Imagination and knowledge with proper effort leads to the path of achievement and success!

Discussion
6. DISCUSSION

The Supralimus-Core® sirolimus eluting coronary stents system (Sahajanand Medical Technologies Pvt. Ltd., Surat, India). It 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.

The development of a new intravascular biodegradable drug eluting stent is a multistep process. Preclinical evaluation of new stent materials and stent construction is fundamental in demonstrating their safety and efficacy before use in human clinical trials. Fortunately, within recent years several guidelines have been published for the preclinical evaluation of new drug eluting stents (Schwartz et al 2002, Schwartz et al 2004). Animal models are necessary when new vascular technologies such as this biodegradable polymer coated drug eluting stents are investigated. The porcine vascular system correlates most closely to the human and is therefore the recommended model (Schwartz et al 2002, Virmani et al 2003). Cytotoxicity and biocompatibility should be undertaken with every new biomaterial. Cell culture models are the most widely used means of demonstrating toxicity and standardized animal implantation tests are essential in biocompatibility testing prior to clinical studies. We have tested in vitro cytotoxicity by using direct contact method, extracts method and indirect agar diffusion method. In all studies Supralimus-Core® stent showed mild to non cytotoxic reaction to fibroblast cells.

Sirolimus, also called rapamycin, was originally developed in 1975 as a macrolide antibiotic. It has potent antifungal, immunosuppressant, and antitumor properties. Sirolimus is an ideal candidate for a stent-based delivery to prevent restenosis (Gummert et al 1999). When used as part of a DES system, sirolimus targets the very cause of in-stent restenosis, proliferating vascular smooth-muscle cells, arresting their proliferation (Beyar and Roguin 2001). Since it does not kill the cells, it avoids the inflammation associated with massive cellular necrosis seen with cytotoxic approaches, such as brachytherapy.
Sirolimus inhibits expression of key cytokines necessary for the smooth muscle cell to progress from the G1 to the S phase of the cell cycle and thus arrests the cell in the G1 phase. Because sirolimus, unlike cytotoxic agents, arrests cellular proliferation, it is referred to as a cytostatic agent (Braun-Dullaeus et al 1998). Because of its lipophilicity, the sirolimus drug passes easily through cell membranes, enabling intramural distribution and prolonged arterial tissue retention. Cellular uptake is enhanced by binding to the cytotoxic receptor FKBP 12, which also may enhance chronic tissue retention of sirolimus.

Biocompatible materials should be less thrombogenic and inflammatory, and are thereby potentially able to reduce neointimal hyperplasia (Babapulle and Eisenberg 2002). The ilimus agents are often blended with synthetic polymers that act as drug reservoirs and elute the active agent over a period of several weeks or months. Unfortunately, many synthetic polymers appear to induce an exaggerated inflammatory response and neointimal hyperplasia in animal models (De Scheerder et al 1995, Van der Giessen et al 1996), so new biomaterials need to be tested for cytotoxicity and biocompatibility before being eligible for further studies. In addition, the interaction of blood with the polymer coated devices induced less response in terms of platelet adhesion, leukocyte adhesion, and activation of the blood coagulation compared to that of the bare metal stent. Therefore, it is likely that the coating of polymer has improved the blood compatibility of the cobalt chromium stents.

The basic tenet of blood stent interactions is that circulating cells do not react directly with the coating or the metallic stent surface (Salzman et al 1994, Horbett et al 1993). Within minutes after stent implantation, soluble proteins will adhere to it and rapidly form a monolayer at the surface of the foreign material. It is therefore to understand, at the molecular level, the dynamic process that regulates protein adsorption. Indeed, proteins will adhere according to their plasma concentrations but also depending on their surface affinity (Salzman et al 1994, De et al 1995). Therefore, there will be a competition between numerous proteins to adhere to the foreign surface. Some surfaces may preferentially absorb albumin, whereas others will tie fibrinogen. The former may promote passivation of the stent surface while the latter may lead to thrombus accumulation. Protein adhesion leads to conformational changes in the protein structure.
initiating cell adhesion, whereas soluble proteins do not interact with circulating cells (Salzman et al 1994, Horbett et al 1993). Inflammatory responses to implant biomaterials are accelerated by leukocyte adhesion and activation (Kaplan et al 1992, DeFife et al 1995). The release of cytokines from the adhered leukocytes can be a major contributing factor that enhances inflammation and restenosis (Welt et al 2002, Inoue et al 2003). In our study, it was found that leukocyte adhesion to the polymer coating stent that was used to load the drug was lower when compared to that of the bare metal stent.

