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Has it really been three years and has it changed?

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This editorial refers to "Three-year follow-up of the Arterial Revascularisation Therapies Study (ARTS-II) – Sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease", by Patrick W. Serruys et al, published in this issue of EuroIntervention.

The importance of longerterm follow-up information has been emphasised repeatedly for full evaluation of the merits of new drugs and new technologies. There are numerous examples in medical literature where an unexpected, uncommon side effect has only been identified in broader patient populations followed for longer periods of time after regulatory approval. In the field of interventional cardiovascular disease, nowhere has this become more relevant than in the evaluation of drug-eluting stents. By design, regulatory approval for drug-eluting stents was based upon small randomised trials in very circumscribed patient populations using discrete outcome metrics which could be measured over a relatively short period of follow-up. During follow-up studies however, the issue of stent thrombosis was 'identified'. Although this phenomenon had been well described with bare metal stents, there was concern that stent thrombosis might be increased with drug-eluting stents. To date, the preponderance of data would indicate that while the overall incidence of stent thrombosis appears to be similar with both the drug-eluting and bare metal stents, the timing may be shifted with slightly more late stent thrombosis occurring in patients with drug-eluting stents. This finding has been responsible for much of the emphasis of longer-term follow up which will become a regulatory requirement.

A second issue of great importance is that new devices are studied and then accepted by regulatory agencies based upon these very circumscribed patient population studies. But when that technology has been proven to be so successful in the small 'pivotal' trials, it is then eagerly adopted for larger, more difficult patient and lesion subsets. This process is the result of efforts by the physician to render the best possible technology to improve patient care and outcome, as well as by the patient and family to indeed receive that care. This process however has led to the increased use of devices in 'off label indications'. This does not necessarily lead to bad care – for example, in the early days of conventional PTCA, the indication for the procedure was treatment of stable patients with subtotal stenosis in large proximal vessels. In one very germane example of an 'off label indication', the results of PTCA alone during acute myocardial infarction (a situation far removed from stable patients with proximal subtotal stenosis) became widely used and has become a guideline Class 1A indication for performance.

One of the largest groups of patients in clinical cardiology are those with severe multivessel disease. Conventional PTCA was tested against coronary artery bypass graft surgery in early randomised and registry trials. In very selected patients with multivessel disease, survival rates and survival free of myocardial infarction were found to be similar between patients undergoing coronary artery bypass graft surgery and those randomised to PTCA. Similarly, conventional bare metal stents and coronary artery bypass graft surgery were studied again in carefully selected small randomised clinical trials. Given the widespread adoption of drug-eluting stents, because of their dramatic effect in improving clinical restenosis measured as target lesion or target vessel revascularisation, it was a forgone conclusion that drug-eluting stents should also be tested in the setting of multivessel disease. Randomised clinical trials have great advantages being free from as much bias as possible. Serruys et al in the current article adapted a different approach. Instead, they used a recent randomised trial, ARTS I of bare metal stents versus coronary artery bypass graft surgery and then used the patient selection and exclusion criteria to develop a cohort comparison group in whom a Sirolimus-eluting stent was placed. The current paper on the three-year follow-up data of ARTS-II is focused on identifying any possible erosion in late clinical outcome with the Sirolimus-eluting stent. While not a randomised trial per se, ARTS-II provides excellent data on the two issues discussed previously, namely longer-term outcome of drug-eluting stents with stent thrombosis and drug-eluting stents in multivessel disease.

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As mentioned by the authors, the PCI procedure in patients in ARTS-II was quite different than PCI in ARTS-I. In general, the patients and the lesions were more complex. For example, 46.6% of patients in ARTS-II underwent treatment of three vessels versus 18.0% of patients in ARTS-I PCI who received the bare metal stent. Another noticeable difference was that diabetes mellitus was more frequent in ARTS-II at 26% versus 17.3%. A final, very important finding relative to the differences in complexity was that in ARTS-II, patients received an average of 3.7 stents and had a mean total stent length of 72.5 mm; while in ARTS-I, it was respectively 2.8 stents and 47.6 mm.

Despite the increased complexity of patients treated with a Sirolimus-eluting stent in ARTS-II, at three years there was no significant difference in overall mortality between ARTS-II, ARTS-I PCI, and ARTS-I coronary artery bypass graft surgery. Crucial data is seen in Figure 2 of this paper with K-Maier curves out to three years for all cause survival (a), freedom from all cause death, stroke, or myocardial infarction (b), freedom from repeat revascularisation (c), and freedom from the combined endpoint of all cause death, CVI, myocardial infarction, or repeat revascularisation. This serie of key figures documents that:

1) There was no difference in mortality between ARTS-II, ARTS-I PCI, and ARTS-I CABG.

2) Patients with Sirolimus-eluting stents had improved death, stroke, or myocardial infarction rates compared with ARTS-I PCI.

3) Repeat revascularisation is still more frequent with Sirolimus-eluting stents versus coronary artery bypass graft surgery although the difference is narrowing.

Stent thrombosis was adjudicated using the ARC definitions. In ARTS-II, 39 patients experienced at least one stent thrombosis either definite, probably, or possible. The rate of definite stent thrombosis was 1.0% within 30 days, 1.6% within one year, 2.1% within two years, and 3.5% at three years of follow-up. Full information on adjudicated ARC stent thrombosis was not available in ARTS-I PCI. It was known however that definite angiographic stent thrombosis occurred in 2.8% of these patients at 30 days. It must be remembered that given the increase over time of stent thrombosis, particularly late stent thrombosis, it is reassuring to note that there was no significant difference in death/myocardial infarction in ARTS-II PCI and ARTS-I PCI at three years of follow-up.

Conclusion

A stated goal of this three year analysis paper was to "assess a possible erosion of the late clinical outcome due to the occurrence of early, late, and very late stent thrombosis". In view of this goal, what can be said?

1) ARTS-II is not a randomised trial which therefore makes the presence of bias harder to factor either in or out.

2) ARTS-II PCI patients were sicker with more complex lesions and received the mean stent length of 72.5 mm, which was significantly longer than patients in ARTS-I PCI.

3) The hard endpoint of all cause mortality at three years was not different between the three groups of patients - ARTS-I PCI, ARTS-I CABG, and ARTS-II PCI.

4) Major adverse cardiac events defined as freedom from all cause death, stroke, or myocardial infarction was significantly better in ARTS-II PCI patients rather than ARTS-I PCI patients.

5) Multivessel disease patients treated with coronary artery bypass graft surgery as compared with Sirolimus-eluting stents have an increased need for repeat revascularisation at three years although the absolute difference of magnitude between these two groups is decreasing.

6) Late stent thrombosis remains an issue but does not appear to affect long-term survival of the selection patients with multivessel disease.