DIABETES SPECIAL ISSUE

cypher™
Sirolimus-eluting Coronary Stent

Clinical Newsletter

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The Impact of Diabetes on Coronary Artery Disease

Atherosclerosis is the most common predisposing factor for coronary artery disease (CAD), and the main underlying cause necessitating revascularisation.[1] In developed countries, atherosclerosis is the leading cause of death and disability, being responsible for more than half of all deaths annually in Europe and the US.[2]

Of the many complications associated with diabetes, CAD is a major cause of morbidity and mortality. Diabetes is an independent risk factor for CAD, and heart disease rates are up to four times higher than in non-diabetics.[3-6] Patients with diabetes are at particularly high risk of coronary events because they generally have more severe CAD than non-diabetics, and a higher incidence of silent ischemia, hyperlipidaemia, and hypertension.[7,8] Furthermore, diabetes worsens both early and late outcomes in acute coronary syndromes. In unstable angina and non Q-wave MI, diabetes independently increases the risk of death by 57%, and 5-year post-MI mortality rates are more than double that of non-diabetics at around 50%.[3,4]

Diabetes is at epidemic levels currently affecting about 150 million people worldwide, and is set to double by 2025.[9] In Europe, the prevalence is 5-7%, and in the US one million new patients are diagnosed each year.[10] Furthermore, diabetes is significantly under diagnosed, with at least 50% of people with diabetes being unaware of their condition.[11]

The abnormal metabolic state that is characteristic of diabetes is associated with arterial dysfunction that promotes atherogenesis and also neointimal hyperplasia after stent implantation. Diabetes alters the function of multiple vessel cell types, including endothelium, smooth muscle cells (SMC), and platelets.[5,12,13]

The effects of chronic hyperglycaemia and excess free fatty acids (a result of insulin resistance) on the endothelium include a decrease in the production and bioavailability of nitric oxide (NO), which plays a pivotal role in inhibiting atherogenesis and protecting the blood vessel. NO is a potent vasodilator that also inhibits SMC proliferation and migration, suppresses platelet activation, and limits inflammation by preventing leukocyte adhesion and migration into the vessel wall.

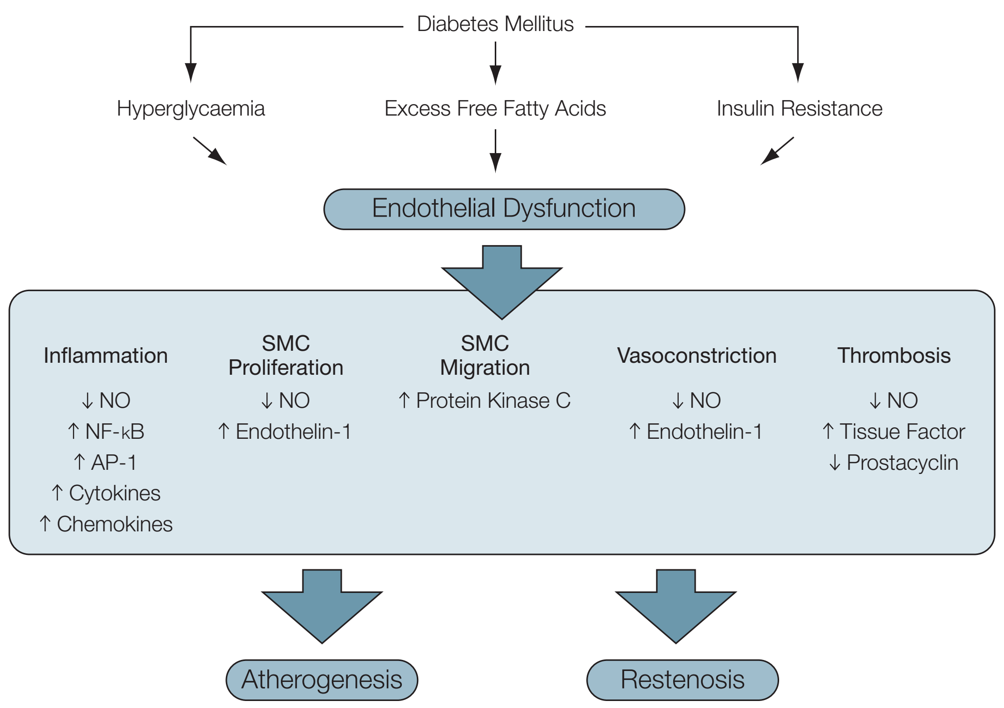
IN THIS ISSUE:

Diabetes-induced endothelial dysfunction also causes an increase in production of vasoconstrictors, pro-inflammatory adhesion molecules, chemokines, and cytokines, a reduction in levels of antiplatelet agents, and an increase in production of procoagulants. Consequently, these adverse events within the endothelium augment vasoconstriction, increase inflammation, and promote thrombosis, which all play a part in atherogenesis.[5]

References:

1. Vliegenhart R et al. The Rotterdam Calcification Study. Stroke 2002; 33 (2): 462-465.
2. The World Health Report 2001, Geneva: WHO 2001.
3. Malmberg K, Yusuf S, Gerstein HC et al. Circulation 2000; 102: 1014-1019.
4. Herlitz J, Karlson BW, Lindquist J et al. Diabet Med 1998; 15: 306-314.
5. Beckman JA et al. JAMA 2002; 287 (19): 2570-2581.
6. Haffner SM et al. N Engl J Med 1998; 339: 229-234.
7. Silva JA et al. Circulation 1995; 92: 1731-1736.
8. Kip KE et al. Circulation 1996; 94: 1818-1825.
9. Amos AF et al. Diabet Med 1997; 17: S7-S85.
10. Mak KH et al. European Heart Journal 2003; 24: 1087-1103.
11. International Diabetes Federation. From idf.org: Facts & Figures 2003.
12. Suesselbeck T et al. Am J Cardiol 2001; 88: 243-7.
13. Kornowski R et al. Circulation 1997; 84: 489-97.

Endothelial Dysfunction in Diabetes



The Challenge for Successful Intervention in Diabetics

In the cath lab, approximately 15-20% of patients undergoing PCI are diabetic – approximately 3 times the prevalence of the general population.

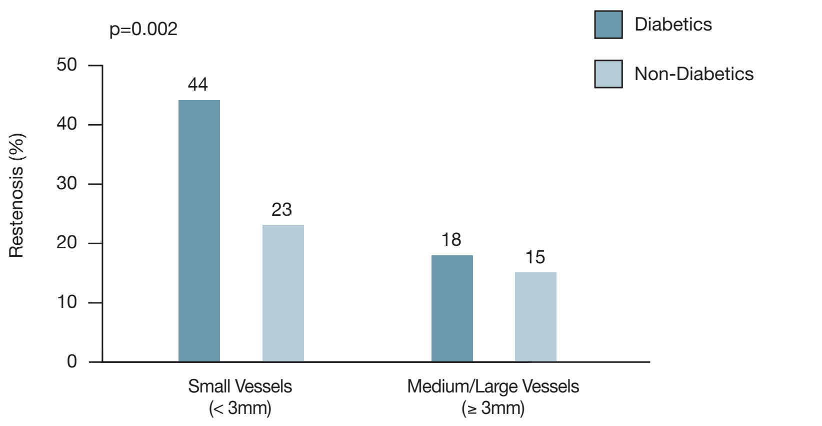
Diabetic patients are particularly difficult to treat because they more often have concomitant coronary risk factors, and their lesions are more complex and severe. CAD lesions in diabetics generally involve more extensive and diffuse disease than non-diabetics, occur in smaller vessels, and are associated with a higher incidence of multivessel and left main disease.[1-3] Furthermore, there is a greater a number of fissured atherosclerotic plaques and more total occlusions in diabetics.[2,3]

Insulin-dependent diabetes mellitus (IDDM) further complicates matters, as lesions are longer and more diffuse than in non-insulin-dependent diabetes mellitus (NIDDM), and are more often associated with multiple vessel disease.

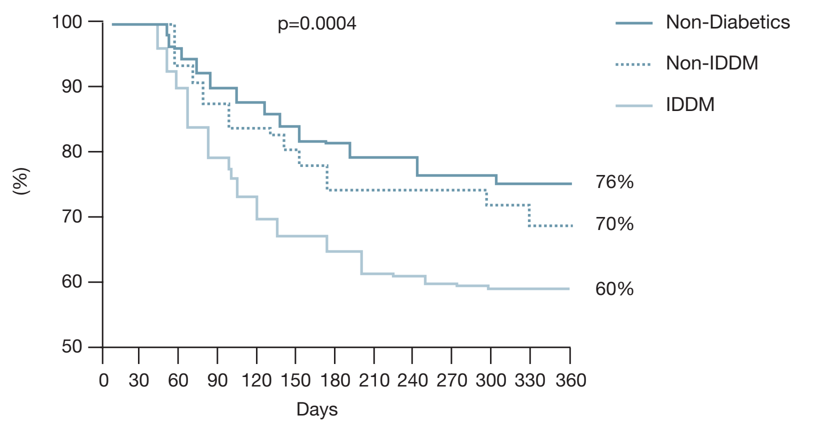
The arterial dysfunction of diabetic vessels also contributes to an exaggerated response to injury following PCI, resulting in increased neointimal hyperplasia post procedure.[4] Consequently, PCI outcomes in diabetics have historically been less favourable than non-diabetics. Balloon angioplasty in diabetic patients is associated with a 2-fold increase in restenosis and repeat revascularisation rates, up to 1.7 times greater risk of AMI and death during hospitalisation, and significantly reduced long-term survival.[5,6] Although bare metal stenting provides benefits over balloon angioplasty such as lower revascularisation, non-fatal MI and death rates,[7] a meta-analysis of more than 4,800 patients demonstrated a consistently higher rate of post-stenting restenosis in diabetics compared to non-diabetics (55% vs. 20%).[8,9] This difference has been shown to be significant for small vessels (<3mm), but not significant for larger vessels.[10] In addition, one-year event free survival rates from TLR and MACE have been shown to be particularly less favourable in IDDM than NIDDM.[11]