Platelet adhesion and activation that lead to α-granule secretion may also influence cell proliferation and inflammation (Mannaioni et al 1997). In our study, it has been observed that platelet adhesion to the polymer coated stent is significantly lower as compared to the bare metal and sirolimus coated stent.

Other than the direct effect of material surface, adhered leukocytes, platelets, and associated cell membrane changes are known to activate intrinsic coagulation (Grunkemeir et al 1998). The shortened PTT of plasma exposed to the uncoated stent may be a consequence of adhered leukocytes and platelets. The activation of intrinsic coagulation is minimal on sirolimus coated stents; therefore it is suggestive that thrombotic complications are less likely during the use of these sirolimus coated stents.

The stent implantation can induce acute local inflammation, which plays a key role in neointimal proliferation and ISR (Celik et al 2009, Kim et al 2005). A brisk early inflammatory response was produced after balloon injury or stent placement with abundant surface-adherent leukocytes of monocyte and granulocyte lineage (Rogers et al 1996, Welt et al 2000). Days and weeks later, macrophages invaded the forming neointima and were observed clustering around the struts, forming giant cells. Inflammatory cells contribute to the neointimal thickening by the generation of reactive oxygen intermediates, production of growth factors and enzymes like cathepsins which are capable of breaking down extracellular constituents and thereby facilitating smooth muscle cell migration (Chen et al 2004, Assoian et al 1987, Sukhova et al 1998). In our study, the mean inflammation score for sirolimus eluting stent was 0.52 ± 0.20, showing no significant difference compared to the polymer coated stent (0.62 ± 0.27). This confirms the findings in previously reported

To check local tolerance of Supralimus-Core\textsuperscript{x} stent, closed patch test for delayed hypersensitivity and Intracutaneous (intradermal) reactivity experiments conducted. In our study we observed Supralimus-Core\textsuperscript{x} stent does not elicit any skin sensitization potential in Guinea pigs and zero irritation score in Intracutaneous (intradermal) reactivity test. The testing for pyrogenic substances of either endotoxin or nonendotoxin origin was carried out in Albino rabbits. The result of the experiment indicated that, the rise in temperature is under acceptable level as per ISO 10993-11, 1993 (E), clause 7.1. The Salmonella Reverse Mutation Assay (Genotoxicity) was conducted using Histidine auxotrophic strains of Salmonella typhimurium tester strains viz. TA97a, TA 98, TA 100, TA 1535 and TA 102. Based on these results it is concluded that Extract of sirolimus eluting stents are not mutagenic in this Salmonella Reverse Mutation Assay.

The Co-Cr stent, compared to the common 316L stainless steel stents, has higher tensile modulus, greater yield strength, greater elongation-to-break and greater density. This make the Co-Cr stent to have the same mechanical stability with thinner stent struts to result in less tissue coverage and greater stent flexibility in curved lesions (Kereiakes et al 2003). Results of a porcine model over 4 weeks clearly showed that using the Co-Cr stent as a base for DES instead of the 316L stainless steel (Suzuki et al 2001, Hong et al 2001, Jabara et al 2006, Grube et al 2004, Carter et al 2006). In our study, the average inflammation score was 0.52 \pm 0.20, indicating only mild intimal inflammation in the segment implanted with Co-Cr sirolimus eluting stent.

