Introduction
Drug-eluting stents (DES) have proven to be highly beneficial in that they dramatically reduce the restenosis rates relative to bare metal stents (BMS). Local delivery of antirestenotic drugs from stent scaffolds is achieved through polymeric coatings. The polymers employed are either biostable or bioabsorbable, although, currently, most of the DES that are on the market are based on biostable polymers (Table 1). Such coatings have to be robust, offer effective drug-release kinetics and, above all, be biocompatible. The following article discusses the role played by polymers in providing these various DES attributes.

Background
The concept behind DES technology is the controlled release of a chemotherapeutic agent from a structurally supportive metallic or organic stent backbone. Arguably, the choice of drug, control of its release kinetics and subsequent tissue effects are the most important components of this technology, and it is the polymer coating that dictates the release kinetics. To date, two different classes of drugs have been successfully employed on DES platforms in order to inhibit neointimal overgrowth:

- The ‘limus’ family of antimitotic drugs – such as sirolimus, zoratolimus and everolimus – which halt cell-cycle progression in the G1 phase.
- Paclitaxel, a microtubule-stabilising drug that interrupts mitotic division in late metaphase, resulting in cell-cycle arrest.

Polymer coatings utilised in coronary drug-release systems
Medically, like other implantable biomaterials, polymers are used typically to provide mechanical support or to serve as a vehicle for the delivery of bioactive agents. In coronary stenting, polymers have been tried as a lone component of a stent backbone, though generally this use has been limited due to inferior radial strength compared with metal alloy stents. On the other hand, since the inception of DES therapy, polymer coating has been the most favoured vehicle for both drug-loading and control-of-release kinetics. Although biostable polymers are employed in most DES, some newer DES systems employ bioabsorbable polymers, which generally comprise of polymers such as polylactic acid (PLA), polyglycolic acid (PGA) and PLGA copolymers. These polymers degrade and get metabolised in the body leaving behind a BMS. However, PLA degrades over 2–3 years and PLGA, depending on the glycolic acid content, can degrade rather too rapidly to result in significant inflammation. As such polymer composition determines degradation kinetics, which in turn largely determines the utility of bioabsorbable polymers.

Polymers may also be classified as hydrophilic or hydrophobic. The former exhibit affinity to water and the latter tend to be averse to water. In the aqueous environment of the body it is only reasonable to expect a...
hydrophilic polymer to generate less interfacial tension relative to a hydrophobic polymer and therefore be more acceptable to the body. However, antiproliferative drugs, such as paclitaxel or sirolimus and its analogues, are highly hydrophobic and it is not feasible to incorporate a hydrophobic drug in a hydrophilic polymer and obtain a controlled and sustained release. As such, it is not surprising that Cypher™ (Cordis Corporation), Taxus™ (Boston Scientific) and Xience V™ (Abbott) were formulated with hydrophobic polymers and attain a controlled and sustained drug release. It is apparent from Table 1 that the constituent monomers that comprise these polymers are all hydrophobic. Nevertheless, it is possible to design polymers with a combination of hydrophobic and hydrophilic monomers such that the hydrophobic components hold and elute the hydrophobic drug in a controlled manner but present a hydrophilic surface in the aqueous body environment to potentially elicit minimal inflammatory response. Indeed, polymers employed in Endeavor™ (phosphorylcholine [PC] polymer) and Resolute™ (BioLinx™ polymer) (both Medtronic, Inc) are more hydrophilic relative to other DES polymers since they contain substantial amounts of water-soluble monomers such as PC and vinyl pyrrolidinone, respectively. The zwitterionic PC head groups associate with a large number of water molecules to provide the hydrophilicity and hence are favoured in the body environment. Similarly, BioLinx has been designed to present a hydrophilic surface with adequate hydrophobic component incorporated to offer a controlled and sustained elution of the drug zotarolimus. Evidence of biocompatibility of PC and BioLinx polymers was borne out in in vitro studies of interactions of activated monocyctic and vascular smooth muscle cells (VSMCs) using real-time-based gene profiling and FACS-BD cytokine array (fig. 1). In addition, the polymer system also promoted viability of endothelial and VSMCs.

