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Evaluation of the efficacy and long-term safety outcomes of first generation drug-eluting stents in off-label indications

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EVALUATION OF THE EFFICACY AND LONG-TERM SAFETY OUTCOMES OF FIRST GENERATION DRUG-ELUTING STENTS IN OFF-LABEL INDICATIONS

by

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ABSTRACT

FDA approval of drug-eluting stents (DES) in 2002, was based on data obtained from several pivotal, short-term (< one year) randomized control trials that evaluated their efficacy in reducing in-stent restenosis when used in treatment of coronary artery lesions compared with bare metal stents (BMS). These trials excluded patients with complex coronary lesions. When the FDA approved use of DES in treatment of coronary artery lesions, the on-label indications only applied to a very limited subset of simple lesions.

Immediate advantages of DES were observed in clinical practice for on-label indications, specifically in their ability to significantly reduce in-stent restenosis after PCI. The increased short-term safety and efficacy seen in on-label clinical cases soon led clinicians to expand the use DES to more complex lesions. These complex indications, not included in the pivotal FDA trials, are considered off-label. Off-label indications include bifurcation lesions, ostial lesions, lesions greater in length and diameter than those approved by the FDA, implantation in saphenous vein grafts, and lesions in the left main coronary artery. Currently, DES use for treatment of lesions presenting off-label indications

may comprise as much as 60% of clinical cases. However, early evidence that DES may play a role in adverse safety outcomes, has led many to question the use of DES outside their on-label indications.

This paper sought to evaluate some of the current research investigating first generation DES use in four different off-label indications: coronary artery bypass graft lesions, saphenous vein graft lesions, ostial lesions, and chronic total coronary occlusions. In particular, it looked at studies, which compared the efficacy and clinical outcomes of DES and BMS treatment of each of the different lesion types.

The results of this evaluation were very promising in that of the four specific off-label indications evaluated, all of them showed to be superior in reduction of neointimal growth and subsequent in-stent restenosis. Additionally, DES treatment of left main coronary artery lesions, saphenous vein graft lesions, and chronic total coronary occlusions showed to be superior in reducing the incidence rate of major adverse cardiac events and target vessel revascularization over various follow-up durations. The only scenario that DES did not prove to be superior to BMSs was the treatment of ostial lesions.

Long-term randomized control trials with large study populations should be performed to further elucidate the effects of DES treatment of specific off-label lesions.

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ABBREVIATIONS

BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
CTO	Chronic Total Coronary Occlusion
DES	Drug-Eluting Stent
FDA	US Food and Drug Administration
HDL	High Density Lipoprotein
ISR	In-Stent Restenosis
LDL	Low Density Lipoprotein
LMCA	Left Main Coronary Artery
Lp(a)	Lipoprotein little a
LST	Late Stent Thrombosis
MACE	Major Adverse Cardiac Events
MI	Myocardial Infarction
NO	Nitric Oxide
PAI-1	Plasminogen Activator Inhibitor-1
PCI	Percutaneous Coronary Intervention
PES	Paclitaxel-Eluting Stent

PRISON	Primary Stenting of Totally Occluded Native Coronary Arteries
RAS	Renin-Angiotensin System
ROS	Reactive Oxygen Species
SCAAR	Swedish Coronary Angiography & Angioplasty Registry
SES	Sirolimus-Eluting Stent
SVG	Saphenous Vein Graft
TNF	Tumor Necrosis Factor
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
ULN	Upper Limit of Normal
VLST	Very Late Stent Thrombosis
VSMC	Vascular Smooth Muscle Cell

Introduction

Coronary Artery Disease

Over one hundred years ago cardiovascular disease was responsible for less than ten percent of death around the world. With advances in medicine infectious diseases as one of the leading causes of morbidity has decreases causing the average age of the population to increase, and with it, the prevalence of cardiovascular disease. Currently, cardiac diseases account for 20-30% of deaths worldwide, and as much as 50% in developed countries, the majority of which are related to coronary artery disease (CAD).[1,2]

Coronary artery disease, also known as coronary heart disease (CHD), is a non-specific term that refers to a variety of pathologies resulting from either a partial or complete occlusion of the coronary vessels.[3] The coronary arteries supply the heart, specifically the myocardium, with oxygenated blood. Development of atherosclerotic lesions in these vessels causes them to become stenotic, reducing blood flow to the heart, leading to symptomatic CAD and myocardial infarction (MI).[2]

While cardiovascular disease still remains a leading cause of death around the world, mortality rates in the United States have recently declined as a result of improved medical prevention and in-hospital treatment of patients with acute coronary pathologies. However, even with this current trend in the US it is expected that prevalence of chronic cardiovascular disease and mortality will

increase with expected increases in cardiovascular risk factors. Among these risk factors is hypertension, which affects more than 30% of the US adult population with another 31% being considered prehypertensive with an above normal blood pressure. These numbers are expected to further increase with population aging.[4] Another major risk factor is Diabetes mellitus, which has been shown to be associated with a more than four-fold increase in death from CAD when compared to patients without the disease.[5] The diabetic population is expected to jump from 171 million to 366 million worldwide between the years 2000 and 2030 due to increasing population age and the obesity epidemic.[6] Other major risk factors for CAD include cigarette smoking, cigarette smoking, and high cholesterol intake (Table 1).[4]

Table 1: **American Heart Association Guide to Risk Factors for CAD.**[4]

Major Independent Risk Factors	**Predisposing Risk Factors**	**Possible Risk Factors**
Cigarette Smoking	Physical Inactivity	Fibrinogen
Hypertension	Obesity	C-reactive protein
Elevated total and LDL cholesterol	Family History of premature CAD	Homocysteine Elevated Lp(a)
Low HDL cholesterol	Ethnicity	
Diabetes mellitus	Psychosocial Factors	
Older age		

Atherosclerosis

The development of CAD was once thought to be the result an unavoidable narrowing of the coronary arteries. Recent investigation shows that stenosis actually arises from a much more complex process of plaque development with the potential to rupture and cause complete occlusion of the arteries leading to MI.[4] The arterial wall is composed of three layers: the *tunica intima*, *tunica media*, and *tunica adventitia*. The innermost layer, the *tunica intima*, consists of an endothelial layer of cells protects the vascular wall and is responsible for regulation of cell proliferation and inflammatory and thrombotic processes. It deviation from normal endothelial cell processes in this layer that leads to the development of atherosclerotic plaques and coronary artery stenosis[7]. The currently accepted "Response-to-injury" theory suggests that atherosclerotic plaques develop in response to damage done to the endothelial layer of a vessel. Inflammation and healing processes occur in the body's effort to heal the damage done to the artery, similar to healing of a wound. It should be noted, however, that although "injury" to the endothelium can be a physical forces, it is much more common that this damage from a biochemical stimulus. All of the aforementioned mentioned CAD high risk factors contribute to increased oxidative damage to the vessel. The generation of reactive oxygen species (ROS) have many effects, but two in particular that initiate the development of coronary artery stenosis. One effect is ROS react with nitric oxide (NO), which acts as a primary anti-atherogenic factor, diminishing its local

availability. Additionally, ROS play a role in initiating signally pathways that stimulate the renin-angiotensin system (RAS), the endogenous endothelin system, and alter the activity of factors. All of these alterations cause the binding and infiltration of the endothelium by inflammatory cells.[8]