It is known that thrombus formation plays a key role in eventual human neointimal hyperplasia. It is now accepted that the thrombus even if small in size, can act as a scaffold to encourage neointimal proliferation simply because activated platelets within the thrombus can generate factors that stimulate smooth cell proliferation (Lowe et al 2001). In our study it was found, neointimal thickness in between strut was less in sirolimus eluting stent (122\pm84 \mu m) compared to polymer coated stents (284\pm181 \mu m).

Sirolimus inhibits in vitro SMC proliferation, induced by basic fibroblast growth factor or platelet-derived growth factor (PDGF) and inhibits migration of stimulated pig.
rat, mouse, and human vascular smooth muscle cells (VSMC), as outlined in several reviews (Marx and Marks 2001, Poon et al 2002). Several studies in experimental animal models have assessed in vivo the antiproliferative effects of the sirolimus eluting stent (SES). In animal models, SES containing 6–1200 µg of sirolimus markedly reduced neointimal area by 23–52% and mean percent stenosis by 27–46%, compared with bare-metal or polymer-coated control stents, 28–30 days after stent implantation (Klugherz et al 2002). Using a porcine models a significant decrease in mean neointimal area was reported 30 days after insertion of a slow-release SES (180 µg) (Aggarwal et al 2002). Our study demonstrates that sirolimus coated stents inhibit strut-associated inflammation and neointimal formation in the porcine coronary model. Our results show a reduction in neointimal area with a sirolimus coated stent with a biodegradable polymer matrix containing 1.4 µg/mm² sirolimus compared with a polymer coated stent.

Biodegradable and non-biodegradable polymers have been used as passive surface coatings or as a matrix for drug loading of stents (Byrne et al 2009). In the present study, a biodegradable polymer was applied to the surface of a stent to serve as a matrix for drug loading. Biodegradable polymers have proven biocompatibility when used as a passive surface coating on stents. The histological data in the porcine model suggest that erodable polymer surface coating is biocompatible at 8 weeks. In the present study also indicate that the used biodegradable polymers appear to be a suitable candidate to serve as a matrix for drug delivery.

Our study demonstrated the antiproliferative of sirolimus drug with coronary stents for preventing post-implant restenosis. The basic mechanism of inhibition of proliferation by sirolimus is common to all cell types and therefore, endothelial cell cultures were used to test the effectiveness of the loaded sirolimus drug. It is well known that endothelial cell attachment and growth is not easy to attain on most biomaterials, however, it was found to grow on bare metal, polymer coated and sirolimus coated stents at 2 hours. In polymer and sirolimus coated stents EC cells attachment were significantly higher compare to bare metal stents at 2 hours. There was no significant difference in EC cells proliferation at 72 hours in among bare metal, polymer coated and sirolimus coated stents. This confirms the findings in previously reported literature (Prasad et al 2005).
The healing stages in stented blood vessels of a normal healthy animal are similar to those in human beings (Virmani et al 2003). This has helped in elucidating the mechanism of arterial response to injury and the inflammation which generally follows angioplasty and stenting. The safety of sirolimus drug eluting stents can also be assessed in animal models, but the evaluation of efficacy remains uncertain and the final true efficacy can be only proved in clinical studies with real patients. As the ideal animal model is unreliable and there is no precise model for vascular diseases, studies with well-characterised animal models only predict how drug eluting stents will probably behave in humans (Schwartz et al 2002).

