstly, it is postulated that stenting of a highly thrombotic lesion in a patient with acute STEMI may result in undersizing of the applied stent or incomplete stent apposition (which is known to be a predictor of stent thrombosis) [33], probably due to the masking effect of thrombus in the vessel. In our study, the treatment with eptifibatide alone or in combination with manual thrombus aspiration was expected to dissolve thrombus and minimize distal embolization, which: 1) allows clear visualization of the true vessel diameter, 2) allows the choice of an appropriate stent size, and 3) eliminates early stent malapposition. Secondly, the maximal stent inflation pressures applied in the EES and CoCr groups were similar (Table 2), which may indicate adequate stent deployment with well-opposed stent struts in the EES group. Thirdly, it is postulated that EES may have a rapid and complete endothelialization. Finally, the stent design of the Xience stents with thin struts, fracture-resistant cobalt chromium stent struts, and low polymer and drug load [34] may also yield specific advantages.

Study limitation

The present study has several limitations. First, the observation period of this study was one month only, and to observe differences with respect to MACE rates and (very) late stent thrombosis rates between the two groups, we need longer follow-up periods. Second, this study was underpowered to detect benefits of EES in 1-month follow up, particularly when the MACE rate in the group of patients treated with the CoCr stent is very low. However, this is the first study that has investigated EES using routine administration of eptifibatide in STEMI patients and therefore this preliminary report may encourage the start of larger randomized trials.

Conclusion

The results of this pilot study indicate that, in a one-month observation period, the use of everolimus-eluting stents is as safe and effective as cobalt chromium stents in patients with acute STEMI undergoing primary PCI with routine administration of intravenous eptifibatide. Future trials with much larger sample size and longer follow-up are necessary to confirm these results.

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Changing from the femoral artery to the radial artery as the preferred access site for primary percutaneous coronary intervention: a real world single center registry data of 1808 consecutive acute ST-elevation myocardial infarction patients

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Abstract

Objective

To compare the short and long-term outcomes of trans-radial (TRA) versus trans-femoral approach (TFA) for primary percutaneous coronary intervention (PPCI) during a complete institutional transition from TFA to TRA as the site of access.

Background

PPCI is the preferred treatment for STEMI patients. Whether the TRA is associated with improved outcomes of the treated patients, as compared to the TFA, remains to be assessed.

Methods

Consecutive STEMI patients (n=1808) who underwent PPCI using TRA (n=1162) and TFA (n=646) from October 2007 to December 2010 were enrolled. By 2007, TRA was used in 25% of PPCI and in 2010 this number was 95%. Primary end-points were cardiovascular death and major adverse cardiac events (MACE) defined as a composite of death, stroke, re-infarction and target vessel revascularization at 30 days and one year.

Results

At 30 days, TRA compared to TFA was associated with less cardiovascular mortality (5.2% vs. 10.5%, OR=0.46; 95% CI=0.32-0.66, p<0.001), less MACE (7.3% vs. 12.5%, OR=0.55; 95% CI=0.39-0.76, p<0.001), less access site complications (0.9% vs. 8.2%; OR=0.11; 95% CI=0.05-0.20, p<0.0001), and less major bleeding (1.1% vs. 4.3%; OR=0.24; 95% CI=0.12-0.46, p<0.001).

At one year, the cardiovascular mortality and MACE were also in favor for TRA compared to TFA group (6.9% vs. 11.5%; OR=0.57; 95% CI=0.41-0.79, p<0.001, and 11.6% vs. 20.1%; OR=0.52; 95% CI=0.40-0.68, p<0.001, respectively).

Conclusion

Complete transition from femoral access to radial access is safe and effective for STEMI patients undergoing PPCI, with favorable effects on short-term and long-term outcomes.

Keywords: trans-radial approach, trans-femoral approach, STEMI, primary PCI.

Introduction

Primary percutaneous coronary intervention (PPCI) is the strategy of choice to re-open the occluded coronary artery, thereby improving the outcome of patients with ST-elevation myocardial infarction (STEMI) [1-3]. Access site selection is an important procedural issue in PPCI. Trans-femoral approach (TFA) has been associated with higher rate of access site bleeding and vascular complications in comparison with trans-radial approach (TRA), particularly so if combined with the aggressive use of antithrombotic and antiplatelet treatment [4,5]. Vascular access site complications have been shown to be associated with worse outcomes [6,7].

Whether there is a possibility to further improve the outcome with radial access instead of femoral access in all-comers STEMI patients remains to be assessed.

Recent randomized trials found that in acute STEMI patients undergoing PPCI, TRA is associated with less bleeding events, lower vascular access site complications, and better clinical outcomes compared with TFA [8,9].

The radial artery offers an advantage that is readily accessible due to its superficial anatomy, regardless of the patient's body mass index, and its close proximity to the radial bone, which makes hemostasis easier [10].

The change of access site strategy, from femoral access to radial access, can overcome most of the problems related to the femoral access [11]. Since 2005, TRA was gradually adopted in our center. TRA became the main access choice in 2009 and has replaced femoral access in most of the elective and emergency PCI procedures.

The objective of this study was to compare the outcomes of a large scale cohort of STEMI patients undergoing PPCI during a period in which both TFA and TRA were used as access sites. All procedures were performed by the same seven high-volume operators experienced in TFA before adopting routine TRA. Thus, although the present study is a retrospective analysis and not a randomized trial, the comparison of TFA and TRA will underestimate the benefits of the TRA approach due to the limited experience of the operators with the relatively new TRA approach.

Patients and Methods

Study population

Between October 2007 and December 2010, a total of 1808 consecutive patients with acute STEMI admitted within the first 12 hours after onset of symptoms who underwent PPCI were enrolled. There were 1162 TRA and 646 TFA patients. During 39 months, all STEMI patients treated at our center were recruited and the procedural and clinical data were recorded in an ongoing registry.

The radial artery access as an alternative to femoral artery access for PPCI was adopted in our center during the period of 2007 to 2010. The TRA was performed in 25% of all PPCI procedures in 2007. In 2010, TRA was used in 95% of all PPCI procedures. Our PPCI registry is representative of our national interventional practice and contains data from 80% of the PPCI procedures performed in the Republic of Macedonia, which has a population of two million residents.

Procedural data was entered into a dedicated database by the interventional cardiologists immediately after completion of the procedure. This database was open for evaluation and audit by the health administration and public health insurance administration.

Transition from femoral access to radial access

All operators went through the TRA learning curve with more than 100 elective PCI procedures per year before using TRA for PPCI. At the beginning of the study (in 2007), TFA was the access chosen in 75% of the cases. In mid-term of the study (transitional period), all operators has changed the access to TRA, and at the end of 2010 TRA was the access site in 95% of the PPCI procedures .

Vascular access

Femoral artery access was obtained with a modified Seldinger technique. After local anesthesia with 3-5 mL 2% lidocaine, the femoral artery was cannulated with a 17G needle and a 0.035 inch guide-wire, followed by a 10 cm 6F introducer sheath placement.

The radial artery was accessed after local anesthesia with 1-1.5 mL of 2% lidocaine, using the counter puncture technique (Seldinger technique) with a 20G plastic iv cannula and a 0.025 inch mini guide-wire of 45 cm, followed by a 6F hydrophilic introducer sheath (Terumo, Fujinomiya, Japan) placement. A spasmolytic agent (5 mg verapamil) was given intra-arterially through the radial sheath.

Interventional procedures

Standard guide-catheters were used to perform PPCI (standard shapes like Judkins, Amplatz, EBU, etc) mostly 6F and occasionally 5F, for both radial and femoral artery access. Standard guide-wires for PPCI, mostly Balance Middle Weight (Abbott Vascular, Santa Clara, CA, USA), and other wires were used according to the case specificity, without preference related to access strategy.

PPCI only on the infarct-related artery was recommended. Infarct-related artery flow was determined before and after the PPCI procedure using the TIMI (Thrombolysis in Myocardial Infarction) score [12]. Stent choice between drug-eluting stent and bare metal stent was left to the operator's discretion. Manual thrombus aspiration was performed in cases with evident high thrombus burden. Data were analyzed by intention-to-treat principle.

Anticoagulation and antiplatelet treatments

Before PPCI, patients were treated with intravenous bolus of unfractionated heparin (100 IU/kg), acetylsalicylic acid (300 mg followed by 100 mg/day indefinitely) and clopidogrel (loading dose of 600 mg followed by 75 mg/day for at least 1 year). When required, abciximab was given by intracoronary or intravenous administration of 0.25 mg/kg (bolus) followed by 0.125 μg/kg/min infusion for 12 hours using a weight-adjusted protocol. After completion of PCI, the weight-adjusted dosage protocol of heparin infusion was continued for 24 hours, and the abciximab infusion was continued for 12 hours. Only in 4.1% of the patients abciximab was used. No fibrinolytic agent was used.

Hemostasis management

For femoral group: Femoral artery sheath was removed at 3-4 hours after insertion, and hemostasis was achieved by manual compression of 15-20 minutes followed by prolonged weight compression placement. Patients must remain in bed thereafter, with restricted mobility, in the following six hours (9-10 hours from sheath insertion). Vascular closure devices were not used.

For radial group: Radial artery sheath was removed immediately after the procedure, and hemostasis was achieved by a simple bandage compression or a TR band (Terumo, Fujinomiya, Japan). Patients had no mobility restriction after the procedure. The simple bandage compression was applied with 4-6 small elastic bands compressing the radial artery at the puncture site. The TR band was applied by inflating 13-15 mL of air at the puncture site. After each hour, TR band was gradually deflated and totally removed after four hours. Patients had no mobility restriction after the procedure.

Study end-points

The primary clinical end-points were cardiovascular death rate and major adverse cardiac events (MACE) at 30 days and 12 months follow-up. Secondary end-points were major vascular access site complications and major bleeding at 30 days. Other baseline, clinical and procedural characteristics such as demographic data, risk factors, first medical contact-to-balloon time, procedural time, procedural success, and fluoroscopy time were recorded and compared between groups. Primary and secondary end-points were judged by an independent clinical event committee of which the members were blinded to the access site for PPCI.

Definitions

Cardiovascular death was defined as: death from acute MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes within 30 days and one year follow-up. MACE was defined as a composite of death, stroke, re-infarction, and target vessel revascularization at 30 days and one year follow up.

Major vascular access site complication was defined as any access site-related hemorrhage requiring red blood cell transfusion, delayed hospital discharge or the need for a surgical vascular repair [13].

TIMI major bleeding was defined as overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a drop in hemoglobin of >5 g/dL (0.5 g/L) or a drop in hematocrit of ≥15% [14].

Door-to-balloon time was defined as the time from admission to the emergency department until the first balloon inflation at the culprit lesion [15].

Procedural success was determined by angiographic success, defined as the achievement of a vessel diameter >80% of normal in the presence of grade 3 TIMI flow [16]. Procedural time was calculated as the time needed from the local anesthesia injection until guide-catheter removal. Fluoroscopy time was also recorded.

Statistical analysis

Data was expressed as mean ± standard deviation for normally distributed numeric variables. If not fitting a normal distribution, data was expressed as median (range). Categorical variables were compared with chi-square test or Fisher's exact test. Student's *t*-test or Mann-Whitney *U*-test was used to compare differences between two groups (continuous data) with normal distribution and not-normal distribution, respectively. Treatment effects between trans-femoral and trans-radial group were analyzed by univariate log-regression and reported as odds ratio (OR) with the corresponding 95% confidence intervals (CI), calculated for the end-points. Time-to-event survival curves are displayed according to the Kaplan-Meier method and compared by Mantel-Cox log rank analysis. All reported p values are two-sided and p values of <0.05 were considered to identify statistically significant differences. All statistical analysis was performed using SPSS 18 (SPSS Inc. Chicago, IL, USA).

Results

During 39 months (between October 2007 and December 2010), 1808 consecutive STEMI patients were treated with PPCI in our center, 1162 patients were treated with TRA (64.3%) and 646 patients with TFA (35.7%). The mean age of the patients was similar in both groups and most of them (75%) were male. Smoking was more common in the TRA patients (55%) than in the TFA group (48%) (p=0.003). The time from symptoms to first medical contact and door-to-balloon time did not differ between the two groups. Patients with cardiogenic shock on initial presentation were similar in both groups. Baseline characteristics are shown in Table 1.

Table 1. Demographic and baseline clinical characteristics in both groups of patients.

Variables	TRA group (N=1162)	TFA group (N=646)	P Value
Demographic characteristics			
Age, years	57.9 ± 10.8	58.3 ± 10.5	0.507
Male	901 (77%)	489 (76%)	0.373
Risk factors			
Hypertension	710 (61%)	389 (60%)	0.647
Diabetes mellitus	236 (20%)	128 (20%)	0.798
Dyslipidemia	425 (37%)	200 (31%)	0.016
Smoker	642 (55%)	310 (48%)	0.003
Family history of CAD	180 (15%)	78 (12%)	0.047
Prior PCI	85 (7%)	62 (10%)	0.089
Clinical presentation			
Anterior MI	579 (49%)	315 (49%)	0.850
Cardiogenic shock	20 (2%)	13 (2%)	0.901
Time frame characteristics			
Time from symptoms to FMC,minute	167 (22-1000)	164 (15-950)	0.368
Door-to-balloon time, minute	50 (8-255)	49 (10-280)	0.684
Procedural time, minute	21.4 ± 7.5	22.8 ± 5.9	0.415
Fluoroscopy time, minute	9.2 ± 6.2	9.8 ± 6.4	0.298

Continous data are presented as mean ± standard deviation or median (range) and categorical data are expressed as numbers (percentage). TRA= trans-radial approach, TFA= trans-femoral approach, CAD= coronary artery disease, PCI= percutaneous coronary intervention, MI= myocardial infarction, FMC= first medical contact.

In both groups, left anterior descending artery was the most frequent infarct-related artery. Although baseline TIMI flow grade 0-1 was lower in the TRA group (74%) than in the TFA group (79%) (p= 0.01), the final TIMI 3 flow was similar in both groups (95% and 94%, respectively). Procedural success was obtained in 95% and 96% in the TRA and TFA group, respectively. Procedural characteristics are shown in Table 2.

Table 2. Characteristics related to intervention procedures.

Variables	TRA group (N=1162)	TFA group (N=646)	P Value
Sheath size			
5F	93 (8%)	0	<0.001
6F	1069 (92%)	646 (100%)	0.002
Culprit lesion			
LAD	570 (49%)	312 (48%)	0.419
LCX	161 (14%)	79 (12%)	0.228
RCA	426 (37%)	255 (39%)	0.084
Diseased vessel			
Multi vessel disease	628 (54%)	340 (53%)	0.187
PCI strategies			
Multivessel PCI	8 (0.7%)	6 (0.9%)	0.911
Reperfusion parameter			
Baseline TIMI flow 0 or 1	856 (74%)	511 (79%)	0.014
Final TIMI flow 3	1104 (95%)	607 (94%)	0.381
Procedural success	1108 (95%)	622 (96%)	0.741

F= French, LAD= left anterior descending artery, LCX= left circumflex artery, RCA= right coronary artery, PCI= percutaneous coronary intervention, TIMI= thrombolysis in myocardial infarction.

During the course of the study, a major shift occurred in access site preference as we changed the strategy from femoral to radial access. The transition from TFA to TRA as the preferred access site for PPCI between October 2007 and December 2010 is illustrated in Figure 1.

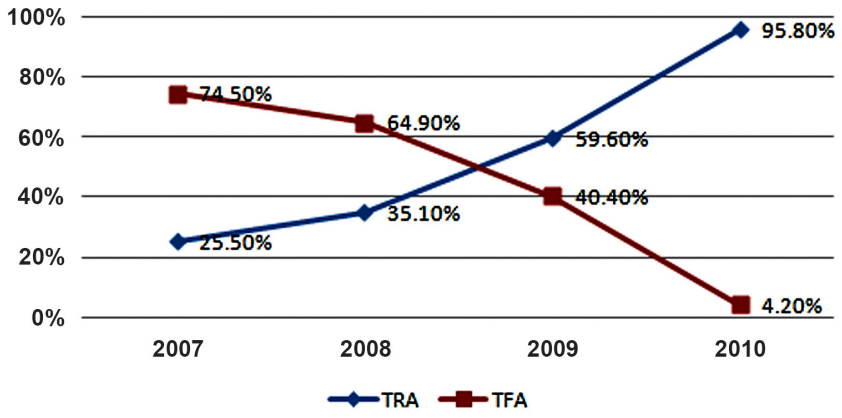

Figure 1. Time courses of the use of TRA and TFA from October 2007 to December 2010.
TRA= trans-radial approach, TFA= trans-femoral approach.

