A Comparison between Bare Metal Stents and Drug-Eluting Stents with Possible Complications of Percutaneous Coronary Intervention


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Abstract

Limitations of percutaneous coronary intervention have been partially overcome with the advent of Drug-eluting stents (DESs), which have offered better results than bare-metal stents (BMSs), and the DESs of second-generation surpass the clinical results of first generation ones. Stent thrombosis (ST) and in-stent restenosis (ISR) are the major late complications of percutaneous coronary intervention. There has been a downward trend in the incidence of ST with the advent of newer stent designs and dual antiplatelet therapy. A few long-term follow-up studies of Biodegradable Vascular Scaffolds failed to show significant benefits, besides showing an increased incidence of stent thrombosis and thus warrant further research. ISR with bare-metal stent implantation is relatively stable, with an early peak of intimal growth and later regression. In contrast, ISR in the case of DES is characterized by a “late catch-up” phenomenon with intimal hyperplasia during long-term follow-up. Neoatherosclerosis with chronic inflammation has become known to play a major role in late stent failure with both BMSs and DESs.

ABBREVIATIONS

CAD: Coronary Artery Disease; PCI: Percutaneous Intervention; DES: Drug-Eluting Stents; BMS: Bare Metal Stents; OCT: Optical Coherence Tomography; IVUS: Intracoronary Ultrasound

METHODS

In order to assess fully the risks and outcomes in the patient with a coronary stent, we first searched the literature for articles giving any indication of current knowledge and clinical practice. Secondly, we examined the literature to identify appropriate case reports and observational series of such patients. Searches for information regarding the issues surrounding the management of these patients were performed using Medline (WINSPR S 5.0) and Pubmed (National Library of Medicine; www.pubmed.gov) with keywords including: percutaneous coronary intervention, balloon angioplasty, coronary artery stents, bare metal stent, drug-eluting stent, cardiac, coronary artery bypass grafting,
Coronary revascularization, pathophysiology, stent occlusion, stent thrombosis, re-stenosis, coagulation, hypercoagulable state, bleeding, haemorrhage, platelet function, monitoring tests, platelet aggregation, thrombocytopenia, platelet transfusion, antiplatelet agents, aspirin, thienopyridines, clopidogrel, ticlopidine, glycoprotein IIB/IIIa receptor inhibitors, loading dose, heparin, low molecular weight heparin, flurbiprofen, aprotinin, antifibrinolytics, recombinant factor seven, neuro-axial block, regional anaesthesia, recommendations, and guidelines.

**INTRODUCTION**

Chronic coronary heart disease (CHD) and acute myocardial infarction are endemic conditions. Coronary artery disease (CAD) is the pathological process of atherosclerosis in coronary arteries and it can be either asymptomatic or symptomatic. 1 out of every 5 deaths in the developed world is due to coronary artery disease, making it the single largest cause of death in developed world [1] and is also one of the leading causes of death in developing world [2]. Thus CAD poses both a significant social burden and economic burden on the healthcare system throughout the world. The rate of therapeutic intervention in CAD patients is 40% [3,4].

Percutaneous coronary intervention (PCI) with coronary stents has become the most widely accepted treatment for symptomatic coronary artery disease and has broadened its applicability [3]. The emergence of drug-eluting stents (DES) in particular has been a major breakthrough in the field of interventional cardiology, which led to significant improvement in the results compared with bare metal stents (BMS) [4]. Drug-eluting stents in combination with antiplatelet and periprocedural antithrombin agents resulted in improved short-term outcomes, [5] but two major late complications namely stent thrombosis (ST) and in-stent restenosis (ISR) still persist even with DES [6]. The incidence of stent thrombosis has significantly reduced with DES compared to BMS, but when such a complication arises, patients present with ST-elevation myocardial infarction (STEMI). [7] Whereas, in-stent restenosis (ISR) which was previously thought be a benign event is now being related to the occurrence of an acute coronary syndrome. Development of neatherosclerosis post-stent placement can be studied with certain in vivo imaging studies, among which intracoronary optical coherence tomography (OCT) is considered to be ideal with better resolution compared to other techniques like intracoronary ultrasound (IVUS) [8].

