TCT 2008: New Data Lead to New Directions in Treating Cardiovascular Disease

Highlights From the 20th Annual Transcatheter Cardiovascular Therapeutics Symposium, October 12-17, 2008, Washington, DC

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The annual Transcatheter Cardiovascular Therapeutics (TCT) symposium is a signature event in the field of interventional cardiology, marked by the dissemination of the latest data from key trials that enables clinicians to incorporate the most advanced percutaneous techniques available for treating cardiovascular disease into their everyday practices. Here we examine recent studies regarding percutaneous coronary intervention (PCI) in patients who have complex disease or acute myocardial infarction and new trials of current and next-generation drug-eluting stents (DES).

Reviewed by Jason Kahn, MA, Gregg W. Stone, MD, FACC, FSCAI, Martin B. Leon, MD, FACC, Caitlin E. Cox, MA, Kim Dalton, MA, Kiersten Feil, PhD, and Gary S. Mintz, MD, FACC, from Columbia University Medical Center, Cardiovascular Research Foundation, New York, NY.

PCI in Complex Disease

SYNTAX

A pair of subgroup analyses from the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial clarified the initial findings released earlier at the European Society of Cardiology annual meeting. One report, from Patrick W. Serruys, MD, PhD, of Thoraxcenter (Rotterdam, the Netherlands), focused on unprotected left main disease.[1] Data showed that at 1 year, the primary endpoint of major adverse cardiac and cerebrovascular events (MACCE, composite of death, stroke, myocardial infarction [MI], and repeat revascularization) was equivalent for PCI and coronary artery bypass graft (CABG) surgery.[1] Stroke was more frequent in the CABG group, and repeat revascularization was more common in the PCI group (Table 1).

However, when patients were stratified by SYNTAX score (a measure of lesion complexity), those with low and intermediate scores still had equivalent rates of MACCE between CABG and PCI, whereas patients with the highest scores experienced a significantly lower MACCE rate with CABG (Table 2).

In a separate analysis of patients with triple-vessel disease, overall 12-month MACCE rates were significantly higher in those who received PCI compared with CABG.[2] (Patients with low SYNTAX scores were an

exception, with similar MACCE rates regardless of whether they were treated with PCI or surgery.) The rates of MI and repeat revascularization were also higher in the PCI arm (Table 3).

ISAR–Left Main

In 2-year follow-up from the Intracoronary Stenting and Antithrombotic Regimen (ISAR)–Left Main trial, Taxus® stents (Boston Scientific Corp., Natick, MA) and Cypher® stents (Cordis Corp./Johnson & Johnson, Inc., Miami Lakes, FL) performed equally well in high-risk patients with unprotected left main disease. There were no significant differences in the rates of target lesion revascularization (TLR) (6.5% for Taxus vs 7.8% for Cypher; P = .49) or mortality (relative risk [RR], 1.14; 95% confidence interval [CI], 0.66-1.94; P = .64).[3] The combined primary endpoint of death, MI, or reintervention was also similar for the 2 stent types (RR, 0.99; 95% CI, 0.69-1.42; P = .96). In addition, the incidence of definite stent thrombosis was low and statistically equivalent in both groups (0.3% for Taxus vs 0.7% for Cypher).

Table 1
Left Main Disease: Outcomes at 1 Year in the SYNTAX Trial

Endpoints	CABG n = 345	Taxus n = 528	*P* Value
MACCE*	13.6%	15.8%	.44
Stroke	2.7%	0.3%	.009
Repeat revascularization	6.7%	12.0%	.02

*Composite of death, stroke, myocardial infarction, and repeat revascularization.
SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events.
Data from Serruys PW.[1]

Table 2
MACCE* Rates by SYNTAX Score† at 1 Year

SYNTAX Score by Tertiles	CABG	Taxus	*P* Value
Low (0-22)	13.0%	7.7%	.19
Intermediate (23-32)	15.5%	12.6%	.54
High (≥ 33)	12.9%	25.3%	.008

