

Transient Ischemic Attack in a High-Risk Cardiovascular Patient with Renal Dysfunction after Treatment with Rivaroxaban and Clopidogrel: A Case Report

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INTRODUCTION

Patients with atrial fibrillation who have experienced acute coronary syndrome that was treated with percutaneous coronary intervention (PCI) represent a challenge in antithrombotic management, in terms of balancing the risks of thrombosis and bleeding. The 2018 update of the Canadian Cardiovascular Society's antiplatelet guidelines recommended triple therapy (an oral anticoagulant [OAC], a P2Y₁₂ inhibitor, and acetylsalicylic acid [ASA]) with reduction in the intensity or dose of the OAC and consideration of dual therapy (OAC and P2Y₁₂ inhibitor) within 1 day to 6 months after PCI following acute coronary syndrome.¹ In contrast, the 2016 atrial fibrillation guidelines of the Canadian Cardiovascular Society recommend triple therapy for 3 to 6 months after PCI in patients with stroke risk defined by a CHADS₆₅ score of 1 or greater.² Triple therapy is associated with a 17.6% frequency of bleeding requiring hospitalization²; dual therapy has been proposed to reduce this risk of bleeding.

The PIONEER-AF-PCI and RE-DUAL-PCI trials assessed the safety of a direct OAC (DOAC) plus a P2Y₁₂ inhibitor relative to the safety of triple therapy.^{3,4} The PIONEER-AF-PCI trial ($n = 2124$ patients) demonstrated a reduction in clinically significant bleeding with rivaroxaban 15 mg dual therapy (or rivaroxaban 10 mg for patients with creatinine clearance of 30–50 mL/min) relative to triple therapy (16.8% versus 26.7%, respectively; $p = 0.002$).³ In the RE-DUAL-PCI trial ($n = 2725$), dabigatran dual therapy was associated with a reduction in clinically relevant bleeding relative to triple therapy (for dabigatran 110 mg, 15.4% versus 26.9%, $p < 0.001$; for dabigatran 150 mg, 20.2% versus 25.7%, $p < 0.001$).⁴ Although these safety outcomes are compelling, and there was no signal for loss of efficacy with dual therapy, these trials were

underpowered to assess thrombosis outcomes.^{3,4} Furthermore, high-risk populations, including patients with renal dysfunction, were underrepresented in these trials.

The case reported here represents the risks of applying evidence for DOAC dual therapy (with limited data for efficacy) to a high-risk cardiovascular patient with renal dysfunction.

CASE REPORT

An 82-year-old, 74-kg man with hypertension, dyslipidemia, coronary artery disease treated with PCI (16 years prior), deep vein thrombosis (17 and 21 years prior), and chronic renal insufficiency (baseline serum creatinine 140 $\mu\text{mol/L}$) was admitted in May 2017 for elective reverse total shoulder arthroplasty. The evening after surgery, while receiving ASA 325 mg daily, the patient experienced non-ST elevation myocardial infarction and acute-on-chronic renal injury (serum creatinine 185 $\mu\text{mol/L}$). A heparin infusion was started, along with clopidogrel 75 mg daily, and the ASA dose was changed to 81 mg daily. New-onset atrial fibrillation was identified on electrocardiography, and amiodarone was initiated. Hematoma of the right shoulder subsequently occurred, and the existing therapy was continued with close observation.

On day 2 after the surgery, the patient exhibited increased confusion and dysphagia; however, the findings of computed tomography (CT) were unremarkable. On day 6, aphasia and right hemiparesis occurred; CT showed an infarct in the left middle cerebral artery of suspected cardioembolic origin. The patient's symptoms recurred throughout the following week, with no changes on repeat CT; the acute renal injury resolved.

*The patient provided consent for publication of this case report.

On day 15, the patient was transferred to cardiac care for recurrent chest discomfort, with electrocardiography showing significant anterolateral ST depression. Coronary angiography revealed severe left main triple-vessel disease, which was treated with bare metal stents in the left main, ostial circumflex, and obtuse marginal arteries. Therapy with heparin, clopidogrel, and ASA was continued for 3 days after the procedure. On day 20 after the initial shoulder surgery, he was switched to rivaroxaban 10 mg and clopidogrel 75 mg daily, planned to continue for 1 year, as per the recommendations of the PIONEER-AF-PCI trial for a patient with creatinine clearance 40 mL/min (by weight-based Cockcroft–Gault equation, for serum creatinine 131 $\mu\text{mol/L}$) (CHADS₆₅ = 4; bleed risk defined by HASBLED score = 3).³ Renal function remained stable after PCI, and the patient did not experience repeat symptoms of stroke. The medications were continued at discharge on day 31.

