

# Recombinant Tissue-Type Plasminogen Activator Use for Ischemic Stroke in the United States

## A Doubling of Treatment Rates Over the Course of 5 Years

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**Background and Purpose**—Recombinant tissue-type plasminogen activator (rtPA) is the only approved therapy for acute ischemic stroke (AIS). In 2004, 1.8% to 2.1% of AIS patients in the United States received rtPA. Given incentives from regulatory agencies and payors to increase rtPA use, we hypothesized that rtPA use in the United States would increase from 2005 to 2009.

**Methods**—AIS cases were defined by exclusion of hemorrhagic stroke and transient ischemic attack International Classification of Diseases 9<sup>th</sup> revision codes (430, 431, 432, and 435) from diagnosis-related groups 14, 15, 524, and 559 discharges. Patients receiving thrombolytics were identified using International Classification of Diseases 9<sup>th</sup> revision code 99.10 (Medicare Provider and Analysis Review and Premier databases) and pharmacy billing records (Premier). Change over time and differences between databases were tested using negative binomial regression.

**Results**—Within Medicare Provider and Analysis Review, thrombolytic use increased from 1.1% in 2005 to 3.4% in 2009 ( $P < 0.001$  for trend). Within Premier, thrombolytic use increased from 1.4% in 2005 to 3.7% in 2009 for all cases ( $P < 0.001$ ). Analysis of pharmacy billing records in Premier for 50-mg or 100-mg doses of rtPA showed that 3.4% of AIS cases were treated in 2009. Inclusion of patients with transient ischemic attack or hemorrhagic stroke International Classification of Diseases 9<sup>th</sup> revision codes who received any thrombolytic as “ischemic stroke patients receiving rtPA” changed the rate of thrombolysis to 5.2%.

**Conclusions**—In 2009, 3.4% to 5.2% of AIS patients in the United States received thrombolytics, approximately double the rate of treatment in 2005. Rapid recognition and transport and quick treatment in the emergency department remain goals for further improving treatment rates. (*Stroke*. 2011;42:00-00.)

**Key Words:** acute stroke ■ thrombolysis

Recombinant tissue-type plasminogen activator (rtPA) remains the only Food and Drug Administration-approved therapy for acute ischemic stroke.<sup>1</sup> Only an estimated 1% to 4% of all ischemic stroke patients in the United States receive rtPA.<sup>2-6</sup> Using the Medicare Provider and Analysis Review (MEDPAR) dataset and a private nationwide hospital database that allows cross-referencing to pharmacy coding, we previously reported that the rate of thrombolytic use for ischemic stroke was increasing slightly from 2001 to 2004 at a rate of 0.04% to 0.09% per year. We estimated the rate of rtPA use in the United States to be 1.8% to 2.1% of ischemic stroke patients in 2004.<sup>6</sup> In this report, we present an update on rtPA use for ischemic stroke from 2005 to 2009 in the United States. We hypothesized that rtPA use for ischemic stroke in the United States would increase from 2005 to 2009.

### Materials and Methods

This was a secondary analysis of existing data. Data were extracted from 2 datasets from fiscal year (FY) 2005 to FY2009: the MEDPAR dataset and the Premier Hospital database (Methods Supplement, <http://stroke.ahajournals.org>). We have previously published thrombolytic treatment estimates in the United States from 2001 to 2004 using identical methodology from the same datasets.<sup>6</sup>

Patients potentially eligible for rtPA treatment based on diagnosis were defined as those with visits within diagnosis-related groups (DRG) 14, 15, 524, and 559 (DRG 14, intracranial hemorrhage or stroke with infarct; DRG 15, nonspecific cerebrovascular accident and precerebral occlusion without infarct; DRG 524, transient cerebral ischemia; and DRG 559, acute ischemic stroke with use of a thrombolytic agent) who did not have a TIA or hemorrhagic stroke discharge International Classification of Diseases 9<sup>th</sup> (ICD-9) revision code (430, 431, 432, and 435). Patients receiving thrombolysis were identified by having an ICD-9 code of 99.10, which denotes thrombolytic use. In addition, pharmacy billing codes within the Premier database were searched for all thrombolytics, which in-

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**Table 1. Estimate of Recombinant Tissue-Type Plasminogen Activator Use for Acute Ischemic Stroke (ICD-9 433, 434, 436) From Premier and Medicare Provider and Analysis Review National Databases**