Primary and secondary end-points

Compared to TFA, the TRA was associated with lower cardiovascular mortality at 30-day and one year (5.2% vs. 10.5%, OR=0.46; 95% CI=0.32-0.66, p<0.001 and 6.9% vs. 11.5%; OR=0.57; 95% CI=0.41-0.79, p=0.001, respectively). The MACE rate at 30-day and one-year were significantly lower in TRA group compared to TFA group (7.3% vs. 12.5%; OR=0.55; 95% CI=0.39-0.76, p<0.001 and 11.6% vs. 20.1%; OR=0.52; 95% CI=0.40-0.68, p<0.001, respectively).

Major vascular access site complications were less frequent in TRA patients than in TFA patients (0.9% vs. 8.2%; OR=0.11; 95% CI=0.05-0.20, p<0.0001). At 30-day follow-up, major bleeding rate occurred less frequently in the TRA group than in the TFA group (1.1% vs. 4.3%; OR=0.24; 95% CI=0.12-0.46, p<0.001). Study end-points are displayed in Table 3.

Table 3. Study end-points in the two groups.

	TRA group (N=1162)	TFA group (N=646)	OR (95% CI)	P Value
Primary end-point				
MACE at 30 days	85 (7.3%)	81 (12.5%)	0.55 (0.39-0.76)	<0.001
MACE at 1 year	135 (12%)	130 (20%)	0.52 (0.40-0.68)	<0.001
Death at 30 days	60 (5.2%)	68 (10.5%)	0.46 (0.32-0.66)	<0.001
Death at 1 year	80 (7%)	74 (11%)	0.57 (0.41-0.79)	0.001
Secondary end-point				
Major vascular access site complication	11 (0.9%)	53 (8.2%)	0.11 (0.05-0.20)	<0.001
Non CABG major bleeding	13 (1.1%)	29 (4.3%)	0.24 (0.12-0.46)	<0.001

MACE= major adverse cardiovascular event, CABG= coronary artery bypass graft, OR= odds ratio, CI= confidence interval.

Event-free survival

The Kaplan-Meier survival curves are shown in Figures 2 and 3. After 30-day and one-year follow-up, the TRA patients had an improved cumulative survival compared to TFA patients (p<0.001 and p=0.001, respectively, by log-rank test). Furthermore, the benefit of TRA was observed in nearly all subgroups of patients (Figure 4).

At one-year follow-up, the overall cardiovascular mortality rate was 10%. The cardiovascular mortality rate was significantly lower in the TRA group than in the TFA group (6.9% vs. 11.5%, p<0.001).

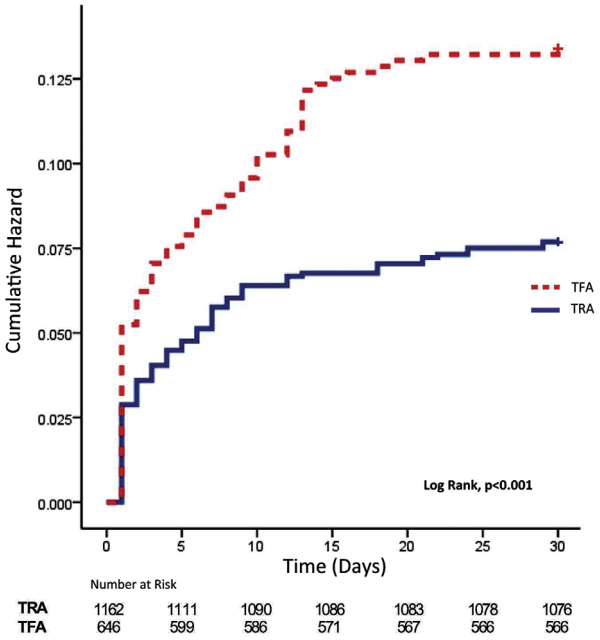

Figure 2. Kaplan-Meier survival curves in the first 30 days.
TRA= trans-radial approach, TFA= trans-femoral approach.

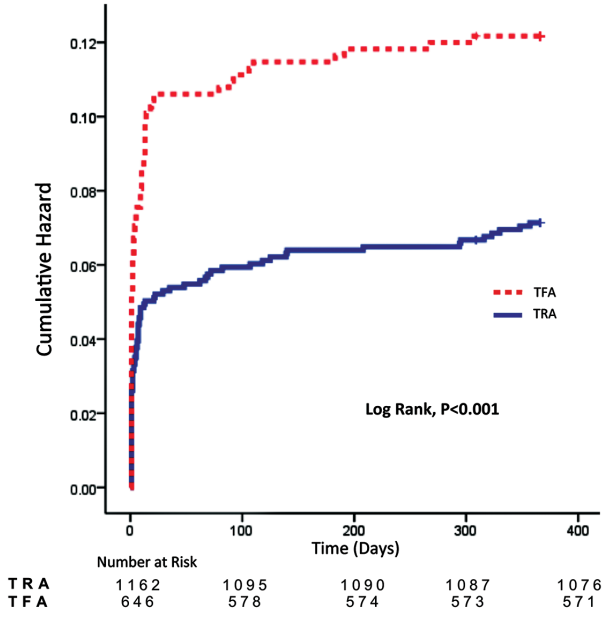

Figure 3. Kaplan-Meier survival curves at one-year follow up.
TRA= trans-radial approach, TFA= trans-femoral approach.

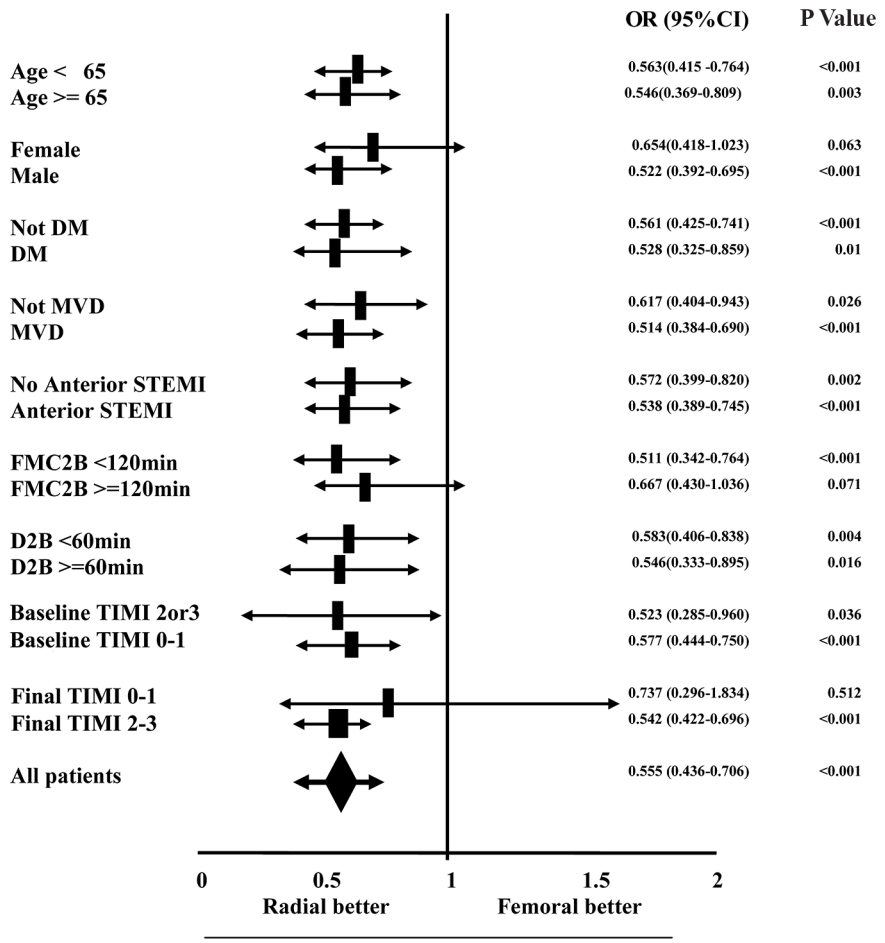

Figure 4. Sub-group analysis of all patients based on access site and its relation to clinical outcome.

OR= odds ratio, DM= diabetes mellitus, MVD= multivessel disease, STEMI= ST-elevation myocardial infarction, FMC2B= first medical contact-to-balloon time, D2B= door-to-balloon time, TIMI= Thrombolysis In Myocardial Infarction.

Discussion

The present study is the first large scale single center report analysing the impact of a transition of the access site from femoral to radial artery on (1) cardiovascular mortality, (2) bleeding events, and (3) one-year clinical outcomes in consecutive STEMI patients undergoing PPCI.

Access site is associated with bleeding events, while bleeding itself has been associated with an increased risk of death and ischemic events [17]. From the present study, the advantage of TRA compared to TFA was observed by a lower MACE rate after 30-day ($p<0.001$) and at

one-year clinical follow-up (p<0.001). Specifically, radial access was associated with lower rates of 30-day and one-year cardiovascular mortality than femoral access (5.2% vs. 10.2%, p<0.001 and 6.9% vs. 11.5%, p<0.001, respectively). The lower 30-day cardiovascular death associated with TRA was also seen in the RIFLE-STEACS study (5.2% vs. 9.2%, p=0.02) [9], as well as in the STEMI subgroup of RIVAL (1.3% vs. 3.2%, p=0.006) [21].

Although the underlying mechanisms of increased mortality of patients suffering from major bleeding remain unclear, a higher ischemic burden has been proposed to be a final common pathway. Local bleeding and femoral site hematoma formation is also thought to lead to systemic activation of pro-thrombotic pathways and activation of the clotting cascade. Cessation of antithrombotic therapies when the patient suffers from blood loss and consequences of blood transfusion in general could further increase the risk of stent thrombosis and subsequent myocardial ischemia and re-infarction [18].

Consistent with the result from the RIVAL study [19], our study shows that TRA is associated with a lower major vascular access site complication rate than TFA. Interestingly, the dramatic reduction of access site complications by TRA was associated with fewer MACE at 30 days compared to the TFA group. The reductions of major bleeding and major access site complications observed in the TRA group most probably affected the short-term and long-term mortality, and were associated with improved clinical outcome.

Since prolonged bed rest itself appears to be a predictor of worse prognosis in coronary artery disease [20], the possibility of a more rapid mobilization as a result of the decrease in access-site complications might have also influenced the outcome difference. Alternatively, it is not unlikely that subclinical bleeding in a less mobile and less active patient after femoral artery instrumentation with resultant hematoma might lead to platelet activation, precipitating intravascular thrombosis. The controversial question is whether relatively minor episodes of bleeding are actually responsible for mortality during follow-up. The reductions in cardiac mortality and bleeding found in the radial arm of the RIFLE-STEACS trial [9] and in the STEMI subgroup of RIVAL trial [21] support the link between mortality and clinically relevant access site bleeding. Further study is required in order to answer this question with confidence.

The advantage of the TRA in PPCI of patients with acute myocardial infarction was also observed in several randomized trials with follow-up periods ranging from 30 days to 2 years. These studies showed a favorable clinical outcome and lower access site complications for TRA compared to TFA [8,9,22,23].

Several studies have argued that the use of vascular closure devices (VCD) for TFA may lower the access site complications [24,25]. Several VCDs have been introduced and tested in clinical trials, but so far none of them have convincingly shown the ability to reduce major vascular complications compared with manual compression. Furthermore, a meta-analysis reported that the use of VCD increases the rate of vascular complications [26]. Recently, in a multicenter registry of 112,340 patients, Trimarchi and colleagues reported that the use of VCDs was associated with an increased risk for the development of retroperitoneal hematoma [27]. The American Heart Association has placed the VCDs when used with the purpose to reduce vascular complications in class III [28]. In our study, we did not use any VCD in any patient.

The HORIZONS-AMI study [5] showed an improved event-free survival in patients undergoing PPCI by the TRA compared with TFA, and confirmed the advantage of the TRA in terms of less hemorrhagic complications.

The present study showed that TRA did not affect the time interval measures, such as door-to-balloon time, procedural time and fluoroscopy time, a result that was shown in another study as well [22]. However, we noticed that the time the TRA procedure takes relates to the operator's experience. Based on our experience, the TRA requires a specific set of skills, and is associated with a significant learning curve. Published data suggest that 100-200 cases are necessary to become proficient in TRA and radial expertise begins to plateau at around 1,000 procedures [10]. Furthermore, the use of a dedicated radial kit (hydrophilic sheath, wire and cannula needle) is the key element in radial artery cannulation, and after dealing with the learning curve catheter manipulation is easier in TRA than in TFA, even for experienced trans-femoral operators.

Other advantages of TRA that have been reported include earlier patient mobilization, reduced procedural and hospital costs [29], and equal operator radiation exposure compared to TFA [30]. Finally, in the present study the advantages of TRA compared to TFA were observed in many subgroups of patients.

The results of this study are consistent with the recent 2012 ESC guidelines on STEMI [31], which state that TRA is preferred over TFA for PPCI, if performed by an experienced operator (Class IIa, Level B).

Limitation

The present study has several limitations. Firstly, this study was not a randomized comparison between TRA and TFA, but compares the outcomes of TRA and TFA in a period in which TRA is increasingly replacing TFA as the access site for PPCI. Secondly, the use of radial access has changed over the course of the study and the learning curve might have resulted in an underestimation of TRA's beneficial effects.

Conclusion

Complete transition from femoral access to radial access is safe and effective in the setting of PPCI in STEMI patients, and has favorable effects on short-term and long-term outcomes. Experienced PPCI centers could further improve their performance by adopting TRA in PPCI interventions in STEMI patients. However, these results should be confirmed in a prospective randomized trial comparing radial and femoral approaches for PPCI in patients with STEMI.

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The use of assist device for the treatment of acute coronary syndrome

The use of intra-aortic balloon pump in a real world setting: a comparison between survivors and non-survivors from acute coronary syndrome treated with IABP. The Jakarta Acute Coronary Syndrome Registry

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Abstract

Background

Real world data on acute coronary syndrome (ACS) patients who received intra-aortic balloon pump (IABP) support remains limited.

Objective

To evaluate the characteristics of ACS patients who received IABP support from a real world ACS registry.

Methods

Patients with ACS (N=121) who received IABP support were enrolled. Characteristics of survivors and non-survivors were compared at 30-days.

Results

Mortality rate of patients with ACS who received IABP support was 47%. The survivors (N=64) had less often cardiogenic shock (p<0.001), more often IABP usage as back-up for a revascularization procedure (p=0.002), less often resuscitation (p=0.043) and less mechanical ventilator support (p<0.001) than non-survivors. The non-survivors had a significantly higher blood leukocyte count (p=0.033), a higher serum creatinine level (p<0.001), a higher blood sugar on admission (p=0.001), higher CK-MB levels after 8-12 hours (p=0.002) and a higher serum uric acid level (p<0.001), but significantly lower left and right ventricular function (p=0.014 and p=0.003, respectively) than survivors. At 30 days, non-ST-elevation (STE) ACS patients had lower mortality rate than STEMI patients (log-rank test, p<0.001) and non-STE ACS patients who had not suffered from cardiogenic shock showed the lowest mortality rate (log-rank test, p<0.001).

By multivariate analysis, a heart rate ≥100 beats per minute prior to IABP insertion was the strongest predictor of 30-day mortality (hazard ratio=5.69; 95% CI= 1.49-21.78; p=0.011).

Conclusion

In ACS patients presenting with either cardiogenic shock, or resuscitated, or patients who needed mechanical ventilation suffered from high mortality, despite the use of IABP. IABP appears to be safe and tended to be favourable in ACS patients who did not suffer from cardiogenic shock, particularly in patients with non-STE ACS. A heart rate of ≥100 beats per minute prior to IABP insertion was the strongest predictor of 30-day mortality.

