Revascularization of diabetic patients: are drug-eluting stents the solution?

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Restenosis and need of repeat revascularization as well as major adverse cardiac events (MACE) are all significantly increased after coronary stenting in patients with diabetes compared to non-diabetic patients. The potential clinical benefit of drug-eluting stents (DES) in this cohort is currently under definition. Both Cypher and Taxus stents in randomized clinical trials and real world post-approval registries appear to be effective with a substantial reduction in MACE and target lesion revascularization compared to control patients. However, despite stability of target lesion revascularization obtained with DES, diabetes continues to be associated with a significant increase in MACE at mid- and long-term follow-up. These data emphasize the role of a fully integrated medical, glycemic and device treatment for optimal outcome in diabetes. In order to develop new guidelines for diabetic treatment, prospective and randomized studies comparing DES with surgical revascularization in three-vessel and/or left main disease are ongoing. Despite significant amelioration obtained with DES the diabetic population remains an unmet need, requiring further basic and clinical research.

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Life expectancy is considerably worse after the diagnosis of diabetes[1]. Diabetes increases the risk of coronary heart disease, stroke, and peripheral vascular disease from 2- to 4-fold[2,3]. Furthermore coronary artery disease in diabetic patients is more extensive and diffuse with an increased prevalence of multivessel disease. Moreover, as an effect of changes in the lifestyle that have accompanied globalization the incidence of this condition is explosively increasing[4].

Despite significant advances in interventional techniques, diabetes still remains an independent predictor of cardiac adverse events after percutaneous coronary interventions. Restenosis and need of repeat revascularization as well as major adverse cardiac events (MACE) are all significantly increased after coronary stenting in patients with diabetes compared to non-diabetic patients[5]. The potential clinical benefits of drug-eluting stents (DES) in this cohort are currently under definition.

Are current drug-eluting stents sufficient to treat diabetes?

The Cypher™ stent. In over 5500 diabetic patients treated with the Cypher stent in randomized clinical trials (RAVEL, SIRIUS, New-SIRIUS, SVELTE, DIRECT, DIABETES) and registries (e-CYPHER, BRIDGE, and WHC Study), the Cypher stent appeared to be safe and effective with a substantial reduction in MACE and target lesion revascularization (TLR) compared to control patients. In an integrated analysis of the randomized pivotal trials the Cypher stent significantly reduced the 8-month in-stent late lumen loss in both insulin and non-insulin-dependent patients (79 and 77% respectively) with sustained clinical benefit (TLR reduction) up to 2 years (Fig. 1).

Quantitative coronary angiography assessments in 222 diabetic patients randomized to the Cypher stent showed a marked inhibitory effect on in-stent neointimal formation. Eight-month late lumen loss was 0.07 mm in the RAVEL trial, 0.29 mm in the SIRIUS trial, 0.22 mm in the New-SIRIUS, and 0.27 mm in the SVELTE trial with a significantly reduced incidence of binary restenosis (from 0 to 8%) compared to the control group (from 41.7 to 54.4%). In the same patient cohort the TLR rate at 270 days ranged from 0 to 6.9%. The 2-year survival free from MACE was > 85%. The efficacy of the Cypher stent in TLR reduction in diabetics was recently confirmed by the DIABETES trial, a multicenter, independent, randomized study carried out at four interventional centers in Spain[6]. The study enrolled 160 diabetic patients (in-