The infiltrating monocytes develop into macrophages and begin to phagocytose low-density lipoprotein (LDL) and become foam cells, which undergo apoptosis. Further development of the plaque occurs when vascular smooth muscle cells (VSMCs) begin to proliferate from the *tunica media* into the intima where they secrete fibrous extracellular matrix encapsulating the accumulated lipids and other cells recruited to the area by the inflammatory pathways.[7,8] Plaque development progresses with further remodeling of the fibrous cap that surrounds the lipid core, which continues to be infiltrated with fat and inflammatory cells. Over time the atherosclerotic lesion invades the lumen of the artery, occluding blood flow to the heart.[7]

Clinically, it is important to understand the behavior of atherosclerotic lesions and their tendency to cause acute cardiac pathologies such as myocardial infarction. While the size of a lesion and the extent to which it occludes a coronary artery has obvious significance, recent studies are particularly focused on plaque vulnerability rather than just size. Vulnerability is of particular importance because as the plaque develops it has the potential to ulcerate and rupture triggering pathways that causes thrombus formation and acute blockage of the artery.[8] Current research has shown that ratio of lipid core

to fibrous cap size plays a key role in determining the vulnerability of atherosclerotic lesions. Specifically, lesions that have a large lipid core with a comparatively less prominent fibrous cap are more likely to rupture in comparison to similarly sized lesions with a higher content of smooth muscle and extracellular matrix development. Plaques made up of greater than 40% lipid are at higher risk for rupture. Similarly, plaques that cause myocardial infarction have been shown to have fibrous caps thinner than 60 μm. One final factor that appears to contribute to the vulnerability of atherosclerotic lesions is the level of macrophage, mast cell, neutrophil and activated leukocyte presence within the nucleus of the lesion. These cells secrete enzymes and tissue factors that break down fibrous matrix and stimulate pro-thrombotic events, which can lead to vascular occlusion and acute ischemic events.[7] Figure 1 illustrates the morphology of stable, unstable and ruptured atherosclerotic plaques.

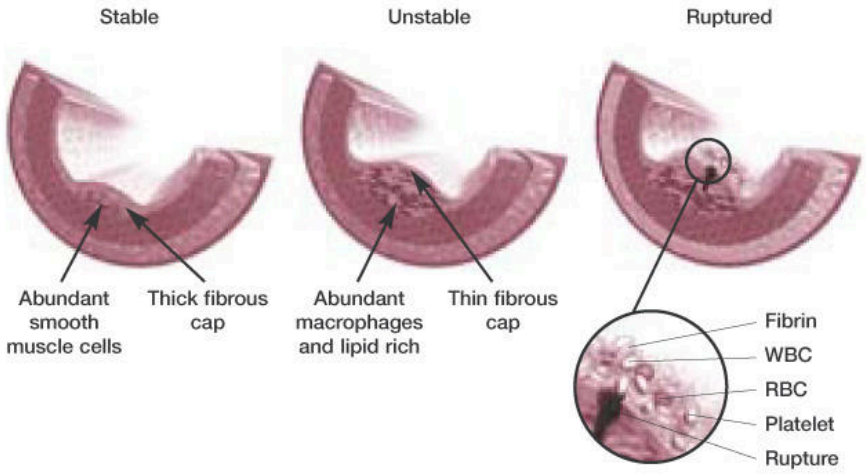

Figure 1: **Morphology of Stable, Unstable and Ruptured Atherosclerotic Plaques.**[4]

Unfortunately, despite the strides made in understanding atherogenesis and the mechanisms responsible for lesion ruptures leading up to acute coronary events, it is still very difficult to predict how these events will present themselves in a clinical setting. A patient with no history of CAD could present with an MI, and go on with complete stability after the event. At the other end of the spectrum, patients often present with rapidly developing angina leading to an acute ischemic event, followed by chronic angina or new infarction within a few weeks or months. Further efforts are currently being made to investigate the mechanisms that are responsible atherosclerotic plaque rupture on both a local and systemic level. Currently, many biomarkers and their role in plaque instability as a systemic inflammatory process are being investigated in hopes of being able to better understand the clinical presentations of acute ischemic events and chronic CAD.[7]

Percutaneous Coronary Intervention

While it remains one of the leading causes of mortality across the globe, dramatic improvements have been made in the treatment of coronary artery disease. Revascularization of coronary vessels affected by CAD was once done through highly invasive surgical procedures involving splitting of the sternum, otherwise known as “open-heart” surgery.[9] While coronary artery bypass graft CABG surgery is still used in many revascularization scenarios, catheter-based percutaneous coronary interventions (PCI) involving balloon angioplasty and

coronary artery stent implantation have become a routine therapy for CAD and MI.[9,10]

Coronary angioplasty is a procedure first developed by Gruntzig in 1977 as an alternative to CABG.[10] The first PCI was performed using a catheter with a balloon at the tip. The balloon was inflated at the site of coronary stenosis in order to dilate the obstructed vessel. Balloon angioplasty was certainly a revolutionary development in revascularization procedures, but it has a major limitation in that the dilated portion of the artery has tendency to constrict during healing, a process called restenosis, which was found to occur in as many as 40% of balloon angiography cases.[10] To solve this problem, coronary stents were developed. Stents are metal, tubular, mesh devices that are placed over the balloon-tipped catheter in collapsed form and expanded at the stenotic portion of a diseased vessel. The stent acts as a mechanical scaffold, reducing the recoil of the arterial wall and allowing the vessel to remain open.[2] While these bare metal stents (BMS) were shown to significantly reduce the rate restenosis and the number of repeat revascularization procedures, in-stent restenosis (ISR) rates still remained between 20-30% at follow-up between 6-12 months post implantation.[11,12] In-stent restenosis is defined as a narrowing of the diameter of a stented vessel by at least 50%, and is caused by excess neointimal formation at the stent site, as opposed to elastic recoil of the vessel seen in restenosis during balloon angiography.[2,12]

In 2002, the US Food and Drug Administration (FDA) approved drug-eluting stents (DES), designed to answer the problem of in-stent restenosis seen in the BMS.[9] Drug-eluting stents are typically comprised of a bare-metal stent, coated with a polymer responsible for carrying drugs, such as sirolimus (CYPHER) and paclitaxel (TAXUS), aimed at disrupting the cellular and molecular pathways responsible for in-stent restenosis.[12] DES have proven to be far superior to the BMS in that they significantly lowered rates of ISR (to around 5%) and necessary repeat revascularization procedures after the initial PCI. DES have also shown promising results for patients who have suffered an acute MI in that treatment with DES has been shown to significantly decrease mortality rates within 2 years of implantation when compared to bare metal stents.[13] Although the results from early, randomized control trials that led to FDA approval of DES in clinical practice, one major drawback has been the long-term safety concerns associated with their use. Specifically, evaluation of clinical cases demonstrates that DES use may be the cause of late stent thrombosis (LST) and very late stent thrombosis (VLST) leading to acute ischemic events.[10] Studies that investigate the clinical effectiveness and long-term safety concerns will be discussed in greater detail later in this paper.

