EDITORIALS

Atrial Fibrillation and PCI — Do We Still Need Aspirin?

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The treatment of patients with atrial fibrillation who undergo percutaneous coronary intervention (PCI) is a common clinical dilemma. Approximately 10 to 15% of patients undergoing PCI have a history of atrial fibrillation.[1] Patients with atrial fibrillation are at increased risk for stroke, and warfarin has been shown to be superior to dual antiplatelet therapy (DAPT) with clopidogrel plus aspirin for the prevention of stroke.[2] However, DAPT has been shown to be markedly superior to aspirin plus warfarin for the prevention of stent thrombosis.[3] This has led to the adoption of triple therapy with DAPT plus warfarin in patients with atrial fibrillation undergoing PCI.

The challenge is that triple therapy is associated with high rates of bleeding.[1] A potential solution is to eliminate aspirin, and this solution was tested in the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting), which showed a lower rate of bleeding with clopidogrel plus warfarin than with triple therapy.[4] Although this finding is intriguing, 573 patients were involved in the WOEST trial, and larger trials would be needed to ensure the safety of stopping aspirin after PCI.

Novel oral anticoagulant drugs have been shown to have at least similar efficacy to warfarin for stroke prevention and to be safer (associated with lower rates of intracranial hemorrhage) than warfarin in patients with atrial fibrillation.[5] Specifically, rivaroxaban, an oral factor Xa inhibitor, administered at a dose of 20 mg daily was proven to be noninferior to warfarin for stroke prevention.[5] In addition, in a randomized trial involving patients with acute coronary syndromes, rivaroxaban administered at a dose of 2.5 or 5 mg twice daily was superior to placebo for the prevention of death from cardiovascular causes, myocardial infarction, or stroke and the prevention of stent thrombosis, but the rate of major bleeding with rivaroxaban plus background DAPT (clopidogrel plus aspirin) was three times as high as the rate with placebo plus background DAPT.[6] It is important to note that these doses of rivaroxaban are not approved for use in the United States.

In this issue of the *Journal*, Gibson et al.[7] report the results of the PIONEER AF-PCI trial (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 triple therapy with DAPT plus a vitamin K antagonist (warfarin) was shown to be associated with a significantly higher rate of bleeding than either therapy with a single $P2Y_{12}$ inhibitor plus low-dose rivaroxaban (15 mg once daily) or therapy with DAPT plus very-low-dose rivaroxaban (2.5 mg twice daily). There were no significant differences among the three groups in the rate of death from cardiovascular causes, myocardial infarction, or stroke or the rate of stent thrombosis; however, the trial was not powered to assess these outcomes. Ischemic stroke occurred in 7 patients receiving a $P2Y_{12}$ inhibitor plus low-dose rivaroxaban, in 6 receiving DAPT plus very-low-dose rivaroxaban, and in 2 receiving DAPT plus warfarin. These differences were not statistically significant; however, the confidence intervals were wide.

PIONEER AF-PCI was designed primarily to

Table 1. Major Randomized Trials Comparing Anticoagulation Strategies for Patients with Atrial Fibrillation Undergoing PCI.*

Trial	No. of Participants	Control	Intervention	Primary Outcome	ClinicalTrials.gov No.
REDUAL-PCI	2800	Aspirin, $P2Y_{12}$ inhibitor, and vitamin K antagonist	Dabigatran (either 110 mg twice daily or 150 mg twice daily) plus $P2Y_{12}$ inhibitor	Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria	NCT02164864
ENTRUST-AF-PCI	1500	Aspirin, $P2Y_{12}$ inhibitor, and vitamin K antagonist	Edoxaban (60 mg once daily) plus $P2Y_{12}$ inhibitor	Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria	NCT02866175
AUGUSTUS	4600	Either aspirin or vitamin K antagonist (2-by-2 factorial design)	Either apixaban (5 mg twice daily) or placebo	Major bleeding and clinically relevant nonmajor bleeding, defined according to ISTH criteria	NCT02415400

* The REDUAL-PCI trial is the Evaluation of Dual Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Atrial Fibrillation That Undergo a PCI with Stenting; the ENTRUST-AF-PCI trial is Edoxaban Treatment versus Vitamin K Antagonist in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; and the AUGUSTUS trial is A Study of Apixaban in Patients with Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart. ISTH denotes International Society on Thrombosis and Haemostasis, and PCI percutaneous coronary intervention.