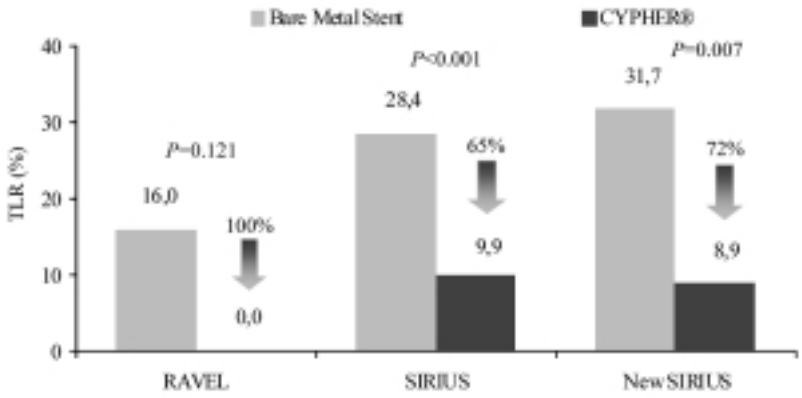
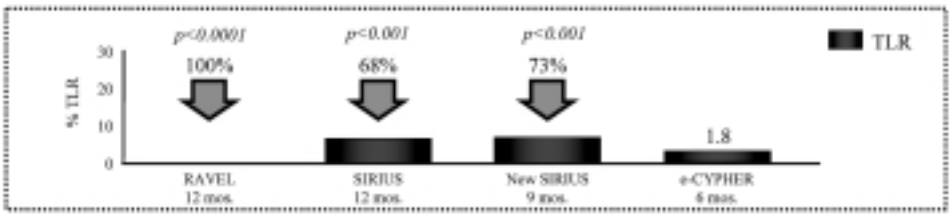


Figure 1. *Major Cordis-sponsored clinical trials in diabetic patients: target lesion revascularization (TLR) at 2 years.*

sulin and non-insulin-treated) with single lesions in the native coronary arteries. Complex lesions and patient cohorts were excluded (in-stent restenosis, bifurcations, recent myocardial infarction, and chronic renal failure). At 9-month follow-up, the use of the Cypher stent was associated with an 88% reduction in late lumen loss (primary endpoint) compared with control patients. Late loss was not affected by type of diabetes. Correspondently the in-segment restenosis rate was significantly reduced in Cypher-treated patients (7.7 vs 33%, $p < 0.001$) as well as the TLR rate (7.5 vs 31.3%, $p < 0.0001$). In addition, at 9-month follow-up the percentage of event-free patients was significantly better in the Cypher arm than in controls (88.7 vs 63.7%, $p < 0.005$). No differences in cardiac death and reinfarction were observed.

The two major limitations of these favorable results are the small total number of treated patients (n = 302) and a single-lesion approach that excluded more complex angiographic and clinical settings. Although real-world post-marketing registries have many intrinsic limitations (observational design, voluntary reporting from physicians, limited auditing, incomplete follow-ups) they are going to fill these two gaps of number and complexity in a short period of time, with critical information collected on safety and efficacy. Actually data on safety and efficacy were reported in diabetic patients from four large post-marketing registries: e-CYPHER and Bridge (supported by Cordis), German Registry and WHC (independently controlled). Total data on more than 6000 diabetic patients treated with the Cypher stent for on- and off-label use were reported. Both sponsored and independent registries showed comparable low event rates in real-world indications at mid-term follow-up. The great majority of the reported data were derived from the multicenter, international e-CYPHER registry (4323 diabetics out of 15 172 patients entered into the database, with 1431 patients with insulin-dependent diabetes) (Fig. 2).

The main clinical and lesion characteristics of the diabetic group were 50% with at least one off-label indication, 47% with acute coronary syndromes – including acute myocardial infarction –, and > 60% with multivessel disease. The averaged vessel size and lesion



		RAVEL	SIRIUS	New SIRIUS	e-CYPHER
Patients (n)	Total 195	19	131	45	4323
IDDM Patients (n)	Total 51	5	38	8	1431
MLD post (mm)		2.43	2.62	2.45	2.8 *
Stented Length (mm)		18.1	21.5	23.3	20.3

Figure 2. *The Cypher stent in diabetic patients (n = 5655). IDDM = insulin-dependent diabetes mellitus; MLD = minimal luminal diameter; TLR = target lesion revascularization. * visual or quantitative coronary angiography estimation.*

