AsiaIntervention 2015;11:99-101 published online ahead of print May 2015

Will the DAPT trial (long-term dual antiplatelet treatment after stent implantation) change my practice?

Chee Tang Chin[1,2], MBChB, MRCP(UK); Davide Capodanno[3], MD, PhD; Philip Urban[4], MD; Alan Ching Yuen Yeung[5], MD; Azeem Latib[6], MD; Sunarya Soerianata[7], MD; Hyeon-Cheol Gwon[8], MD; William Wijns[9]*, MD; Andrew Ong[10], MD, PhD

1. National Heart Centre Singapore, Singapore; 2. Duke-NUS Graduate Medical School, Singapore; 3. Ferrarotto Hospital, University of Catania, Catania, Italy; 4. Hôpital de La Tour Meyrin, Geneva, Switzerland; 5. Stanford University, Stanford, CA, USA; 6. San Raffaele Scientific Institute, Milan, Italy; 7. National Cardiovascular Center, Harapan Kita Hospital, Jakarta, Indonesia; 8. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; 9. Cardiovascular Research Center, Aalst, Belgium; 10. Westmead Hospital, Sydney, Australia

Introduction

Dual antiplatelet therapy (DAPT) combining aspirin with an adenosine diphosphate receptor inhibitor has significantly reduced the incidence of ischaemic events, including stent thrombosis, after percutaneous coronary intervention, and is thus strongly recommended by international practice guidelines[1,2]. However, less clear has been the optimal duration for which DAPT should be recommended, especially in the context of a drug-eluting stent (DES) implantation, where previous reports have implicated an association with increased late stent thrombosis events after DAPT has been stopped. In addition, this issue is further influenced by the exposure of the patient to an increased risk of bleeding while on DAPT.

The DAPT study was therefore designed to evaluate the benefits and risks of continuing a patient on DAPT beyond 12 months after coronary stenting[3]. This study was distinct from prior studies in that it was powered to detect a difference in stent thrombosis rates, and was composed of five individual studies with similar protocols involving eight different devices and pharmaceutical companies.

Briefly, the DAPT study was an international, multicentre, prospective, blinded, placebo-controlled study that included 9,961 patients who had successfully completed 12 months of DAPT after coronary stenting without a significant ischaemic or bleeding event, and who were then randomly assigned to either continuing on DAPT for a further 18 months, or stopping DAPT and continuing on aspirin alone[4]. The two co-primary efficacy endpoints were stent thrombosis and major adverse cardiovascular and cerebrovascular events (MACCE) (a composite of death, myocardial infarction, or stroke) during the period from 12 to 30 months. The primary safety endpoint was moderate or severe bleeding. Patients who were randomised to continuing DAPT after the initial 12 months, as compared with patients who discontinued DAPT, had reduced rates of stent thrombosis (0.4% vs. 1.4%; hazard ratio [HR] 0.29, 95% confidence interval [CI] 0.17 to 0.48; p<0.001) and MACCE (4.3% vs. 5.9%; HR 0.71, 95% CI: 0.59 to 0.85; p<0.001). The rate of myocardial infarction (MI) was also reduced with prolonged DAPT (2.1% vs. 4.1%; HR 0.47; p<0.001). However, both the rates of death from any cause (2.0% vs. 1.5%; HR 1.36, 95% CI: 1.00 to 1.85; p=0.05) and moderate or severe bleeding (2.5% vs. 1.6%, p=0.001) were higher in the prolonged DAPT group as compared to the group where DAPT was stopped at 12 months **(Figure 1)**.

This important and potentially practice-changing study was discussed in the first ever "Will this trial change my practice?" session at AsiaPCR 2015. The objectives of this new session format were succinctly outlined by W. Wijns, who explained to the audience the

*Corresponding author: Cardiovascular Center Aalst, Moorselbaan 164, B-9300 Aalst, Belgium.
E-mail: William.Wijns@olvz-aalst.be

