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Use of intravenous tissue plasminogen activator and hospital costs for patients with acute ischaemic stroke aged 18–64 years in the USA

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ABSTRACT

Introduction: Intravenous tissue plasminogen activator (IV tPA) is a globally recommended treatment for patients with acute ischaemic stroke. We examined IV tPA use among patients aged 18–64 years with a primary diagnosis of acute ischaemic stroke in the USA and inpatient costs per hospitalisation by IV tPA use status among these patients.

Methods: Using the 2010–2013 MarketScan Commercial Claims and Encounters Inpatient Data, we identified 39 149 hospitalisations with a primary diagnosis of acute ischaemic stroke. We verified those with and without IV tPA by ICD-9 procedure code 99.10. We estimated trends in IV tPA use by applying logistic regression. The average inpatient costs per acute ischaemic stroke hospitalisation were assessed for subpopulations. We examined costs per acute ischaemic stroke hospitalisation using multivariate regression models controlling for IV tPA status, age, gender, urbanisation, geographic region, Charlson comorbidity index, length of hospital stays (LOS) and discharge status.

Results: 2546 hospitalisations (6.5%) used IV tPA. IV tPA use increased over time (2010 vs 2013; OR 1.50). Average inpatient costs per acute ischaemic stroke hospitalisation were $20 331 ($31 369 for the IV tPA group, $19 563 for the non-tPA group). From multivariate analyses, higher costs per acute ischaemic stroke hospitalisation were associated with longer LOS, non-home discharge destination, and IV tPA use, which might be correlated with severity of stroke.

Conclusions: Findings suggest that IV tPA use has increased in recent years while the inpatient costs per acute ischaemic stroke hospitalisation using IV tPA are substantial. Those findings are useful in better understanding the overall economic burden of stroke, short-term cost implications of using IV tPA, and for estimating the accurate cost-effectiveness of stroke treatments.

INTRODUCTION

Intravenous (IV) infusion of tissue plasminogen activator (tPA) is the only US Food and Drug Administration (FDA) approved IV thrombolytic for acute ischaemic stroke.[1] After the FDA approval in 1996, the American Heart Association/American Stroke Association (AHA/ASA) recommended IV thrombolysis with tPA for patients with acute ischaemic stroke who are eligible to be treated within 0–3 h after symptom onset and recently expanded the recommendation to use IV tPA for selected patients within 3–4.5 h after the onset of acute ischaemic stroke.[1–3] Other organisations have similarly recommended treatment within 0–4.5 h after acute ischaemic stroke onset.[4–6]

The recommendations were based on a strong body of clinical evidence from several trials, including the National Institute of Neurological Disorders and Stroke tPA trial, Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke trial, Stroke in Thrombolysis Study, and the European Cooperative Acute Stroke Study I, II and III.[7–12] These trials confirmed that the use of IV tPA within 0–4.5 h after the onset of stroke could be used safely and improved clinical outcomes 3 months post-stroke.

Although some studies examined inpatient costs of stroke by type of stroke, diagnosis status, age group and discharge destination,[13 14] no study has examined the inpatient costs for acute ischaemic stroke by IV tPA status, especially for patients younger than 65 years of age. The purpose of this study is to estimate inpatient costs per acute ischaemic stroke hospitalisation from the healthcare payers' perspective by IV tPA use status and patient characteristics, and to examine sociodemographic factors affecting IV tPA use to identify characteristics of those who have limited access to IV tPA.

METHODS

We identified all inpatient hospitalisations with a primary diagnosis of acute ischaemic

stroke (International Classification of Diseases, Ninth Revision, Clinical Modifications (ICD-9-CM) diagnosis codes 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 436) from the 2010–2013 MarketScan Commercial Claims and Encounters Inpatient Database. In each year, the data contain several million individuals, including employees, their spouses and dependants, covered by employer-sponsored private health insurance.[15] The database has been used to estimate hospitalisation costs for various health conditions.[14 15] Owing to a relatively low prevalence of acute ischaemic stroke in adults younger than 65 years of age and a markedly low level of IV tPA use among those who have acute ischaemic stroke, we pooled 4 years MarketScan data to increase our sample size for analyses.

