Drug-eluting stents and late stent thrombosis

See **Articles** page 937

3 years after the first description of four cases of coronary stent thrombosis occurring late after insertion of drug-eluting stents,[1] in today's *Lancet* Christoph Stettler and colleagues[2] report a comprehensive meta-analysis of randomised trials that compared sirolimus and paclitaxel drug-eluting stents with each other or with bare-metal stents. They used a collaborative network analysis that combines studies that directly compare the two drug-eluting stents with studies in which each drug-eluting stent is compared with a bare-metal stent. 38 trials with follow-up of between 6 months and 4 years were analysed, with a focus on stent thrombosis as an endpoint. No difference in total mortality was seen between the sirolimus, paclitaxel, or bare-metal stents. Repeat revascularisation of target lesions was reduced to a greater extent with sirolimus than with paclitaxel, and both drug-eluting stents were better than a bare-metal stent. However, there was an apparent increase in late (after 30 days) stent thrombosis with the stent eluting paclitaxel.

Although meta-analyses are only as good as the studies included, and about a third of the time they fail to predict the outcome of a subsequent large clinical trial testing the same hypothesis,[3] Stettler and colleagues' study is the best current comparison of the two drug-eluting stents. Similar results were reported in another meta-analysis that included only the head-to-head trials of such stents.[4] An emerging issue with the plethora of meta-analyses is the complexity of the statistics. Although many clinicians have a good working knowledge of standard statistical methods, which equips them to analyse most research results, few understand the differences between the network or mixed-treatment comparison in Stettler's study and other meta-analytical methods.

The Academic Research Consortium's meaning of definite stent thrombosis, as used by Stettler and colleagues, required confirmation by angiography or autopsy. This standardised but restrictive definition is useful for comparing different types of stent, but will substantially underestimate the true rate of thrombosis, which also includes many events classified as probable and some as possible stent thrombosis. Most trials in the analysis, and in particular the early ones contributing the longest follow-up, enrolled patients and lesions at low risk of recurrent cardiac events, including thrombosis. After 12 months, with data available from two-thirds of the 18 000 patients, only 48 documented episodes of definite late stent thrombosis took place (eight with bare-metal stents, 14 with sirolimus-eluting stents, and 26 with paclitaxel-eluting stents).

How do these findings relate to real-world practice? Drug-eluting stents are often used in higher-risk patients, such as in those with diabetes or renal failure, and higher-risk lesions, such as long lesions, chronic occlusions, bifurcation lesions, and vein-graft lesions. These patients and lesions, at increased risk of restenosis with bare-metal stents, are under-represented in or excluded from the randomised trials. Unfortunately, many of the predictors for increased restenosis with bare-metal stents also predict increased late thrombosis with drug-eluting stents.[5] Daemen and colleagues reported a late thrombosis rate, to 3 years after insertion, of 0·6% per year with routine drug-eluting stents for coronary interventional procedures.[6] Of concern, there was no apparent flattening of the cumulative stent-thrombosis curve over time, which suggests that the risk might be ongoing. Interventional cardiologists are definitely worried; in the USA, sales of sirolimus-eluting and paclitaxel-eluting stents have both dropped by more than 40%.

Are there other predictors of late thrombosis in drug-eluting stents? Intravascular ultrasonography in patients presenting with late thrombosis shows that a technical problem at stenting, most commonly inade-

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Paclitaxel-eluting stent

quate stent expansion or stent apposition to the vessel wall, contributed to thrombosis.[7] Operators need to use meticulous insertion techniques, perhaps aided by intravascular ultrasonography if there is any angiographic uncertainty about the procedural result. Those patients with a reduced response to antiplatelet drugs seem to be at increased risk.[8] Although premature discontinuation of dual antiplatelet therapy also predicts stent thrombosis, few data are available for how long clopidogrel should be administered and the current 12-month recommendation is empirical.

Can a patient's future risk of thrombosis be assessed after the stent is implanted? As seen at autopsy and by angioscopy, drug-eluting stents have delayed and incomplete re-endothelialisation compared with bare-metal stents.[9] Optical coherence tomography might aid individual risk stratification; it cannot establish stent endothelialisation but does provide accurate information about coverage of stent struts.[10]

Are there better ways of overcoming the problem of restenosis with bare-metal stents? The next generation of stents that elute zotarolimus and everolimus have encouraging results from preclinical and early clinical studies, but need adequately powered trials with at least medium-term follow-up to establish efficacy and safety. Although bioabsorbable stents still have some drawbacks related to radial strength and absorption rates, early-stage clinical results are promising.[11] Finally, bare-metal stents with oral drug therapy could re-emerge as a viable alternative to drug-eluting stents. Sirolimus is effective for the prevention of restenosis when given orally, but this use is limited by toxicity.[12] The insulin-sensitising and antiproliferative drugs, rosiglitazone and pioglitazone, reduce restenosis in bare-metal stents when given orally to patients with and without diabetes.[13] Recently, celecoxib was also shown to reduce restenosis in lesions treated with a paclitaxel-eluting stent.[14] That drugs which possibly increase cardiovascular risk when given long term have emerged as candidates to reduce restenosis is an interesting paradox. Because a short-term course is probably all that is needed, oral treatment plus a bare-metal stent might yet be part of the answer.

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1 McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364:** 1519–21.
2 Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* 2007; **370:** 937–48.
3 LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med* 1997; **337:** 536–42.
4 Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary disease. *J Am Coll Cardiol* 2007 (in press).
5 Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005; **293:** 2126–30.
6 Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* 2007; **369:** 667–78.
7 Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation* 2007; **115:** 2426–34.
8 Buonamici P, Marcucci R, Migliorini A, et al. Impact of platelet reactivity after clopidogrel administration on drug-eluting stent thrombosis. *J Am Coll Cardiol* 2007; **49:** 2312–17.
9 Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol* 2006; **47:** 2108–11.
10 Takano M, Inami S, Jang I-K, et al. Evaluation by optical coherence tomography of neointimal coverage of sirolimus-eluting stent three months after implantation. *Am J Cardiol* 2007; **99:** 1033–38.
11 Erbel R, Di Mario C, Bartunek J, and for the PROGRESS-AMS (Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents) Investigators. Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicentre trial. *Lancet* 2007; **369:** 1869–75.
12 Rodriguez AE, Granada JF, Rodriguez-Alemparte M, et al. Oral rapamycin after coronary bare-metal stent implantation to prevent restenosis: the prospective, randomized oral rapamycin in Argentina (ORAR II) study. *J Am Coll Cardiol* 2006; **47:** 1522–29.
13 Rosmarakis ES, Falagas ME. Effect of thiazolidinedione therapy on restenosis after coronary stent implantation: a meta-analysis of randomized controlled trials. *Am Heart J* 2007; **154:** 144–50.
14 Koo B-K, Kim Y-S, Park K-W, et al. Effect of celecoxib on restenosis after coronary angioplasty with a Taxus stent (COREA-TAXUS trial): an open-label randomised controlled study. *Lancet* 2007; **370:** 567–74.

Trials of venous thromboembolism prevention

In today's *Lancet*, Bengt Eriksson and colleagues report the RE-NOVATE trial on prevention of venous thromboembolism after total hip replacement.[1] This trial is in many important methodological respects exemplary: it is an international multicentre study, with robust randomisation, double-dummy blinding, central outcome-adjudication with imaging, and prespecified statistical analyses, and was reported according to

See **Articles** page 949