Addition of Clopidogrel to Aspirin and Fibrinolytic therapy for ST-Segment Elevation Myocardial Infarction

Thesis

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بسم الله الرحمن الرحيم

(اقرأ و ربك الأكرم, الذي علم بالقلم, علم الانسان ما لم يعلم.)

صدق الله العظيم

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Contents

List of abbreviations

ACC	American College Of Cardiology	***MBG***	Myocardial blush grade
ADP	Adenosine Diphosphate	***MI***	Myocardial infarction
AHA	American Heart Association	***NSTEMI***	Non ST elevation myocardial infarction
CK	Creatine kinase	***NO***	Nitric Oxide
CK-MB	MB fraction of Creatine Kinase	***P value***	Significance
CRP	C-Reactive Protein	***PCI***	Percutaneous intervention
DM	Diabetes mellitus	***PGI_2***	Prostaglandin I-2
ECG	Electrocardiogram	***PTCA***	Percutaneous transluminal coronary angioplasty
FH	Family history	***RCA***	Right coronary artery
GP	Glycoprotein	***rt-PA***	Recombinant tissue plasminogen activator
HTN	Hypertension	***SK***	Streptokinase
IRA	Infarct-related artery	***STEMI***	ST segment elevation myocardial infarction
LAD	Left anterior descending artery	***TIMI***	Thrombolysis in myocardial infarction
LCX	Left circumflex artery	***TIMI FC***	TIMI frame count
LIPIDM	Dyslipidemia	***TNK***	Tenecteplase
LMWH	Low molecular weight heparin	***T-PA***	Tissue plasminogen activator
MACE	Major adverse cardiac events	***UFH***	Unfractionated heparin

List of tables

List of figures

Introduction

The benefit of fibrinolytic therapy for myocardial infarction with ST-segment elevation is limited by inadequate reperfusion of the infarct-related artery in a sizable proportion of patients. Initial reperfusion fails to occur in approximately 20 percent of patients [1-3] and is associated with a doubling of mortality rates.[4] The artery becomes re-occluded in an additional 5 to 8 percent of patients during their hospitalization, and this event is associated with an increase in mortality rates by a factor of nearly three.[5]

Platelet activation and aggregation play a key role in initiating and propagating coronary-artery thrombosis. An important paradox associated with the use of fibrinolytic therapy is its procoagulant potential, mainly through the release of a pool of trapped thrombin during the course of clot lysis.[6-8] However, conflicting data exist concerning the capacity of fibrinolytic agents to activate platelets directly.[6,9]

Regardless of the controversial evidence on this subject, exposure of the clot bound thrombin during fibrinolysis is an extremely potent platelet agonist, promoting platelet activation and aggregation.(10) Consequently, the above mentioned hypercoagulative state associated with AMI itself, as well as the procoagulant effect of fibrinolytic agents (the "thrombolytic paradox"), make the use of adjunctive antithrombin and antiplatelet therapies absolutely mandatory for the achievement of satisfactory and permanent myocardial reperfusion.[10]

In the Second International Study of Infarct Survival, conducted in patients with acute myocardial infarction, aspirin reduced the odds of death from vascular causes by 23 percent and the odds of reinfarction by 46 percent. [11] Aspirin has also been shown to reduce the rate of angiographic re-occlusion by 22 percent, as compared with placebo. [12]

Clopidogrel is an adenosine diphosphate receptor antagonist, a class of oral antiplatelet agents that block the P2Y component of the adenosine diphosphate receptor and thus inhibit the activation and aggregation of platelets.[13] Clopidogrel has been shown to prevent death and ischemic complications in patients with symptomatic atherosclerotic disease, patients who have undergone percutaneous coronary intervention, and patients with unstable angina or myocardial infarction without ST-segment elevation.

A major remaining question is whether the addition of clopidogrel is beneficial in patients who have myocardial infarction with ST-segment elevation [14-16] and who are receiving a standard fibrinolytic regimen, including aspirin.

Aim of the Work

The aim of this study will be to assess the benefit of adding clopidogrel to aspirin and fibrinolytic therapy for those patients who has myocardial infarction with ST-segment elevation.

The primary end point will be the patency of the infarct-related artery assessed by coronary angiography 3 to 8 days after the infarction.