Preclinical studies of sirolimus eluting stents show a range of biological effects on arterial wall healing, inflammation, and neointimal growth. Studies of 28 days (Klugherz et al 2002, Suzuki et al 2001) or longer (Carter et al 2004) showed significant suppression of neointimal growth with rapamycin-eluting stents compared with polymer-coated stents or BMSs. Other preclinical studies that used systemic delivery of paclitaxel or everolimus showed delayed healing, with significantly decreased endothelialization at 28 days (Farb et al 2002, Kolodgie et al 2002). However, in a present study we found partial re-endothelialization at 8 weeks in the both the group, with minimal angiogenesis, necrosis, haemorrhage, and thrombosis/fibrin/fibrinoid deposits. There were no significant re-endothelialisation differences documented in other studies (Suzuki et al 2001, Costa and Simon 2005). However, this observation contradicts the previously reported literature where SES showed delayed re-endothelialisation (Frey et al 2008). The delayed vascular healing in sirolimus eluting stent is due to its antiproliferative activity as a result of blocking the cell cycle at the G1 phase (Finn et al 2007). Sirolimus also inhibits the migration and proliferation of endothelial progenitor cells, thereby contributing to the delay in re-endothelialisation (Fukuda et al 2005). Our analysis was done at 8 weeks. A possible explanation to this observation may be the relatively short period at which the analysis was performed. A final concern with drug-eluting stent coatings is the potential for endothelial toxicity, since delayed re-endothelialization promotes thrombus formation and late vessel occlusion. In our study re-endothelization was only mildly affected by the intramural delivery of sirolimus. These data supports similar findings in the porcine model showing
no effect on endothelialization by sirolimus eluting stents (Suzuki et al 2001). There was no significant difference in the peristrut fibrin deposition between the two groups of our study. In a pooled analysis of data from four trials comparing SES with BMS, no significant difference was found between the two in rates of stent thrombosis (Spaulding et al 2007).

By conducting in vitro and in vivo animal biocompatible and safety studies, it confirmed that sirolimus coated Supralimus-Core® stent is non-cytotoxic at the 1.4 \( \mu g/\text{mm}^2 \) concentrations. Our findings also document that the feasibility of a Supralimus-Core® sirolimus eluting stent, and the efficacy data support the notion that stent-based sirolimus delivery via a biodegradable polymer matrix is a promising approach for the prevention of restenosis.

In vivo pharmacokinetic results examined in male New Zealand white rabbit which show a sirolimus levels in blood immediately after 1 day of stent implantation were 2.4 ng/ml. Necropsy at 3rd day (72 hours) showed 0.8 ng/ml but at 7th day it was below LLOQ (0.5 ng/ml). Tissue levels varied from 0.6 to 4.0 ng/mg tissue wet weight over the first 7 days with a maximum mean value of 4 ng/mg at 1st day of implantation. At 15 days after implantation, tissue Sirolimus levels were between 0.7 - 2.1 ng/mg. This range was reduced to 70 %, at 28th day after implantation (0.2 to 0.6 ng/mg tissue). Implantation of sirolimus eluting stents in animal model, shows that \( C_{\text{max}} \) were closely dose-proportional and comparable with standard Cypher stent. The arterial reaction to overlapping Cypher sirolimus eluting stent or Taxus paclitaxel eluting stent examined in rabbits, circulating levels of paclitaxel at 0.5 hours to 9 days after stent deployment were generally below the detection limit of 0.02 ng/mL. Drug concentration of paclitaxel at the stent treatment site at 1 (n = 3) and 8 (n = 3) days averaged 1.7 and 1.3 ng/mg tissue, respectively (p = NS). In contrast, tissue concentrations of sirolimus at the stented site averaged 4.52 (n = 6) and 1.56 (n = 6) ng/mg tissue at 1 and 8 days, respectively (p = 0.03), whereas whole-blood concentrations peaked at 0.5 hours (13.31 ng/mL; n = 6), declined to 4.58 ng/mL at 24 hours (n = 6) and 0.90 ng/mL at 8 days (n = 3) (Finn et al 2005).

In porcine coronary artery model, whole-blood concentration of sirolimus (Cypher stent) peaked at 1 hour (2.63±0.74 ng/mL) after stent deployment and declined below the
lower limit of detection (0.4 ng/mL) by 3 days. The total arterial tissue level of sirolimus was 97±13 ng/artery, and the residual stent content was 71±10 μg at 3 days. The amount of residual sirolimus on the stent at 3 days was 43% of the initial quantity loaded on the stent. These data document the ability to deliver a potentially therapeutic arterial tissue concentration of sirolimus and insignificant levels in the systemic circulation with the nonerodible copolymer matrix (Suzuki et al 2001).