Keywords: IABP, ACS, survivor, non-survivor.

Introduction

The intra-aortic balloon pump (IABP) was introduced nearly five decades ago [1], as a simple but effective device to increase coronary perfusion, reduce afterload and reduce myocardial work [2,3]. Since then, IABP has become the most widely used form of mechanical circulatory support for patients with acute myocardial infarction (AMI) complicated by cardiogenic shock.

The American College of Cardiology and American Heart Association guidelines for the management of patients with ST-segment elevation myocardial infarction (STEMI) [4], and the American College of Cardiology Foundation/American Heart Association/the Society for Cardiovascular Angiography and Interventions guidelines for percutaneous coronary intervention [5] strongly recommend supportive treatment with an IABP in patients with cardiogenic shock (class I), whereas the European Society of Cardiology (ESC) guidelines on management of AMI in patients presenting with STEMI [6] now has given IABP a class IIb recommendation. However, the real utilization rate of IABP in STEMI patients complicated by cardiogenic shock is still low (20-39%) [7,8] and the results from the recently published IABP-SHOCK II trial [9] showed that the use of IABP in patients with AMI complicated by cardiogenic shock does not improve survival as compared to medical therapy.

Those findings now strongly challenge the recommendations of the guidelines thus, more data is needed to establish the role of IABP in the daily management of acute coronary syndrome (ACS) patients. Furthermore, the body of evidence supporting IABP in the real world ACS patients remains limited. Therefore, we studied the outcome of patients who received IABP treatment based on clinical judgment in our series of ACS patients from a real world local registry, outside the setting of a randomized controlled trial, including patients with and without cardiogenic shock in whom an IABP was inserted.

Patients and Methods

This study was an observational retrospective analysis. Data was collected from the Jakarta Acute Coronary Syndrome Registry of patients in the Intensive Cardiovascular Care Unit (ICVCU) of National Cardiovascular Center Harapan Kita, Jakarta, Indonesia, from the period of August 2008 to July 2012, involving 121 consecutive patients with ACS in whom an IABP was used.

Inclusion criteria were: All ACS patients (STEMI and non-STE ACS) presenting with and without cardiogenic shock, in whom an IABP was inserted and early revascularization was planned. The indications for IABP insertion in the non-cardiogenic shock group were: 1) recurrent acute pulmonary edema despite optimal medical treatment, 2) adjunct to complex revascularization procedures, 3) recurrent prolonged chest pain despite optimal medical treatment, and 4) persistent refractory malignant arrhythmia.

Intra-aortic balloon pump insertion technique

The IABP was inserted according to the standard technique. After local anesthesia with 10 mL of 2% lidocaine, the femoral artery was cannulated using a 17 G needle (modified Seldinger technique) and a 0.024 inch J-shaped guide-wire was inserted and advanced until

the level of the aortic arch, followed by a 7.5F or 8F introducer sheath placement. The balloon was advanced gently over the guide wire into the descending aorta and the tip of the catheter was positioned 1-2 cm distal to the origin of the left subclavian artery, followed by guide wire removal. The catheter was flushed with a heparin solution when the catheter is in the standard position. The access site choice for insertion (left or right femoral artery) was left to the operator's discretion. After insertion, 5000 IU bolus heparin was given in all patients. Choice of revascularization (PCI on culprit lesion only, multivessel PCI or CABG) was at the operator's discretion. Balloon size was determined using a height-adjusted protocol: body height of 152-162 cm (34 mL) and 162-183 cm (40 mL).

IABP initiation and weaning protocol

The balloon catheter was connected to the console and purged with helium. The central lumen of the catheter was connected to a pressure transducer and the pressure wave form was monitored.

Correct timing of balloon inflation and deflation during the cardiac cycle is vital for an optimal counterpulsation effect of IABP, initiated with 1:1 electrocardiographic triggering (R-wave triggered). However, the trigger ratio was selected depending on the hemodynamic status. The auto-pilot mode was used in most patients. The IABP was weaned by reduction of trigger ratio every 1-4 hours, from 1:1 to 1:2 to 1:3. If 1:3 ratio was tolerated for 4 hours, the device was turned to standby mode and removed.

Study end-points

The end-point was all cause mortality rate at 30-day follow-up. The blood pressure and heart rate before IABP insertion, blood leukocyte count, blood hemoglobin, glucose, creatinine, uric acid and cardiac biomarkers, echocardiographic variables (left ventricular ejection fraction (LVEF) and right ventricular function), history of cardiopulmonary resuscitation, and use of mechanical ventilation support were also assessed as well as in-hospital bleeding events, stroke, acute limb ischemia and/or vascular access site complications. Neither the Maquet nor Arrow company had any involvement in the study.

Definitions

Cardiogenic shock was defined as a systolic blood pressure <90 mmHg for >30 minutes or need for infusion of catecholamines/inotropics to maintain a systolic pressure >90 mmHg with signs of tissue hypoperfusion such as cold extremities, clammy skin and extremities, and/or oliguria with urine output of less than 30 mL per hour [10].

LVEF was measured with two-dimensional echocardiography using the modified Simpson's rule [11] and right ventricular function was measured by ultrasound using tricuspid annular plane systolic excursion (TAPSE) [12].

In-hospital bleeding criteria were defined according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) criteria [13] for classifying the severity of bleeding complications and are described as: 1) severe or life-threatening bleeding: intracranial bleeding or bleeding that causes substantial hemodynamic compromise

requiring treatment; 2) moderate bleeding: bleeding which needs blood transfusion; 3) minor bleeding: other bleeding, neither requiring transfusion nor causing hemodynamic compromise.

Stroke was defined as: new ischemic stroke event (rapidly developed clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours) occurring during the observation period [14].

Acute limb ischemia was defined as: sudden decrease in limb perfusion which could threaten limb viability, classified as type I (viable), type IIa (marginally threatened), type IIb (immediately threatened) and type III (irreversible). Duplex ultrasonography of the lower limb was used to confirm the diagnosis [15].

Vascular access site complication was defined as any puncture site-related bleeding (at the IABP insertion site) and/or hematoma ≥5 cm in diameter at the IABP insertion site.

Cardiac biomarkers

Creatine kinase-MB (CK-MB) level in plasma was measured by immunoinhibition assay (Roche Hitachi 912, Mannheim, Germany) after arrival in the emergency department and 8-12 hours after admission. Serum troponin T concentration was measured with the cTnT assay from Roche Diagnostics (Mannheim, Germany). The lowest cTnT value to be measured reliably with this assay is 0,03 μg/L which is the lowest cTnT concentration that can be measured reproducibly with the between-run coefficient of variation of 10%.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation (SD) or median (range). Categorical variables are expressed as percentages or as proportions. Normally distributed numerical variables were compared by Student's *t*-test, skewed distribution data by Mann-Whitney *U*-test and categorical variables by Chi-square test or Fisher's exact test.

Multivariate analysis was performed by Cox regression to identify the predictor(s) of 30-day mortality. Cumulative survival was assessed by the Kaplan-Meier method. Differences between the two groups were analyzed using the log-rank test. A p-value of <0.05 was considered statistically significant. All computations were performed using a statistical package (SPSS version 17.0, SPSS Inc. Chicago, IL, USA).

Results

Characteristics of patients

The median age of the patients was 58 years ranging from 30 to 85 years, and most patients (91%) were male. STEMI was diagnosed in 51% and non-STE ACS in 49% of patients. Baseline characteristics of the patients are presented in Table 1.

Table 1. Demographic and baseline clinical characteristics.

Variables	All patients (N=121)
Demographics characteristics	
Age, years	58 (30-85)
Male gender	110 (91%)
Body surface area, m^2	1.75 (1.37 – 2.48)
Risk factors	
Hypertension	68 (56%)
Dyslipidemia	60 (49%)
DM	54 (45%)
Current smoking	81 (67%)
Cardiac history	
Previous MI	63 (52%)
Previous PCI	26 (21%)
Previous CABG	1 (0.8%)
Clinical presentation	
STEMI	62 (51%)
Non STEMI	44 (36%)
UAP	15 (12%)
Cardiogenic shock	53 (44%)
Procedure during hospitalization	
Coronary angiography	108 (89%)
Primary PCI	17 (14%)
Fibrinolytic therapy	3 (2.5%)
30-days mortality	57 (47%)

DM= diabetes mellitus, MI= myocardial infarction, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, STEMI= ST-elevation myocardial infarction, UAP= unstable angina pectoris.

Fifty-three patients (44%) presented with cardiogenic shock. Table 2 shows the clinical characteristics and indications for IABP insertion in survivors and non-survivors during 30-days follow-up.

Table 2. Demographic and baseline clinical characteristics between survivors and non-survivors.

	Survivors (N=64)	Non-Survivors (N=57)	P Value
Demographic characteristics			
Age, years	55 (30-85)	61 (36-75)	NS
Male gender	58 (91%)	52 (91%)	NS
Body surface area, m^2	1.75 (1.38-2.32)	1.75 (1.37-2.48)	NS
Risk factors			
Hypertension	35 (55%)	33 (58%)	NS
Dyslipidemia	35 (55%)	25 (44%)	NS
DM	26 (41%)	28 (49%)	NS
Current smoking	41 (64%)	40 (70%)	NS
Cardiac history			
Previous MI	35 (55%)	28 (49%)	NS
Clinical presentation			
STEMI	24 (37%)	38 (67%)	0.001
Cardiogenic shock	17 (26%)	36 (63%)	<0.001
Location of MI			
Anterior	20 (31%)	26 (46%)	NS
Indication for IABP treatment			
Cardiogenic shock	17 (26%)	36 (63%)	<0.001
Recurrent pulmonary edema	5 (8%)	3 (5%)	NS
Prolonged chest pain	7 (11%)	3 (5%)	NS
Refractory malignant arrhythmia	4 (6%)	3 (5%)	NS
Adjunct to complex revascularization	31 (48%)	12 (21%)	0.002
Mechanical complication			
Interventricular septal rupture	0 (0)	2 (3%)	NS
Blood pressure, mmHg			
Systolic blood pressure	113 (70-191)	114 (70-160)	NS
Diastolic blood pressure	73 (43-113)	70 (37-100)	NS
Heart rate on admission, beats/minute	93 (51-146)	98 (50-168)	NS
Laboratory parameter			
Hemoglobin, g/dL	13 ± 2.1	14 ± 2.0	NS
Leucocyte count, /μL	10,565 (3900-62,380)	12,500 (6190-25,200)	0.033
Creatinine, mg/dL	1.10 (0.5-11)	1.6 (0.8-10)	<0.001
Calculated CCT	69 (5.9-178)	42 (4.8-133)	<0.001
Glucose, mg/dL	144 (82-554)	194 (72-488)	0.001
Initial CK-MB, U/L	30 (2-628)	47 (3-1965)	NS
CK-MB after 8-12 h, U/L	42 (9-724)	136 (7-1388)	0.002
Initial Troponin T, ng/mL	0.5 (0.01-16)	1.1 (0.03-25)	NS
Uric acid, mg/dL	6.1 (2.6-11)	8.1 (3.5-15.4)	<0.001

Echocardiography parameters			
LVEF, %	37 (14-70)	30 (15-76)	0.014
TAPSE, cm	1.9 (1.1-2.6)	1.6 (0.6-2.7)	0.003
Cardio-pulmonary resuscitation	6 (9%)	13 (23%)	0.043
Mechanical ventilator support	15 (23%)	39 (68%)	<0.001
Coronary angiography	62 (97%)	46 (81%)	0.004
Revascularization			
PCI	28 (44%)	29 (51%)	NS
CABG	27 (42%)	7 (12%)	<0.001
Manual thrombectomy	9/62 (14%)	7/46 (15%)	NS
Number of diseased vessels			
1	8/62 (13%)	2/46 (4%)	
2	7/62 (11%)	11/46 (24%)	NS
3	47/62 (76%)	33/46 (72%)	
Culprit vessel			
LAD	59/62 (95%)	45/46 (98%)	
LCX	48/62 (77%)	39/46 (85%)	NS
RCA	49/62 (79%)	36/46 (78%)	
LM	25/62 (40%)	16/46 (35%)	
Anticoagulation			
Unfractionated heparin	16 (25%)	10 (17%)	
Enoxaparin	22 (34%)	16 (28%)	NS
Fondaparinux	15 (23%)	10 (17%)	

DM= diabetes mellitus, MI= myocardial infarction, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, STEMI= ST-elevation myocardial infarction, CCT= calculated clearance test, CK-MB= creatine kinase-MB isoform, LVEF= left ventricular ejection fraction, TAPSE= tricuspid annular plane systolic excursion, LAD= left anterior descending artery, LCX= left circumflex artery, RCA= right coronary artery, LM= left main artery. NS= not significant.

Mechanical complications occurred in two patients, and both presented with cardiogenic shock. In survivors (N=64) cardiogenic shock less often occurred (p=0.001) and IABP was more often used as an adjunct to complex revascularization procedures (p=0.002) than in non-survivors. Survivors had less often a history of resuscitation (p=0.043) and less mechanical ventilator support (p<0.001) than non-survivors. Most patients had triple vessel coronary artery disease, including the cardiogenic shock patients. The characteristics of the subpopulation with cardiogenic shock are depicted in Table 3.

Antiplatelet and anticoagulation regimen

The antiplatelet and anticoagulation regimen were identical in the survivors and non-survivors groups. All patients received 160 mg salicylic acid and 300 mg loading dose of clopidogrel on admission. For patients who underwent PCI, a loading dose of 600 mg clopidogrel was given and intravenous unfractionated heparin was administered (100 IU/kg or 50-60 IU/kg if a GPIIb/IIIa inhibitor was used). During hospitalization, enoxaparin was given in 31%, fondaparinux in 20%, and unfractionated heparin in 21% of the patients (Table 2).

Table 3. Characteristics of cardiogenic shock patients treated with IABP.

	Cardiogenic shock patients (N=53)
Age, years	56 (30-72)
Risk factors	
Hypertension	29 (57%)
Dyslipidemia	19 (36%)
DM	24 (45%)
Current smoking	36 (68%)
STEMI	38 (72%)
Heart rate, beats/minute	100 (50-168)
Creatinine, mg/dL	1.50 (0.70-10)
LVEF, %	30 (15-76)
Mechanical complication	2 (4%)
Triple vessel coronary artery disease	33/44 (75%)

DM= diabetes mellitus, STEMI= ST-elevation myocardial infarction, LVEF= left ventricular ejection fraction.

Study end-points

At 30 days follow-up, the overall mortality of the study population was 47%. Compared to survivors, the non-survivors had significantly higher:

- blood leukocyte counts (p=0.033)
- serum creatinine levels (p<0.001)
- serum glucose levels on admission (p=0.001)
- serum CK-MB levels after 8-12 hours (p=0.002), and
- serum uric acid levels (p<0.001).

The non-survivors had a significant lower LVEF (p=0.014) and TAPSE (p=0.003) than the survivors (Table 2). Survivors and non-survivors did not differ with respect to in-hospital bleeding and stroke rate, but four cases of acute limb ischemia were found in the non-survivors group (Table 4). After multivariate analysis, a heart rate ≥100 beats per minute prior to IABP insertion was the strongest predictor of 30-day mortality (hazard ratio=5.69; 95% CI=1.49-21.78; p=0.011) (Table 5).

Table 4. Safety end-points of the study.

	Survivors (N=64)	Non-survivors (N=57)	P Value
In-hospital bleeding*			
Severe or life-threatening	1 (1.5%)	5 (9%)	NS
Moderate	13 (20%)	7 (12%)	NS
Minor	6 (9%)	10 (17%)	NS
Stroke	1 (1.5%)	1 (2%)	NS
Acute limb ischemia	0 (0)	4 (7%)	0.046
Vascular access site complication	2 (3%)	3 (5%)	NS

*In-hospital bleeding was according to GUSTO criteria. NS= not significant.

Table 5. Multivariate predictors of 30-day mortality of ACS patients treated with IABP.