*Composite of death, stroke, myocardial infarction, and repeat revascularization.
†A measure of lesion complexity.
MACCE, major adverse cardiac and cerebrovascular events; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; CABG, coronary artery bypass graft.
Data from Serruys PW.[1]

Table 3
Triple-Vessel Disease: Outcomes at 1 Year in the SYNTAX Trial

Endpoints	CABG n = 549	Taxus n = 546	*P* Value
MACCE*	11.2%	19.1%	< .001
MI	2.6%	5.2%	.04
Repeat revascularization	5.4%	14.7%	< .001

*Composite of death, stroke, myocardial infarction, and repeat revascularization.
SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.
Data from Mohr F.[2]

FAME

The Fractional Flow Reserve Versus Angiography for Guiding PCI in Patients With Multivessel Coronary Artery Disease (FAME) trial investigated whether routine use of fractional flow reserve (FFR) measurements to identify ischemic vessels that require stenting significantly improves clinical outcome in patients with multivessel disease. The multicenter study randomized 1000 patients with stenoses at or greater than 50% in at least 2 of 3 major epicardial vessels to angiographically guided PCI or FFR-guided PCI. In the FFR arm, only those stenoses with an FFR at or less than 0.80 were stented.

One-year results, reported by Nico H. J. Pijls, MD, PhD, of Catharina Hospital (Eindhoven, the Netherlands), demonstrated that, compared with angiographically guided treatment, FFR guidance resulted in better clinical outcomes (Table 4).[4] In addition, use of FFR reduced the number of stents implanted per patient, the volume of contrast agent used, and the overall cost.

Table 4
Adverse Events at 1 Year in the FAME Trial

Endpoints	Angiography n = 496	FFR n = 509	*P* Value
MACE*	18.4%	13.2%	.02
Death or MI	11.1%	7.3%	.04

*Composite of death, MI, and repeat revascularization.
FAME, Fractional Flow Reserve Versus Angiography for Guiding PCI in Patients With Multivessel Coronary Artery Disease; FFR, fractional flow reserve; MACE, major adverse cardiac events; MI, myocardial infarction.
Data from Pijls NHJ.[4]

PCI in Acute Myocardial Infarction

HORIZONS AMI

Long-term outcomes from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS AMI) trial, the largest study to focus on the optimal use of stents and anticoagulation therapy in patients with ST-segment elevation myocardial infarction (STEMI), were reported for the first time at TCT 2008.[5] This randomized, multicenter trial compared bivalirudin with heparin plus a glycoprotein IIb/IIIa inhibitor in 3602 patients, of whom 3000 were randomized to receive Taxus paclitaxel-eluting stents or Express® bare-metal stents (Boston Scientific Corp., Natick, MA).

In the stent cohort, patients treated with Taxus had significantly less ischemia-driven TLR. Risk of major adverse coronary events (MACE, a composite of all-cause death, reinfarction, stent thrombosis, or stroke) was equivalent between both treatment groups (Table 5). Angiographic follow-up was available for 1204 patients and showed that binary restenosis per lesion was significantly lower in the Taxus group than in the Express group (10.0% vs 22.9%; $P < .0001$).

In addition, Roxana Mehran, MD, of Columbia University Medical Center (New York, NY) announced 1-year outcomes from the pharmacologic cohort of HORIZONS AMI that extended the trial's initial 30-day results, published earlier this year.[6] At 1-year follow-up, net adverse clinical events were 2.6% lower in the bivalirudin group versus the heparin group (15.7% vs 18.3%; $P = .03$). Major bleeding was 5.8% with bivalirudin versus 9.2% with heparin ($P < .0001$), and MACE was 11.9% in both groups. In addition, there was a significant 1.4% reduction in all-cause mortality at 1 year with bivalirudin ($P = .029$).[7] Further analyses showed no interaction between drug and stent type for clinical outcomes at either 30 days or 1 year.

