National US Estimates of Recombinant Tissue Plasminogen Activator Use
ICD-9 Codes Substantially Underestimate

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**Background and Purpose**—Current US estimates of recombinant tissue plasminogen activator (rt-PA) use have been based either on extrapolation of regional studies or on administrative database estimates, both of which may have inherent biases. We sought to compare the utilization of rt-PA in acute ischemic stroke in the MEDPAR database to another national hospital database with drug utilization information.

**Methods**—Cases were defined as DRG 14, 15, and 524 and ICD-9 code 99.1, which indicates cerebral thrombolysis, for fiscal year 2001 to 2004. Additionally, the Premier database was queried for rt-PA utilization documented in pharmacy records in those patients admitted for stroke. Change over time and difference between databases were tested using Poisson regression.

**Results**—When comparing databases, rt-PA use, as identified by ICD-9 code 99.1, was only documented in 0.95% of stroke cases in 2004 in MEDPAR, and 1.2% in the Premier database, which slightly increased by 0.04% to 0.09% over time. Analysis of pharmacy billing records increased the estimate to 1.82%. Exclusion of cases younger than 65 years excluded 43% of cases treated with rt-PA. In 2004, 12.7% of cases receiving thrombolytic had either a TIA or a hemorrhagic stroke ICD-9 code.

**Conclusions**—We estimate the rate of rt-PA use in the United States to be 1.8% to 2.1% of ischemic stroke patients. The rate of thrombolytic use for ischemic stroke was slightly increasing between 2001 and 2004 at a rate of 0.04% to 0.09% per year. A significant proportion of patients treated with rt-PA are likely miscoded as either TIA or hemorrhagic stroke. We conservatively estimate that 10,800 to 12,600 patients received rt-PA in 2004. *(Stroke. 2008;39:924-928.)*

**Key Words:** acute stroke treatment ■ epidemiology ■ tPA
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 6 hospitalizations 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.12 All hospitalizations are entered into the database for all payors, not just Medicare.

Cases potentially eligible for rt-PA treatment based on diagnosis were defined as those patient visits with a hospital discharge code of 433, 434, or 436, within DRG 14 and 15 (DRG 14: intracranial hemorrhage or stroke with infarct and DRG 15: nonspecific CVA and cerebrovascular accident), and DRG 524 (transient cerebral ischemia). DRG 524 was created in 2003 and aims to identify TIA as distinct from DRGs 14 and 15. Those patient visits with hemorrhagic stroke or TIA ICD-9 codes (430, 431, and 432) were excluded. Cases receiving thrombolysis were identified by having an ICD-9 code of 991, which denotes thrombolytic use. In addition, pharmacy billing codes within the Premier database were searched for all thrombolytics, which included 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 fiscal years (FY) 2001 to 2004, the total number of cases, and the proportion of cases treated with rt-PA, was estimated for each database. For the Premier database, estimates were based on the entire sample, and separately for those aged ≥65 years so that rates could be compared directly between Premier and MEDPAR.

A sensitivity analysis was conducted to explore how the estimated rate of thrombolytic usage would be impacted by including patients coded with a diagnosis of TIA or hemorrhagic stroke, ie, those cases with DRG 14, 15, and 524 that received thrombolysis and had either a TIA (435) or a hemorrhagic stroke (430, 431, and 432) ICD-9 code. Diagnoses that might have warranted thrombolytic therapy were evaluated in patients with these diagnoses, including acute myocardial infarction, acute pulmonary embolus, acute thrombosis in extremity, and dialysis catheter declotting (ICD-9 410.x1, 996.7x, 444.22, 415.19).

