JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 2, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2015.11.024

EDITORIAL COMMENT

Is Prolonged DAPT Apt or a Study in Zero-Sum Games?*

David R. Holmes, Jr, MD, Charanjit S. Rihal, MD

Interventional cardiology has focused on issues of adjunctive therapy since the initial case of percutaneous transluminal coronary angioplasty was performed by Andreas Grüntzig in September 1977. Several issues bear emphasis: 1) the need to mitigate or eliminate the initial adverse effects of mechanically disrupting the vascular architecture of an atherosclerotic coronary artery; 2) prevention of subsequent events such as early elastic recoil and the later development of restenosis; 3) promoting re-endothelialization after placing either a permanent metallic or now a bioabsorbable structure for scaffolding; 4) local drug delivery to enhance arterial healing and prevent stent thrombosis (ST) with its markedly increased associated risk of mortality and morbidity; and finally 5) preventing other adverse coronary events in areas remote from the initial target lesion or vessel.

These adjunctive strategies have evolved over the course of time: pioneers in the early stages of interventional therapy development will recall such diverse agents as dextran, colchicine, steroids, and a variety of both anticoagulant and antiplatelet drugs. Some of these strategies either did not work, were not needed, or were associated with increased adverse events.

A number of different principles of adjunctive therapy have been substantiated and embedded in guidelines, namely that dual antiplatelet agents are necessary to improve the outcomes of now ubiquitously used drug-eluting coronary stents. However, important issues remain, not the least of which is the duration of the antiplatelet therapy following intervention as the interplay between risks and benefits tightens. This area and its interpretation have been rendered more complex by the fact that antiplatelet agents may also be used as a cornerstone for secondary prevention of other lesions remote from the stented arterial segment.

Despite an abundant literature that has grown up around these issues, with multiple studies and now multiple meta-analyses, it remains a moving target as new knowledge accumulates (1–8). Currently, the answer remains unclear to the point where the American College of Cardiology/American Heart Association recommendations in the past have focused on longer term >6 months of dual antiplatelet therapy (DAPT), whereas the European Society of Cardiology recommendations have typically focused on shorter-term DAPT administration: ≤6 months in patients with stable coronary artery disease. Interestingly, these somewhat different guideline recommendations have been reached by the authors of both guidelines who have had access to the same literature. Considerations in reaching these recommendations take into account baseline patient acuity, extent of coronary disease, predicted bleeding risk, and type of stents implanted. However, even taking these into account, European Society of Cardiology guidelines usually recommend a somewhat shorter duration of DAPT, although both sets of guidelines place increasing emphasis on the importance of individualizing treatment based on consideration of the risk-benefit ratio (9,10).

SEE PAGE 138

In this issue of *JACC: Cardiovascular Interventions*, the study by Hermiller et al. (11) focuses on one aspect of the published pivotal multicentered randomized trial DAPT, which included 25,682 patients after coronary stenting (12,13). Details of that study are important, including the fact that following stent

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

implantation, all patients were treated with DAPT for 1 year. If at the end of 1 year, no adverse events had been identified, patients were then randomized to either continued DAPT with a thienopyridine (clopidogrel or prasugrel) plus aspirin, or placebo plus aspirin for an additional 18 months. Hermiller et al. (11) focus on a post-hoc analysis of 4,703 patients initially been treated with an everolimus-eluting stent (EES). This is an important group for several reasons, but predominantly because EES was the most common drug-eluting stent used during the period of this study (47.2%), and EES have been found to be associated with particularly low rates of ST thought to be an important mechanism of adverse coronary events following drug-eluting stent implantation (14).

In this current analysis (11), continued thienopyridine administration did not reduce the overall incidence of clinically relevant adverse ischemic events (death, myocardial infarction [MI], stroke 4.3% vs. 4.5%, p = 0.42). On the risk side of the equation, continued thienopyridine was associated with increased moderate/severe bleeding (2.5% vs. 1.3%, hazard ratio [HR]: 1.79, 95% confidence interval [CI]: 1.15 to 2.80; p = 0.01). Subgroup analyses of the findings in this post-hoc analysis substantiated some of the major conclusions reached in the initial manuscript namely (10,11) continued thienopyridine was associated with a further reduced rate of ST (0.3% vs. 0.7%, HR: 0.38, 95% CI: 0.15 to 0.97; p = 0.04) and myocardial infarction (2.1% vs. 3.2%, HR: 0.63, 95% CI: 0.44 to 0.91; p = 0.01), but a higher risk of death (2.2% vs. 1.1%, HR: 1.80, 95% CI: 1.11 to 2.92; p = 0.02). This issue of increased mortality with longer-term clopidogrel has been the subject of concern and was dominantly related to malignancy. Recently the Food and Drug Administration has concluded that the preponderance of data does not suggest that clopidogrel increases the risk of either cancer or death related to cancer (15). It does, however, point to the risks of subgroup analyses and zero-sum games.

