POLYMER FREE DRUG-ELUTING STENTS VERSUS DURABLE POLYMER DRUG-ELUTING STENTS IN ELECTIVE PERCUTANEOUS CORONARY INTERVENTIONS IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE PATIENTS: A SINGLE CENTER PROSPECTIVE COMPARATIVE STUDY

Thesis Submitted for Partial Fulfilment of the MD Degree in Cardiology

Presented by

Sherif Mohammad Aziz Abdalazeem Altoukhy

M.Sc. Cardiology, Ain Shams University

Under supervision of

Prof. Mohammad Awad Ahmed Taher

Professor of Cardiology, Ain Shams University

Prof. Mohsen Fahmy Metwally Aly

Professor of Cardiology, Ain Shams University

Prof. Walid Abdelazim Mohammad Elhammady

Professor of Cardiology, Ain Shams University

Dr. Basem Alsaid Mohammad Enany

Assistant Professor of Cardiology, Ain Shams University

Dr. Ahmed Abdul Moneim Abdul Salam Rezq

Lecturer of Cardiology, Ain Shams University

Ain Shams University

Cairo, 2018

سورة البقرة الآية: ٣٢

Acknowledgment

First and foremost, I feel always indebted to ***Allah****, the Most Kind and Most Merciful.*

I would like to express my respectful thanks and gratitude to ***Prof. Mohammad Awad Ahmed Taher,*** *Professor of Cardiology - Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made the completion of this work possible.*

I am also delighted to express my deepest gratitude and thanks to ***Prof. Mohsen Fahmy Metwally Aly,*** *Professor of Cardiology, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to ***Prof. Walid Abdelazim Mohammad Elhamady,*** *Professor of Cardiology, Faculty of Medicine, Ain Shams University, for his great help, active participation and guidance.*

I wish to introduce my deep respect and thanks to ***Dr. Basem Alsaid Enany,*** *Assistant Professor of Cardiology, Faculty of Medicine, Ain Shams University, for his continuous support in this work.*

I would like to express my hearty thanks to ***Dr. Ahmed Abdul Moneim Abdul Salam Reza,*** *Lecturer of Cardiology, Faculty of Medicine, Ain Shams University, for his support, kindness, supervision and cooperation in this work.*

Sherif Mohammad Aziz
Abdalazeem Altoukhy

List of Contents

List of Tables

List of Figures

List of Figures (Cont...)

List of Abbreviations

Abbreviation	Full term

ACC *.....American College of Cardiology*
ACS *..... Acute coronary syndrome*
ADP *..... Adenosine diphosphate*
AES *..... Amphilimus-eluting stent*
AHA *..... American Heart Association*
ARC *..... Academic Research Consortium*
BA9 -DCS *..... Biolimus -A9 polymer free coated stent*
BMS *..... Bare-metal stent*
BP *..... Biodegradable polymer*
BVS *..... Bioabsorbable vascular scaffold*
CABG *..... Coronary artery bypass grafting*
CD4 *..... Cluster of differentiation 4*
CE *.....Conformité Européene (European conformity)*
CI *.....Cardiac index*
CI *.....Confidence interval*
CRP *.....C-reactive protein*
DAPT *..... Dual antiplatelet therapy*
DEB *..... Drug-eluting balloon*
DES *..... Drug-eluting stent*
DM *.....Diabetes mellitus*
DS *..... Diameter stenosis*
EACTS *..... European Association for Cardiothroacic Surgery*
ECS *..... Endothelial progenitor cell capture stent*
EES *..... Everolimus eluting stent*
EF *.....Ejection fraction*
ELISA *..... Enzyme-linked immunosorbent assay*
EPC *..... Endothelial progenitor cells*
ESC *..... European Society of Cardiology*
FDA *..... Food and Drug Administration*

List of Abbreviations (Cont...)

Abbreviation	Full term
HDL	*High density lipoprotein*
HsCRP	*High sensitivity C-reactive protein*
HTN	*Hypertension*
IL-6	*Interleukin-6*
IL-12	*Interleukin-12*
IQR	*Interquartile range*
ISA	*Incomplete stent apposition*
ISR	*In stent restenosis*
IVUS	*Intravascular ultrasound*
JNC	*Joint national committee*
LAD	*Left anterior descending artery*
LCx	*Left circumflex artery*
LDL	*Low density lipoprotein*
LIMA	*Left internal mammary artery*
LLL	*Late lumen loss*
LMCA	*Left main coronary artery*
LST	*Late stent thrombosis*
LV	*Left ventricle*
MACEs	*Major adverse cardiac events*
mg	*Milligram*
MI	*Myocardial infarction*
ml	*Milliliter*
ng	*Nanogram*
NO	*Nitric oxide*
NSTACS	*Non-ST acute coronary syndrome*
NSTEMI	*Non-ST elevation myocardial infarction*
OCT	*Optical coherence tomography*
OM	*Obtuse marginal branch*
OR	*Odds ratio*

List of Abbreviations (Cont...)

