6-months Follow-up after Stenting of Matched Occluded and Non-occluded Coronary Arteries

Thesis

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Presented by

Mohammed Ismael Ali Hassan
(M.B., B. Ch)

Supervised by

Doctor/ Sherif Samir Mostafa EL-Zahwy
Assistant Professor of Cardiology.
Faculty of Medicine-Ain Shams University.

Doctor/ Ahmed Mohammed EL-Mahmoudy
Lecturer of Cardiology.
Faculty of Medicine-Ain Shams University

Ain Shams University
Faculty of Medicine
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Introduction

Flow-limiting stenosis is the most serious and important complication of Coronary atherosclerosis that leads to myocardial ischemia and/or myocardial infarction (MI) ***(Piscione et al., 2002).***

Chronic total occlusion (CTO) is defined as obstruction of a native coronary artery with no luminal continuity and with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or I for more than or equal to one month duration ***(Olivari et al., 2003).***

Percutaneous coronary intervention (PCI) of chronic total occlusion (CTO) is one of the major challenges in interventional cardiology ***(Safian et al., 1988).***

Balloon angioplasty of coronary occlusions as opposed to non-occluded coronary lesions had been associated with a significantly higher 6-months restenosis rate ***(Berger et al., 1996).***

Stenting as opposed to balloon angioplasty of non-occluded coronary lesions as well as coronary occlusions had a lower restenosis rate ***(Sirnes et al., 1996).***

Aim of the Work

To evaluate the 6-months clinical outcome and occurrence of Major adverse cardiac events (MACE) following successful stenting of matched occluded and non-occluded coronary arteries.

Atherosclerosis and Coronary Artery Disease

Introduction

The prevalence of coronary artery disease (CAD) is approximately one-third to one-half that of total cardiovascular diseases (CVD).

The most common cause of angina pectoris is coronary atherosclerosis with a severe stenosis obstructing blood flow leading to myocardial ischemia ***(Gibbons et al., 2002).*** The atherosclerotic coronary lesion is a lipid-containing plaque (also known as an atheroma) in the intima of the artery. Atheroma formation is secondary to a complex set of mechanisms only partially understood, involving endothelial dysfunction, lipoprotein deposition, infiltration by inflammatory cells, cellular proliferation, especially smooth muscle cells and matrix deposition ***(Stuart and Ellestad, 1980).***

This mechanism may start at an early age. Endothelial dysfunction is thought to be the initial step in atherosclerosis. Endothelial dysfunction may result from the injurious effects of free radicals caused by tobacco smoking or from the effects of low-density lipoprotein (LDL), cholesterol, hypertension, diabetes, infectious agents, genetic factors, or a combination of these factors. Endothelial dysfunction results in increased endothelial permeability to lipoproteins, increased expression of

adhesion molecules and release of chemotactic factors that attract inflammatory cells (monocytes, macrophages, lymphocytes) and smooth muscle cells and facilitate their migration into the arterial wall ***(Daly et al., 2006).***

The fatty streak results from the deposition of macrophages, lymphocytes and smooth muscle cells into the arterial wall. In the arterial wall, macrophages containing LDL form 'foamy cells' and release cytokines and free radicals causing more local damage and attracting more cells. As more foamy cells, inflammatory cells and smooth muscle cells accumulate in the arterial wall, the fatty streak will grow in size and will tend to form a fibrous cap surrounding a lipid core (fibrofatty plaque or atheroma) ***(Ezzati et al., 2002).***

The cap consists of connective tissue and the lipid core includes foamy cells, leukocytes and debris. As the plaque grows in size, it will push its way towards the lumen of the artery. When it is large enough to interfere with blood flow, ischemia and angina will result. Stable atheromas have a collagen-rich, thick fibrous cap, abundant smooth muscle cells and fewer macrophages and usually result in chronic stable angina. Atheromas with thin caps, large necrotic core and abundant macrophages tend to be less stable (vulnerable plaque) with a tendency to rupture, resulting in acute coronary syndromes, including MI ***(Thadani, 2004).***

Atherosclerosis is responsible for almost all cases of CAD. This insidious process begins with fatty streaks that are

first seen in adolescence, these lesions progress into plaques in early adulthood and culminate in thrombotic occlusions and coronary events in middle age and later life ***(Wilson, 1994).***

A variety of factors, often acting in concert, are associated with an increased risk for atherosclerotic plaques in coronary arteries and other arterial beds, risk factor assessment is useful in adults to guide therapy for dyslipidemia, hypertension, diabetes and multivariate formulations can be used to help estimate risk for coronary disease ***(Ridker, 1999).***

Sex and age

Cardiovascular risk factors promote coronary disease in either sex at all ages but with different strengths.