ZEST AMI

In the Prospective Randomized Comparison of Zotarolimus-Eluting Stents, Sirolimus-Eluting Stents, and Paclitaxel-Eluting Stents in Patients With Acute Myocardial Infarction (ZEST AMI), the Cypher stent demonstrated less late loss and a lower rate of restenosis than the Taxus stent or the Endeavor® zotarolimus-eluting stent (Medtronic, Inc., Santa Monica, CA) in patients undergoing primary PCI.[8] Cheol Whan Lee, MD, PhD, of Asan Medical Center (Seoul, South Korea) randomized 328 STEMI patients to receive Cypher, Taxus Liberté™, or Endeavor stents.[8] The single-blind trial was stopped early ahead of its target sample size (1482 patients) because of slow enrollment.

At 8-month follow-up, the Cypher stent showed the lowest rate of in-stent and in-segment late loss compared with the other 2 DES (Table 6). At 12 months, there was no difference in the primary endpoint of MACE among the 3 stents (Cypher, 9.1%; Taxus, 9.1%; Endeavor, 11%; $P = .804$), or in rates of death and recurrent MI.

Table 5
HORIZONS AMI: 1-Year Outcomes

	Taxus DES n = 2257	Express BMS n = 749	*P* Value
Ischemic TLR	4.5%	7.5%	.002
MACE*	8.1%	8.0%	.92

*Composite of death, reinfarction, stroke, or stent thrombosis.
HORIZONS AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; DES, drug-eluting stent; BMS, bare-metal stent; TLR, target lesion revascularization; MACE, major adverse cardiac events.
Data from Stone GW.[5]

Table 6
Late Loss at 8-Month Follow-Up in the ZEST AMI Trial

	Cypher n = 110	Taxus n = 110	Endeavor n = 108	*P* Value
In-segment (mm)	0.3	0.47	0.46	.029
In-stent (mm)	0.3	0.52	0.73	< .001

ZEST AMI, Zotarolimus-Eluting Stents, Sirolimus-Eluting Stents, and Paclitaxel-Eluting Stents in Patients With Acute Myocardial Infarction.
Data from Lee CW.[8]

PREPARE
The Prospective Randomized Trial of Proximal (PREPARE) study, which included 284 STEMI patients, demonstrated that early, complete ST-segment resolution was better in those treated with the Proxis™ proximal embolic protection system (St. Jude Medical, Inc., St. Paul, MN) compared with controls.[9] The difference in ST-segment resolution immediately after primary PCI was found to be statistically significant (P = .009), according to presenter Karel T. Koch, MD, PhD, of the Academic Medical Center, University of Amsterdam (Amsterdam, the Netherlands), but this difference narrowed as time progressed.

Current and Next-Generation DES

ISAR-TEST 2
According to recent results from the Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents (ISAR-TEST 2) trial, polymer-free stents eluting both probucol and sirolimus—so-called "Dual DES"—achieved similar rates of restenosis and in-stent late lumen loss as Cypher stents. In addition, both Cypher and the Dual DES performed better than the Endeavor stent.[10]

ISAR-TEST 2 randomized 1007 patients with de novo coronary lesions to the Dual DES, Cypher, or Endeavor stents. In-segment binary angiographic restenosis (primary endpoint) and ischemic TLR were both similar between the Dual DES and Cypher groups. However, Endeavor showed significantly less favorable results than Dual DES for both of these outcomes (Table 7). Late lumen loss was also similar for Dual DES versus Cypher (0.23 mm vs 0.26 mm; P = .78) and was significantly better with Dual DES versus Endeavor (0.23 mm vs 0.58 mm; P < .001).

SORT-OUT III
In early results from the randomized Comparison of Zotarolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With Coronary Artery Disease (SORT-OUT III) trial involving 2333 patients, the Endeavor stent was associated with significantly higher rates of restenosis, TLR, MI, and definite stent thrombosis than the Cypher stent.[11]

At 9-month follow-up, patients in the Endeavor group had significantly higher rates of restenosis (hazard ratio [HR], 6.59; 95% CI, 2.57-16.9; P < .0001) and TLR (HR, 4.19; 95% CI, 2.10-8.35; P < .0001), as well as MI (HR, 3.47; 95% CI, 1.14-10.5; P = .03). Definite stent thrombosis also was more frequent in the Endeavor arm (HR, 4.62; 95% CI, 1.33-16.1; P = .02). There was no significant difference in cardiac mortality between the 2 groups (HR, 2.17; 95% CI, 0.75-6.24; P = .14).