Abbreviation	Full term
PAI-1	*Plasminogen-activator inhibitor 1*
PCI	*Percutaneous coronary intervention*
PCWP	*Pulmonary capillary wedge pressure*
PDLLA	*poly-D,L-lactide*
PES	*Paclitaxel-eluting stents*
PF-DES	*Polymer free drug-eluting stent*
PF-PES	*Polymer free paclitaxel-eluting stent*
PF-SES	*Polymer free sirolimus-eluting stent*
PLLA	*Poly-L-lactic acid*
POBA	*Percutaneous old balloon angioplasty*
PP	*Permanent polymer*
PTCA	*Percutaneous transluminal coronary angioplasty*
RCA	*Right coronary artery*
RCTs	*Randomized controlled trials*
RES	*Rapamycin-eluting stent*
RR	*Risk ratio*
SAM	*Self-assembled monolayer*
SCAD	*Stable coronary artery disease*
SD	*Standard deviation*
SES	*Sirolimus eluting stent*
SMC	*Smooth muscle cells*
ST	*Stent thrombosis*
STEMI	*ST elevation myocardial infarction*
SVG	*Saphenous venous graft*
SWMA	*Segmental wall motion abnormalities*
TLF	*Target lesion failure*
TLR	*Target lesion revascularization*
TOR	*Target of Rapamycin*
TVR	*Target vessel revascularization*
UA	*Unstable angina*
VLST	*Very late stent thrombosis*
vs.	*versus*
ZES	Zotarolimus-eluting stent

INTRODUCTION

The development of DES has been pioneered through a combination of the increased understanding of the biology of restenosis, the selection of drugs that target one or more pathways in the restenotic process, controlled-release drug delivery strategies, and the use of the stent as a delivery platform. This helped in reducing the major drawback of using bare metal stents (BMS) ***(Abizid and Costa, 2010).***

Although first-generation DES Cypher and Taxus have effectively achieved their main goal, reducing restenosis across virtually all lesion and patient subsets, their safety has been limited by suboptimal polymer biocompatibility, delayed stent endothelialization leading to late and very late thrombosis, and local drug toxicity ***(Iakovou et al., 2005 and McFadden et al., 2004).***

The permanent presence of these polymers has been correlated to the inflammatory responses and local toxicity in preclinical analysis ***(Abizid and Costa, 2010)***. Consequently, the focus of clinical research has been on the development of novel drug carrier systems including biodegradable polymers and non-polymeric stent surfaces. Additional improvements include the development of more modern platforms and the use

of novel anti-proliferative agents or reduced doses of current approved anti-proliferative drugs ***(Serruys et al., 2010).***

The main issue is: Will polymer free stents reduce the incidence of very late stent thrombosis, thereby lessening the need for long term dual anti platelet therapy? In addition, if so, is there a penalty to pay in terms of target lesion and target vessel revascularization? ***(Bailey et al., 2012)***.

A large body of evidence suggests that inflammation plays a key role in the pathogenesis of atherosclerosis. The chronic inflammatory process can develop into an acute clinical event by the induction of plaque rupture, leading to acute coronary syndromes ***(Libby et al., 2002).***

C-reactive protein (CRP) has been the most extensively studied, and subsequent works demonstrated that it was a risk marker in both acute coronary syndromes and in patients with myocardial ischemia. Moreover it takes part directly in the atherosclerotic process ***(Zebrak et al., 2002 and Topol, 2003).***

It was concluded that CRP was an independent predictor of adverse cardiac events in patients with stable coronary artery disease irrespective of the presence of significant atherosclerotic lesions ***(Arroyo-Espliguero et al., 2009 and Worthley et al., 2006).***

Vascular injury during percutaneous coronary intervention (PCI) is associated with a systemic inflammatory

response and a rise in CRP serum level, and the degree of inflammation has been shown to correlate with the cardiovascular risk ***(Jae Rhee et al., 2008).***

Most of the clinical trials in the literature focused on comparing the clinical outcome between permanent polymer and polymer free drug eluting stents, but there is little data about the inflammatory effect of the permanent polymer versus polymer free drug eluting stents in association with the clinical outcome.

Accordingly, our study aims at comparing the inflammatory responses and the clinical outcomes after percutaneous interventions, using permanent polymer versus polymer free DES in patients with SCAD. High sensitivity CRP will be our marker to assess that inflammatory response.

AIM OF THE WORK

The aim of this study is to compare the inflammatory response of polymer free versus permanent polymer drug-eluting stents in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention, and the effect of this inflammatory response on the 6 month clinical outcomes & major adverse cardiac events.

Chapter 1
EVOLUTION OF CORONARY STENTS

In the modern era, percutaneous coronary intervention (PCI) is a globally adopted standard therapy that continues to advance based on best medical practice and evolving scientific data. It is now one of the most common medical procedures performed in the United States, with over 600,000 performed annually ***(Roger et al., 2012).***

In 1929, Forssmann performed the first human cardiac catheterization on himself, using a urinary catheter to measure heart pressures ***(Forssmann, 1929)***. This was followed by Cournand and Richards who evolved right heart catheterization to a standard diagnostic tool ***(Cournand and Ranges, 1949)***. For their pioneering work, and so diagnostic catheterization became an established tool for invasive hemodynamic assessment.

In 1953, Seldinger developed a safe percutaneous catheterization technique ***(Seldinger, 1953)***, and in 1958, the first selective coronary angiogram was performed by Sones, giving rise to the concept of diagnostic coronary angiography ***(Sones, 1958)***.

In 1964, the first peripheral angioplasty case was performed by Dotter who, working with Judkins, used multiple catheters of increasing diameter to expand the lumen of an