In the selection process of the study sample (n=60 417, figure 1), we excluded: (1) patients with repeat hospitalisations with a primary diagnosis of acute ischaemic stroke during the study period because patients with a prior stroke within 3 months are not recommended for IV tPA[1] and patients with repeated hospitalisations due to stroke may not be typical patients and require intensive care; (2) patients with missing variables of interest such as residence region or discharge destination, main independent variables in our study, and enrollee ID, which was used to define repeated acute ischaemic stroke hospitalisations during the study period; (3) patients younger than 18 or older than 64 years of age because the data mainly covered patients younger than 64 years, and patients younger than 18 years are not recommended for IV tPA[1]; (4) hospitalisations associated with a capitated health insurance plan because total payment does not reflect the medical services provided for each health condition; (5) hospitalisations with intra-arterial tPA by using ICD-9-CM procedure code 99.10 (injection or infusion of thrombolytic agent) and 39.74 (endovascular removal of obstruction from head and neck vessels) and (6) hospitalisations with a cost below the 1st or above the 99th centile to reduce the influence of extreme values on the cost estimates.

Hospitalisations associated with IV tPA were identified by using ICD-9-CM procedure code 99.10. Our main outcome measure was the total hospital cost per hospitalisation from the healthcare payers' perspective, which

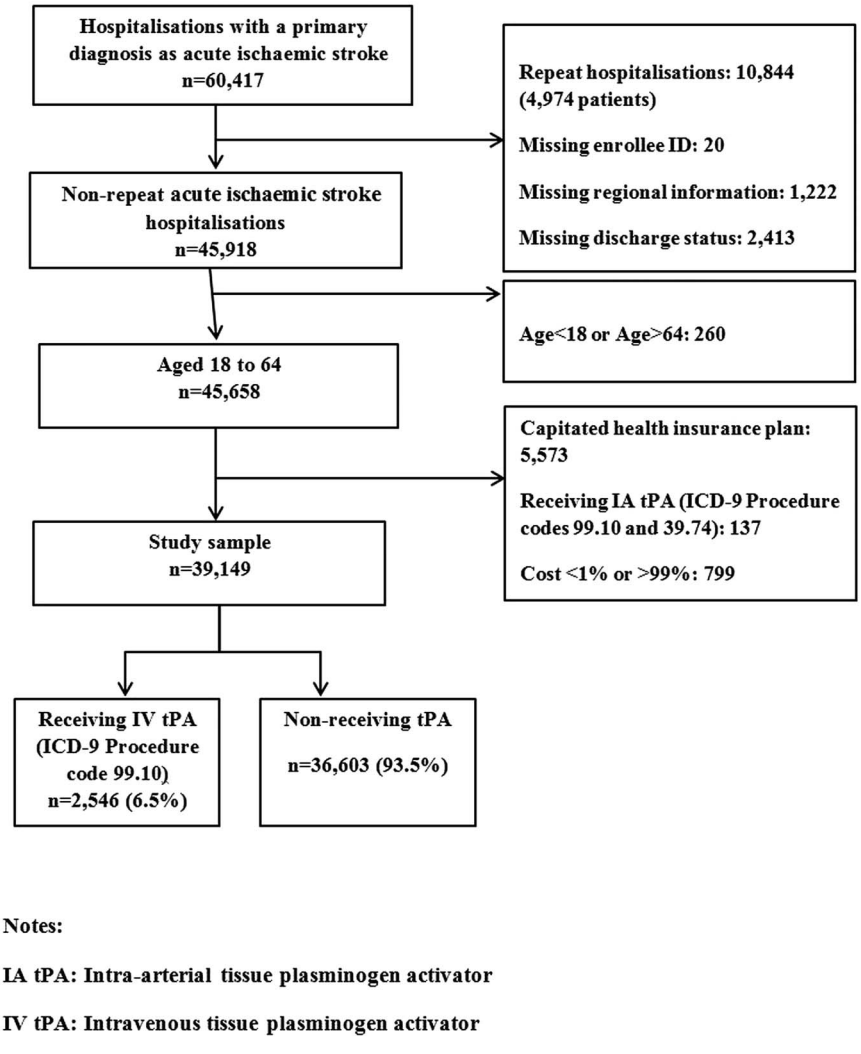

Figure 1 Study population selection process from the 2010–2013 MarketScan Commercial Claims and Encounters Inpatient Database. ICD, International Classification of Diseases; IV tPA, intravenous tissue plasminogen activator.