On the day after discharge, the patient was readmitted with facial drooping, dysphagia, and right-side hemiparesis; CT showed no significant change. The diagnosis was recurrent transient ischemic attack, which prompted a switch to warfarin, with maintenance of the clopidogrel therapy (75 mg daily). The anti-Xa level calibrated for rivaroxaban was not measured, although steady-state drug concentrations were assumed. In follow-up with the neurologist in October 2017, it was noted that the patient continued to have infrequent episodes of aphasia, with subtherapeutic international normalized ratio (INR), following initiation of warfarin. This problem has since resolved, and the patient has not had recurrent stroke or transient ischemic attack, and subsequent INR values have been therapeutic.

DISCUSSION

The suitability of DOAC dual therapy for this high-risk patient is limited, as his medical conditions were not well represented in the available trials,^{3,4} reducing the external validity of the efficacy outcomes. Given the small subset of patients with renal insufficiency in the trials, initial management with warfarin might have been more appropriate as a well-established option for stroke prophylaxis in patients with atrial fibrillation and declining renal function.

The 2 published trials of DOAC dual therapy would have excluded this patient because of risks of stroke and/or bleeding. More specifically, the PIONEER-AF-PCI trial³ excluded patients with a history of stroke; in addition, 254 (35.8%) of the patients in the dual-therapy experimental arm were 75 years of age or older, and 130 (18.5%) patients had non-ST elevation myocardial infarction. One hundred and ninety-four (28.8%) of the patients had creatinine clearance of 30–60 mL/min; however, data for the subgroup with creatinine clearance of 30–50 mL/min, who would have received 10 mg rivaroxaban, were not published. The composite rate of death from cardio-

vascular causes, myocardial infarction, or stroke was 6.5% for patients receiving dual therapy versus 6.0% for those receiving triple therapy, although the study was underpowered to demonstrate significance for this comparison.³ The primary composite safety outcome was significantly lower with dual therapy (16.8% versus 26.7%, $p = 0.002$), and was driven by bleeding that required medical attention (13.5% versus 19.9%, $p = 0.001$) rather than major or minor bleeding. Furthermore, the subgroup analysis of clinically significant bleeding for the rivaroxaban 10 mg group was not published. In the RE-DUAL-PCI trial,⁴ patients with a stroke in the month before screening were excluded. Patients with previous stroke constituted 11% of the population, 16% had renal disease, the indication for PCI was unstable angina for 19.9% and non-ST elevation myocardial infarction for 20.7%, and the mean stroke risk defined by CHA₂DS₂-VASc score was 3.7 in the dabigatran 110 mg group.⁴ The combined dabigatran 110 mg and 150 mg arms demonstrated non-inferiority for the composite end point of thrombosis, death, or unplanned revascularization relative to triple therapy (13.7% versus 13.4%, $p = 0.005$); however, this composite end point was higher for the dabigatran 110 mg arm (15.2% versus 13.4%, $p = 0.30$).⁴ The primary composite safety outcome was significantly different between dual and triple therapy (for dabigatran 110 mg, 15.4% versus 26.9%, $p < 0.001$; for dabigatran 150 mg, 20.2% versus 25.7%, $p < 0.001$), which was maintained for the component of major bleeding (for dabigatran 110 mg, 5.0% versus 9.2%, $p < 0.001$; for dabigatran 150 mg, 5.6% versus 8.4%, $p = 0.02$); however, results for clinically relevant, nonmajor bleeding were not reported. It is unclear whether the outcomes of these trials, in terms of both efficacy and safety, can be extrapolated to similar patients of advanced age with a history of stroke and renal dysfunction.

Future trials may further elucidate the role of DOAC dual therapy. The AUGUSTUS trial (ClinicalTrials.gov identifier NCT02415400, completed November 2018) and the ENTRUST-AF-PCI trial (ClinicalTrials.gov identifier NCT02866175, estimated completion June 2019) are assessing the safety of apixaban and edoxaban dual therapy, respectively. Neither of these trials is assessing efficacy as a primary outcome, and application of their results to high-risk patients, such as the one described here, may be limited.

The patient described here was ultimately treated with warfarin-based dual therapy to balance his high risk of stroke with the risk of bleeding. In patients with high thrombotic risk, elevated bleeding risk, or a complex interplay of these 2 factors, ongoing critical evaluation of recent and emerging evidence is needed to determine optimal antithrombotic therapy.

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