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Review Article

Drug eluting stents: To evolve or dissolve?

Brig Prashant Bharadwaj, VSM[a,*], Gp Capt D.S. Chadha[b]

[a] Consultant (Medicine & Cardio), Military Hospital (Cardio Thoracic Center), Pune 411040, India
[b] Senior Adviser (Medicine & Cardio), Military Hospital (Cardio Thoracic Center), Pune 411040, India

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ABSTRACT

Currently, percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is the most commonly employed modality in the treatment of patients with coronary artery disease. PCI has come of age over the last four decades with enormous forays in the technology and drugs which have greatly enhanced its capability. Angioplasty and bare metal stents were plagued by high failure rates on account of restenosis leading to repeat revascularization procedures. Insights into pathophysiology of instent restenosis (ISR) and neointimal hyperplasia triggered the development of DES. The dreamlike remarkable reduction in ISR with DES was enthusiastically welcomed. Soon thereafter emerged the spectre of very late stent thrombosis (VLST) with DES. VLST was a new entity seen predominantly with DES and pathological insights as to the cause was instrumental in the development and efficacy of new generation DES. This review will highlight the evolution and present day DES for coronary interventions.

Introduction

Percutaneous coronary intervention (PCI) with stenting today represents the standard of care in the treatment of patients with coronary artery disease. The first path-breaking modality to treat coronary stenosis was percutaneous coronary angioplasty (PTCA) in 1977 with a catheter improvised in his kitchen by Gruntzig.[1] PTCA was fraught with a 50% failures at one year which was on account of acute elastic recoil, plaque prolapse and constrictive remodelling on account of balloon mediated vascular injury. This balloon-mediated injury had an initial phase similar to wound healing with platelet adhesion, fibrin deposition and cellular infiltrate to be followed by a subsequent phase re-endothelisation, smooth muscle cell (SMC) migration and proliferation.

Bare metal stents (BMS) – the rise and fall

The quandary of restenosis with PTCA was addressed by the next innovation in the form of a metallic stent implant in the coronary in 1986 by Sigwart et al.[2] The deployed stent promptly sealed disrupted plaques and splinted angioplasty induced dissection with resultant plaque stabilisation. The stanchion provided by the metal platform resulted in acute gain in vessel calibre and offset the vessel recoil and constrictive remodelling. This resulted in significantly reduced rates in restenosis

* Corresponding author.
E-mail address: prashantbharadwaj@gmail.com (P. Bharadwaj).
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to 20% (11–40%) with BMS. Stent implantation was quickly adopted as the default strategy in PCI but soon lost their sheen on account of two drawbacks in the form of stent thrombosis (ST) and instent restenosis (ISR).

(a) *Stent thrombosis (ST)*: ST is the acute and complete thrombotic occlusion of a coronary stent. ST occurred in up to 25% of the cases within the first 14 days in early experience.[3] ST is a very serious clinical event typically resulting in ST-elevation myocardial infarction (MI) in 70–80% of cases[4] with mortality rates that may be as high as 20–40%.[5] Aggressive initial attempts to tackle ST with high dose heparin, dextran and urokinase infusions lead to considerable morbidity and mortality with major bleeding occurring in up to 9% of the cases. Two developments were salutary in reducing the incidence of ST to less than 1%: firstly the institution of dual anti-platelet therapy and secondly the use of high balloon pressures during stent deployment to maximise their apposition. The battle of early stent failures on account of ST was won and this unfolded the second worrisome area of ISR.

(b) *Instent restenosis (ISR)*: The delayed temporal response to the higher degree of vascular injury on account of implantation of stents in the first month initially comprises mild luminal thrombus formation on account of platelet aggregation and fibrin deposition to be followed by inflammatory cellular infiltrate, SMC migration and collagen deposition that constitutes neo-intimal hyperplasia (NIH). NIH with BMS peaked at 6 months and was the cause of ISR. The clinical presentation of ISR is usually angina but in a third may be an acute MI.