The molecular architecture of the polymers is important in providing a robust coating, and it is imperative that a polymer coating is tough and adheres well to the stent surface (fig. 2). It should not crack or peel when the stents are often tracked through hard calcified lesions in the vasculature. Softer, elastomeric segments in the coating polymer eliminate cracking but, in excess, can also lead to a balloon-sticking problem. Those hard glassy blocks in the polymer not adequately compensated with elastomeric components can lead to brittle coatings that crack. Regarding drug elution,
softer polymers enhance the drug-elution rate, whereas hard polymers can either sequester the drug or drastically impede the elution rate. Furthermore, it is important that if a polymer blend is employed, the component polymers are either miscible, or mutually compatible, so as not to phase separate. Phase-separated polymer systems are often unable to provide diffusion-controlled kinetics because of preferential migration of drugs into phases of different physicochemical characteristics.

The importance of drug-release kinetics to DES efficacy
The control of drug release is central to the effectiveness of DES technology and the main reason behind the incorporation of polymer coating into DES devices. Evidence on the importance of release kinetics can be seen in the comparative performance of a number of current DES platforms. The history of DES development provides some insights into the importance of this dynamic to antirestenotic efficacy.

Limus-eluting stents
Early clinical trials with sirolimus-eluting stents compared fast-release stents (FRS; 100% drug release at <15 days) with slow-release stents (SRS; 80% at 30 days) using otherwise identical stent platforms and drug dosages. Although the FRS showed somewhat superior NIH suppression at initial 4-month follow-up, the durability of this antirestenotic efficacy to 12 months appeared more sustained with SRS – which was ultimately the product chosen to come to market (the Cypher stent). Comparison of the next-generation limus-eluting DES also confirms the importance of early release kinetics. On one hand, the Endeavor stent employs a fast-release protocol (~95% at 10 days) to deliver its drug load to the arterial tissue early where it is retained for 28 days owing to its relatively high lipophilicity. Against this, Resolute, with the same drug load (1.6 μg per mm² of stent surface) as Endeavor, elutes 85% of its zotarolimus content over the first 60 days post-procedure, and the remainder of the drug by 180 days. The gradual release of drug from Resolute stent produces a more tightly constrained drug level in the tissue, but sustaining it for a longer duration resulting in low TLR rates, low late loss and zero thrombosis at 2 years in the Resolute I clinical trial. Similarly, the Xience V stent displays a slower drug-release profile (40–50% at 10 days; 80% at 30 days) and displays a very similar degree of antirestenotic efficacy to the Cypher stent.

The ISAR-TEST-3 trial also provided an interesting illustration of the importance of early drug-release kinetics. This study randomised patients to otherwise identical fast-release polymer-free sirolimus-eluting stents or slow-release biodegradable polymer stents and compared their performance with those of Cypher stents. Although both investigative stents release a similar proportion of drug (80–90%) at 30 days, a more rapid release of sirolimus in the first 10 days resulted in an inferior performance efficacy compared with the Cypher stent; whereas a slower early release of sirolimus resulted in a similar antirestenotic efficacy to Cypher.

Paclitaxel-eluting stents
The Taxus stent operates to a very different and much slower drug-release model compared with the limus-agent platforms already considered. The Taxus II trial tested slow- (10% at 30 days; remainder sequestered indefinitely) and moderate-release (25% at 30 days; remainder sequestered indefinitely) DES platforms. The moderate-release formulation had a rapid initial burst, with an eight-fold higher release of paclitaxel in the first 10 days. Overall, however, the antirestenotic performance of both was very similar, indicating that a dosing threshold for NIH inhibition had been reached with the slow-release model; this was the formulation subsequently brought to market.
The assessment of DES polymer effects

A number of limitations should be considered when assessing the accumulated evidence on vascular responses to DES implantation in both animals and humans.