length visually estimated were 2.8 and 17.6 mm respectively. The use of Cypher stents in diabetic patients in routine clinical practice yields comparable results to those observed in randomized clinical trials in both insulin-dependent and non-insulin dependent diabetic groups[7]. On- and off-label use in diabetic patients was associated with only a slight but still significant increase in repeat revascularization at 6 months compared to non-diabetic patients. However diabetic patients receiving a Cypher stent in the real world continue to have higher MACE and cardiac mortality rates at 6 months independently of an effective control of in-stent restenosis (Fig. 3). The MACE rate at 6 months was 5.9% in insulin-dependent and 3.3% in non-insulin-dependent diabetic patients (p = 0.001), including death (3.2 vs 1.5%, p = 0.03), myocardial infarction (1.6 vs 1.0%, p = 0.2), and ischemic TLR (1.5 vs 1.3%, p = 0.7). These results were obtained with the evidence that the adjunctive medical treatment in real-world diabetics is still far from being optimal (66% discharged on statins, 54% on beta-blockers, and 55% > 3 months of double antiplatelet regimen – aspirin + clopidogrel/ticlopidine).

The main limitations of the existing data are due to the low number of Cypher stents implanted per patient (average 1.4) that does not represent a full revascularization procedure in multivessel diabetic patients (the majority) and in the relatively short length of the treated lesions (average 17 mm) that is excluding diabetic patients with diffuse disease, a quite common situation to be faced in this patient cohort.

Are the present sirolimus doses enough for diabetics?

The recently reported 6-month clinical, angiographic and intravascular ultrasound results from the First in Man three-dimensional study (prospective, randomized, multicenter trial, Cordis a Johnson & Johnson Company), comparing double vs single-dose sirolimus stents in diabetic patients, failed to show any additional benefit of increasing the sirolimus dose with DES (TLR 10.7 vs 3.6%, p = NS; restenosis rate 7.4 vs 4.3%, p = NS; in-stent late loss 0.25 ± 0.54 vs 0.18 ± 0.30 mm, p = NS) with one subacute thrombosis (2%) in the double-dose group (Abizaid A., TCT 2004, unpublished data). Even if the 2-year follow-up is still ongoing, it seems at present that there is no need for further dose escalation with DES to counteract the exaggerated neointimal response in diabetics.

The Taxus™ stent. The use of Taxus polymer-eluting stents in > 2600 diabetic patients in controlled randomized trials (TAXUS I, II, IV and VI) and real-world post-approval registries (WINSDOM, MILESTONE II, ARRIVE) has demonstrated TLR benefit and low reintervention rates independently of the diabetic status (Hermiller J.B., and Russell M.E., TCT 2004, unpublished data).

However all trials evaluating paclitaxel-eluting stents in the TAXUS clinical program were not specifically designed to prospectively assess the Taxus stent response in diabetic patients. Overall, a total of 2289 patients had been treated in these pivotal and confirmation randomized trials, including 458 diabetic subjects (control, n = 242; Taxus, n = 216). The number of enrolled diabetic patients increases as trial inclusion criteria expand to higher complexity (lesions, procedures, and patients). Nevertheless among the enrolled diabetic patients only 154 were requiring insulin (control, n = 83; Taxus, n = 71). In a recently presented *post-hoc* meta-analysis (TAXUS II, IV and VI) based on pooling of individual data points, the 12-month TLR rate was significantly lower in all patients treated with the Taxus stent, regardless of the presence or absence of diabetes (Fig. 4). A Breslow-Day test for homogeneity of odds ratios among the pooled studies was used to demon-

