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Three tribes go to war – latest DES results

Results presented at the ACC merely emphasised rivalry in the DES war. Whilst Cordis and Boston Scientific continued their war of words, related to the findings from the ARTS II, SIRTAX and TAXUS V trials, Medtronic announced promising data regarding its Endeavor system – which was at the point of recieving the CE mark at the time of going to press.

ACCORDING TO Cordis's rivals, results from the REALITY Trial, comparing the Cypher stent (Cordis) and the Taxus stent (Boston Scientific), presented at the American College of Cardiology (ACC) Annual Scientific Session, failed to meet its primary endpoint of proving Cypher's superiority to Taxus.

Sponsored by Cordis Corporation, the REALITY Trial is a prospective, randomised study involving 1,386 patients at 90 hospitals centers in Europe, Latin America and Asia. In the REALITY trial, patients were included if they had up to two de novo lesions with a primary lesion of at least 15mm in length in small vessels (2.25 to 3.0mm in diameter). The two study arms were well balanced in terms of standard patient characteristics including age, sex and prior heart attack. Patients were also well balanced in terms of number of diseased arteries and the location of the lesions. On average, patients receiving the Cypher Stent had 1.91 stents, while those receiving Taxus had 1.94 stents. The REALITY trial is one of several randomised controlled trials, including the ISAR-DIABETES and SIRTAX studies, comparing the two drug-eluting stents in different patient populations.

REALITY

Results from the REALITY trial found that the Cypher Sirolimus-eluting Coronary Stent was associated with development of significantly fewer blood clots at the stent site than the Taxus Paclitaxel-eluting Coronary Stent. This was not in the intention-to-treat analysis, but in the actual treatment, with events seen in 0.4% versus 1.8% of patients, respectively (p=0.196), due to one patient assigned to a Cypher stent receiving a Taxus stent instead.

"In this study, the incidence of stent thrombosis was 78% lower with the Cypher Stent than with the Taxus Stent," said Principal Investigator, Dr Marie-Claude Morice, Head of Interventional Cardiology at the Institut Hospitalier Jacques Cartier, Massy, France. "As this is the first head-to-head trial to observe a difference in the rate of stent thrombosis, these results raise concerns and demand further investigation. While we see that the two drug-eluting stents were comparable in terms of the primary endpoint of restenosis, we also observed that patients who received the Cypher Stent had a significantly larger vessel diameter inside the stent after eight months of follow-up, which is

Marie-Claude Morice

important because the vessel diameter determines the amount of blood that is delivered to the heart muscle," noted Morice.

According to Cordis several key angiographic measurements favoured the Cypher Stent at the eight month follow-up endpoint of the study. The minimum lumen diameter was significantly larger, while the late loss and mean% diameter stenosis were both significantly lower with the Cypher Stent. "There is a growing body of meaningful and predictive data to examine about the Cypher Stent," said Dr Dennis Donohoe, Vice President, Worldwide Regulatory and Clinical Affairs, Cordis. "Time and again, researchers continue to find that the Cypher Stent offers benefit for many types of patients and lesions in the near- and long-term, improving health and quality of life."

Boston Scientific Corporation welcomed the results, which reaffirmed the safety and efficacy of its Taxus Express2 paclitaxel-eluting coronary stent system. Boston's Chief Operating Officer, Paul LaViolette, said that while REALITY failed to meet its primary endpoint, "we were particularly pleased to see that it reaffirmed the safety of the Taxus stent system. There were 'no significant differences' in safety endpoints between the Cypher and Taxus systems, according to the presentation. The absence of any significant differences in the safety endpoints within the intent-to-treat patient population once again reaffirms the excellent safety profile of approved drug-eluting stents. The reported early stent thrombosis rates for both arms are well within the previously established safety profile for both technologies."

"Despite the fact that this trial was

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ESC issues PCI guidelines

THE EUROPEAN SOCIETY OF CARDIOLOGY (ESC) has released the first European Guidelines on Percutaneous Coronary Interventions (PCI). According to these guidelines, PCI can now be regarded as the first option for a larger group of patients with acute coronary syndromes (ACS) than before. Recent technical and pharmacological improvements have developed PCI into a procedure that can be safely and effectively applied to patients with various types of coronary lesions and patients with and without myocardial infarction (MI). The ESC guidelines on PCI represent the consensus of a Task Force of European experts, chaired by Professor Sigmund Silber of the Gemeinschaftspraxis Hospital, Munich, Germany. Silber outlines the highlights of the guidelines and summarises the recommendations, whilst outlining the rationale behind their timing and their relevance to the European healthcare arena.