	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009
<b>MEDPAR</b>					
Total no. of ischemic stroke cases DRG 14/15/524/559	254 530	236 258	223 483	217 798	213 888
No. with ICD-9 code 99.10 (%)	2908 (1.1)	4793 (2.0)	5320 (2.4)	6013 (2.8)	7201 (3.4)
<b>Premier Database</b>					
Total no. of ischemic stroke cases, DRG 14/15/524/559, age older than 65 y	37 878	41 622	41 730	42 285	44 259
No. with ICD-9 code 99.10 (%)	459 (1.2)	842 (2.0)	979 (2.3)	1266 (3.0)	1509 (3.4)
No. with pharmacy billing for thrombolytic (%)*	844 (2.2)	1124 (2.7)	1246 (3.0)	1548 (3.7)	1857 (4.2)
Total no. of cases, DRG 14/15/524/559, all ages	55 402	61 168	61 560	62 754	66 080
No. with ICD-9 code 99.10 (%)	774 (1.4)	1417 (2.3)	1628 (2.6)	1944 (3.1)	2418 (3.7)
No. with pharmacy billing for thrombolytic (%)*	1343 (2.4)	1852 (3.0)	2036 (3.3)	2391 (3.8)	2952 (4.5)

DRG indicates diagnosis-related group; FY, fiscal year; ICD-9, International Classification of Diseases 9<sup>th</sup> revision; MEDPAR, Medicare Provider and Analysis Review. \*Including alteplase 100 mg, alteplase 50 mg, alteplase 20 mg, alteplase misc, reteplase, tenecteplase, urokinase, excluding streptokinase, and alteplase 1 mg.

cluded alteplase, reteplase, urokinase, and tenecteplase. Finally, to estimate thrombolytic therapy specific to stroke treatment, the query was limited to alteplase, 50-mg and 100-mg vials, to rule out use for declotting central lines, for example. For FY2005 to FY2009, the total number of cases and the proportion of cases treated with rtPA were estimated for each database. For the Premier database, estimates were based on the entire sample and separately for those aged 65 years or older, so that rates could be compared directly between Premier and MEDPAR.

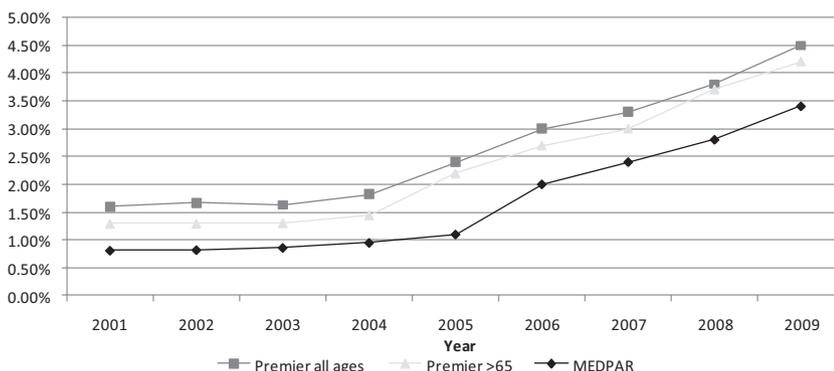
Previously, we found that  $\approx 13\%$  of cases receiving thrombolytics were coded as TIA or hemorrhagic stroke.<sup>6</sup> Therefore, we explored how the estimated rate of thrombolytic usage would be impacted by including patients with a diagnosis code of TIA or hemorrhagic stroke, ie, those within DRG 14, 15, 524, and 559 who received thrombolysis and had either a TIA (435) or a hemorrhagic stroke (430, 431, and 432) ICD-9 code. Ultimately, our summary estimate of rtPA use among AIS patients in the United States was based on the range obtained from pharmacy billing codes within the Premier database.<sup>6</sup> Differences in proportions were tested using the  $\chi^2$  statistic. Change in rates of thrombolytic use over time and differences between databases were tested using negative binomial regression.