Variables	HR	95% CI	P Value
Age (>65 years)	0.85	(0.36 – 2.03)	0.722
Male gender	1.15	(0.29 – 4.48)	0.844
Risk Factors			
Diabetes mellitus	3.19	(1.01 – 10.08)	0.048
Hypertension	3.11	(1.31 – 7.42)	0.010
Dyslipidemia	0.47	(0.16 – 1.36)	0.163
Current smoking	1.79	(0.63 – 5.04)	0.272
Prior myocardial infarction	1.35	(0.52 – 3.56)	0.537
Anterior wall infarction	1.12	(0.46 – 2.71)	0.807
Systolic pressure <90 mmHg	0.58	(0.23 – 1.45)	0.245
Heart rate ≥100 beats/minute	5.69	(1.49 – 21.78)	0.011
Creatinine level >1.5 mg/dL	1.31	(0.67 – 2.55)	0.427
Leukocyte count >11,000 /μL	0.97	(0.41 – 2.36)	0.963
Blood glucose ≥200 mg/dL	0.87	(0.37 – 2.04)	0.751
LVEF <35%	1.70	(0.83 – 3.48)	0.144
Triple vessel disease	0.64	(0.29 – 1.39)	0.257

LVEF= left ventricular ejection fraction, HR= hazard ratio, CI= confidence interval.

Survival functions

At 30 days, non-STE ACS patients had lower mortality rate than STEMI patients (log-rank test, p<0.001) (Figure 1A). Patients with cardiogenic shock, either STEMI or non-STE ACS, had a significantly higher mortality rate than the STEMI and non-STE ACS patients without cardiogenic shock (log-rank test, p<0.001). Patients with the lowest mortality rate were the non-STE ACS patients who had an indication for IABP other than cardiogenic shock

(Figure 1B). Finally, patients with a heart rate ≥100 beats per minute prior to IABP insertion had a higher mortality rate than the patients with a heart rate <100 beats per minute (log-rank test, p<0.001) (Figure 1C).

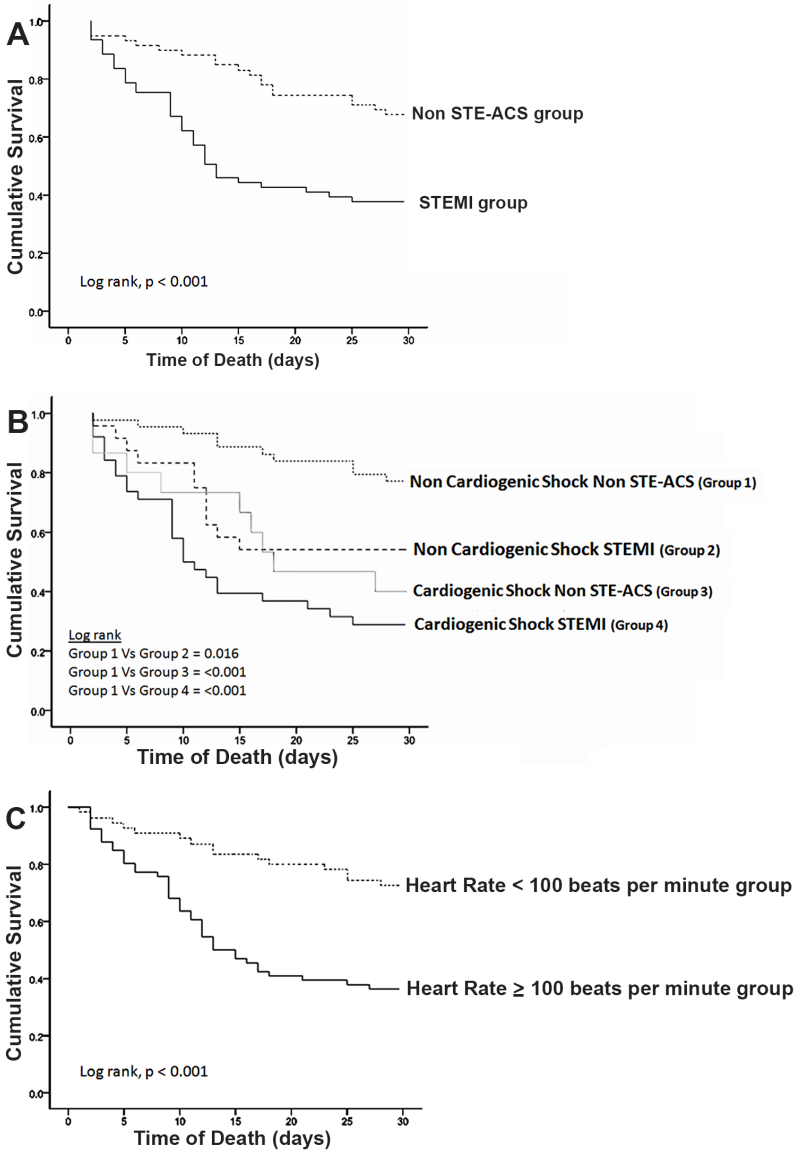

Figure 1. Kaplan-Meier survival curves for all cause of death in the first 30 days among patients with: STEMI and non-STE ACS treated with IABP (A); in patients with STEMI and non-STE ACS with and without cardiogenic shock treated with IABP (B); and in STEMI and non-STE ACS patients having high heart rate (≥100 bpm) and lower heart rate (<100 bpm) prior to IABP insertion (C).

Discussion

In the real world, IABP is used not only for patients presenting with cardiogenic shock complicating an AMI, but also in a variety of ACS conditions such as refractory ventricular failure, cardiac support for patients undergoing high risk general surgery, refractory unstable angina [16], refractory malignant arrhythmia despite optimal medical treatment [17], adjunct to revascularization [18,19] and/or bridging to a heart transplant [20].

The main findings of this study are: despite the lack of support for IABP treatment in cardiogenic shock patients, we observed a favourable safety profile and a tendency to good performance of IABP treatment in: 1) ACS patients without cardiogenic shock; 2) IABP as an adjunct to revascularization procedures; 3) ACS patients without resuscitation; and 4) patients who did not need mechanical ventilator support. As expected, we also found that non-STE ACS patients had better 30-day survival than STEMI patients.

IABP in cardiogenic shock patients

The incidence of cardiogenic shock complicating an AMI is around 7.2% [21,22] and is associated with high mortality (50-80%) [23]. More recently, several randomized studies and registries reported a mortality of 42-48% [24,25], despite emerging innovative treatment modalities. Mortality rates may differ among the trials which may be due to the differences in criteria of cardiogenic shock. The high mortality rate in AMI patients with cardiogenic shock has led most IABP trials to enroll patients with cardiogenic shock only.

The mortality rate of AMI patients with cardiogenic shock in our study was higher than the mortality rate in the IABP group of the IABP SHOCK II trial [9] (63% vs. 39.7%). Several conditions may explain these differences. Compared to the IABP group in the IABP SHOCK II trial, the group of patients with cardiogenic shock in our study population had a higher risk profile as evident in a higher proportion of diabetes mellitus (45% vs. 35%), higher median heart rate (100 beats per minute vs. 92 beats per minute), higher median creatinine level (1.5 mg/dL vs. 1.3 mg/dL), more frequently triple vessel disease (75% vs. 52%), and lower LVEF (30% vs. 35%).

In patients with ACS it was shown that diabetes mellitus [26], heart rate [27], creatinine level [28], triple vessel disease [29] and low LVEF [30] are associated with high mortality rates. Moreover, patients with mechanical complications were included in our study. On the other hand, the IABP SHOCK II trial has more patients with a history of resuscitation (45% vs. 16%) than our study.

The survival curves showed that patients who might benefit most from IABP treatment appear to be: 1) non-STE ACS patients, particularly the non-STE ACS patients without cardiogenic shock, who had a lower mortality rate than the STEMI patients without cardiogenic shock, 2) non-STE ACS patients with cardiogenic shock, and 3) STEMI patients with cardiogenic shock. These findings deserve further investigation by means of a larger multi-center randomized trial to establish the true efficacy and safety of IABP in ACS populations.

Survivors versus non-survivors

We observed that non-survivors more often presented with cardiogenic shock with lower

LVEF and lower TAPSE than survivors. The higher CK-MB levels after 8-12 hours found in the non-survivors and its relation to the lower left and right ventricular functions needs to be investigated further. Moreover, higher blood leukocyte count, higher serum creatinine and higher serum uric acid concentrations in the non-survivors might explain the higher risk profile of this group and this merits further investigation as well. However, the safety profile did not differ between survivors and non-survivors except for the four patients with acute limb ischemia in the non-survivors group, which may reflect their more serious disease at baseline.

Predictors of 30-day mortality

After multivariate analysis, we found that a heart rate ≥100 beats per minute prior to IABP insertion was a strong predictor of 30-day mortality. Morrow et al. also showed the importance of heart rate as a predictor of 30-day mortality in STEMI patients [28]. The pathophysiological mechanism through which a higher heart rate adversely affects mortality remains unclear. The significance of sympathetic activity has become evident after sympathetic blockade that leads to a lower heart rate [31]. Thus, the results of the present study may alert us to manage patients with high heart rate on admission (e.g., ≥100 beats per minute) more aggressively.

The results of a meta-analysis [32] and the IABP SHOCK II trial [9] showed no benefits of IABP in AMI patients with cardiogenic shock, which is in agreement with our results. Thus, the recommendations of the ACCF/AHA/SCAI and ACC/AHA guidelines [4,5] regarding IABP treatment in cardiogenic shock patients may be challenged. Importantly, it should be noted that in the real world practice, the use of IABP is not restricted to AMI patients suffering from cardiogenic shock. Randomized studies are needed to investigate the efficacy of IABP treatment in ACS patients without cardiogenic shock.

Limitations

This study was designed as an observational retrospective analysis with its inherent limitations.

Conclusion

In ACS patients (1) presenting with cardiogenic shock, or (2) were resuscitated, or (3) who needed mechanical ventilation, the short-term mortality remains high, despite the use of an IABP. IABP appears to be safe and potentially favourable in ACS patients without cardiogenic shock, particularly in patients presenting with non-STE ACS. A heart rate of ≥100 beats per minute prior to IABP insertion was the strongest predictor of 30-day mortality.

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Trans-radial approach for coronary procedures

Nitroglycerin plus diltiazem versus nitroglycerin alone for spasm prophylaxis with trans-radial approach

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Abstract

Objective

The aim of this study was to compare the efficacy of nitroglycerin and diltiazem versus nitroglycerin alone in preventing radial artery spasm (RAS) during transradial coronary procedures.

Background

Spasm after trans-radial access decreases procedural success. Multiple spasmolytics are used to prevent spasm. Individual efficacy of these agents is not conclusively established.

Methods

One hundred and fifty patients undergoing coronary procedures through radial artery were enrolled and randomized into two groups of 75 patients each. Patients in Group A received 200 µg nitroglycerin plus 2.5 mg diltiazem intra-arterially, and Group B patients received 200 µg nitroglycerin plus placebo (saline). Blood pressure (BP) and heart rate (HR) were recorded at baseline and for 5 minutes after cocktail was given. Clinical signs of RAS, such as pain and resistance during catheter maneuver, were recorded in both groups during the procedure.

Results

Systolic and diastolic BP decreased significantly in Group A compared to Group B after cocktail was given ($p<0.01$ and $p<0.22$, respectively). There were no significant changes in HR in either group. There was no significant difference in the incidence of clinical RAS between Group A (diltiazem plus nitroglycerin) versus Group B (nitroglycerin alone) (5% vs. 7%; $p=1.000$). Furthermore, we found higher incidence of local burning pain in the forearm in patients that receive intra-arterial diltiazem plus nitroglycerin compared to nitroglycerin alone (21% vs. 9%; $p=0.041$).

Conclusion

Diltiazem plus nitroglycerin showed no advantage compared to nitroglycerin alone in prevention of RAS in trans-radial approach.

Keywords: radial artery spasm, spasmolytic, nitroglycerin, diltiazem.

Introduction

The use of the trans-radial approach (TRA) for coronary intervention has increased tremendously over the past 5 years worldwide. It has been shown that TRA has become popular due to its lower vascular complication rates, reduced procedural costs, earlier patient mobilization, and equivalent procedural success [1-4]. TRA has been shown to lower mortality in ST-segment elevation myocardial infarction patients [5,6].

The most common complication of TRA is radial artery spasm (RAS), which can lead to serious complications and is a predictor of procedural failure [7,8]. Therefore, spasmolytic cocktail is needed to prevent RAS during coronary procedures in TRA [9]. In clinical practice, RAS is manifested by resistance during manipulation of intra-arterial equipment and by patient reporting pain in the forearm [10,11]. RAS is observed more frequently during the early phase of the operator's learning curve, as well as patient and operator apprehension. Experienced operators report a low incidence of manifest RAS

The most commonly used vasodilator cocktail consists of nitroglycerin and a calcium-channel blocker [10,12]. There is uncertainty whether combination pharmacotherapy (calcium-channel blocker plus nitroglycerin) might have an advantage over single agent (nitroglycerin alone) in preventing RAS. Furthermore, diltiazem is known to cause an uncomfortable burning sensation in the forearm. The aim of this study was to compare the efficacy of nitroglycerin and diltiazem versus nitroglycerin alone in preventing RAS during trans-radial coronary procedures.

Methods

This study was designed as single-center, prospective, randomized, placebo-controlled trial (consecutive eligible patients are randomized to receive nitroglycerin plus diltiazem or nitroglycerin plus placebo). One hundred and fifty patients were included in the study (75 patients for each group). The operators and personnel were blinded to the treatment assignment.

All eligible patients were assigned to receive 200 µg nitroglycerin plus diltiazem (Group A) or 200 µg nitroglycerin plus placebo (Group B). All drugs were given intra-arterially through the radial sheath. The study protocol was approved by the local ethics committee, and all patients provided written informed consent.

Patients with severe left ventricular dysfunction (left ventricular ejection fraction <30%), severe bradycardia (heart rate <40 bpm), second or third degree atrioventricular block, or hypotension (SBP <90 mm Hg) with or without cardiogenic shock were excluded.

Transradial access

All patients had a positive Allen's test. The radial artery was punctured using either counter-puncture technique or anterior-puncture technique based on operator preference. After the insertion of a 0.025" guidewire, a 5 or 6F short hydrophilic sheath (10 cm) was introduced into the radial artery.

Blood pressure (BP) and heart rate (HR) monitoring

Arterial BP and HR were recorded before the administration of spasmolytic cocktails and at 5 minutes after the administration of spasmolytic cocktails. Baseline BP was recorded from the manifold pressure monitoring through the radial sheath before injection of cocktails. Baseline HR was derived from the electrocardiogram monitor. After the injection of either nitroglycerin plus diltiazem or nitroglycerin plus placebo, the BP and HR were recorded continuously. The largest change was recorded.

Cocktail administration

All patients were randomized before the procedure began. Patients in Group A received 200 µg nitroglycerin in 2 mL normal saline with 2.5 mg diltiazem in 10 mL of normal saline, and Group B patients received 200 µg nitroglycerin in 2 mL saline with 10 mL saline as placebo. All drugs were given intra-arterially through the radial sheath.

Coronary procedures

Coronary angiography and percutaneous coronary intervention (PCI) were performed according to the standard techniques. A 0.035" x 260 cm-long guidewire was used to deliver or exchange catheters. The first choice catheter was 5F Optitorque for diagnostic procedures and the Judkins Right 3.5 x 6F (for right coronary artery) and EBU 3.5 x 6F catheters (for left coronary artery) in all PCI cases. All patients received intravenous unfractionated heparin 5000 IU for diagnostic procedure and 100 IU/kg if PCI was planned.

Procedural variables, including number of punctures, vasovagal reaction, procedural success, resistance during catheter maneuver, local forearm pain, and procedural time, were recorded. Demographic data were recorded.