When the FDA evaluated the first generation of drug-eluting stents for approval, they based their decision for commercialization on results of multiple randomized control trials. Data from these trials delineated reductions of IRS and the necessity for repeat revascularizations when compared with bare metal

stents, which was enough to warrant approval of DES use in clinical practice. Because many common clinical cases that generally present with more complexity were excluded from the early trials comparing BMS and DES, the FDA only considers a narrow spectrum of indications to be “on-label.”[14] The on-label indications for the first approved Sirolimus-eluting stent included de novo lesions no longer than 30 mm in native coronary arteries of between 2.5 and 3.5 mm in diameter. However, CAD more often than not presents as a much more complex pathology than is covered by the on-label DES indications. In fact more than 50% of uses are considered off-label.[14] Table 2 summarizes the criteria for FDA approved on-label use and frequent off-label indications for use of DES. Use of DES in off-label cases assumes that the effectiveness of this treatment in on-label scenarios carries over to more complex diseases processes. The validity of this assumption is still under much investigation, since these cases were not substantially represented in the pivotal trial populations. Safety and long-term adverse effects of DES use in complex CAD patients is still yet to be fully understood.[14]

Table 2: **On-Label and Off-Label Indications for DES Use.**[14]

On-Label Indications	Off-Label Indications
Single lesion treated	>1 lesion treated
Lesion <30 mm in lenth	Total stent length >36 mm
Reference vessel diameter >2.5 mm and <3.75	Bifurcation Lesion
Lesion in native coronary artery	Coronary Artery Bypass Graft Lesion
	Baseline creatine kinase MB >3 ULN
	Maximum balloon diameter >4 mm
	Chronic Total Coronary Occlusion
	Ejection Fraction <25%
	Left Main Coronary Artery Lesion

Specific Aims and Goals

Due to fact that data from randomized control trials investigating off-label DES use is limited, coupled with evidence that DES use may be associated with stent thrombosis, concerns about the long-term safety and efficacy of DES in these scenarios is a major concern. While there are some studies that have begun to evaluate the use of DES in off-label cases, comprehensive analysis of these situations is far from complete. A study by Win *et al.* (2007) compared the clinical outcomes of DES and BMS use in varying off-label situations.[14] Their studied showed DES use might be associated with adverse effects. However this

study, along with others like it, have many limitations including the fact that they neglect to account for varying degrees of complexity amongst different lesions.[14]

The goal of this paper is provide an evaluation of clinical outcomes and safety concerns associated with off-label first generation DES use in a lesion specific manner. Due to the fact that different subsets of coronary artery lesions vary in complexity it is not effective to compile them all into one category. This paper plans to examine recent studies that compare the efficacy and safety of DES and BMS use in treatment of left main coronary artery lesions, saphenous vein graft lesions, ostial lesions, and chronic total coronary occlusions. Obtaining data for use of off-label indications in a case-by-case manner could be very helpful in making treatment decisions in a clinical setting. Additionally, this study plans to point out some of the limitations of current research in hopes of guiding future research efforts on the use of drug-eluting stents.

Drug-Eluting Stents

Design

Before discussing their use in clinical settings it is important to examine the basic design of drug-eluting stents. The design of the stent is critical for ensuring that, once implanted, it is able to maintain patency of the vessel while also effectively delivering the desired drug to the vessel wall and not drastically compromising the normal function of the vessel.[12] Most first generation stents have either a modular or slotted-tube design, and are made from inert metals, usually stainless steel. However, recent technological advances have led to some stents being made from metallic alloys, which allows for thinner struts with increase in strength.[2] They must also be collapsible, as to fit on the tip of a balloon-tip catheter and through arteries during angiography. When the stent expands it must exhibit minimal shortening and conform to the inner wall of the vasculature without deforming the vessel. Currently, both SES and PES drug eluting stents have closed cell, slotted tube design with sinusoidal struts, joined by flexible, N-shaped link segments (Figure 2).[12] Due to long-term safety concerns, specifically stent thrombosis (discussed in the next section), associated with first generation DES, a lot of current research is ongoing in an effort to evaluate stent structure and the role it plays in clinical pathologies.[12]

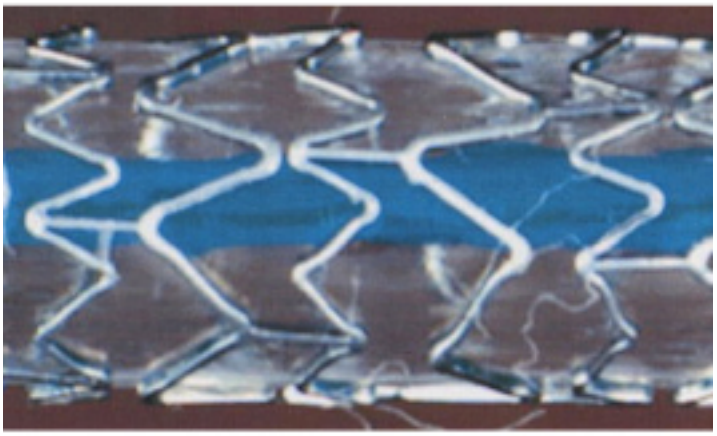

Figure 2: **Taxus Express PES.**[12]

Since the purpose of the drug-eluting stent is to deliver a drug to the local environment of the coronary lesion, the drug must be loaded on to the stent and released in a controlled manner. The most common method of loading the drug onto the framework of the stent, in current practice, is to coat the metal with a thin layer of permanent, synthetic polymer, which has been pre-loaded with a specified concentration of the desired drug. Pre-loading of the drug is performed by mixing the drug with the polymer so that it becomes “trapped” in the polymer matrix. Once the stent has been implanted in to the vessel the drug is released by simple diffusion. The type of polymer used regulates diffusion rate. Obviously the polymers used to should, ideally, be biologically inert so that it does not trigger a thrombotic or inflammatory pathway.[12] The types of drugs used in first generation DESs and their intended mode of action is discussed later on in this section.

