EuroIntervention

Observational studies of drug-eluting stents – some are more equal than others

David Austin[1,2], MRCP; Keith G. Oldroyd[3], MD, FRCP, FSCAI; Jill P. Pell[1]*, MD, FESC

1. Department of Public Health and Health Policy, University of Glasgow, Glasgow, United Kingdom; 2. Darlington Memorial Hospital, Darlington, County Durham, United Kingdom; 3. Department of Cardiology, West of Scotland Regional Heart and Lung Centre, Glasgow, United Kingdom

Dr Austin and Prof Pell have received research funding from Boston Scientific. Dr Oldroyd has received speaker and consultancy fees from Boston Scientific, Medtronic and Cordis.

This editorial refers to Daemen et al "The relative safety and efficacy of bare-metal and drug-eluting stents in low and high risk patient subsets".

Observational studies analysing outcome following percutaneous coronary intervention (PCI) with drug-eluting stents (DES) and bare-metal stents (BMS) have been a growth industry since concerns were first raised regarding late outcomes with DES. Analysis of non-randomised data relies on statistical adjustment or matching, with the enduring problems of unknown confounding factors and potential bias. Some authors have suggested observational analyses contributed to a misleading picture following the World Congress in Cardiology in September 2006.[1] Despite this, observational outcome studies have accrued in the subsequent period and with some justification.

Randomised controlled trials (RCTs) are the gold standard in establishing a causal relationship between treatment and outcome, but are time consuming, costly and selective, limiting their generalisability. In the case of the DES versus BMS RCTs they were underpowered to detect differences in hard clinical end-points and between sub-groups. Thus when late stent thrombosis became an issue, particularly among more complex patients not studied in the pivotal trials,[2,3] the analysis of "real world" outcomes in large registries became imperative. Advantages of this approach include the ability to study patients representing routine clinical practice in a relatively short time-frame. However, due to the potential pitfalls of non-randomised comparisons a critical approach to study design should always be maintained. In particular, registry studies should be scrutinised for relevance of baseline data; control group employed; systems for ascertaining and defining clinical outcomes; extent of follow-up; and appropriateness of statistical methods employed. Nonetheless observational studies have played a key role, not only expanding the patient groups in which DES and BMS have been compared, but also in providing clinically important information on the need for longer durations of dual antiplatelet therapy in DES[4] and the natural history of stent thrombosis.[2]

Sequential cohorts and four year follow-up in Rotterdam

In this issue of EuroIntervention, Daemen et al add to this important and expanding body of literature.[5] Using registry data from the Thoraxcenter, Rotterdam, 6,129 patients treated in sequential cohorts with BMS, sirolimus-eluting Cypher® stents (SES, Cordis Corp., Miami, FL, USA) or paclitaxel-eluting Taxus™ stents (PES, Boston Scientific Corp., Natick, MA, USA) were compared. By employing a policy of treating all patients with DES (initially all SES from April 2002, and then all PES from February 2003) the authors have a unique and powerful set of data with up to four years follow-up. Given the concern regarding very late stent thrombosis risks with DES this is an important advance. Furthermore, data that correspond closely with the ARC definition of "definite" stent thrombosis were available; such detail is usually absent from "real

* *Corresponding author: Department of Public Health and Health Policy, University of Glasgow, 1 Lilybank Gardens, Glasgow, G12 8RZ, United Kingdom E-mail: j.pell@clinmed.gla.ac.uk*

world" outcome studies. Daemen et al also provide mortality data though administrative databases, a method that is comprehensive and clearly unbiased to treatment type. In the absence of an end-point committee, it could be argued that all-cause mortality so defined is the most accurate and clinically relevant safety outcome.[6,7]

The 100% penetrance of a given stent type during each period of study is also a further positive feature. The authors argue that with parallel recruitment of BMS and DES as in many other registries, operator and procedural factors affecting stent choice may introduce selection bias that is difficult to reconcile with statistical techniques. Sequential registries are not without their own issues however, and may introduce other types of bias related to secular trends in the selection of patients for PCI; adjuvant therapies (variable duration of clopidogrel therapy); operator technique and practice (variable rates of planned angiographic follow-up); available technology (cobalt-chromium thin-strut BMS and newer stent platforms for DES); and other unmeasured aspects of local clinical practice. The impact of the changing selection of patients for PCI over time is apparent in the measured patient characteristics during each study period. The need for statistical adjustment is therefore not obviated, and as with all such studies unadjusted results should be interpreted with due caution.

Findings and implications

The principal findings of Daemen et al corroborate other recent long-term follow-up studies. In common with the most extensive existing meta-analysis of selected patients[8] no difference in mortality was noted between DES and BMS groups. This is clearly reassuring given the complexity of patients treated (including a large proportion "off-label"). These findings add to other recent observational analyses either showing equivalent or reduced overall mortality with DES in unselected or higher risk groups.[9-13]

Consistent with meta-analysis,[8] very late-stent thrombosis was more common in DES, though overall stent thrombosis was no different after statistical adjustment. This is a key finding. PES and SES showed similar benefit in reducing target vessel revascularisation (TVR) compared with BMS although, as with previous registry studies, the absolute risk reduction was less than that seen within RCTs.[8-11,13]

Beyond this, the results are less consistent. Despite the authors' claim of a "strong trend" towards lower mortality with SES over PES, the adjusted hazard ratio 1.16 (confidence interval 0.88-1.53) suggests no difference between the groups. There was apparently a statistically significantly lower incidence of cardiac death in the SES group compared to PES – a finding derived from death certificate coding. This is difficult to reconcile with the lack of any difference between SES and PES for overall death, myocardial infarction or stent thrombosis. Previous meta-analysis have suggested a lower target lesion revascularisation rate with SES over PES;[8] in contrast this study showed no difference in efficacy between types of DES (TVR hazard ratio=0.99 [confidence interval 0.77-1.28]). Therefore we see little evidence from this study to support "real world" differences in safety or efficacy between SES and PES.

