"An idea that is developed and put into action is more important than an idea that exists only as an idea"

Introduction
2. **INTRODUCTION**

Cardiovascular disease is increasing in prevalence in many regions of the world. It is responsible for major disability in developed and developing countries. Worldwide, it is estimated that death from CHD will increase 100% in men and 80% in women from 1990 to 2020, with the majority of that increase coming from Asia, Africa, and Latin America. Similarly, disability-adjusted life-years lost will increase 107% in men and 74% in women worldwide (Murray et al 1996). Cardiovascular disease includes common conditions, such as coronary heart disease, stroke, hypertension, and heart failure, and those less common, such as congenital heart disease, cardiomyopathy, and peripheral vascular disease.

Cardiovascular disease is a major cause of death globally and coronary artery disease is one of the major causes of premature deaths in modern and industrialized countries. In 2005, the World Health Organization reported that cardiovascular diseases caused 17.5 million (30%) of the 58 million deaths globally. Cardiovascular Diseases such as ischemic heart disease and strokes are the largest causes of death in developing countries and are one of the main contributors to disease burden. Coronary artery disease is a major cause of death all over the world (Shepherd et al 1995). CVD in India cause 3 million deaths in a year accounting for 25% of all mortality (Mukherjee 1995). IHD is the leading cause of death in India (Reddy 1993). Moreover, research on Indian Asians living abroad indicates a 40% higher risk of IHD mortality than that for Europeans (Balarajan 1996). It has been estimated that CAD will emerge as a single target contributions to mortality in India by 2010, accounting for nearly one third of all deaths. CAD prevalence was predicted, 60% of the world’s patients with heart disease will be in India by 2010 (Kohn 2008). Age standardized CVD death rates (per 100,000) in middle-aged (30–69 years) are low in developed countries such as Canada (120) and Britain (180) and high in developing countries Brazil (320), China (280), Pakistan (400), Nigeria (410), Russia (680) and India (405) (WHO, 2005). The present burden of CVD related deaths and quality of life indicators a need for effective prevention as well as therapeutic management of these patients. It is extremely essential to control the growing trend of coronary diseases in the world population and the increasing burden of CAD in developing countries should be dealt through public awareness
programs and preventive health care management (Boutayeb and Boutayeb 2005). Statistics suggest that South Asians seem more naturally vulnerable to heart disease than other ethnic groups. Even after adjusting for all known risk factors; South Asians in Canada appeared to have a higher rate of heart disease than Europeans or Chinese living there (Levy and Kannel 2000).

CAD is characterized by the presence of atherosclerotic plaques that progressively narrow the coronary artery lumen and impair antegrade myocardial blood flow. The reduction in coronary artery flow may be symptomatic or asymptomatic, occur with exertion or at rest, and culminate in a myocardial infarction, depending on obstruction severity and the rapidity of development (Hatmi et al 2007).

In 1964, Dotter and Judkins described the first angioplasty. Thirteen years later, Andreas performed the first balloon coronary angioplasty, a revolutionary treatment that leads to the birth of a new specialty, interventional cardiology. Coronary stents, which were first developed in the mid-1980s, have ultimately replaced “plain old balloon angioplasty” (POBA). Interventional cardiologists are faced with a wide choice of coronary stents to implant. This choice ranges from conventional bare metal stents (BMS) and drug eluting stents (DES). DES with biodegradable polymers, polymer-free, DES with novel coatings, dedicated bifurcation stents, self-expanding stents, and biodegradable stents (Garg and Serruys 2010).

Restenosis was always considered to be the major drawback of PCI (Serruys et al 2006). The occurrence of restenosis was significantly lowered by the introduction of DESs. However, a considerable number of clinical studies on DES with appropriate follow-up suggest a small but significant increase of late and very late stent thrombosis an event that is of considerable clinical importance as it is associated with high mortality (Kastrati et al 2007, Iakovou et al 2005). Furthermore, the current use of DESs is limited by the need for prolonged dual antiplatelet therapy, which is currently recommended for 12 months following PCI with DESs, compared to 4 weeks for BMSs (Grines et al 2007).

