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EDITORIAL COMMENT

Bleeding and Quality of Life*

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It is well-recognized that bleeding during hospitalization for acute coronary syndrome (ACS) or following percutaneous coronary intervention is associated with an increased risk of subsequent adverse outcomes, including death, myocardial infarction (MI), stroke, and stent thrombosis (1-3). Therefore, bleeding prevention is now recognized as just as important a goal as prevention of ischemic events. Risk stratification for in-hospital bleeding and antihemorrhagic management is a Class I recommendation in the guidelines (4,5). Despite the availability of standardized definitions of bleeding, developed by the Bleeding Academic Research Consortium (BARC), various definitions have been used in clinical trials to assess bleeding for both in-hospital and post-discharge periods. BARC definitions have been well-validated and are particularly suited for assessment of post-discharge bleeding, enabling collection of patient reports (6-8). However, most studies showing associations between bleeding and outcomes have focused on major bleeding events. Even in those reports demonstrating an impact of minor bleeding on outcomes, the definitions of minor bleeding would be classified as greater than BARC type 2 (3). The BARC definition enables the identification of clinically very minor bleeding, BARC type 1, that does not require medical care or hospitalization.

Although the impact of bleeding on clinical outcomes has been well documented, the data on quality of life (QOL) after ACS are scarce. The latter is of particular interest in the context of recommendations for prolonged dual antiplatelet therapy (DAPT) with more potent $P2Y_{12}$ inhibitors (4,9). In this issue of the *Journal*, Amin et al. (10) analyze the prevalence and impact of bleeding on QOL and health utilities in 9,290 acute MI patients in the TRANSLATE-ACS (Treatment with ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome) registry treated with percutaneous coronary intervention and discharged on DAPT. The primary outcome was the 6-month EQ-5D (a standard 5-question QOL tool) index score and secondary EQ-5D visual analog scale (VAS), also at 6 months. The magnitude of difference in QOL was estimated by using Cohen's d index. The entire spectrum of post-discharge BARC bleeding types was analyzed, and the following comparisons were made: none versus any bleeding, BARC type 1, BARC type 2 to 4, and BARC type 3 to 4.

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The investigators demonstrated a high prevalence of any BARC bleeding (24.2%) and its association with worse 6-month health-state utilities and QOL. The degree of impairment increased in a stepwise fashion with bleeding severity. However, the follow-up period of 6 months in the study was relatively short. In contrast, recent evidence demonstrated an ischemic benefit associated with prolonged DAPT for 2 to 3 years following the occurrence of an acute coronary event. Therefore, we definitely need better identification of bleeding risk to maximize the risk/benefit ratio given that therapy with prolonged DAPT has also been associated with a definite increased risk of severe bleeding compared with aspirin monotherapy. The increased use of prolonged DAPT in clinical practice, even in patients with high ischemic and low bleeding risk, will likely increase the incidence of bleeding. In the current registry, most patients were treated with clopidogrel (68%). However,

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current guideline recommendations for more potent $P2Y_{12}$ inhibitors than clopidogrel along with the evidence of anti-ischemic benefits from prolonged DAPT will affect bleeding incidence with resulting consequences of decreased QOL.

Amin et al. (10) applied contemporary tools for estimating QOL and health status. The EQ-5D index score, based on the U.S. population preference weights validated for ACS, examined various QOL domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. QOL was also assessed with the EQ-5D VAS to self-estimate overall health status of each patient. Importantly, BARC bleeding was independently associated with EQ-5D index score and a lower QOL according to the VAS at 6 months. Both scores declined in a stepwise fashion with increasing BARC bleeding severity. The decrement in EQ-5D and Cohen's d index were similar to the effect sizes observed for cancers. Therefore, the decrease in QOL associated with bleeding was clinically meaningful.

