REVIEW ARTICLE

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Management of Antithrombotic Therapy after Acute Coronary Syndromes

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Because of rapidly changing guidelines in response to multiple clinical trials of new therapies, the management of antithrombotic agents for patients after an acute coronary syndrome is becoming increasingly complex. Patients and clinicians must make treatment decisions by weighing the antithrombotic benefits of antiplatelet agents and the anti-ischemic benefits of anticoagulant agents against the risk of bleeding, including severe, life-threatening bleeding. Treatment decisions should be individualized by incorporating additional variables in this risk–benefit assessment, including but not limited to demographic characteristics of the patient, examination findings, laboratory testing, and imaging, as well as the patient's values and preferences.

The pathobiology of acute coronary syndromes is characterized by disruption of coronary atherosclerotic plaque through fissure, erosion, or rupture, resulting in activation of platelets and the coagulation system; the clinical result is myocardial ischemia or infarction, depending on the extent of coronary-artery occlusion.[1,2] Acute coronary syndromes are initially categorized on the basis of the 12-lead electrocardiogram (ECG), with patients separated into two treatment pathways: one for patients with ST-segment elevation (STE) and one for patients without persistent STE. This initial ECG-guided risk stratification drives most treatment decisions during hospitalization and is also important for prognosis and treatment recommendations after discharge.

Every year, an estimated 720,000 people in the United States are hospitalized with an acute coronary syndrome or have a fatal coronary heart disease event.[3] Advanced age and coexisting conditions are characteristic of patients presenting with an acute coronary syndrome; more than 60% of hospital admissions for acute coronary syndromes involve patients over the age of 65 years. Large clinical trials that are the basis for clinical practice guidelines might not enroll patients who are as diverse as those seen in clinical practice. In particular, older adults, women, and racial or ethnic minority groups continue to be underrepresented in contemporary clinical trials of treatment approaches for patients with acute coronary syndromes.[4] Registry and other observational data may serve as valuable tools for studying the effects of guideline-recommended therapies in a diverse patient population.

The recommended initial care of all patients with acute coronary syndromes consists of rapid diagnosis, risk assessment and stratification, treatment of ischemic symptoms, initiation of antithrombotic therapies with antiplatelet and anticoagulant agents, and risk-based triaging for the timing of invasive strategies.[5-8] On the basis of extensive clinical trial data, the scales are tipped toward an intensive approach to reducing thrombotic complications with aggressive use of antiplatelet and anticoagulant agents during this initial phase of an acute coronary syndrome.

For most high-risk patients presenting with acute coronary syndromes, current U.S. and European guidelines favor an early invasive approach.[9] Subsequent management requires individualized approaches to antithrombotic treatments, with the benefits weighed against the risk of bleeding (Fig. 1).

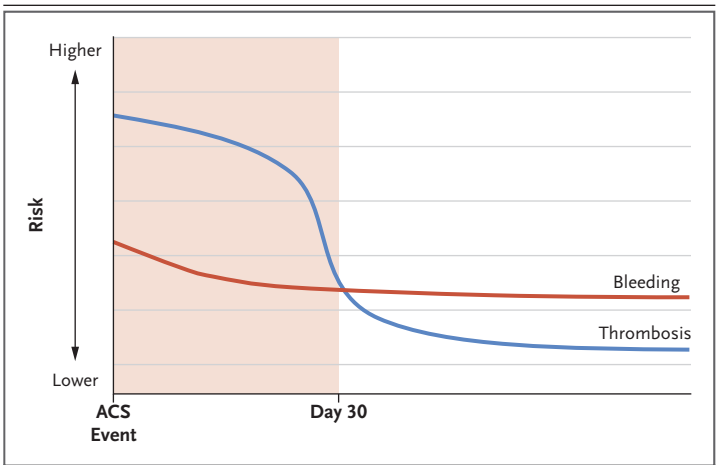

Figure 1. Risks of Thrombosis and Bleeding after an Acute Coronary Syndrome (ACS).