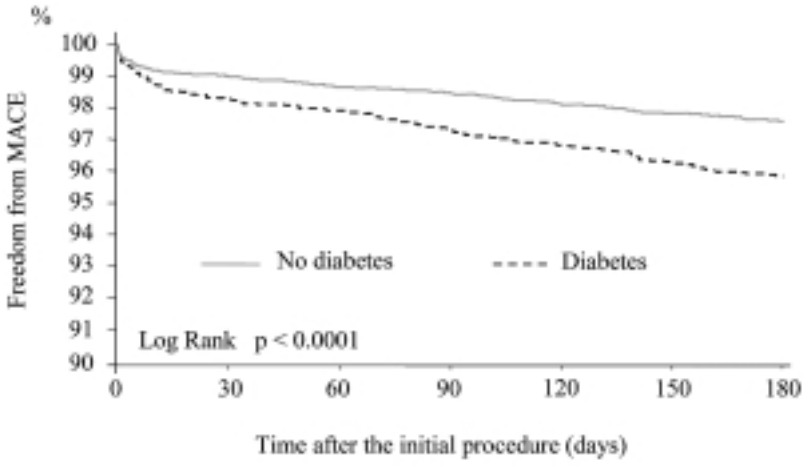


Figure 3. *Six-month survival free from major adverse cardiac events (MACE).*

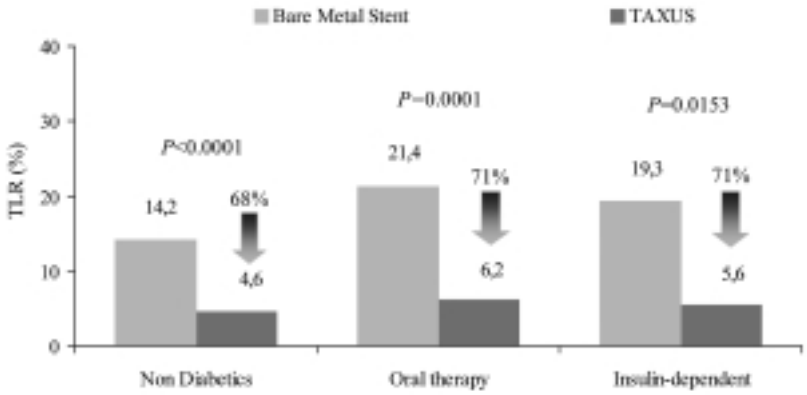


Figure 4. *Taxus clinical trials in diabetic patients: target lesion revascularization (TLR) at 12 months.*

strate independency from dose formulation (slow release vs moderate release) and stent platform (NIR vs Express). Similar results were also observed in the reduction of in-segment restenosis (Hermiller J.B., TCT 2004, unpublished data).

In addition investigators reported a similar value of late lumen loss in diabetic as well as non-diabetic patients treated with the Taxus stent (0.33-0.36 mm), significantly better compared to the value reported in the control arm (0.70-0.78 mm). The Taxus stent had a favorable impact both in reducing TLR and reintervention rate in all the diabetic subgroups, including those with proteinuria (as a marker of advanced disease) and suboptimal glycemic control (serum glycosylated hemoglobin > 7.0%). Additional prospective trials are warranted in order to validate this retrospective pooled analysis.

To date more than 2300 diabetic patients were entered in Taxus stent peri/post-approval registries (WISDOM, MILESTONE II, ARRIVE) (Russell M.E., TCT 2004, unpublished data).

The WISDOM transitional registry was initiated in 2002 as part of a limited commercial launch of the Taxus stent system, to assess the usage patterns of the first Taxus slow-release formulation. As an international, multicenter, prospective, observational registry, WISDOM collected and analyzed data via website on 778 patients (260 diabetic patients, 33.4% of the total population). All patients received source data verification on selected parameters while patients with reported cardiac events had source data verification on all data points. A single Taxus stent was used in 91% of the target lesions, with an averaged lesion length of 15.9 mm. The 12-month follow-up was obtained in 92% of patients. In diabetic compared to non-diabetic patients the reported MACE rate was 9.8 vs 2.9% (death 4.3 vs 1.2%, reinfarction 2.7 vs 0.4% and target vessel revascularization 4.0 vs 1.1%).

A real-world practice patient and lesion complexity was recently evaluated in the MILESTONE II Registry. On a global basis, this registry enrolled 3688 patients at 164 centers in 32 countries. MILESTONE II had a 96% of follow-up at 6 months and 40% monitoring of the enrolled patients. All reported events were reviewed and adjudicated by an independent medical reviewer. In the diabetes cohort (33.9% of all patient population, n = 1251; insulin-dependent diabetics, n = 309), the MACE rate was 7.2% (cardiac death 2.1%, reinfarction 1.5%, reinterventions 3.6%), while stent thrombosis (angiographically confirmed thrombotic events including all deaths < 30 days without obvious causes) was 1.4%. The lower rates for cardiac events in observational registries are to be expected given differences in study design and execution between controlled trials and registries.

