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Platelet Reactivity and Risk of Ischemic Stroke After Coronary Drug-Eluting Stent Implantation

From the ADAPT-DES Study

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ABSTRACT

OBJECTIVES The authors sought to investigate the association between $P2Y_{12}$ reaction units (PRU) and the risk of ischemic stroke (IS) after successful coronary drug-eluting stents (DES) implantation.

BACKGROUND The association between platelet reactivity on clopidogrel and the risk for ischemic cerebrovascular events remains unclear.

METHODS Incidence, predictors, and prognostic impact of IS were evaluated among patients enrolled in the multicenter, prospective ADAPT-DES (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents) study. By protocol, patients were maintained on aspirin for 2 years and clopidogrel for at least 1 year. Baseline platelet reactivity on clopidogrel and aspirin were assessed by means of VerifyNow point-of-care assay after successful DES implantation.

RESULTS Among 8,582 patients enrolled, 68 (0.8%) had an IS during 2-year follow-up. Across the spectrum of PRU, rates of IS were progressively greater as patients transitioned from the lowest quintile of PRU (more $P2Y_{12}$ receptor inhibition; 2-year rate of 0.51%) to the highest quintile of PRU (less $P2Y_{12}$ receptor inhibition; 2-year rate of 1.34%; adjusted $p = 0.04$). PRU >208 was independently associated with higher risk of IS at 2 years (adjusted hazard ratio 1.81; 95% confidence interval 1.08 to 3.04; $p = 0.03$). The association between higher PRU and risk for IS was also consistent in patients with versus without high CHA_2DS_2-VASc score ($p_{interaction} = 0.30$) and in those on or off oral anticoagulation at discharge ($p_{interaction} = 0.99$). Occurrence of IS was strongly associated with increased risk of all-cause mortality at 2 years (adjusted HR: 4.16; 95% CI: 1.95 to 8.87; $p < 0.0001$).

CONCLUSIONS Higher PRU was associated with increased risk of IS after coronary DES implantation. Ensuring adequate platelet $P2Y_{12}$ receptor inhibition may reduce the risk of IS in this patient population. (Assessment of Dual AntiPlatelet Therapy With Drug Eluting Stents [ADAPT-DES]; NCT00638794) (J Am Coll Cardiol Intv 2018;■:■–■)

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ABBREVIATIONS AND ACRONYMS

ARU = aspirin reaction unit(s)

CI = confidence interval

DAPT = dual antiplatelet therapy

DES = drug-eluting stent(s)

HR = hazard ratio

HS = hemorrhagic stroke

IS = ischemic stroke

PCI = percutaneous coronary intervention

PRU = $P2Y_{12}$ reaction unit(s)

ST = stent thrombosis

After percutaneous coronary intervention (PCI) with drug-eluting stents (DES), a period of dual antiplatelet therapy (DAPT) combining a $P2Y_{12}$ receptor inhibitor and aspirin is recommended to prevent the occurrence of stent-related thrombotic complications (1). The pathobiological rationale of DAPT post-PCI is predicated on the need to protect the stented vascular segment while vascular healing and stent strut endothelialization are ongoing (1,2). Additionally, platelet inhibition may prevent the development of atherothrombosis arising from atherosclerosis progression and acute plaque changes occurring outside the stented vascular segment, within the coronary vasculature, and possibly throughout the systemic arterial system (3,4). A significant interindividual variability in platelet response to clopidogrel has been described and has been attributed to genetic and epigenetic factors that influence pharmacokinetic and pharmacodynamic properties of clopidogrel (5,6). As such, high on-clopidogrel platelet reactivity has been widely described as a strong independent predictor of increased risk of stent thrombosis (ST) and myocardial infarction after PCI (5,6).

Stroke is a devastating clinical event associated with substantial morbidity and mortality (7). Patients with coronary artery disease are also at an increased risk of ischemic stroke (IS) due to concomitant atherosclerotic disease within the extra- and intracranial arterial system or due to cardiogenic embolism (7–9). Whether the degree of residual $P2Y_{12}$ receptor inhibition influences the risk of IS in a PCI population, in which the primary indication of DAPT is the prevention of coronary-related events, remains unclear. Therefore, in the largescale ADAPT-DES (Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents) study, we sought to investigate the association between platelet reactivity on clopidogrel and aspirin and the risk of IS in patients with coronary artery disease who underwent successful DES-PCI.

METHODS

STUDY DESIGN AND OBJECTIVES. The ADAPT-DES study was a prospective, multicenter registry specifically designed to determine the association between platelet reactivity and ST after DES implantation. The design and major outcomes of the ADAPT-DES study have been previously described (6). In brief, a total of 8,582 all-comers patients were prospectively enrolled at 11 sites in the United States and Germany.

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