Diabetes and low, high density lipoprotein (HDL)-cholesterol/total cholesterol ratio operate with greater power in women ***(Kannel and McGee, 1979).***

The incidence of a myocardial infarction is increased sixfold in women and threefold in men who smoke at least 20 cigarettes per day compared to subjects who never smoked ***(Prescott et al., 1998).***

Systolic blood pressure and isolated systolic hypertension are major risk factors at all ages in either sex ***(Chobanian et al., 2003).***

Obesity or weight gain promotes or aggravates all the atherogenic risk factors ***(Hung et al., 1990),*** and physical inactivity worsens some of them, predisposing subjects of all ages to coronary events ***(Dannenberg et al., 1989).***

Family history

Family history is a significant independent risk factor for coronary artery disease, particularly among younger individuals with a family history of premature disease ***(Sesso et al., 2001).***

Family history was evaluated in a prospective study from the Physician's Health Study of 22,071 men followed for 13 years and the Women's Health Study of 39,876 women followed for 6.2 years. Compared to no parental history of an MI, a maternal history, a paternal history, and both maternal and paternal history was associated with a relative risk of cardiovascular disease of 1.71, 1.40, and 1.85 in men and 1.46, 1.15, and 2.05 in women. A history of paternal MI at an age <60 years was associated with a greater risk of cardiovascular disease than infarction at a later age, in comparison any maternal history of infarction was associated with a greater risk ***(Murabito et al., 2005).***

Lipids and lipoprotein

Lipids, principally cholesterol and triglycerides, are the water insoluble compounds that require larger protein containing complexes called lipoproteins to transport them in

blood. The protein components of the lipoprotein are known as apolipoproteins or apoproteins. Evidence for the pathogenic importance of serum cholesterol has largely come from randomized trials which showed that reductions in total and LDL-cholesterol levels (almost entirely with statins) reduce coronary events and mortality when given for primary and secondary prevention ***(Sacks et al., 1996).***

Hypertension

Hypertension is a well-established risk factor for adverse cardiovascular outcomes, including: CAD, mortality and stroke ***(Lewington et al., 2002).*** In the worldwide INTERHEART study of patients from 52 countries, hypertension accounted for 18% of the population at risk of a first MI ***(Yusuf et al., 2004).***

Systolic blood pressure is at least as powerful a coronary risk factor as the diastolic blood pressure, particularly in older patients, and isolated systolic hypertension is now established as a major hazard for coronary heart disease and stroke. There is also evidence that the pulse pressure which is determined primarily by large artery stiffness is a predictor of risk ***(Franklin et al., 2001).***

Diabetes mellitus

Insulin resistance, hyperinsulinemia, and elevated blood glucose are associated with atherosclerotic cardiovascular disease ***(Norhammar et al., 2002).*** In an analysis of over

13,000 participants in the Copenhagen Heart Study, the relative risk of incident of MI or stroke was increased two to three fold in those with type 2 diabetes, and the risk of death was increased two fold, independent of other CAD risk factors. In addition, a significant number of patients with an acute MI have previously undiagnosed diabetes. In the worldwide INTERHEART study of patients from 52 countries, diabetes accounted for 10 percent of the population at risk of a first MI ***(Al-Delaimy et al., 2004).***

The all-cause mortality risk associated with diabetes is comparable to the all-cause mortality risk associated with a prior MI. While the causes of death are not equally frequent in these groups (Cardiovascular death is more frequent after MI, while non-Cardiovascular death is more frequent in patients with diabetes), the 2002 National Cholesterol Education Program report designated diabetes a CAD equivalent, thereby elevating it to the highest risk category ***(Vaccaro et al., 2004).***

In addition to the importance of diabetes as a risk factor, diabetics have a greater burden of other atherogenic risk factors than non-diabetics, including hypertension, obesity, increased total-to-HDL-cholesterol ratio, hypertriglyceridemia and elevated plasma fibrinogen. The CAD risk in diabetics varies widely with the intensity of these risk factors ***(Almdal et al., 2004).***

Obesity

Obesity is associated with a number of risk factors for atherosclerosis, cardiovascular disease and cardiovascular mortality. These include hypertension, insulin resistance and glucose intolerance, hypertriglyceridemia, reduced HDL-cholesterol, and low levels of adiponectin. However, in an analysis of data from 4780 adults in the Framingham Offspring Study, obesity as measured by body mass index (BMI) significantly predicted the occurrence of coronary heart disease and cerebrovascular disease after adjusting for traditional risk factors ***(Calle et al., 1999).***