**Coronary stents**

**Bare Metal Stents (BMSs):** Bare metal stents are coronary stents without any coating. They are primarily classified on the basis of the delivery system and structural design. BMSs can either be self-expanding or balloon expandable and are classified into three basic design groups: coil stents (circular coil-shaped metal wires or strips), slotted tube stents (metal tubes with laser cuts), tubular mesh stents (wires arranged to form a tubelike meshwork) [9]. They can be further classified based on stent composition (stainless steel, nickel chromium alloy, cobalt chromium alloy), strut patterns and stent dimensions.

Most of the currently available BMSs are made of cobalt-chromium alloy, allowing better navigability and greater mechanical strength. Another recent advance is the development of platinum chromium BMS, with improved mechanical performance compared to cobalt-based stents [10].

Although studies have shown better long-term outcomes with DES compared to BMSs, [11] BMSs are still being considered in certain scenarios like a vessel with a large diameter, high bleeding risk and situations preventing the use of dual antiplatelet therapy (DAPT) for recommended duration. In elderly patients undergoing PCI DES with a short duration DAPT is proven to have better outcomes than BMS with a similar duration of DAPT [12].

**Drug Eluting Stents (DESs)**

Drug Eluting Stents are metallic coronary stents (stainless steel or cobalt chromium), with a polymer coating embedded with an anti-proliferative drug, which helps in drug elution into the vessel wall over a period of time after stent implantation.

**First-generation DESs:** The sirolimus-eluting stent (SES-CYPHER) was the first DES to be approved by the FDA in 2003. Sirolimus is an antifungal macrolide, which by controlled release from G1 to S phase, prevents the progression of the cell cycle from G2 to M phase by stabilization of microtubules. This results in the prevention of cellular proliferation and neointimal hyperplasia. Studies like RAVEL trial [13] and SIRIUS trials [14] established the superiority of SES over BMSs in the reduction of rates of Target Vessel Revascularization (TVR) and in-Stent Restenosis (ISR). Likewise, PES was shown to be better compared to BMSs. Metaanalysis study comparing the efficacy of both these DESs showed better results with SES compared to PES in terms of inhibition of neointimal hyperplasia and prevention of in-stent thrombosis [16].

**Second-generation DESs**

Everolimus-eluting stents (EES) contain everolimus which is a cell cycle inhibitor derived from sirolimus COMPARE trial, [17] a randomized study comparing EES with paclitaxel-eluting stent (PES) showed that the rates of myocardial infarction, TVR, stent thrombosis and major adverse cardiac events (MACE) at 5 years were lower in the EES patient group. This combined with results of other studies like SPIRIT trials has resulted in a major shift away from the use of the paclitaxel-eluting stent and replaced by EES. Whereas EXCELLENT trial, comparing the efficacy of EES with sirolimus-eluting stent (SES) showed similar results in both the patient groups but a recent update of this study showed results in favor of EES in terms of delayed safety events [18].

Another available second-generation DES is Zotarolimus-eluting stent (ZES). The superiority of this stent compared to bare metal stents in the clinical outcomes and long-term reduction of the rate of target vessel revascularization was clearly proven in the ENDEAVOR II trial [19]. Final 5-year follow-up results from ENDEAVOR III, [20] a randomized trial comparing ES-ZES with SES showed that the rates of target lesion revascularization and target vessel failure were similar in both groups, whereas the
incidence of major adverse cardiovascular events (MACE) was lower with ZES. Similar results were shown in the late follow-up study of ENDEAVOR IV trial [21] comparing ES-ZES with PES. Second ZES is Endeavor Resolute (ER), with a different polymer named BioLinx and it features extended release of drug from the stent. A recent multicenter observational study in patients with multi-vessel coronary artery disease comparing the benefits of ER and ES showed similar safety profile and outcome results during a 12-month clinical follow-up [22].

Other recent ZESs which are considered by a few as third generation DESs are the Resolute Integrity with better deliverability and conformability and the Resolute Onyx with greater visibility, low crossing profile, and better delivery system [23,24].