Firstly, due to the limited resolution of conventional angiography and intravascular ultrasound, as well as the practical constraints of direct angioscopy, there are a limited number of methods available to directly assess the long-term effects of DES and nonerodable polymers on arterial healing. Most of our information comes from two sources: preclinical animal models (in particular rabbit and porcine) and human autopsy studies. There have been recent advances in imaging techniques – specifically regarding optical coherence tomography – which are certainly encouraging and will likely provide important information on vascular responses to stent implantation in the future.

Secondly, much of the available clinical data, and to a lesser extent preclinical studies, compared DES platforms (i.e. stent plus polymer plus drug) with BMS (stent only) controls. As such it is often difficult to definitively attribute an observed ‘DES effect’ to either active drug or carrier polymer.

Differences in inflammation between biodegradable and biostable polymer-coated stents

The inflammatory response to most biodegradable polymer-coated stents is dictated by their biological sequences of degradation. For example, PLA-based polymer stents show a considerably low inflammatory response early after implantation in different animal models (fig. 3). As soon as the polylactide chain starts to degrade into shorter fragments or its monomers, a dramatic change in the biological vascular environment is observed. Due to chemical reactions with the polymer and pH changes in the vascular tissue surrounding the polymer, the cellular and acellular responses to the polymer are accumulating. It is likely that proinflammatory growth factors and cytokines induce inflammatory cell recruitment and infiltration to the tissue adjacent to the degrading polymer. The primary goal is to reduce the burden of foreign body; thus, the predominant inflammatory reaction is a nonspecific immune reaction dominated by monocytes and macrophages. Many of these macrophages form multinucleated giant cells to cope with the bulk of polymer fragments. As a consequence of persisting inflammation and sustained release of pro-inflammatory cytokines, a new formation of microvessels, termed neovascularisation, is commonly observed. The result of this is frequently a reinforcement of the already existing inflammatory response until the resorption process is completed. Ultimately, the inflammatory response is reduced as the polymer has degraded. The histopathological

![Diagram illustrating the fundamental differences of histopathological reactions occurring after implantation.](image-url)
differences among other biodegradable polymers are mainly characterised by the differences in the pace of degradation and the biocompatibility of the individual monomers (fig. 4).

In contrast, most biostable polymers vary in their degree of inflammation early after stent implantation (fig. 3).28-30. There has been a large variety of different biostable polymers that have been adopted by cardiovascular device companies for the use as drug carriers on stents31-35. They can be grouped in many ways, starting from the chemical structure of their respective monomers to their complex three-dimensional structure, which determines their biochemical behaviour. Lately, they have been divided into polymers with a predominance of hydrophilic versus hydrophobic surface characteristics likely to render them more or less biocompatible. However, the type and degree of the inflammatory response to biostable polymers is determined by various factors, including the stability of the polymer in vivo, the inertness at relevant biological conditions and the capability of allowing a regenerative tissue growth. Hence, most of the biostable polymers provoke an inflammatory process dominated by leukocytes. Early after stent implantation, neutrophils get deposited at the polymer sites that ultimately strengthen the pro-inflammatory milieu in the surrounding tissue. Monocytes and macrophages are commonly observed, however, and limited mostly to the polymer coating itself. In contrast to most biodegradable polymers, the inflammatory reaction persists, and is likely to find a balance after the nonspecific immune response has resolved, or leads to a prolonged, more specific hypersensitivity response involving T lymphocytes and eosinophils (fig. 4).31,36. To date, the detailed factors resulting in a hypersensitivity response remain to be elucidated.