Data in the present study support the observations in experimental animals. Sirolimus is highly protein bound with a steady-state volume of distribution in transplant patients of 12 ± 5 L/kg (Zimmerman and Kahan 1997). Oral daily dosages of 2-5 mg in transplant patients result in steady-state trough blood levels of 8.6-17.3 ng/mL, reflecting an availability of only 8-14% (MacDonald et al 2000). Metabolism is predominantly via the liver and intestines. After bolus IV dosing, peak plasma concentrations occur within 2 minutes. Thus the peak whole blood levels achieved in the present study (2.22 ng/mL) are quite low and short lived when compared with therapeutic anti-rejection levels.

In human pharmacokinetic study, data showed that sirolimus concentration rises rapidly in Japanese patients compared with American patients. Chronic whole-blood levels achieved in renal transplant patients treated with sirolimus was 8 to 17 ng/mL, and a therapeutic window of 5 to 15 ng/mL is recommended for patients at standard risk of rejection (Otsuka et al. 2005, Windecker et al. 2003, Klugherz et al. 2002). The Sirolimus oral dose was adjusted to achieve target whole blood trough sirolimus concentrations of 10 to 15 ng/mL (chromatographic method) throughout the 12-month study period. Our finding of the pharmacokinetic study is that systemic levels of sirolimus eluted by the Supralimus-Core® sirolimus eluting stent are lower compared with oral immunosuppressive therapy. Results from Supralimus-Core® sirolimus eluting coronary stent’s pharmacokinetic study showed limited systemic exposure up to a total dose of 250 μg. From the above available pharmacokinetic data the systemic exposure of sirolimus from Supralimus-Core® Stent is comparable with Cypher sirolimus eluting coronary stent system (USFDA approved stent) and below the minimum therapeutic blood level of 5 ng/mL. In the present study, patients who were treated with sirolimus eluting stents had low, but measurable, sirolimus blood levels for at least 14 days after deployment, with systemic exposure being proportional to
the number and length of stents received. This rapid elimination is similar to that reported for sirolimus eluting stents tested in rabbits, where blood concentration of Sirolimus range 8.1-13.1 ng/ml after 1 hour of post implantation and reduced to 1.1-1.5 ng/ml after 48 hours. Necropsy at 3rd day (72 hours) showed 0.8 ng/ml but at 7th day it was below LLOQ (0.5ng/ml).

The individual maximal concentration (C max) measured in the present human pharmacokinetic study, 4.13 ng/mL, was found in one patient with the higher dose of sirolimus drug (249μg) who received a combination of 2 sirolimus eluting stents. This is in agreement with the observation of a proportional correlation between the loading sirolimus dose of the stents and the systemic exposure. Residual differences are the result of intersubject variability in pharmacokinetic parameters (e.g., drug clearance) and differences in patient characteristics.

In Cypher® sirolimus eluting stent, the average peak blood concentration for patients receiving two stents was about twice the concentration as was observed in patients receiving one stent (one stent, 0.57±0.12 ng/mL vs. two stents 1.05±0.39 ng/mL, p < 0.05). The higher concentration in Supralimus-Core® may be because of difference in polymers. In Supralimus-Core® biodegradable polymers used while in Cypher stent permanent polymers are used. The sirolimus AUC0-t after implantation of a single Cypher stent was 55.13±15.49 ng.h/mL, while in Supralimus-Core® stent after implantation of a single stent was 128.84±75.40 ng.h/mL. The C max and AUC are proportional to the dose in the range of 57 to 250 μg following Supralimus-Core® stent implantation.

In the present study, patients who were treated with Supralimus-Core® stents had low, but measurable, sirolimus blood levels for at least 7 days after deployment, with systemic exposure being proportional to the number of stents received.