In the first 30 days after an ACS event, the benefits of intensive antithrombotic therapy generally outweigh the increased risk of bleeding. However, this benefit dissipates with additional time after the ACS event, favoring a therapeutic approach that considers the risks of both bleeding and thrombosis.

ANTIPLATELET AGENTS

Dual antiplatelet therapy (DAPT), typically aspirin (acetylsalicylic acid) combined with an adenosine diphosphate (ADP) inhibitor such as clopidogrel, prasugrel, or ticagrelor, is the cornerstone of management after an acute coronary syndrome. Multiple clinical trials have shown that this combination significantly lowers the risk of recurrent ischemic events, including stent thrombosis, among patients who have had acute coronary syndromes. However, this risk reduction comes at the cost of an increased risk of bleeding.

The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial established the benefit of clopidogrel added to aspirin in patients presenting with acute coronary syndromes.[10] Although clopidogrel remains the most commonly used $P2Y_{12}$ inhibitor in the United States, clinical practice guidelines in both the United States and Europe favor more potent, next-generation $P2Y_{12}$ inhibitors, such as ticagrelor and prasugrel, given that in head-to-head comparisons, clinical trials have shown the superiority of these next-generation inhibitors over clopidogrel in reducing ischemic events.[5] These agents have a faster onset of action and result in more predictable and more potent platelet inhibition, with fewer drug–drug interactions. Genetic polymorphisms leading to a loss of function of the CYP2C19 isoenzyme may result in higher platelet reactivity with clopidogrel and are associated with a higher incidence of major adverse cardiovascular and cerebrovascular events (MACCE).[11-13] However, routine genetic or platelet-function testing is not usually performed or recommended, given the lack of evidence supporting a change in clinical outcomes.[14,15]

The 2014 American College of Cardiology (ACC)–American Heart Association (AHA) guidelines recommend either clopidogrel or ticagrelor for the management of a non-STE acute coronary syndrome, with a preference for ticagrelor. Prasugrel is recommended mainly when a percutaneous coronary intervention (PCI) is planned in patients who are not considered to be at high risk for bleeding. This recommendation is based on findings from TRITON-TIMI (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction) 38.[15-17] PLATO (Study of Platelet Inhibition and Patient Outcomes) documented a benefit of ticagrelor over clopidogrel for patients at moderate-to-high risk for ischemia with or without revascularization.[17,18] The 2020 European Society of Cardiology (ESC) treatment guidelines for non-STE acute coronary syndromes preferentially recommend ticagrelor or prasugrel as the standard treatment for all patients presenting with an acute coronary syndrome (class I recommendation, level of evidence B) unless this agent is contraindicated.[19] We typically favor ticagrelor, given the broad study population in PLATO, coupled with the greater reduction in mortality with ticagrelor than with clopidogrel.

In 2019, the ISAR-REACT (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment) 5 trial randomly assigned 4018 patients presenting with acute coronary syndromes to either ticagrelor (loading dose given right away) or prasugrel (loading dose given right away for STE myocardial infarc-

tion and loading dose given after delineation of coronary anatomy for other acute coronary syndromes).[20] The investigators concluded that prasugrel was superior to ticagrelor, with a lower rate of death, myocardial infarction, or stroke at 1 year and no increase in the risk of bleeding. However, this study was limited by its open-label design, high rates of ticagrelor discontinuation (perhaps due, in part, to the dyspnea associated with ticagrelor), and a modest sample size. The ESC guidelines recommend considering prasugrel over ticagrelor for patients with non-STE acute coronary syndromes who undergo PCI (class IIa recommendation, level of evidence B).[19]

