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In search of the "IDEAL" left main coronary stent and DAPT regimen

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Percutaneous coronary intervention (PCI) is being increasingly used in patients with left main coronary artery disease (LMCAD). An individual patient data pooled meta-analysis from 4 large-scale randomised trials of PCI with drug-eluting stents (DES) vs coronary artery bypass graft surgery (CABG), in 4,394 LMCAD patients, showed no significant differences in 5-year or 10-year mortality between the approaches[1]. PCI resulted in lower 30-day rates of stroke and large procedural myocardial infarctions (MI), but higher rates of spontaneous MI and repeat revascularisation procedures during follow-up. Formal quality-of-life studies have shown better early quality-of-life with PCI than with CABG, with comparable late outcomes after both procedures[2]. Thus, PCI with contemporary DES is a valid approach for selected patients with LMCAD in whom revascularisation can be safely accomplished.

Can the results of PCI in general and LM-PCI in particular be further improved? Toward this goal numerous studies have investigated different polymer types coating the stent backbone and the optimal duration of dual antiplatelet therapy (DAPT) after DES. Bioabsorbable polymers (BP) that are completely metabolised within several months after implantation were introduced to replace durable polymers (DP) to reduce long-term polymer-induced inflammation and hypersensitivity reactions. However, while first-generation DPs were prone to these complications (necessitating long-term reliance on DAPT)[3], second-generation DPs were developed that are more biocompatible and may even have thromboresistant properties. Prior randomised trials have thus found no early or late differences in safety or effectiveness between contemporary BP-DES and DP-DES[4]. As regards DAPT duration, although randomised trials have demonstrated that prolonged DAPT reduces late stent thrombosis and MI after DES, it also increases major bleeding, the occurrence of which has been associated with at least an equal risk of attributable mortality[5]. A cottage industry has thus developed to characterise the relative risks of ischaemia vs bleeding in individual patients treated with DES to tailor post-PCI antiplatelet therapy strategies.

Unfortunately, few patients with LMCAD were enrolled in these prior trials and generalisability of their results cannot be assumed. On one hand the LMCA is typically a short, large-calibre vessel that has a relatively low rate of restenosis and stent thrombosis. However, when these events do occur, they may have serious consequences given the large amount of myocardium subtended.

It is with this background that van Geuns et al for the IDEAL-LM investigators[6], reported in this issue, randomised 818 patients with LMCAD to a BP platinum chromium everolimus-eluting

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stent (BP-PtCr-EES) with 4 months of DAPT vs a control DP cobalt chromium everolimus-eluting stent (DP-CoCr-EES) with 12 months of DAPT. With observed event rates of 14.6% vs 11.4% respectively, they concluded the BP-DES was non-inferior to the DP-DES for the 2-year composite of all-cause death, MI, or ischaemia-driven target vessel revascularisation. Of note, MI rates were similar and there were no stent thromboses in either arm between 4 and 12 months (the time period during which the DAPT durations differed). Major bleeding was inexplicably increased in the short-DAPT group, principally after 4 months. Are these results sufficiently robust to recommend a BP-PtCr-EES with 4 months of DAPT as the standard of care after LM-PCI?

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Although this study was very well done, several considerations preclude definitive conclusions. First, the randomisation scheme allowed 2 elements to vary: stent type and DAPT duration. While a 2x2 factorial randomisation would have been preferred as it would have allowed discrimination of the differing effects of these 2 conditions, the present study design necessitates we consider the results of the "strategic" use of a specific BP-DES with 4-month DAPT compared with a specific DP-DES with 12-month DAPT. Second, the declaration of non-inferiority was based on an absolute non-inferiority margin (or "delta") of 7.5%. The anticipated 2-year control arm event rate was 20%. This planned margin thus allowed acceptance of a relative 37.5% worse outcome with the test strategy, which might be considered acceptable given the well-established utility of short DAPT in reducing bleeding[5]. However, as is frequently the case in many randomised trials, the 2-year control event rate of 11.4% was lower than anticipated, resulting in a 1-sided upper 95% confidence interval (CI) for the observed difference of 7.18%; p=0.04 for non-inferiority. This "positive" result is fragile at best as: 1) it is based on a relative margin of 7.5/11.4=66%, which is unacceptably high, especially for LM-PCI; and 2) even with this liberal margin, non-inferiority would not have been met had it been tested using a standard 1-sided upper 97.5% margin (rather than the 1-sided upper 95% margin as tested). Moreover, the present study had relatively few exclusion criteria. While this is laudable, it precludes subgroup analysis in meaningful numbers of patients at very high ischaemic risk (e.g., high SYNTAX scores or 2-stent treatment of the distal LM bifurcation) or very high bleeding risk (e.g., advanced age, chronic oral anticoagulation use), in whom the benefits vs risks of longer-term DAPT might have emerged. Thus, from this trial we cannot conclude that 4-month DAPT should become the new standard of care after LM-DES, nor should BP-DES be preferred over DP-DES for LM-PCI, especially given the signal for a higher rate of adverse events with the BP-DES/4-month DAPT combination.

Presently, DAPT is recommended for 6 months after PCI in stable CAD and for 12 months after PCI in acute coronary syndromes, with allowances to shorten or prolong DAPT duration depending on the relative risks of ischaemia vs bleeding. Neither the EU nor the US guidelines state a preference for DP-DES vs BP-DES in any clinical scenario. On the basis of IDEAL-LM demonstrating similar risks of stent thrombosis and MI between 4 and 12 months, we believe it reasonable to extend the standard DAPT duration recommendations to patients undergoing LM-PCI. However, given the divergent 2-year composite adverse event rates, greater uncertainty remains as to whether all stent geometries are interchangeable for complex LM morphologies. Of note, neither stents with heightened radial force nor ultrathin strut stents were tested in this trial, the latter of which have some clinical advantages after non-LM-PCI[7]. Thus, the search for the ideal LM coronary stent and DAPT regimen continues. Nonetheless, LM-PCI outcomes may be further improved by: the mandatory use of intravascular imaging guidance[8]; appropriate (image-guided) lesion preparation; applying best techniques for complex distal LM bifurcations (e.g., double kissing crush[9] until others are proved as effective); strategies to reduce procedural and late bleeding (radial intervention, selective use of bivalirudin, and yes, optimising DAPT duration); effective identification of non-LM targets to treat (currently based on physiology, in the future possibly also based on plaque vulnerability); and concerted efforts to initiate and ensure adherence to intensive secondary preventative measures.

Conflict of interest statement

G.W. Stone has received speaker honoraria from Pulnovo, Infraredx, and Amgen; has served as a consultant to Valfix, TherOx, Robocath, HeartFlow, Ablative Solutions, Vectorious, Miracor, Neovasc, Abiomed, Ancora, Elucid Bio, Occlutech, CorFlow, Apollo Therapeutics, Impulse Dynamics, Vascular Dynamics, Shockwave, V-Wave, Cardiomech, and Gore; and has equity/options from Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, Valfix, and Xenter; his daughter is an employee at Medtronic. Institutional disclosure: G.W. Stone's employer, Mount Sinai Hospital, receives research support from Abbott, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Shockwave, Vascular Dynamics, and V-wave. C. Bohra has no conflicts of interest to declare.

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