



Canadian Cardiovascular Congress

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Update on Drug-eluting Stents in Percutaneous Coronary Intervention

Toronto - According to a large Canadian observational study, late mortality and adverse clinical outcomes following percutaneous coronary intervention are independently associated with various clinical factors. However, better survival out to seven years was associated with the use of drug-eluting stents (DES). While DES appear protective in the long term, two studies presented at a recent major congress comparing two DES indicated significant differences in outcomes. A third study investigated the potential for improving the anti-restenosis effect by incorporating a second active agent in a polymer-free DES.

Toronto – Une vaste étude d'observation canadienne a établi que divers facteurs cliniques sont des prédicteurs indépendants du décès ou d'une issue défavorable survenant à retardement à la suite d'une intervention coronarienne percutanée. Une augmentation du taux de survie à sept ans a toutefois été associée à l'utilisation de tuteurs médicamenteux. Si ces tuteurs semblent exercer un effet protecteur à long terme, deux études visant à comparer un tuteur médicamenteux de première génération et un tuteur similaire de deuxième génération ont néanmoins mis au jour des différences significatives quant aux résultats. Le résidu de polymère – que laissent tous les tuteurs médicamenteux dans l'artère coronaire à long terme – a été incriminé dans les effets indésirables tardifs. L'incorporation d'un deuxième agent actif à un tuteur médicamenteux sans polymère est une option éventuelle que l'on explore afin de réduire le taux de resténose.

By Wayne Kuznar

A large observational study of Canadian patients has revealed that late mortality and adverse clinical outcomes following percutaneous coronary intervention (PCI) were independently associated with various clinical factors such as older age, severe heart failure, renal dysfunction and diabetes, in addition to incomplete revascularization and suboptimal angiographic results. Among other findings, the use of a drug-eluting stent (DES) was associated with better survival out to seven years.

These results were derived from a clinical database of 12,662 consecutive patients undergoing PCI in Canada, who were followed for an average of 3.6 years (range: 0 to 7.75 years). Among the independent predictors of late mortality were:

- Age per decade older than 49 years (hazard ratio [HR]: 1.48; $P < 0.001$).
- Urgent priority (HR: 1.36; $P < 0.001$).
- Primary PCI (HR: 1.51; $P = 0.007$).
- Shock (HR: 3.22; $P < 0.001$).
- LV grade 3 (HR: 1.75; $P < 0.001$).
- LV grade 4 (HR: 2.93; $P < 0.001$).
- New York Heart Association class IV heart failure (HR: 1.85; $P < 0.001$).
- Renal dysfunction (HR: 1.78; $P < 0.001$).
- Diabetes (HR: 1.75; $P < 0.001$).
- Incomplete revascularization (HR: 1.68; $P < 0.001$).
- Residual stenosis greater than 20% (HR: 1.29; $P = 0.002$).

Implantation of a DES was protective, with a HR for late mortality of 0.74 ($P < 0.001$), as was use of a glycoprotein IIb/IIIa inhibitor (HR: 0.8; $P = 0.006$).

More detailed results of this study will be reported during an oral session here on Wednesday.

Investigating DES Differences

While long-term outcomes favour DES, results from two studies recently presented at the 2008 Transcatheter Cardiovascular

Therapeutics (TCT) Conference, October 12-17, 2008, in Washington, DC, comparing sirolimus-eluting stents to zotarolimus-eluting stents indicated significant differences in outcomes. In patients with coronary artery disease (CAD), there was an excess risk of stent thrombosis for those receiving zotarolimus-eluting stents.

SORT-OUT III Results

Nine-month results from the SORT-OUT III trial (Plenary Session 20, Late Breaking Clinical Trials III, 11:00) revealed that patients with CAD who were implanted with a sirolimus-eluting stent had significantly lower rates of restenosis, target lesion revascularization (TLR), MI, and definite stent thrombosis than patients who received a zotarolimus-eluting stent, according to Dr. Jens Flensted Lassen, Skejby Hospital, Aarhus, Denmark.

SORT-OUT III was the first large-scale, randomized, head-to-head trial of the two types of DES. It included 2333 patients. Because the study was designed to reflect daily clinical practice, angiographic follow-up or study-related patient contact was not scheduled. The trial employed a "patient-driven" system for reporting events, available through the comprehensive network of Danish registries and databases, explained Dr. Lassen.

Patient and lesion characteristics were similar in the two arms. Approximately half of the patients in each group had stable angina as their indication for PCI and about 38% in each group had non-ST-elevation MI or unstable angina. Those randomized to the zotarolimus-eluting stent were more likely to have had prior PCI.

