Secondary Stroke Prophylaxis with Clopidogrel Produces Sufficient Antiplatelet Response

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Background: Antiplatelet therapy is a cornerstone prevention strategy for secondary ischemic stroke (IS) and transient ischemic attack (TIA). Yet, a proportion of patients who receive antiplatelet therapy experience recurrent ischemic cerebrovascular events. A recent meta-analysis found an increased risk of recurrent stroke in clopidogrel- or aspirin-treated patients with ischemic stroke who had high on-treatment platelet reactivity (HTPR). Few studies have focused specifically on clopidogrel HTPR. Therefore, the aim of this study was to examine the relationship between clopidogrel HTPR and recurrent ischemic events in a population of Danish patients with IS. *Methods:* We performed a prospective observational study to evaluate the relationship between HTPR defined as platelet reaction units >208 and a composite primary endpoint of recurrent stroke, TIA, acute myocardial infarction (AMI), or vascular death over a 2-year follow-up period. *Results:* A total of 142 patients were included in the final statistical analysis, but only 3 patients (2.1%) demonstrated clopidogrel HTPR. The median time of on-treatment platelet testing was 75 days. Recurrent IS, TIA, AMI, or vascular death occurred in 14 patients (10%). Of these, 1 new ischemic event (AMI) occurred in a HTPR patient. There was no difference in the frequency of new ischemic events between the HTPR and non-HTPR groups (P = .27); moreover, the number of patients with HTPR was too small for statistical analysis. *Conclusions:* Clopidogrel HTPR does not seem to be a major contributor to recurrent ischemic events in Danish ischemic stroke patients.

Key Words: Antiplatelet therapy—cerebrovascular disease—clopidogrel—high on-treatment platelet reactivity—stroke

Introduction

Antiplatelet therapy is a cornerstone prevention strategy for secondary ischemic stroke (IS) and transient ischemic attack (TIA). Yet, a proportion of patients who receive antiplatelet therapy experience recurrent ischemic cerebrovascular events.[1] It has been proposed that insufficient platelet inhibition despite antiplatelet therapy might account for a proportion of those patients with recurrent stroke or cardiovascular events, even though it has been questioned if antiplatelet resistance exists.[2] There are several hypothesis of insufficient platelet inhibition: Intrinsic (genetic variables, increased release of ADP, and alternate pathways of platelet activation) and extrinsic factors (nonadherence to treatment, under/inappropriate dosing of clopidogrel, and drug interactions).[3-6]

High on treatment platelet reactivity (HTPR) is defined as patients despite treatment with antiplatelet drugs still have normal or near-normal ex vivo platelet aggregation.

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In 1993, Grotemeyer evaluated recurrent vascular events (IS, TIA, acute myocardial infarction [AMI], and vascular death) in 180 patients with IS who were treated with 500 mg acetylsalicylic acid 3 times per day for a period of 24 months. Patients with aspirin resistance measured at inclusion showed a 10-fold increase in the risk of a vascular event compared to aspirin responders.[7] The diagnostic evaluation of patients with IS and the ability to treatment concurrent illnesses have notably improved since 1993, making these results inapplicable to current clinical practice.

A more recent meta-analysis similarly found an increased risk of recurrent stroke in patients with IS and HTPR during aspirin or clopidogrel therapy.[8] Yet, few studies have specifically investigated clopidogrel HTPR, and most are observational studies. One systematic review reported clopidogrel HTPR in 8%-61% of patients with IS,[9] suggesting that HTPR is possibly a major cause of recurrent stroke.

The aim of this study was to investigate the relationship between recurrent ischemic vascular events (a composite end-point of IS, TIA, AMI, and vascular death) and HTPR in patients with IS treated with clopidogrel 75 mg/day over a 2-year follow-up period.

