ACKNOWLEDGMENT

It is a great thing to feel success and have the pride of achieving all what is always aspired. However, one must not forget all those who usually help and push him onto the most righteous way.

I would like to express my endless gratitude and appreciation to ***Prof. Dr. Nireen Okasha,*** *Professor of Cardiology, Ain Shams University, the person who gave me the honor to be her student and for her great effort. She really helped me by her precious opinions and contributive comments that served much in the construction of this work. She was always there to care, support, help, encourage and provide constructive pieces of advice in every possible way.*

My deep thanks also to ***Dr.Mohammed Abd El Zaher****, Lecturer of Cardiology, Faculty of Medicine, Ain Shams University, for his support during the early period of the study.*

At last, I would like to thank my family; my father, my mother, my wife & my daughter for being always there for me.

MOHAMMED KAMEL

AIM OF THE WORK

To compare the effect of giving the 600-mg loading dose of clopidogrel, (***(taken immediately befor the procedure)***, with the standard 300-mg loading dose therapy, (***taken 12 hours befor the procedure)*** as regards

1. Measurement of percentage of inhibition of ADP-induced platelet activity.
2. Periprocedural elevation of the cardiac biomarker Ck-MB.
3. 3 months follow up for ***MACE*** .

- Primary end point : (occurrence of death, MI, target vessel revascularization or stent restenosis).
- Secondary end point: (occurrence of bleeding, hemorrhage, or decrease in platelet count).

بسم الله الرحمن الرحيم

(وقل اعملوا فسيرى الله عملكم و رسوله و المؤمنون)

صدق الله العظيم

Effect Of 2 Different Loading Doses Of Clopidogrel (600mg Vs 300mg) On Inhibition Of ADP-Induced Platelet Activation In Patients Undergoing Elective Coronary Intervention

Thesis for partial fulfillment to master degree of cardiology

Submitted by

Mohammed Kamel Ragab

M.B.B.Ch.

Under supervision of

Prof. Dr. Nireen Khalifa Okasha

Professor of cardiology

Ain Shams University

Dr. Mohammed Abd El Zaher Abd Allah

Lecturer of Cardiology

Ain Shams University

Cairo

Ain Shams University

Faculty of Medicine.

2013

Introduction

Atherothrombosis, which is sudden disruption of atherosclerotic plaque leading to platelet activation with superimposed thrombus formation, is the common link between the clinical manifestations of arterial vascular disease including ischemic stroke and acute coronary syndromes, such as unstable angina (UA) and acute myocardial infarction (MI). Cardiovascular, cerebrovascular, and peripheral artery diseases (PAD) all share the common underlying pathophysiology of atherosclerosis**.** ***(Steinhubl et al., 2005).***

Effective platelet inhibition at the time of percutaneous coronary intervention (PCI) with stent placement reduces the risk of periprocedural myocardial infarction (MI*).* ***(Hochholzer et al., 2005).***

Pharmacological inhibition of platelets with a combination of aspirin and a thienopyridine is a key strategy for the prevention of recurrent ischemic events in patients with acute coronary syndromes and those

undergoing percutaneous coronary intervention ***(Wiviott et al., 2007).***

Clopidogrel has become a mainstay of the pharmacological therapy for patients with atherosclerotic cardiovascular disease, especially in those undergoing percutaneous coronary interventions. Despite the widespread use of clopidogrel, several aspects of its pharmacokinetics, optimal dosing and length of therapy, and its drug interactions are still unclear ***(Kastrati et al., 2004).***

Clopidogrel inhibits platelet aggregation. It decreases the incidence of coronary artery stent thrombosis and is approved for reduction of myocardial infarction, stroke, and vascular death in patients with atherosclerotic vascular disease ***(Lau et al., 2003).***

CHAPTER 1

Atherothrombosis

1.1 What is atherothrombosis ?

The term 'atherothrombosis' was originally coined to define thrombosis occurring at a site of an atherosclerotic plaque. It may involve multiple arterial beds and is the major cause of myocardial infarction (MI), stroke and vascular death ***(Zimarino and Caterina, 2008).***

Atherothrombosis describes the occurrence of both atherosclerosis and thrombosis in an artery, a common feature of peripheral arterial disease ***(Mohler, 2007).***

Atherothrombosis, characterised by atherosclerotic lesion disruption with superimposed thrombus formation, is the major cause of acute coronary syndromes (ACS) and cardiovascular death ***(Viles-Gonzalez et al., 2004).***

Allam et al,(2009) performed whole body , 6-slice CT on 20 mummies housed in the Egyptian National Museum . Definite atherosclerosis was present in 5 of 16 mummies (31%) ***(Zaki, 2011).***

The presence of atherosclerosis in in those young mummies makes us wonder if there is a risk factor that has not been identified yet, and we may understand atherosclerosisless less well than we think, as it is now proved that atherosclerosis is a progressive disease that starts from birth ***(Milei et al., 2010).***

1.2 Pathophysiology of atherosclerosis and atherothrombosis:

Endothelial dysfunction is a systemic, reversible disorder considered the earliest pathologic process of atherothrombosis ***(Weiss et al., 2002).***

Endothelial injury caused by shear stress, hypertension, diabetes or smoking is an important factor in the initiation and progression of arterial disease ***(Kam and Nethery, 2003).***

The atherosclerotic coronary lesion is a lipid-containing plaque (also known as an atheroma) in the intima of the artery ***(Abrams, 2005)***.