assess safety and to generate hypotheses about clinical outcomes but not to definitively assess clinical outcomes. According to the results of PIONEER AF-PCI, the elimination of aspirin from triple therapy or the use of very-low-dose rivaroxaban with DAPT resulted in a lower rate of bleeding than did the use of triple therapy. However, the efficacy of these strategies for the prevention of stroke or stent thrombosis is still uncertain. Specifically, the effectiveness of rivaroxaban administered at a dose of 2.5 mg twice daily for stroke prevention in patients with atrial fibrillation is uncertain, so this regimen cannot be recommended without further data. It is also possible that the elimination of aspirin from triple therapy could be associated with a 25% increase in the risk of stent thrombosis, but this trial does not have the power to assess this outcome. Although these data add to the results of the WOEST trial regarding the elimination of aspirin from triple therapy, clinicians should individualize therapy on the basis of a patient's risk for bleeding and stent thrombosis until the results of larger trials are available. A trial sample size of approximately 14,000 patients would be needed to provide adequate power for the assessment of ischemic outcomes, including the risk of stroke and stent thrombosis.

Finally, $CHADS_2$ scores are used to stratify patients with nonvalvular atrial fibrillation according to risk of stroke, and patients with a $CHADS_2$ score of 0 or 1 (on a scale ranging from 0 to 6, with higher scores indicating a higher risk of stroke) are still most likely to be best served by treatment with DAPT alone given their low risk of stroke. In addition, the safety of combining ticagrelor or prasugrel with oral anticoagulants is still uncertain; very few patients in PIONEER AF-PCI received these agents.

Three ongoing multicenter randomized trials (Table 1) involving patients with atrial fibrillation undergoing PCI are being conducted to compare the effects of novel oral anticoagulants plus a $P2Y_{12}$ inhibitor (without aspirin) with the effects of triple therapy with DAPT plus a vitamin K antagonist. However, these trials are not designed to assess ischemic outcomes; they target bleeding. In conclusion, more than 100,000 patients with atrial fibrillation undergo PCI in the United States annually, and simple, low-cost, randomized trials would help to determine the best possible regimen for these patients.

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

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Acute Otitis Media — The Long and the Short of It

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Acute otitis media is the second most common reason for a child to visit his or her primary care physician and the most common reason for prescribing an antibiotic agent to a child.[1] Over the past 40 years, substantial progress has been made in understanding the epidemiology, bacteriology, risk factors, and natural history of acute otitis media.[2] The introduction of pneumococcal vaccines, the 7-valent vaccine (PCV7) in 2000 and the 13-valent vaccine (PCV13) in 2010, has resulted in a decrease in the incidence of acute otitis media attributable to the pneumococcal vaccine serotypes.[3] Despite this decrease, acute otitis media remains prevalent, especially among young children. The characteristic manifestations of acute otitis media include otalgia, fever, otorrhea, crankiness, poor sleeping, conductive hearing loss, and vestibular dysfunction. Both intratemporal and intracranial complications may occur, including mastoiditis, subperiosteal abscess, sigmoid-sinus thrombosis, epidural abscess, facial-nerve palsy, otitic hydrocephalus, and sensorineural hearing loss resulting in serious injury and, rarely, death.[4]

Oral antibiotics, with symptomatic management of otalgia and fever, are the standard of care for patients with acute otitis media, although close observation with available rescue antibiotics, especially in older children, has also been advocated.[2] Empirical therapy is based on the well-documented bacteriology of acute middle ear disease — *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, and *Moraxella catarrhalis* are the most commonly isolated middle-ear pathogens. However, as the prevalence of pneumococcal serotypes represented in PCV7 and PCV13 has declined, other nonvaccine pneumococcal serotypes and less common pathogens, including *Alloiococcus otitidis*, *Staphylococcus aureus*, *S. pyogenes*, and *Pseudomonas aeruginosa*, are increasingly being isolated in patients with acute otitis media.[5,6]

Recommendations for the duration of antibiotic therapy for acute otitis media vary from 5 to 10 days.[7] A shorter duration of antibiotic therapy is desirable to reduce antibiotic resistance, decrease the risk of adverse events, improve adherence, and lessen expense. This issue of the *Journal* presents the results of a prospective, double-blind study conducted by Hoberman et al.,[8] which randomly assigned 520 otherwise-healthy children, 6 to 23 months of age, with strictly defined acute otitis media to receive either 10 days of amoxicillin–clavulanate or 5 days of amoxicillin–clavulanate followed by 5 days of placebo. In their study, children who were treated with amoxicillin–clavulanate for 5 days were more likely to have clinical failure than those who were treated for 10 days (34% vs. 16%; difference, 17 percentage points [based on unrounded data]; 95% confidence interval, 9 to 25). In addition, on the Acute Otitis Media–Severity of Symptoms scale (scores range from 0 to 14, with higher numbers indicating more severe symptoms) at days 6 to 14, the 5-day group had less-favorable mean symptom scores than the 10-day group (1.61 vs. 1.34, P=0.07).