DURATION OF DAPT

The recommended duration of DAPT after an acute coronary syndrome and PCI is a moving target.[21] For most patients, DAPT is recommended for a minimum of 12 months after an acute coronary syndrome; exceptions include patients for whom surgery is urgently needed, anticoagulation is needed for atrial fibrillation, or the risk of bleeding is too high for other reasons, such as thrombocytopenia, liver disease, or renal disease. A daily aspirin dose of 75 to 100 mg is recommended in the ESC guidelines,[6,19] whereas the ACC–AHA guidelines recommend a daily dose of 81 to 325 mg.[5] The adequate dose of aspirin for long-term therapy in patients with coronary artery disease is currently being studied in a pragmatic clinical trial, ADAPTABLE (Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-Term Effectiveness), with results expected in 2021.[22]

When patients with an acute coronary syndrome stop DAPT to undergo coronary-artery bypass grafting (CABG), they should resume DAPT after surgery for at least 12 months.[21] This is frequently overlooked after surgery. Patients who are treated medically for an acute coronary syndrome (and do not undergo stenting) also have an anti-ischemic benefit from DAPT.[23] Extending DAPT beyond 12 months leads to a decrease in the risk of ischemic complications, with a commensurate risk of increased bleeding.[24] The DAPT Study, which compared 30 months with 12 months of DAPT after coronary stenting, showed that the reduction in MACCE was greater among study participants who presented with acute coronary syndromes than among those with more stable coronary artery disease and was also greater in the group treated for 30 months than in the group treated for 12 months.[25] The rate of bleeding was higher in the 30-month group. Similarly, the PEGASUS-TIMI (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction) 54 trial showed that the continuation of ticagrelor therapy for more than 12 months after an acute myocardial infarction reduced MACCE but also increased bleeding.[26] Patients with complex coronary anatomy, other vascular disease, or untreated residual coronary disease who are not at high risk for bleeding may benefit from a longer duration of DAPT, particularly if they have not had a major bleeding event during 1 year of DAPT.

The alternative approach of discontinuing aspirin instead of the $P2Y_{12}$ inhibitor has been studied in several recent trials.[27-30] For example, the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial compared DAPT (aspirin plus ticagrelor) with ticagrelor monotherapy after 3 months of DAPT. More than half the study patients had presented with an acute coronary syndrome before undergoing PCI. At 1 year, the rate of clinically significant bleeding was lower and ischemic events were not increased with ticagrelor monotherapy as compared with ticagrelor plus aspirin. Likewise, in the TICO (Ticagrelor Monotherapy after 3 Months in the Patients Treated with New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome) trial, after 3 months of DAPT with ticagrelor and aspirin, a strategy of continuing ticagrelor alone (without aspirin), as compared with ongoing DAPT, resulted in few primary end-point events (a composite of bleeding and ischemic events).[31] A major limitation of the TICO study was the small number of observed events, which meant that the investigators were unable to quantify the benefit of a reduction in bleeding and the risk of increased ischemic events, including stent thrombosis. A recent meta-analysis by O'Donoghue et al. similarly concluded that discontinuation of aspirin with continued $P2Y_{12}$ monotherapy (after 1 to 3 months of DAPT) reduced the risk of bleeding and was not associated with an increased risk of ischemic events among patients presenting with acute coronary syndromes.[27] This is an evolving area

of investigation, but most of the currently available data support the view that early, highly intensive DAPT can be safely de-escalated over time, with aspirin withdrawn and the $P2Y_{12}$ inhibitor continued, to provide ischemic protection while reducing the risk of bleeding.

De-escalation of DAPT by switching from more potent $P2Y_{12}$ inhibitors such as prasugrel or ticagrelor to clopidogrel may be considered in certain circumstances, such as a high risk of bleeding or a need for oral anticoagulation. De-escalation should be avoided in the first 30 days after the acute coronary syndrome or PCI because of the high risk of thrombotic complications, as well as clinical trial data supporting the use of the more potent, newer agents over clopidogrel. Clinical trial data that can provide guidance for de-escalation protocols are lacking.[19]

ANTICOAGULANT THERAPY

Current clinical practice guidelines recommend the combination of DAPT and anticoagulant therapy for hospitalized patients with acute coronary syndromes, irrespective of whether invasive or conservative treatment strategies are planned. Parenteral anticoagulant agents — enoxaparin, bivalirudin, fondaparinux, or unfractionated heparin — are a class I recommendation for treatment during the initial period (up to 48 hours after the event or until PCI is performed).[5] The choice of anticoagulant may be guided by concurrent decision making regarding the use and timing of an early invasive strategy. For example, a patient for whom an invasive strategy is planned, with a very rapid transition (within a few hours) to the catheterization laboratory for PCI, might best be treated with unfractionated heparin or bivalirudin, whereas a patient for whom a medical strategy is planned might be more appropriately treated with enoxaparin or fondaparinux.