Definitions

Primary end-point was defined as the occurrence of RAS. Vasovagal reaction (cardioinhibitory as well as vasodepressor) was defined as symptomatic hypotension and/or bradycardia after cocktail administration, associated with nausea and/or flushing, that required additional therapy including aggressive volume repletion. Procedural success was defined as completion of the intended procedure via the initial access site. Local burning pain was defined as burning sensation experienced by the patient in the forearm that was used for the access, without the presence of catheter resistance. RAS was defined as resistance during catheter maneuver, inability to freely manipulate the catheter, and/or difficulty in removing the catheter with the presence of concomitant forearm pain during the procedure. Total procedural time was calculated from local anesthetic injection to introducer sheath removal.

Statistical analysis

Data were expressed as mean ± standard deviation for normally distributed numeric variables, and as median (range) for continuous variables not fitting a normal distribution, while percentages were used for categorical variables. The Chi-square test was used to compare categorical variables and Student's *t*-test or Mann-Whitney *U*-test were used to

compare differences between the two groups. Using 80% study power and a probability of 0.05, a minimum of 65 patients were needed in each group for evaluating an effect on the primary end-point of RAS using a 10% incidence of RAS. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 17.0. A study flow chart can be seen in Figure 1.

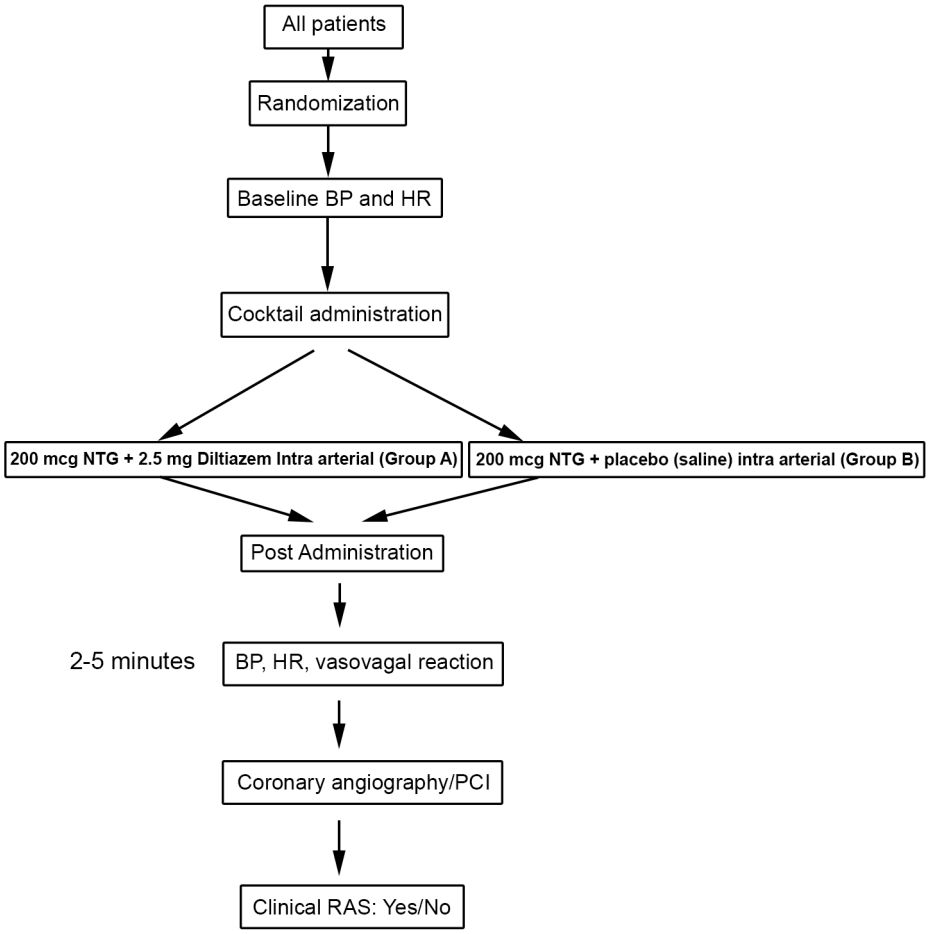

Figure 1. Study flow chart.
NTG= Nitroglycerin, RAS= radial artery spasm, BP= blood pressure, HR= heart rate.

Results

Baseline characteristics including type of procedure, access site, number of punctures, and total procedural time between the groups are shown in Table 1. There were no significant differences noted in clinical and procedural variables between the two groups.

Table 1. Baseline characteristics of all patients.

	Group A (Nitroglycerin plus Diltiazem) N=75	Group B (Nitroglycerin plus Placebo) N=75	P Value
Clinical Variables			
Age (years)	58.8 ± 11.3	57.7 ± 9.4	0.499
Male	54 (72%)	54 (72%)	1.000
BMI (kg/m^2)	25 (20-44)	24 (17-42)	0.090
Procedure			
Diagnostic	64 (85%)	62 (83%)	0.656
PCI procedure	11 (15%)	13 (17%)	
CAD risk factor			
Hypertension	42 (56%)	37 (49%)	0.414
Diabetes mellitus	28 (37%)	30 (40%)	0.737
Dyslipidemia	0 (0%)	3 (4%)	0.245
Smoking	1 (1%)	4 (5%)	0.367
LVEF (%)	60 (30-75)	50 (30-65)	0.062
Procedural variables			
Access site			
RRA	71 (95%)	71 (95%)	1.000
LRA	4 (5%)	4 (5%)	
Number of punctures			
Single puncture	52 (69%)	43 (57%)	0.127
Multiple punctures	23 (31%)	32 (43%)	
Sheath size			
5F	65 (87%)	61 (81%)	0.373
6F	10 (13%)	14 (19%)	
Number of catheters used			
Single catheter	62 (83%)	58 (77%)	0.414
Multiple catheters	13 (17%)	17 (23%)	
Total procedural time (minutes)			
Diagnostic	9 (5-29)	10 (5-30)	0.473
PCI procedure	25 (14-60)	20 (13-55)	0.884
Procedural success	75 (100%)	75 (100%)	NS

Continous data presented as mean ± standard deviation or median (range) and categorical variables as number and percentages. RRA= right radial artery, LRA= left radial artery, PCI= percutaneous coronary intervention, BMI= body mass index, LVEF= left ventricular ejection fraction, NS= not significant.

The differences of BP and HR between the two groups before and after cocktail administration are shown in Table 2. After cocktail administration, systolic and diastolic BP in Group A were significantly lower than in Group B.

Table 2. Blood pressure and heart rate profile before and after cocktail was given.

	Group A (Nitroglycerin plus Diltiazem) N=75	Group B (Nitroglycerin plus Placebo) N=75	P Value
Systolic BP (mm Hg)			
At baseline	162.68 ± 27.68	161.12 ± 27.54	0. 730
After cocktail	124.56 ± 21.30	141.24 ± 26.15	<0.001
Diastolic BP (mm Hg)			
At baseline	80.11 ± 11.03	78.31 ± 13.61	0. 375
After cocktail	71.60 ± 11.21	75.88 ± 11.45	0.022
Heart rate (bpm)			
At baseline	81.69 ± 18.37	81.61 ± 17.27	0.978
After cocktail	86.61 ± 18.05	84.69 ± 18.08	0.516

Data presented as mean ± standard deviation. Student's *t*-test was used to analyze differences between groups. BP= blood pressure, bpm= beats per minute.

The incidence of local pain was significantly higher in the diltiazem group (p=0.041). The incidences of vasovagal reaction, local pain, and clinical signs of RAS are shown in Table 3.

Table 3. Differences between groups in the incidence of vasovagal reaction, local pain, and clinical radial artery spasm.

	Group A (Nitroglycerin plus Diltiazem) N=75	Group B (Nitroglycerin plus Placebo) N=75	P Value
Vasovagal reaction	2 (3%)	0 (0%)	0.497
Local burning pain	16 (21%)	7 (9%)	0.041
Clinical sign of RAS	4 (5%)	5 (7%)	1.000

RAS= radial artery spasm.

Discussion

The radial artery is a muscular artery with concentric layers of smooth muscle cells (SMC) found predominant in the tunica media [15]. RAS occurs due to contraction of SMC in response to activation of the predominant α-1-adrenoreceptors and, to a lesser extent,

α-2-adrenoreceptors. These receptors are stimulated by circulating catecholamines and by mechanical stimuli (catheter or wire manipulation), pain sensation due to multiple punctures, or anxiety [7]. The radial artery has been classified as a type III artery [16] and has a higher receptor-mediated contractility (to endothelin-1 and angiotensin II) [17], hence a higher risk of spasm compared to other vessels.

The incidence of RAS during transradial procedures varies from 10%-12%. In current practice, intra-arterial calcium-channel blocker and nitroglycerin are the most common drug combination used to prevent RAS [10,12]. Diltiazem is a high-specificity L-type calcium channel blocker that inhibits the influx of extracellular calcium ions during membrane depolarization of cardiac and vascular SMCs, resulting in dilation of the coronary and systemic arteries, including the radial arteries [13].

Our study showed a higher incidence of local burning pain in patients who received intra-arterial diltiazem plus nitroglycerin compared to nitroglycerin alone (21% vs. 9%; p=0.041). This may be due to acidic pH of diltiazem solution, versus vasodilatory action causing burning pain. Diltiazem-induced vasodilatation not infrequently causes a raised urticarial rash on the flexor aspect of the forearm.

Nitroglycerin exerts its vasodilator effect through nitric oxide (NO) stimulating guanylate cyclase and cGMP formation in the vascular SMCs [14]. This study showed that nitroglycerin and diltiazem caused a decrease in mean systolic and diastolic BP. This is probably because of a synergistic effect of nitroglycerin and diltiazem in causing systemic vasodilatation.

Some studies have found that addition of intra-arterial diltiazem to nitroglycerin after TRA showed lower incidence of RAS than with nitroglycerin alone [9,11], but our study did not show the advantage of adding diltiazem (5% vs. 7%; n.s). We believe that minimal number of puncture attempts in the radial artery, use of a hydrophilic guidewire, use of an universal catheter with fewer catheter exchanges, and short duration of the procedure are more responsible for a reduced tendency to develop RAS in our patients than the addition of diltiazem to nitroglycerin. When the incidence of RAS is expected to be higher, such as during the early part of the operator's and institution's learning curve, with an unusually anxious patient, with procedures requiring multiple catheter exchanges, or with longer procedure duration due to adverse anatomy, diltiazem may be needed in addition to nitroglycerin.

Incidence of RAS decreases with increasing operator's experience [7,18-20]; procedures performed by experienced operators may be successfully completed with RAS prevention provided by nitroglycerin alone.

Study limitations

Diagnosis of clinical RAS was made by the presence of resistance during catheter movement, inability to freely manipulate the catheter, and/or difficulty in removing the catheter with the presence of forearm pain during the procedure, which was subjective. To decrease the subjectivity bias, the operators were blinded to the treatment group. These signs and symptoms of RAS could also be encountered with other conditions that increase the resistance to catheter movement, such as atherosclerosis, vessel tortuosity, or small-caliber of the radial artery; hence, a radial angiogram was acquired when these problems were encountered to

eliminate these anatomic reasons for resistance and pain, and angiographic presence of stenotic segments suggestive of spasm were observed. The operators participating in this trial were very experienced in the transradial technique and hence results of this study may not be applicable to less experienced operators.

Conclusion

Diltiazem plus nitroglycerin showed no significant advantage compared to nitroglycerin alone, as a vasodilator to prevent RAS in patients undergoing coronary procedures performed by operators with experience in the trans-radial approach.

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Prognostic markers in acute coronary syndrome

Serum uric acid as an independent predictor of cardiovascular events in patients with acute ST-elevation myocardial infarction

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Abstract

Background

There is uncertainty whether serum uric acid level can be used as a prognostic marker in acute ST-elevation myocardial infarction (STEMI) patients. Furthermore, there is a need to find a simple, less expensive but accurate marker that can be used in rural areas where fibrinolytic treatment is the first choice of acute reperfusion therapy. We studied the association of serum uric acid levels with cardiovascular events in patients with acute STEMI receiving fibrinolytic treatment.

Methods

Seventy-five patients with acute STEMI, eligible for fibrinolytic therapy, were enrolled in this cohort study. After a night of fasting, serum uric acid level was measured. The composite of re-infarction, heart failure, urgent revascularization, recurrent angina and death during 1-month clinical follow-up was the primary end-point of the study.

Results

STEMI patients in the lowest quartile of uric acid levels (<4.8 mg/dL) and those in the highest quartile of uric acid levels (>7.3 mg/dL) had a cardiovascular event rate of 8% and 20%, respectively. Elevated serum levels of uric acid (>7.3 mg/dL) were an independent and significant risk factor of cardiovascular events [Hazard Ratio=3.10, $p<0.024$].

Conclusion

In patients with acute STEMI treated with fibrinolytic therapy, serum uric acid concentration is an independent predictor of 30-day cardiovascular events.

Keywords: uric acid, myocardial infarction, predictor, cardiovascular event.

Introduction

Previous trials suggest that serum uric acid concentration might be an independent predictor of major adverse cardiac events (MACE) in patients with coronary artery disease (CAD) or only an indirect marker of adverse events due to the association between serum uric acid concentration and other cardiovascular risk factors [1-5].

As to the mechanisms behind this association, high serum uric acid concentration may increase platelet reactivity [6], and may promote inflammatory responses [7,8], which may promote thrombosis and aggrevate its consequences. There is uncertainty about the role of serum uric acid concentration in patients with acute coronary syndrome and whether it could be used as a prognostic marker in acute ST-elevation myocardial infarction (STEMI) patients.

Furthermore, there is a need to find a simple and accurate prognostic marker that could be used in a remote area where fibrinolytic therapy is the first choice of acute reperfusion therapy (as part of a pharmaco-invasive strategy) in non PCI-capable hospitals, particularly in developing countries.

To explore the relation between serum uric acid and myocardial infarction, we investigated the predictive role of serum uric acid concentration on the risk of MACE in 75 consecutive patients with acute STEMI who received fibrinolytic treatment.

Methods

Study design

Seventy-five consecutive patients were enrolled in this single center prospective cohort study. All patients were recruited in the emergency department of National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. The inclusion criteria were acute STEMI patients ≤12 hours of onset, and eligible for fibrinolytic therapy. Fibrinolytic therapy was performed using intravenous streptokinase (1.5 million units, given in 30 to 60 minutes). One month clinical follow-up was done by a dedicated medical practitioner by phone contact and medical record study, who was blinded to the baseline characteristics of patients. The primary end-point of the study was the composite of re-infarction, heart failure, urgent revascularization, recurrent angina and death.

Participation of all subjects was voluntary and written, and informed consent was obtained from each subject. This study has been approved by the institutional review committee and the local medical ethics committee.

Baseline measurements and definitions

In all 75 subjects, blood samples were drawn under standardized conditions after overnight fasting. After 10 minutes at room temperature, samples were centrifuged at 4,000 rpm for 10 minutes. Serum uric acid concentration was determined by enzymatic calorimetric test (Roche, Germany). Diabetes mellitus was diagnosed in patients with a history of oral antidiabetic or insulin medication or fasting blood glucose >125 mg/dL at study entrance. Hypertension was diagnosed by the Joint National Committee VII criteria on hypertension or if currently taking antihypertensive treatment. Dyslipidemia was diagnosed in patients with a history of lipid-lowering medication or a total cholesterol level >200 mg/dL, LDL-C >130 mg/dL, HDL-C

<40 mg/dL, and triglycerides >150 mg/dL. A positive family history of premature CAD was diagnosed if the patient had a first degree relative in whom CAD had developed before the age of 65 years.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and percentages were used for categorical variables. Serum uric acid levels were presented in quartiles: first quartile <4.8 mg/dL, second quartile from 4.8 to 6.2 mg/dL, third quartile from >6.2 to 7.3 mg/dL, and fourth quartile range >7.3 mg/dL.

Chi-square test was used to compare categorical variables. Student's *t*-test or Mann-Whitney *U*-test were used to compare differences between the highest and lowest uric acid quartile. Univariate and multivariate regression analyses were performed to identify independent predictors of cardiovascular events. Cumulative event-free survival was assessed by the Kaplan-Meier method. A p-value of <0.05 was considered statistically significant. All computations were performed using a statistical package (SPSS 13.0).

