ABSTRACT
In the 26 years since Gruntzig introduced a simple balloon angioplasty technique, percutaneous coronary intervention has made extraordinary progress and has now surpassed bypass surgery in frequency. The area of coronary stenting has been the focus of intense research. One of the major problems encountered after stenting is an exaggerated vascular neointimal proliferation called in-stent stenosis. The evolution of drug-eluting stents has helped in reducing the incidence of in-stent stenosis by almost half. A number of pharmacological agents have been tried in coronary stents with varying degrees of success; many more are being developed and tested. Serious doubts have been expressed about the pharmacoeconomics of drug-eluting stents compared with bare metal stents, because of the huge disparity in costs. Drug-eluting stents, which can be grouped under both device and instrument, have thrown up interesting challenges for clinical trials. The future could see the development of more compact devices with the help of diverse fields such as nanotechnology, microelectronics and advanced materials technology.


INTRODUCTION
Coronary artery disease (CAD) accounts for approximately 25% of total deaths in the developed world and 15% in the developing world.1 In India, the prevalence of CAD is said to be around 3.9%.2 The multiple approaches to treatment involve lifestyle changes such as diet, exercise, meditation, etc., and medications such as antiplatelet and hypolipidaemic drugs as well as intervention procedures. The major interventional treatment options for CAD are percutaneous coronary intervention (PCI), which includes mainly percutaneous transluminal coronary angioplasty (PTCA), and coronary artery bypass graft (CABG) surgery. In 1964, Dotter and Judkins proposed the concept of implanting intravascular stents to support the arterial wall following coronary angioplasty.3 The first implantation of a stent in a human was performed in 1986 by Sigwart et al. (Schneider Wallstent).4 The Palmaz–Schatz stent was approved by the FDA in 1994 after two randomized control trials (STRESS and BENESTENT) showed better clinical and angiographic outcomes with its use.5,6 In the early days, stents were not widely used because of an unacceptably high incidence of thrombotic complications. Consequently, drug-eluting and drug-coated stents were developed. Their introduction has broadened the spectrum of indications for angioplasty, with a shift towards PCI from medical and surgical treatments for patients with CAD. Current data show that more than 90% of PTCA procedures use stents.7

RESTENOSIS OR IN-STENT STENOSIS
One of the major problems encountered after stenting is an exaggerated vascular neointimal proliferation—namely restenosis or, more specifically, in-stent restenosis. It occurs in 15%–40% of cases,8 and has a high recurrence rate in those with more severe and associated disease conditions. The aetio-pathogenesis of restenosis and its severity differs from primary stenosis (Fig. 1). Whereas stenosis is mostly an atherosclerotic lesion in the native vessel wall, restenosis is a reduction in lumen size after PTCA. In-stent stenosis could be categorized as a special form of restenosis that occurs exclusively after stent insertion, though both terms are used interchangeably. Metallic stent struts activate platelets and macrophages through cytokines and growth factors as well as by upregulation of genes and metalloproteinases, leading to in-stent stenosis.9 It

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depends almost entirely on intimal thickening as opposed to constriction of the vessel from the outside, known as negative remodelling, which is the main reason for restenosis after PTCA without stenting. The pathophysiological features of in-stent stenosis are the targets of therapeutic strategies.\(^{10}\)

**DRUG-ELUTING STENTS (DES)**

Stents have undergone several changes since their introduction 19 years ago, and improvements in design and better adjuvant medical therapy have made stent placement near mandatory in a majority of angioplasty procedures. Stents have evolved through three generations:

*First:* Uncoated stents or bare stents made of surgical-grade stainless steel

*Second:* Coated stents with carbon or gold attached to the stent surface

*Third:* Drug-eluting stents (DES) with polymer coatings that act as drug reservoirs.\(^{11}\)

DES are coated stents that release single or multiple bioactive agents which are deposited in or affect blood vessels, cells, plaque or the surrounding tissues. They provide high concentrations of a drug at the site of action, thereby decreasing the chances of systemic toxicity. The first-in-man (FIM, 2001) trial showed zero restenosis after sirolimus-eluting stent implantation.\(^{12}\) Paclitaxel-eluting stents have also been shown to decrease restenosis. Today, both sirolimus- and paclitaxel-eluting stents are known to have similar efficacy in reducing restenosis. In contrast to the lack of success with systemic drug therapy in preventing restenosis, DES have been successful in suppressing local neointimal proliferation that is responsible for angiographic and clinical restenosis.\(^{13}\) In India, both paclitaxel- and sirolimus-eluting stents are available since 2002 and are widely used.