Differences in proportions were tested using the Chi-square statistic. To test for trends, the Chi-square was partitioned into that attributable to regression over time and that attributable to other sources of heterogeneity.13

### Results

The total number of DRG 14, 15, and 524 admissions contained within each database are presented in Table 1 (excluding hemorrhagic stroke and TIA ICD-9 codes), as well as the estimated rates of thrombolytic use based on the ICD-9 code 99.10. For each year, the rate of thrombolytic use tended to be lower when estimated using the MEDPAR database than when using the comparable subset of the Premier database (patients aged greater than or equal to 65), but this was only significant in 2002 (P=0.029). Within the Premier database, consideration of pharmacy billing codes also increased the rate of thrombolytic use, to a maximum of 1.82% in 2004. Exclusion of patients younger than 65 missed 43% of thrombolytic treatments in FY 2004.

Within MEDPAR, the rate of thrombolytic use increased by 0.04% per year (P<0.001). Within the Premier database, when considering only ICD-9 and DRG codes and patients aged ≥65 years, the rate increased by 0.08% per year (P=0.003). When considering pharmacy billing codes in those aged ≥65 years, the rate increased by 0.09% per year (P=0.006). A similar rate was observed when including all patients (P=0.002).

Patterns of thrombolytic therapy drug utilization within the Premier database 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. However, even using the most conservative estimate with only Alteplase 50 mg or 100 mg, the estimated rate

| Table 1. Estimation of Thrombolytic Use for Acute Ischemic Stroke (ICD-9 433, 434, 436), Premier and MEDPAR National Databases |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
|                             | FY 2001        | FY 2002        | FY 2003        | FY 2004        |
| MedPAR                      |                |                |                |                |
| Total number of ischemic stroke cases DRGs 14/15/524 | 291 022        | 284 551        | 274 124        | 263 328        |
| Number with ICD-9 code 99.10 (%) | 2362 (0.81%)   | 2344 (0.82%)   | 2344 (0.86%)   | 2502 (0.95%)   |
| Premier DATABASE (sample)   |                |                |                |                |
| Total number of ischemic stroke cases, DRGs 14/15/524, age >65yo | 40 301         | 43 435         | 42 130         | 39 971         |
| Number with ICD-9 code 99.10 (%) | 354 (0.88%)    | 403 (0.93%)    | 386 (0.92%)    | 421 (1.05%)    |
| Number with pharmacy billing for thrombolytic (%)* | 510 (1.30%)    | 563 (1.30%)    | 553 (1.31%)    | 579 (1.45%)    |
| Total number of cases, DRG 14/15/524, all ages | 54 772         | 59 893         | 58 570         | 56 129         |
| Number with ICD-9 code 99.1 (%) | 572 (1.04%)    | 632 (1.06%)    | 616 (1.05%)    | 646 (1.20%)    |
| Number with pharmacy billing for thrombolytic (%)* | 875 (1.60%)    | 1002 (1.67%)   | 956 (1.63%)    | 1021 (1.82%)   |

*Including Alteplase 100 mg, Alteplase 50 mg, Alteplase 20 mg, Alteplase misc, retevase, tenecteplase, urokinase, excluding streptokinase and Alteplase 1 mg.
of use in 2004 was still substantially higher than that based on the ICD-9 code 99.1: 901 treatments of alteplase 50 mg or 100 mg versus 646 treatments based on ICD-9 codes (28% missed).

Within MEDPAR, we found 681 patients during the 4-year period that were coded as either TIA or hemorrhagic stroke and also coded as receiving thrombolytic therapy (681/1 113 025 claims total). Of these 681, 34% were given TIA codes, 56% were given intracerebral hemorrhage codes, and 10% were given either subarachnoid hemorrhage or other hemorrhagic stroke codes. The sensitivity analysis found that inclusion of these patients as “ischemic stroke patients receiving rt-pa” increased our estimated rate of thrombolytic therapy to 2.1%. None of these patients were given ICD-9 codes for other conditions that might warrant thrombolysis (such as pulmonary embolus, acute MI, etc).

Within Premier, during 2004 alone we found 130 of 37 144 cases coded as either TIA or hemorrhagic stroke that received some form of thrombolytic, which accounts for 12.7% of total thrombolytic treatments (Table 2). Four of these patients had a “complications of dialysis catheter” diagnosis code that might have referred to thrombolytic therapy to recanalize occluded dialysis shunts, but none had codes for other acute disease processes that might require thrombolysis.