Stent Thrombosis

Much debate and research has gone into investigating whether or not long-term safety concerns associated with the use of DES are valid. While first-generation drug-eluting vascular scaffolds like the sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) have exhibited major strides towards reducing ISR and target lesion revascularization (TLR) when compared to bare metal stents, the primary concern today is their association with late LST and VLST.[15] Late stent thrombosis is considered any thrombus that occurs between 30 days and one year post PCI, while late stent thrombosis is any thrombus occurring later than one year post implantation.[16] In 2007, the Academic Research Consortium recommended standardized definitions of stent thrombosis. These standardized definitions were adopted and used in a meta-analysis of eight different clinical trials that investigated the long-term follow-up of patients receiving treatment with SES and PES. Analysis showed that occurrence of VLST was significantly higher in cases treated with DES compared with BMS. Interestingly, and contrary to findings from earlier studies, prior to having the standardized definitions of LST and VLST, this meta-analysis found no difference between DES and BMS rates of LST. Further evaluation by other studies has since supported these findings.[12]

Although their use is relatively new to clinical practice, recent studies have more thoroughly examined some of the longer-term outcomes of patients treated with DES. Wenaweser *et al.* looked at a total of 8,146 patients who underwent

PCI with either SES or PES from the Bern-Rotterdam registry for a follow-up period of four years.[17] The cumulative incidence of definite stent thrombosis at the end of four-year follow-up was 3.3%. Additionally, the cumulative incidence of occurrence of probable and definite stent thrombosis was 5.7%. Interestingly, the annual occurrence of stent thrombosis increased at a steady 0.53% (between 0.4 and 0.6 annually) up to four years post PCI.[17] A more recent study has corroborated the Bern-Rotterdam registry data. Sarno *et al.* performed a follow-up of 21,717 patients in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR).[18] Results of this study showed an annual rate of stent thrombosis of 0.50% and a cumulative incidence of definite thrombosis of 1.3% during a two-year follow-up period.[18]

Vascular Responses to Drug-Eluting Stents

Very late stent thrombosis has had an overshadowing effect on DESs and the enthusiasm generated around their ability to reduce the rate of ISR and TLR. Understanding the mechanism of DES and their effect on the arterial wall is of paramount importance when it comes to determining whether DES or BMS is the best treatment option, especially in off-label indications. As previously mentioned, DESs were designed to combat the problem of in-stent restenosis seen in BMS. Both first generation DES, SES and PES, rely on the same approach of delivering antiproliferative drugs to the endothelium to inhibit neointimal growth. In doing so, both drugs also have an inhibitory effect on endothelial regrowth.

Sirolimus has also been linked with impairing growth and differentiation of endothelial stem cells, though whether or not this leads to endothelial dysfunction in atherosclerotic lesions is still unknown.[19]

SES and PES, the primarily used first-generation DES, both achieve reduction of restenosis by disrupting different molecular pathways involved in VSMC proliferation. Sirolimus is designed to disrupt mTOR, the target of rampamycin, and prevents the degradation of a cyclin-dependent kinase inhibitor involved in smooth muscle cell growth and differentiation in the arterial wall. Additionally, it deacitivates p70 S6 kinase pathway activity, an key regulatory step in the cell cycle response to growth factors, leading to stunted endothelial cell development.[19]

Similarly, paclitaxel acts to suppress endothelial and smooth muscle cell proliferation and migration to the vascular wall by interrupting microtubule function during mitosis. Interestingly, unlike sirolimus, paclitaxel also causes significant fibrin deposition as well as macrophage infiltration. At higher concentrations arterial wall breakdown occurs and smooth muscle cell depletion occurs. All of these factors may play a significant role in causing stent thrombosis especially since increased macrophage concentration could lead to an inflammatory response.[19]

The delayed healing of the endothelial lining in coronary arteries seen with these first generation DES is of paramount importance to understanding the association between DES and stent thrombosis. In addition to acting as a simple

structural lining to the coronary vessel, endothelial cells also provide the vasculature with regulatory factors for mediating thrombotic cascades. One study using cultured endothelial cells showed that sirolimus and paclitaxel exhibited increases in plasminogen activator inhibitor (PAI)-1, which is involved in regulating the clotting cascade.[20] Interestingly sirolimus' inhibition of mTOR also indirectly contributes to a local prothrombogenic and proinflammtory environment surrounding the stent. Inhibition of this target increases thrombin and tumor necrosis factor (TNF)-α expression in the endothelial cells. In addition to increased macrophage infiltration, paclitaxel also activate c-Jun NH_2-terminal kinase, an important signaling molecule for monocyte regulation of the proinflammatory environment. Dysfunction with anti-thrombotic pathways, in conjunction with evidence that both types of DES enhance a local proinflammatory environment, greatly enhances the risk of thrombosis.[19]

Delayed endothelial growth and dysfunction may only be one of the many factors leading to late stent thrombosis, Finn *et al.* note that none of the cases examined demonstrating LST had complete endothelialization.[19] Otsuka *et al.* examined 46 human autopsy cases exhibiting 62 separate coronary lesions treated with first generation DES for longer than 30 days. Stent thrombosis had occurred at 28 of these lesions. In their study they looked at stent strut coverage as a means of evaluating the amount of endotheliazation. Results showed that in the DES lesions, the mean number of struts, the ratio of uncovered struts to total struts per section and the average stent length without neointimal coverage were

all greater in thrombosed lesions than the non-thrombosed lesions. These findings further support the notion that DES targeting of neointimal growth may directly play a role in stent thrombosis. Furthermore, they observed that the distance between struts in thrombosed lesions was significantly less than in non-thrombosed lesions, and that in sections where average strut distance was lower there was less endothelial coverage of the stent. Decreased endothelial growth may be a function of local drug concentration and since the drugs are loaded onto the struts of the stent, shorter distances could lead to higher local concentrations. Also since the sirolimus and paclitaxel are lipophilic drugs, their retention and local concentration can be greatly affected by the differences in plaque morphology.[15] These differences in plaque morphology and disease progression are an extremely important consideration, especially extrapolating the efficacy and safety of on-label DES use to their use in off-label cases.

Off-Label Use

FDA approval of first generation drug-eluting stents was based on results from randomized clinical trial with short-term follow-up (<1 year). These trials showed extremely promising results in terms of drug-eluting stents' ability to reduce in-stent restenosis and target lesion revascularization in the coronary arteries without increases in adverse cardiac events often seen in bare metal stent use. These trials, however, were limited to, from a clinical perspective, uncomplicated coronary artery lesions (Table 2) and were not designed evaluate long-term safety concerns like stent thrombosis.[19] The advantage of on-label DES use was almost immediately accepted and their clinical use quickly expanded to applications outside of the FDA approved situations.[21] Due to the complexity of CAD in real-world practice, coronary lesions cannot be classified within the originally approved criteria more often than not. Because of this off-label applications such as DES implantation in the left main coronary artery (LMCA), bifurcation lesions, ostial lesions, chronic total occlusions, in-stent restenosis, severely calcified lesions, lesions of unapproved length, saphenous vein grafts, and use in cases of acute MI, all of which are "off-label," comprise about 60% of uses in today's practice.[19,21] Effectiveness and long-term safety of off-label DES remains a major concern because of the increasing complexity that these lesions occur in comparison to the approved indications. While some early studies suggest that there are adverse effects and reduced efficacy associated

with off-label use, very little research has compared DES and BMS in specific lesion types to provide a more comprehensive insight into off-label outcomes.[21] The following sections will take a more in-depth look at current research aimed at investigating first generation DES use in specific off-label indications and their clinical outcomes when compared with BMSs.

