EDITORIALS

Triple Therapy for Atrial Fibrillation after PCI

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The management of atrial fibrillation in patients who have undergone percutaneous coronary intervention (PCI) for the treatment of coronary-artery disease is a common and difficult challenge. In patients with atrial fibrillation, oral anticoagulation is administered to reduce the risk of stroke. In patients who have undergone PCI, dual antiplatelet therapy is administered to prevent major adverse cardiovascular events and stent thrombosis. The use of triple therapy is common in clinical practice; one in four older patients with atrial fibrillation who have had an acute myocardial infarction receives triple therapy.[1] Although triple therapy may minimize the risk of stent thrombosis and ischemic events, it is associated with a risk of fatal and nonfatal bleeding that is nearly four times as high as the risk with warfarin therapy alone[2] and a risk of intracranial hemorrhage that is two times as high as the risk with dual antiplatelet therapy.[1] Furthermore, shortening the course of triple therapy does not substantially reduce the bleeding risk.[3] Thus, although triple therapy may prevent ischemic events, it also has the potential to cause considerable harm in many patients.

In this issue of the *Journal*, Cannon et al.[4] report the results of the open-label, randomized, noninferiority RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention). In the RE-DUAL PCI trial, 2725 patients with atrial fibrillation who had undergone PCI were randomly assigned, in a 1:1:1 ratio, to receive triple therapy with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and aspirin (for 1 to 3 months), dual therapy with dabigatran at a dose of 110 mg twice daily plus a $P2Y_{12}$ inhibitor, or dual therapy with dabigatran at a dose of 150 mg twice daily plus a $P2Y_{12}$ inhibitor. The rate of the primary end point — the occurrence of International Society on Thrombosis and Hemostasis (ISTH) major or nonmajor clinically relevant bleeding — was lower in the 110-mg dual-therapy group than in the triple-therapy group (hazard ratio, 0.52; 95% confidence interval [CI], 0.42 to 0.63; $P<0.001$ for noninferiority) and was also lower in the 150-mg dual-therapy group than in the corresponding triple-therapy group (hazard ratio, 0.72; 95% CI, 0.58 to 0.88; $P<0.001$ for noninferiority). There were markedly lower rates of intracranial bleeding in the 110-mg and 150-mg dual-therapy groups (0.3% and 0.1%, respectively) than in the triple-therapy group (1.0%). Both dual therapies were noninferior to triple therapy with respect to the composite efficacy end point of death, myocardial infarction, stroke, systemic embolism, or unplanned revascularization. Therefore, the RE-DUAL PCI trial showed that dual therapy with dabigatran plus clopidogrel or ticagrelor resulted in a risk of bleeding that was significantly lower than the risk with triple therapy. Furthermore, dual therapy with dabigatran was noninferior to triple therapy with respect to the prevention of ischemic events.

How do we place the results from the RE-DUAL PCI trial in the context of currently available evidence? Two other randomized trials have directly compared dual therapy with triple therapy after PCI in patients with atrial fibrillation: the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting)[5] and 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 Sub-