Methods

We performed an observational follow-up study on the risk of recurrent stroke, TIA, AMI, or vascular death in patients with IS who were treated with clopidogrel 75 mg/day; specifically, outcomes were compared among patients with HTPR (platelet reaction units [PRU] >208) and non-HTPR patients (PRU ≤208). The study was conducted at the Neurovascular Centre of Zealand University Hospital in Denmark. A stroke physician prescreened the medical records of all admitted patients with suspected acute ischemic stroke for eligibility between December 2012 and November 2016.

The inclusion criteria were acute IS or TIA; treatment with clopidogrel 75 mg/day; ≥18 years of age; no prior history of stroke, cancer, or increased risk of bleeding; and a life expectancy of >2 years. The exclusion criteria were current treatment with a vitamin K antagonist, non-vitamin K antagonist oral anticoagulant (NOAC), or antiplatelet therapy other than clopidogrel at the time of inclusion, increased risk of bleeding, carotid stenosis, and inability to give informed consent. Patients with atrial fibrillation or cancer detected during follow-up were excluded from the analysis since antiplatelet treatment is insufficient stroke prophylaxis in patients with atrial fibrillation and cancer-related coagulopathies result in an increased risk of stroke and vascular events, respectively. Patients who met the inclusion and exclusion criteria were invited to attend a screening visit in the outpatient clinic; during this visit, a physician collected the patient's medical history, concomitant medications, laboratory results, results of imaging performed during a recent admission, and performed a clinical physical examination (Fig 1). If eligible, blood samples were taken for clopidogrel HTPR evaluation. Experienced personnel (the study physician) performed blood sampling by antecubital venipuncture using a Vacutainer Safety-lok system (Becton

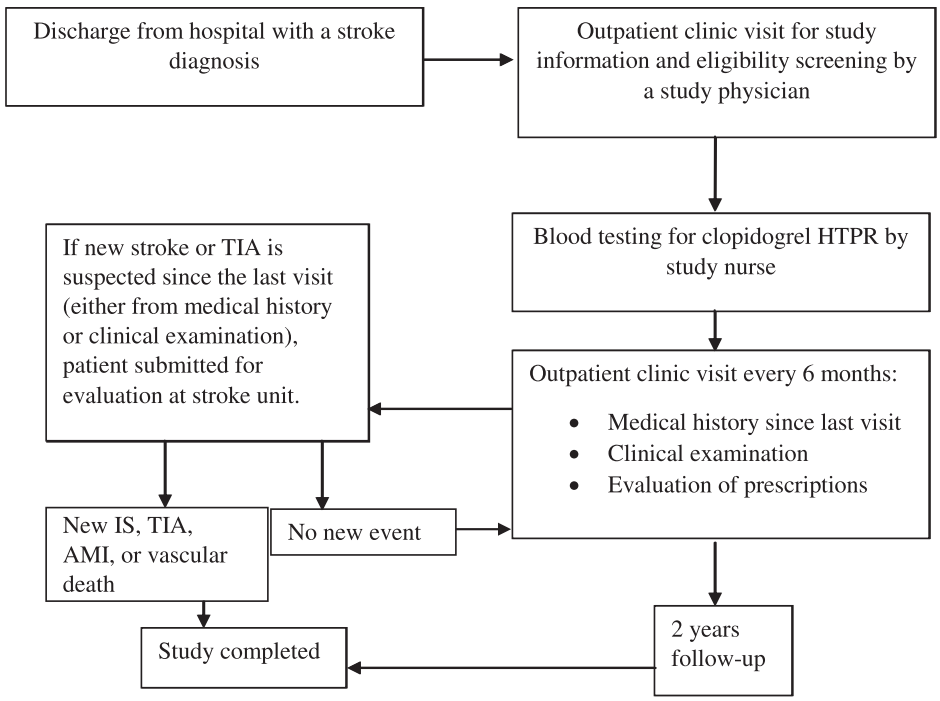

Figure 1. *Study design. AMI, acute myocardial infarction; HTPR, high on therapy platelet activity; IS, ischemic stroke; TIA, transient ischemic attack.*