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Striking a Balance: Individualizing Antithrombotic Therapy After Myocardial Infarction

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In this issue of Trends in Cardiovascular Medicine, Park et al. provide a comprehensive review of oral antithrombotic therapy for secondary prevention of ischemic events following non-ST segment elevation myocardial infarction¹. The authors correctly point out that the totality of evidence currently available from clinical trials supports the concept that we should be individualizing therapy to optimize the benefit of reducing recurrent ischemic events as well as minimizing the risks of bleeding. While this may be intuitive, physicians are currently “left on an island” so to speak with regards to this decision making process. Validated clinical tools are lacking to assist with understanding the long-term risks and benefits of these therapies in the individual patient who has recently suffered an acute coronary syndrome. In contrast, physicians instituting chronic anticoagulation in patients with non-valvular atrial fibrillation can rely on the CHA2DS2-VASc score to quantify the risks of future thromboembolic events and employ the HAS-BLED score to quantify bleeding risks^{2,3}. Unfortunately, similar long-term risk assessment tools are not available to assist the clinician in deciding on the optimal treatment strategy for secondary prevention in patients with a prior myocardial infarction.

In relation to employing antithrombotic therapy for secondary prevention in coronary artery disease, it is important to realize that not all patients with a history of an acute coronary syndrome have the same risk for recurrent ischemic events. Like arterial thromboembolism in atrial fibrillation, specific patient populations such as the elderly, patients with concomitant diabetes mellitus, renal impairment, peripheral arterial disease, heart failure, and history of prior stroke or transient ischemic attack have a significantly higher risk of recurrent events than those without any of these risk factors⁴. The Global Registry of Acute Coronary Events (GRACE) score has been proposed to identify the risk of future ischemic events in individual patients⁵. Nevertheless, this tool has only been validated for short-term follow-up after discharge (< 6 months). In addition, it does not include many of the aforementioned co-morbid conditions that are associated with increased risk nor does it

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include procedural related characteristics that may further increase risk in patients that have undergone PCI⁵. It stands to reason that for patients with a moderate to high risk of recurrent ischemic events, there may be benefit in more aggressive or prolonged antithrombotic regimens. This has been suggested in the recently published Veterans Administration observational study by Thukkani et al. which demonstrated a reduction in very late death and myocardial infarction in patients with diabetes who received clopidogrel for more than 12 months following insertion of a drug eluting stent⁶. Clinical trials have demonstrated similar outcomes including The Dual Anti-platelet Therapy (DAPT) study which demonstrated a benefit in reducing ischemic events with prolonged dual anti-platelet therapy > 12 months, and the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2 TIMI 51) trial which demonstrated a reduction in ischemic events with the addition of anticoagulant therapy with Rivaroxaban in patients with a recent acute coronary syndrome^{7,8}. However, in both of these studies, the benefit in decreasing cardiovascular risk was counterbalanced by the finding that prolonging dual anti-platelet therapy, or the addition of anticoagulant therapy, was associated with increased rates of bleeding. Thus, bleeding risk may largely negate the overall beneficial effects of these medications in many patients when administered on a long term basis. The CRUSADE (Can Rapid risk stratification of Unstable angina Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines) score was developed to determine the risk of major in-hospital bleeding events in patients presenting with a non-ST segment-elevation myocardial infarction but has not been validated to determine the risk on a long term basis after discharge⁹. Recently Généreux et al. published a post-hoc analysis of the Assessment of Dual Antiplatelet Therapy with Drug Eluting Stents (ADAPT-DES) registry. They demonstrated that patients who received clopidogrel for at least 1 year and aspirin indefinitely had a post-discharge risk of bleeding over the subsequent 2 years of 6.6%. This was associated with a 5-fold higher adjusted risk for mortality¹⁰. They also identified independent risk factors for post-discharge bleeding including older age, anemia, prior vascular disease, low platelet reactivity, and complex coronary anatomy¹⁰. It is important to recognize that these risk factors are dynamic and frequently change over the course of follow-up after an event. Furthermore, many of the same risk factors associated with increased bleeding are also associated with an increased risk for future ischemic events creating a clinical conundrum.

While we have made considerable advances in demonstrating the short-term benefit of antithrombotic therapy following acute coronary syndromes in randomized clinical trials, clinical tools need to be developed and validated to accurately quantify both the risk of recurrent ischemic events as well as the risks of bleeding in the individual patient. These will help us to predict who would benefit from a more or less aggressive antithrombotic strategy after a myocardial infarction. Once developed, clinical trials will need to establish their predictive utility over prolonged periods of follow-up.

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