To maximise the success of PCI in diabetics, these findings suggest the need for a modality that is safe and effective in small vessels and long lesions. Furthermore, therapy needs to be active against the key components of vascular dysfunction in diabetics – namely chronic inflammation, smooth muscle cell proliferation and migration, and increased thrombotic activity – in order to prevent the exaggerated neointimal hyperplasia seen in this patient group.

Restenosis Rates (Bare Metal Stenting)



MACE-Free Survival (Bare Metal Stenting)



References:

1. Kornowski R et al. Am J Cardiol 1998; 98: 1298-304.
2. Silva JA et al. Circulation 1995; 92: 1731-1736.
3. Kip KE et al. Circulation 1996; 94: 1818-1825.
4. Kornowski R et al. Circulation 1997; 84: 489-97.
5. Stein B et al. Circulation 1995; 91:979-89.
6. Kip KE et al. Circulation 1996; 94: 1818-1825.
7. Van Belle E et al. J Am Coll Cardiol 2002; 40: 410-7.
8. Schofer J et al. J Am Coll Cardiol 2000; 35: 1554-9.
9. Karam C, Fajadet J et al. Cath Cardiovasc Intervent 2000; 50: 170-4.
10. Suesselbeck T et al. Am J Cardiol 2001; 88: 243-7.
11. Abizaid et al. JACC 1998;

Meeting Therapeutic Needs in Diabetics

The cellular activities of diabetic vessels involve more inflammation, SMC proliferation, and SMC migration than non-diabetic vessels, which are responsible for the higher rates of restenosis and ischaemic events in diabetic patients.

The CYPHER Stent is ideally suited to the treatment of diabetic lesions, most notably because of the mechanism of action of the eluted drug. Sirolimus is a highly effective anti-proliferative immunosuppressant that has demonstrated a triple mechanism of action in preventing neointimal hyperplasia. It reduces inflammatory activity by blocking the activation and proliferation of inflammatory cells; it inhibits SMC proliferation through a targeted cytostatic mechanism of action; and it inhibits SMC migration from the arterial wall into the lumen. These actions counter the cellular hyperactivity that occurs in diabetic patients by acting specifically against the key components of diabetic vascular dysfunction.

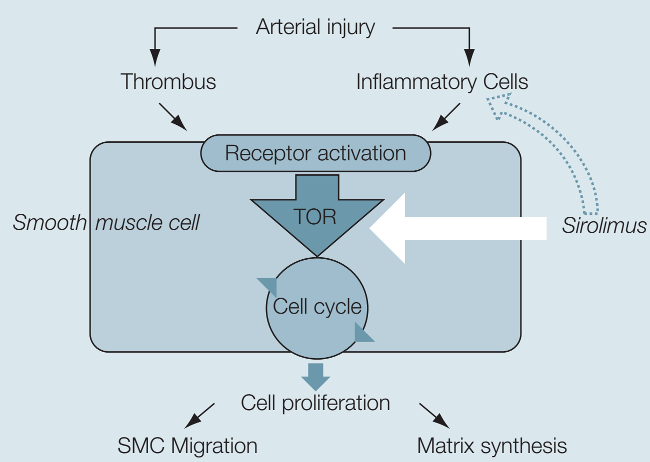
Furthermore, the selective cytostatic mechanism of action of sirolimus avoids tissue necrosis and related secondary inflammation that may cause thickening of the adventitia (peri-stent thickening) seen with cytotoxic agents. The cytostatic action of sirolimus also allows normal healing of the vessel wall through re-endothelialisation after implantation. Pre-clinical studies have shown that the rate of re-endothelialisation with the CYPHER Stent is the same as a bare metal stent.This provides vascular protection against the risk of thrombosis, which is particularly high in diabetics.

