Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, KwaZulu-Natal 3935, South Africa (M-LN, TB); Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, UK (M-LN); and Department of Population and International Health, Harvard School of Public Health, Boston, Massachusetts, USA (TB)
mnewell@africacentre.ac.za

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Thrombosis: the last frontier of coronary stenting?

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In 1991, Serruys and colleagues[1] reported a 24% incidence of thrombotic stent occlusion 6 months after implantation into human coronary arteries. At the time, many cardiologists thought that bare-metal stents would soon disappear from clinical use. However, 2–3 years later, improved antiplatelet regimens, better stents, and better implantation techniques came into use. The incidence of stent thrombosis dropped to about 1·2% and, despite the rare but poorly quantified occurrence of late stent thrombosis (figure), overall the problem was thought to be solved.

15 years later, an intense debate has resurfaced, which questions whether current drug-eluting stents (with their potent antirestenotic effect and potential for delayed local vascular healing) are associated with an excess of thrombotic problems. In today's *Lancet*, Joost Daemen and colleagues[2] report the risk of early and late stent thrombosis after implantation of coronary drug-eluting stents in clinical practice. The researchers followed up a cohort of 8146 patients, who were treated in two large academic hospitals (in Rotterdam, the Netherlands, and Bern, Switzerland), for a mean 1·7 years. The incidence of early stent thrombosis (ie, occurring ≤30 days after implantation) was 1·1%, as recorded by angiography. More importantly, the incidence of late stent thrombosis (ie, >30 days after implantation) was a steady 0·6% of patients a year.

Daemen and colleagues' decision to focus on angiographically proven events can only have underestimated the true incidence of stent thrombosis, and

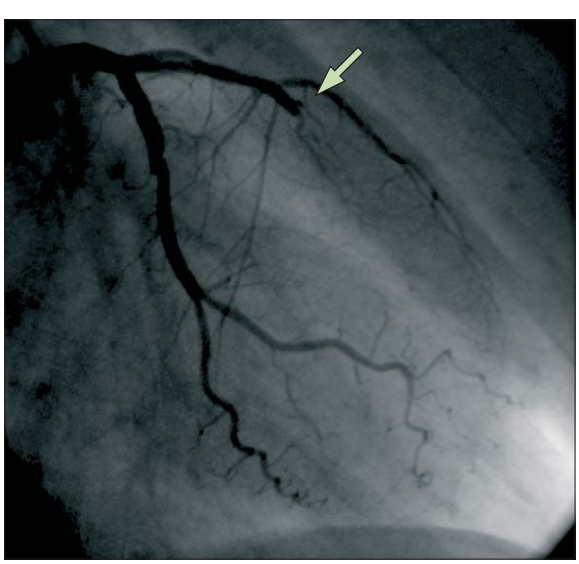

Figure: **Stent thrombosis (arrow) of left anterior descending coronary artery 3 years after implantation of bare-metal device**

follow-up remains incomplete (28% of patients not contacted at 1 year and 81% not contacted at 3 years). However, these data are important, and suggest a low but persistent risk of thrombotic events associated with drug-eluting stents, at least up to 3 years after implantation. Daemen's findings differ substantially from those of previous randomised trials, for which the frequency of stent thrombosis was 0·6% at 1 year after implantation[3] and was low in subsequent years (about 0·2% in most trials,[4] but not all[5]).

Daemen and colleagues are correct to highlight the limited interpretation of their recorded higher incidence of late stent thrombosis during the first year after implantation of paclitaxel-eluting stents compared with those that elute sirolimus, given the non-randomised design, important baseline differences between groups, and unequal follow-up between groups. Furthermore, meta-analysis[6] of controlled comparisons of paclitaxel-eluting stents and sirolimus-eluting stents at 6–13 months of follow-up showed no significant difference in stent thrombosis (1·1% *vs* 0·9%, respectively).

A universal real-life situation does not exist: every hospital has specific referral patterns, processes to select patients, financial constraints, and differing clinical expertise and opinions. The data from Daemen and colleagues are one extreme: both hospitals in the study had unrestricted access to drug-eluting stents, and took a deliberate decision to use them as a default for all patients who needed stent implantation. For example, patients presenting with acute coronary syndrome (59% of the cohort) were treated routinely with drug-eluting stents. A recent randomised trial[7] showed that the risk of stent thrombosis at 1 year in the setting of acute myocardial infarction, although not different for drug-eluting and bare-metal stents, can be as high as 3·4%.