Less clearly defined is the value of longer-term anticoagulation after discharge. The addition of anticoagulant therapy in the immediate period after an acute coronary syndrome reduces the risk of recurrent thrombotic events but increases the risk of bleeding. In the pre-DAPT era, clinical trials showed that the addition of warfarin to aspirin decreased the risk of MACCE but was associated with a risk of major bleeding.[32] However, given the challenges of maintaining warfarin levels within a therapeutic range, warfarin is not recommended for the management of residual thrombotic risk after an acute coronary syndrome.

Several studies have investigated the additive value of direct oral anticoagulants (DOACs) for long-term management of acute coronary syndromes after hospital discharge. The APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial, which compared standard-dose apixaban (5 mg twice daily, or 2.5 mg twice daily for patients with renal disease) with placebo, was terminated early because of a marked increase in the risk of major bleeding, including intracranial hemorrhage, with no significant difference in the primary outcome of MACCE.[33,34] Because of the increased risk of bleeding seen with standard-dose anticoagulant therapy, the ATLAS ACS 2–TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome 2–Thrombolysis in Myocardial Infarction 51) trial tested low-dose anticoagulation (2.5 mg or 5 mg of rivaroxaban) versus placebo in patients with acute coronary syndromes, most of whom were receiving DAPT.[35] The trial showed that the rivaroxaban strategy was associated with a decreased risk of death, myocardial infarction, and stroke but with an increased risk of major bleeding complications. The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial provides further support for the benefit of low-dose anticoagulation (rivaroxaban at a dose of 2.5 mg twice daily), in addition to low-dose aspirin, in the longer-term care of patients who have been hospitalized with stable coronary artery disease, peripheral arterial disease, or both.[36] In all, the available evidence suggests that there is a dose-dependent risk of bleeding with DOACs after an acute coronary syndrome and a decrease in the risk of MACCE, but except in the case of very carefully selected patients with a high ischemic risk, the strategy of combining DAPT with low-dose DOAC has not been widely used.

Between 5% and 10% of patients with atrial fibrillation are referred for PCI.[37] Atrial fibrillation itself can be a risk factor for myocardial infarction, given the shared cardiometabolic risk profiles and increasing prevalence with age. It is estimated that atrial fibrillation develops in up to 20% of patients with acute coronary syn-

dromes,[38] and these patients have higher stroke rates and in-hospital mortality than patients without atrial fibrillation.[39-41]

In observational studies, patients treated with triple therapy (aspirin, a $P2Y_{12}$ receptor inhibitor, and an oral anticoagulant) after an acute coronary syndrome were at high risk for bleeding.[42-44] Triple therapy with a more potent antiplatelet agent such as prasugrel is associated with an even higher risk.[45] The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial compared DAPT and warfarin with clopidogrel (at a dose of 75 mg a day) and warfarin.[46] Without aspirin, fewer bleeding complications were noted, although the study was not powered to detect differences in the less frequent ischemic outcome of stent thrombosis. The trial suggested, but did not prove, that an effective strategy that balances the anti-ischemic benefit against the risk of bleeding in patients with atrial fibrillation and a recent acute coronary syndrome event might be the combination of a $P2Y_{12}$ inhibitor and a DOAC.