was the sum of payments received by all providers associated with a hospitalisation. All costs were inflated to 2013 US dollars using the Consumer Price Index (CPI) in Medical Care from the Bureau of Labor Statistics.[16]

First, we examined factors affecting IV tPA use, including age, gender, urbanisation, region, Charlson comorbidity index (CCI), and year of hospitalisation, by using logistic regression. Next, we examined average inpatient cost per hospitalisation associated with acute ischaemic stroke. We conducted univariate comparisons of the average inpatient cost per hospitalisation for the IV tPA and the non-tPA groups using t tests. Comparisons were conducted for each sociodemographic group as well as for all patients. Last, we examined factors affecting hospitalisation cost associated with acute ischaemic stroke using ordinary least squares. IV tPA use, age, gender, urbanisation, region, length of hospital stays (LOS), CCI, discharge destination and year of hospitalisation were used as independent variables. The CCI was derived by using secondary diagnosis codes of up to 18 different conditions, which partly captured the severity of overall health.[17] We further examined the impact factors on the hospitalisation cost by LOS, which could be highly correlated with severity of stroke. We used three categories of LOS (<2, 2–4 and 5 or more days) for analyses. All statistical analyses were performed using SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

Among the 39 149 hospitalisations during the study period, 2546 hospitalisations received IV tPA (6.5%). This IV tPA group differed significantly from the non-tPA group (n=36 603) across most sociodemographic characteristics (age, urbanisation, region, CCI, LOS and discharge destination) (table 1). Those who received IV tPA were younger, more likely to live in an

Table 1 Sample characteristics of patients aged 18–64 years with a primary diagnosis of acute ischaemic stroke by intravenous tissue plasminogen activator (IV tPA) therapy status (%), 2010–2013 MarketScan Commercial Claim Inpatient Database

		tPA status		
	Total (N=39 149)	Non-tPA group (N=36 603)	IV tPA group (N=2546)	p Value
Age, years				
18–44	12.7	12.6	14.7	<0.01
45–54	28.6	28.7	28.4	0.81
55–64	58.6	58.7	56.8	0.06
Average (years)	54.3	54.3	53.8	<0.01
Gender				
Female	41.6	41.6	41.6	0.99
Male	58.4	58.4	58.4	0.99
Metropolitan statistical area				
No	18.0	18.4	12.5	<0.01
Yes	82.0	81.6	87.5	<0.01
Region				
West	12.4	12.2	14.4	<0.01
Northeast	17.3	17.4	16.7	0.35
North central	27.5	27.5	28.0	0.57
South	42.8	43.0	41.0	0.05
Charlson comorbidity index				
0–2	33.8	33.7	34.6	0.39
3–4	44.7	44.4	49.2	<0.01
5 or higher	21.5	21.9	16.2	<0.01
Average (index)	3.25	3.26	3.14	<0.01
Length of stay, days				
<2	16.6	17.2	7.5	<0.01
2–4	55.4	55.4	56.3	0.36
≥5	28.0	27.4	36.2	<0.01
Average (days)	4.1	4.1	4.6	<0.01
Discharge destination				
Home	74.9	75.5	67.2	<0.01
Rehabilitation facility	14.0	13.5	21.1	<0.01
Short-term hospital/SNF/other*	9.0	9.0	8.4	0.29
Expired	2.1	2.0	3.3	<0.01

*SNF stands for skilled-nursing facility. Other discharge status includes transferring to a federal hospital, critical access hospital, hospice, long-term care facility, and all other discharge status.

urban area, more likely to be discharged to a rehabilitation facility, less likely to be discharged to home, and had a longer LOS than those who did not receive IV tPA. Those who did not receive IV tPA had a higher CCI than those receiving IV tPA.