Results

Serum uric acid levels

Baseline characteristics of all patients are shown in Table 1. The mean ± standard deviation serum uric acid level was 6.28 ± 1.68 mg/dL. Serum uric acid level did not differ between women and men (6.38 ± 1.57 mg/dL vs. 6.26 ± 1.71 mg/dL, p=0.83, respectively).

Compared with the lowest quartile of uric acid (Table 1), the highest quartile was associated with more use of diuretics (13% vs. 4%, p=0.027), whereas there was only a trend toward a higher level of serum creatinine in the highest uric acid quartile (1.22 ± 0.32 mg/dL vs. 1.06 ± 0.26 mg/dL, p=0.109). No statistically significant differences were observed in the location of myocardial infarction (MI) and use of angiotensin converting enzyme inhibitor between the patients in the lowest and the highest uric acid quartiles.

Table 1. Demographic and baseline clinical and laboratory characteristics of all patients and the patients in the lowest and highest quartiles of serum uric acid levels.

Variables	All Patients (N=75)	Lowest Uric Acid Quartile* (N=16)	Highest Uric Acid Quartile* (N=18)	P Value
Age (years)	53.68 ± 7.72	53.12 ± 7.71	52.72 ± 6.95	0.873
Body mass index (kg/m2)	22.99 ± 2.76	22.38 ± 2.45	22.95 ± 1.73	0.442
Male gender	63 (84%)	15 (20%)	15 (20%)	0.347
Prior myocardial infarction	4 (5%)	2 (2%)	0 (0)	0.122
Risk factor				
Family history	18 (24%)	6 (8%)	3 (4%)	0.169
Smoker	39 (52%)	8 (10%)	8 (10%)	0.746
Hypertension	40 (53%)	9 (12%)	9 (12%)	0.715
Diabetes mellitus	16 (21%)	6 (8%)	4 (5%)	0.329
Dyslipidemia	52 (69%)	13 (17%)	12 (16%)	0.336
Door-to-needle time (minute)	57.88 ± 43.56	59.43 ± 41.43	51.88 ± 46.08	0.276
Symptoms-to-reperfusion time (minute)	297.28 ± 154.44	288.18 ± 173.43	264.38 ± 139.70	0.661
Anterior MI	47 (63%)	10 (13%)	14 (18%)	0.329
Lipid profile				
Total cholesterol (mg/dL)	209.70 ± 44.00	214.18 ± 54.25	217.16 ± 41.77	0.857
LDL-cholesterol (mg/dL)	136.80 ± 40.08	144.25 ± 49.54	148.77 ± 33.35	0.754
HDL-cholesterol (mg/dL)	42.93 ± 10.70	43.25 ± 12.05	43.55 ± 11.25	0.939
Triglyceride (mg/dL)	152.57 ± 69.95	134.06 ± 51.60	135.50 ± 41.58	0.769
Creatinine (mg/dL)	1.03 ± 0.28	1.06 ± 0.26	1.22 ± 0.32	0.109
Medication at enrollment				
Diuretic	21 (28%)	3 (4%)	10 (13%)	0.027
ACE inhibitor	52 (69%)	10 (13%)	15 (20%)	0.169
Statin	41 (54%)	9 (12%)	8 (10%)	0.492
Beta blocker	23 (30%)	6 (8%)	7 (9%)	0.934
MACE	43 (57%)	6 (8%)	15 (20%)	0.006

*Uric acid quartiles: first quartile range <4.8 mg/dL, second quartile range 4.8 to 6.2 mg/dL, third quartile range >6.2 to 7.3 mg/dL, fourth quartile range >7.3 mg/dL. Data are expressed as percentages of patients or mean ± SD.
The p value is given for the comparison of lowest versus highest uric acid quartile, for normally distributed, continuous variables by *t* test, for skewed continuous variables by Mann-Whitney *U*-test, and for categorical variables by Pearson's chi-square test.
MACE= major adverse cardiac event, MI= myocardial infarction, ACE= angiotensin converting enzyme.

Cardiovascular events

During one month follow-up, MACE occurred in 43 patients (57%), of whom 7 patients (17%) were women. Heart failure was the most common event (55%). In the lowest uric acid

quartile (<4.8 mg/dL), the MACE rate was 8% while in the highest quartile (>7.3 mg/dL), the MACE rate increased to 20% (p=0.006).

Patients having serum uric acid concentration in the highest quartile had a hazard ratio for MACE of 3.24, relative to the patients having serum uric acid in the lowest quartile (95% CI=1.25-8.41, p=0.016) (Table 2). Multivariate Cox regression analysis showed that a serum uric acid concentration in the fourth quartile (>7.3 mg/dL) was an independent predictor of cardiovascular event with HR of 3.10 (p=0.024), and stronger than resting heart rate >100 beats/min, anterior location of MI, and use of beta-blocker (Table 3).

Table 2. Univariate predictors of cardiovascular events.

Variables	HR (95% CI)	P Value
Age (>65 years)	1.0 (0.24-4.18)	0.990
Body mass index (>25 kg/m^2)	0.86 (0.41-1.81)	0.705
History of CAD	0.36 (0.05-2.68)	0.244
History of MI	0.79 (0.19-3.27)	0.748
Risk factor		
Family History	0.76 (0.36-1.59)	0.477
Diabetes mellitus	1.25 (0.61-2.55)	0.524
Hypertension	0.69 (0.38-1.26)	0.238
Dyslipidemia	0.80 (0.42-1.52)	0.500
Smoker	0.94 (0.52-1.72)	0.862
Heart rate >100 beats/minute	2.11 (1.08-4.14)	0.029
Anterior location of infarction	2.29 (1.15-4.57)	0.018
Door-to-needle time >30 min	0.56 (0.29-1.06)	0.078
Symptoms-to-reperfusion time >240 min	1.00 (0.54-1.85)	0.977
Lipid profile		
Total cholesterol >200 mg/dL	1.15 (0.61-2.16)	0.654
HDL-cholesterol <40 mg/dL	1.09 (0.60-2.00)	0.763
LDL-cholesterol >130 mg/dL	1.34 (0.72-2.50)	0.344
Triglyceride >150 mg/dL	0.71 (0.37-1.36)	0.310
Serum creatinine >1.5 mg/dL	0.98 (0.35-2.75)	0.976
Medication at enrollment		
Beta blocker	0.55 (0.27-1.13)	0.107
ACE Inhibitor	1.67 (0.82-3.39)	0.154
Statin	0.61 (0.33-1.12)	0.118
Uric acid		
Second quartile (4.8-6.2 mg/dL)	1.34 (0.47-3.77)	0.575
Third quartile (>6.2-7.3 mg/dL)	1.79 (0.68-4.73)	0.234
Fourth quartile (>7.3 mg/dL)	3.24 (1.25-8.41)	0.016

Variables with p value <0.25 were entered in the multivariate Cox regression analysis; All uric acid quartile were entered in the multivariate Cox regression analysis. CAD= coronary artery disease, MI= myocardial infarction, HR= hazard ratio, CI= confidence interval.

Table 3. Multivariate analysis of cardiovascular event.

Variables	HR (95% CI)	P Value
History of CAD	0.38 (0.04-3.23)	0.382
History of hypertension	1.00 (0.48-2.08)	0.985
Heart rate >100 beats/minute	2.31 (1.03-5.19)	0.041
Anterior location of infarction	2.93 (1.06-8.07)	0.038
Door-to-needle time >30 minute	0.70 (0.32-1.53)	0.377
Use of beta blocker	0.39 (0.17-0.92)	0.033
Use of ACE Inhibitor	0.66 (0.21-2.04)	0.472
Use of statin	0.89 (0.44-1.79)	0.759
Second quartile of uric acid	1.55 (0.51-4.63)	0.433
Third quartile of uric acid	2.10 (0.78-5.68)	0.141
Fourth quartile of uric acid	3.10 (1.16-8.29)	0.024

CAD= coronary artery disease, ACE= angiotensin converting enzyme, HR= hazard ratio, CI= confidence interval.

Kaplan-Meier event-free survival curves clearly showed that patients with highest quartile of serum uric acid level had a significantly lower cumulative event-free survival than those with other quartiles (log-rank test, p=0.026) (Figure 1).

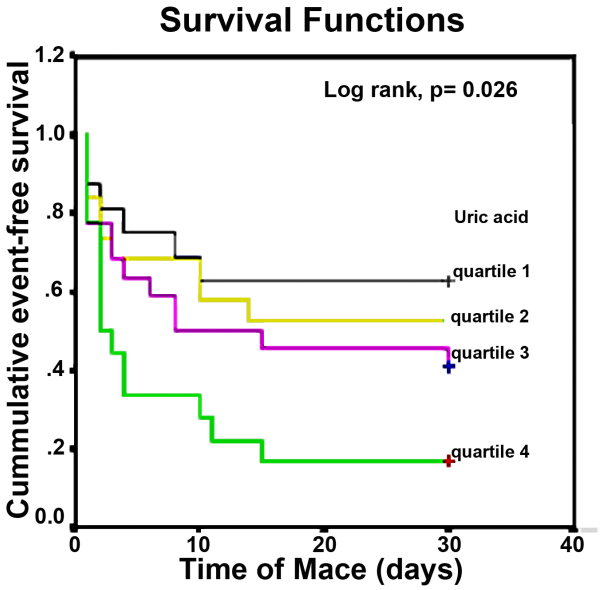

Figure 1. Kaplan Meier event-free survival curves.

Discussion

This is the first study that focuses on the role of serum uric acid levels in patients with acute STEMI treated with fibrinolytic therapy. Serum uric acid levels can be measured at low cost in almost all hospitals in the world, especially in developing countries, where many hospitals have no facilities to measure other expensive prognostic markers such as high sensitive C-reactive protein, brain-type natriuretic peptide, interleukin-6, and many others. This study documents and validates that a high serum uric acid level (>7.3 mg/dL) is a strong and independent predictor of cardiovascular events in post fibrinolytic patients with acute STEMI. The measurement of serum uric acid concentration in this study provides information independently of, and better than, other well-established parameters such as age, prior MI, history of hypertension, history of diabetes mellitus, resting heart rate, anterior STEMI, and symptoms-to-reperfusion time [9].

Several epidemiologic studies have suggested an association between serum uric acid concentration and CAD [10,11]. Urate is one of the products of the lysosomal enzymatic degradation of glycoprotein-urate complexes. The urate links to the lysosomal membrane via hydrogen bonds, causing membrane lysis. Uric acid potently stimulates vascular smooth muscle cell proliferation in vitro, an effect mediated by stimulation of mitogen-activated protein kinase, cyclooxygenase-2, and platelet-derived growth factor [10]. Other theory involves uric acid as a mediator of inflammation by directly activating complement factors [12]. Xanthine oxidase, the rate-limiting enzyme for the formation of uric acid, has been found in endothelial cells and smooth muscle cells of arteries. The resultant uric acid may result in free radical injury to the vessel wall [7,13,14]. These actions are believed to contribute to the development of degenerative vascular disease [7], and might increase the risk of acute thrombosis. Furthermore, uric acid is a general marker of cell death [15] and elevated serum uric acid is linked with obesity, dyslipidemia [16], hypertension, insulin resistance [17], male gender, aging, menopause [18], excessive alcohol intake and diuretic use [19]. Moreover, the serum uric acid level may reflect the activity of the xanthine oxidase pathway, which has the potential to contribute to the progression of left ventricular dysfunction by interfering with myocardial energetics and myofilament calcium sensitivity [10]. Treatment with allopurinol, an inhibitor of xanthine oxidase, improves endothelium-dependent vasodilation in the forearm circulation and was associated with reduced oxidant stress in patients with chronic heart failure [14].

Other trials showed that the relation between serum levels of uric acid and cardiovascular disease is generally stronger in women than in men [20,21]. However, Maxwell et al. [6] demonstrated that men had a significantly higher serum uric acid concentration than women (5.5 ± 1.3 mg/dL vs. 4.2 ± 1.4 mg/dL, $p<0.0001$). Our study, consisting of 12 female patients (16%) did not show any difference compared to males (6.26 ± 1.71 mg/dL vs. 6.38 ± 1.57 mg/dL, n.s). Also, there were no differences in traditional risk factors between patients with high and with low serum uric acid levels. Using data from the Framingham study, Culleton et al. [4] reported that serum uric acid concentration is an independent risk factor in patients with CAD. After adjustment for age, they found an increased risk of MACE in women only, but after additional adjustment for cardiovascular disease risk factors, serum uric acid concentration was not independently associated with death from cardiovascular disease or death from all

causes. They concluded that uric acid has no causal role in the development of CAD and that any apparent association with these outcomes is probably due to the association of uric acid levels with other risk factors.

Our study presents the results of an observational study in patients with clinically proven CAD (acute STEMI), whereas in the Framingham study [2,4] and NHANES I [11] epidemiologic follow-up studies, primarily healthy persons were included, which is a different approach and may explain some of the different results. Furthermore, a recent study from Ndrepepa et al. [22] concluded that elevated levels of uric acid is an independent predictor of 1-year mortality in patients with acute coronary syndrome treated with percutaneous coronary intervention, thus strengthening the prognostic value of uric acid, not only for short term, but also for a longer follow-up period.

In some developing countries that use the pharmaco-invasive approach for their AMI system of care (fibrinolytic treatment in pre-hospital setting with an invasive procedure back-up), this simple, inexpensive and accurate prognostic marker might be used for further risk stratification. Thus, in STEMI patients the role of allopurinol in the treatment of hyperuricemia needs further evaluation.

Study limitations

The prognostic role of serum uric acid concentration in this small group of patients needs to be confirmed by larger studies.

Conclusion

The serum uric acid concentration is an independent predictor of 30-days cardiovascular events in patients with acute STEMI treated with fibrinolytic therapy.

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Blood leukocyte count on admission predicts cardiovascular events in patients with acute non ST-elevation myocardial infarction

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Submitted

Abstract

Background

We aimed to test the hypothesis that blood leukocyte count adds prognostic information in patients with acute non ST-elevation myocardial infarction (non-STEMI).

Methods

A total of 585 patients with acute non-STEMI (TIMI risk score ≥3) were enrolled in this cohort retrospective study. Blood leukocyte count was measured immediately after admission in the emergency department. The composite of death, re-infarction, urgent revascularization and stroke during hospitalization was defined as the primary end-point of the study.

Results

The mean age of the patients was 61 ± 9.6 years and most of them were male (79%). Using multivariate Cox regression analysis involving seven variables (history of smoking, hypertension, heart rate >100 beats/minute, serum creatinine level >1.5 mg/dL, blood leukocyte count >11,000 /μL, use of beta-blocker and use of ACE inhibitor), leukocyte count >11,000 /μL demonstrated to be a strong predictor of the primary end-point (HR=3.028; 95% CI=1.69–5.40, p<0.001).

Conclusion

Blood leukocyte count on admission is an independent predictor of cardiovascular events in patients with acute non-STEMI.

Keywords: leukocyte, acute non-STEMI, predictor.

Introduction

Inflammation plays an important role in the course of atherosclerosis including acute plaque rupture leading to thrombosis, manifested as acute coronary syndrome (ACS) [1-3]. The leukocyte is one of the inflammatory biomarkers [4], and quantification of leukocyte density in blood is available in almost all laboratories worldwide. Leukocytosis affects acute thrombosis by mechanisms involving inflammation that will induce a hypercoagulability state and microvascular obstruction, leading to a more extensive infarction [5].

Many studies have shown that leukocytosis is a predictor of cardiovascular events in healthy individuals [6-8], and in patients with a history of myocardial infarction [9-11], but another study failed to find such an association [12]. Studies that observe an association between blood leukocyte count and cardiovascular events in the developing countries are scarce. As the clinical laboratories in most developing countries lack the routine assay of established inflammatory markers, such as interleukins and C-reactive protein (CRP), these laboratories need a simple, reliable, inexpensive but accurate marker is to be measured routinely in daily management of infarct patients to identify patients who are at increased risk for subsequent cardiovascular events.

This study was designed to observe the predictive role of baseline leukocyte count on in-hospital cardiovascular events in patients with acute non ST-segment elevation myocardial infarction (non-STEMI).