A coronary DES essentially has 3 components—stent, coating and bioactive agent. The main challenge in designing a DES is to achieve a compatible relationship among these 3 components.

**Coating: The differentiator between bare stents and DES**

The coating is essentially a drug carrier vehicle that permits elution of the drug into the vessel wall at the required concentrations and kinetic profile with the purpose of uniform delivery of the drug to the underlying tissue. The selection of a non-inflammatory, inert coating matrix has been a major obstacle to the development of DES. Stents may be either actively or passively coated. The first substance that was loaded directly onto the bare metal of the stent was heparin, and is an example of passive coating.\(^{14}\) Paclitaxel, prostacyclin and tacrolimus can also be directly coated onto the metal. In active coating, a polymer coating matrix is present which acts as a reservoir and facilitates prolonged drug delivery. Sustained release of up to 3 weeks is necessary to prevent smooth muscle migration and proliferation.

**Bioactive agents**

The ideal antirestenotic agent for local delivery should have the following properties:

1. Potent antiproliferative effects
2. Non-interference with vascular healing
3. Wide therapeutic index

Bioactive agents can be classified according to their properties.

1. Immunosuppressive: Sirolimus, everolimus, mycophenolic acid, tacrolimus
2. Antiproliferative: Actinomycin D, paclitaxel, taxanes
3. Anti-inflammatory: Dexamethasone, prednisolone, tranilast
4. Antithrombotic: Glycoprotein IIb/IIIa antagonists, heparin, iloprost, hirudin
5. Extracellular matrix inhibitors: Batimastat
6. Prohealing agents: Oestrogen
7. Others: Statins

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**Fig 2. Mechanisms of vessel wall injury**

- **VEGF** vascular endothelial growth factor
- **MMP** matrix metalloproteinase
Some agents such as sirolimus may affect multiple targets in the restenotic process.

**STENTS ELUTING IMMUNOSUPPRESSIVE AGENTS**

The limited success with ionizing radiation therapy led to the use of immunosuppressive agents in stents. Different classes of immunosuppressive agents such as xenobiotics (sirolimus, cyclosporin and its analogues) and antimetabolites (mycophenolate mofetil) have been tried with varying degrees of success.

**Sirolimus-eluting stents**
Sirolimus has antifungal, immunosuppressive and antimitotic properties. The sirolimus–FK binding protein complex binds to a specific cell cycle regulatory protein, the mammalian target of enzyme rapamycin (mTOR), and inhibits its activation resulting in decreased growth factor- and cytokine-induced cell division. There are two forms of drug formulations: fast-release (<15-day drug release) and slow-release (28-day drug release). Only slow-release formulations are commercially available.

**Tacrolimus-eluting stents**
Tacrolimus is a hydrophobic immunosuppressive agent that acts by preventing activation of the T cells. Initial in vitro and in vivo studies have failed to demonstrate inhibition of smooth muscle cell proliferation.

**Mycophenolic acid-eluting stents**
Mycophenolic acid is the active metabolite of mycophenolate mofetil, and has both antineoplastic and immunosuppressive properties. Preliminary results suggest no beneficial effects when used in coronary stents, but results of ongoing studies are awaited.

**Paclitaxel-eluting stents**
Paclitaxel is a microtubule stabilizing agent with potent antitumour activity. Many different platforms that use polymer coatings or surface modifications to cause paclitaxel to adhere onto the stent surfaces have been utilized over the past 2 years. Paclitaxel exerts its antiproliferative effects at concentrations much lower than those used for the treatment of cancer.

**Angiopeptin-eluting stents**
Somatostatin, an angiopeptin analogue, has been shown to reduce tissue response to several growth factors. In humans, systemic administration of angiopeptin has improved the clinical outcome after angioplasty but showed no effect in restenosis.

**Tyrosine kinase inhibitor-eluting stents**
The results of clinical studies on the use of these agents are awaited.

**Actinomycin D-eluting stents**
Actinomycin D is an anticancer drug that selectively inhibits RNA synthesis. Clinical trials using this drug were stopped prematurely because its use led to a high incidence of repeat revascularization.

**Stents eluting anti-inflammatory agents**
Anti-inflammatory agents were considered an obvious target to prevent restenosis because of the role of inflammatory cells in the pathological process. However, clinical trials failed to demonstrate major benefits.

