# Clopidogrel Resistance after Minor Ischemic Stroke or Transient Ischemic Attack is Associated with Radiological Cerebral Small-Vessel Disease

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*Background:* The objective of this study was to compare nonresponders (NR) and responders (R) to clopidogrel with respect to presence of microvascular and macrovascular pathology in a cohort of patients with recent minor ischemic stroke (IS) or transient ischemic attack (TIA). *Methods:* Seventy-two patients treated with clopidogrel after IS or TIA were evaluated 1 month after onset. Platelet aggregation was measured by multiple electrode aggregometry (Multiplate). Nonresponse was defined according to recent consensus. The degree of cerebral small-vessel disease (cSVD) was evaluated on computed tomography scans of the brain using Fazekas scale for white matter changes. Carotid atherosclerosis was evaluated by ultrasound or computed tomography/magnetic resonance angiography. *Results:* Twenty-two percent of patients were NR. Moderate to extensive cSVD was more common for NR than R, 56% versus 25%, odds ratio 3.9 (1.2-12), $P = .03$. Correspondingly, 39% of patients with cSVD were NR versus 14% of patients with no or mild cSVD. No differences were found between NR and R in prevalence or severity of carotid atherosclerosis. NR had higher platelet aggregation response than R after stimulation with arachidonic acid or thrombin receptor–activating peptide, indicating a general platelet hyperreactivity. In a univariate analysis, hypertension, previous IS, glucose intolerance, pulse pressure above median, and presence of moderate to extensive cSVD were associated with the NR phenotype. *Conclusions:* Nonresponsiveness to clopidogrel after minor IS or TIA is associated with radiological cSVD but not with carotid atherosclerosis. *Practice/implications:* Measurement of platelet function is warranted in patients with cSVD. Larger studies on alternative or tailored antiplatelet treatment for these patients should be initiated. **Key Words:** Clopidogrel resistance—ischemic stroke—TIA—cerebral small-vessel disease—hypertension.


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## Introduction

Ischemic stroke (IS) is a heterogeneous disease with varying pathology. Large-artery atherothrombosis and small-vessel thrombotic disease are the two most common causes aside from cardioembolism. Large-artery atherothrombosis is a macrovascular disease resulting from rupture of atherosclerotic plaque in large- to medium-sized arteries, often with artery-to-artery embolization to cerebral vessels. Small-vessel thrombotic IS, or lacunar infarcts, are generally caused by cerebral small-vessel disease (cSVD). This condition affects small penetrating arteries and arterioles typically 30-300 μm in diameter. The etiology is not fully known but hypertensive arteriolosclerosis and cerebral amyloid angiopathy are the most common underlying conditions.[1] Pathological changes include segmental subendothelial protein accumulation and breakdown of the vessel wall architecture. Functionally, cSVD is coupled to endothelial dysfunction and increased permeability of the blood–brain barrier.[2,3] In addition to lacunar infarcts, cSVD may manifest as white matter changes (WMC), cerebral microbleeds, and enlarged perivascular spaces on brain imaging. cSVD has also been associated with intracerebral hemorrhage (ICH).

Secondary prevention with antiplatelet treatment is given both after large-artery atherothrombotic and small-vessel thrombotic IS. Present guidelines recommend either clopidogrel as monotherapy or aspirin combined with extended-release dipyridamole.[4] These treatments are considered equally effective in large cohorts with IS.[5] However, it is well known that the response to clopidogrel treatment shows strong individual variation and that a significant portion of patients with cardiovascular disease are effectively "clopidogrel resistant."[6-8] Being nonresponder to clopidogrel (often called "high on-treatment platelet reactivity") with high residual platelet aggregation in vitro is coupled to an increased risk of new cardiovascular events in meta-analyses.[9-11] In a recent study on clopidogrel-treated patients with minor IS or transient ischemic attack (TIA), we found a high prevalence of glucose intolerance and insulin resistance.[12] NR also displayed higher platelet aggregation response to arachidonic acid, suggesting a general platelet hyperreactivity, as has been found by others.[13,14]

Platelet interactions with the vessel wall and circulating blood cells, and the influence of such interactions on cardiovascular disease, have attracted increasing research interest the last decade. Notably, there is mounting evidence that platelets are involved in the initiation and progression of atherosclerosis.[15] The role of platelets in cSVD is less clear, but widespread endothelial dysfunction in small vessels may enhance platelet activation through platelet/endothelial cell interactions. Because the total area of interaction is larger in microvascular beds than in arteries, microvascular pathology such as cSVD may have a stronger influence on platelet reactivity than macrovascular atherosclerosis. The aim of this hypothesis-generating study was to compare the prevalence of macrovascular and microvascular pathology for NR and responders (R) to clopidogrel in a cohort of patients with recent minor IS or TIA. Vascular risk factors were also evaluated. We show that nonresponsiveness to clopidogrel is associated with radiological presence of moderate to extensive cSVD but not with carotid atherosclerosis or other types of large-vessel disease.

## Methods

### *Study Population*

Patient recruitment has been described previously.[12] From the ongoing StrokeDiabetes trial at Danderyd Hospital, Stockholm, Sweden (Clinical Trial No: NTC01648985), all patients treated with clopidogrel 75 mg once daily as monotherapy and who completed platelet function tests at the follow-up visit 1 month after symptom onset were included. This resulted in a study population of 72 patients with minor IS or TIA (of 144 recruited to the StrokeDiabetes trial). Included are 61 of 66 patients from our previous work.[12] Five patients were excluded for the present analysis: 2 who had platelet function tests only from the subacute phase, 2 receiving dual antiplatelet treatment with clopidogrel and aspirin, and 1 with diagnosis other than acute IS or TIA after detailed workup. The patient cohort was similar to the Swedish stroke population in risk factor profile and medication, with the exception of age (see Results). The study was approved by the local ethics committee. All patients gave oral and written informed consent to participation before inclusion. Details on the study population are given in Table 1.

Patients were enrolled at the time of acute cerebrovascular event (0-19 days, median 2 days after onset). At inclusion, demographic and anthropometric measures were recorded and routine laboratory tests as well as platelet reactivity were assessed. At the follow-up visit (20-51 days after inclusion, median 34 days), platelet reactivity was reassessed and variables of glucose metabolism were evaluated. Patient recruitment was blinded to all test results and computed tomography (CT) analyses.

### *Multiple Electrode Aggregometry*

Platelet aggregation in whole blood was assessed using the multiple electrode aggregometry (MEA) device, which is an established method to assess platelet responsiveness to clopidogrel.[7] Blood samples were taken after an overnight fast, 1-3 hours after intake of medication including the daily dose of clopidogrel 75 mg. Blood was sampled from an antecubital vein after rest in semi-reclining position with minimal stasis. Samples were