With the increasing use of DOACs for the management of atrial fibrillation, several trials have now documented a reduction in bleeding when a DOAC and a $P2Y_{12}$ inhibitor are used together, as compared with warfarin-based triple therapy, in patients undergoing PCI. PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention), in which patients were randomly assigned to one of two rivaroxaban strategies (low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor or very-low-dose rivaroxaban plus a $P2Y_{12}$ inhibitor and low-dose aspirin) or triple therapy with warfarin, showed a lower rate of bleeding with each of the rivaroxaban treatment strategies than with triple therapy.[47] Similarly, RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) randomly assigned patients to receive dabigatran with a $P2Y_{12}$ inhibitor or warfarin-based triple therapy.[48] Both these studies confirm that DOACs result in less bleeding than warfarin in high-risk patients with atrial fibrillation for whom PCI is required.

Most recently, the AUGUSTUS (Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation) trial evaluated the independent effects of the oral anticoagulant apixaban and aspirin in patients with atrial fibrillation and a recent acute coronary syndrome or PCI (within the previous 14 days).[49] Apixaban resulted in a lower bleeding rate than warfarin, and aspirin led to a higher bleeding rate than placebo. In a secondary analysis from this trial, aspirin appeared to reduce ischemic events only up to 30 days after the acute coronary syndrome.[50] The ENTRUST-AF PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial provides support for another DOAC as an option for patients with atrial fibrillation requiring antiplatelet therapy after PCI.[51] Alternatively, the 2019 ACC–AHA–Heart Rhythm Society practice guidelines for managing atrial fibrillation recommend the use of DAPT alone after an acute coronary syndrome in patients who have atrial fibrillation and a CHA_2DS_2-VASc score of 0 to 1 (on a scale of 0 to 9, with higher scores indicating a greater risk of stroke).[38]

For patients with an acute coronary syndrome and atrial fibrillation, the totality of the evidence favors a short duration of triple therapy in most cases and then dual antithrombotic therapy with a $P2Y_{12}$ inhibitor (clopidogrel) and a DOAC for at least 12 months.[52] The results of the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial suggest that rivaroxaban monotherapy may be a safe alternative for longer-term management of atrial fibrillation and stable coronary artery disease (at least 1 year after PCI or bypass surgery).[53]

INDIVIDUALIZING TREATMENT DECISIONS

It is important to remember that the evidence base informing practice guidelines reflects population-level data. However, many patients seen in clinical practice do not perfectly meet trial inclusion criteria and have sociodemographic, clinical, or other characteristics that require special consideration.[4] Patients may not weigh bleeding, ischemic, or thromboembolic risks equally or in the same way that clinicians do.

Tools are available to help inform shared de-

cision making about antithrombotic therapies after an acute coronary syndrome. For example, the DAPT score weighs patient and procedural characteristics to determine whether continuing DAPT beyond 12 months would provide a favorable risk–benefit profile (Table 1).[25,54,55] On the basis of derivation cohorts (and validation studies), the risk–benefit profile would favor aspirin monotherapy beyond 12 months for patients with a DAPT score of less than 2 (on a scale from –2 to 10). Patients with a DAPT score of 2 or higher would have a greater reduction in ischemic risk with prolonged DAPT. The DAPT score has also been validated for patients with a prior myocardial infarction, who have an increased risk of late ischemic complications.[56] A newer scoring system for use with more contemporary patient cohorts is being developed to aid in decision making about long-term treatment.[57] However, available risk prediction models that integrate ischemic and bleeding risks have not been prospectively validated in randomized clinical trials, and their use in clinical practice is variable. Clinicians might weigh the risks of ischemia versus bleeding by balancing individual bleeding characteristics such as advanced age, low body weight, and noncardiac coexisting conditions (e.g., cancer and kidney or liver disease) against characteristics associated with high ischemic risk, such as diabetes and diffuse atherosclerotic coronary disease on angiography. Of course, some of the characteristics that are associated with an increased risk of bleeding are also associated with an increased ischemic risk, the most obvious one being advanced age. Clinical judgment regarding risks versus benefits is critical in making these decisions about antithrombotic therapy (Table 2).