Left Main Coronary Artery Lesions

The left main coronary artery supplies as much as three-quarters of the heart with oxygenated blood. This means that when this vessel becomes occluded patients are usually symptomatic and at risk of major adverse cardiovascular events, which include acute myocardial infarction and death.[22] Traditionally, CAD in this vessel has been treated with coronary artery bypass surgery. PCI with DES is usually indicated in cases where the patient is at a high risk for surgical complications or is affected by other advanced pathologies such as chronic obstructive pulmonary disease (COPD).[23]

Not long after the FDA approval of DES did researchers begin looking at their efficacy in treating LMCA stenotic lesions. One of the first studies to compare the outcomes of DES to BMS in LMCA lesions was published in 2005. In this study Seung-Jung Park *et al.* observed 102 patients who received elective implantation of SESs for treatment of *de novo* LMCA lesions showing symptomatic disease or greater than 50% diameter reduction during angiography.[24] This group was compared to 121 control-group patients who

received BMS for the same inclusion criteria. Periprocedurally, there were no incidents of MACE, stent thrombosis, or the need for emergency CABG surgery in either group. Similar to the clinical trials that lead to the FDA approval for on-label use, at 6-month follow-up patients who received treatment with SES exhibited significantly lower ISR, compared to the BMS control group (7.0% versus 30.3%, $p<0.001$). Even more promising were the results at 12-month follow-up, which showed freedom from MACE (death, myocardial infarction, and TLR) was significantly higher in cases using SES compared to BMS (98.0 ± 1.4% versus 81.4 ± 3.7%, $p = 0.003$, Figure 3). There were no deaths or MI in either group, but two and 22 TLRs in the SES and BMS control groups, respectively.[24]

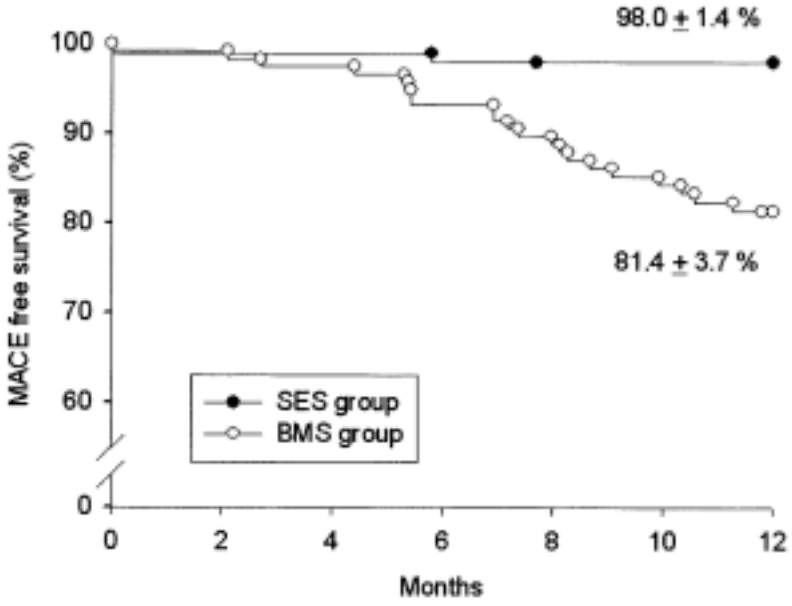

Figure 3: **Kaplan-Meier curves for one-year MACE-free survival rates in patients treated with SES and BMS for LCMA Lesions**. Figure taken from Park *et al.* (2005).[24]

The results of this early study are certainly promising in that they show the success of SES in treating LMCA lesions without any incidence of adverse effects at one year. Moreover, comparison of the baseline characterization of the lesions in each group showed that lesions treated with SES were more pathologically complex in that they exhibited more multivessel involvement, bifurcation lesions and longer lesion length on average. Other studies up to this point, specifically reports from the RESEARCH registry, had suggested favorable clinical outcomes with DES use in LMCA lesions. However, the study by Park *et al.* was one of the first with enough cases to demonstrate statistical power.[24] One major limitation of this investigation, however, is that it only followed patients up to one year after implantation. While this does provide insight into the occurrence of LST after DES use, it does not allow us to evaluate the long-term safety concerns.

More recently, Kubo *et al.* presented data from a study that followed 250 patients who received LMCA lesion treatment with DES from 2003 to 2005 for seven years after stent implantation and compared them to BMS patients.[25] Results from this study showed that the incidence of death and MI was similar between both stent groups while the incidence of TLR at seven-year follow-up was significantly less in the DES group compared to the BMS group. Specifically, TLR was significantly lower in years one through four in the DES group, and similar between both groups between years four and seven.[25] This study reaffirms the results seen in the study by Park *et al.* (2005) showing that there

was no increased MACE risk associated with DES treatment of LMCA stenosis, while having the added benefit of reducing TLR. The obvious advantage to this later study is that it provides a better insight into the long-term efficacy and safety concerns by having a much longer follow-up than the original study.

Saphenous Vein Graft Lesions

Saphenous vein aortocoronary bypass grafts (SVG) are used in almost all CAPG surgeries.[26] The saphenous vein is a long, superficial vein found in the leg that is used as the conduit for revascularization in bypass surgeries described in the previous section.[27] SVGs, unfortunately, are associated with a high rate of failure and often need to be revascularized by PCI or another CABG. However, due to the fact, that repeat CABG is more difficult than the original CAPG, stent placement in SVG lesions has become intervention of choice in clinical situations.[26] Because of the high failure rate of SVGs, as much as 10% of all PCI procedures are done on these graft lesions, yet, because of their poor representation in the early pivotal trials of DESs, they are still considered an off-label indication.[28]

While bare metal stents have proven to be more effective than the original balloon angiography interventions, there is a significantly higher risk of restenosis associated with their use in SVG lesions than in native coronary artery lesions. The development and early of success of DESs in reducing ISR, has been particularly exciting for SVG lesions. However, several factors make SVGs more

than native coronary arteries making it very difficult to anticipate whether the effects of DESs can be extrapolated. The progression of the atherosclerotic process, the mechanism of ISR with more thrombosis, and increased rate of plague progression are all characteristics of SVG vessels that make them more pathologically complex.[26,28]

As of 2008 there had been five retrospective studies that evaluated the use of DESs in treating SVG lesions in comparison to BMSs.[26] Collectively, these studies evaluated the major adverse cardiac events, ISR, TLR and target vessel revascularization (TVR) for an intermediate-term (6-12 months) follow-up. Results from four of the five studies showed that, when compared to BMS implantation, use of DESs showed significant reduction in the incidence of MACE (including MI) at both six- and twelve-month follow-up.[29–32] Furthermore, the study by Ge *et al.* demonstrated that DES implantation significantly lowered the incidence of ISR, TLR, and TVR up to six months.[29] Only one retrospective study performed before 2008 did not show significant reduction in MACE. Chu et al. found no statistical difference in the incidence of clinical events in 48 DES and 57 BMS treated lesions at one-year follow-up (21% vs 18%, respectively, $p = 0.84$).[33]

There are several drawbacks to these retrospective studies. The first is that each of them used a small number of cases, which yields a limited amount of data. Secondly, two of these studies only had a six-month follow-up period, while the other three only followed for up to one year. As described earlier, many of the

adverse effects believed to be associated with DES use often happen further from the time of stent implantation than one year. To obtain a more comprehensive picture of SVG PCI effectiveness longer follow-up time is a necessity. Lastly, these are only retrospective studies. To be able to better understand the statistical validity of the difference seen in clinical outcomes, randomized controlled trials need to be performed.