BBC ONE
According to presenter David Hildick-Smith, MD, of the Sussex Cardiac Centre (Brighton, UK), a simple stenting strategy with DES was superior to a complex strategy for unselected bifurcation lesions.[12] The British Bifurcation Coronary Study: Old, New, and Evolving Strategies (BBC ONE) randomized 500 patients with bifurcation lesions to 2 strategies: a simple strategy involving main-vessel DES implantation with kissing inflation and T-stenting plus provisional side-branch stenting (n = 250) or a complex strategy involving total lesion coverage with either culotte or crush techniques (n = 250), according to operator preference.[12]

At 9-month follow-up, the primary composite endpoint of death, MI, or target vessel failure was significantly lower with the simple strategy (8.0% vs 15.2%; P = .009), as was the individual endpoint of MI (3.6% vs 11.2%; P = .001). Rates of target vessel revascularization and death were also lower with the simple strategy, but the differences were not statistically significant.

Periprocedural MACE, meanwhile, was substantially higher with the complex strategy (7.6% vs 2.0%; RR, 3.8; 95% CI, 1.5-10.0; P = .003). Procedural endpoints demonstrated improved times and better resource utilization with the simple strategy (Table 8). ■

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Table 7
ISAR-TEST 2 Outcomes

	Dual DES* n = 333	Cypher n = 335	Endeavor n = 339	*P* Value†
Angiographic restenosis	11.0%	12.0%	19.3%	.002
TLR	6.8%	7.2%	13.6%	.001

**P* value was not significant for Dual DES vs Cypher.
†*P* values for Dual DES vs Endeavor.
ISAR-TEST, Intracoronary Stenting and Angiographic Restenosis–Test Equivalence Between 2 Drug-Eluting Stents; DES, drug-eluting stent; TLR, target lesion revascularization.
Data from Byrne RA.[10]

Table 8
Procedural Endpoints in the BBC ONE Trial

	Complex Strategy n = 250 mean (SE)	Simple Strategy n = 250 mean (SE)	*P* Value
Procedure time (min)	78 (1.9)	57 (1.6)	< .001
Fluoroscopy time (min)	22 (0.8)	15 (0.7)	< .001
Diamentor (cGy cm^2)	7900 (350)	6140 (300)	< .001
No. of guidewires used	3.11 (0.08)	2.21 (0.06)	< .001
No. of balloons used	3.97 (0.11)	2.26 (0.09)	< .001
No. of stents used	2.21 (0.07)	1.17 (0.04)	< .001

BBC ONE, British Bifurcation Coronary Study: Old, New, and Evolving Strategies; SE, standard error.
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Main Points

- Patients with unprotected left main disease who underwent percutaneous coronary intervention or coronary artery bypass graft surgery had equivalent rates of major adverse cardiac and cerebrovascular events (composite of death, stroke, myocardial infarction, and repeat revascularization) at 1 year.
- In patients with multivessel disease, use of fractional flow reserve measurements to identify ischemic vessels that require stenting resulted in better outcomes than angiographically guided treatment at 1 year.
- In a large study focusing on the optimal use of stents and anticoagulation therapy in patients with ST-segment elevation myocardial infarction (STEMI), patients treated with Taxus paclitaxel-eluting stents had significantly less ischemia-driven target lesion revascularization than patients treated with Express bare-metal stents.
- A study of STEMI patients demonstrated that early, complete ST-segment resolution was better in subjects treated with the Proxis proximal embolic protection system compared with controls.
- In a study using drug-eluting stents (DES) to treat patients with de novo coronary lesions, polymer-free stents eluting both probucol and sirolimus—so-called "Dual DES"—achieved similar rates of restenosis and in-stent late lumen loss as Cypher stents. In addition, both Cypher and the Dual DES performed better than the Endeavor stent.
- In a study of patients with bifurcation lesions, a simple stenting strategy with DES was superior to a complex strategy for treatment of unselected lesions.

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