The secondary end-points will be:

1. The 30-day MACE (recurrent angina, reinfarction, or death) at 30 days.
2. The incidence of major bleeding.

Chapter (1)

Myocardial Infarction

Epidemiology:

Coronary heart disease is the leading cause of death Worldwide, with myocardial infarction a common manifestation of this disease.

In 2006, approximately 1.2 million Americans sustained a myocardial infarction. [17] Of these, one quarter to one third had a myocardial infarction with ST-segment elevation (STEMI). [18, 19]

Of all patients having a myocardial infarction, 25 to 35% will die before receiving medical attention, most often from ventricular fibrillation. [20]

The prognosis is considerably better and has improved over the years: in-hospital mortality rates fell from 11.2% in 1990 to 9.4% in 1999. [18] Most of the decline is due to decreasing mortality rates among patients with myocardial infarction with ST-segment elevation, [19] as a consequence of improvements in initial therapy, including fibrinolysis and PCI. In an analysis by the National Registry of Myocardial Infarction, the rate of in-hospital mortality was 5.7% among those receiving reperfusion therapies, as compared with 14.8% among those who were eligible for but did not receive such therapy. [21]

Definition:

Myocardial infarction can be defined from a number of different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristics.[22] It is accepted that the term myocardial infarction reflects death of cardiac myocytes caused by prolonged ischemia.

Clinical presentation of acute myocardial infarction [22]

The typical symptoms of acute myocardial infarction include severe chest, epigastric, or arm pain/ discomfort with exertion or at rest. Usually lasting for more than 20 minutes and is not relieved by rest or nitrates.

The discomfort may develop in the central or left chest and then radiate to the arm, jaw, back or shoulder.

The discomfort is usually not sharp or highly localized and may be associated with dyspnea, diaphoresis, nausea, vomiting or light-headedness.

The discomfort is not affected by moving the muscles of the region where the discomfort localized, nor is it worsened by deep inspiration.

The discomfort is not positional in nature. Symptoms can also include unexplained nausea and vomiting, persistent shortness of breath secondary to left ventricular failure and unexplained weakness, dizziness, lightheadedness or syncope, or a combination of these.

Atypical presentation when the discomfort develops in the epigastrium (often confused with indigestion), arm, shoulder, wrist, jaw or back, without occurring in the chest.

Acute MI which occur without chest pain I knows as silent infarction, it is mostly limited to the elderly and diabetic patients.

Diagnosis of acute Myocardial infarction.

ECG

The ECG may show signs of myocardial ischemia, specifically ST and T changes, as well as signs of myocardial necrosis, specifically changes in the QRS pattern. A working definition for acute *evolving* myocardial infarction in the presence of clinically appropriate symptoms has been established as[22]

(1) Patients with ST-segment elevation in at least 2 contagious leads, i.e. new ST-segment elevation at the J point with the cut-off points measuring ≥0.2 mV in V1 through V3 and ≥0.1 mV in other leads. (STEMI), or

(2) Patients without ST-segment elevation, i.e. ST-segment depression or T wave abnormalities. Non as non St Elevation myocardial infarction (NSTEMI).

In addition, new-onset left bundle branch block in the settings of symptoms consistent with acute MI may indicate a large, anterior wall acute infarction.[23].

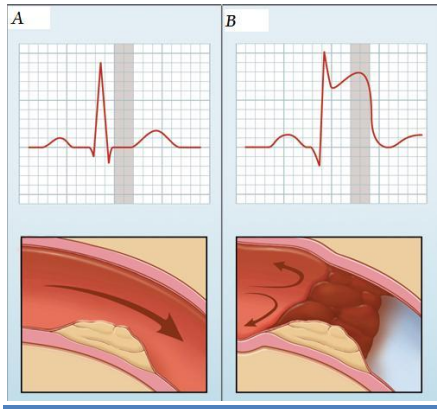

Figure 1: *Total occlusion of coronary artery producing transmural ischemia and ST segment elevation in the corresponding ECG lead.*

Biomarkers [22]

- The preferred cardiac markers are troponin I or T because of their specificity

- CK-MB has lower specificity than troponins T and I, but may be used

- Myoglobin or CK-MB isoforms should be considered for rapid diagnosis

- Total CK, aspartate transaminase (serum glutamate oxaloacetate transaminase) and LDH have low specificityand are less satisfactory.