**Corticosteroid-eluting stents**
Multiple trials involving corticosteroid-eluting stents have assessed the efficacy of steroid-eluting stents, but none have proved clinically beneficial. Dexamethasone stents have been approved for clinical use in Europe.

**Tranilast-eluting stents**
Tranilast, N-(3, 4-dimethoxy cinnamoyl) anthranilic acid, has been shown to inhibit proliferation and migration of vascular smooth muscle cells in experimental models. Systemic use of this agent for prevention of restenosis has been disappointing.

**STENTS ELUTING ANTITHROMBOTIC AGENTS**

Though vessel injury with resulting platelet aggregation and thrombus formation plays a prominent role in the development of restenosis, antithrombotic pharmacological approaches have been proven to be ineffective in preventing restenosis. Nitrous oxide and glycoprotein IIb/IIIa inhibitors have been used as stent coatings, but their efficacy is yet to be proved.

**STENTS ELUTING EXTRACELLULAR MATRIX MODULATORS**

Matrix metalloproteinases (MMP) have the ability to digest collagen and facilitate smooth muscle cell migration. Batimastat, a non-specific MMP inhibitor, as well as other MMP inhibitors have been shown to inhibit neointimal hyperplasia in animal models. However, in human trials they have not shown significant benefits.

**STENTS ELUTING PROHEALING AGENTS**

There are reports suggesting that endothelialization of stents with a functional endothelium reduces the restenotic process. In a recent study, implantation of endothelial progenitor cell (EPC) capture stents showed promising results; there was no increase in major adverse cardiac and cerebrovascular events (MACCE). Nitric oxide, vascular endothelial growth factor, and 17-β-oestradiol have all been tested as prohealing and antirestenotic agents, but the results are conflicting.

**ADVANTAGES OF DES**

The main benefit of DES is the prevention of restenosis. In the case of PTCA, initial restenosis rates were as high as 30%–40%; they decreased to 20%–25% with bare stents and are now <10% with DES. Stents are currently used for complicated lesions, and in high risk patients. In spite of this, complication rates have decreased significantly (restenosis, mortality, myocardial infarction and emergency CABG). DES can be safely and effectively placed in most lesions without predilatation, reducing the cost and procedural time. Since the drug and stent are delivered as a complex, its action begins at the time of vessel injury, and additional interventions or manipulations are not needed.
DES AND STENT THROMBOSIS

Even though DES have decreased restenosis rates by almost one-fourth, restenosis remains high in a subset of patients who have lesions in difficult anatomical sites such as vessel bifurcations and side branches (25% after 6 months).25 Also, late thrombosis (1 year later) occurs after the use paclitaxel- and sirolimus-eluting stents following discontinuation of antiplatelet therapy.26 Restenosis rates ranging from 15% to 30% have been reported in diabetic patients who have undergone DES placement.27 Histological analysis of vessels with paclitaxel-coated stents showed reduced healing of the vessel wall and chronic low-grade inflammation and intraintimal haemorrhage.28 These aspects have raised the concern that a delayed loss of the initial benefit with DES can occur after 3–4 years in terms of restenosis and major adverse cardiac events. Though these are isolated reports in a few patients, they merit attention since DES have been in use for about 2 years and there are no data on the long term restenosis rates.29

SAFETY AND EFFICACY OF DES: THE DEBATE

Since DES is a combination product, it presents the combined challenges of a drug and a device. The pharmacokinetics of DES consist of local, regional and systemic effects. Though the purpose of DES is local delivery, drugs can reach detectable systemic levels. Studies indicate that after insertion of a single sirolimus stent, 10% of the level used for immunosuppression is reached. Animal studies have shown that there is a dose-dependent cytotoxic effect with DES, which results in impaired wound healing.28 However, such studies in patients with CAD are lacking. Patient studies are difficult in real world situations; therefore, adequate pharmacokinetic testing data are not available. Another major drawback is the lack of a reliable animal model as different models have not provided consistent results in humans. A consensus group has recommended certain parameters for in vivo estimation of the pharmacokinetics of DES. These include (i) full temporal characterization of drug release and better definition of the therapeutic window, (ii) levels of drug in arterial and myocardial tissue proximal and distal to the stent, (iii) justification of proposed clinical drug dose and release characteristics by preclinical data, and (iv) use of a minimum of 5 time points examining release from 3 separate stents to determine the $t_{1/2}$.30

