One of the most common conundrums in all of cardiovascular medicine pertains to the care of patients with atrial fibrillation who need percutaneous coronary intervention. Both dual antiplatelet therapy (DAPT) and oral anticoagulant therapy would seem to be necessary to reduce risks of stent thrombosis and thromboembolism, respectively. However, with intensification of the antithrombotic regimen, there is an inevitable tradeoff with more bleeding. Two modest-sized randomized trials, WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) and ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen: Testing of a Six-Week Versus a Six-Month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-Eluting Stenting), have shown that double therapy (single antiplatelet therapy plus full-dose vitamin K antagonists) appeared to provide similar efficacy and reduced bleeding compared with triple therapy (DAPT plus full-dose vitamin K antagonists). Curiously, even a signal of less ischemic/thrombotic complications occurred with double therapy, although these 2 trials were clearly not powered for efficacy end points. It remained possible, however, that excess bleeding with triple therapy overwhelmed any potential gain in efficacy. Furthermore, the role, if any, of the novel oral anticoagulants (NOACs), instead of vitamin K antagonists such as warfarin, remained poorly characterized.

In this issue of Circulation, Gibson et al have published the key data from the PIONEER AF-PCI (An 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) trial. A total of 2124 stented patients with atrial fibrillation were randomized to 1 of 3 groups: reduced-dose rivaroxaban 15 mg daily plus a P2Y₁₂ for 12 months (Group 1); rivaroxaban 2.5 mg twice a day with stratification to a prespecified duration of DAPT of 1, 6, or 12 months (Group 2); or the control arm of dose-adjusted vitamin K antagonists daily with a similar DAPT stratification as above (Group 3). The primary end point for this post hoc analysis was all-cause mortality or recurrent hospitalization because of an adverse event. This clinically relevant and important composite end point was significantly lower in both experimental arms than in the control arm: 34.9% in Group 1 and 31.9% in Group 2 versus 41.9% in Group 3. Mortality rates were similar in the 3 arms. The salutary effects seen in Groups 1 and 2 were caused by reductions in hospitalizations for both bleeding and cardiovascular causes, with no significant effect on other types of hospitalizations. No significant differences were found between the 2 experimental arms.

The results of this post hoc analysis from the PIONEER study build substantially on the findings regarding the primary end point of TIMI (Thrombolysis In Myocardial Infarction) major bleeding, TIMI minor bleeding, or bleeding requiring medical atten-
tion, which was significantly lower in Groups 1 and 2 compared with Group 3. The secondary end point of cardiovascular death, myocardial infarction, or stroke was similar in all 3 arms. Thus, from the PIONEER data to date, significant benefits can be realized from abandoning the strategy of full-dose triple therapy, with no apparent downside.

A much greater appreciation of bleeding has emerged in recent years. Obviously, fatal or intracranial bleeding would provide a direct causal pathway for the now well-known association between bleeding and death. Bleeding may be associated with partial or complete interruption or cessation of the various components of the antithrombotic regimen. Other medications, such as statins and beta blockers, are sometimes also stopped and may or may not be resumed. Transfusions, either appropriately or inappropriately, may be administered. Hospitalizations frequently occur around major bleeding episodes, leading to a series of tests and procedures, an increase in the risk of nosocomial infections, or other adverse sequelae from being admitted to the hospital. Thus, through direct and indirect pathways, bleeding requiring hospitalization can cause major morbidity, including of a cardiovascular nature. Supportive of this latter hypothesis, in the PIONEER study, although the relative risk reduction in recurrent hospitalization for the rivaroxaban arms compared with the conventional triple therapy arm was greater for bleeding events, the absolute risk reduction in recurrent hospitalization was greater for cardiovascular events.

The APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events - 2: A Phase 3, Randomized, Double-Blind, Evaluation of the Safety and Efficacy of Apixaban in Subjects With a Recent Acute Coronary Syndrome) trial clearly demonstrated that in patients with high-risk acute coronary syndromes, triple therapy with aspirin, clopidogrel, and full-dose apixaban resulted in an unacceptable degree of major bleeding, such that the data safety monitoring board terminated the trial. Despite a large increase in serious bleeding, including a numeric excess in fatal and intracranial bleeding, no consistent signal of efficacy was found. ATLAS ACS 2-TIMI 51 (A Randomized, Double-Blind, Placebo-Controlled, Event-Driven Multicenter Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects With a Recent Acute Coronary Syndrome) was also an acute coronary syndrome trial. In this randomized study, low (5 mg BID) and very low (2.5 mg BID) doses of rivaroxaban versus placebo were studied largely on a background of aspirin and clopidogrel. The doses tested were much lower than full-dose anticoagulation with rivaroxaban, and, of note, the very low dose was again studied in PIONEER. The low dose in ATLAS ACS 2-TIMI 51 was associated with a significant reduction in the primary ischemic end point and cardiovascular and all-cause mortality. Major bleeding, including intracranial bleeding, was increased in both dosing arms of ATLAS ACS 2-TIMI 51 in this placebo-controlled trial. Putting aside any potential differences in the oral anticoagulants studied, it appears that full-dose anticoagulation when combined with DAPT in APPRAISE-2 provided no benefit but caused clear harm, the low-dose anticoagulation arm of ATLAS ACS 2-TIMI 51 reduced nonfatal ischemic events but increased major bleeding, and the very low-dose anticoagulation arm from ATLAS ACS 2-TIMI 51 showed a reduction in fatal events despite an increase in major bleeding. Thus, this cross-trial comparison provided suggestive evidence, at least in acute coronary syndromes, that full-dose triple therapy was a poor strategy. PIONEER validates that concern in atrial fibrillation. Ongoing trials of NOACs, such as COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) (https://clinicaltrials.gov, unique identifier: NCT01776424), which is examining the role of very low-dose anticoagulation with rivaroxaban combined with antiplatelet monotherapy in coronary and peripheral artery disease, will help flesh out the role of reduced-dose NOACs across the atherothrombotic spectrum.

It is interesting to note that even when the duration of full-dose triple therapy was 6 weeks in ISAR-TRIPLE, a large percentage of the bleeding had already occurred. Thus, abbreviating the course of full-dose triple therapy does not diminish the risks of bleeding as much as physicians like to believe. Of course, if a patient passes this early potent bleeding stress test, then the subsequent risk rate of bleeding is lower but may still be substantial in terms of cumulative risk over time. These early and late bleeding risks seem to be particularly high in older patients.

Another development concomitant with advances in our understanding of anticoagulation and the introduction of NOACs into widespread clinical practice has been the evolution in stenting. Second-generation drug-eluting stents truly are an advance, and in addition to having low restenosis rates, they appear to have lower stent thrombosis rates compared with first-generation drug-eluting stents or even older bare metal stents. This reduction in stent thrombosis is true for late and very late stent thrombosis, but it also has been demonstrated with respect to early stent thrombosis, at least with certain second-generation drug-eluting stents.

Some have speculated that in the patient in whom conventional full-dose triple therapy is being contemplated, such as the patient with atrial fibrillation who has an acute coronary syndrome or is receiving percutaneous coronary intervention, left atrial appendage closure may provide the best option to address thromboembolic risk and bleeding simultaneously. While logical, large randomized trials are necessary to compare these closure...
appropriate NOAC dosing. It is important to note that in most randomized clinical trials to guide antithrombotic decisions with the best available data. The open-label design is another limitation, but with several different dosing arms, full blinding would have been challenging. The exclusion criteria of creatinine clearance <30 mL/min means that the results cannot directly be extrapolated to these difficult-to-treat patients, in whom few data are available from randomized clinical trials to guide appropriate NOAC dosing. It is important to note that in PIONEER, patients with creatinine clearance of 30 to 50 mL/min received 10 mg of rivaroxaban daily, not 15 mg. In addition, clopidogrel was the predominant P2Y₁² utilized in PIONEER, and further study is necessary to understand fully how to integrate NOAC use with prasugrel and ticagrelor.

Indeed, other ongoing trials are evaluating patients with atrial fibrillation undergoing stenting or with acute coronary syndromes, such as RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Atrial Fibrillation That Undergo a Percutaneous Coronary Intervention With Stenting) with dabigatran, AUGUSTUS (An Open-label, 2 x 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) with apixaban, and ENTRUST-AF-PCI (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) with edoxaban, although none may be powered to provide definite evidence about efficacy. However, if there is no substantial heterogeneity, perhaps pooling the data may provide further clarity about the optimal antithrombotic cocktail. For the time being, in patients not in clinical trials, full-dose oral triple therapy with dual antiplatelet agents and full-dose anticoagulation should be avoided as a routine practice.

**DISCLOSURES**

Dr Bhatt discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee, including the ongoing RE-DUAL PCI), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor, Today’s Issue), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), Slack Publications (Chief Medical Editor, Cardiology Today’s Issue), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical; Trustee: American College of Cardiology; Unfunded Research: FlowCo, PlX Pharma, Takeda.

**AFFILIATIONS**

From Brigham and Women’s Hospital Heart & Vascular Center, Harvard Medical School, Boston, MA.

**FOOTNOTES**

Circulation is available at http://circ.ahajournals.org.
REFERENCES


O PIONEERS! - The Beginning of the End of Full Dose Triple Therapy with Warfarin?

Deepak L. Bhatt

_Circulation_ published online November 14, 2016;
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2016/11/14/CIRCULATIONAHA.116.025923.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/