**Recent Advances**

Despite the majority of the previously mentioned studies with favorable results, an incidence of hypersensitivity reactions associated with DES is an area of active debate [25, 26]. A few studies also report fracture of ZESs leading to in-stent restenosis and late thrombosis [27,28]. Knowledge of these effects prompted extensive research for the development of the advanced completely biodegradable scaffolds and biodegradable polymer coated stents.

**Biodegradable Vascular scaffolds (BVS):** Biodegradable vascular scaffolds (BVS) represent a major advance in the field of percutaneous coronary intervention [29]. They are similar to DESs in terms of providing mechanical support to prevent elastic recoil and drug delivery to prevent restenosis but have an additional advantage of complete resorption of the stent over years allowing complete vascular healing and restoration of normal endothelial structure and function.

Absorb and Dissolve are currently available. A Series of five randomized ABSORB trials studied the efficacy of Absorb BVS, eluting everolimus. Both ABSORB I: Cohort A and Cohort B (with improved scaffold design) trials [30, 31] demonstrated good efficacy and safety profile of Absorb BVS.

Another advance in the field of BVS is the introduction of metallic bioabsorbable magnesium based stent that degrades by oxidation-reduction reactions.

**Biodegradable Polymer-Coated Stents:** Several first and second generation DESs are now available with biodegradable polymers like the Nobori biolimus eluting stent, BioMatrix biolimus eluting stent, Synergy everolimus-eluting stent, Desynevo biolimus eluting stent, Ultimaster sirolimus eluting stent, and Jactax paclitaxel-eluting stent. Short-term results of various studies failed to show a significant reduction in the rates of myocardial infarction and stent thrombosis with biodegradable polymer DESs compared to permanent polymer DESs [32].

**Complications**

**Stent Thrombosis (ST):** Stent thrombosis is a relatively uncommon complication of PCI but it can be fatal. It is multifactorial. Lesion related factors include ruptured plaques and necrotic lipid cores (in patients with ST-elevation MI), length, diameter and location of the lesion. Patients with the acute coronary syndrome are particularly at higher risk of ST either with BMS or DES. Patients with lesions located at bifurcations and in LAD are highly predisposed to stent thrombosis. Among the procedure-related factors, incomplete stent strut coverage poses a major risk for ST due to poor endothelialization of the implanted stent. Other procedure-related factors include stent malapposition, stent under expansion, and usage of longer stents. Patient-related factors include advanced age, various medical comorbidities and failed compliance with dual antiplatelet therapy. These factors in addition to selection and continuation of dual antiplatelet therapy play a role in the occurrence of late ST. Delayed re-endothelialization and late stent malapposition saw with first-generation DES pose a significant risk for late stent thrombosis. Neoatherosclerotic plaques develop in DES earlier than BMS and the concept of neo-atherosclerosis is relatively new compared to other causes [33].

**Clinical presentation of ST:** Clinical presentation of ST varies from unstable angina to ST elevation MI often leading to death in a majority of cases.

**Drug Eluting Stents and ST:** Although the first-generation DES significantly decreased cardiac mortality there were concerns regarding the increased incidence of late stent thrombosis, particularly after the discontinuation of dual antiplatelet therapy.

**In-Stent restenosis (ISR)**

Besides stent thrombosis, ISR is another major limitation of PCI with coronary stenting. ISR is defined as re-narrowing of vessel diameter of more than 50% as evidenced by coronary angiography or more than 70% of the reference vessel area in cross section on intravascular imaging. ISR may develop due to the early elastic recoil of the vessel, constrictive vascular remodeling or neo-intimal hyperplasia. Multiple factors are responsible for the enhanced pathogenesis of ISR including patient-related (increasing age, diabetes) and procedure-related factors (small vessel diameter, longer stents, usage of BMS and first-generation DES). Similar to other causes of stent failure, like stent thrombosis, neoatherosclerosis also plays a role in the pathogenesis of ISR. This, in particular, is greater with DES compared to BMS [34].

**Clinical Presentation of ISR**

When compared to ST, the clinical course of ISR is relatively benign in most cases, presenting commonly as a progressive recurrent angina.

