Usefulness of statin pretreatment to prevent contrast-induced nephropathy in diabetic patients with renal impairment undergoing elective percutaneous coronary intervention

Thesis for partial fulfillment of master's degree of cardiology
submitted by

Mohammed Mahmoud Samy Monzaly
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Under supervision of

Prof. Dr. Hany Mohammed Awadalla
Assistant Professor of Cardiology
Ain Shams University

Dr. Ahmed Mamdoh Ismail
Lecturer of Cardiology
Ain Shams University

Ain Shams University
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Mohammed Mahmoud Samy

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List of Abbreviations

χ^2	: Chi-square
ACEI	: Angiotensin-converting enzyme inhibitors
CABG	: Coronary artery bypass surgery
CAD	: Coronary artery disease
CI	: Confidence interval
CIN	: Contrast-induced nephropathy
CK	: Creatine kinase
CKD	: Chronic kidney disease
CM	: Contrast medium
COX-2	: Cyclo-oxygenase
CrCl	: Creatinine clearance
CRP	: C-reactive protein
eGFR	: Estimated glomerular filtration rate
eNOS	: Endothelial nitric oxide synthase
GFR	: Glomerular filtration rate
HDL	: High-density lipoprotein
HMG-CoA	: 3-hydroxy-3-methylglutaryl coenzyme A reductase
ICAM-1	: Intercellular adhesion molecule-1
IV	: Intravenous
LDL	: Low-density lipoprotein
LOX-1	: Lectin-like oxidized LDL-1 receptor
MMPs	: Matrix metalloproteinases
MRI	: Magnetic resonance imaging
NAC	: N-acetylcysteine
NO	: Nitric oxide
NSAIDS	: Non-steroidal anti-inflammatory drugs
NSF	: Nephrogenic systemic fibrosis
OR	: Odds ratio
PCI	: Percutaneous coronary intervention
SAA	: Serum amyloid A
SCr	: Serum creatinine
SD	: Standard deviation

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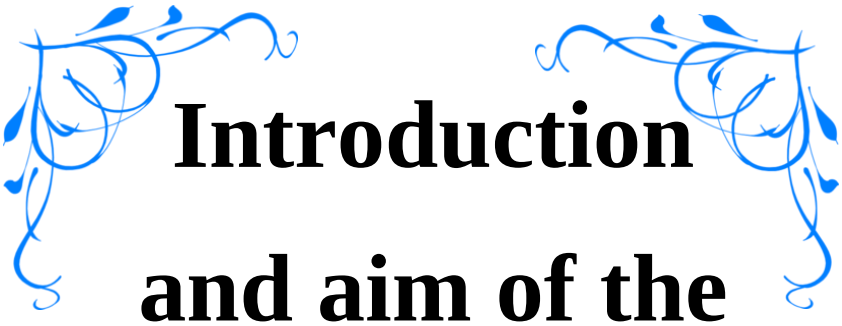

Introduction and aim of the work

Introduction

Contrast-induced nephropathy (CIN) represents an increasing healthcare burden and challenge as the frequency of diagnostic imaging and interventional studies increase, particularly among populations at risk of developing CIN. As the population ages, decreased renal function and increased atherosclerotic cardiovascular disease become more prevalent. Increasing levels of obesity with resultant metabolic syndrome and adult diabetes mellitus also increases the population at risk for CIN ***(Katholi, 2009).***

CIN accounts for 10 to 15% of hospital-acquired acute renal failure. It may rarely lead to irreversible renal function loss and it represents the third most common cause of in-hospital acute renal failure after decreased renal perfusion (42%) and post-operative acute renal failure (18%) **(*Perrin et al, 2012).***