**Discussion**

We found that the rate of thrombolytic use for ischemic stroke in the United States slightly increased between 2001 and 2004, which was statistically significant, no matter how the treatment rates were assessed; however, the increases in treatment rates of 0.04 to 0.09% per year were disappointingly small. We also discovered that by analyzing pharmacy billing records, we were able to detect 25% to 30% more patients treated with thrombolytic than by using administrative ICD-9 codes to estimate rates of use. Finally, exclusion of younger patients from administrative databases risks miss-
ing a substantial portion of rt-PA–treated ischemic stroke patients, in our study the proportion was up to 43%.

We also unexpectedly found that 12.7% of patients that received thrombolytic therapy for ischemic stroke were likely miscoded as hemorrhagic stroke or TIA. Although we cannot be certain that the thrombolytic was not given for another reason, such as an intracranial bleed after receiving thrombolytics for myocardial infarction, the lack of any other diagnostic coding for these other acute vascular thromboses suggests that the lytic was given primarily for ischemic stroke symptoms. Patients coded with hemorrhagic stroke codes may represent hemorrhagic transformation after receiving lytics, as we suspect the distinction between “hemorrhagic transformation” and “primary intracerebral hemorrhage” were not well understood by administrative billing staff. Future estimations of hemorrhagic transformation rates using administrative data would be extremely difficult without detailed record review. For TIA, we note that by excluding those patients labeled as “TIA” by billing administrators, we are likely excluding those patients with the best clinical response to the medication. However, including all TIAs in the denominator for rt-PA utilization, when resolving symptoms is a contraindication to rt-PA use, does not seem reasonable. Retrospective analyses of TIA need to examine DRGs 14, 15, and 524, because TIA was included in DRG 14 and 15 until 2003.

Our best US national estimate of rt-PA use for ischemic stroke is 1.8 to 2.1% in 2004. The upper limit includes those patients that we believe were miscoded ischemic stroke patients in the numerator, whereas the lower limit excludes them. If these estimates are extrapolated to current national estimates of stroke incidence of about 600,000 ischemic strokes in the United States each year, we conservatively estimate that 10,800 to 12,600 patients received rt-PA in 2004.

Limitations of our analysis include the use of administrative databases for rt-PA use estimates. Both the Premier and MEDPAR databases are based on DRG coding, which is determined by billing personnel, and not medical personnel chart review. We note that there is no other way to obtain national level estimates of use, and regional estimates are often subject to referral biases. Another limitation is that we are not able to distinguish the mode of delivery for the rt-PA. The ICD-9 code 99.1 likely is mostly intravenous rt-PA, but may include intraarterial as well. There is a slight difference in the payor mix between the MEDPAR and Premier databases, as approximately 15% of Medicare beneficiaries with managed care plans were excluded from MEDPAR, whereas all payors were included in Premier. However, the impact of patient insurance status on rates of tpa use is unknown, further studies should evaluate socioeconomic factors in rt-pa use for ischemic stroke.

The recent approval of the new DRG 559 in October of 2005 for acute stroke patients treated with rt-PA in October of 2005 by CMS increased the payment to hospitals for acute stroke patients by an average of $6700 to more than $11,500 (Figure). A recent study has confirmed that the new DRG significantly improves the cost-to-reimbursement ratio at a hospital in Scottsdale, Arizona, for patients treated with rt-PA. The institution of the new DRG, the establishment of formal primary stroke centers, and the various state-wide initiatives to standardize acute stroke care may lead to increased rt-PA use over time. Artifactual increases may also occur as billing personnel become more aware of the rt-PA treatment codes now linked to increased hospital reimbursement. However, we are hopeful that the increased reimbursement will cover the hospital costs for these sicker, resource needy patients. We also hope that it will stimulate the growth of organized stroke systems of care, and eventually improve patient outcome.
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Disclosures

None.

References

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