The next forays were targeted against NIH. The therapeutic option of controlling the cellular proliferation was intuitive and was accomplished and ensured by local delivery of anti-proliferative drugs. Concomitantly it was important to have the optimal and desired drug concentrations coinciding with the period when NIH occurred. This temporo-spatial profile of drug delivery was done by coating the metal platform with a polymer which in turn served as the drug delivery carrier. The evolution of PCI is given in Fig. 1.

First generation drug-eluting stents (DES) – the new kid in town!

The first DES to be launched were in 2002 and they were the sirolimus eluting stent (SES) – Cypher® stent and the paclitaxel eluting stent (PES) – Taxus® stent. Early DES versus BMS trials demonstrated DES superiority with significantly reduced rates of target lesion revascularisation (TLR) and angiographic restenosis to less than10% in the RAVEL trial,[6] the SIRIUS trials,[7] and the TAXUS trials.[8] Consequently, both first-generation DES, the SES and the PES received approval by the regulatory bodies in Europe and the USA in 2002/2003. Following the success of initial clinical trials of first-generation DES there was a rapid and fervent expansion to their use in almost 90% of PCI over the next 3 years. Simultaneously these DES were also used for 'off-label' indications in complex lesions such as small vessels, long and tortuous lesions, chronic total occlusions and left main disease. The euphoria was tempered by the occurrence of ST after a year of implantation of these DES called very late stent thrombosis (VLST). Case reports and preliminary data from the large Swedish Coronary Angiography and Angioplasty Register (SCAAR), and other groups[9] noted a significant increase in VLST. The 4-year rates of VLST were 1.2% in SES vs 0.6% in BMS ($p = 0.20$) and 1.3% in PES vs 0.9% in BMS ($p = 0.30$). Furthermore, the risk of VLST (0.4–0.6% per year) continued for another 5 years. The causes of VLST were ascribed to a distinct and different kind ISR seen with DES as compared to BMS as shown in Table 1. The DES ISR delayed healing, impaired endothelisation, allergic reactions, inflammation, vascular dysfunction and neo-atherosclerosis in the stented segment of the coronary artery. Among these neo-atherosclerosis was a new and a perilous phenomenon.

Table 1 – Instent restenosis – BMS vs DES.

	BMS	DES
Smooth muscle cell (SMC) content	Rich	Hypocellular
Proteoglycan content	Moderate	High
Peri-stent inflammation	Occasional	Frequent
Complete endothelisation	3–6 months	Up to 4years
Neo-atherosclerosis	Infrequent and late	Frequent and accelerated
Angiography	Diffuse pattern	Focal pattern
Late luminal loss	6–8 months	Up to 5 years

Neo-atherosclerosis

Neo-atherosclerosis is the development of an atherosclerotic plaque inside an implanted coronary stent. Histopathologically, the process is characterised by three main stages: (i) early foamy macrophage infiltration, (ii) manifest atherosclerotic plaque development, and (iii) necrotic core plaque formation with or without thin fibrous caps. Although neo-atherosclerosis is also observed after bare metal stenting, it occurs earlier and more frequently after stenting with DES (35% vs 10%). The primary cause is the delayed and variable endothelisation

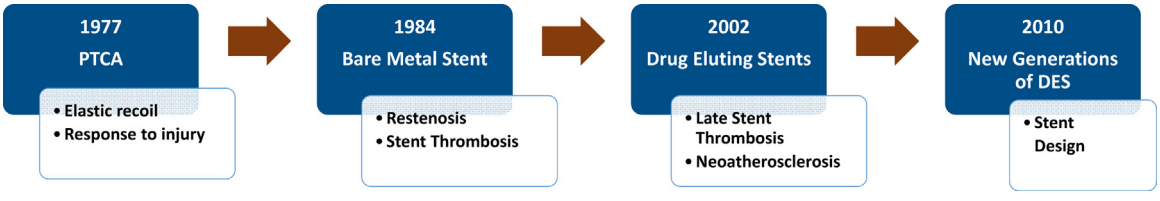

Fig. 1 – The evolution of PCI.