Methods

Study population

Data was collected from the Jakarta Acute Coronary Syndrome Registry database involving 585 patients admitted to the emergency department of the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. The inclusion criteria were all patients diagnosed with moderate to high-risk acute non-STEMI (TIMI risk score ≥3) who were hospitalized between January 2008 and December 2010. Patients with known history of infection or systemic inflammation during the last two weeks before admission, or patients with liver disease, or patients with hematologic disease at admission were excluded.

Diagnosis of acute non-STEMI was based on (1) typical chest discomfort in the preceeding 48 hours, (2) the absence of ST-segment elevation, and (3) the presence of at least one of the following criteria: (a) positive serum marker of myocardial necrosis, defined as troponin T values above the 99th percentile of a healthy reference population, and (b) electrocardiographic indices of ischemia consisting of transient ST-segment depression (≥0.05 mV) or T-wave inversion (≥0.1 mV) in two or more contiguous leads.

TIMI risk score [13] was calculated as the sum of each of the following variables of which its presence contributes one point to the total score: age 65 years or older, at least 3 risk factors for coronary artery disease, prior coronary stenosis of ≥50%, ST-segment deviation on electrocardiogram at presentation, at least two anginal events in the prior 24 hours, use of acetylsalicylic acid in the preceeding week, and elevated cardiac marker levels in serum. Moderate and high-risk patients are defined when having TIMI score of 3-4 and 5-7, respectively. To investigate a homogenous study population, only moderate-to-high risk patients (TIMI risk score ≥3) were included in the study.

Laboratory determination

Immediately after admission venous blood samples were taken in tubes containing EDTA. One blood sample was used to measure the blood leukocyte count using flow cytometry (Sysmex Corporation, Kobe, Japan). In plasma samples cardiac troponin T was assayed using a chemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA), and creatine kinase-MB activity was measured using an immuno-inhibition assay (Roche Diagnostics Corporation).

Study end-point

Primary end-point of the study is major adverse cardiovascular event (MACE) defined as the composite of death, re-infarction, urgent revascularization, and stroke during hospitalization, as judged by an independent clinical event committee of which the members were blinded to the laboratory results. This study has been approved by the local institutional review committee and all patients have given written informed consent.

Statistical methods

Continuous variables are presented as mean values ± standard deviation (SD) or median (range) if not fitting a normal distribution. Categorical variables were expressed as percentages or proportions. The cut-off value for blood leukocyte count was determined using the receiver operator characteristic (ROC) test, based on a specificity of 70% and a sensitivity of 50%. A leukocyte count of 11,000/μL was chosen as the cut-off point. Normally distributed variables were compared by Student's *t*-test, skewed distribution data by Mann-Whitney *U*-test and categorical variables by Pearson's chi-square test. Univariate and multivariate Cox regression analyses were performed to identify whether a variable is a predictor of cardiovascular events. Variables with p value <0.25 in univariate analysis were entered in the multivariate analysis. To detect a reduction of MACE by at least 16%, each group should contain at least 85 patients at a study power of 80% and a probability of 5%. A p value <0.05 was considered as statistically significant. All computations were performed using a statistical package (SPSS version 13.0, SPSS Inc, Chicago, IL, USA).

Results

Most patients were men (79%) and the mean age was 61 ± 9.6 years. The mean leukocyte count was 10,382 ± 4,007 /μL. On admission, patients with a leukocyte count >11,000 /μL had higher heart rate (p<0.001), a higher CK-MB level on admission (p<0.001) and a higher creatinine level (p=0.014) than patients with a leukocyte count ≤11,000 /μL (Table 1).

During the hospitalization period, MACE occurred in 52 patients (9%). Incidence of MACE was significantly higher in patients with a leukocyte count >11,000 /μL than in patients with a leukocyte count ≤11,000 /μL (16% vs. 5%, p<0.001).

Table 1. Demographic and clinical characteristics including baseline blood chemistry of patients with acute non-STEMI divided into two groups having blood leukocyte count >11,000 /µL and ≤11,000 /µL.

Variables	All Patients (N=585)	Leukocyte count ≤11,000 /µL (N=397)	Leukocyte count >11,000 /µL (N=188)	P Value
Age (years)	61 ± 9.6	61.3 ± 9.6	60.0 ± 9.4	0.223
Male gender	462 (79%)	306 (77%)	156 (82%)	0.102
Systolic blood pressure (mmHg)	142.5 ± 29	143.3 ± 29	140.9 ± 28	0.383
Heart rate (beats/minute)	90 ± 23.8	87 ± 23	97 ± 24	<0.001
Prior myocardial infarction	97 (16%)	66 (17%)	31 (16%)	0.947
Risk factor profile				
Family history	148 (25%)	106 (27%)	42 (22%)	0.231
Smoker	141 (24%)	89 (22%)	52 (27%)	0.230
Hypertension	423 (72%)	287 (72%)	136 (72%)	0.990
Diabetes mellitus	220 (38%)	141 (35%)	79 (42%)	0.104
Dyslipidemia	277 (47%)	192 (48%)	85 (45%)	0.529
Lipid Profile				
Total cholesterol (mg/dL)	188 ± 50	190 ± 49	184 ± 50	0.313
LDL-cholesterol (mg/dL)	123 ± 42	124.3 ± 42	120 ± 42	0.420
HDL-cholesterol (mg/dL)	37.8 ± 12	38.2 ± 12	36.8 ± 11	0.235
Triglyceride (mg/dL)	142 ± 91	146 ± 93	133 ± 86	0.060
CK-MB (U/L)	25 (3 – 523)	23 (4 – 324)	32 (3 – 523)	<0.001
Troponin T >0.03 µg/L	512 (88.6)	342 (86)	170 (90)	0.142
Creatinine (mg/dL)	1.4 ± 0.9	1.38 ± 0.9	1.52 ± 1.1	0.014
Length of stay (days)	8.77 ± 7.14	8.82 ± 6.7	8.68 ± 7.8	0.501
Coronary angiography	221 (38%)	161 (40%)	60 (32%)	0.042
PCI	79 (13%)	54 (13%)	25 (13%)	0.262
CABG	29 (5%)	22 (5%)	7 (3%)	0.696
Medication at enrollment				
ACE Inhibitor	313 (53%)	205 (51%)	108 (57%)	0.188
Beta-blocker	373 (64%)	273 (68%)	100 (53%)	<0.001
MACE	52 (9%)	21 (5%)	31 (16%)	<0.001

Continous data presented as mean ± standard deviation or median (range) and categorical variables as number and percentages. MACE= major adverse cardiac event, CK-MB= creatine kinase-MB, PCI= percutaneous coronary intervention, CABG= coronary artery bypass grafting, ACE= angiotensin converting enzyme.

In univariate analysis, patients with leukocyte count >11,000 /µL had an increased cardiovascular events compared to patients with leukocyte count ≤11,000 /µL (hazard ratio=3.17, 95% CI=1.81-5.57, p<0.001), and in multivariate analysis, the hazard ratio was 3.028 (95% CI=1.69–5.40, p< 0.001) (Tables 2 and 3).

Table 2. Univariate predictors of cardiovascular events.

Variables	HR (95% CI)	P Value
Age (>65 years)	0.913 (0.50 – 1.63)	0.759
Male gender	1.085 (0.54 – 2.17)	0.818
History of MI	0.915 (0.42 – 1.96)	0.820
Risk Factor profile		
Family History	0.774 (0.39 – 1.51)	0.453
Diabetes mellitus	1.240 (0.70 – 2.17)	0.453
Hypertension	0.701 (0.39 – 1.24)	0.227
Dyslipidemia	1.089 (0.61 – 1.93)	0.772
Smoker	0.749 (0.51 – 1.08)	0.130
Systolic blood pressure <100 mmHg	0.853 (0.26 – 2.78)	0.792
Heart rate >100 beats/minute	1.425 (0.80 – 2.54)	0.229
Lipid Profile		
Total cholesterol >200 mg/dL	1.202 (0.57 – 2.51)	0.625
HDL-cholesterol <40 mg/dL	0.780 (0.37 – 1.61)	0.501
LDL-cholesterol >130 mg/dL	1.210 (0.58 – 2.51)	0.609
Triglyceride >150 mg/dL	0.883 (0.37 – 2.10)	0.779
Creatinine >1.5 mg/dL	1.958 (1.10 – 3.47)	0.022
Leukocyte count >11,000 /μL	3.178 (1.81 – 5.57)	<0.001
Medication at enrollment		
Beta-blocker	0.676 (0.38 – 1.17)	0.167
ACE Inhibitor	0.638 (0.36 – 1.11)	0.116

Variables with p value <0.25 were entered into multivariate Cox regression analysis. MI= myocardial infarction, ACE= angiotensin converting enzyme, HR= hazard ratio, CI= confidence interval.

Table 3. Multivariate predictors of cardiovascular events.

Variables	HR (95% CI)	P Value
History of smoking	0.727 (0.49 – 1.06)	0.101
Hypertension	0.410 (0.15 – 1.09)	0.076
Heart rate >100 beats/minute	1.803 (0.71 – 4.56)	0.214
Creatinine >1.5 mg/dL	1.642 (0.90 – 2.97)	0.102
Leukocyte count >11,000 /μL	3.028 (1.69 – 5.40)	<0.001
Use of beta-blocker	0.775 (0.43 – 1.37)	0.384
Use of ACE inhibitor	0.575 (0.32 – 1.02)	0.058

ACE= angiotensin converting enzyme, HR= hazard ratio, CI= confidence interval.

Discussion

In this study involving 585 patients with acute non-STEMI we found a strong relationship between leukocyte count on admission and incidence of cardiovascular events during hospitalization. This result is consistent with a study from Cannon and colleagues [10] who showed that patients with acute myocardial infarction or high risk unstable angina pectoris with a leukocyte count >10,000/μL had a high mortality rate.

Several mechanisms explain how leukocytosis affects coronary heart disease through multiple pathologic mechanisms that mediate inflammation: (1) Leukocytes may cause endothelial cell injury by proteolytic and oxidative damage, (2) leukocytes may plug the microvasculature, (3) leukocytes may induce hypercoagulability [5], and (4) leukocytes may induce increased expression of Tissue Factor on monocytes [14]. It is hypothesized that these mechanisms may cause activation of intrinsic and extrinsic pathways of the coagulation system [15], leading to thrombus formation [16] and infarct expansion [5]. The prognostic value of inflammatory markers is observed accross a wide clinical spectrum of atherosclerotic diseases [17].

In this study, the higher MACE rate in patients with a leukocyte count >11,000 /μL could be explained by several reasons. Firstly, patients with a leukocyte count >11,000 /μL may have larger infarct size as shown by higher initial CK-MB level in the group with high leukocyte count than in the group with low leukocyte count (32 vs. 23 U/L, $p<0.001$), and deserves further investigation. Secondly, heart rate on admission was higher in patients with a leukocyte count >11,000 /μL ($p<0.001$) than in the patients with low leukocyte count, and in patients with acute myocardial infarction heart rate on admission is an established risk factor [18]. Thirdly, the baseline creatinine level was significantly higher in the patients with a leukocyte count >11,000 /μL than in the patients with low leukocyte count, and the GRACE study has demonstrated that elevated creatinine levels are a risk factor for developing cardiac events [18]. After adjustment of all those variables and other variables such as history of smoking, hypertension, use of beta-blocker and use of ACE inhibitor, a leukocyte count >11,000 /μL proved to be a strong predictor of in-hospital cardiovascular events. Thus, for patients with acute non-STEMI having a blood leukocyte count >11,000 /μL aggressive treatment seems clearly indicated. In Jakarta, Indonesia, the group of patients with acute non-STEMI is larger than the group of patients with STEMI [19].

As the measurement of leukocyte count is cheap, rapid and available in almost every laboratory worldwide, the leukocyte count might be used as an additional marker for immediate bed side risk stratification of patients with non ST-elevation ACS, and particularly in rural areas where other established markers such as interleukin-6, interleukin-1β, and CRP are not available.

Study limitation

Several limitations of the present study should be considered. The design of the study was a retrospective analysis and data was collected from an existing registry. Furthermore, the assay of additional inflammatory markers such as CRP is lacking which would have strengthened the role of the leukocyte count in the present study.

Conclusion

The blood leukocyte count on admission is an independent predictor of cardiovascular events in patients with acute non-STEMI.

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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.

Samenvatting, Conclusies en Toekomstperspectief

Samenvatting

Cardiovasculaire ziekten zijn wereldwijd een belangrijke, zo niet de belangrijkste oorzaak van sterfte, en dit geldt ook voor Indonesië. Elke verbetering van het zorgsysteem voor patiënten met acuut hartinfarct is een bijdrage aan het terugdringen van dit hoge sterftecijfer. Dit proefschrift laat analyses zien van gegevens van patiënten met acuut coronair syndroom (ACS) welke gegevens zijn opgeslagen in een lokaal patiëntenregister (het Jakarta Acuut Coronair Syndroom registratiesysteem). Aan de hand van deze analyses is duidelijk geworden dat de farmaco-invasieve aanpak van reperfusie in patiënten met ACS mogelijk is in Jakarta na implementatie van een nieuw netwerk van diagnostische en therapeutische protocollen. Dit netwerk is specifiek gericht op de zorg voor patiënten met acuut hartinfarct voordat ze het ziekenhuis hebben bereikt en tijdens hun verblijf in het ziekenhuis (**hoofdstuk 2.1**).

Na de invoering van dit netwerk, genaamd Jakarta Hartbewaking Netwerk, zijn de implementatie en effectiviteit van de behandelingsprotocollen voor patiënten met acuut ST-segment elevatie myocardinfarct (STEMI) geëvalueerd door de kwaliteitsindicatoren en prestatiematen te analyseren. **Hoofdstuk 2.2** toont aan dat het aantal patiënt-verwijzingen van andere ziekenhuizen naar het ontvangende ziekenhuis significant is gestegen, hetgeen gepaard is gegaan met een toegenomen aantal primaire percutane coronaire interventies (PCI's) in het ontvangende ziekenhuis en een toegenomen aantal patiënten die na aankomst in het ziekenhuis al binnen 30 minuten gecatheteriseerd werden. Echter, er waren geen verbeteringen waar te nemen in (1) het aantal patiënten dat laat arriveerde in het ziekenhuis, (2) het aantal patiënten dat na aankomst in het ziekenhuis niet snel angioplastie onderging (gedotterd werd) en (3) het aantal patiënten dat in het ziekenhuis overleed. Het is duidelijk dat er verdere verbeteringen moeten worden aangebracht aan de protocollen voor de pre-hospitale fase, met name het systeem waarmee het electrocardiogram wordt verzonden naar het ontvangende ziekenhuis en in de protocollen die operationeel zijn in het ziekenhuis.

Een belangrijke uitdaging in de behandeling van patiënten met STEMI is de verbetering van de uitkomst van acute reperfusietherapie, zoals primaire PCI (**hoofdstuk 3**). Het is bekend dat PCI als mechanische reperfusietherapie de voorkeursbehandeling van patiënten met acuut STEMI is. Een risico hierbij is embolizatie van het distale vaatbed door losgemaakt atherotrombotisch materiaal dat leidt tot obstructie van de microcirculatie, suboptimale reperfusie en verhoogd risico op overlijden. **Hoofdstuk 3.1** bevat een overzichtsverhaal over het behandelen van trombus tijdens primaire PCI. Dit overzichtsverhaal behandelt oude en nieuwe strategieën die zijn ontwikkeld om trombus in een coronair arterie te bestrijden teneinde embolizatie van het distale vaatbed te voorkómen. De beschikbare technieken zijn: (1) gebruik van glycoproteine IIb/IIIa remmers (GPI's), (2) gebruik van manuele en mechanische trombus-opvang catheters, (3) gebruik van beschermingsinstrumenten en (4) gebruik van stents die specifiek ontwikkeld zijn om trombus op te vangen. Dit hoofdstuk sluit af met een praktische gids voor trombus-opvang en een praktisch klinisch algoritme dat te gebruiken is tijdens primaire PCI.