One of the most pertinent points of the ESC guidelines is that thrombolysis for MI can be administered within the first three hours after onset of chest pain, if no catheter lab is

Sigmund Silber

accessible, preferably within 90 minutes. Thrombolysis, however, should not be regarded as the final treatment stage: even if successful, thrombolysis should still be followed by invasive diagnosis and treatment, if applicable. A patient may feel fine after thrombolysis, but there is significant evidence that he/she should still undergo cardiac catheterisation, optimally within 24 hours after successful thrombolysis.

Due to the differences in the infrastructure between the US and Europe, the ESC guidelines differ from those of the US (issued by the American College of Cardiology and American Heart Association), when addressing issues of time and distance to catheter laboratories.

The European guidelines are based on the likelihood that most patients can reach a catheter laboratory, preferably within 90 minutes after first medical contact, if an appropriate network logistic has been established.

Furthermore, the ESC guidelines do not demand cardiac surgery on-site for PCI, since so many more hospitals are in a position to offer high-quality PCI. These guidelines aim to present all the relevant evidence on PCI in order to help physicians weigh the risks and benefits of diagnostic and therapeutic procedures in their daily clinical decision-mak-

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ESC issues PCI guidelines

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ing. The practically oriented recommendations address when to perform PCI on the basis of currently available, peer-reviewed, published data, derived from randomised and non-randomised clinical studies. A top-line summary of these recommendations follows:

1 PCI can be considered a valuable initial mode of revascularisation in all coronary artery disease patients with objective large ischemia, and this is the case for every lesion subset except chronic total occlusions that cannot be crossed.
2 The addition of stents and newer adjunctive medications has improved PCI outcome. The decision to recommend PCI or CABG surgery will be guided by technical improvements in cardiology or surgery, local expertise and patients preference.
3 Until proven otherwise, PCI should be used only with reservation in diabetics with multi-vessel disease and in patients with unprotected left main stenosis (although developments in drug-eluting stents may eventually alter this situation).
4 Patients presenting with NSTE-ACS (unstable angina or myocardial infarction without ST-segment elevation) have to be stratified first for their risk of acute thrombotic complications. A clear benefit from early angiography (<48 hours) and, when needed, PCI or CABG surgery, has been reported only in the high-risk groups.
5 Deferral of intervention does not improve outcome. Routine stenting is recommended on the basis of the predictability of the results and its immediate safety.
6 In patients with STEMI (ST-segment elevation – myocardial infarction), primary PCI within 12 hours after onset of chest pain should be the treatment of choice in patients presenting in a hospital with PCI facility and an experienced team.
7 Patients with contra-indications to thrombolysis or no signs that thrombolysis is working within 45-60 minutes after administration should be immediately transferred for PCI, as this might be their only option in order to ensure the swift opening up of the coronary artery.
8 In cardiogenic shock, emergency PCI for complete revascularisation may be life-saving and should be considered at an early stage.
9 Randomised trials have noted that transfer of the patients for primary PCI to a heart attack centre have observed a better clinical outcome than thrombolysis. This has been observed despite the delay, due to transportation, between randomisation and the start of the treatment.
10 The superiority of primary PCI over thrombolysis seems to be especially clinically relevant, for the time interval between three and 12 hours after onset of chest pain or other symptoms, on the basis of its superior preservation of myocardium. Furthermore, with increasing time to presentation, MACE rates increase after thrombolysis, but appear to remain relatively stable after primary PCI. Within the first three hours after onset of chest pain or other symptoms, both reperfusion strategies seem equally effective in reducing infarct size and mortality. Therefore, thrombolysis is still a viable alternative to primary PCI, provided that it can be delivered within three hours after onset of chest pain or other symptoms.
11 Primary PCI compared with thrombolysis significantly reduced stroke. Overall, the recommendation is for primary PCI over thrombolysis in the first three hours of chest pain, in order to prevent stroke, and in patients presenting three-12 hours after the onset of chest pain, to salvage myocardium as well as preventing stroke.
12 At present, there is no evidence to recommend facilitated PCI.
13 After successful thrombolysis, to improve patient outcome, the use of routine coronary angiography within 24 hours and PCI (if applicable) is recommended. This applies even if the patient is asymptomatic and without demonstrable ischemia.
14 If a PCI centre is not available within 24 hours, patients who have received successful thromblysis, with evidence of spontaneous or inducible ischemia before discharge, should be referred to coronary angiography and revascularised accordingly, independent of maximal medical therapy.