Atheroma formation is secondary to a complex set of mechanisms only partially understood, involving

endothelial dysfunction, lipoprotein deposition and oxidation in the arterial wall, infiltration by inflammatory cells, cellular proliferation, especially smooth muscle cells and matrix deposition ***(Shaper et al., 1984).*** This mechanism may start at an early age. Endothelial dysfunction is thought to be the initial step in atherosclerosis ***(Elveback et al., 1986)***

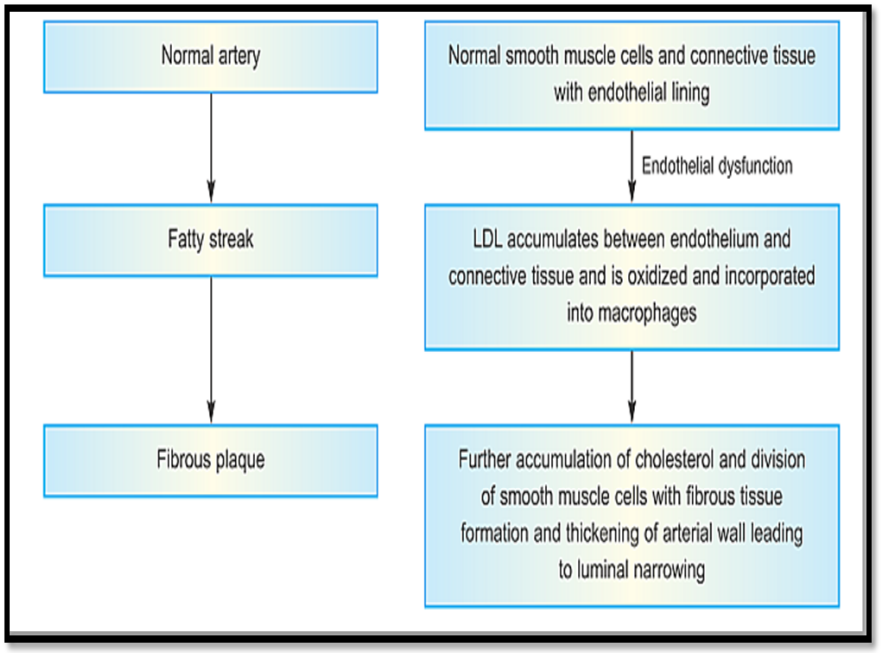
The atherosclerotic and thrombotic processes appear to be interdependent and could therefore be integrated under the term "atherothrombosis" a broader term that includes both atherosclerosis and its thrombotic complications **(Figure 1) (*Sarembock et al., 2007*)**.

In a certain proportion of cases, platelet-initiated mural thrombosis progresses to a degree causing impairment of flow or the total occlusion of the vessel, phenomena at the basis of acute coronary syndromes (ACS)**. *(Zimarin and Caterina, 2008)*.**

Atherothrombosis begins with the development of an atherosclerotic plaque within the arterial intima. Rupture or erosion of the plaque exposes thrombogenic components to the flowing blood, causing platelets to

adhere to the damaged area. Thrombi may then become incorporated into the plaque, increasing its size and rapidly decreasing the arterial lumen. ***(Zimarino and Caterina, 2008).***

Figure 1. *Steps in the development of atheroma.* ***(Sarembock et al., 2007).***



- **Plaque structure:**

Mature atherosclerotic plaques are composed of a variable amount of lipid core and a connective tissue matrix cap ***(Witztum, 1994).*** The cap consists of connective tissue and the lipid core includes foamy cells, leukocytes and debris. Stable atheromas have a collagen-rich, thick fibrous cap, abundant smooth muscle cells and fewer macrophages and usually result in chronic stable angina (*figure 2).* Atheromas with thin caps, a large necrotic core and more macrophages tend to be less stable (vulnerable plaque) with a tendency to rupture ***(Lambert 1991).***

- **High-risk atherothrombotic plaque:**

Inspite of a common pathophysiologic pathway, atherosclerotic lesions are very heterogeneous and the "high-risk plaque" of each vascular bed has unique characteristics ***(Corti et al., 2003).***