Hoofdstuk 3.2 beschrijft een onderzoek naar het concept “hoe eerder, hoe beter” met betrekking tot toediening van GPI voor primaire PCI. Wij onderzochten het moment waarop toediening van eptifibatide moet worden gestart. De resultaten van vroege toediening van eptifibatide (≤30 minuten na opname in het ziekenhuis) zijn vergeleken met de resultaten van relatief late toediening van eptifibatide (>30 minuten na opname in het ziekenhuis). De pre-procedurele doorgankelijkheid van de aan het infarct gerelateerde coronair arterie was het primaire eindpunt. In deze patiëntengroep, voornamelijk patiënten met STEMI die laat arriveerden in het ziekenhuis, konden wij geen verbetering in de pre-procedurele doorgankelijkheid van de aan het infarct gerelateerde coronair arterie constateren in de groep met vroege toediening van eptifibatide vergeleken met de groep met relatief late toediening van eptifibatide. Beide groepen toonden ook geen verschillen in serum CK-MB 8-12 uur na stentplaatsing, noch verschillen in linkerkamer ejectiefractie.

Het gerandomiseerde klinische onderzoek dat wordt gepresenteerd in **hoofdstuk 3.3** moest nagaan in hoeverre de werkzaamheid en veiligheid van een 2e-generatie drug-vrijmakende stent (van het everolimus type) gunstiger zijn dan die van de al veel langer verkrijgbare stalen stent in patiënten met acute STEMI die primaire PCI ondergingen met routine eptifibatide toediening. Na een periode van 30-dagen bleken de patiënten met de everolimus-type stent niet te verschillen van de patiënten met de stalen stent met betrekking tot optreden van ernstige complicaties, stenttrombose, bereiken van TIMI flow 2 of 3, en bereiken van myocardiale “blush” graad 2 of 3.

Recent is de keuze met betrekking tot de punctieplaats van de PCI-catheter een punt van onderzoek geworden binnen de interventie cardiologie en deze keuze is tussen de *arteria radialis* (trans-radiale benadering, TRA) en de *arteria femoralis* (trans-femorale benadering, TFA). De TFA in STEMI patiënten is geassocieerd met hoge doseringen anti-trombotische en bloedplaatjes-remmende farmaca die vaak bloedingen ter plaatse van de punctieplaats veroorzaken. Al eerder is aangetoond dat bloedingen ter plaatse van de punctieplaats zijn geassociëerd met toegenomen risico op cardiale complicaties en sterfte. **Hoofdstuk 3.4** toont aan dat verandering van de punctieplaats van de PCI-catheter van de *arteria femoralis* naar de *arteria radialis* geassocieerd was met een significante reductie van cardiale complicaties en/of sterfte in de eerste 30-dagen na PCI met circa 50%. Een jaar na PCI waren cardiale complicaties en/of sterfte nog steeds in het voordeel van TRA vergeleken met TFA, met reducties van 40-50%. Vergeleken met TFA was TRA geassocieerd met een lager risico op bloedingen ter plaatse van de punctieplaats (respectievelijk 8,2% en 0,9%; $p<0,0001$) en een lager risico op ernstige bloedingen (respectievelijk 4,3% en 1,1%; $p<0,001$).

In de afgelopen 50 jaar is de intra-aortale ballonpomp (IABP) een standaardmethode voor mechanische ondersteuning van de hartfunctie geworden binnen de acute cardiologische zorg, met name in patiënten met ACS. Helaas zijn de bewijzen dat gebruik van IABP in patiënten met ACS binnen een standaard ziekenhuis gunstig is relatief schaars. In **hoofdstuk 4.1** analyseren wij de karakteristieken van patiënten met ACS van wie de hartfunctie werd

ondersteund met behulp van IABP. Vergeleken met de patiënten die de eerste 30 dagen na opname niet overleefden, bleken de patiënten die de eerste 30 dagen wel overleefden (1) minder vaak cardiogene shock te hebben, (2) vaker IABP ondersteuning te krijgen na een revascularizatie procedure, (3) minder vaak resuscitatie te ondergaan, en (4) minder vaak kunstmatig te worden beademd.
In patiënten met non-ST-elevatie (STE) ACS trad de eerste 30 dagen na opname minder sterfte op dan in STEMI patiënten. Patiënten met non-STE ACS zonder cardiogene shock vertoonden de minste sterfte vergeleken met de andere ACS patiënten. Verder vonden we dat de hartfrequentie vóór aanbrengen van de IABP een voorspeller was van de sterfte in de eerste 30 dagen na opname.

Tijdens catheterisatie via de *arteria radialis* is een spasmolytische behandeling van de *arteria radialis* nodig om ernstige complicaties te vermijden. Spasme van de *arteria radialis* (RAS) is een voorspeller van falen van de procedure. Tijdens catheterisatie via TRA wordt een combinatie van nitroglycerine en diltiazem, een calcium kanaal blokker, het meest gebruikt als spasmolytische behandeling. Maar het is onbekend of deze combinatie zoveel beter is dan elk van de twee farmaca afzonderlijk. De resultaten beschreven in **hoofdstuk 5.1** geven aan dat de combinatie van nitroglycerine en diltiazem geen voordeel biedt boven nitroglycerine alleen bij de preventie van RAS.

Hoofdstuk 6.1 beschrijft dat de serum concentratie van urinezuur gebruikt kan worden als voorspeller van prognose na acuut STEMI in 75 patiënten die fibrinolytische therapie hadden ondergaan. Dit prospectieve, observationele onderzoek heeft twee interessante resultaten opgeleverd: (1) in STEMI patiënten in het laagste kwartiel (<4,8 mg/dL) en in het hoogste kwartiel urinezuur concentraties (<7,3 mg/dL) waren de risico's op ernstige cardiovasculaire complicaties respectievelijk 8% en 20% (p=0,006); (2) meting van de urinezuur concentraties in serum geeft prognostische informatie die onafhankelijk is van, en van meer betekenis is dan andere reeds bekende prognostische factoren zoals leeftijd, eerder hartinfarct, hypertensie of diabetes mellitus in de voorgeschiedenis, hartfrequentie in rust, voorwandinfarct en de tijd die verstreken is tussen ontstaan van pijn op de borst en optreden van reperfusie.

In **hoofdstuk 6.2** beschrijven wij dat in patiënten met acuut non-STEMI een leukocytenaantal >11.000 per µL bloed bij opname een onafhankelijke voorspeller was van ernstige cardiovasculaire complicaties tijdens de ziekenhuisopname. Hieruit is geconcludeerd dat non-STEMI patiënten die na opname een leukocytenaantal >11.000 per µL bloed hebben onmiddellijk intensief behandeld moeten worden om hun prognose gunstig te beïnvloeden.

De kwaliteit van pre-klinische en klinische zorg voor patiënten met een acuut hartinfarct in Jakarta is afhankelijk van een goed georganiseerd zorgsysteem dat specifiek gericht is op snelle diagnostiek, snelle verwijzing naar een ziekenhuis met PCI-faciliteit, en snelle reperfusietherapie. Dit systeem, het Jakarta Hartbewaking netwerksysteem, is in dit proefschrift op zijn functionaliteit getest door gebruik te maken van een registratiesysteem

waarin kwaliteitsindicatoren en prestatiematen de huidige zorgpaden met betrekking tot infarctpatiënten kwalificeren. Dit registratiesysteem, het Jakarta Acuut Coronair Syndroom registratiesysteem, stelt ons steeds in staat om te zien (1) hoe goed er gewerkt is, (2) wat er beter kan en (3) wat er nodig is om het beter te maken.

Conclusies

1. Het Jakarta Hartbewaking netwerksysteem is ontwikkeld om de zorg voor patiënten met acuut hartinfarct in Jakarta te verbeteren.
2. Teneinde de kwaliteit van zorg voor patiënten met acuut hartinfarct in Jakarta te verhogen, moeten de protocollen in de verwijzende en ontvangende ziekenhuizen worden verbeterd en moet een electrocardiogram direct worden verzonden naar het ontvangende ziekenhuis.
3. Selectieve trombusafzuiging is een attractief concept, is eenvoudig uitvoerbaar en verbetert mogelijk de prognose in het eerste jaar na opname.
4. Om het meest gunstige moment te vinden waarop eptifibatide moet worden toegediend vóór aanvang van PCI, zijn er grotere gerandomiseerde onderzoeken nodig, bij voorkeur met patiënten met STEMI die worden opgenomen binnen 2 uur na begin van klachten.
5. In een cohort van STEMI patiënten die met primaire PCI zijn behandeld is het gebruik van een everolimus-type stent in combinatie met intraveneuse toediening van eptifibatide even veilig en effectief gebleken als het gebruik van een standaard metalen stent, althans in de eerste maand na opname.
6. Een volledige omschakeling van *arteria femoralis* naar *arteria radialis* als route voor catheters voor coronair angioplastie in patiënten met acuut STEMI is veilig en effectief, en heeft gunstige effecten op de korte en lange termijn.
7. IABP heeft bewezen veilig te zijn en lijkt gunstige resultaten te hebben in ACS patiënten zonder cardiogene shock, met name in patiënten die worden opgenomen met acuut hartinfarct zonder ST-segment elevaties op het ECG (non-STEMI).
8. De combinatie van diltiazem en nitroglycerine liet geen significant voordeel zien vergeleken met nitroglycerine alleen met betrekking tot het voorkómen van RAS in patiënten die coronaire procedures ondergingen via de *arteria radialis* route door interventie-cardiologen die veel ervaring hadden met deze route.
9. In STEMI patiënten die reperfusie ondergaan met behulp van fibrinolytische therapie, is de urinezuurconcentratie in serum een onafhankelijke voorspeller van ernstige cardiovasculaire complicaties tijdens het verblijf in het ziekenhuis. Deze eenvoudige, goedkope en nauwkeurige bepaling kan dus nuttig zijn voor risicostratificatie van infarctpatiënten in ontwikkelingslanden die vooral fibrinolytische therapie toepassen in patiënten met acuut hartinfarct.
10. In non-STEMI patiënten bleek de leukocytendichtheid in bloed bij opname een onafhankelijke voorspeller van ernstige cardiovasculaire complicaties tijdens het verblijf in het ziekenhuis. Dus, patiënten met acuut non-STEMI die een leukocytendichtheid in bloed hebben van >11.000/μL moeten niet afwachtend maar intensief behandeld worden.

Toekomst perspectief

Zorgsysteem voor patiënten met acuut hartinfarct

In de acute fase van een acuut hartinfarct zijn een snelle diagnose en vroege reperfusietherapie factoren die de infarctgrootte beperken en ernstige complicaties voorkómen. Een goed georganiseerd netwerksysteem voor de zorg van patiënten met acuut hartinfarct maakt een gestandaardiseerde behandeling volgens de meest recente richtlijnen mogelijk die leidt tot optimale zorgkwaliteit. Professionele samenwerking tussen huisarts, ambulance medewerkers en medewerkers in regionale ziekenhuizen en in centra met geavanceerde reperfusiemogelijkheden (primaire PCI) is essentiëel voor de ontwikkeling van goede lokale en regionale protocollen voor de behandeling van infarctpatiënten. Door in een registratiesysteem diagnostische en therapeutische informatie van patiënten met acuut hartinfarct te verzamelen en te evalueren, ontstaan nieuwe inzichten over (1) te verbeteren zaken en (2) de aanpak van deze verbeteringen.

Primaire percutane coronaire interventie

Primaire PCI is de beste behandeling van patiënten met acuut ST-segment elevatie myocardinfarct (STEMI). Voor het beste resultaat van primaire PCI zijn een aantal strategieën beschikbaar die in de toekomst verder moeten worden onderzocht. Hiertoe behoren (1) wanneer en langs welke weg behandelen met glycoprotein IIb/IIIa remmers, (2) wel of niet gebruik maken van catheters die trombus in de aan het infarct gerelateerde coronaire arterie verwijderen, (3) stentkeuze zoals stalen stents, drug-vrijmakende stents en stents, speciaal ontworpen om trombus vast te zetten en af te schermen van het lumen, (4) keuze van de route voor catheters voor coronair angioplastie in patiënten met acuut hartinfarct zoals de *arteria radialis* en *arteria femoralis* die voorlopig het gunstigst uitpakt voor de *arteria radialis*, en (5) wel of niet gebruik maken van de intra-aortale ballonpomp (IABP), met name in infarctpatiënten zonder cardiogene shock. De resultaten van verder onderzoek zullen leiden tot een wereld-wijde consensus over de uitvoering van de beste cardiovasculaire geneeskunde voor de samenleving.

Trans-radiale toegang voor cardiovasculaire interventies

In de huidige cardiologische praktijk is de trans-radiale benadering voor cardiovasculaire interventies zoals primaire PCI en angioplastie in de *arteria carotis* een alternatief geworden voor de trans-femorale benadering. De trans-radiale benadering vereist een specifieke deskundigheid die door ervaring is aan te leren. We verwachten dat in de komende jaren de trans-radiale benadering in de meeste catheterisatiekamers zal worden gekozen als de beste benadering voor cardiovasculaire interventies in hoofd- en hartstreek.

Biomarkers in patiënten met acuut coronair syndroom (ACS)

Biomarkers spelen een belangrijke rol in de diagnostiek en risicostratificatie van patiënten met ACS. De ideale biomarkers die voldoen aan de volgende specificaties moeten nog verder worden onderzocht: (1) detecteren myocardiale necrose in een vroeg stadium, (2) zijn geschikt voor risicostratificatie, (3) geven progressie van de ziekte aan, en (4) geven aan

welke therapie optimaal is. Met name in ontwikkelingslanden is er behoefte aan eenvoudige, goedkope en accurate biomarkers aangezien de biomarkers met bewezen kwaliteit veelal te duur zijn.

De beste praktijk van cardiovasculaire geneeskunde is gebaseerd op resultaten die verkregen zijn in klinische onderzoeken en zijn gedocumenteerd in wereld-wijd geldende consensus documenten en/of richtlijnen. De zorg voor patiënten met acuut hartinfarct zal steeds weer worden verbeterd, onder andere door steeds nieuwe therapeutische ingrepen, hetgeen zal leiden tot verbeterde prognoses van deze patiënten.

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Curriculum Vitae

Surya Dharma, MD, FIHA, FICA, FAPSIC, FESC, FSCAI was born on August 27th 1970 in Medan, North Sumatera, Indonesia. Elementary, junior and high school years were spent in Medan. In 1990, he went on to study Medicine at the Faculty of Medicine, University of North Sumatera, Medan, Indonesia. After obtaining his medical degree in 1996, he worked as a general practitioner and the head of the public health service in Kelila, Jayawijaya district, Irian Jaya/Papua Province from 1997-2000. During his work, he received an award from the local government for his dedication and active involvement in the "flying doctor" program in the area of Jayawijaya mountain, Papua. In 2001, he started the cardiology training at the Department of Cardiology and Vascular Medicine, University of Indonesia, Jakarta, Indonesia. After finishing the cardiology training in 2005, he went to Banda Aceh, Indonesia, worked as a cardiologist in a local government hospital for three months, as a volunteer for the Tsunami relief and get an award from local authority. In 2006, he started the interventional cardiology fellowship at the Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands, under the supervision of Prof. dr. J.W. Jukema. During his training, he was involved in several clinical trials, specifically about fractional flow reserve and intravascular ultrasound. In 2007 until now, he worked in National Cardiovascular Center Harapan Kita at the Department of Cardiology and Vascular Medicine, Faculty of Medicine, University of Indonesia, Jakarta. From March to June 2011, he followed the advanced trans-radial interventional cardiology fellowship in SAL Hospital and Medical Institute, Ahmedabad, India. In May 2012, he was also following the advanced training on trans-radial and trans-ulnar carotid angioplasty in Medical Faculty, University Clinic of Cardiology, University of St. Cyril & Methodius, Skopje, Macedonia. During the training, he was actively involved in several studies described in this thesis.

Currently, he is the head of the emergency and intensive cardiovascular care unit of the National Cardiovascular Center Harapan Kita, Jakarta and act as the principal investigator of the Jakarta Acute Coronary Syndrome registry and Jakarta Cardiovascular Care Unit Network System.

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