**Drug-Eluting stents and ISR**

Risk of ISR is higher with BMS implantation ranging from 20 to 40 percent. With the introduction of the incidence of ISR has significantly come down.

**Abruption Closure**

The incidence of abrupt closure has declined from 3% in the balloon angioplasty era to 0.3% in current days. The common mechanism of abrupt closure is dissection followed by thrombus formation while vasoconstriction is a rate mechanism of closure. Patient-related factors in abrupt closure include unstable angina, multi-vessel disease, female gender, and chronic renal failure.
Abrupt closure results in acute ischemia manifesting as ECG changes, hypotension, bradycardia, chest pain, and ventricular arrhythmias. The priority lies in stabilizing hemodynamics and relieving ischemia [35].

**DISSECTION**

Dissection is split or tears in the wall of the artery which compresses or compromises the lumen of the artery resulting in a reduced flow. This complication should be recognized early as initial treatment improves vessel patency and patient outcome.

In the current era, the main causes of iatrogenic coronary dissection are guided catheter-induced dissection, spiral dissection, and stent edge dissection [36].

Common types of dissection include:

a) Guide catheter dissection - associated with deep engagement of large catheters into smaller, diseased arteries.

b) Spiral dissection - can be spontaneous or iatrogenic. Iatrogenic dissection is much more common, which may result from forceful contrast injection into an unrecognized tissue plane following catheter-induced injury.

c) Stent edge dissection - The exact mechanism of stent edge dissection is unknown, but it has been hypothesized that a false lumen is created after initial disruption from stent struts deployed at high pressure [36].

**CORONARY PERFORATION**

Coronary perforation, defined as evidence of extravasation of contrast medium or blood from the coronary artery, is a serious complication with an incidence of less than 1.0%. Responsible for 20% of cases referred for emergency CABG.

Coronary perforation is induced mainly due to guidewire penetration and vessel rupture. Recanalisation of CTO has become a common setting for perforation, usually due to small guidewire perforations with increasing use of stiffer and hydrophilic guide wires [37].

**CORONARY SPASM**

Recent studies have shown impaired coronary vasomotion in the persistent region and development of coronary artery spasm (CAS) after sirolimus-eluting stent and paclitaxel-eluting stent implantation.

CAS in the absence of obstructive coronary disease is an inflammatory process characterized by the presence of inflammatory markers like monocytes and high levels of C-reactive protein [38].

**NO-REFLOW PHENOMENON**

There is a group of patients who seem not to benefit fully from the prompt restoration of antegrade flow, as they fail to show resolution of the indirect signs of ischemia such as electrocardiographic (ECG) changes and improvements in perfusion abnormalities. These patients also present an angiographic phenomenon characterized by evidence of slow-flow in the affected vessel (Thrombolysis in Myocardial Infarction [TIMI] flow equal to or less than 2) and lack of contrast uptake “blush” by the subtended myocardium, leading to a potential dissociation between coronary revascularization and myocardial perfusion in STEMI.

Originally, it was thought prolonged ischemia and extensive myocardial damage led to microvascular (capillary bed) damage, resulting in incomplete reperfusion. More recently, other factors have been thought to play a role in the development of no-reflow, specifically distal embolization of the plaque/thrombus following balloon inflation [39].

**PSEUDONEUROUSYM**

The development of a coronary pseudoaneurysm after stent deployment is a rare phenomenon, and little is known regarding the prognosis. When a drug-eluting stent (DES) is used, this complication poses a potentially serious problem due to the inhibitory effect of the drug on healing within the surrounding vascular tissue [40].

**CONCLUSION**

Stent thrombosis and In-stent restenosis still remain major challenges following the percutaneous coronary intervention. Second generation DESs have overcome the drawbacks of BMS and first-generation DES, up to a certain extent. Bioresorbable polymers and bioresorbable vascular scaffolds still require evidence from extended long-term follow-up studies, in view of recently reported an increased incidence of thrombosis. Neoatherosclerosis plays a significant role in the development of late stent failure due to various causes.

**REFERENCES**


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