"The field of PCI is constantly and rapidly evolving," explained Silber, "We are always waiting for the next study and development. Following each new study, we need to re-evaluate our thinking and clinical practice. With the wealth of recent landmark studies and developments in the field of PCI, the ESC feels that it is the appropriate moment to review the data released to date and offer guidance on the recommended procedures. We [the Task Force on PCI of the ESC] believe it is time to set the European guidelines on PCI. We want to acknowledge and present the incredible amount of recent developments, studies and data on PCI. Following this recent peak in activity, it is the optimal moment to issue these guidelines and we expect that our recommendations should remain valid for at least two to three years".

Spearately, the British Cardiovascular Intervention Society (BCIS) has revealed that the third set of PCI 'Guidelines' (Percutaneous coronary intervention: recommendations for good practice and training) will appear as a supplement to Heart Journal in June 2005 both as a paper supplement and on eHeart. Previous guidelines that appeared in 1996 and 2000 have been updated to reflect contemporary practice. This set of guidelines includes new sections on training, informed consent and a core evidence base.

This is the third set of guidelines produced by the BCIS and the British Cardiac Society (1,2). Following the last set of guidelines published in 2000, PCI activity in the UK has increased from 33,652 to 53,261 (60% in three years) such that the PCI:CABG ratio has increased to 2.1:1. The BCIS claims the impact of drug eluting stents has been profound, and the Department of Health is investigating the feasibility of primary PCI for acute myocardial infarction. Changes in the structure of NHS funding are likely to focus attention on cost effective therapies and will require physician engagement and sensitive handling if rapid and appropriate growth in cardiovascular intervention continues.

The ESC has recommended that the anticoagulant, bivalirudin (tradename Angiox in Europe and Angiomax in US), replace heparins (unfractionated or low-molecular weight) in patients undergoing PCIs. In the guidelines, the authors reviewed data across a wide range of studies of bivalirudin in PCI, including the REPLACE-2 trial, which examined bivalirudin performance compared to the combination of heparin with platelet blockers known as GP IIb/IIIa inhibitors. The guidelines state, "REPLACE-2 determined the efficacy and safety of bivalirudin monotherapy compared with heparin plus GP IIb/IIIa blockade with regard to protection from periprocedural ischaemic and haemorrhagic complications in patients undergoing PCI." The guidelines noted death rates in REPLACE-2, stating, "...after one year, mortality showed a lower trend in the bivalirudin group (1.89%) compared with the heparin plus GP IIb/IIIa group (2.46%, P=0.16)."

In addition, regarding bivalirudin, the ESC guideline authors, "unanimously recommended as a replacement for UFH (and LMWHs) in patients with heparin-induced thrombocytopenia (HIT)". HIT occurs when a patient exposed to heparin forms heparin antibodies, which may cause severe immune reactions if the patient is exposed to heparin again.

Bivalirudin is marketed as Angiox in Europe by Nycomed Group and Grupo Ferrer. The Medicines Company markets bivalirudin as Angiomax in the US. Angiox is currently approved in the US and the EU, as well as several other territories. Angiomax is a direct thrombin inhibitor with a naturally reversible mechanism of action. In clinical trials, Angiomax has demonstrated reductions in both ischemic and bleeding complications compared to heparin as the foundation anticoagulant in the contemporary catheterisation lab setting. These reductions in ischemic and bleeding complications remain evident even in high-risk patients. In the EU, the approved indication for Angiox is as an anticoagulant for patients undergoing PCI. In the US, Angiomax is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

Hakan Bjorklund, Nycomed CEO said, "The favourable review and recommendation by the ESC is a recognition of the clinical evidence for Angiox. It reflects that improved patient outcomes and simplified treatment has been demonstrated across several trials. We expect that this development will significantly and positively affect the continued introduction of Angiox in Europe."

Controversy over DES in complex lesions

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were also significantly reduced compared with patients treated with a bare metal stent. This reduction appears to have been driven by the reduction in TLR – as seen in other DES trials. The in-stent restenosis rate was 5.7 vs. 50.6, p<0.0001 with the in-segment restenosis rate of 11.8 vs. 52.5, p <0.001.