## Results

The total number of DRG 14, 15, 524, and 559 admissions contained within each database (excluding hemorrhagic stroke and TIA ICD-9 codes) and the estimated rates of thrombolytic use based on the ICD-9 code 99.10 and pharmacy billing codes are presented in Table 1. The Figure depicts increases in rtPA use in the United States from 2001

through 2009 using pharmacy billing codes (Premier) and ICD-9 codes (MEDPAR). Thrombolytic use was similar in both the MEDPAR and Premier groups during the study period. Using ICD-9 code 99.10 within the MEDPAR database, thrombolytic use increased by 28% per year from 1.1% in FY2005 to 3.4% in FY2009 ( $P < 0.001$  for trend). Using ICD-9 code 99.10 within the Premier database, thrombolytic use increased by 24% per year from 1.4% in FY2005 to 3.7% in FY2009 for all discharged patients ( $P < 0.001$  for trend), and from 1.2% to 3.4% in patients aged older than 65 years ( $P < 0.001$  for trend). Exclusion of patients younger than 65 years in Premier excluded 38% of cases treated with thrombolytics. Consideration of pharmacy billing codes within the Premier database significantly increased the rate of thrombolytic use by 33% compared with use of ICD-9 code 99.10 only for the entire study period ( $P < 0.001$ ). Overall, the rate of thrombolytic use for all patients within Premier increased from 2.4% in FY2005 to 4.5% in FY2009 ( $P < 0.001$  for trend; Table 1).

Patterns of thrombolytic therapy drug utilization within the Premier database for FY2009, the most recent year with complete data available, are presented in Table 2. All thrombolytic use (including such drugs as tenecteplase and urokinase) was substantially higher than the use of Alteplase 50-mg or 100-mg vials. Using the most conservative estimate with only Alteplase 50 mg or 100 mg, the estimated rate of



**Figure.** National estimates of recombinant tissue-type plasminogen activator (rtPA) use in the United States.

**Table 2. Thrombolytic Drug Utilization Stratified by International Classification of Diseases 9<sup>th</sup> Revision Ischemic Versus Nonischemic Coded Cases, Premier Database, Fiscal Year 2009**

Thrombolytic	Ischemic Stroke Cases ICD-9 433, 434, 436	TIA or Hemorrhagic Stroke Cases ICD-9 430, 431, 432, 435
Total discharges	66 080	44 046
Primary or secondary ICD-9 procedure 99.10	2418	283
Billed for thrombolytic (excluding streptokinase)*	2952	538
Alteplase, Activase VL 100 mg	1636	220
Alteplase, Activase VL 50 mg	604	104
Alteplase, Activase VL 20 mg	18	3
Alteplase, Activase VL 1 mg	897	227
Alteplase misc	28	...

ICD-9 indicates International Classification of Diseases 9<sup>th</sup> revision; TIA, transient ischemic attack.

\*For all thrombolytics, including alteplase, reteplase, urokinase, and tenecteplase.

thrombolytic use in 2009 was 3.4%. Within Premier, during 2009 alone we found 283 of 44 046 (0.6%) patients with cases coded as either TIA or hemorrhagic stroke that received some form of thrombolytic, which accounts for 10.5% of total thrombolytic treatments (Table 2). Inclusion of these patients as “ischemic stroke patients receiving rtPA” changed our estimated rate of thrombolytic therapy from 4.5% to 5.2% using pharmacy billing codes.

Within MEDPAR, we found 1008 patients during the 5-year period with cases that were coded as either TIA or hemorrhagic stroke and also coded as receiving thrombolytic therapy (1008/692 480 or 0.15% of total TIA/hemorrhagic stroke claims). The proportion of patients with cases coded as TIA or hemorrhagic stroke and also coded as receiving thrombolytic therapy did not significantly change during the study period (2005: 141/149 189 or 0.1%; 2006: 189/142 664 or 0.1%; 2007: 209/138 138 or 0.2%; 2008: 199/133 002 or 0.1%; 2009: 270/129 487 or 0.2%). In 2009, inclusion of these patients as “ischemic stroke patients receiving rtPA” who had miscodes of TIA or hemorrhagic stroke increased our estimated rate of thrombolytic therapy from 3.4% to 3.8%.

## Discussion

We found that the rate of thrombolytic therapy use among acute ischemic stroke discharges in the United States approximately doubled from 2005 to 2009 (Figure). This is strikingly different from our previous report, which found essentially no difference in rtPA treatment rates between 2001 and 2004 (Figure). This more recent increase in treatment was consistent using either pharmacy billing records or ICD-9 codes to estimate thrombolytic use. We conservatively estimate that 3.4% to 5.2% of ischemic stroke patients in the United States received thrombolytic therapy in 2009, repre-

senting double the 1.8% to 2.1% who received thrombolytics in 2004.<sup>6</sup> The upper limit of our estimate represents any thrombolytic use and includes patients who we believe had cases that were miscoded as TIA or hemorrhagic stroke in the numerator, whereas the lower limit excludes these patients and is limited to Alteplase 50 mg or 100 mg only. It is also possible that cases of “hemorrhagic stroke” coded as receiving rtPA were cases of hemorrhagic conversion of ischemic stroke miscoded as hemorrhagic stroke. However, because of the fact that there is no separate code for hemorrhagic transformation of ischemia, we are unable to isolate these cases. If our estimated treatment rates are extrapolated to the ≈700 000 ischemic strokes in the United States each year,<sup>7</sup> we estimate that 23 800 to 36 000 patients received rtPA in 2009.

