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EDITORIALS

Optimal duration of dual antiplatelet therapy after stent implantation in patients with or without diabetes

Shorter may be better

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A topic of much research and debate within cardiology has been the optimal duration of dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor to prevent stent thrombosis and further atherosclerotic progression after percutaneous coronary intervention and implantation of a drug eluting stent. Recently, large randomised controlled trials and observational studies have been conducted in an attempt to determine the optimal duration of DAPT, but the results were conflicting or inconclusive.[1-7] Indicative of the implications, this area of cardiovascular research has had an effect on a broad range of clinical practice guidelines.[8-11] The common consensus among experts has been that there is no "one size fits all" approach and no common rule for the duration of DAPT after placement of a drug eluting stent, but it is likely to be a case of "the longer the better." The current recommendation is for 12 months of DAPT, but there are claims that this is actually of uncertain value.[12]

The study by Gargiulo and colleagues[13] in *TheBMJ* (doi:10.1136/bmj.i5483) adds some clarity to the debate on the duration of DAPT. In a individual patient level meta-analysis, data were pooled from 11 473 well matched randomised patients from six large, multicentre, randomised controlled trials assessing short term (≤6 months) versus long term (12 months) DAPT after insertion of a drug eluting stent for stable ischaemic heart disease or acute coronary syndrome.[1-6] Not surprisingly, diabetes was identified as an independent predictor of major adverse cardiac events (MACE)—defined as cardiac death, myocardial infarction, or definite or probable stent thrombosis (according to criteria from the Academic Research Consortium[14]) at one year after implantation of a drug eluting stent. Perhaps the most notable finding of this meta-analysis was that long term DAPT did not decrease the risk of MACE at one year compared with short term DAPT in patients with diabetes (32% of the cohort) and also in those without. Additionally, higher rates of bleeding (defined according to commonly used criteria[2-16]) were observed with long term DAPT, irrespective of diabetes status. The researchers' use of individual patient level data, prespecified subgroup analyses, and sensitivity analyses make this a rigorous assessment with high internal validity, and allowed conduct of extended analysis. However, the patients within the trial cohorts included in this analysis were prescribed clopidogrel and aspirin for DAPT only. Studies involving analysis of aspirin plus newer antiplatelet agents (prasugrel and ticagrelor) were not included.

This study complements work conducted so far on the use of DAPT after implantation of a drug eluting stent. Such work includes a study most recently reported by the authors, in which a pooled analysis of patient level data from four randomised controlled trials was performed in all patients undergoing short term versus longer term DAPT.[17] The finding was that short term DAPT was associated with similar rates of MACE but lower rates of bleeding after stent implantation.[17] The present study[13] is an extension of this work and looks at an important and increasing population—patients with diabetes who are at higher risk of ischaemic or thrombotic events and for whom prolonged and even lifelong DAPT treatment could be beneficial.[18]

The findings of Gargiulo and colleagues are important and increasingly so because of the exponential increase in the global prevalence of diabetes mellitus (particularly type 2 diabetes), owing to risk factors related to increasingly poor lifestyles and the emerging epidemic of obesity. Despite limitations, this study provides robust data that contribute considerably to the debate around DAPT duration, and could contribute towards reaching a consensus for optimal length of treatment. It also highlights the fact that having diabetes itself does not necessarily equate to a requirement for longer duration of DAPT and that this can actually do more harm than good.

Understanding the optimal duration of DAPT after percutaneous coronary intervention and stent implantation is of clear clinical and economic importance. Reducing costs to healthcare systems resulting from medication provision, increased patient surveillance, and the occurrence of adverse events (such as ischaemic events from insufficient treatment and bleeding events from prolonged treatment) is critical. Perhaps even more important, however, is the need to minimise the burden of treatment placed on patients (and possibly on their carers and families) with the requirements of strict treatment adherence and caution that comes in association with (potentially life threatening) side effects and reduced quality of life. In context,

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the findings of Gargiulo and colleagues are hypothesis generating but are promising. Further work is needed, for example, by large, prospective, randomised controlled trials or broader, patient level meta-analyses including newer $P2Y_{12}$ inhibitors. Confirmation of Gargiulo and colleagues' findings could have a significant and definitive effect on clinical practice and management guidelines for the optimal duration of DAPT after percutaneous coronary intervention and implantation of a drug eluting stent for the treatment of coronary artery disease and acute coronary syndrome.

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1 Valgimigli M, Campo G, Monti M, et al. Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation* 2012;125:2015-26. doi:10.1161/CIRCULATIONAHA.111.071589 pmid:22438530.

2 Feres F, Costa RA, Abizaid A, et al. OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA* 2013;310:2510-22.pmid:24177257.

3 Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation* 2012;125:505-13. doi:10.1161/CIRCULATIONAHA.111.059022 pmid:22179532.

4 Kim BK, Hong MK, Shin DH, et al. RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol* 2012;60:1340-8. doi:10.1016/j.jacc.2012.06.043 pmid:22999717.

5 Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol* 2014;64:2086-97. doi:10.1016/j.jacc.2014.09.008 pmid:25236346.

6 Gilard M, Barragan P, Noryani AAL, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol* 2015;65:777-86. doi:10.1016/j.jacc.2014.11.008 pmid:25461690.

7 Timmis A, Rapsomaniki E, Chung SC, et al. Prolonged dual antiplatelet therapy in stable coronary disease: comparative observational study of benefits and harms in unselected versus trial populations. *BMJ* 2016;353:i3163. doi:10.1136/bmj.i3163 pmid:27334486.

8 Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention* 2015;10:1024-94. doi:10.4244/EIJY14M09_01 pmid:25187201.

9 Levine GN, Bates ER, Blankenship JC, et al. American College of Cardiology Foundation American Heart Association Task Force on Practice Guidelines Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44-122. doi:10.1016/j.jacc.2011.08.007 pmid:22070834.

10 Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [correction in: *J Am Coll Cardiol* http://dx.doi.org/10.1016/j.jacc.2016.07.715]. *J Am Coll Cardiol* 2016;68:1082-115. doi:10.1016/j.jacc.2016.03.513 pmid:27036918.

11 Levine GN, Bates ER, Blankenship JC, et al. American College of Cardiology Foundation American Heart Association Task Force on Practice Guidelines Society for Cardiovascular Angiography and Interventions. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol* 2011;58:e44-122. doi:10.1016/j.jacc.2011.08.007 pmid:22070834.

12 Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials [correction in: *BMJ* 2016;355:i5600]. *BMJ* 2015;350:h1618. doi:10.1136/bmj.h1618 pmid:25883067.

13 Gargiulo G, Windecker S, da Costa BR, et al. Short term versus long term dual antiplatelet therapy after implantation of drug eluting stent in patients with or without diabetes: systematic review and meta-analysis of individual participant data from randomised trials. *BMJ* 2016;355:i5483.

14 Cutlip DE, Windecker S, Mehran R, et al. Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344-51. doi:10.1161/CIRCULATIONAHA.106.685313 pmid:17470709.

15 Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II Trial. *Ann Intern Med* 1991;115:256-65. doi:10.7326/0003-4819-115-4-256 pmid:1906692.

16 Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123:2736-47. doi:10.1161/CIRCULATIONAHA.110.009449 pmid:21670242.

17 Palmerini T, Sangiorgi D, Valgimigli M, et al. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. *J Am Coll Cardiol* 2015;65:1092-102. doi:10.1016/j.jacc.2014.12.046 pmid:25790880.

18 Mauri L, Kereiakes DJ, Yeh RW, et al. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014;371:2155-66. doi:10.1056/NEJMoa1409312 pmid:25399658.