Patients aged 45–64 years, living in a rural area, or who had a higher CCI were less likely to receive IV tPA (table 2). Those who lived in the Northeast or South regions (compared with those who lived in the West) were also less likely to receive IV tPA (OR 0.82 (95% CI 0.71 to 0.94) and 0.86 (0.76 to 0.97), respectively). Use of IV tPA had increased over time (year 2011 vs 2010; OR 1.21 (95% CI 1.07 to 1.37); year 2012 vs 2010; OR 1.26 (95% CI 1.12 to 1.42); year 2013 vs 2010; OR 1.50 (95% CI 1.33 to 1.70)).

Across all hospitalisations, the average inpatient cost per hospitalisation with a primary diagnosis of acute ischaemic stroke was $20 331 (table 3). Cost for the non-tPA group averaged $19 563 per hospitalisation while the cost averaged $31 369 per hospitalisation among those who received IV tPA. The mean difference in inpatient cost per hospitalisation between the IV tPA and the non-tPA groups was $11 806 and increased with age and LOS.

LOS, discharge destination and use of IV tPA were the three most significant factors in our analysis associated with inpatient costs per acute ischaemic stroke hospitalisation (table 4). LOS of 5 or more days were associated with an additional $18 822 per hospitalisation compared to LOS of <2 days. Hospitalisations with a primary diagnosis of acute ischaemic stroke that resulted in a non-home discharge destination were found to have a significantly higher hospital cost compared to those with a home discharge destination ($5002 for discharging to a rehabilitation facility; $6407 for discharging to a short-term hospital, skilled-nursing facilities, or other non-home facilities; $19 438 for expired). Use of IV tPA was associated with increased hospital costs of $9195 (p value <0.01, (95% CI $8546 to $9844)) per acute ischaemic stroke hospitalisation. The average increase in the inpatient cost per hospitalisation associated with IV tPA was $7453 (95% CI $6328 to $8577) for LOS of <2 days; $9386 (95% CI $8842 to $9929)) for LOS of 2–4 days; and $9409 (95% CI $7656 to $11 163) for LOS of 5 or more days.

Table 2 OR of receiving intravenous tissue plasminogen activator (IV tPA) for patients aged 18–64 years with a primary diagnosis of acute ischaemic stroke, 2010–2013 MarketScan Commercial Claim Inpatient Database (n=39 149)

	OR	95% CI
Age, years		
18–44	1.00	
45–54	0.87*	(0.76 to 0.99)
55–64	0.86*	(0.76 to 0.97)
Gender		
Female	1.00	
Male	1.01	(0.93 to 1.10)
Metropolitan statistical area		
No	1.00	
Yes	1.58**	(1.40 to 1.78)
Region		
West	1.00	
Northeast	0.82**	(0.71 to 0.94)
North central	0.90	(0.79 to 1.03)
South	0.86*	(0.76 to 0.97)
Charlson comorbidity index		
0–2	1.00	
3–4	1.08	(0.99 to 1.18)
5 or higher	0.72**	(0.64 to 0.82)
Year		
2010	1.00	
2011	1.21**	(1.07 to 1.37)
2012	1.26**	(1.12 to 1.42)
2013	1.50**	(1.33 to 1.70)

*Statistical significance at the p<0.05.
**Statistical significance at p<0.01.

DISCUSSION

In this study, we found that estimated hospitalisation costs for patients with acute ischaemic stroke were substantial. Average inpatient cost per hospitalisation of acute ischaemic stroke was $20 331. The use of IV tPA was significantly associated with age, metropolitan statistical area, region, CCI and year of hospitalisation. Owing to known contraindications for the use of IV tPA, the finding that those with a high CCI group were less likely to receive IV tPA than the low CCI group was expected.[1] Higher use of IV tPA among those who lived in a metropolitan statistical area is most likely related to increased timely access to a stroke centre.