DOI: 10.4244/AIJY15M05_01

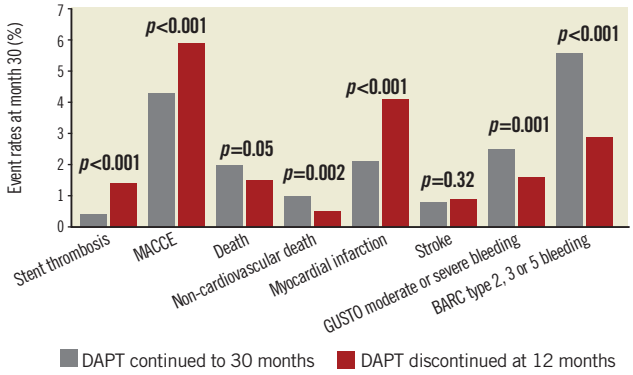

Figure 1. *Clinical event rates in the two randomisation groups at month 30 (%). Stent thrombosis, MACCE and myocardial infarction are significantly lower with DAPT continued to 30 months, while bleeding, as well as non-cardiovascular death is increased.*

need to achieve a detailed understanding of the results of a particular published trial that may impact on their clinical practice, the importance of being able to evaluate the relevance of new results for the treatment of their patients, and the importance of being able to share current and future practice with colleagues from around the world. The expert panel at the session comprised colleagues from Asia, Australia, North America, and Europe and was therefore in a unique position to provide a global appraisal of the study and its relevance to an international audience.

W. Wijns proceeded to put into context the relevance of the study to daily clinical practice by presenting a case study of an actual patient from the DAPT study. He then polled the audience to determine practice patterns with regard to DAPT duration before the results of the DAPT study were known. The following three choices were presented to the audience: 1) stop DAPT no later than one year; 2) continue DAPT beyond one year whenever possible; or 3) decide on a case-by-case basis. Only a small minority of the audience stated their preference for stopping DAPT no later than one year. This differed significantly from the panel, as most of the panel members indicated their preference for option 1 (stop no later than one year). The majority of the audience supported either option 2 or option 3, about 50% each.

With the clinical context firmly established, A. Ong presented a concise summary of the rationale for DAPT post coronary stenting and the evolution in practice patterns over time prior to the publication of the DAPT study. A meta-analysis by Bulluck and colleagues demonstrated firstly the lack of studies examining a DAPT duration of 12 versus 24+ months, and, secondly, showed that, although there was no advantage in terms of reducing mortality, MI, or stent thrombosis, a prolonged DAPT duration of at least 24 months was associated with more bleeding incidents than a DAPT duration of 12 months[5]. However, because only two small studies were included in this analysis, the results were more likely to be hypothesis-generating rather than definitive, hence emphasising the importance and relevance of the DAPT study.

This was therefore the context for D. Capodanno's in-depth review of the DAPT study design, results and interpretation. He showed that, although the study was an international multicentre effort, the majority of sites were from the USA. There were no sites from Asia in the study. He then highlighted the study protocol and its impact on the final study population. Because the DAPT study was attempting to answer the question of the effect of prolonging DAPT beyond 12 months, by design it was necessary to enrol and randomise patients who were event-free for the first 12 months on DAPT after coronary stenting. As such, from the initial 22,866 patients who were enrolled after the index DES stenting procedure, only 9,961 were finally randomised. Patients were not randomised for a variety of reasons, including having had a clinical event, but a significant number were also not randomised because of non-adherence, withdrawal of consent, or loss to follow-up. From the published data of events during the 12 months post coronary stenting (i.e., before randomisation), the DAPT study population could be characterised as a low-risk population, with respect to both ischaemic and bleeding risks.

The event curves for the two arms in the DAPT study were shown and discussed in detail. Two observations were highlighted. 1) The event curves diverged early on, but also appeared to converge in the observational period after DAPT had been stopped in the prolonged DAPT arm, thus suggesting a possible "rebound" phenomenon. 2) More than half (55%) of the MI events were not related to stent thrombosis and thus by implication occurred at a non-stented site.

In the DAPT study, more than one third of patients had a "first-generation" paclitaxel or sirolimus-eluting stent placed. Although subgroup analysis showed a significant interaction between stent type and MACCE, there was no significant interaction with stent thrombosis. In fact, generally there was a consistent treatment effect in most subgroups favouring prolonging DAPT for reducing stent thrombosis and MACCE, especially MI. The issue of all-cause mortality which showed a numerical excess (mainly from trauma, bleeding, or cancer-related deaths) in the prolonged DAPT arm was presented. The issue of cancer-related deaths was further defined by the DAPT study investigators who performed a *post hoc* analysis and reported more cancers at baseline in the prolonged DAPT arm. Furthermore, they also published a meta-analysis of DAPT vs. aspirin studies and reported no mortality benefit favouring either management strategy[6].