Table 1. Calculation of the DAPT Score.*

Variable	Points
Age (yr)	
≥75	–2
65–74	–1
≤64	0
Diabetes mellitus	1
Current cigarette smoker	1
Prior MI or PCI	1
MI at presentation	1
CHF or left ventricular ejection fraction <30%	2
Stent diameter <3 mm	1
PCI of vein graft	2
Paclitaxel-eluting stent	1

* The score for dual antiplatelet therapy (DAPT) ranges from –2 to 10. A score of 2 or higher suggests that the magnitude of the benefit from a reduction in ischemic events is greater than the risk of bleeding with DAPT continued for more than 12 months. CHF denotes congestive heart failure, MI myocardial infarction, and PCI percutaneous coronary intervention.

For evaluation of the efficacy and safety of new therapies, there are no substitutes for comparative, randomized clinical trials. Because randomized, controlled trials typically have stringent

Table 2. Suggested Approaches to Antithrombotic Treatment after an ACS Event.*

Time after ACS Event	Default Strategy	Patients with High Ischemic Risk	Patients with High Bleeding Risk	Patients with Concomitant Atrial Fibrillation†
≤1 mo	Aspirin and newer-generation $P2Y_{12}$ inhibitor	Aspirin and newer-generation $P2Y_{12}$ inhibitor	Aspirin and newer-generation $P2Y_{12}$ inhibitor	Aspirin, clopidogrel, and DOAC‡
>1 mo to 12 mo	Aspirin and newer-generation $P2Y_{12}$ inhibitor	Aspirin and newer-generation $P2Y_{12}$ inhibitor	Any $P2Y_{12}$ inhibitor alone	Clopidogrel and DOAC
>12 mo	Any $P2Y_{12}$ inhibitor alone	Aspirin and newer-generation $P2Y_{12}$ inhibitor, or switch to aspirin and low-dose rivaroxaban	Any $P2Y_{12}$ inhibitor or aspirin	DOAC

* Aspirin is given at a dose of less than 100 mg. In this table, prasugrel and ticagrelor are considered newer-generation $P2Y_{12}$ inhibitors. ACS denotes acute coronary syndrome, and DOAC direct oral anticoagulant.
† Recommendations are for patients with nonvalvular atrial fibrillation (those who do not have mechanical heart valves and do not have moderate-to-severe mitral stenosis).
‡ Consider withdrawing aspirin before hospital discharge for patients who are at high risk for bleeding.

enrollment criteria, evidence from nonrandomized, observational studies can also be useful. Some medications, although highly effective, may have unacceptable side effects or involve a disutility (e.g., a requirement for twice-a-day dosing) that can adversely affect adherence to the therapeutic regimen. In fact, contemporary evidence suggests that almost a quarter of patients discontinue antiplatelet therapy prematurely after an acute coronary syndrome. Their reasons include side effects, treatment complexity, cost, and drug interruption for noncardiac procedures.[21,58-61]

FUTURE DIRECTIONS

Several areas are under active investigation. Almost all the reported studies of DAPT and triple therapy after an acute coronary syndrome have assessed the combination of clopidogrel plus aspirin. We do not know the adequate duration of DAPT with more potent, newer-generation $P2Y_{12}$ inhibitors. Newer-generation stents, which have essentially replaced bare-metal stents, are likely to require less potent platelet inhibition, yet the benefits of antithrombotic therapy after an acute coronary syndrome are independent of stenting. Active clinical trials are evaluating investigational agents that might improve the risk–benefit balance of current antithrombotic strategies. In addition, we need more rigorous and pragmatic clinical trials that recruit populations as diverse as the patients we care for in clinical practice, with broad representation of race or ethnic group, sex, coexisting conditions, age, and sociocultural characteristics.

CONCLUSIONS

A one-size-fits-all approach is not suited to the management of antithrombotic therapies after an acute coronary syndrome. A careful assessment of thrombotic risk versus bleeding risk is required for each patient as part of a tailored, potentially dynamic treatment plan that uses the tools of risk stratification in the context of the patient's values and preferences.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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