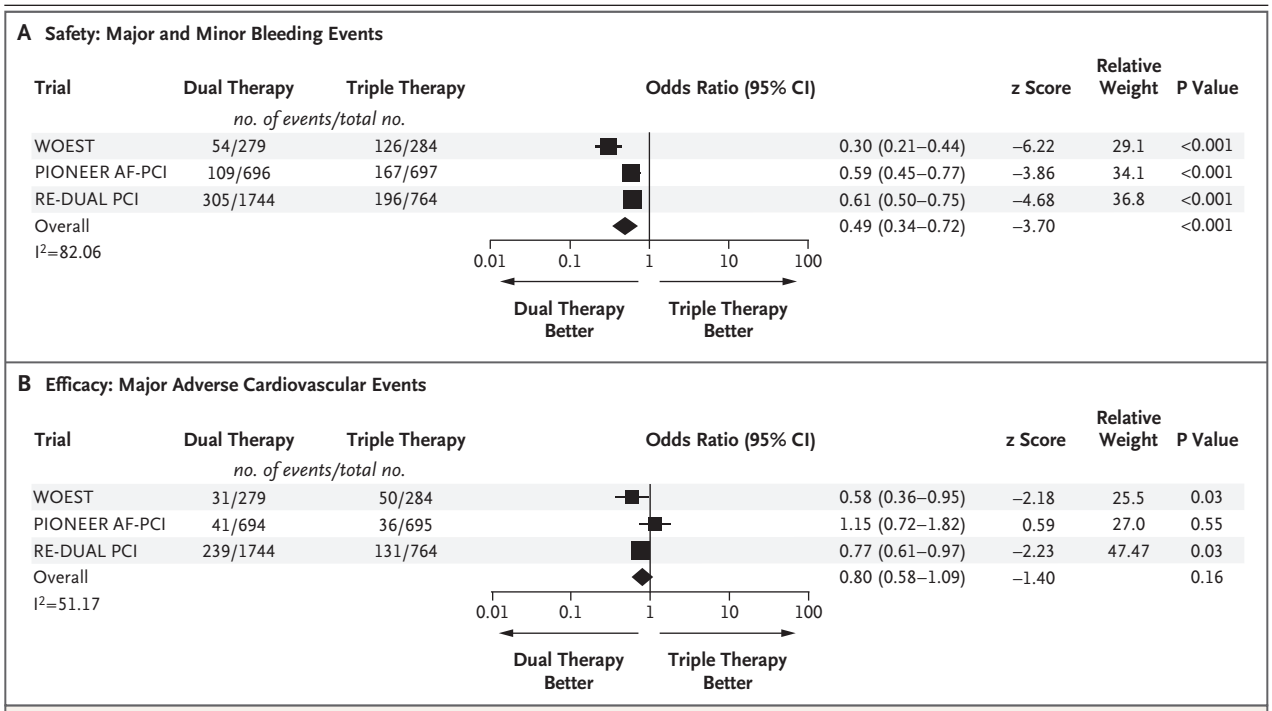

Figure 1. Meta-Analyses of Results from Three Major Trials of Dual Therapy versus Triple Therapy.

Shown are meta-analyses of results from three major trials: the WOEST trial (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting),[5] 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),[6] and the RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention).[4] Each of these trials compared dual therapy (oral anticoagulation plus a $P2Y_{12}$ inhibitor) with triple therapy (oral anticoagulation plus a $P2Y_{12}$ inhibitor and aspirin). Panel A shows the meta-analysis of results for combined bleeding events: any TIMI (Thrombolysis in Myocardial Infarction), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and BARC (Bleeding Academic Research Consortium) bleeding events in the WOEST trial; TIMI major and minor bleeding events in the PIONEER AF-PCI trial; and ISTH (International Society on Thrombosis and Hemostasis) major and clinically relevant nonmajor bleeding events in the RE-DUAL PCI trial. Panel B shows the meta-analysis of results for combined major adverse cardiovascular events: death, myocardial infarction, stroke, revascularization, or stent thrombosis in the WOEST trial; death, myocardial infarction, stroke, or stent thrombosis in the PIONEER AF-PCI trial; and death, myocardial infarction, stroke, systemic embolism, or unplanned percutaneous or surgical revascularization in the RE-DUAL PCI trial. The meta-analyses were performed with the use of the DerSimonian and Laird method for random effects. Significant heterogeneity was identified in both analyses, as indicated by the I^2 values. In general, I^2 values of 25%, 50%, and 75% are considered to indicate low, moderate, and high degrees of heterogeneity, respectively. Relative weights are based on the inverse of the observed variance of the treatment effect within studies and between studies.

