Late-Breaking Trial Results Presented in Stockholm

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The 23rd Annual Meeting of the European Society of Cardiology (ESC) took place in Stockholm from September 1 to 5, 2001. The attendance at this year's ESC meeting was its largest ever, and the Congress was conducted in conjunction with the 36th Annual General Meeting of the Association of European Pediatric Cardiology. The highlights of the ESC Congress were the late-breaking trials, where several important studies in interventional cardiology and management of acute myocardial infarction were presented.

The Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de novo Native Coronary Artery Lesions (RAVEL) trial, which was presented by Dr. M.C. Morice, received the greatest attention.[1] The study was a multicenter, randomized trial of 238 patients who were randomized to receive a drug-eluting stent versus a standard stent (Bx velocity). The drug used was rapamycin, a macrolytic antibiotic that eluted from the stent with a half life of 2 weeks. The primary endpoint was 6-month angiographic late loss. Secondary endpoints were binary restenosis and major adverse clinical events (MACE). Results at 210 days showed a dramatic reduction in restenosis with no measurable late loss (–0.06 mm) in the drug-eluting stent group and a late loss of 0.8 mm in the standard stent group ($P < .01$). The binary restenosis rates were 0% and 26%, respectively. MACE occurred in 3% of the drug-eluting stent group and 27% of the standard group ($P < .001$). The selection criteria were restricted to patients with de novo lesions in native vessels 2.5 mm to 3.5 in diameter and lesions less than 18 mm in length. The results overall are dramatic and significantly superior to prior interventions to reduce restenosis, including radiation therapy.

For the moment, enthusiasm should be tempered by the study's limitations, including short follow-up, relatively small number of patients included, and most importantly, the selection criteria that restricted the study to lesions that would have an intrinsically lower risk for restenosis. These results support prior nonrandomized studies by Sousa and Serruys,[2] and if these results are duplicated in the larger ongoing clinical trial in the United States—the Sirolimus-Coated Velocity Stent in Treatment of Patients with de novo Coronary Artery Lesions (SIRIUS) trial, which is planning to enroll more than 1100 patients—this could mark the end of restenosis as a significant clinical problem. Questions awaiting answers include the impact of drug-eluting stents in situations with higher risks of restenosis, including small vessels, long lesions, and diabetic patients. If the results of subsequent trials with rapamycin or other agents, including paclitaxel, tacrolimus, and Taxol, are positive, this would undoubtedly result in an expansion of the technique, with angioplasty applied to patients with

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more severe coronary anatomy as well as patients who have milder disease. The end of coronary artery restenosis as a disease entity may now be in sight.

The results of the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT) 3 trial were also presented at the ESC.[3] A total of 6095 patients with acute myocardial infarction were randomized to full-dose tenecteplase (TNK) plus enoxaparin, half-dose TNK plus unfractionated heparin plus full-dose abciximab, or TNK plus unfractionated heparin. The primary endpoint was 30-day mortality in-hospital, reinfarction, or refractory ischemia. The study showed a significant reduction in the primary endpoint in first two study groups (11.4 vs 11.1 vs 15.4; $P = .001$). Although mortality was not significantly different among the groups, the significance of the primary endpoint was due to reinfarction and recurrent ischemia. Major bleeding was slightly more frequent in the first two groups than in the latter group (3% vs 4.3% vs 2.1%; $P < .005$). The study demonstrates that adjuncts to TNK are beneficial and, most important, shows that both enoxaparin (a low-molecular-weight heparin) and abciximab are effective when combined with TNK. These results parallel the report from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) V trial, where 16,580 patients were randomized to reteplase or one half-dose reteplase plus abciximab. Overall, there was no difference in the primary endpoint, but there was a significant reduction in reinfarction and urgent percutaneous coronary intervention with the combination of reteplase and abciximab. The very low mortality of 5.8% may partially explain the lack of a difference in the primary endpoint. The results of ASSENT-3 and GUSTO-V confirm the safety and efficacy of abciximab with either TNK or reteplase and the benefits of enoxaparin when added to TNK in patients with acute MI.

Drug-eluting stent development could mark the end of restenosis as a significant clinical problem.

The Warfarin Reinfarction Study (WARIS) II trial also addressed the use of anticoagulant therapy and acute MI. In this study, 3630 patients with acute MI (50% Q-wave MI) were randomized to aspirin, warfarin (international normalized ratio [INR] between 2.8 and 4.2), or aspirin plus lower-dose warfarin (INR between 2 and 2.5). The primary endpoint of death, MI, or cerebrovascular accident over 1 year was significantly lower in the warfarin and warfarin-plus-aspirin groups compared to the aspirin-alone group (16.7% and 15% vs 20% respectively; $P < .005$).

The results of ASSENT-3 and GUSTO-V confirm the safety and efficacy of abciximab with either TNK or reteplase and the benefits of enoxaparin.

Likewise, any cardiovascular event was lower in the first two groups. Major bleeding was slightly higher, but not at a clinically significant level (0.58% vs 0.58% vs 0.15%, $P < .001$). This trial again raises the issue of the value of long-term warfarin therapy following acute MI and is supportive of older trials demonstrating the superiority of warfarin over aspirin.

Taken together, these studies of adjunctive therapy in acute MI infarction support the use of aggressive anticoagulation and antiplatelet regimens and are likely to change our clinical practice with the more liberal use of low-molecular-weight heparin and warfarin in acute MI. ■

References

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Main Points

- The RAVEL trial demonstrated a dramatic reduction in restenosis with a rapamycin-eluting stent compared with a standard stent.
- The ASSENT-3 trial showed that enoxaparin (a low-molecular-weight heparin) and abciximab are effective when combined with tenecteplase.
- The WARIS II trial's results support older trials demonstrating the superiority of warfarin over aspirin following acute myocardial infarction.