Finally the ARRIVE periapproval registry is evaluating in the United States greater complexity in Taxus stenting procedures. Among the 2586 consecutive patients enrolled (795 diabetic patients, 30.7% of the entire population), 17.3% had multivessel disease treated, while the average stent length per patient was 30.6 mm. ARRIVE reported a 99% follow-up at 30 days. The 30-day MACE rate was of 2.7%, including site-reported cardiac death, myocardial infarction and reintervention of the target vessel. An acceptable early safety outcome with low rates of stent thrombosis and target vessel reintervention was reported. The 1-month adjudicated MACE rate was 4.1% (cardiac death 1.4%, myocardial infarction 1.8%, need for repeat procedures 0.9%), while stent thrombosis was 1.3%.

At present time there are no data available to demonstrate the superiority of one DES system over another in diabetics with *de novo* lesions. In the prospective, randomized head-to-head comparison of the Reality study, having as primary endpoint the 8-month in-lesion angiographic restenosis, the diabetics represent 28% (n = 388) of the all 1386 patients enrolled. Although this equivalence study was not specifically designed to analyze extremely complicated patient and lesion settings, the results in diabetics are going to be remarkable for effective decision-making.

In summary both the Cypher and Taxus stents in diabetic patients with a lesion length ranging from 9 to 16 mm and a vessel size between 2.3-3.0 mm, are safe and

effective acutely. DES in diabetes are associated only with a slight increase in TLR at 6 months compared to non-diabetic treated patients. However, despite stability of TLR obtained with DES in diabetic as well as non-diabetic patients, diabetes continues to be associated with a significant increase in MACE including death, myocardial infarction and stent thrombosis at mid- and long-term follow-up[7] (and Hermiller J.B., and Russell M.E., TCT 2004, unpublished data).

What is the risk of increased stent thrombosis as more complex lesions and patient cohorts are treated with drug-eluting stents?

Stent thrombosis results from a series of complex interactions involving the presence of a thrombogenic surface, the damage to the vessel wall, the altered blood flow, and the activation of platelet and coagulation cascades. Antiplatelet agents have been shown to be effective in reducing early thrombotic events with bare metal stent (BMS)[8]. In the modern era (second-generation stents + high pressure deployment + dual antiplatelet therapy) BMS thrombosis within 30 days is approximately 0.5% (95% confidence interval 0.3-0.8) in large clinical practice and 0.9% (95% confidence interval 0.6-1.1) in pooled analysis from multicenter trials[9]. However, the rate of acute and subacute stent thrombosis is substantially increased in higher-risk lesion and patient cohorts[10]. Does the use of DES necessarily imply an increased risk of stent thrombosis? In a pooled analysis of the major clinical trials carried out with the Cypher stent in low-mid risk lesion and patient cohorts, including small vessels and in-stent restenosis, only 9 thrombotic events (acute-subacute and late) out of 1394 patients were reported. In more recent data from the routine use of DES (Cypher and Taxus) in 2227 high-risk patients[11], stent thrombosis continues to occur at an acceptable rate (1.2%). However renal failure (odds ratio 11.5), bifurcation lesions (odds ratio 7.2), and diabetes (odds ratio 3.4) were significant predictors of higher stent thrombosis. Real-world thrombotic failure may be due to extreme patient complexity or an increased thrombogenic profile.

Actually, the 6-month results collected from the e-CYPHER registry confirm the safety of sirolimus-eluting stents in diabetes[7]. Nevertheless stent thrombosis is higher in insulin-dependent vs non-insulin-dependent diabetic patients (2.38 vs 0.96%, p = 0.001). This difference is mainly due to the increased rate of subacute stent thrombosis (Fig. 5), predominantly occurring within 12 days of sirolimus-eluting stent implantation.

As a consequence insulin-dependent diabetes remains an independent predictor of all MACE components and stent thrombosis at 6 months[12]. The increased rate of stent thrombosis in insulin-dependent compared to non-insulin-dependent patients suggests meticulous attention to the periprocedural antithrombotic therapy (Table I).

Table I. Predictors of stent thrombosis at multivariate analysis.