Clinical data
Initial reports of late adverse events following DES therapy were anecdotal in nature. An early pathological case report from Virmani et al concerned a 58-year old patient who died of acute circumflex vessel stent thrombosis 18 months following Cypher implantation31. Sectioning of the coronary arteries revealed the absence of neointimal regrowth and signs of significant arterial wall toxicity at the stented segment, such as malapposition and aneurismal dilatation of the vessel wall, and diffuse predominantly T lymphocyte and eosinophil infiltration with occasional giant cells. Collectively, these changes were consistent with a hypersensitivity reaction, although an isolated giant-cell reaction was also noted adjacent to polymer fragments which had become detached from the stent backbone. In general, however, such a marked hypersensitivity reaction is not typical for DES-associated delayed vascular healing. As the resolution of clinically practicable invasive and noninvasive imaging techniques is insufficient to characterise the extent of vascular healing, most of our understanding of impaired vascular healing post-DES implantation comes from autopsy studies of patients who succumbed for cardiac or noncardiac reasons at a time point following coronary stenting. A report from Joner et al compared autopsy specimens from 23 patients with prior DES implantation (at >30
days) with 25 matched controls with a previously implanted BMS\textsuperscript{57}. All cases came from a registry of 484 stent specimens submitted to the CVPath (Gaithersburg, MD, USA) for pathological consultation. DES specimens (Cypher and Taxus) showed greater delayed healing compared with BMS: fibrin deposition score (2.3±1.1 vs. 0.9±0.8; p≤0.001) and endothelial coverage (55.8±26.5 vs. 89.8±20.9; p≤0.001). In addition, DES specimens were more likely to have evidence of late stent thrombosis (LST; 14/23 patients vs. 2/25 patients). In all 14 DES patients with late thrombosis, delayed healing appeared to be a principal contributing factor.

Interestingly, however, 11 of 14 patients had evidence of a second pathological risk factor for LST, suggesting that a ‘dual-hit’ was often necessary to provoke a thrombotic event. The contribution of drug and polymer to these cases of delayed healing is difficult to definitively define. In three of 11 cases there was evidence of a full-blown chronic hypersensitivity reaction, which may have been a direct response to residual polymer. In the remainder of cases the relative contribution of drug effects and response to nonerodable polymer are unclear.

Information relating to the prevalence of delayed arterial healing in patients who remain well post-coronary intervention is beyond the scope of an autopsy study. Indirect evidence, however, may be construed from a large-scale serial angiographic follow-up study\textsuperscript{18}. In this study patients receiving Cypher, Taxus and ISAR polymer-free DES underwent surveillance coronary angiography at two time points post-DES implantation, namely 6–8 months and 2 years. In 1580 lesions with paired follow-up, delayed late luminal loss was a systematic feature of DES therapy (0.12±0.49 mm between 6–8 months and 2 years) – a finding which illustrates that across large numbers of DES-treated patients, arterial healing is an ongoing process beyond 6–8 months. This contrasts markedly with data from the BMS era where neointimal volume peaked at 3–6 months and thereafter volumes of restenotic plaque tended to remain stable or indeed contract slightly due to completion of vessel wall healing\textsuperscript{19–41}. Interestingly, there seemed to be device-specificity to this phenomenon; late NIH progression was not observed with the polymer-free DES platform.

Conclusion

Polymers, as either biostable or biodegradable multimers of complex molecules, have revolutionised interventional cardiology by introducing the possibility of a controlled release of antirestenotic compounds for the treatment of obstructive atherosclerotic coronary lesions. The necessity of controlled drug release was impressively shown in a series of early preclinical studies evaluating precursors of currently available DES. While a landmark improvement was achieved with the advent of polymer science in interventional cardiology, initial attempts at controlled drug release were hampered by the concerns regarding biocompatibility and delayed vascular healing. Without a doubt, the further improvements with second-generation DES were among those factors attributable to advancements in polymer chemistry that partly resumed the trust of interventional cardiologists.

To date, we have just started to learn about the complex interactions in vascular biology that are likely to play a major role in the long-term success of any interventional treatment, and the diversity of therapeutic potentials offered by polymeric DES will certainly continue to determine the evolution of interventional cardiology.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not necessarily reflect those of the publishers, editor-in-chief, editorial board and supporting company. KU is President of Biopolymer Designs, Inc, and a consultant to Medtronic, Inc. RM acknowledges support by a research fellowship in atherothrombosis from the European Society of Cardiology. The funding authority had no input into the preparation of the manuscript. MD is consultant to Abbott Vascular, Medtronic, Inc, Biotronik and Mlemecience GmbH.

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