JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 14, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.06.002

EDITORIAL COMMENT

Dual-Antiplatelet Therapy

Why Stop Now?*

Alice K. Jacobs, MD, Zoran S. Nedeljkovic, MD

Dual-antiplatelet therapy (DAPT), comprising a combination of aspirin with a $P2Y_{12}$ receptor inhibitor, is prescribed following coronary stent implantation to reduce the risk for stent thrombosis and ischemic atherothrombotic events (1,2). The recommended duration of DAPT is based on the type of stent and the clinical presentation (3). DAPT is usually continued for a minimum of 1 month following bare-metal stent implantation and 12 months following drug-eluting stent procedures. However, recent studies and meta-analyses, particularly those involving newer, second-generation drug-eluting stents, have demonstrated comparable safety and efficacy of shorter duration DAPT compared with the standard 12-month regimen (4,5). Furthermore, extending DAPT beyond 12 months heightens the dilemma as to whether any additional reduction in ischemic risk (very late stent thrombosis and myocardial infarction) is offset by the increased risk for bleeding that accompanies prolonged therapy (5,6). Hence, a more recent focused update on the duration of DAPT in patients with coronary artery disease has been published to help incorporate newer data and revise existing guidelines (7).

Although it has been shown that adherence to guideline recommendations improves outcomes, particularly in patients with acute coronary syndromes (8), clinical circumstances arise that lead to transient interruption or, alternatively, complete cessation of DAPT, regardless of the intended duration of therapy. Complicating this issue is whether the withdrawal of DAPT itself, the specific clinical circumstance leading to withdrawal (e.g., surgery, noncompliance, bleeding), or both raise the risk for adverse cardiovascular events. Moreover, although it has been reported that women are less adherent to guideline-recommended medical therapy than men (9), sex-based differences in bleeding rates, with women demonstrating higher bleeding complications following percutaneous coronary intervention (PCI), have been well described (10). The impact of this observed increase in risk for bleeding, coupled with DAPT-related bleeding risk and its influence on adherence, represents an important area of study in women treated with PCI.

SEE PAGE 1461

In this issue of *JACC: Cardiovascular Interventions*, Yu et al. (11) examine the differences in clinical outcomes following cessation of DAPT in women compared with men enrolled in the PARIS (Patterns of Non-Adherence to Antiplatelet Regimens in Stented Patients) registry, a prospective, observational, multicenter study of patients undergoing PCI with stent implantation (12). DAPT cessation was classified on the basis of whether 1 or both medications were stopped because of: 1) physician-recommended discontinuation; 2) interruption for surgery (with reinstitution of DAPT within 14 days); or 3) disruption, further defined as physician-recommended because of bleeding or nonrecommended and due to noncompliance. Of note, the overall major adverse cardiac events (MACE) rate at 2-year follow-up was 11.5%, and 74% of these events occurred while patients were taking DAPT. Compared with patients who remained on DAPT, those with discontinuation had lower MACE risk, whereas those with interruption had similar risk and those with disruption had higher risk, the latter of which attenuated after 7 days. These findings highlight

*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 the Evans Department of Medicine, Boston University School of Medicine, and the Section of Cardiology, Boston Medical Center, Boston, Massachusetts. Dr. Jacobs is the site principal investigator for one study funded by AstraZeneca. Dr. Nedeljkovic has reported that he has no relationships relevant to the contents of this paper to disclose.

the importance of the relationship between the mode of cessation and the incidence of adverse events.

In the present study, these observations were extended to capture sex-based patterns and consequences of cessation of DAPT. Overall, women were more likely than men to have DAPT cessation (59.1% vs. 55.9%), especially disruption (17.4% vs. 13.2%), and female sex was an independent predictor of both discontinuation and disruption at 2 years. The effect of DAPT cessation on clinical events was similar in both women and men and varied according to reason. In particular, disruption was associated with an increased risk for both bleeding and ischemic events, but women had a nearly 2-fold risk for all-cause mortality and significantly increased bleeding. After adjustment for differences in clinical and treatment characteristics in addition to DAPT cessation episodes, female sex remained an independent predictor of bleeding but not ischemic events.

Notwithstanding the lack of factors associated with bleeding risk (frailty, renal disease, anemia) and medication adherence (ethnic, social, geographic, and economic), which were not captured, this study, with its thoughtful design and carefully analyzed and adjudicated outcomes, adds to prior observations that highlight sex-based differences in adherence to prescribed medications (13) and higher bleeding rates in women following PCI (10). However, this report further elucidates the incidence and impact of different modes of cessation of DAPT in both women and men, documenting a higher occurrence of physician-recommended cessation as well as worse outcomes in women. The reasons for this sex-based difference in the incidence of bleeding likely relate to older age and a higher prevalence of frailty, vascular disease, and chronic kidney disease in women. Its importance is underscored by leading to DAPT cessation; failure to prescribe a thienopyridine at discharge following PCI because of bleeding has been associated with MACE at 1 year (14).