Sirolimus is a peptide that was isolated in 1975 from the bacteria strain Streptomyces hygroscopicus found in a soil sample on Easter Island (known locally as Rapa Nui). Its use in intracoronary stenting was based on the premise that the
antiproliferative properties of the drug would inhibit the neointimal hyperplasia (NIH) associated with restenosis following stent implantation. The first drug successfully embedded into a coronary stent was sirolimus (Rapamycin®; Wyeth), a potent immunosuppressant of T-lymphocytes that also inhibits human vascular smooth muscle cell proliferation and migration, without causing cellular toxicity. Moreover, rapamycin reduces matrix synthesis and inhibits inflammation in injured vessels. Since then, a number of new analogs of the ‘limus family’ are in development of or are in clinical trials to create the next generation of these stents in this series. Some of these analogs have different modes of action and are introduced on newer stent platforms with or without polymer support in order to optimize their drug effects. Other drugs in limus category are everolimus, zotarolimus, biolimus, pimecrolimus and tacrolimus.

The first clinical use of DES technology began with the introduction of the Cypher™ stent (Cordis, Johnson and Johnson) through initial first-in-man studies as well as in subsequent clinical trials leading to the device’s approval in Europe in 2002 and the United States in 2003. In Cypher™ stent system, poly-n-butyl methacrylate durable polymer technology used for drug elution that has been shown to cause inflammation and fibrin deposition as well as endothelial dysfunction and delayed endothelialization (Joner et al 2006). Poly-n-butyl methacrylate is hydrophobic and causes monocytes to adhere to its surface and produce cytokines such as monocyte chemotactic protein-1, plasminogen activator inhibitor-1, and tissue factor. Persistence of this pro-inflammatory polymer is hypothesized to be a potential major contributor to late stent thrombosis events (Wykrzykowska et al 2009).

The first-generation coronary stents were composed of 316L stainless steel. An alternative to stainless steel is cobalt chromium, which exhibits superior radial strength and improved radio-opacity, allowing for thinner stent struts that may reduce restenosis (Kastrati et al 2001, Pache et al 2003, Kereiakes et al 2003). Thinner struts can also lead to a reduction in device profile and, hence, an improvement in stent deliverability to the target lesion. The cobalt-chromium alloy has superior mechanical properties compared with traditional 316L stainless steel, including greater strength and increased density. The strut
thickness has been shown to be an important determinant of the long-term restenosis rate (Briguori et al 2002, Kastrati et al 2001, Pache et al 2003, Rittersma et al 2004).

In-stent restenosis is due to neointimal hyperplasia as a result of smooth muscle migration and proliferation as well as extracellular matrix deposition. Elastic vascular recoil and constrictive arterial remodelling also contribute to this process. The stents cause a mechanical injury to the arterial wall. This incites an acute inflammation in the vessel wall with the release of cytokines and growth factors which in turn induce multiple signalling pathways to activate smooth muscle migration and proliferation (Forrester et al 1991).

Durable polymer coatings have proven to be a successful method for drug loading and drug release, the key determinants of DES efficacy in clinical practice. However, an important limitation of durable coatings is the undetermined effect on arterial healing. Several animal and human studies have identified durable polymer coatings as a possible stimulus for hypersensitivity reactions and nidus for chronic inflammation. These pathological mechanisms may play an important role in the predisposition for very late stent thrombosis and delayed restenosis (Byrne et al 2009, Cook et al 2009, Cook et al 2007).

In order to address durable polymers limitations; biodegradable polymers have been developed with the potential for controlled drug release combined with a biodegradation process, which ultimately leaves only the bare-stent platform behind. In addition to biocompatibility, other properties of these polymers, makes them uniquely suitable for other applications: thermo plasticity, high strength, controlled crystallinity, controlled degradation rates, controlled hydrophilicity, and proven non toxicity. They have the advantage of not requiring surgical removal after they serve their intended purposes. In case of elimination of biodegradable polymers, the polymeric chains are cleaved by hydrolysis to form monomeric acids and are eliminated from the body through the Kreb’s cycle, primarily as carbon dioxide and water in urine.