Several risk factors may aggravate CIN, the most important risk factor is pre-existing impaired renal function. Patients with baseline serum creatinine (SCr) levels between 2.0 and 2.9 mg/dL have more than 7-fold increased risk of developing CIN whereas patients with SCr values above 3.0 mg/dL have more than 12-fold increased risk of developing CIN. Diabetic patients also have more than 5-fold increased risk of developing CIN. Other risk factors include hypertension, increased age, acute myocardial

infarction within 24 hours before administration of the contrast agent and congestive heart failure ***(Paraskevas et al, 2010).***

Contrast-induced nephropathy is defined as an absolute increase of serum creatinine (SCr) more than 0.5 mg/dL (>44 mmol/L) or a relative increase in SCr $\geq$ 25% from baseline SCr within 48 hours after contrast administration in patients undergoing elective percutaneous coronary intervention ***(Perrin et al, 2012).***

There has been considerable interest in the development of preventative strategies to reduce the risk of contrast-induced renal deterioration in high risk populations. Among these measures, pharmacologic prophylactic strategies based on antioxidant properties have received considerable attention in recent years.
Statins have recently been shown to possess pleiotropic effects that include antioxidant properties ***(Jo et al, 2008).***

Six years ago, a preliminary report supported that pre-procedural statin treatment in patients undergoing cardiac catheterization was associated with improved SCr levels compared with control ***(Paraskevas et al, 2010).***

More recently, 2 clinical studies have reported positive findings for the effect of statins on CIN prevention in patients undergoing coronary interventions. These findings, however, remain tentative because of study limitations that include retrospective designs, heterogeneous patient populations, and

significant differences in baseline risk factors between groups being compared ***(Jo et al, 2008).***

Aim of the work

Assessment of the efficacy of pre-procedural treatment with high dose atorvastatin (80 mg) in preventing contrast-induced nephropathy (CIN) in diabetic patients with renal impairment undergoing elective percutaneous coronary intervention (PCI).

Review of literature

Chapter One:

Statins

The discovery of the statins by Akira Endo and colleagues in 1976 opened the door to a new era in preventive cardiology. The importance of this discovery was recently underscored by Endo's receipt of the 2008 Albert Lasker Clinical Medical Research Award. By inhibiting the biosynthesis of endogenous cholesterol, the statin drugs lower elevated blood cholesterol levels much more effectively than any of the dietary or drug regimens that were available before Endo's discovery. Moreover, they have proved to be remarkably free of serious side effects ***(Steinberg, 2009).***

The hypothesis that elevated blood cholesterol levels represent an important cause of atherosclerosis and coronary heart disease, the "lipid hypothesis" was controversial for many years. Skepticism about the hypothesis persisted in some quarters despite a steadily growing body of supportive evidence from experimental studies in animals, striking findings in human kindreds with familial hypercholesterolemia, consistent epidemiologic correlations, and several small (but nevertheless impressive) clinical trials. In contrast, by the 1960s many or most leaders in the field of lipoprotein and atherosclerosis research were convinced that the accumulated evidence justified intervention to lower blood cholesterol levels ***(Steinberg, 2009).***

Recent research has shown that inflammation plays a key role in coronary artery disease (CAD) and other manifestations of

atherosclerosis. Immune cells dominate early atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit acute coronary syndromes ***(Hansson, 2005).***

Since their early introduction, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have become among the most effective and widely used medications for reducing cardiovascular risk. The value of statins in primary and secondary prevention has been established in a broad spectrum of clinical scenarios; at one end of the spectrum are those without known vascular disease ***(Thavendiranathan et al, 2006).***

Randomized clinical trials have consistently shown that statins reduce cardiovascular event rates. The favorable effects of statins extend across a range of levels of low-density lipoprotein (LDL) cholesterol, with no apparent lower threshold for a benefit ***(Ridker et al, 2008).***

In parallel, imaging trials have shown that intensive statin regimens slow the progression of coronary atherosclerosis and may even result in disease regression in some patients ***(Nissen et al, 2006).*** Accordingly, guidelines for cardiovascular disease prevention have increasingly emphasized that lowering LDL cholesterol levels with statins is the primary goal of lipid-modulating therapy ***(Reiner et al, 2011).***