

Aspirin Versus Clopidogrel for Type 2 Diabetic Patients with First-Ever Noncardioembolic Acute Ischemic Stroke: Ten-Year Survival Data from the Athens Stroke Outcome Project

Haralampos Milionis, MD, PhD,* George Ntaios, MD, PhD,†
 Vasileios Papavasileiou, MD,‡ Konstantinos Spengos, MD, PhD,§
 Efstathios Manios, MD, PhD,|| Moses Elisaf, MD, PhD,* and
 Konstantinos Vemmos, MD¶

Background and objective: Diabetes mellitus is associated with an increased risk of stroke and poor outcome following a stroke event. We assessed the impact of discharge treatment with aspirin versus clopidogrel on the 10-year survival of patients with type 2 diabetes after a first-ever noncardioembolic acute ischemic stroke (AIS). *Methods:* This was a post hoc analysis of the Athens Stroke Outcome Project. Study outcomes included death, stroke recurrence, and a composite cardiovascular disease (CVD) end point (recurrent stroke, myocardial infarction, unstable angina, coronary revascularization, aortic aneurysm rupture, or sudden death). Kaplan–Meier survival curve and Cox regression analyses were performed. *Results:* A total of 304 (93 women) diabetic patients receiving either aspirin (n = 197) or clopidogrel (n = 107) were studied. The 10-year survival was better in clopidogrel-treated patients than in aspirin-treated patients (19 deaths [17.7%] for clopidogrel versus 55 deaths [27.9%] for aspirin; log-rank test: 4.91, $P = .027$). Similarly, clopidogrel was associated with a favorable impact on recurrent stroke (12 events [11.2%] for clopidogrel versus 39 events [19.7%] for aspirin; log-rank test: 4.46, $P = .035$) and on the composite CVD end point (21 events [19.6%] for clopidogrel versus 54 events [27.4%] for aspirin; log-rank test: 4.17, $P = .041$). In the multivariable analysis, the beneficial effect of clopidogrel over aspirin on both primary and secondary end points was independent of age, gender, the presence of CVD or CVD risk factors, and stroke severity. *Conclusions:* Our findings indicate a favorable effect of clopidogrel at discharge compared with aspirin in preventing death, recurrent stroke, and CVD events in diabetic patients with a first-ever noncardioembolic AIS. **Key Words:** Aspirin—clopidogrel—diabetes—outcome—stroke.
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From the *Departments of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece; †Department of Internal Medicine, University of Thessaly, Larissa, Greece; ‡Stroke Service, Department of Neurosciences, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; §Department of Neurology; ||Department of Clinical Therapeutics, School of Medicine, University of Athens, Athens, Greece; and ¶Hellenic Stroke Organization, Athens, Greece.

Received January 12, 2017; revision received April 30, 2017; accepted June 29, 2017.

Address correspondence to Haralampos Milionis, MD, PhD, Department of Internal Medicine, School of Medicine, University of Ioannina, 45110 Ioannina, Greece. E-mail: hmilioni@uoi.gr.

1052-3057/\$ - see front matter

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<http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.06.052>

Introduction

Diabetes mellitus is an independent risk factor for stroke. Diabetic patients have at least twice the risk of stroke compared with nondiabetic subjects.¹ It has been shown that ischemic stroke risk increases by 3% with every year of diabetes duration. On the other hand, stroke is a leading cause of death in this population because as much as 20% of patients with diabetes will die from stroke.¹

Of note, in the setting of type 2 diabetes, the active management of cardiovascular risk factors other than tight glucose control, such as hypertension and dyslipidemia, has been documented to improve outcome following a stroke.² Most authorities suggest the use of low-dose aspirin (75-162 mg/day) for the secondary prevention of cerebrovascular and cardiovascular events in all diabetic patients, a position that is supported by the results of 2 large meta-analyses.^{3,4} However, there are no specific recommendations for patients with stroke with diabetes with regard to antiplatelet treatment. What is more, there is a paucity of data regarding the efficacy of antiplatelet agents other than aspirin in the context of ischemic stroke of nonembolic source in the diabetic patient.⁵

In the present study, we assessed the effect of aspirin versus clopidogrel treatment on the 10-year survival in patients with type 2 diabetes who experienced a first-ever noncardioembolic acute ischemic stroke (AIS).

Methods

The present study is a post hoc analysis of the Athens Stroke Outcome Project involving type 2 diabetic patients who were hospitalized due to AIS and had an indication to receive antiplatelet therapy (lacunar, atherothrombotic, and miscellaneous etiology strokes). The study protocol prospectively included mortality data as well as early and late cardiovascular events, namely, stroke recurrence, myocardial infarction, unstable angina, coronary revascularization, aortic aneurysm rupture, peripheral atherosclerotic artery disease, and sudden death.

Study Population

We evaluated a series of consecutive patients with first-ever AIS who were admitted to the acute stroke unit and the general medicine and neurology wards of our institutions since January 1, 1998. The study protocol was based on the Athens Stroke Outcome Project, a computerized prospective observational data bank. After an extensive workup (brain imaging and vascular and cardiac studies as indicated), the patients were classified into stroke subtypes. According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, ischemic stroke was classified based on etiopathogenetic mechanisms into the

following groups: large-artery atherosclerotic stroke, cardioembolic stroke, small-artery occlusion or lacunar infarction, infarction of other determined origin, and infarction of undetermined cause.^{6,7}

Cardiovascular risk factors were documented in all cases. Medical history of diabetes mellitus, coronary artery disease, peripheral artery disease, atrial fibrillation and other cardiac arrhythmias, and dyslipidemia was recorded. Medical treatments before admission were also recorded.

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). An initial brain computerized tomography scan and a 12-lead electrocardiogram were immediately performed, and a Doppler ultrasonography of the carotid arteries was performed during the first 24 hours of hospitalization. A second computerized tomography or a magnetic resonance imaging scan was later performed and films were evaluated by 2 independent neuroradiologists. A history of hypertension was defined as a systolic blood pressure higher than 140 mm Hg with or without a diastolic blood pressure higher than 90 mm Hg (on ≥ 2 occasions), or the use of antihypertensive treatment before the index event. Current smoking was considered present when a subject had been smoking on a daily basis before the stroke. The presence of diabetes mellitus was defined as a fasting blood glucose level higher than 7.0 mmol/L (on more than 1 occasion) or receiving oral hypoglycemic agents or insulin before the occurrence of the stroke. Dyslipidemia was defined by history, medical treatment, or when a cholesterol concentration of 6.2 mmol/L or higher, or a high-density lipoprotein cholesterol of .9 mmol/L or lower, or a triglyceride level of 2.3 mmol/L or higher (based on cutoff values for high risk of coronary heart disease according to National Cholesterol Education Program Adult Treatment Panel [NCEP-ATP] III) was detected the day after admission.⁸ A history of a transient ischemic attack was defined as a temporary, focal neurological deficit presumably related to ischemia and lasting less than 24 hours, as diagnosed by a neurologist. A history of coronary heart disease (angina pectoris, unstable angina, and myocardial infarction), heart failure, heart valve disease, and arrhythmias was assessed by questionnaire and relevant medical confirmation. The study protocol was approved by the Local Ethics Committee (Alexandra's Hospital) and informed consent was obtained from all participants.

Choice of Antiplatelet Treatment

All patients were treated with aspirin upon admission, which was continued for at least 10 days or until discharge (100 mg daily, after a 325 mg loading dose). Postdischarge treatment with aspirin was prescribed in the majority of patients. Clopidogrel (75 mg daily) was administered as an alternative to aspirin in subjects with a history of hypersensitivity or a major

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