D. Capodanno summed up his review by stating that, although there was a significant reduction in stent thrombosis, MACCE, and MI with prolonged DAPT, this was at the expense of more bleeding events. In addition, the benefit in MI appeared to be not solely confined to the stented segment. There appeared to be a rebound phenomenon or withdrawal of protection after DAPT was discontinued at 30 months, with the event curves approaching each other. Finally, he emphasised that these results would apply to low-risk patients who have tolerated one year of DAPT after stent placement with no ischaemic or bleeding events.

The audience asked whether the study results could be generalised to an Asian population, bearing in mind that there were no

Asian sites in the study, that Asian patients may have a different bleeding profile compared to Western patients, and that "first-generation" DES had long been discontinued in Asia. In response, H.C. Gwon echoed these concerns by stating that bleeding had been well established as being associated with mortality and adverse outcomes, and that with newer-generation DES the risk of ischaemic events was much less and hence the risk-benefit ratio might not be in favour of prolonging DAPT duration. P. Urban shared his concern with regard to bleeding, especially in the context of the DAPT study which, he pointed out, showed an excess of deaths in the treatment arm which had more bleeding events. Other issues raised included the potentially diverging effects in subgroups such as the elderly (>75 yrs), or non-diabetics. P. Urban and D. Capodanno emphasised that, although these were interesting observations, they were ultimately only hypothesis-generating and should not inform treatment decisions.

The session concluded with the final clinical outcome of the initial case study from the trial. A. Ong summarised the session by stating again that overall the DAPT study had not shown any mortality benefit with regard to prolonging DAPT beyond 12 months as compared to stopping at 12 months. Although there was benefit in reducing stent thrombosis and MI, this was at the expense of bleeding, including nuisance bleeding, which may impact on quality of life.

To close the session, the panel members emphasised that, as with all important studies, data from the DAPT study would continue to inform clinical practice beyond the results included in the main manuscript. Of particular interest and importance would be further data and analyses with regard to patient presentation (acute coronary syndromes versus stable coronary artery disease), predictors of increased bleeding risk, and also factors associated with recurrent MI, be they related to the index stenting procedure or at another coronary site.

So, will the DAPT trial results change practice in the Asia-Pacific region?

A repeat poll of the audience indicated that the results of the DAPT study would not change their current clinical practice patterns. As to the colleagues participating in the discussion, the vast majority were already continuing DAPT beyond one year or at least considering it on a case-by-case basis. The DAPT trial now brings evidence in support of this practice.

As to the panel members, nearly all remained reluctant to continue DAPT beyond one year in all patients in the absence of mortality benefit. Following the release of the DAPT trial results, however, they will more often consider continuation of DAPT on a case-by-case basis for treatment of patients with high ischaemic and low bleeding risks.

Acknowledgements

We are indebted to A. Banning, N. Bowers and A.H. Gershlick for kindly providing the clinical case history for discussion during the session.

Conflict of interest statement

C.T. Chin has received an honorarium from AstraZeneca and has ongoing research collaborations with Eli Lilly and Daiichi Sankyo. P. Urban is a consultant for Biosensors, and has received honoraria from Abbott Vascular and Edwards Lifesciences, and institutional grant/research support from Boston Scientific. W. Wijns has received institutional research grants from Boston Scientific, Cordis J&J, Medtronic, Terumo and AstraZeneca. The other authors have no conflicts of interest to declare.

References

1. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 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. *Circulation.* 2011; 124:e574-651.

2. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann FJ, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS guidelines on myocardial revascularization. *EuroIntervention.* 2015;10: 1024-94.

3. Mauri L, Kereiakes DJ, Normand SL, Wiviott SD, Cohen DJ, Holmes DR, Bangalore S, Cutlip DE, Pencina M, Massaro JM. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. *Am Heart J.* 2010;160: 1035-41.

4. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014;371:2155-66.

5. Bulluck H, Kwok CS, Ryding AD, Loke YK. Safety of short-term dual antiplatelet therapy after drug-eluting stents: An updated meta-analysis with direct and adjusted indirect comparison of randomized control trials. *Int J Cardiol.* 2015;181:331-9.

6. Elmariah S, Mauri L, Doros G, Galper BZ, O'Neill KE, Steg PG, Kereiakes DJ, Yeh RW. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet.* 2015;385:792-8.