Comparison Between the Effect of Stand-alone Intracoronary Bolus of Tirofiban versus Intravenous Bolus Followed by Infusion as Adjunctive Antiplatelet Therapy on the Outcome of Primary Coronary Intervention in Patients with Acute ST Segment Elevation Myocardial Infarction.

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LIST OF ABBREVIATIONS

AMI	**Acute myocardial infarction**
ACC	**American colleague of cardiology**
ACCP	**American colleague of clinical pharmacy**
ACE	**Angiotensin converting enzyme**
ACEP	**American Colleague of Emergency Physicians**
ACS	**Acute coronary syndrome**
ACT	**Activated clotting time**
ADA	**American diabetes association**
AHA	**American Heart Association**
aPPT	**Activated partial thromboplastin time**
ASA	**Acetyl salicylic acid**
BP	**Blood pressure**
CABG	**Coronary artery bypass grafting**
CAD	**Coronary artery disease**
CADILLAC	**Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications**
CAPTIM	**Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction trial**
CBC	**Complete blood count**
CHD	**Coronary heart disease**
CHF	**Congestive heart failure**
CK	**Creatine kinase**
CPB	**Cardiopulmonary bypass**
CRP	**C-reactive protein**
CTFCs	**Corrected TIMI frame counts**
cTnI	**Cardiac troponin I**
CVA	**Cerebrovascular accident**

DANAMI	**Danish Multicenter Randomized Study on Thrombolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction**
DIC	**Disseminated intravascular coagulopathy**
DM	**Diabetes mellitus**
ECG	**Electrocardiogram**
ED	**Emergency department**
ER	**Emergency room**
ESC	**European Society of Cardiology**
FBS	**Fasting blood sugar**
FH	**Family history**
FTT	**Fibrinolytic Therapy Trialists**
GP IIb/IIIa	**Glycoprotein IIb/IIIa**
HDL	**High density lipoprotein**
HIT	**Heparin induced thrombocytopenia**
HTN	**Hypertension**
IC	**intracoronary**
ICH	**Intracranial hemorrhage**
IHD	**Ischemic heart disease**
IRA	**Infarct related artery**
IV	**intravenous**
LAD	**Left anterior descending artery**
LBBB	**Left bundle branch block**
LCA	**Left coronary artery**
LCX	**Left circumflex artery**
LDL	**Low density lipoprotein**
LM	**Left main**
LMWH	**Low molecular weight heparin**
LV	**Left ventricle**
LVEF	**Left ventricular ejection fraction**
MACCE	**Major adverse cardiovascular and cerebrovascular events**
MBG	**Myocardial blush grade**

NRMI	**National registry of myocardial infarction**
NSAIDS	**Non-steroidal anti-inflammatory drugs**
NSTEMI	**Non-ST segment elevation myocardial infarction**
№	**Number**
P	**Probability of chance (significance)**
PCI	**Percutaneous coronary intervention**
PTCA	**Percutaneous transluminal coronary angioplasty**
RBBB	**Right bundle branch block**
RCA	**Right coronary artery**
RCTs	**Randomized controlled trials**
RESTORE	**Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis trial**
RV	**Right ventricle**
SD	**Standard deviation**
STEMI	**ST segment elevation myocardial infarction**
TFGs	**TIMI flow grades**
TIGER-PA	**Tirofiban Given in the Emergency Room before Primary Angioplasty**
TIMI	**Thrombolysis in myocardial infarction**
t-PA	**Tissue plasminogen activator**
TVR	**Target vessel revascularization**
UA	**Unstable angina**
UFH	**Unfractionated heparin**
US	**United states**
TVR	**target vessel revascularization**
VD	**Vessel disease**
VS	**Versus**
WHO	**World health organization**

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Introduction

Introduction

Reperfusion of acute myocardial infarction (MI) has generally been approached in 1 of 2 ways - fibrinolysis or primary angioplasty**.** Primary percutaneous coronary intervention (PCI) achieves reperfusion through mechanical recanalization of the infarct related artery (IRA) rather than through lysis of the coronary thrombus with pharmacologic agents (Li et al 2000). Time to recanalization and adequacy of restoration of perfusion were found to be pivotal determinants of a favorable outcome with either approach. (Dauerman et al, 2003)