Multiple studies have demonstrated that the immunosuppressive efficacy and incidence of adverse effects of sirolimus are correlated with blood concentration (Kovarik et al 2006, Baldelli et al, 2005). The adverse effect profile of sirolimus includes hypercholesterolemia, renal disorders, anaemia, thrombocytopenia, leucopenia, infections, gastrointestinal, and neurologic disorders (Mabasa and Ensom 2005). In this cohort, none of these effects have been reported after stent implantation. No correlation was found
between higher sirolimus levels (up to 4.13ng/mL) and ischemia-driven MACE (cardiac death, myocardial infarction, ischemia-driven target lesion revascularization by coronary artery bypass graft, or percutaneous coronary intervention), of course keeping in mind that it is only a small cohort. Therefore, it is unlikely that the systemic sirolimus exposure found in our study, with concentrations less than 4.13 ng/mL, would be sufficient to result in sirolimus drug related adverse events, even when multiple stents are used.

For most patients, whole blood concentrations initially increased to reach a maximum at about 1 to 12 hours after stent implantation. Thereafter, whole blood concentrations decreased biphasically; an initially fast distribution/elimination phase was followed by a slower elimination phase. The biphasic distribution is the result of initial distribution to the tissues and subsequent elimination from the blood. This is achieved by means of drug-biodegradable polymer blend base layer followed by hydrophilic (PVP) top layer. It is hypothesized that top PVP layer hydrolyzes rapidly (within 2-3 hours after stent implantation) promoting the release of the drug at a higher rate. This initial burst is intended to prevent adverse biochemical reactions (inflammation and neo-intimal hyperplasia) that arise due to intervention procedure. As blood concentrations increase rapidly after stent placement, the initial release of sirolimus from the stent must be higher that the net drug distribution to the tissues and its clearance from the blood. At the peak concentration, the release of drug from the stent equals its distribution to the tissues and clearance from the blood. After the peak, the clearance of sirolimus from the blood is higher that its release from the stent and sirolimus concentrations decreases. Apparently, the high release from the stent is only temporary because no steady-state or plateau concentration is observed.

By conducting animal and human pharmacokinetic studies, it concluded that Supralimus-Core® stent allow higher local drug concentrations at lesion sites while avoiding systemic toxicity.

The main function of metallic stents is to scaffold the vessel wall and prevent early elastic recoil and acute vessel closure. The need for this property is limited to the period ranging from the time of PCI to several months, thereafter, when the stented segment is fully endothelialized and vascular damage has healed. Beyond this period, the scaffolding
properties of the stent are probably unnecessary. Their permanent presence induces chronic inflammation between the metal and surrounding tissue (Farb et al 2002), which causes in-stent neointimal hyperplasia and thrombogenesis. Further, metallic stents prevent the lumen expansion associated with late favourable remodelling sometimes seen following balloon angioplasty (Hoffmann et al 1996, Konig et al 2002), impair the vessel geometry, and interfere with surgical reinterventions (Kornowski et al 1998) and with recently developed coronary imaging modalities such as multi slice computed tomography and magnetic resonance imaging. These imaging modalities may become the default non-invasive diagnostic tool for CAD patients in the near future (Dewey et al 2006). To fulfil the short-term need for scaffolding vessel walls and overcome the aforementioned drawbacks of metallic stents, the concept of bioabsorbable polymer stents is attractive.

Acute stent recoil has been observed following balloon deflation in normal and disease coronary arteries, and the degree varies by stent design. Newer-generation 316L-SS stent designs have enabled reduced strut thickness while retaining radial strength and minimizing recoil, but with significant loss of radiopacity, leading to reduced visibility. Cobalt-Chromium alloys have enabled a reduction in stent strut thickness to around 60-90 μm while retaining modest radiopacity, but due to higher elastic properties, have been associated with greater stent recoil.