Important considerations of large datasets such as these relate to the number needed to treat for either benefit or harm and the tremendous statistical power these large numbers deliver to detect small differences that may or may not be clinically important. How to interpret these findings?

1. This is a post-hoc study with the inherent limitations in such an approach.
2. Subgroup analyses is a zero-sum game because of the issue of the potential to find some results based on chance alone.
3. The authors, however, are to be commended for this analysis in which they "suggest that the therapeutic window for benefit vs. risk of continued thienopyridine therapy may be narrow." Specifically, the number needed to treat to benefit 1 person for ST was 235 patients over 18 months, whereas the number needed to treat to benefit 1 person for MI was 98 over 18 months; by contrast, the number need to treat for harm from moderate or severe bleeding was 84.

These numbers are compelling as medicine moves increasingly towards patient-centric care because any treatment strategy requires evaluation of risks and benefits. These numbers also form part of the background of the difference between guidelines and clinical practice. As devices become increasingly effective, risks from adjunctive therapy such as bleeding may weigh more heavily in making individualized therapeutic decisions. It must also be remembered that not all subsequent cardiovascular events are the result of stent-related problems. This was highlighted in the PEGASUS (Prevention of Cardiovascular Events [e.g., Death From Heart or Vascular Disease, Heart Attack, or Stroke] in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) trial TIMI-54 (Thrombolysis In Myocardial Infarction-54) (16), which evaluated 21,162 patients 1 to 3 years post-MI who were randomly assigned to either ticagrelor of placebo. In this study, the primary composite endpoint of cardiovascular death, MI, or stroke was improved in patients treated with ticagrelor, although bleeding was higher. Accordingly, it is possible that longer-term DAPT, particularly in patients with extensive disease or an acute coronary syndrome, may benefit from more extensive, more prolonged medical therapy irrespective of whether a stent is present or not.

What then could be concluded from this analysis is well stated by the authors: "ongoing analyses will delineate the individual predictors of the risk and benefit of late continuation of (DAPT) treatment as well as the absolute impact of late ischemic and bleeding events and overall quantity and quality of life." Accordingly, for some patients, prolonged DAPT may be apt, but this must be based on individualized risk-benefit assessment.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. David Holmes, Jr., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: Holmes.david@mayo.edu.

REFERENCES

1. Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomized trials. Lancet 2015;385:2371–82.

2. Giustino G, Baber U, Satori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation; a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2015;65:1298–310.

3. Palmerini T, Sangiogri 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.

4. Spencer FA, Prasad M, Vandvik PT, et al. Longer- versus shorter-duration dual-antiplatelet therapy after drug-eluting stent placement: a systematic review and meta-analysis. Ann Intern Med 2015;163:118–26.

5. Elmariah S, Mauri L, Doros G, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet 2015;385:792–8.

6. Lee CW, Ahn JM, Park DW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. Circulation 2014;129:304–12.

7. Collet JP, Silvain J, Barthelemy O, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomized trial. Lancet 2014;384:1577–85.

8. Campo G, Tebaldi M, Vranckx P, et al. Short-versus long-term duration of dual antiplatelet therapy in patients treated for in-stent restenosis: a PRODIGY trial substudy (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia). J Am Coll Cardiol 2014;63:506–12.

9. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2014;35:2541–619.

10. Cutlip D, Nicolau JC. Antiplatelet therapy after coronary artery stenting. 2015. Available at: http://www.uptodate.com. Accessed November 27, 2015.

11. Hermiller JB, Krucoff MW, Kereiakes DJ, et al. Benefits and risks of extended dual antiplatelet therapy after everolimus-eluting stents. J Am Coll Cardiol Intv 2016;9:138–47.

12. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

13. Kereiakes DJ, Yeh RW, Massaro JM, et al. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial. JAMA 2015;313:1113–21.

14. Palmerini T, Kirtane AJ, Serruys PW, et al. Stent thrombosis with everolimus-eluting stents: meta-analysis of comparative randomized controlled trials. Circ Cardiovasc Interv 2012;5:357–64.

15. FDA drug safety communication. FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death. 11-6-2015. Available at: http://www.fda.gov/drugs/drugsafety. Accessed November 27, 2015.

16. Bonaca MP, Bhatt DL, Cohen M, et al. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372:1791–800.

KEY WORDS drug-eluting stent(s), dual-antiplatelet therapy, stent thrombosis