PCI in patients with acute myocardial infraction (AMI) has been shown to be preferable to thrombolytic therapy in terms of patient survival, higher rates of patency in the IRA, and lower rates of reinfarction and stroke (Weaver et al 1997, Zijlstra et al 1999). These benefits of PCI can be further enhanced by administration of platelet glycoprotein IIb/IIIa inhibitors abciximab (Collet et al 2001), or eptifibatide (Blankenship et al 1997, Cohen et al 2000).

Tirofiban stands out as a useful adjunct to PCI because it is a small non-peptide molecule, somewhat similar to eptifibatide, and does not elicit an adverse immune reaction (Batchelor et al 2002). Compared with abciximab, its advantages as an adjunct therapy for PCI are lower cost and no overt bleeding complications (Gunasekara et al 2006).

Distal embolization of atherothrombotic material during PCI is associated with impaired myocardial perfusion, abnormal left ventricular function, and higher mortality. At high local concentrations, glycoprotein IIb/IIIa receptor

antagonists have been demonstrated to promote clot disaggregation in vitro (Pinto et al 2005).

Intracoronary bolus application of tirofiban is reported to be associated with superior clinical prognosis compared with the standard intravenous bolus application of tirofiban in patients with ST segment elevation myocardial infarction (STEMI) undergoing primary PCI (Yang et al 2007)**.**

Chapter 1

ACUTE MYOCARDIAL INFARCTION

Acute myocardial infarction (AMI or MI), commonly known as a heart attack, is a disease state that occurs when the blood supply to a part of the heart is interrupted. The resulting ischemia or oxygen shortage causes damage and potential death of heart tissue. It is a medical emergency, and the leading cause of death for both men and women all over the world (Luepker et al., 2003).

Definition of myocardial infarction:

Last updated definition of AMI is the "Universal Definition of Myocardial Infarction" conducted by Thygesen et al (2007) on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction:

Criteria for Acute Myocardial Infarction: The term myocardial infarction should be used when there is evidence of myocardial necrosis (myocardial cell death) in a clinical setting consistent with myocardial ischaemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

1. Symptoms of ischaemia.
2. ECG changes indicative of new ischaemia (new ST-T changes or new left bundle branch block [LBBB]).
3. Development of pathological Q waves in the ECG.
4. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

• Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. (Thygesen et al., 2007).

• For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 x 99th percentile URL have been designated as defining PCI-related myocardial infarction. A subtype related to a documented stent thrombosis is recognized. (Thygesen et al., 2007).

• For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or

angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related myocardial infarction.

• Pathological findings of an acute myocardial infarction.

Criteria for Prior Myocardial Infarction. Any one of the following criteria meets the diagnosis for prior myocardial infarction:

1. Development of new pathological Q waves with or without symptoms.
2. Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischaemic cause.
3. Pathological findings of a healed or healing myocardial infarction. (Thygesen et al ., 2007)

Clinical Classification of Different Types of Myocardial Infarction:

Based on the universal definition of myocardial infarction: myocardial infarction was further classified into 5 different clinical types: (Thygesen et al., 2007)

Type 1 (Spontaneous):

Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

Type 2 (Secondary):

Myocardial infarction secondary to ischaemia due to either

increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension

Type 3 (Sudden death):

Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new STelevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

Type 4a (PCI):

Myocardial infarction associated with PCI

Type 4b (Stent thrombosis):

Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

Type 5 (CABG):

Myocardial infarction associated with CABG. (Thygesen et al., 2007)

Epidemiology:

Myocardial infarction is a common presentation of ischemic heart disease. Ischemic heart disease is the leading cause of death in developed countries, but third to AIDS and lower respiratory infections in developing countries (Cause of Death - UC Atlas of Global Inequality, 2006).