We also found that IV tPA was one of the factors which affected hospitalisation costs of acute ischaemic stroke. The significant difference in hospitalisation costs between the IV tPA and the non-tPA groups in the current study was consistent with previous estimates in cost-effectiveness of IV tPA studies from the USA. A previous study by Fagan *et al*[18] estimated that the hospitalisation cost among the IV tPA group was $1747 higher than the cost for the non-tPA group in 1996 US dollars. A recent study estimated that the use of IV tPA increased the cost per hospitalisation by $4423 ($2750 for tPA cost; $467 for consult physician cost; and $1206 for intensive care unit (ICU) cost) than the non-tPA group, using the 2010 hospital billing data from South Carolina.[19] Also, a third study by Boudreau *et al*[20] showed that the estimated cost associated with IV tPA therapy, including drug, administration and monitoring costs, was $6083 in 2011 US dollars by using Medicare reimbursement rates while this study's estimates are IV tPA associated costs including possible complications.

Another cost-effectiveness study by Tung *et al*[21] used the hospitalisation costs with and without IV tPA from nationwide estimates of Medicare costs with a retrospective approach from a study by Young *et al*,[22] which was

Table 3 Average hospital costs ($2013) for patients aged 18–64 years with a primary diagnosis of acute ischaemic stroke by intravenous tissue plasminogen activator (IV tPA) status, 2010–2013 MarketScan Commercial Claim Inpatient Database

		IV tPA status		
	Total (N=39 149)	Non-tPA group (A) (N=36 603)	IV tPA group (B) (N=2546)	Differences (B–A) (p Value)
Total	20 331	19 563	31 369	11 806 (<0.01)
Age, years				
18–44	22 316	21 581	31 347	9767 (<0.01)
45–54	20 165	19 456	30 428	10 972 (<0.01)
55–64	19 981	19 182	31 845	12 663 (<0.01)
Gender				
Female	20 210	19 450	31 137	11 687 (<0.01)
Male	20 417	19 644	31 534	11 891 (<0.01)
Metropolitan statistical area				
No	18 683	18 091	31 220	13 129 (<0.01)
Yes	20 693	19 895	31 390	11 495 (<0.01)
Region				
West	24 419	23 572	34 735	11 164 (<0.01)
Northeast	21 456	20 753	32 005	11 252 (<0.01)
North central	19 770	19 048	29 949	10 901 (<0.01)
South	19 056	18 270	30 895	12 625 (<0.01)
Charlson comorbidity index				
0–2	17 833	17 119	27 842	10 723 (<0.01)
3–4	21 293	20 384	33 063	12 679 (<0.01)
5 or higher	22 253	21 661	33 745	12 084 (<0.01)
Length of stay, days				
<2	11 882	11 638	19 934	8296 (<0.01)
2–4	16 218	15 560	25 525	9965 (<0.01)
≥5	33 469	32 611	42 822	10 211 (<0.01)
Discharge destination				
Home	17 065	16 440	27 164	10 724 (<0.01)
Rehabilitation facility	28 766	27 618	39 330	11 711 (<0.01)
Short-term hospital/SNF/other*	29 710	28 939	41 613	12 674 (<0.01)
Expired	40 574	40 633	40 055	−578 (0.87)

All numbers except p values are 2012 US dollar.
*SNF stands for skilled-nursing facility. Other discharge status includes transferring to federal hospital, critical access hospital, hospice, long-term care facility and all other discharge status.

similar to the approach in our study, for their model. The adopted hospital costs associated with IV tPA was $9417 in 2010 US dollars.[21] The costs are closely akin to our results but are far different from the cost estimate from Boudreau *et al*.[20] The higher cost of the IV tPA group in our study and in the study by Tung *et al*[21] might be due to costs associated with IV tPA other than the drug, administration and ICU monitoring costs.