Dose-ranging studies of sirolimus-eluting stents have shown the drug to be effective at low doses, but not harmful at high doses i.e. sirolimus has a broad therapeutic window.

This means that for long diffuse lesions in the diabetic patient, overlapping CYPHER Stents can be safely deployed without a risk of local tissue toxicity and necrosis. In addition, in small vessel lesions typical of diabetes patients, the closed-cell diameter adaptive design of the CYPHER Stent ensures consistent drug delivery to the artery wall to maximise inhibition of neointimal hyperplasia.

To summarise, the combination of drug and platform of the CYPHER Stent fulfils the therapeutic needs of PCI in diabetics by providing effective control of the processes that lead to neointimal hyperplasia, and a suitable modality for the treatment of long lesions and small vessels commonly encountered in these patients.

Action of Sirolimus on Inflammatory Cells, and SMC Activation and Migration



TOR = Target of Rapamycin (Sirolimus)

Unmatched Outcomes in Diabetics

The pharmacological benefits of sirolimus confer excellent outcomes in diabetics. The RAVEL study gave the first indication of the outstanding efficacy of the CYPHER Stent in this difficult patient subset. Nineteen diabetic patients received the CYPHER Stent, and although the lesions were not too long (9.74mm), they occurred in small vessels (RVD 2.52mm). Remarkably, results mirrored those of the total population, with a virtual elimination of late loss (0.08mm) and 0% in-segment restenosis at 6 months. Clinical follow-up at 12 months revealed a 0% TLR rate compared to 36% for control.[1]

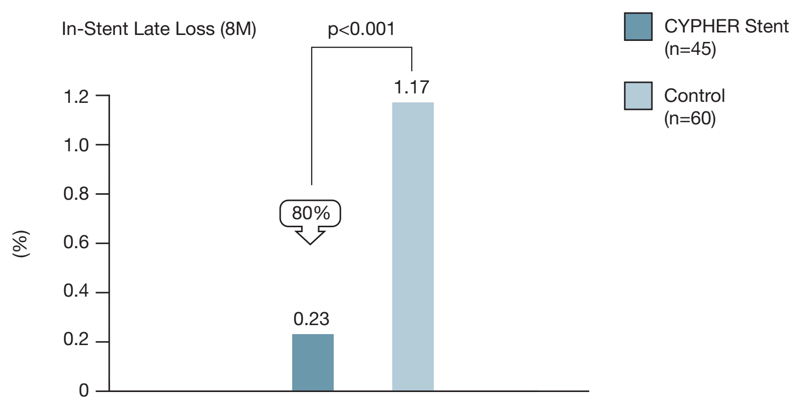
In comparison to RAVEL, the US SIRIUS trial studied more complex patients (increased multivessel disease and prior PCI/CABG), longer and more complex lesions, and frequent overlapping stents. Despite this, results in the diabetic subgroup were exemplary (n=131). In the CYPHER arm, diabetic patients had long lesions (14.07mm) in small vessels (RVD 2.73mm). In-stent late loss (0.29mm vs. 1.20mm control) and in-stent restenosis (8.3% vs. 48.5% control) at 8 months were dramatically reduced by 76% and 83% respectively. A 69% reduction in TLR at 9 months (6.9% vs. 22.3% control) held up at 12 months (8.4% vs. 26.4% control), translating into a total of 180 TLR events prevented per 1000 treated patients over the first year.[2]

More recently, pooled results from the European E-SIRIUS and Canadian C-SIRIUS trials, known as “New SIRIUS”, were presented at this year’s TCT. In New SIRIUS, 45 diabetic patients received the CYPHER Stent. Compared to SIRIUS, diabetic lesions were longer (14.8mm) and occurred in smaller vessels (RVD 2.49mm). However, outcomes in diabetics, as well as the whole population, were improved due to refinements in operator technique. The New SIRIUS diabetic subset showed outstanding reductions in late loss, binary restenosis, and TLR. At 8 months, in-stent late loss was reduced by 80% (0.23mm vs. 1.17mm control), while in-stent restenosis was reduced by 90% (5.4% vs. 54.5% control) and in-segment restenosis reduced by 81% (10.8% vs. 56.4% control). TLR at 9 months was reduced by 73% (7.0% vs. 26.0% control), which meant that for every 1000 patients treated, 190 would avoid a repeat procedure with the CYPHER Stent over the same period.[3]

