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Drug eluting stents in left main stem stenosis: patients will pay the price

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This editorial refers to "Revisiting the Incidence and Temporal Distribution of Cardiac and Sudden Death in Patients Undergoing Elective Intervention for Unprotected Left Main Coronary Artery Stenosis in the Drug Eluting Stent Era" by Marco Valgimigli et al published in this issue of EuroIntervention.

In the current issue of this journal, Valgimigli and colleagues report a pooled analysis of 340 patients receiving drug eluting stents (DES) for unprotected left main coronary artery (LMCA) stenosis[1]. This seminal study is important for three reasons. It not only constitutes the largest series of such patients reported in the literature, but by describing the combined experience of leading experts, using only DES, it represents 'state of the art' practice in interventional cardiology. Nevertheless, of several qualifications which apply to the superficially encouraging results, the most important is the very limited duration of follow-up (a duration of six to twelve months, but enthusiastically described by the authors as 'mid-term'). The main danger, however, is the very real risk that patients will yet again pay the price for professionals to re-learn why, after promising early results, previous attempts at stenting in LMCA stenosis succumbed not only to high re-intervention rates but, more importantly, to excess mortality.

Background to CABG and stenting in LMCA stenosis

Both randomised trials and large observational studies, from over two decades ago, consistently demonstrated a marked survival advantage for CABG versus medical treatment in LMCA stenosis[2,3]. Since then, there have been significant advances in both medical therapy (applicable to both medical and surgical groups) and surgical techniques (particularly the widespread use of the internal mammary artery graft). Nevertheless, the size of the survival benefit of revascularisation in LMCA stenosis (up to at least six years[3]) has ensured that CABG has remained the "gold standard" treatment in eligible patients with LMCA stenosis.

However, with the introduction of percutaneous coronary intervention (PCI), LMCA stenosis was soon considered a potentially suitable target because of its proximity in the coronary circulation and its relatively large diameter. This approach, however, ignored three key factors which strongly predicated against long-term success of PCI for this lesion. Rather than the more suitable ostial or shaft lesions, over 90% of LMCA stenosis are bifurcation lesions[4,5], around half of which have significant calcification[5] and both of these factors predict poorer technical outcomes with PCI[6]. Furthermore, around 90% of patients have simultaneous multi-vessel coronary disease[4,5] when CABG produces far better survival than PCI[7-10].

Initial attempts at PCI with balloon angioplasty in LMCA stenosis were prone to vessel dissection, but the ability of bare metal stents (BMS) to prevent this complication encouraged renewed efforts. Despite early satisfactory results, continuing high rates of mortality and the need for further revascularisation led to abandonment of stenting except in patients who were not surgical candidates[11,12]. Indeed, on the basis of these results both the ESC[13] and ACC[14] guidelines state that PCI is largely contra-indicated in patients with LMCA stenosis except in those who are ineligible for CABG.

Current practice of PCI in LMCA stenosis

One recent survey reported that up to 30% of patients in Europe and 20% of patients in the USA now undergo PCI with stents for LMCA stenosis[4]. Yet interpretation of the appropriateness and results of such practice is virtually impossible. As in the current pooled study[1], it is rarely reported what proportion of these patients are ineligible for CABG (this is important because patients who are at high risk for CABG are inevitably also at high risk for PCI), and

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what proportion have distal/bifurcation lesions and simultaneous multi-vessel coronary artery disease. This is compounded by very short term follow-up, frequently less than a year, despite – and as acknowledged in the current report[1] – the continuing limitations of stents, both BMS and DES, well beyond a year.

Results with surgery

In the United Kingdom in 2003 the mortality for over five thousand patients undergoing CABG for LMCA stenosis was 3%[15]. However, as this figure included all patients including one third who were high risk (because of the urgency of the operation, advanced age and/or or poor left ventricular function) this mortality rate could be improved by simply excluding higher risk patients.

Another consideration is that LMCA stenosis may lend itself particularly well to the use of bilateral internal mammary artery (IMA) grafts. The angiographic patency of both IMA placed to the left sided coronary vessels is over 95% at one week and at seven years after CABG[16]. And this superior angiographic patency may translate into a significant survival benefit. In a meta-analysis of over 15,000 CABG patients receiving single or bilateral IMA grafts and matched for age, gender, diabetes and left ventricular function we reported a significant survival benefit in patients with bilateral IMA grafts, with a HR of 0.82 for death (or a NNT of 13-16 patients)[16]. And such a surgical approach appears safe and feasible. Indeed in a current randomised trial of bilateral versus single IMA grafts (ART Trial), sponsored by the Medical Research Council and British Heart Foundation of the United Kingdom, in over 2000 patients operated in 22 centres in 5 countries the overall 30 day mortality is 1.2%[17].