When we compared inpatient cost estimates from our study with the cost estimates from the previous study by Fagan *et al*,[18] we found a large increase in the inpatient costs per acute ischaemic stroke hospitalisations, especially among those who received IV tPA therapy. The short-term hospitalisation cost for the IV tPA group increased from $16 671 in 1996 US dollars[18] to $31 369 (table 3) in 2013 US dollars. The cost for hospitalisations not using tPA also increased ($14 923 in 1996 US dollars[18] vs $19 563 (table 3) in 2013 US dollars), but the hospital cost increase among hospitalisations not using tPA was much smaller than the increase among hospitalisations using IV tPA (non-tPA vs IV tPA; $4640 vs $14 698). The short-term hospital cost increased by 31% and by 88% among the non-tPA group and IV tPA group, respectively, while there was an 86% increase in the average price of medical care between 1996 and 2013 in the USA (CPI in Medical Care 228.2 in 1996 vs 425.1 in 2012).[16]

This asymmetric increase in hospital costs could be caused by multiple factors. First, the drug price of tPA has increased over time. The wholesale price of tPA was $2750 in 1996 US dollars[18] and was $6525 in 2013 US dollars.[20] Although tPA drug cost paid by hospitals could be lower than the wholesale price, the wholesale price can serve as an indicator of the price paid by hospitals. Next, despite decreasing LOS for both the IV tPA and the non-tPA groups over time, LOS of the non-tPA group decreased more than the LOS of the IV tPA group during the past 20 years. Acute ischaemic stroke hospitalisations not using tPA reported average LOS of 12.4 days in 1995[18] and 4.1 days (table 1) during 2010–2013, while acute ischaemic stroke hospitalisations using IV tPA reported average LOS of 10.9 days in 1995[18] and

Table 4 Marginal effect of receiving intravenous tissue plasminogen activator (IV tPA) on hospital costs ($2013) for patients aged 18–64 years with a primary diagnosis of acute ischaemic stroke, 2010–2013 MarketScan Commercial Claim Inpatient Database

		Length of stay		
	Total (N=39 149)	<2 days (N=6489)	2–4 days (N=21 696)	≥5 days (N=10 964)
tPA				
Non-tPA group	Ref.	Ref.	Ref.	Ref.
IV tPA group	9195**	7453**	9386**	9409**
Age, years				
18–44	Ref.	Ref.	Ref.	Ref.
45–54	−1860**	−1354**	−1078**	−3722**
55–64	−2555**	−1817**	−1610**	−4948**
Gender				
Female	Ref.	Ref.	Ref.	Ref.
Male	724**	140	279*	1934**
Metropolitan statistical area				
No	Ref.	Ref.	Ref.	Ref.
Yes	1186**	382	630**	2982**
Region				
West	Ref.	Ref.	Ref.	Ref.
Northeast	−3894**	1409**	−2523**	−10 853 **
North central	−4737**	−67	−3660**	−11 129 **
South	−5879**	−461	−4611**	−12 945 **
Charlson comorbidity index				
0–2	Ref.	Ref.	Ref.	Ref.
3–4	1140**	511*	927**	2045**
5 or higher	739**	782**	939**	933
Length of Stay, days				
<2	Ref.			
2–4	3858**	–	–	–
≥5	18 822 **			
Discharge destination				
Home	Ref.	Ref.	Ref.	Ref.
Rehabilitation facility	5002**	8013**	4171**	6642**
Short-term hospital/SNF/other‡	6407**	873*	2120**	10 942 **
Expired	19 438 **	11 937 **	19 058 **	23 561 **
Year				
2010	Ref.	Ref.	Ref.	Ref.
2011	502*	653*	608**	77
2012	762**	934**	734**	396
2013	1523**	1507**	1345**	1659*
Constant	14 420 **	11 123 **	17 507 **	37 332 **

*Statistical significance at p<0.05
**Statistical significance at p<0.01.
‡SNF stands for skilled-nursing facilities. Other discharge status includes transferring to federal hospital, critical access hospital, hospice, long-term care facility, and all other discharge status.

4.6 days (table 1) during 2010–2013. Lastly, the in-hospital care after IV tPA most likely increases the hospital cost. After receiving IV tPA, most patients are monitored in an ICU or specialised stroke unit which adds to the cost.

