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Review

Novel bioabsorbable polymer and polymer-free metallic drug-eluting stents

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ABSTRACT

The introduction of drug-eluting stents (DES) significantly reduced angiographic restenosis and the clinical need for revascularization following percutaneous coronary intervention. However, concerns remain regarding the long-term safety and efficacy of DES. The use of durable polymers for drug elution that have limited biocompatibility is thought to contribute toward DES failure, by promoting an adverse local inflammatory response and vascular toxicity. Biodegradable polymer and polymer-free metallic stents represent two novel technological solutions to this challenging clinical problem. This review summarizes the available clinical evidence supporting the use of either biodegradable polymer or polymer-free DES platforms.

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Introduction

Coronary stents were introduced >25 years ago in an effort to mitigate the risk of acute vessel closure and reduce recoil/early restenosis associated with 'plain old balloon angioplasty' (POBA) [1]. Although short-term procedural outcomes were improved, bare-metal stents (BMS) were prone to development of in-stent restenosis (ISR), a new entity resulting from diffuse proliferation of neointimal tissue within the stented segment [2]. Early angiographic studies of BMS found ISR rates around 25% [3], fueling the need for therapies that inhibit neointimal growth. The addition of anti-proliferative drug coatings to the metallic stent frame, carried in a permanent 'durable' polymer (DP) layer, heralded the arrival of the drug-eluting stent (DES). Anti-proliferative agents, including sirolimus and paclitaxel, were the most successful of initial attempts to prevent neointimal cellular replication by cytostatic and cytotoxic actions [4]. Early randomized trials confirmed significant reduction in rates of ISR with use of DES, principally due to significant reductions in neointimal tissue volume [5,6]. These results led to widespread adoption and use of DES, resulting in percutaneous coronary intervention (PCI) becoming the most commonly performed invasive medical procedure worldwide.

Concerns with drug-eluting stent use

Despite clear reductions in ISR rates following DES implantation, pooled data from randomized trials suggested that rates of death and myocardial infarction (MI) at long-term follow-up were not reduced, when compared with BMS [7]. The long-term safety of DES was then questioned when registry data and meta-analyses [8,9] began demonstrating increased incidence of MI and very-late (>1 year after implantation) stent thrombosis (VLST) [10,11] with estimated annual risk of VLST approximately 0.2–0.6% and importantly not diminishing with time [12]. Although VLST remains infrequent, it is associated with very poor outcomes [13]. Furthermore, despite widespread use of DES, patients continue to experience high rates of target lesion revascularization (TLR), with studies showing that around 1 in 10 patients receiving early-generation devices required repeat procedure within 5 years [14,15]. Lack of long-term efficacy and device safety concerns, coupled with increasing urgent/emergent presentations and uncertainty of the efficacy of PCI compared with optimal guideline-driven medical therapy [16], have led to a net downturn in elective PCI procedure volume.

Drug-eluting stent failure

DES failure is a multi-factorial process involving patient-specific, pharmacological, procedural, and mechanical/biological factors [17]. Although many of these factors cannot be modulated, precise DES implantation and optimization during implantation is crucial. Studies have consistently found that DES under-expansion is not only common, but may be associated with increased risk of ISR [18] and stent thrombosis (ST) [19]. Geographical miss, where deployed stents fail to cover the entire target plaque longitudinally, also appears to be important with such lesions often exhibiting higher rates of adverse events [20,21]. Mechanical factors, related to the stent itself, also appear to play a role; stent fracture is associated with restenosis in ~60% of cases [22], and there are reports that microscopic disruption (e.g. peeling or cracking) of the polymer/drug coating may result in failure to inhibit neointimal growth and lead to restenosis [23]. Increased stent strut thickness also increases restenosis in BMS [24,25], as thick struts induce subtle alterations to coronary blood flow, resulting in low or oscillatory wall shear stress regions downstream of the strut that act to promote platelet accumulation, cytokine release, and neointimal growth [26]. Late DES failure may also be precipitated by the development of in-stent neoatherosclerosis, which can be identified through use of invasive imaging modalities including optical coherence tomography [27]. Although neoatherosclerosis appears more common following BMS [28], macrophage infiltration and necrotic core formation has been observed as early as 4 months after DES implantation [29]. As such, neoatherosclerosis remains an ongoing safety concern and further research into its mechanism and strategies to mitigate risk are required.

Delayed arterial healing, following PCI with DES, is also thought to be an important driver for adverse clinical events [30,31]. A combination of clinical, pathological, and animal studies have demonstrated that poor arterial healing, often characterized by delayed re-endothelialization, hypersensitivity, eosinophilic infiltration, and chronic inflammation, is associated with VLST [32,33]. Although the exact pathological processes underlying hypersensitivity reactions and delayed arterial healing remain obscure, one potential etiological agent implicated in this phenomenon may be the durable polymer left coating the stents when drug-elution has completed [32].

In the hope of improving clinical outcomes, considerable effort and resources have been committed into designing technologies that might negate the requirement for durable polymers in metallic DES manufacture. In effect, leaving a BMS after the time required for the drug-elution to be completed. This review will detail those platforms that are currently, or soon to be, commercially available and explore the existing clinical data supporting their use.

Biodegradable polymer drug-eluting stents

As DP-DES have been implicated in delayed arterial healing, developing a polymer that would disappear after drug elution may be advantageous. This was highlighted by data from the SCAAR registry, where the annual risk of VLST was lower in BMS compared with DES after 1 year [34] with several manufacturers having developed biodegradable polymer (BP)-DES over recent years. A list of existing commercially available systems can be found in Table 1, together with their material construct, drug delivered, strut thickness, and biodegradable polymer utilized where known.

Biomatrix

The Biomatrix DES (Biosensors Europe, Morges, Switzerland) is a thick-strut (150 μm) 316L stainless steel stent with a coating composed of 50:50 poly-l-lactic acid (PLLA) and biolimus-A9 mix. Biolimus is approximately ten times more lipophilic than sirolimus, thereby easily crossing the cell membrane to achieve

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