	OR (95% CI)	p
Clinical		
Insulin-dependent diabetes	3.24 (1.79-5.62)	< 0.0001
ACS at presentation	2.32 (1.28-4.51)	0.009
Age (1 year older)	1.03 (1.01-1.06)	0.01
Lesion calcifications (heavy/moderate)	1.95 (1.15-3.27)	0.01
Procedural		
Non-SES also implanted	3.95 (1.48-8.80)	0.002
Post-procedure TIMI flow < 3	3.82 (1.37-8.91)	0.0045
Post-procedure MLD (1 mm larger)	0.59 (0.40-0.94)	0.02

Logistic fixed model: predictors chosen by stepwise procedure using an entry criterion of 0.20 with a stay criterion of 0.10. ACS = acute coronary syndrome; CI = confidence interval; MLD = minimal luminal diameter; OR = odds ratio; SES = sirolimus-eluting stent; TIMI = Thrombolysis in Myocardial Infarction.

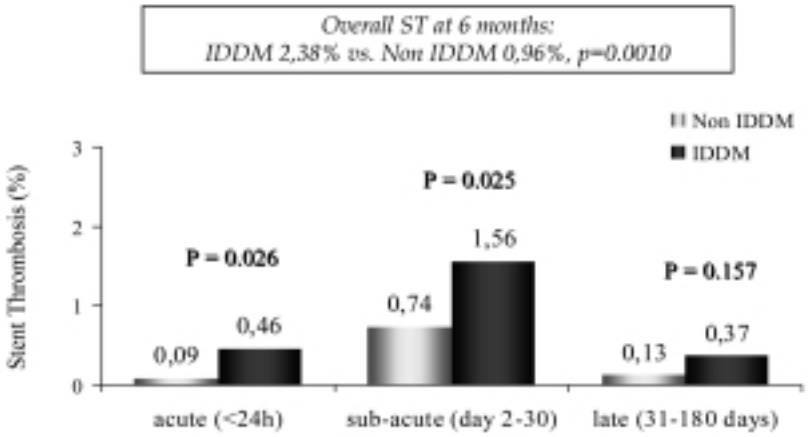


Figure 5. *Cypher stent thrombosis (ST) in diabetes. All cases with reported death, acute myocardial infarction, target lesion revascularization or ST were reviewed and adjudicated by the Clinical Events Committee. IDDM = insulin-dependent diabetes mellitus.*

What is biologically different among diabetic patients in terms of their response to stenting?

In animal models, depending upon drug potency and polymer biocompatibility, DES may suppress the neointimal growth at the cost of a delayed healing process, with a lower rate of endothelial stent coverage, more persistent fibrin deposits, and an increased inflammatory response[13]. Until recently, we have had limited access to diagnose vascular response in living patients. A high-resolution coronary artery imaging modality (Angioscopy, Optical Coherence Tomography) has the potential to address important *in vivo* vessel responses to different stent design and components[14].

In vivo angioscopic images of DES in diabetes at different time points of follow-up detect very thin non-uniform coverage of these stents, with increased fibrin around the stent struts. No major thrombi were observed at the DES level in diabetic and non-diabetic patients. These findings suggest a need for further improvements toward a more prompt and functionally complete coverage of DES as well as a more effective antithrombotic therapy in diabetics.