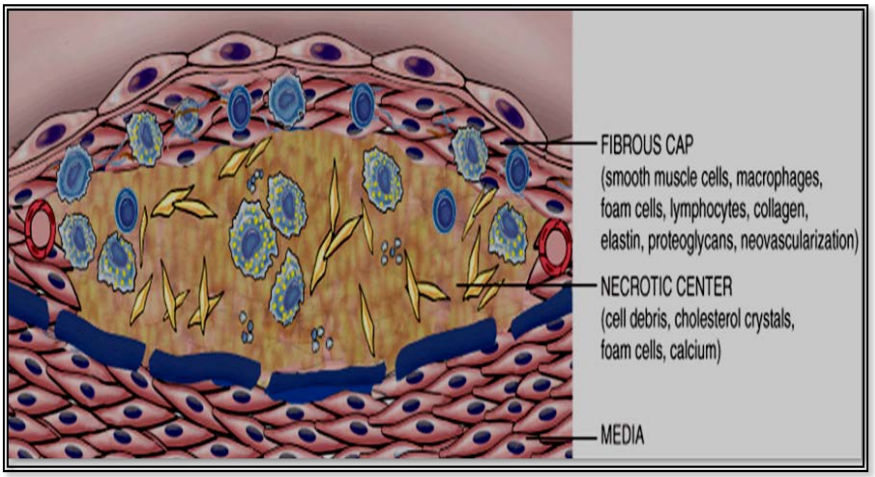


Figure 2. *Schematic depiction of the major components of well developed intimal atheromatous plaque overlying an intact media.* ***(Kannel and Wilson, 1995***).

The plaques prone to instability and rupture have a large lipid core, a low density of smooth muscle cells, a high concentration of inflammatory cells and a thin fibrous cap covering the lipid core compared with stable plaques. The plaque prone to rupture descriptive term is thin-cap fibroatheroma (TCFA) has been suggested ***(Bassand et al., 2007).***

In contrast to coronary artery vulnerable plaques characterized by high lipid content and a thin fibrous cap, high-risk plaques of the carotid arteries tend to be fibrotic and severely stenotic ***(Fayad and Fuster, 2001).***

More recently, the anatomic characterization of vulnerable plaque has been possible. Postmortem and intravascular ultrasound studies have demonstrated a greater lipid core, thinner fibrous cap, and a high density of inflammatory cells in complex ruptured plaques ***(Shah, 2003)***.

- **Plaque disruption:**

The ruptured plaque is a plaque with deep injury with a real defect or gap in the fibrous cap that had separated its lipid-rich atheromatous core from the flowing blood, thereby exposing the thrombogenic core of the plaque. Exposure of the thrombogenic lipid-rich core in plaque rupture may lead to thrombosis which covers the rupture site and extends into the lumen ***(Thim et al., 2008).***

It has long been appreciated that ACS is the manifestation of sudden plaque rupture with subsequent occlusive or subocclusive thrombus formation, leading to distal myocardial ischemia or myonecrosis ***(Ambrose et al.,1985*** *and* ***Chew & White, 2004).***

- **Consequences of plaque rupture:**

Rupture or erosion of the fibrous cap exposes the highly thrombogenic collagenous matrix and lipid core to the circulation and leads to platelet accumulation and activation. This, in turn, leads to fibrin deposition, thrombus formation and, at its most extreme, vessel occlusion**.** If the lesion ruptures or erodes platelets rapidly accumulate and intravascular thrombosis can occur, leading to the acute coronary syndromes of unstable angina and myocardial infarction ***(figure 3) (Weissberg , 2000)***.

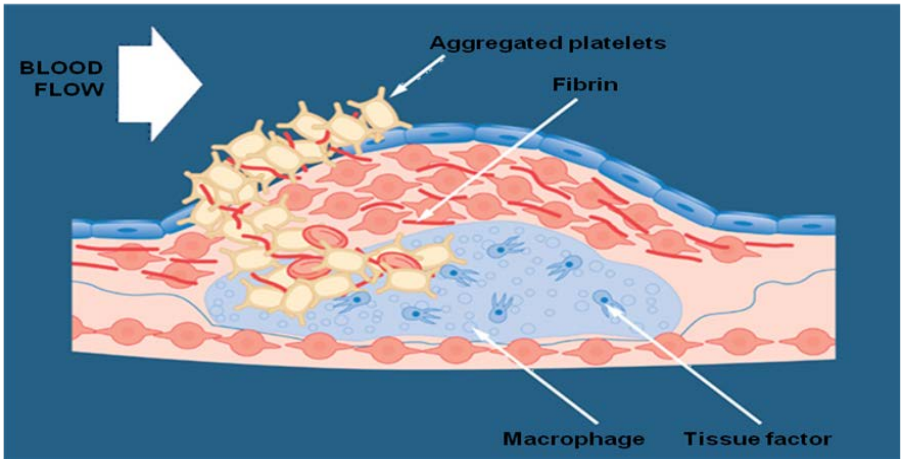


Figure 3. Plaque Disruption Leading to Atherothrombosis Formation. *Adapted from: Falk E et al. Circulation 1995; 92: 657–71.*