The current study enabled the assessment of very minor (close to nuisance) BARC type 1 bleeding, defined as "bleeding that does not cause the patient to seek medical care or hospitalization and is not actionable." In contrast to the harder endpoints of BARC type 2 (hospitalization), BARC type 3 (hemoglobin drop/transfusion), and BARC type 5 (fatality) bleeding, identification of BARC type 1 bleeding in clinical trials will require more effort than chart review. BARC 1 bleeding occurred in 9.1% of patients during 6-month follow-up in the current study, and there was a significant independent association between BARC type 1 bleeding and decreased QOL expressed by both scales. BARC type 1 bleeding negatively influenced all EQ-5D QOL domains, none of which are trivial endpoints.

In the TRIUMPH (Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction) registry of 3,560 post-MI patients treated with DAPT for 1 year, the same group of investigators demonstrated that BARC type 1/nuisance bleeding was common (37.5% during 12 months) and independently associated with worse QOL (11). The latter high frequency of BARC type 1 bleeding with more prolonged therapy and its consequences should be taken into consideration when making decisions regarding optimization of DAPT duration. In earlier single-center studies, investigators showed that nuisance bleeding had a negative impact on antiplatelet therapy adherence (12,13). The latter raises potential criticism for the definition of BARC type 1 bleeding as "not actionable" when, in fact, the patient may "take action" and discontinue medication without seeking medical attention. Self-discontinuation of DAPT places patients at risk for recurrent ischemic events, including stent thrombosis. BARC type 1 bleeding, although not correlated with mortality, is clinically relevant.

Less severe forms of bleeding as reported by patients have not been rigorously collected and adjudicated in current clinical trials. The clinical relevance of this "low-grade" bleeding mandates recording these bleeds, particularly in studies of new and more potent antiplatelet and antithrombotic agents as well as in studies investigating optimal duration of therapy. Standardized surveys used to assess bleeding complications in patients with hematologic disorders may facilitate identification of specific signs of bleeding. Less severe forms of bleeding should also be considered in clinical practice for individualizing decisions regarding antiplatelet and anticoagulation therapy.

The current TRANSLATE-ACS registry analysis holds important implications for clinical practice and future clinical trials. It expanded the impact of bleeding from clinical outcomes to QOL, documented the usefulness of the entire spectrum of BARC bleeding definitions, and encouraged more proactive assessment of all bleeding, including the BARC type 1/nuisance-type bleeding.

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REFERENCES

1. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774–82.

2. Rao SV, O'Grady K, Pieper K, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. J Am Coll Cardiol 2006;47:809–16.

3. Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. Eur Heart J 2009;30:655–61.

4. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2015 Aug 29 [E-pub ahead of print].

5. 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.

6. 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.

7. Ndrepepa G, Schuster T, Hadamitzky M, et al. Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 2012;125:1424–31.

8. Kikkert WJ, van Geloven N, van der Laan, et al. The prognostic value of Bleeding Academic Research Consortium (BARC)-defined bleeding complications in ST-elevation myocardial infarction: a comparison with the TIMI (Thrombolysis in Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) and ISTH (International Society on Thrombosis and Haemostasis) bleeding classifications. J Am Coll Cardiol 2014; 63:1866–75.

9. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J 2015 Aug 31 [E-pub ahead of print].

10. Amin AP, Wang TY, McCoy L, et al. Impact of bleeding on quality of life in patients on DAPT: insights from TRANSLATE-ACS. J Am Coll Cardiol 2016;67:59–65.

11. Amin AP, Buchuwar A, Reid KJ, et al. Nuisance bleeding with prolonged dual antiplatelet therapy after acute myocardial infarction and its impact on health status. J Am Coll Cardiol 2013; 61:2130–8.

12. Roy P, Bonello L, Torguson R, et al. Impact on "nuisance" bleeding on clopidogrel compliance in patients undergoing intracoronary drug eluting stents implantation. Am J Cardiol 2008;102:1614–7.

13. Ben-Dor I, Torguson R, Scheinowitz M, et al. Incidence, correlates, and clinical impact of nuisance bleeding after antiplatelet therapy for patients with drug eluting stents. Am Heart J 2010;159:871–5.

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