In previous human clinical trials, acute stent recoil varied between 3% and 15% following Wiktor or Palmaz-Schatz stent implantation (Serruys et al 1991, De Jaegere et al 1994, Haude et al 1993, Fischman et al 1994, Rechavia et al 1995, Bermejo et al 1998). The wide range of BMS recoil was related in part to differences in stent material and design and in part to the difference in definitions of recoil. Stent recoil was usually defined as the difference between the last inflated maximum balloon diameter and the MLD post-stent implantation. However, usage of minimum variables, proposed by previous investigators, has the potential for assessing only a part of the stented segment, because the balloon does not expand uniformly, causing asymmetric stent expansion. To reflect the behaviour of the vessel wall of the entire stented segment, we used mean variables and defined acute stent recoil as the difference between the mean diameter of the last inflated balloon and the mean luminal diameter immediately after the last balloon deflation. Low
recoil (the ability of a stent to maintain its initial expansion diameter) is clinically desirable to reduce the risk of subsequent malapposition or restenosis. Malapposition may increase risk of subsequent late stent thrombosis. Our study was a prospective, single-centre, non-randomized study. A total of 19 patients were treated with sirolimus-eluting coronary stent system implantation for de novo native coronary artery lesions. Our study demonstrated that the acute percent stent recoil of the Supralimus-Core® sirolimus eluting stent was 0.08 mm (2.42%), which is less than the Promus Xience V recoil (4.6%) and Endeavor (5.1%), and also in line with previously reported in vivo conventional metallic stent recoil (Serruys et al 1991, de Jaegere et al 1994, Haude et al 1993, Fischman et al 1994, Rechavia et al 1995, Bermejo et al 1998, Menown et al 2010). We observed recoil of Supralimus-Core® stent is less than the USFDA approved stents (Xience V and Endeavor) and has greatest radial strength.

Efficacy of sirolimus-eluting stent using stainless steel platform and biostable polymer has been well documented in medical literature (Kereiakes et al 2003, Morice et al 2002, Moses et al 2003, Schofer et al 2003, Lee et al 2007, Ge et al 2007). 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 as well as influence late loss and restenosis. Supralimus-Core® stent as a strut thickness of 60µm (thin strut) which is also likely to improve long-term angiographic result as has been shown in ISAR STERE0 study (Kastrati et al 2001).

First-in-man (MAXIMUS study) was a single-centre, prospective and non-randomized. Total 105 patients enrolled in the study. Repeat angiography was performed 8 months post stent implantation and analyzed by independent core laboratory. The study demonstrated a late loss of 0.39± 0.33mm in-stent and 0.33± 0.35mm in-segment. This was somewhat higher than previous studies of SESs with stainless steel platform, significantly high percentages of unfavourable demographic and angiographic factors (eg. Diabetes 37%, hypertension 48%, type C lesion 6.7%, ≥ 28mm lesion 20% and small vessel 3 mm ≤ 84%) who partly be responsible for this higher late loss. However this slightly higher late loss at angiographic QCA follow-up did not result in significant increase in-binary
restenosis rate. In fact the restenosis rate and TLR were lower than study demonstrating relatively lower angiographic late loss (Weisz et al 2009). The first generation sirolimus eluting stent have used permanent (non-degradable) polymers. Persistence of polymers in the coronary artery after the elution of drug may become the source of inflammation in the artery. This may partly explain the higher incidence of late and very late thrombosis. It is inherently logical that disappearance of polymer after complete drug elution would be highly desirable (Tanguay et al 1994). ISAR-TEST 3 trial which compared outcomes of DES with biodegradable-polymer, no-polymer, and permanent-polymer sirolimus eluting stents showed best outcomes with biodegradable polymer (Mehilli et al 2008). The present study used biodegradable polymer as vehicle for sirolimus-eluting Co-Cr stent showed 100% procedural success and very low in-hospital MACE. Long-term safety was also well demonstrated at 1 year with low MACE rate of 7%.

In a first-in-man study of real life patients 'All comers' with a very high percentage of clinical and angiographic follow-up with independent core lab analysis. The binary angiographic restenosis rate in-stent and in-segment was 3.3% and 4.6% respectively. The incidence of any major adverse cardiac event (MACE) at 30 days, 8 months and 12 months was 1%, 6% and 7% respectively. The Supralimus-Core® stent is effective in reducing neointimal hyperplasia.