Mehilli *et al.* (2012) were one of the first to compare first generation DES and BMS treatment of SVG lesions in a multicenter randomized controlled trial powered for clinical endpoints.[28] Their study included 303 patients receiving DES treatment and 307 patients receiving BMS (610 total patients), and examined the combined incidence of MACE at a one-year follow-up. Thirty patients were lost at one-year follow up without any significant difference between the DES and BMS groups (15 DES patients, 15 BMS patients; $p = 0.97$). The incidence of the primary endpoint of death, MI, or TLR was lower in DES group (44 patients versus 66 patients for BMS), but this was mainly due to difference in TLR, not death or MI. There was no significant difference in the number of deaths or incidence of MI between the DES and BMS groups (15 versus 14 respectively). The incidence of TLR was 19 in the DES group and 37 in the BMS group, indicating almost a 50% reduction. This was largely attributed to the drug-induced effect on the endothelial layer at the molecular level seen during angiographic follow-up in about two-thirds of the cases. Results from this trial are summarized in Figure 4.[28]

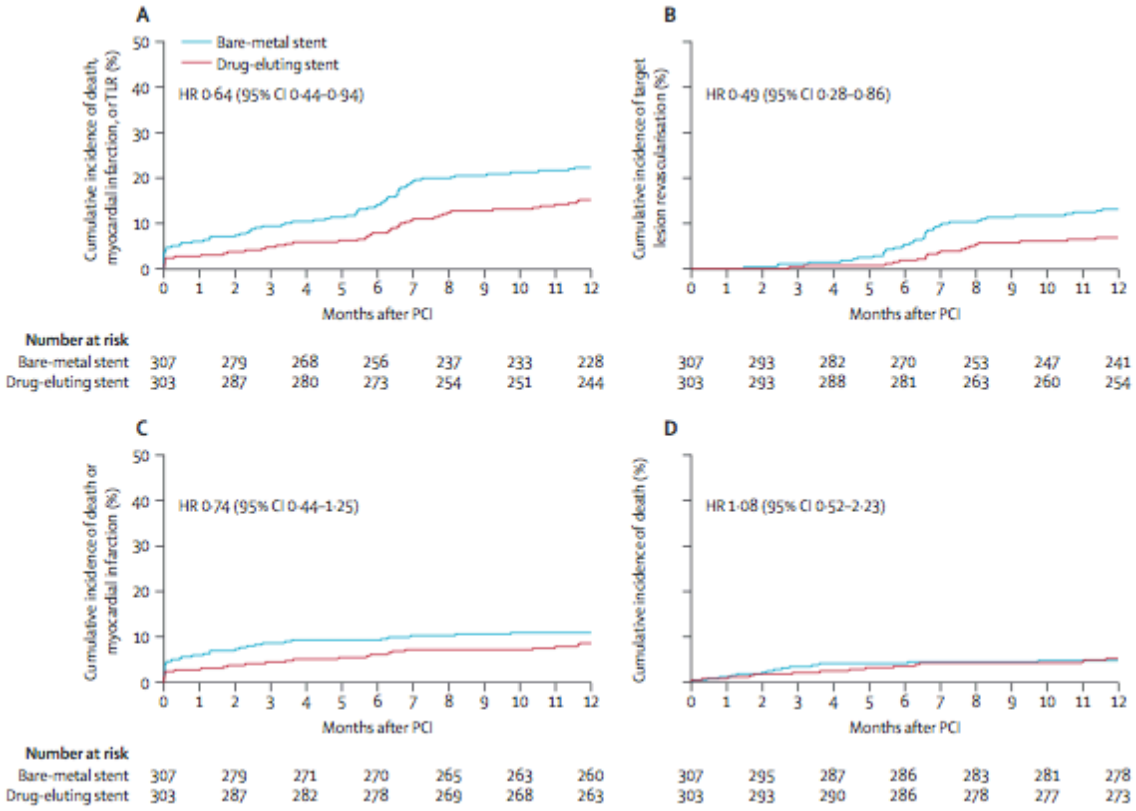

Figure 4: **One-year Cumulative rates of outcomes in patients assigned to receive DES or BMS for SVG lesions**. Kaplan-Meier Curves shown for (A) the primary composite endpoint (composite death, MI, TLR); (B) the secondary endpoint of TLR; (C) secondary endpoint of all-cause death; and (D) combined endpoint of death or MI. HR=Hazard Ratio. Figure taken from study by Mehilli *et al.* (2011).[28]

The results from this multicenter randomized control trial are promising in that they corroborate data from the previous retrospective analysis. Despite greater complexity usually associated with SVGs and the concern that DES efficacy in on-label indications not being transferable to this specific off-label scenario, their use in this trial indicate superior efficacy compared to BMS. Restenosis and failure of SVGs are a major limitation of using SVG to treat

LMCA disease. Significant reduction of restenosis associated with drug-eluting stent treatment in these trials could play a prominent role in clinical decision making of treating diseased grafts, especially considering the complications of repeat CABG surgeries.[28] One additional finding from the randomized control trial worth noting is that there was no difference in the occurrence of definite or probable stent thrombosis seen between two groups. As a matter of fact, the number of incidences was actually less in the DES group than in the BMS group (three versus five, respectively).[28] This is of obvious significance due to the fact that stent thrombosis a primary long-term safety concern of DES use in off-label scenarios. However, clinical follow-up of more than one year should be done to see if this trend continues for a longer duration.

Ostial Lesions

The next type of off-label coronary lesion that will be examined are ostial lesions. In particular one multicenter prospective observational study comparing DES and BMS treatment of ostial lesions and the results from a lesion specific meta-analysis will be evaluated. The coronary ostia are the regions where the left and right main coronary arteries originate from the ascending aorta just above the aortic valve. An ostial lesion is classified as an atherosclerotic plaque that develops at the origin of a coronary artery.[34] These specific types of lesions are one of the more pathologically complex confronted in CAD. They are usually associated with a higher degree of plaque calcification, varying blood flow

patterns at the region of the lesion, and increased elastic recoil from the wall of the aorta. However, despite these added risks, as many at 20% of cases receiving treatment for off-label coronary vessel disease indications are for ostial lesions.[34]

The first study to be examined was performed by Vasaiwala *et al.* (2012) and compares the treatment outcomes of ostial coronary lesions with drug-eluting stents and bare metal stents for a three-year follow-up period.[34] This study took a multicenter prospective observational approach and performed follow-up at one month, six months, and then at one, two and three years post-PCI. They looked at death, MI and repeat revascularization procedures as clinical end points at each follow-up. Treatment of 464 ostial lesions was attempted with BMS and 351 lesions with DES. There was no significant difference in the location or vessel diameter where lesions occurred. After completion of three-year follow-up the incidence of clinical endpoints were not different at statistically significant level. BMS treated lesions showed higher rates of death, while DES treated patients showed higher rates of MI and repeat revascularization. While not related to the long-term safety, it should be noted that periprocedural in-hospital death was significantly higher in BMS implantation, while all other MACE showed no statistical differences at this time point.[34]

The results from this study are similar to those found in a lesion-specific meta-analysis, performed by Beohar *et al*., of four reports evaluating clinical endpoints associated with DES treatment of ostial lesions. The four included

studies collected outcomes of death, MACE, MI, TLR, and thrombus at six- to 12-month follow-up and incidence of MI at three-years.[21] Rates of death, stent thrombosis, and TLR were not significantly different between patients receiving DES and BMS treatment at six- to 12-month follow-up, corroborating findings from Vasaiwala *et al.*[21,34] Unfortunately, no data on the incidence of MI in BMS cases was collected in any of the included reports, leaving statistical comparison to DES cases impossible.[21]

Chronic Total Occlusions

The final off-label indication that will be evaluated here is the use of drug-eluting stents in chronic total coronary occlusions. Specifically, the randomized Primary Stenting of Totally Occluded Native Coronary Arteries (PRISON) II study and case-control study published by De Felice *et al.* in 2013 will be examined.

