

Editorial

The drug-eluting stent controversy: a new example of an old pattern?

For any treatment introduced into clinical practice, it can only be hoped that the rigorous testing the treatment undergoes before release has identified any associated adverse effects. But the recent high-profile withdrawal of treatments from clinical use — such as Vioxx — and the recent debate on the long-term safety of drug-eluting stents (DES)[3][5] calls into question whether the current level of pre-release assessment is adequate. DES were used with great enthusiasm when first introduced in 2002. However, since 2006, several reports have highlighted an increased risk of late (>30 days) and very late (>1 year) stent thrombosis associated with DES use.[1][2][3][4][5] a risk that was not evident after the initial trials.

Percutaneous coronary angioplasty is the most common treatment used to achieve revascularisation in coronary artery disease.[6] Stents were originally introduced in 1987 to reduce complications of balloon angioplasty. Patrick Serruys and colleagues determined in 1991 that the original bare-metal stents were associated with a 24% incidence of stent thrombosis after 6 months.[7] However, improvements in antiplatelet regimens, development of better stents, and refinement of the implantation techniques led to a drop in stent thrombosis to 1.2%.[2] Consequently, the main complication of coronary stents became clinical restenosis, an excessive healing response that causes the stented vessel to re-occlude. DES releasing cytostatic or antimetabolic agents were developed with a view to reducing restenosis. However, inhibition of cell division delays and may even prevent healing. It has also been suggested that delayed re-endothelialisation of the DES actually increases stent thrombosis by prolonging the prothrombotic stimulus created by a breached endothelium.[8] Other factors may also be involved in the pathogenesis of stent thrombosis, such as sub-optimal stent-positioning techniques, a local hypersensitivity reaction, and the increased endothelial expression of prothrombotic surface proteins as a result of the stent.[8]

If the risk of in-stent thrombosis associated with DES is real, why was it not detected sooner? One reason may be related to the choice of end points in the early trials. RCTs, such as the RAVEL study, examined a composite outcome of all-cause mortality, MI, and target vessel revascularisation,[9] which it was assumed would reflect restenosis rather than thrombosis of the vessel. However, when the components of this composite were assessed individually, an increased risk of in-stent thrombosis with DES use was revealed. The BASKET trial[10] was a small RCT looking at cardiac death, non-fatal MI, and clinically driven, restenosis-related target vessel revascularisation as separate, primary end points; BASKET is set apart from other RCTs as it was designed to examine real-world use of DES, and low-risk patients were excluded from the population. The investigators found that treatment of 100 people with DES was associated with 3.3 late deaths or MIs, and prevention of 5 target vessel revascularisation events. These results were echoed by the meta-analysis of Edoardo Camenzind and colleagues, which examined similar end points of real-world DES use.[4] More recent meta-analyses have found that rates of all-cause mortality and MI are equivalent for DES and bare-metal stents, findings supported by a recent observational study.[11] When it is considered that DES decrease restenosis, the overall lack of benefit suggests that any mortality benefit conferred by a reduction in restenosis is offset by other factors.

Although the original clinical appeal of DES was that they justified the use of stents in more complex lesions, the majority of RCTs have predominantly focused on low-risk lesions in low-risk people. However, the initial enthusiasm surrounding DES led to their widespread “off-label” use in complex, high-risk lesions, and in the RCTs and observational studies examining real-world DES use the risk of late stent thrombosis was higher with DES. This raises the possibility that the observed increased risk of stent thrombosis emerged from the over-enthusiastic

use of DES in complex lesions. In 2007, Joost Daemen and colleagues[1] measured the incidence of late stent thrombosis in a cohort of 8146 people who were followed for a mean of 1.7 years; they found that 0.6% of people per year developed late stent thrombosis. A review of earlier RCTs reported that incidences were typically 0.6% for the first year, followed by 0.2% per year for the following 2 years.[12] In the investigation carried out by Daemen, DES were used as a default first-line option for all people who required stent implantation.[1] As DES were originally tested and approved for a subset of low-risk lesions, their use as a first-line option represents an extreme example of “off-label” DES use: the lack of a control group receiving bare-metal stents was a weakness of this study. Similar results were reported in a recent Canadian observational study.[5] Andrew Philpott and colleagues measured death or repeat revascularisation as a composite end point in over 6000 people receiving either a bare-metal stent or a DES, again in a real-world setting.[5] Philpott found that DES use decreased the relative risk of the outcome at 1 year, but increased the relative risk over the subsequent 2 years. An important confounding factor in all these observational studies has been the difficulty in separating the effects of the stents, good or bad, from effects created by the timing and extent of associated drug therapy.

Why would the use of stents in more complex lesions create an increased risk of late stent thrombosis? One reason is that the underlying risk of thrombosis is already higher. Complex lesions are themselves more prone to thrombosis, and often reflect a more severe underlying prothrombotic disease state. For example, 59% of the cohort in the study conducted by Daemen received DES to treat acute coronary syndrome, a setting in which the risk of stent thrombosis with any stent type is known to be high.[13] More complex lesions also require the use of more and longer stents; the surface area of blood vessel exposed to the drug is therefore increased. It is known that DES length is a risk factor for stent thrombosis,[14] which suggests that there is a “dose-response” effect: the greater the surface area exposed to the drug, the greater the risk of late stent thrombosis. This proposal is supported by the data reported by Daemen and colleagues who found that the average number (2 v 1.1–1.4) and length (36 mm v 22 mm) of stents implanted were higher than in previous studies.[1]

When an adverse effect of a treatment is identified, its impact on clinical practice must also be assessed. If DES increase the risk of late stent thrombosis, how should they be used? There is still insufficient evidence to answer this question. The risk of late stent thrombosis needs to be carefully assessed in large-scale studies that can establish whether this risk is universal, or occurs only with certain types of lesion. Prolonged use of antiplatelet therapy may provide protection from late stent thrombosis, and should be investigated further. All adverse outcomes must be examined in the context of the threat posed by coronary artery disease itself. The risk of late stent thrombosis also needs to be interpreted in the context of other treatment options. Emerging data from RCTs, such as the SYNTAX trial,[15] indicate that CABG is associated with better outcomes (fewer cardiac or cerebrovascular events and repeat revascularisations) than angioplasty at 1 year in more severe disease. Taken together, the data indicate that increased complexity of the underlying lesion limits the usefulness of angioplasty in general, and DES in particular, and that these limits must be carefully defined.

The increased risk of late stent thrombosis may have been detected sooner if outcomes such as cardiac death and non-fatal MI had been assessed as individual primary outcomes in the early RCTs of DES. Also, as it is a known complication of stent use in general, it could be argued that stent thrombosis should have been studied in greater detail as part of the safety assessment, even if increased stent thrombosis with DES was not anticipated. Some of the risk from late stent thrombosis may have emerged from the over-enthusiastic initial use of DES in more complex lesions; RCT results should always be extrapolated with caution. A final lesson is perhaps to learn from the patterns of history. Treatments are often greeted with enthusiasm when they first appear, only to fall into disfavour when adverse effects are found. Then, with time, some of these treatments return with a use that is more limited and clearly defined. To avoid this pattern, adverse effects should be actively sought, and introduction of the

treatment should be gradual, so that experience and evidence can be built and the treatment can find its proper niche.

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