- Elevation of troponin or CK-MB is defined as a value exceeding the 99th centile of a reference control group

- Sampling of troponins or CK-MB should be done at presentation, at 6–9 hours, and at 12–24 hours.

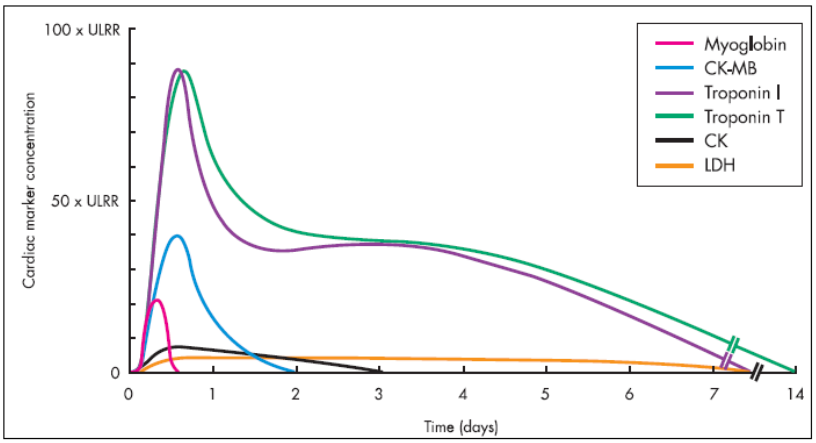

Figure Kinetic profiles of cardiac markers following ST elevation myocardial infarction. These profiles are schematic and do not differentiate between patients with early reperfusion and those with persistent occlusion of the infarct related artery. When there is early reperfusion, cardiac marker concentrations rise more rapidly, peak earlier and at a higher value, and return to the reference range more rapidly.

Figure 2: *Kinetic profile of cardiac markers following ST elevation myocardial infarction*

Modified from: The Joint European Society of Cardiology/American College of Cardiology Committee. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology for the redefinition of myocardial infarction. *Eur Heart J* 2000; **21**:1502–13.

Pathogenesis of STEMI

The ST segment elevation Myocardial infarction refers to that kind of infarction in which the ischemic changes involve the whole thickness of the myocardial muscle, with the characteristic ST-T changes. Appearance of Q waves later on indicates myocardial necrosis.

Coronary arterial occlusion due to plaque rupture and superimposed thrombosis is the cause of most cases of STEMI. [24]

Atherosclerotic Plaque:

The pathogenesis of coronary atherosclerosis is multifactorial.[25] Broadly, endothelial injury and dysfunction result in the adhesion and transmigration of leukocytes from the circulation into the arterial intima as well as the migration of smooth-muscle cells from the media into the intima, thus initiating the formation of an atheroma or atherosclerotic plaque.[25, 26]

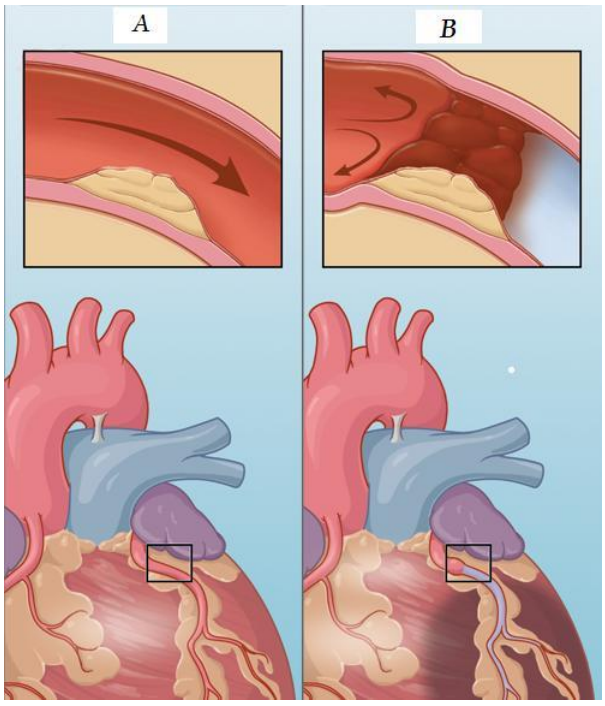

Figure 3: *(A) atherosclerotic plaque narrowing the lumen of the coronary artery without obstruction, (B) Plaque rupture and thrombus formation with total occlusion.*