A confluence of factors may account for the significantly increased rtPA use for ischemic stroke in the United States. In October 2005, a new DRG was approved by the United States Centers for Medicare and Medicaid Services. DRG 559 (acute ischemic stroke with use of a thrombolytic agent) increased the payment to hospitals for acute stroke patients to \$11 500 compared to \$6400 for DRG 14 (intracranial hemorrhage or stroke with infarct) and \$4900 for DRG 15 (nonspecific cerebrovascular accident or precerebral occlusion without infarct). This financial incentive, along with the establishment of formal certification of primary stroke centers by the Joint Commission, the various statewide initiatives to standardize acute stroke care, and the aggressive Get With The Guidelines campaign by the American Heart Association, may have contributed to the increased treatment rates. Notably, the increase in treatment rates began in FY2005, before approval of DRG 559, suggesting that higher reimbursement was not the primary factor driving increased treatment rates.

Limitations of our study include the use of administrative datasets to estimate thrombolytic use. Both the Premier and MEDPAR databases use DRG coding, which is determined by billing personnel and thus is prone to the inherent errors of not using medical personnel for chart review. However, no other practical means of obtaining nationwide estimates of thrombolytic for ischemic stroke use are available. Single centers that report exceptionally high treatment rates likely have a referral bias, and the usually more accurate population-based studies likely reflect local practices and are often not generalizable to the nation as a whole. Thus, despite their inherent limitations, nationwide administrative databases remain a useful tool for estimating trends in national practice. Inclusion of TIA and hemorrhagic stroke patients in the upper limits of our estimates may have significantly overestimated rtPA use. In our previous report, we examined patients with the TIA or hemorrhagic stroke discharge diagnoses to assess whether alternative diagnoses (eg, acute myocardial infarction, pulmonary embolus, and others) may have accounted for thrombolytic therapy. None of the patients had alternative diagnoses to account for thrombolytic use.<sup>6</sup> Another limitation is that we are not able to distinguish the mode of delivery for the rtPA. We also were unable to ascertain appropriateness of patient selection for treatment. Last, we did not examine the potential impact of payor source and socioeconomic factors on the likelihood of rtPA treatment.

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### Disclosures

Opeolu Adeoye is a member of the Genentech Speakers' Bureau (modest). Dawn Kleindorfer is a member of the Genentech Speakers Bureau (modest).

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## FINAL PROOF

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## SUPPLEMENTAL MATERIAL

MEDPAR is a claims-based dataset that contains fee-for-service Medicare-eligible inpatient hospital discharge in the United States. Nearly all US residents with age greater than or equal to 65 years old are eligible for Medicare, as are all patients with end-stage renal disease or solid organ transplant, and all patients that have been totally disabled for more than 24 months. Medicare beneficiaries in managed care plans (roughly 15% of Medicare enrollment in 2005) are not captured in the MEDPAR data. Hospitalizations are categorized by the Diagnosis Related Group (DRG), which describes the primary reason for admission as determined by the billing personnel. The DRG is based on the primary and secondary International Classification of Diseases, version 9 (ICD-9) codes, which identifies diagnoses and procedures for patients, both old and new. Reimbursement to hospitals is based primarily on the DRG weights.

The Premier Hospital dataset is a privately-owned dataset that contains data from 506 hospitals across the United States. Premier is currently partnered with the FDA to study drug utilization in hospitalized patients. Therefore, all billing and administrative coding information can be cross-linked to hospital pharmacy billing records. The Premier database represents approximately 1 in 5 hospital discharges in the United States each year, and preliminary comparisons between participating Premier hospitals and patient characteristics and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) proved to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis, and primary procedure groups.<sup>1</sup> All hospitalizations are entered into the database for all payors, not

just Medicare. While the DRG definitions changed in 2008 to the MS-DRGs, for consistency in comparison to previous years, we used the DRG definitions for this analysis. This was possible because the Centers for Medicare and Medicaid Services (CMS) maintained DRG categorization on the MEDPAR file, and the Premier database also maintained DRG categorization.

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