Metabolic syndrome

Patients with the constellation of abdominal obesity, hypertension, diabetes and dyslipidemia are considered to have the metabolic syndrome (also called the insulin resistance syndrome or syndrome X). Individuals with metabolic syndrome have a markedly increased risk of coronary artery disease ***(Wilson et al., 2008).***

Potential benefits of risk factors modification

The importance of identifying people at risk is that many of the important risk factors for CVD are modifiable by specific preventive measures. In the worldwide INTERHEART study of patients from 52 countries, nine potentially modifiable factors accounted for over 90 percent of the population at risk of a first

MI. These included smoking, dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol consumption and regular physical activity ***(Yusuf et al., 2004)***

Chronic Total Occlusion

Definition of CTO

Definition of coronary CTO must consider the degree of lumen narrowing, antegrade blood flow, grade and age of the occlusion.

CTOs are characterized by significant atherosclerotic vessel narrowing with lumen compromise resulting in either complete interruption of antegrade blood flow as assessed by coronary arteriography (TIMI grade 0 flow) also known as (true) total occlusions, or with minimal contrast penetration through the lesion without distal vessel opacification (TIMI grade I flow), which is known as (functional) total occlusions ***(Stone et al., 2005).***

In coronary angiography, total coronary occlusion is identified as an abrupt termination of the epicardial vessel, antegrade and/or retrograde collaterals may be present and are helpful in quantifying the length of the totally occluded segment ***(Zidar et al., 1996).***

TIMI 0 Flow

The identification of TIMI 0 flow is not as straightforward as in recent post-MI occlusions, for which the TIMI classification was originally developed.

Antegrade contrast filling of the segment beyond the occlusion does not preclude TIMI 0 flow within the occluded segment. Non-intraluminal ipsilateral bridging collaterals may give antegrade flow and the false impression of a functional incomplete occlusion. Their presence should be differentiated from TIMI 0 flow within the occluded segment by careful frame-by-frame assessment in different angiographic planes ***(Srivata et al., 1997).***

The presence of intraluminal channels plays a role in facilitating crossing of occlusions. Pathology shows that they are often below the threshold of angiographic resolution ***(Katsuragawa et al., 1993).***

Antegrade contrast filling of the segment beyond the occlusion flow, in the absence of ipsilateral bridging collaterals and even when the occluded vessel segment shows no intraluminal contrast filling, indicates a functional CTO ***(Di Mario et al., 2007).***

Occlusion Duration

In the absence of serial angiograms, the duration of coronary occlusion is difficult to specify with certainty and instead must be estimated from available clinical information related to the timing of the event that caused the occlusion as acute MI or sudden change in angina pattern with ECG changes consistent with the location of the occlusion. However, in many

patients the age of the CTO cannot be determined with confidence ***(Stone et al., 2005).***

There are three levels of certainty as regard the occlusion duration

Certain (angiographically confirmed):

A previous angiogram (for instance, before a previous CABG operation or after an acute myocardial infarction) confirm the presence of TIMI 0 flow for ≥3 months.

Likely (clinically confirmed):

Objective evidence of an acute myocardial infarction in the territory of the occluded artery without other possible culprit arteries ≥3 months before the current angiogram.

Possible (undetermined):

CTO with TIMI 0 flow & angiographic anatomy suggestive of longstanding occlusion (collateral development, no contrast staining) with stable angina symptoms unchanged in the last 3 months or evidence of silent ischemia.

In case of recent acute ischemic episodes (acute MI or unstable angina or worsening effort angina), a culprit artery other than the occluded vessel should be present.

The temporal criterion used to define a CTO duration has varied widely, typically ranging from >2 weeks ***(Werner et al., 2003)*** to >3 months ***(Zidar et al., 1996)*** which in part explains interstudy differences in lesion characteristics and procedural success. In general, a total occlusion of duration ≥ 3 months may be considered chronic ***(Stone et al., 2005).*** Lesions can be classified as CTOs when there is TIMI 0 flow within the occluded segment and angiographic or clinical evidence or high likelihood of an occlusion duration ≥ 3 months ***(Di Mario et al., 2007).***

Prevalence of CTO in the population and in patients undergoing angioplasty

The true prevalence of CTO in the general population is unknown because a certain proportion of patients with CTO is either asymptomatic or minimally symptomatic and never undergoes diagnostic coronary angiography ***(Stone et al., 2005).***

However, among patients with known or suspected coronary artery disease undergoing coronary angiography, chronic total occlusions (CTO) are common and found in approximately one-third of patients ***(Zidar et al., 1996),*** and they account for 10% of all percutaneous revascularization ***(Hoye et al., 2005).***

According to data from the 1997-1999 National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry, CTOs are most prevalent in the right coronary artery and least