Further analyses for heterogeneity should be interpreted with caution – a large number of statistical comparisons were performed and these findings should be viewed as exploratory. Most notably perhaps, patients treated in the context of ST-elevation MI (STEMI) were seen to have little benefit in terms of TVR with DES compared to BMS. In addition, STEMI as an indication for PCI was a strong predictor of stent thrombosis, leading to the suggestion that DES use is debatable in such patients. It is important to consider these findings in the context of both a previous meta-analysis[14] and a recent propensity-score matched study[13] of STEMI patients that indicated clinical efficacy without major safety concerns for combined DES versus BMS.

Conclusion

Observational studies have played a key role in evaluating the safety and "real world" efficacy of DES. Daemen et al add to the increasingly consistent body of literature suggesting at least equivalent, or perhaps better long-term mortality, with DES in routine clinical practice and maintained reductions in TVR. Elsewhere, we would argue that the findings do not support the theory of differential safety and efficacy of SES and PES in routine clinical practice.

References

1. Cook S, Meier B. Have we been misled by the ESC DES firestorm? *Eurointerv.* 2008;3:535-537.

2. Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW. 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;369:667-678.

3. Win HKM, Caldera AE, Maresh K, Lopez J, Rihal CS, Parikh MAM, Granada JFM, Marulkar S, Nassif D, Cohen DJM, Kleiman NS, for the EVENT Registry Investigators. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA.* 2007;297:2001-2009.

4. Eisenstein EL, Anstrom KJ, Kong DF, Shaw LK, Tuttle RH, Mark DB, Kramer JM, Harrington RA, Matchar DB, Kandzari DE, Peterson ED, Schulman KA, Califf RM. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA.* 2006;297:159-168.

5. Daemen J, van Twisk P-H, Kukreja N, van Domburg RT, Boersma E, de Jaegere PP, Serruys PW. The relative safety and efficacy of bare-metal and drug-eluting stents in low and high risk patient subsets. *EuroInterv.* 2008;4:464-474.

6. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol.* 1999;34:618-620.

7. The West of Scotland Coronary Prevention Study Group. Computerised record linkage: Compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. *J Clin Epid.* 1995;48:1441-1452.

8. Stettler C, Wandel S, Allemann S, Kastrati A, Morice MC, Schomig A, Pfisterer ME, Stone GW, Leon MB, de Lezo JS, Goy JJ, Park SJ, Sabate M, Suttorp MJ, Kelbaek H, Spaulding C, Menichelli M, Vermeersch P, Dirksen MT, Cervinka P, Petronio AS, Nordmann AJ, Diem P, Meier B, Zwahlen M, Reichenbach S, Trelle S, Windecker S, Juni P. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet.* 2007;370:937-948.

9. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, Hopkins R, Tarride JE, Blackhouse G, Lazzam C, Cohen EA, Goeree R. Effectiveness and safety of drug-eluting stents in Ontario. *N Engl J Med.* 2007;357:1393-1402.

10. Marzocchi A, Saia F, Piovaccari G, Manari A, Aurier E, Benassi A, Cremonesi A, Percoco G, Varani E, Magnavacchi P, Guastaroba P, Grilli R, Maresta A. Long-term safety and efficacy of drug-eluting stents: two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation.* 2007;115:3181-3188.

11. Austin D, Oldroyd KG, McConnachie A, Slack R, Eteiba H, Flapan AD, Jennings KP, Northcote RJ, Pell ACH, Starkey IR, Pell JP. Drug-eluting stents versus bare-metal stents for off-label indications: a propensity score-matched outcome study. *Circ Cardiovasc Intervent.* 2008;1:45-52.

12. Shishehbor MH, Goel SS, Kapadia S, Bhatt DL, Kelly P, Raymond RE, Galla JM, Brener SJ, Whitlow PL, Ellis SG. Long-term impact of drug-eluting stents versus bare-metal stents on all-cause mortality. *J Am Coll Cardiol.* 2008;52:1041-1048.

13. Mauri L, Silbaugh TS, Garg P, Wolf RE, Zelevinsky K, Lovett A, Varma MR, Zhou Z, Normand SL. Drug-eluting or bare-metal stents for acute myocardial infarction. *N Engl J Med.* 2008;359:1330-1342.

14. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, Di Lorenzo E, Kaiser C, Tierala I, Mehilli J, Seyfarth M, Varenne O, Dirksen MT, Percoco G, Varricchio A, Pittl U, Syvanne M, Suttorp MJ, Violini R, Schomig A. Meta-analysis of randomized trials on drug-eluting stents vs. bare-metal stents in patients with acute myocardial infarction. *Eur Heart J* 2007;28:2706-13.