Why PCI is unlikely to ever equal the results of CABG for LMCA stenosis

There are three reasons why it is unlikely that PCI, even with DES, will ever match the success of CABG over the longer term for patients with LMCA stenosis.

(i) The proven survival benefit of CABG over the long term is because of its ability to protect whole zones of proximal myocardium as the graft is placed to the mid coronary vessel rather than the more proximal location of stents (which leaves the vessel susceptible to restenosis or distal de novo lesions)[7-10].

(ii) PCI frequently results in incomplete revascularisation and this adversely affects survival proportional to the incompleteness of revascularisation[18].

(iii) Three large meta-analyses have shown no clinical advantage in terms of survival or reduction in myocardial infarction with DES vs BMS because although DES reduce angiographic rates of restenosis compared to BMS, they are (unlike CABG) ineffective against *de novo* lesions[19-21].

The importance of follow-up

What is the true rate of re-stenosis of DES in LMCA stenosis? The evidence in the literature is conflicting because few studies have complete angiographic follow-up. Indeed, in the current pooled study only 69% of patients underwent repeat angiography at six to twelve months (and it is noteworthy that are we are not told the rate of restenosis in these patients)[1]. In a recent study by Price and colleagues who reported complete angiographic follow-up of fifty patients (94% with distal LMCA stenosis) receiving DES, restenosis increased from 34% at three months to 44% at nine months[22]. Most importantly, as restenosis was frequently asymptomatic, Price and colleagues cautioned that serial angiographic follow up was necessary. Their recommendation was supported in an accompanying editorial by Baim et al who wrote that "without that safety net, one would expect an up-tick in late mortality events resulting from unrecognised restenosis in this critical location."[23] These recommendations argue strongly against the more complacent view advocated in the current pooled analysis[1]. And probably angiographic follow-up should continue beyond a year, in view of the increasing recognition of late stent failure and thrombosis[24] in such a vital position.

Summary and conclusion

LMCA stenosis carries major adverse prognostic implications. CABG provides well established survival benefits over the long term because of its ability to protect whole zones of proximal myocardium, and should remain the preferred option in eligible patients and particularly in those with bifurcation LMCA stenosis and associated multi-vessel coronary disease. PCI has an important role in those who are ineligible for or refuse CABG, but mandates careful follow-up. Although the intensity, invasiveness and duration of follow-up is not yet agreed, the fact that restenosis is frequently asymptomatic should sound a very important cautionary note.

References

1. Valgimigli M, Chieffo A, Lefevre T, Colombo A, Morice MC, Serruys PW on behalf of the Executive Committee of the Syntax Study. Revisiting the incidence and temporal distribution of cardiac and sudden death in patients undergoing elective intervention for unprotected left main coronary artery stenosis in the drug eluting stent era. *Eurointervention* 2007; 434-443.

2. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; 344:563-70.

3. Caracciolo EA, Davis KB, Sopko G, Kaiser GC, Corley SD, Schaff H, Taylor HA, Chaitman BR. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASS experience. *Circulation* 1995; 91:2335-44.

4. Kappetein AP, Dawkins KD, Mohr FW, Morice MC, Mack MJ, Russell ME, Pomar J, Serruys PW. Current percutaneous coronary intervention and coronary artery bypass grafting practices for three-vessel and left main coronary artery disease. Insights from the SYNTAX run-in phase. Eur J Cardiothorac Surg. 2006 Apr;29(4):486-91.

5. Ragosta M, Dee S, Sarembock IJ, Lipson LC, Gimple LW, Powers ER. Prevalence of unfavorable angiographic characteristics for percutaneous intervention in patients with unprotected left main coronary artery disease. *Catheter Cardiovasc Interv* 2006; 68(3):357-62.