At nine months, patients randomized to the zotarolimus-eluting stent had significantly higher rates of restenosis HR: 6.59; $P < 0.0001$), TLR (HR: 4.19; $P < 0.0001$), MI (HR: 3.47; $P = 0.03$), and definite stent thrombosis (HR: 4.62; $P = 0.02$). There were no significant differences between groups in overall

mortality and cardiac mortality, although trends favoured the sirolimus-eluting stent on these end points.

“I was surprised that there was that amount of stent thrombosis [with the zotarolimus-eluting stent] during antiplatelet therapy,” remarked Dr. Lassen, who added that the results from SORT-OUT III represent only “half the story,” with the rest of the story to be told with longer follow-up.

Western Denmark Registry

However, the safety signals with the zotarolimus-eluting stent were also apparent at two years of follow-up in the Western Denmark registry of 6122 CAD patients implanted with either the zotarolimus-eluting stent or the sirolimus-eluting stent.

The registry showed significantly higher all-cause mortality and a strong trend toward higher cardiac mortality with the zotarolimus-eluting stent. Also, definite stent thrombosis, TLR and in-segment restenosis were all significantly higher compared with the sirolimus-eluting stent.

The adjusted risk ratios in patients receiving zotarolimus-eluting stents were 1.34 for all-cause mortality ($P=0.02$), 1.83 for cardiac mortality ($P=0.06$), 1.01 for MI ($P=0.87$), 1.78 for definite stent thrombosis ($P<0.05$), 2.39 for TLR ($P<0.0001$), and 2.44 for in-segment restenosis ($P<0.0001$).

Lead investigator Dr. Leif Thuesen, Aarhus University Hospital, noted that he was surprised that safety was not better with the zotarolimus-eluting stent—“we expected the opposite.” Because the zotarolimus-eluting stent is flexible and easier to implant than the sirolimus-eluting stent, it may have been the chosen stent for patients with more complex lesions, adding a potential selection bias to the registry data, according to study investigators.

It may be difficult to adjust for patient and operator selection bias when analyzing data from registries, but nevertheless, “the definite stent thrombosis was quite a significant finding,” noted Dr. Thuesen.

SORTing OUT the Findings

According to Dr. Thuesen, the stent thrombosis observed with the zotarolimus-eluting stent in the Western Denmark registry might actually be “aggressive restenosis” rather than stent

thrombosis. The more rapid endothelialization with the stent leads to significant late lumen loss, which may be a marker for aggressive restenosis.

Differentiating restenosis from stent thrombosis may be difficult, noted Dr. Lassen. He suggested that the stent thromboses causing acute coronary syndromes in the recipients of the zotarolimus-eluting stents were probably driven by restenosis.

According to Dr. Alexandra Laskey, Columbia University, New York, late lumen loss may not be harmful in a “simple” patient population, “but in complex patients, you begin to test the device and you understand the device. You do not ultimately know the final performance of a device until you go into these kinds of studies in complex patients.”

ISAR-TEST 2

A third comparison presented at TCT—the ISAR-TEST 2 randomized trial (Plenary Session 20, Late Breaking Clinical Trials III, 11:45)—showed higher rates of restenosis for patients with CAD who were assigned to the zotarolimus-eluting stent compared with the rapamycin-eluting stent and a polymer-free dual drug-eluting stent (probuco and rapamycin) according to Dr. Robert Byrne, Deutsches Herzzentrum, Munich, Germany.

A total of 1007 patients were randomized to receive one of the three stents. The primary end point, binary angiographic restenosis, occurred in 19.3% of patients randomized to the zotarolimus-eluting stent, a significantly ($P=0.002$) higher rate than the 11.0% randomized to the dual drug-eluting stent. The rate of the primary end point was 12.0% with the rapamycin-eluting stent, which was not significantly different than the rate with the dual-drug-eluting stent.

Clinical restenosis and angiographic restenosis followed the same pattern—significantly higher rates in the zotarolimus-eluting stent arm compared with the dual-drug-eluting stent arm, and no significant difference between the rapamycin-eluting stent arm and the dual-drug-eluting stent arm. No significant differences between arms in the rates of death/MI, MI, or definite stent thrombosis was observed.

Further exploration of the dual-drug polymer-free stent approach is warranted with longer-term accrual of results. □

Please plan to attend:

Oral Presentation #1066. “Late Outcomes Following Percutaneous Coronary Intervention: Results from 12,662 Consecutive Patients.” Wednesday, October 29, 2008; 10:00-10:15, Room 714 A.

This session is accredited and co-developed as an Accredited Group Learning Activity under Section 1 of the framework of Continuing Professional Development options as defined by the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada (RCPSC).

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