Before the PRISON II study was performed, no randomized control trials had been conducted to gather data on the effectiveness of DES in chronic total coronary occlusions (CTO).[35] In this trial, 200 patients were randomly assigned to receive either BMS treatment or SES treatment for CTO. Angiographic restenosis was the primary end point of the study, with a number of secondary end points, which included MACE. Unfortunately, this randomized control trial only had a six-month follow- up term. Results did show that the sirolimus-eluting stent group did show significantly lower rates of angiographic restenosis, TLR and all major MACE at six-month follow-up.[35] With such a short follow-up period, however, it is

difficult to use the results of this study in clinical practice, especially when it is the long-term safety and efficacy of off-label DES use that is of paramount concern.

De Felice *et al.* investigated the persistence of the superior efficacy of the DES treatment of CTO, demonstrated in the PRISON II trial, at five-year follow-up. Their study consisted of 315 (298 data points collected due to 17 lost post-PCI) patients who underwent successful CTO PCI. Only patients who had occlusion of a native coronary artery for longer than three months were eligible for inclusion. Of the 315 patients, 156 received implantation with either paclitaxel- or sirolimus-eluting stents and 159 patients received BMS implantation. The endpoints included MACE (death and MI) and TLR, which were collected at one, three and five years post-procedure.[36]

As previously mentioned 298 of the original 315 patients in the study completed the five-year follow-up term. At one-year post-PCI, the incidence rate of MACE was significantly lower in patients treated with DES compared to BMS (2% versus 20%). The rate of incidence of TLR was also significantly lower in DES patients. At three-year follow-up MACE (23% for BMS versus 8% for DES) TLR incidence rates (20% for BES versus 6% for DES) were still significantly lower DES patients. At five-year follow-up, DES continued to show significantly reduced incidence of MACE when compared to BMS (15.6% versus 31%, respectively. Additionally, TLR incidence rates were still lower in DES (8%) when compared to the BMS group (33%). In addition to looking at MACE and TLR endpoints, the researchers also collected data on stent thrombosis over the five-

year period and found that stent thrombosis occurred in 12 patients with six definite VLST cases in the DES group. While there was no statistically significant difference between DES and BES stent thrombosis, there was a marked increase in the DES group compared to the BES group, which had seven stent thrombotic events and three LST events.[36]

Despite the fact that this was a case-control study and not a randomized control trial, the results found by De Felice *et al.* provide some very valuable insight into DES use for CTO in clinical practice.[36] The five-year follow-up term provides a much better look into long-term efficacy of the PCIs. Drug-eluting stents use in this study showed superiority when compared to bare metal stents in reducing the incidence adverse clinical outcomes when, making a strong case for their use in this particular off-label indication. One alarming finding of the study, however, was the fact that stent thrombosis, and in particular VLST, was higher than in the BMS group. Although the rate of restenosis was not significantly different between the two treatment groups, six cases of VLST were found in the DES group compared to zero in the BMS group. As described in previous section, increased incidence of LST and VLST in the use of drug-eluting stents in both on- and off-label situations is a prominent concern. This makes this finding particularly concerning.[36]

DISCUSSION

Conclusions

Since their approval by the FDA in 2002, drug-eluting stents have proven to be superior to bare metal stents, especially in reduction of in-stent restenosis and the need for target lesion revascularization.[14] The pivotal trials that led to the approval of DES, however, excluded patients with complex lesion pathology. This led to the approval of DES use in only simple coronary lesions presenting with a small range of characteristics. These indications are known as the on-label indications. Due to the immediate recognition of DES' efficacy in limited in-stent restenosis, their use in complex, off-label indications become common in clinical practice. Some estimates show that off-label use may account for as much as 60% of all DES PCIs.[21] However, because the pivotal FDA trials only evaluated efficacy of simple coronary lesions in a short-term follow-up period, the long-term efficacy and safety of DES in off-label situations have been a primary concern. To date, some research has shown that DES use has been associated with stent thrombosis, which can lead to MACE like death and MI. Little clinical data exists evaluating the long-term clinical outcomes of DES use in off-label indications in a lesion-specific manner.

This particular study sought to evaluate some of the current research investigating first generation DES use in four different off-label indications: coronary artery bypass graft lesions, saphenous vein graft lesions, ostial lesions,

and chronic total coronary occlusions. Evaluating the treatment outcomes in a lesion-specific manner is much more valuable in a clinical setting because it allows for a more focused insight when making treatment decisions on a case-by-case basis. Stenotic lesions, more often than not, come with varying degrees of complexity and comorbidities. Research that puts all off-label indications into one category is too broad and does not allow for the identification of problems in specific scenarios. As some of the current research has shown, DES use in some off-label situations is much more effective and safe than in others.

This evaluation of some of the current investigation of the effectiveness of first generation drug eluting stents in various off-label situations led to some interesting findings. Data from the lesion specific studies that we found comparing first generation DES to bare metal stent uses all corroborated data from the pivotal FDA trials that showed incidence rates of ISR were significantly diminished in DES groups when compared to BMS groups, in all four off-label lesion types. This reduction was expected because both sirolimus- and paclitaxel-eluting stents are designed to target pathways that lead to neointimal growth at the endothelial layer of the vasculature. The magnitude of reduction in these trials has been shown to be as much as 50-70% when compared to BMSs.[28] While the efficacy of DESs in reducing neointimal growth in off-label situations is not really at question it is important to point out that their efficacy is not reduced in these situations.

With regards to the incidence of major adverse cardiac events, included death, MI, and the need for target lesion revascularization, the studies we evaluated actually showed that, contrary to initial concerns, use of DESs in treatment of off-label lesion indications did not result in increased rates of incidence when compared to BMS treatment. In fact DES use in left main coronary artery lesions, SVG lesions and CTOs appeared to be superior to BMS use. In LMCA lesions DES treatment, Park *et al.* (2005) showed that freedom from MACE was significantly lower when compared to BMS treatment, with no incidence of death or MI at one-year follow-up.[24] Even more promising was data presented by Kubo *et al.*, which showed that the incidence of TLR in these types of lesions was still lower in DES treatment at significant level through seven-year follow-up.[25] This seven-year follow-up study is of particular importance because it is one of the first to show the long-term outcomes of LMCA treatment with DES implantation. This demonstrates that DES is a superior treatment choice over BMS for this type of lesion without risk of diminishing patient safety.