There is skepticism about the universal benefits of the use of stents. Recent reviews indicate that there is no evidence of a difference in mortality between patients receiving DES and those treated with bare metal stents at 1 year; however, there was a reduction in event rates with DES. Though CABG is more expensive than bare metal stenting in multivessel disease and may have higher immediate risks, over time the cost differential gets reduced and long term outcomes favour CABG over stenting.31

DES: PRESENT REGULATORY STATUS IN INDIA

Issues regarding the safety, efficacy, quality and cost aspects of coronary stents have been discussed widely among the medical fraternity and were raised in the Indian Parliament. The Ministry of Health and Family Welfare, Government of India, notified the guidelines for import and manufacture of medical devices including stents (S.O. 1468 (E) dated 6/10/2005). Control over manufacture of these devices would be exercised by the Drug Controller General of India under the said Rules. According to the notification, if a device incorporates a medicinal product which is intended to act upon the body along with the device, data on the safety, quality and usefulness of the medicinal substance used should be furnished. Additional data on compatibility of the device with medicinal products are required if the device is intended to deliver medicinal products. Further, if the device is to be manufactured in India, the manufacturers have to adhere to strict norms which are more or less similar to the manufacture of pharmaceutical products.32

THE PHARMACOECONOMIC ASPECTS OF DES

Another factor that needs to be considered is the pharmacoeconomics of DES. The list price of the sirolimus-eluting stent in Europe is US$ 2500. In India, a DES costs nearly Rs 130 000 (US$ 5000) whereas a bare stent costs only one-fourth of this. This high price relative to bare stents, as well as the absence of incremental reimbursement in most countries, has been an obstacle to more widespread utilization of DES. However, it is estimated that the treatment of restenosis costs US$ 8000–28 000 per episode, and it could be economically viable to use DES for patients who need stenting, especially if only one stent is used and the patients’ risk of restenosis is high.33

CHALLENGES IN CLINICAL TRIALS

The rapid evolution of stent design, deployment approaches and adjunctive therapy have led to challenges in clinical practice patterns and data interpretation, necessitating consideration of major issues while comparing data from different clinical trials. While trials on sirolimus-eluting stents cover an identical group utilizing one single device (Cypher™, Cordis J&J, NJ), those on paclitaxel-eluting stents represent a non-homogeneous group that includes both non-polymer based and polymer-based devices. This makes the results of the second group of studies more difficult to interpret and analyse. Also, care is needed while extrapolating the data from these studies to a large and diverse population base from a low risk population. It is not ethically permissible to conduct studies of a new device on a high risk population, thereby limiting the assessment of a new device on more extreme parameters such as death or myocardial infarction.34

Another difficulty is defining the most appropriate end-point and the duration of the study. In various clinical trials, angiographic and clinical data have been compiled at different time points (4, 6, 8, 9, or 12 months). The most commonly used end-point is the restenosis rate, but this gives limited information on whether the effect of a device on neointimal proliferation is essentially restraining or inhibitory. The use of stents for a wide variety of clinical indications, many of which have not been evaluated in randomized studies, is another problem.35 Absolute restenosis rates with DES have been higher in those with diabetes and when used in small vessels, in-stent restenosis lesions and bifurcation lesions.36

It is therefore not clear how the available clinical trials reflect the real life situation when the stents are used in patients with a wide variety and severity of disease. Until now no trial has been adequately powered to evaluate the benefits within subgroups with different risk factors.37 Therefore, there is an urgent and clear need for randomized clinical trials with simple end-points that truly reflect the real clinical situation. This could help in achieving more uniformity of trials and better analysis of benefits with various models of stents.
FUTURE TRENDS

Several critical breakthrough technologies account for the remarkable progress in the field of interventional cardiology in the past 3 decades: intracoronary stents have increased success rates and reduced restenosis, adjunctive antiplatelet therapy has reduced periprocedural complications, and restenosis after stent placement has been effectively treated with local radiation. The role of other agents with potential benefits (e.g., statins, adenosinivirus-mediated arterial gene transfer, tyrosine kinase inhibitors, L-arginine, abicipabim, angiopoetin, r-PEG-hirudin and iloprost) as well as biodegradable stents may be tested in the future. The rapidly developing fields of nanotechnology, microelectronics, and advanced materials technology will enable the surface engineer to design molecular-specific surfaces for a new generation of vascular devices. 

REFERENCES