Several systems that maintain the integrity and patency of the normal vasculature are impaired in diabetes, including platelet, endothelial function, coagulation, and fibrinolysis. Thus, the balance of normal hemostasis is shifted to favor thrombosis. Platelets in diabetic patients exhibit reduced membrane fluidity, which may reflect changes in the lipid membrane components or protein glycation[15]. In addition arachidonic acid metabolism is increased leading to enhanced thromboxane A_2 production and contributing to increased platelet sensitivity[16]. Platelets in diabetic patients produce less nitric oxide and prostacyclin, which normally inhibit platelet-endothelium interactions and promote endothelium-mediated vasodilation. The nitric oxide synthase concentration is less than half that measured in platelets of non-diabetic patients[17]. Furthermore platelets in diabetic subjects contain reduced antioxidant levels, which tend to be associated with increased aggregability[18]. Further, patients with type 1 and type 2 diabetes have increased populations of platelets expressing activation-dependent adhesion molecules, such as the activated glycoprotein IIb/IIIa, lysosomal glycoprotein 53, thrombospondin, and P-selectin[19]. The increased expression of glycoprotein IIb/IIIa is consistent with the enhanced fibrinogen binding and aggregability seen in platelets of diabetics[20]. Finally serum fibrinogen levels are elevated in many patients with type 1 or type 2 diabetes. Platelet reactivity may have prognostic implications: the event probability (myocardial infarction, target vessel revascularization) is based on the capacity of binding fibrinogen in response to adenosine diphosphate. In high reactivity patients insulin-dependent diabetes mellitus is the only baseline characteristic significantly represented[21]. In addition recent data have shown that diabetic patients continue to have a higher platelet adhesion and aggregation even at 1 month of standard double antiplatelet regimen (clopidogrel 300 mg loading dose followed by 75 mg/day + aspirin 100 mg/day)[22]. This may explain the increased risk of early stent thrombosis observed in diabetes when treated with DES, suggesting the use of higher clopidogrel doses or more meticulous periprocedural pharmacological approach in this subset of patients.

Diabetic patients with multivessel disease: are drug-eluting stents the solution?

At 7 years the BARI trial showed an excess of > 20 deaths for every 100 diabetic patients revascularized by percutaneous techniques compared to bypass surgery[23]. These findings provided a compelling evidence to conclude that diabetic patients with multivessel disease requiring an intervention are best treated with bypass surgery. Novel developments in percutaneous coronary intervention might translate into a significant improved outcome to offset the advantage of bypass surgery originally seen in BARI and further confirmed in ARTS I with the use of BMS[24].

ARTS II was recently completed as a single-arm study in multivessel disease patients treated with the Cypher stents: 607 patients; 26% diabetics, left anterior descending coronary artery mandatory, 54% of three-vessel disease were historically controlled against the bypass surgery and BMS arms of the ARTS I trial[25]. On average 3.6 lesions per patient were treated with the Cypher stent, with a total stent length of 73 mm per patient. The event-free survival at 6 months (including freedom from death, reinfarction, cerebrovascular accident and repeated procedure) was significantly better in ARTS II DES-treated patients (93.6%) compared to the BMS cohort of the ARTS I (80%, $p < 0.001$). As a consequence, the Cypher stent in multivessel disease seems to be able to counteract the increasing rate of in-stent restenosis, usually accompanying a multiple number of BMS placement. However long-term follow-up results and data on diabetics are not available yet and they need to be substantiated in efficacy and durability.

Two major prospective, randomized trials are going to approach shortly all the remaining clinical issues on the use of DES in diabetic patients with multivessel disease: the FREEDOM and the SYNTAX trials. The FREEDOM trial is investigating in multivessel disease diabetic patients the impact of a combination of multivessel stenting with the Cypher or Taxus stents and abciximab, compared to bypass surgery with respect to 3-year death, myocardial infarction, and stroke (Farkouh M., TCT 2004, unpublished data). The study is recruiting 2400 patients. All concomitant therapies shown to be beneficial are encouraged, including clopidogrel,

angiotensin-converting enzyme inhibitors, beta-blockers, and statins. Multiple medical targets are planned: serum glycosylated hemoglobin < 7.0%, low-density lipoprotein cholesterol < 100 mg/dl, and blood pressure < 130/80 mmHg).

On the other hand, the SYNTAX trial, ready for approval, is going to test in a head-to-head comparison the Taxus stent vs surgical revascularization in 1500 patients with *de novo* three-vessel disease and/or left main disease (Stone G.W., TCT 2004, unpublished data). To provide real-world answers to these questions in order to develop new guidelines all ongoing study and consensus team agreement will be used.

Conclusion

These data emphasize the role of a fully integrated medical, glycemic and device treatment for diabetes mellitus. Despite significant amelioration obtained with DES in controlling post-stent proliferative local response, the diabetic population remains an unmet need requiring further targeted basic and clinical research.

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