Treatment of SVG lesions has proved to be complex due to differences in disease progression when compared to native coronary arteries. These differences have made clinicians weary about safety of DES use in these types of lesions. We examined a report that summarized the results of five retrospective studies comparing DES and BMS treatment of SVG plaques. Again DES proved to significantly reduce the level of ISR and MACE at both six- and twelve-month follow-up. Results from a randomized control trial by Mehilli *et al.*

(2012), also showed similar results at one-year follow-up. Although these studies did not look past one-year post-PCI, the advantage of having data from a randomized control trial should not be undervalued. This trial was one of the first incidences in which differences in lesion pathology were accounted for by subject randomization, which further solidifies the data that shows that DES treatment of SVGs is superior to BMS treatment.[28]

Similar results were found in the incidence rates of MACE with DES treatment of CTOs. Again, results showed significant reduction in the rates TLR and MACE in DES treated lesions at six-month follow-up in the PRISON II trial.[35] These findings were further corroborated by De Felice *et al.*, whose case-control study showed that DES treatment was superior to BMS use at one-, three- and five-year follow-up.[36] The longer follow-up term provides valuable insight into the safety of DES use in this situation. One concern that arose from this study however was the increased incidence in stent thrombosis seen in DES patients. Although there was no statistically significant difference in the occurrence of stent thrombosis throughout the five-year study, six of the DES patients exhibited occurrence of VLST compared to zero cases in BMS patients.[36] Since stent thrombosis is of paramount concern when considering the use of DES treatment, randomized control trials with long-term follow-up and enough patients to demonstrate statistical significance should be performed to provide see if stent thrombosis is a legitimate concern in treatment of chronic total occlusions.

Of the four off-label lesion indications evaluated in this paper, ostial lesions were the only type in which DES treatment demonstrated clinical superiority compared to BMS. At three-year follow-up patients treated with DES and BMS showed similar rates of death, MI and repeat revascularization procedures at the target vessel. Of the four coronary lesion types examined, ostial lesions are usually the most pathologically complex, which may contribute to the findings that DES and BMS treatments were similar. Higher degree of plaque calcification, varying blood flow patterns at the lesion site, and increased vascular recoil at the lesion site are several characteristics that make PCI of ostial lesions increasingly difficult.[34] Increased lesion complexity in these cases was evident in the research seeing as how rate of successful stent implantation was much lower in ostial lesion PCI procedures compared to the other studies that were evaluated. Intrinsic lesion complexity probably caused problems in both stents, leading to similar outcomes.

A look at several current, lesion-specific studies shows that the concern over adverse clinical outcomes in off-label drug use may be somewhat overestimates. While this is only a preliminary review of some of the data that compares DES use to BES use in treatment of coronary lesions, results show that DESs may be clinically superior to BMSs in SVG lesions, LMCA lesions and CTOs in reducing in-stent restenosis and decreasing incidence of MACE. While ostial lesion treatment with DESs and BMSs showed no significant difference it is reassuring to know DES did not increase the risk of MACE in these patients.

Observations made in the studies presented in this paper, are far from complete, but they could be very valuable towards guiding research into lesion-specific outcomes in future clinical trials.

Limitations

A lot of the limitations of this paper are largely due to limitations in the studies that were evaluated for the different off-label indications. Firstly, there were very few randomized control trials that compared the efficacy of drug-eluting and bare metal stents. In this paper only a total of two randomized control trials were presented. The advantage of randomized control trials, especially when comparing cases in clinical situations, is that they randomize which patients will be allotted into the different treatment groups, which eliminates baseline differences in patient characteristics. To give an example, in the study by Park *et al.* (2005) comparing DES and BES treatment of LMCA lesions, patients in the SES group were found to have more advanced disease progression than those in the BMS group. These differences included more multivessel coronary artery disease, more bifurcation lesions, longer lesion length, and smaller reference diameter. All of these characteristics could have a significant confounding effect on the clinical outcomes observed in the treatment group.[24]

Another limitation of the studies presented here was the duration of follow-up. As mentioned, one of the main concerns with DES treatment is the long-term

safety of these devices when implanted in off-label situations specifically with regards to late and very late stent thrombosis. A lot of the studies included in this paper, and many that were excluded, only followed patients for a six-month or one-year period. The obvious limitations of these studies are that they do not follow patients for enough time to gain comprehensive insight into the long-term treatment outcomes. In real world clinical situations it is of paramount importance for treatment of CAD to have a lasting clinical effect. It has been well established already that DES are superior to BMS in reduction of short-term outcomes like in-stent restenonsis. A lot of the current studies fail to follow patients for a long enough duration to have a clinical significance.

One of the limitations of this paper is that it is not entirely comprehensive. Only four of the off-label indications for drug eluting stents were chosen for evaluation. Decision to do so was based on several factors. One was that these off label situations were very commonly encountered in clinical practice. The second was that at least some long-term data was obtainable for these off-label indications. Many of the off-label indications that were excluded had data of treatment with a follow-up period of six months or less, which was deemed too short to have relevance in this evaluation. Finally, these four off-label scenarios were chosen because there was research that directly compared DES use to BMS use in each of these situations. While many studies looked at DES use in other off-label indications, they often times compared the efficacy of two different DES or looked only at DES in their analysis.

Another limitation of this paper is that it only looked at the efficacy and long-term clinical outcomes of first generation drug-eluting stents, specifically sirolimus- and paclitaxel-eluting stents. Currently, there are second and third generation devices that use different drugs and stent platforms which are being used in trials that have shown promising results in eliminating some of the safety concerns with earlier stents.[12] However, because most of the research investigating use of these drug-eluting stents is in relatively early phases, they were excluded from this paper.

One final limitation of this study is that we did discuss the use of anti-clotting medication post PCI. Due to the fact that many studies had a high level of difficulty evaluating compliance with drug therapy after discharge from the hospital, data collection was far too inconsistent to be considered in this paper. However, this is certainly an area of future research that should be evaluated.

Future Directions

In continuance of what has been observed in this paper, future research should focus on performing randomized control trials of different off-label indications that are commonly encountered in clinical practice. These trials should include a large population of patients to have enough statistical power to allow results to be significant. Additionally, these trials should have a long-term follow-up of at least five years in order to allow for the evaluation of long-term efficacy and safety of DES use in specific off-label situations. Since off-label

indications comprise a large amount of the PCI procedures in current practice, having data from randomized control trials will be extremely valuable in whether or not to use DESs in treatment of different coronary artery disease patients on a case-by-case basis.

Finally, as technology continues advance in the design of drug eluting stents, it is important that these stents be evaluated in studies similar to those described for first generation drug-eluting stents to evaluate their safety and long-term efficacy in different clinical scenarios. Of particular interest is the polymer-free drug eluting stent. The durable polymer currently found on first generation DESs may play a role in delaying vascular healing leading to some adverse effects in the vasculature. Currently, investigation of the polymer-free Biolimus A9-coated stent in clinical cases is taking place.[2] These research efforts should continue in an on-going effort to make stents as safe and effective as possible.

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