Investigators from DIABETES, an independent, multi-centre, prospective, randomised trial and the first drug-eluting stent trial with a 100% diabetic patient population, presented follow-up data that showed the beneficial effect seen at six months with Cypher was sustained out to 12 months. Involving 160 diabetic patients from four Spanish Centres (Madrid, Barcelona, Valladolid and Vigo) the patient population is remarkable in so much as they combine the risk factors of diabetes with the smallest diameter lesions ever studied (mean vessel diameter of 2.34 mm, with significantly smaller vessels treated in the IDDM group – 2.21 mm in the Cypher arm and 2.26 mm in the control arm). The average lesion length was 15.0 mm.

At one-year, the investigators revealed TLR rates of 7.5% for the Cypher arm (n=80) versus 35% for the bare metal stent control arm (n=80), p<0.0001. Similarly MACE rates of 11.3% vs. 38.8% in favour of Cypher were recorded, p<0.0001. (See Table 10)

Table 10: DIABETES Trial 1-year results

	SES (n=80)	BMS (n=80)	P value
Death, n (%)	1* (1.3)	2** (2.5)	0.5
Q-MI, n (%)	1 (1.3)	0 (0)	0.3
Non-Q MI, n (%)	1 (1.3)	6 (7.5)	0.1
TLR, n (%)	6 (7.5)	28 (35)	<0.0001
MACE, n (%)	9 (11.3)	31 (38.8)	<0.0001

* Cardiac rupture / sudden death ** Refractory heart failure

In further analysis, examining TLR and diabetes status, the investigators found statistically significant reductions in both NIDDM patients (7.4% vs. 32.1%, p=0.009, and IDDM 7.7% vs. 40.7%, p=0.001). These remarkable findings translate into Percent Freedom from TLR of 92.5% for Cypher and 65% in the bare metal control group (as measured by Breslow Test <0.001). The investigators also reported no late stent thromboses out to one-year (on clopidogrel treatment), and one-month after its discontinuation.

In summary, the two independent studies, DIABETES and ISAR-DIABETES, together with data from the integrated analysis of six other Cypher trials, serve to highlight the excellent outcomes with the Cypher stent in this difficult-to-treat group at high risk of repeat revascularisation.

As reported elsewhere in this edition of *Cardiovascular News*, new head-to-head trial results presented at this year's ACC comparing Cypher Sirolimus-eluting stent with the paclitaxel-eluting Taxus stent now appear also to validate Edelman and Campbell's hypothesis for drug-eluting stents.

Table 8: Integrated CYPHER trial Information

Studies	RCT vs BMS	Pts	Study Location	Angio F/up (Mos)	Clin F/up (Mos)	APT (Mos)	Core Lab	CEC
SIRIUS	Y	*de novo*	US	8	9, 12, 24	3	BW	HCRI
E-SIRIUS	Y	*de novo*	EU	8	9, 12, 24	2	BW	HCRI
C-SIRIUS	Y	*de novo*	CA	8	9, 12, 24	2	BW	HCRI
DIRECT	N	*de novo*	US	8	9	3	BW	HCRI
SVELTE	N	*de novo* & SV	EU/LA	8	9	2	BW	HCRI
RAVEL	Y	*de novo*	EU/LA	6	6, 12, 24, 36	2	CS	CS

RCT – Randomised controlled trial, BMS – Bare Metal Stent, SV – Small Vessel, NA – North America, EU – Europe, US – United States, LA – Latin America, BW – Brigham & Women's, HCRI – Harvard Clinical Research Institute, CS – Cardialysis

Table 9: Cypher Trials DM Patients

Studies	DM Pts		Gender (M%)		Age (Yrs)		IDDM pts	
	CYPHER	Control	CYPHER	Control	CYPHER	Control	CYPHER	Control
SIRIUS	131	148	64%	59%	63.4	62.1	38	44
E-SIRIUS	33	48	64%	60%	62.7	62.7	7	11
C-SIRIUS	12	12	50%	83%	64.9	58.8	1	2
DIRECT	70	-	73%	-	61.9	-	16	-
SVELTE	27	-	74%	-	63.4	-	2	-
RAVEL	19	25	68%	80%	63.6	63.0	5	5
INTEGRATED	292	233	67%	63%	63.0	62.2	69	62