Although several factors associated with the increased bleeding risk in women following PCI have been defined, the etiology of sex-based differences in cardiovascular medication adherence is more difficult to discern (15). It has been postulated that the higher rate of adverse outcomes in women in comparison with men with cardiovascular disease is attributable to biological differences and treatment disparities as well as socioeconomic and psychosocial factors, the latter not usually evaluated in clinical trials but which may lead to differences in compliance with therapy. Caretaker responsibilities, prevalence of anxiety and depression, and lower education levels have been implicated.

With advances in interventional technology, including newer generation drug-eluting stents and newer antiplatelet agents, it is expected that the sex gap in MACE will continue to narrow, and the optimal duration of DAPT will continue to evolve. A better understanding of sex-based differences and disparities in treatment and outcomes in patients undergoing PCI, and the recognition of different correlates of mortality and MACE in women and men (16), can allow more refined and targeted therapies to achieve durable safety and efficacy. The increased physician-recommended discontinuation of DAPT in the present study, which was associated with a lower risk for MACE, underscores this concept. As new evidence continues to inform our guidelines, it is likely that we will be able to shorten the overall duration of DAPT in select patient subsets, including women, without compromising net clinical benefit. The relatively small overall contribution of DAPT cessation to cardiac risk and the acceptable outcomes associated with discontinuation and interruption seen in this study may negate the concept that longer duration is better, particularly in stable and low-risk patients.

Determining when to stop DAPT following PCI rests on a complex interplay among patient characteristics including sex, procedural factors, recommended duration of therapy, the prompting issue, and the mode and timing of cessation. Large-scale clinical trials, inclusive of patients treated in contemporary practice and properly sized for endpoints within each mode of cessation, will teach us how best to manage patients across the spectrum of risk. Tools that predict risk will help identify those with more favorable risk/benefit profiles who may derive an overall benefit from prolonged DAPT (17), and ultimately a personalized approach when the promise of big data is realized, will likely provide the best outcomes. Armed with these findings, we may finally provide an evidence-based answer to the question “Why stop now?”

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Alice K. Jacobs, Section of Cardiology, Boston Medical Center, 88 East Newton Street, Boston, Massachusetts 02118-2393. E-mail: alice.jacobs@bmc.org.

REFERENCES

1. Schomig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med 1996;334:1084–9.

2. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of

multicenter coronary stent clinical trials. Circulation 2001;103:1967–71.

3. Levine GN, Bates ER, Blankenship JC, et al. 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.

4. 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.

5. 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. BMJ 2015;350:h1618.

6. 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.

7. 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. J Am Coll Cardiol 2016 Mar 23 [E-pub ahead of print].

8. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. JAMA 2006;295:1912–20.

9. Smolina K, Ball L, Humphries KH, Khan N, Morgan SG. Sex disparities in post-acute myocardial infarction pharmacologic treatment initiation and adherence: problem for young women. Circ Cardiovasc Qual Outcomes 2015;8:586–92.

10. Yu J, Mehran R, Grinfeld L, et al. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. Catheter Cardiovasc Interv 2015;85:359–68.

11. Yu J, Baber U, Mastoris I, et al. Sex-based differences in cessation of dual-antiplatelet therapy following percutaneous coronary intervention with stents. J Am Coll Cardiol Intv 2016;9:1461–9.

12. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

13. Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. Am Heart J 2013;165:665–78.

14. Maree AO, Margey RJ, Selzer F, et al. Renal insufficiency, bleeding and prescription of discharge medication in patients undergoing percutaneous coronary intervention in the National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry. Cardiovasc Revasc Med Mar 11 2016 [E-pub ahead of print].

15. Joynt KE, Mega JL, O'Donoghue ML. Difference or disparity: will big data improve our understanding of sex and cardiovascular disease? Circ Cardiovasc Qual Outcomes 2015;8:S52–5.

16. Pendyala LK, Torguson R, Loh JP, et al. Comparison of adverse outcomes after contemporary percutaneous coronary intervention in women versus men with acute coronary syndrome. Am J Cardiol 2013;111:1092–8.

17. Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735–49.

KEY WORDS dual-antiplatelet therapy, percutaneous coronary intervention, women