The benefit of intravenous recombinant tissue-type plasminogen activator (rt-PA) for the treatment of acute ischemic stroke is well established.\(^1,2\) Unfortunately, the rates of rt-PA use among US patients with ischemic stroke remain quite low. Previously, our group published the rate of rt-PA use among ischemic stroke patients within the large Premier database, which is a 15% sampling of US hospitals that cross-references drug use with administrative data. The rate of rt-PA use was extremely low and did not increase from 2001 to 2004.\(^3\) This was despite rt-PA being approved for use in the US since 1996. More recently, we found that the rates of rt-PA have begun to slowly increase from 1.4% in fiscal year (FY) 2001 to 4.5% in FY 2009 (Figure 1).\(^4\) The timing of this increase seemed to coincide with primary stroke center certification by the Joint Commission in the United States in 2004, although this is only an association rather than definitive causality. Rates of rt-PA use did not seem to be affected by increased reimbursement given to hospitals for care of rt-PA–treated patients (instituted in 2006), as we had originally hypothesized.

To explore the impact further of hospitals becoming certified as primary stroke centers, we used the Medicare Provider Analysis and Review (MEDPAR) database to evaluate rt-PA rates at the hospital level. This database includes all fee-for-service hospitals in the United States, and patients are included if they are Medicare-eligible (aged, >65 years or permanently disabled). Within this database, hospital characteristics associated with higher rates of rt-PA use included larger bed size, urban location, and Northeast and West geographic location within the United States in FY 2009.\(^5\) We then compared rt-PA use between hospitals that became primary stroke centers during the study period of FY 2006–2010 to those hospitals that were not certified. As expected, hospitals that became stroke centers had higher rates of rt-PA treatment than those that did not become certified (5.0% versus 1.4%) in FY 2010. Rates of treatment increased steadily during the 3 years before and the 3 years after certification (Figure 2).\(^6\)

However, even with these substantial improvements in our systems of care, we are still not treating the vast majority of ischemic stroke patients with rt-PA. This is most certainly related to the eligibility of stroke patients for this acute reperfusion therapy. Within the large, biracial population of 1.3 million people in the Greater Cincinnati/Northern Kentucky region, only 8% of 2308 ischemic stroke patients would have been eligible for intravenous rt-PA in 1994,\(^7\) applying American Heart Association acute stroke management guideline criteria. The most common reason for exclusion from rt-PA was related to time from symptom onset to presentation, as only 23% of stroke patients arrived within 3 hours from symptom onset.\(^8\) This finding is very similar to many other large studies, as reviewed by Majersik et al.\(^9\) The other most common exclusion was mild symptom severity at presentation. The inclusion/exclusion criteria for rt-PA are currently being reviewed by stroke experts to verify whether all are medically necessary and which criteria warrant further

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From the Department of Neurology (D.K., F.d.l.R.L.R., B.K., P.K. O.A.), Department of Emergency Medicine (O.A.), University of Cincinnati, Cincinnati, OH; and Department of Neurology, Indiana University, Bloomington, IN (J.M.).

Correspondence to Dawn Kleindorfer, MD, University of Cincinnati, 260 Stetson St, Ste 2300, Cincinnati, OH 45267. E-mail dawn.kleindorfer@uc.edu

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Figure 1. National estimates of recombinant tissue-type plasminogen activator (rt-PA) use in the United States.
study. If some of these criteria were not required, it is possible that the percentage of eligible patients, and thereby the number of stroke patients receiving this therapy, would increase. For example, treating patients with mild stroke deficits could potentially at least double the rate of rt-PA use. However, further study is needed to determine the benefit of rt-PA within this population.

An exclusion criterion recently reconsidered was the extremely limited time window for giving lytic therapy. In 2008, the European Cooperative Acute Stroke Study (ECASS)-III study successfully expanded the time window for acute treatment with thrombolytic therapy from 0 to 3 hours to 0 to 4.5 hours from symptom onset. This prompted the American Heart Association to publish an advisory statement recommending treatment in the expanded time window of 3 to 4.5 hours, in the setting of ECASS-III eligibility criteria (age, <80 years; no oral anticoagulants regardless of serum coagulation testing, no patients with a history of both diabetes mellitus and a prior stroke, and National Institutes of Health Stroke Scale must be <25). This expanded time window within a population, however, leads to the disappointing finding that this expansion adds very few additional eligible stroke patients. In the Greater Cincinnati/Northern Kentucky population, the combination of the expanded time window and the additional ECASS-III exclusion criteria, would have only led to an additional 0.6% more ischemic stroke patients becoming eligible for rt-PA in 2005. This is related to the bimodal distribution of times that ischemic stroke patients present to medical attention. Only 9% of all stroke patients arrive in the 3- to 8-hour time window. Stroke patients tend to arrive very early or quite late. This finding has also been confirmed in other populations. Furthermore, the Federal Drug Administration denied approval of the expanded time window for the approved uses of rt-PA, which may further minimize the impact of the expanded time window.

In summary, the rate of rt-PA use in ischemic stroke patients remains low in the United States. This is most likely related to eligibility for thrombolytic therapy, especially the very short time window in which it can be given. Unfortunately, expanding the time window by a few hours does not seem to dramatically improve this eligibility. Rigorous study of other exclusion criteria is needed, such as mild stroke severity, as expansion of other criteria has the potential to increase thrombolytic therapy treatment rates dramatically and potentially improve long-term disability for stroke patients. At the hospital level, primary stroke center certification seems to have a powerful and sustained association with higher rates of rt-PA use, and further study of the impact of the newly instituted comprehensive stroke center certification, and advances, such as telemedicine, is needed.

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Figure 2. Recombinant tissue-type plasminogen activator (rt-PA) use rates by quarter, pre, and post primary stroke center (PSC) certification, compared with non–stroke center hospitals during the same timeframe (ranging from FY 2001 to 2010).


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