Although this study and the existing literature consistently found that acute ischaemic stroke hospitalisations using IV tPA encountered higher hospital costs than acute ischaemic stroke hospitalisations not using tPA, IV tPA within 0–3 h after the onset of stroke has been shown to be a cost-saving strategy in the long term because of the long-term benefit of IV tPA resulting in less disability.[16 18 19] In addition, IV tPA improves the quality adjusted life years (QALYs) for acute ischaemic stroke survivors.[16 18–20]

Another positive finding is the increased use of IV tPA in recent years. Our study shows that, on average, 6.5% of hospitalisations were associated with IV tPA therapy during 2010–2013. The OR confirmed that, even in this short study period, the proportion of patients with acute ischaemic stroke who received IV tPA therapy increased each year, with the odds of receiving IV tPA increasing by 21% from 2010 to 2011, by 26% from 2010 to 2012, and by 50% from 2010 to 2013. In the late 1990s, nationally only 2–3% of patients with stroke received IV tPA.[23] In the 2000s, the national estimates increased from 1% to

5%,[24–26] but still a few patients with acute ischaemic stroke received IV tPA. Our estimates of the use of IV tPA may be conservative due to the fact that most patients experiencing acute ischaemic stroke are likely to be covered by Medicare and are not included in this study.

We want to emphasise that accurate hospital cost information can be used as a key input for cost-effectiveness analyses of treatments for acute ischaemic stroke. Cost-effectiveness evaluations of public health programmes are sensitive to cost information as well as health outcomes achieved from the programmes. Unlike IV tPA from 0 to 3 h after the onset of acute ischaemic stroke, which consistently showed the improvement of health outcomes and the long-term cost-saving impact among patients with IV tPA, IV tPA from 3 to 4.5 h after the onset of stroke increased short-term and long-term costs. Two studies examining the cost-effectiveness of IV tPA between 3 and 4.5 h after the onset of stroke in the USA showed that IV tPA improved QALYs but increased the lifetime cost. Although IV tPA from 3 to 4.5 h after the onset of stroke is recommended by AHA/ASA, IV tPA use for the extended time window is not approved by FDA yet.[27]

In addition, inpatient cost per hospitalisation with IV tPA is important baseline information for studying the cost-effectiveness of advanced stroke treatment, such as intra-arterial (IA) thrombectomy as an adjunct to IV tPA. Additional cost-effectiveness analyses of IV tPA are needed to provide more information, which will be helpful for decision-makers, and the findings of this study could be an important input for further cost-effectiveness analyses of IV tPA.

There are some limitations in this study. First, while the median age of patients with stroke in stroke trials was 68 years,[16] it is limited to patients aged 18–64 years because of the characteristics of the data set used by us. In addition, the study sample included only those who were covered by private insurance and does not reflect hospitalisations for those with Medicare or without any insurance. Since hospital costs with and without IV tPA for adult patients who were younger than 65 years had not been included in previous study samples, we believe that this study is a reasonable complement to previous estimates using Medicare reimbursement rates.[20]

Second, MarketScan does not provide data about severity of stroke. Since IV tPA is not recommended for those who have very mild stroke, the non-tPA group may include those for whom IV tPA is not recommended. However, we indirectly considered the severity of stroke through analyses with LOS categories and controlling for a CCI and hospital discharge destination. Last, hospitalisations with IA therapy could not be separately examined because of the very low frequency (n=137). Despite these limitations, our study derived a reasonable estimate of hospitalisation costs with and without IV tPA.

CONCLUSIONS

This study found that IV tPA use, which can improve health outcomes of acute ischaemic stroke survivors, increased in recent years. However, inpatient cost per acute ischaemic stroke hospitalisation is substantial, especially for those who received IV tPA. Despite the fact that many studies have claimed that IV tPA is cost-effective or cost-saving in the long-term, the immediate hospitalisation costs by IV tPA use in a younger population have not been rigorously evaluated. Future cost-effectiveness studies of stroke treatments should consider such information as inputs, especially when studying the cost-effectiveness of IV tPA alone versus in combination with IA therapy.

Contributors HJ planned the study, performed data analyses and wrote the manuscript. MGG helped plan the study, commented on medical issues and contributed to the revision of the manuscript. GW supervised the study and contributed to the revision of the manuscript.

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