jects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention).[6] In the WOEST trial, among patients who had a long-term indication for oral anticoagulation (69% of whom had atrial fibrillation), those who were randomly assigned to receive dual therapy (clopidogrel and warfarin) had a significantly lower rate of bleeding, with no apparent increase in thrombotic events, than those who were assigned to receive triple therapy. In the WOEST trial, patients were not treated with non–vitamin K antagonists or $P2Y_{12}$ inhibitors other than clopidogrel, whereas in the PIONEER AF-PCI trial, 2124 patients were randomly assigned, in a 1:1:1 ratio, to one of three groups, including one group that received dual therapy with rivaroxaban (15 mg daily) plus a $P2Y_{12}$ inhibitor and one group that received triple therapy with dose-adjusted warfarin. In the PIONEER AF-PCI trial, dual therapy with rivaroxaban was associated with lower risks of Thrombolysis in Myocardial Infarction (TIMI) major and minor bleeding than was triple therapy with warfarin. Similar to the WOEST trial, the PIONEER AF-PCI trial was not powered to detect differences in the prevention of ischemic events, but no excess events were noted with dual therapy.

The RE-DUAL PCI trial is now the third direct head-to-head comparison of dual therapy with triple therapy. Similar to its predecessors, it also shows a significantly lower risk of bleeding with dual therapy and no apparent major increase in ischemic or major adverse cardiovascular events.

There were several differences among these three trials. The most important differences were the duration of triple therapy and the anticoagulants used in each study (warfarin in the WOEST trial, rivaroxaban in the PIONEER AF-PCI trial, and dabigatran in the RE-DUAL PCI trial). However, an informal meta-analysis of the results of these three large trials, performed with the use of the DerSimonian and Laird method for random effects (Fig. 1), shows that the odds of major and minor bleeding with dual therapy are half the odds with triple therapy (odds ratio, 0.49; 95% CI, 0.34 to 0.72; $P<0.001$; $I^2=82.06$). The risk of bleeding is clearly lower with dual therapy than with triple therapy; however, we must consider the cost — is there an increase in ischemic events with dual therapy? Although it is important to acknowledge the heterogeneity of these trials, the meta-analysis suggests that the risk of major adverse cardiovascular events (e.g., death, myocardial infarction, revascularization, thromboembolic events, or stent thrombosis) is not higher with dual therapy than with triple therapy. At worst, there may be a 9% relative increase in risk (odds ratio, 0.80; 95% CI, 0.58 to 1.09; $P=0.16$; $I^2=51.17$), a difference that is far smaller than the margin used to establish the noninferiority of non–vitamin K antagonists to warfarin in pivotal studies (i.e., a hazard ratio of 1.38 to 1.46).[7,8]

No single trial has been adequately powered to completely rule out an increase in ischemic events with dual therapy versus triple therapy. However, the consistency across these three major trials and the significantly lower risk of bleeding with dual therapy make it hard to argue that triple therapy should be used routinely. The aggregate evidence suggests that the net clinical benefit of dual therapy should give cardiologists confidence to drop aspirin when they are using a contemporary PCI strategy with drug-eluting stents. Moving forward, the key questions will be: What combination of drugs should be included in dual therapy, and how will we test this strategy?

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

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JAK Inhibitors Taking on Psoriatic Arthritis

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Psoriasis is a chronic inflammatory skin disease that affects 2 to 4% of the population.[1] Inflammatory arthritis develops in approximately 30% of patients with psoriasis and can have a major effect on activities of daily living and quality of life.[2] Peripheral joint involvement in patients with psoriatic arthritis can be oligoarticular or polyarticular and can cause joint destruction. Several medications are used to treat psoriatic arthritis, and the choice of agent and the timing of administration in the course of the disease depend on disease manifestations, their severity, and prognostic factors.[2] Therapy typically involves the sequential use of nonsteroidal antiinflammatory drugs (NSAIDs) and intraarticular glucocorticoids and, later, disease-modifying antirheumatic drugs