

The Burden of Diabetes and the Chance of a Previous Stroke: Thrombolysis for Recurrent Stroke in Diabetics

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Background: Intravenous thrombolysis with recombinant tissue plasminogen activator is still not approved by the European Medicines Agency for patients with diabetes mellitus and previous stroke. We assessed functional benefit and potential risk of thrombolysis in patients with diabetes and previous stroke and the influence of age, preexisting diabetic damage, as well as acute and chronic hyperglycemia on outcome, symptomatic intracranial hemorrhage, and in-hospital mortality. **Methods:** We analyzed 527 consecutive patients treated with thrombolysis for acute stroke. Poor outcome was defined as deterioration of prestroke modified Rankin Scale (mRS) to 3 or greater at discharge. Symptomatic intracranial hemorrhage was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study criteria. **Results:** Of the patients, 35.9% were diabetic and 33.2% had previous stroke. Of these patients, 14.4% were diabetics with previous stroke (index group). The rate of patients with poor functional outcome at discharge, symptomatic intracranial hemorrhage, or mortality did not differ between the index group and patients with either diabetes or previous stroke in 2 × 2 comparisons. Diabetics with first-ever stroke showed significantly more symptomatic intracranial hemorrhage (9.7%, $P < .001$) than the other groups, poorer functional recovery ($P = .036$), and the highest rate of mortality (12.4%, $P < .001$). Significant predictors for poor outcome were age ($P < .001$) and HbA1c ($P = .013$), for symptomatic intracranial hemorrhage HbA1c ($P = .006$) and for mortality acute hyperglycemia ($P = .001$) and age ($P = .004$). **Conclusion:** Diabetics with previous stroke should not be withheld from intravenous thrombolysis. The risk of complications derives primarily from poor long-term metabolic control rather than from acute hyperglycemia or from previous stroke. **Key Words:** Intravenous thrombolysis—diabetes—previous stroke—outcome—symptomatic intracranial hemorrhage.

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Introduction

Diabetes mellitus (DM) is a widespread metabolic disease in industrial nations, with up to 10% prevalence in adults.¹ Ischemic stroke (IS) represents one of the most frequent and disabling consequences of diabetic vasculopathy. Epidemiological studies have confirmed DM as a strong independent risk factor for IS² of all subtypes. In this respect DM is a strong risk factor for recurrent stroke.³ Yet, due to potential hemorrhagic complications as a result of hyperglycemia and cerebral microangiopathy, recombinant tissue plasminogen activator (rtPA) for intravenous thrombolysis (IVT) is not approved in Europe for patients with

DM and previous stroke (PS).⁴ Even if this contraindication might be treated more generously in today's clinical practice, the current approval restriction results in insecurities in acute stroke care.

Our study aims to add knowledge to risks and benefits of IVT in patients with DM and PS. The first objective was to examine complications and functional outcome of patients with DM and PS after IVT. Furthermore, we objected to illuminate if acute or chronic hyperglycemia or preexisting micro- and macrovascular diabetic damage can predict outcome or the risk of complications.

Methods

The local institutional ethical review committee approved the study. We extracted all consecutive patients from our prospectively collected stroke database who underwent IVT for acute IS as exclusive acute therapy from January 2013 to July 2015. All patients underwent standardized stroke treatment and workup according to national guidelines.^{5,6} Cerebrovascular risk factors,^{7,8} medication, and risk factors for hemorrhagic complications after IVT⁹ were assessed. Patients with PS were identified by a known history of IS or by a postischemic lesion greater than 1.5 cm¹⁰ on cranial computed tomography or magnetic resonance imaging. Microangiopathy was defined as multiple or confluent white matter lesions or multiple chronic lacunar lesions. Symptomatic intracranial hemorrhage (SICH) was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria.¹¹ Diabetics were identified by a known history of DM, by taking antidiabetic medication, or by fulfilling WHO criteria.¹² Acute hyperglycemia was defined as a plasma glucose greater than 140 mg/dL¹³ within 24 hours from admission. Poor outcome was defined as deterioration of prestroke modified Rankin Scale (mRS)

to 3 or greater at discharge. Excellent outcome was considered as mRS of 0 or 1 at discharge.

Statistical analysis was performed using SPSS 22.0 (IBM Corp., Armonk, NY). We compared the following groups: (i) diabetic patients with PS (DM+/PS+); (ii) diabetic patients without PS (DM+/PS-); (iii) nondiabetic patients with PS (DM-/PS+); and (iv) patients without DM or PS (DM-/PS-). Group comparisons were done by a multidimensional χ^2 test or Fisher's exact test for nominally scaled variables. In case of significant differences between the groups, 2×2 comparisons were done through 4-field χ^2 tests or Fisher's exact tests. For ordinal scaled variables we employed a Kruskal-Wallis test and in case of significant results a Mann-Whitney *U* test for comparison of 2 groups. For metric variables we performed a unifactorial variance analysis followed by Scheffé tests. For 2×2 comparisons, we conducted Bonferroni corrections. To test the influence of potential outcome predictors we conducted a logistic regression analysis with stepwise backward exclusion of nonsignificant parameters. A *P* value <.05 was considered to indicate statistical significance.

Results

Patient Characteristics

Of 527 included patients, 35.9% (189) were diabetic and 33.2% (175) had PS. The combination of DM and PS (group i) was found in 14.4% (76); 21.4% (113) had DM without PS (group ii); 18.8% (99) had PS without DM (group iii); and 45.4% (239) presented with neither DM nor PS (group iv; see Fig 1).

Diabetics showed significantly ($P < .001$) higher levels of HbA1c, higher levels of plasma glucose at admission, and a higher rate of acute hyperglycemia than nondiabetic patients, whereas diabetics with PS or without PS did not differ in each. Patients with DM and PS had

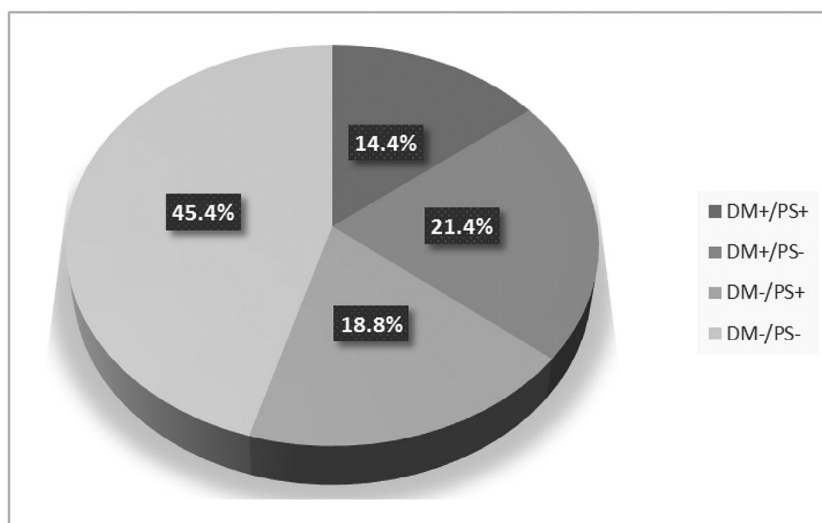


Figure 1. Proportions of diabetes mellitus and previous stroke or the combination of both in the study collective. Abbreviations: DM+/PS+, diabetic patients with previous stroke; DM+/PS-, diabetic patients without previous stroke; DM-/PS+, nondiabetic patients with previous stroke; DM-/PS-, nondiabetic patients without previous stroke.

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