The second-generation DES that are currently approved by the U.S. FDA utilize Co-Cr, and elute “limus” drugs with the aid of more biocompatible polymers than are found on the first-generation DES. The second-generation DES have more biocompatible
polymers, and although they have already demonstrated impressive safety results at medium-term follow-up (Garg et al 2009, Stone et al 2009), additional improvements are anticipated from the newer metallic durable polymer DES that have been developed. DES using biodegradable polymers for drug release represents the next technological modification and preliminary results are favourable and demonstrate similar angiographic and clinical efficacy as first-generation DES (Raber and Windecker 2010).

Preclinical testing in animal models is the mainstay of the regulatory process to determine the safety and efficacy of these stents before human use. Porcine and rabbit models are extensively evaluated as they predict human responses as the stages of healing are similar even though the temporal response to healing is significantly prolonged in humans (Virmani et al 2003). The consensus report concerning FDA approval of the DES recommended the use of the pig model to allow the assessment of these devices in the vascular bed for which they were intended. The deployment of the DES in coronary arteries, it was argued, would enable study of the effects of high doses of drug in the myocardium and of any emboli phenomenon associated with the DES polymer and drug. In addition, the rate of proliferation of smooth muscle cells and endothelium might be slower in the rabbit model than in the pig model (Nakazawa et al 2007, Schwartz et al 2002).

Arterial healing after DES implantation is multifactorial. With the next generation of DESs, it is therefore extremely important that such factors as endothelialization, inflammation, release kinetics, and neointimal reduction be examined in preclinical testing models. It is accepted that biological effects seen in cell culture do not necessarily correlate with in vivo activity. However, if the biological effects of the agent to be eluted are examined in cell culture, such experiments should use vascular endothelial and smooth muscle cells over a range of doses in a logarithmic scale. Although human cells are preferable, they may be less practical, so that porcine or rabbit cells will suffice. There is no perfect animal model of human vascular disease. The coronary arteries in crossbred or miniswine, or rabbit iliac arteries are suitable because the size, access, and injury response appear similar to human vessels, and therefore may permit device evaluation before
clinical evaluation. The porcine model of choice is the normolipemic domestic crossbred or miniswine coronary artery (Schwartz et al 2008).

Stenting provide vessel wall scaffolding and prevent early elastic recoil and restenosis as compare to balloon angioplasty (Tanimato et al 2007). The Geometric arterial remoulding may be contributing factor to restenosis in human coronary artery. In coronary arteries, acute stent recoil has been tarnished contributor for inadequate stent expansion and final stent area is a significant forecaster for subsequent clinical event and restenosis. Compared with metallic stents, bioabsorbable polymer stents could have a lower radial strength, resulting in more stent recoil after implantation, because polymers are more elastic than metal. Acute recoil reduces the mean lumen diameter and it may contributor for late restenosis (Rodriguez et al 1993).

Efficacy of sirolimus-eluting stent using stainless steel platform and biostable polymer has been well documented in clinical studies publications. The Co-Cr stent platform provides flexibility for easy delivery, conformability and scaffolding that adapts vessel to the blood. Hence using Co-Cr as stent platform is likely to improve technical and procedural success of sirolimus eluting stent (Ge et al 2007).

The Supralimus-Core® sirolimus eluting coronary stents system (Sahajanand Medical Technologies Pvt. Ltd., Surat, India) is a newly developed sirolimus eluting coronary stent coated on L605 cobalt chromium bare metallic stent platform. The Supralimus-Core® sirolimus eluting stent comprises the following four components: the L605 cobalt chromium (Co-Cr) thin-strutted stent; biodegradable polymers (Poly L-Lactide, Poly DL-Lactide-co-Glycolide, and Polyvinyl Pyrrolidone), a potent immunosuppressant agent sirolimus; and the highly flexible stent delivery system.

Overall objectives of the study

> Preclinical study

- To evaluate safety and efficacy of novel Supralimus-Core® sirolimus eluting coronary stent in preclinical testing methods like cytotoxicity,
cytocompatibility, hemocompatibility, local tolerance, intradermal reactivity, pyrogen, Genotoxicity, histopathological, biofunctional and pharmacokinetics.

▷ Clinical study

- To determine in vivo acute recoil of the vessel wall immediately and early after sirolimus eluting coronary stent system implantation in de novo native coronary artery lesions in comparison with in vitro recoil.
- Evaluation of pharmacokinetic, safety and efficacy of the sirolimus Eluting Coronary Stent System in de novo native coronary artery lesions.