Furthermore, the total length of an implanted drug-eluting stent is a risk factor for stent thrombosis,[3] and complex procedures were often done in both Bern and Rotterdam, with an overall mean of two stents and 36 mm of total stent length per patient. These findings differ substantially from two pivotal randomised trials,[8,9] for which the mean number of stents per patient was 1·4 and 1·1, respectively, and the mean total stent length was 22 mm in both trials. These factors, in addition to others, explain why the reported incidence of early and late stent thrombosis is higher than 1·1–1·3% at 3 years in the controlled trial setting,[4] or is higher than 0·9% at 1 year in a multicentre registry.[10]

Do these findings imply that drug-eluting stents are dangerous and that their use should be restricted to low-risk patients and lesions? We think that Daemen and colleagues' data do not allow an answer, because there is no control group that has been given an alternative intervention (eg, medical treatment, bare-metal stenting, or bypass surgery). However, several issues help put the information into perspective. First, the natural history of coronary artery disease, even with secondary prevention measures, remains a greater threat to patients than do the potential events related to the stented segment of coronary artery.[11] In Daemen's study, documented stent thrombosis accounted for 32% of myocardial infarctions, but for only 2% of deaths. Second, duration of dual antiplatelet therapy varied during enrolment in both centres. A longer course of therapy for all patients or improved compliance with prescribed treatment, or both, might have had a protective effect. Third, a decreased incidence of restenosis with drug-eluting stents might not only lead to better angina control and fewer repeat procedures, but might also help to prevent major adverse events such as acute coronary syndromes and myocardial infarction.[12] Fourth, alternative approaches have their own limitations. For example, the occlusion rate of surgical saphenous vein grafts is 3–12% within the first month and is about 40% at 10 years.[13]

Thus, if implantation of a drug-eluting stent seems to increase the risk of late stent thrombosis in high-risk patients, better or safer treatment options do not necessarily exist today. Comparison of Daemen and colleagues' data with those from previous series of bare-metal stents[14] is not meaningful because the selection of patients and lesions for percutaneous revascularisation has changed substantially over the past 5–10 years. The situation should be clarified by ongoing randomised trials with endpoints of efficacy and safety and with long-term follow-up that enable direct comparison of different drug-eluting stents (ie, the PROTECT trial) or of drug-eluting stents versus coronary surgery (ie, the SYNTAX and FREEDOM trials), and by large multicentre registries (ie, e-SELECT and OLYMPIA).

Moreover, today's technology drive may soon improve drug-eluting stents and their antithrombotic properties (eg, with use of resorbable drugs, polymers, and perhaps resorbable stents), removing the need for cumbersome long-term antiplatelet therapy and preventing the rare but devastating occurrence of late stent thrombosis.

Philip Urban, Edoardo De Benedetti
Cardiovascular Department, La Tour Hospital, 1217 Geneva, Switzerland
philip.urban@latour.ch

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HIV/AIDS in China: the numbers problem

China has been widely criticised for its failure to respond to the HIV/AIDS threat and for systematic suppression of information about the size of the problem.[1,2] Thus Zunyou Wu and colleagues' report in today's *Lancet* of the way in which China has responded to HIV/AIDS will surprise many.[3] Their thorough review shows how much progress has been made, and how, given the political and cultural context, the Chinese response has evolved in a measured and mainly appropriate way.

Wu and colleagues show how early efforts emphasised enforcement of laws against high-risk behaviour, but that later lessons from effective interventions in other countries (eg, needle-exchange programmes in Australia and condom campaigns for sex workers in Thailand) have led to a more evidence-based approach. The process of policy development might not have been as neat as that presented because of tensions, particularly those between public-health officials and the police and those within public security over the management of illegal drug use and prostitution. However, the recently announced AIDS Prevention and Control Regulations[4] are a good example of evidence-based policy, even if their implementation is highly variable across China.

The most surprising feature of HIV/AIDS in China is how it has attracted such attention and large amounts of external funding, given that the proportion of the

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Panos Pictures

Patient with AIDS in China