6. Hoye A, Iakovou I, Ge L, van Mieghem CA, Ong AT, Cosgrave J, Sangiorgi GM, Airoldi F, Montorfano M, Michev I, Chieffo A, Carlino M, Corvaja N, Aoki J, Rodriguez Granillo GA, Valgimigli M, Sianos G, van der Giessen WJ, de Feyter PJ, van Domburg RT, Serruys PW, Colombo A.

Long-term outcomes after stenting of bifurcation lesions with the "crush" technique: predictors of an adverse outcome. *J Am Coll Cardiol.* 2006 May 16;47(10):1949-58.

7. Taggart DP. Surgery is the best intervention for severe coronary artery disease. *BMJ* 2005; 330:785-6.

8. Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation* 2004;109:2290-5.

9. Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, Culliford AT, Isom OW, Gold JP, Rose EA. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005;352:2174-83.

10. Smith PK, Califf RM, Tuttle RH, Shaw LK, Lee KL, Delong ER, Lilly RE, Sketch MH Jr, Peterson ED, Jones RH. Selection of surgical or percutaneous coronary intervention provides differential longevity benefit. *Ann Thorac Surg.* 2006;82(4):1420-8.

11. Takagi T, Stankovic G, Finci L, Toutouzas K, Chieffo A, Spanos V, Liistro F, Briguori C, Corvaja N, Albero R, Sivieri G, Paloschi R, Di Mario C, Colombo A. Results and long-term predictors of adverse clinical events after elective percutaneous interventions on unprotected left main coronary artery. *Circulation* 2002;106:698-702.

12. Brueren BR, Ernst JM, Suttorp MJ, ten Berg JM, Rensing BJ, Mast EG, Bal ET, Six AJ, Plokker HW. Long term follow up after elective percutaneous coronary intervention for unprotected non-bifurcational left main stenosis: is it time to change the guidelines? *Heart* 2003;89:1336-9.

13. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyllo W, Urban P, Stone GW, Wijns W; Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. *Eur Heart J.* 2005 Apr;26(8):804-47.

14. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB 3rd, Morrison DA, O'Neil WW, Schaff HV, Whitlow PL, Williams DO, Antman EM, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions Writting Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:156-75.

15. Keogh BE, Kinsman R. Fifth national adult cardiac surgical database report 2003. Dendrite Clinical Systems (Henley-on Thames, Oxfordshire, UK) 2004.

16. Taggart DP, D'Amico R, Altman DG. Effect of arterial revascularisation on survival: a systematic review of studies comparing bilateral and single internal mammary arteries. *Lancet.* 2001;358:870-5.

17. Taggart DP, Lees B, Gray A, Altman DG, Flather M, Channon K; ART Investigators. Protocol for the Arterial Revascularisation Trial (ART). A randomised trial to compare survival following bilateral versus single internal mammary grafting in coronary revascularisation [ISRCTN46552265]. *Trials.* 2006 Mar 30;7:7.

18. 7. Hannan EL, Racz M, Holmes DR, King SB 3rd, Walford G, Ambrose JA, Sharma S,Katz S, Clark LT, Jones RH. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation.* 2006 May 23;113(20):2406-12.

19. Babapulle MN, Joseph L, Belisle P, Brophy JM, Eisenberg MJ. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. *Lancet* 2004;364:583-91.

20. Hill R, Bagust A, Bakhai A, Dickson R, Dundar Y, Haycox A, Mujica Mota R, Reaney A, Roberts D, Williamson P, Walley T. Coronary artery stents: a rapid systematic review and economic evaluation. *Health Technol Assess* 2004;8(35):iii-iv, 1-242.

21. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs. bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J* 2006 Oct 4[Kappetein1];

22. Price MJ, Cristea E, Sawhney N, Kao JA, Moses JW, Leon MB, Costa RA, Lansky AJ, Teirstein PS. Serial angiographic follow-up of sirolimus-eluting stents for unprotected left main coronary artery revascularization. *J Am Coll Cardiol.* 2006 Feb 21;47(4):871-7.

23. Baim DS, Mauri L, Cutlip DC. Drug-eluting stenting for unprotected left main coronary artery disease: are we ready to replace bypass surgery? *J Am Coll Cardiol.* 2006 Feb 21;47(4):878-81.

24. Rihal CS, Raco DL, Gersh BJ, Yusuf S. Indications for coronary artery bypass surgery and percutaneous coronary intervention in chronic stable angina: review of the evidence and methodological considerations. *Circulation* 2003; 108(20):2439-45.