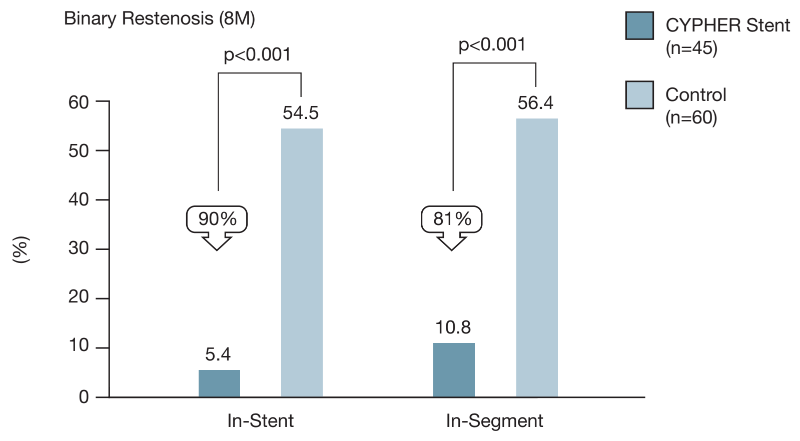
The latest results for e-CYPHER, the first ever post-marketing surveillance registry of a drug-eluting stent, were also presented at TCT this year. To date, this 'real world' registry has included 2385 patients with diabetes, 545 of whom have so far completed 6-month clinical follow-up. Lesions were particularly long (18.0mm), and occurred in vessels with an average RVD of 2.80mm. With exceptionally low rates of TLR (3.1%) and MACE (9.4%), it seems the remarkable efficacy and safety of the CYPHER Stent in diabetics seen in clinical trials is reproducible in routine clinical practice.[4]

In summary, the CYPHER Stent has been studied in more diabetic patients than any other drug-eluting stent, including 428 in randomised controlled trials (295 underwent angiographic follow-up) and 545 in the e-CYPHER registry. Overall, the CYPHER Stent achieved a virtual elimination of in-stent late loss (~0.2-0.3mm) and provided outstanding clinical benefit (TLR reduced by ~70%) in clinical trials, which have been confirmed in real world clinical practice.

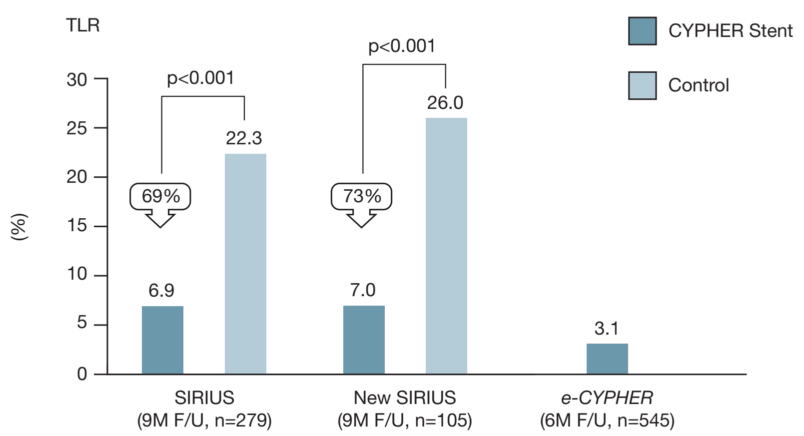
New SIRIUS Diabetics



New SIRIUS Diabetics



Diabetic Subsets



References:

1. Cordis. Data on file 2003.
2. SIRIUS results presented at TCT 2002.
3. New SIRIUS results presented at TCT 2003.
4. *e-CYPHER* results presented at TCT 2003.

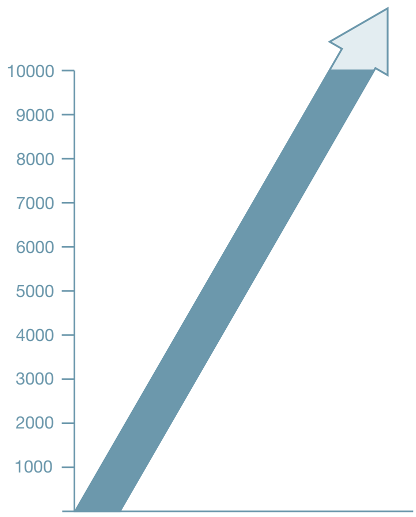
Clinical milestones

January 2004	February 2004	March 2004
—	—	**RAVEL** 3 years follow-up, ACC **FIM** 4 years follow-up, ACC **SVELTE** 8 month angiographic follow-up, ACC

NEXT ISSUE:

- Real-world experience in challenging indications

Already implanted in over 10,000 patients worldwide in clinical trials.



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a Johnson & Johnson company