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ORIGINAL RESEARCH

Regional Disparity of Reperfusion Therapy for Acute Ischemic Stroke in Japan: A Retrospective Analysis of Nationwide Claims Data from 2010 to 2015

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BACKGROUND: We aimed to determine whether a regional disparity exists in usage of reperfusion therapy (intravenous recombinant tissue plasminogen activator [IV rt-PA] and endovascular thrombectomy [EVT]) and post-reperfusion 30-day mortality in patients with acute ischemic stroke, and which regional factors are associated with their usage.

METHODS AND RESULTS: We retrospectively investigated 69 948 patients (mean age±SD, 74.9±12.0 years; women, 41.4%) with acute ischemic stroke treated with reperfusion therapy between April 2010 and March 2016 in Japan using nationwide claims data. Regional disparity was evaluated using Gini coefficients for age- and sex-adjusted usage of reperfusion therapy and 30-day post-reperfusion in-hospital death ratio in 47 administrative regions. The association between regional factors and reperfusion therapy usage was evaluated with fixed-effects regression models. During the study period, Gini coefficients showed low inequality (0.11–0.15) for use of IV rt-PA monotherapy and IV rt-PA and/or EVT and extreme inequality (0.49) for EVT usage in 2010, which became moderate inequality (0.25) by 2015. The densities of stroke centers and endovascular specialists, as well as market concentration, were associated with increased usage of reperfusion therapy whereas the proportion of rural residents and delayed ambulance transport were negatively associated with usage. Inequality in the standardized death ratio after EVT was extreme (0.86) in 2010 but became moderate (0.29) by 2015; inequality was low to moderate (0.17–0.23) for IV rt-PA monotherapy and IV rt-PA and/or EVT.

CONCLUSIONS: Scrutinizing existing data sources revealed regional disparity in reperfusion therapy for acute ischemic stroke and its associated regional factors in Japan.

Key Words: ischemic stroke ■ reperfusion therapy ■ regional disparity

Stroke is a major cause of death or functional disability worldwide.[1,2] Establishment of stroke systems of care is an imminent public health issue across the world.[3] In recent years, effective treatments for acute stroke have been developed, which have led to improvement of post-stroke outcomes.[4–6] Among these, recanalization of the occluded arteries within the therapeutic time window is the most effective therapy to reduce ischemic damage and thus, improve clinical outcomes after ischemic stroke.

Currently, 2 types of reperfusion therapies are performed as a standard therapy for acute ischemic stroke: intravenous recombinant tissue plasminogen activator (IV rt-PA) and endovascular thrombectomy (EVT).[4,6,7] However, the therapeutic time window of IV rt-PA and EVT is limited, and their effects are time-dependent. Therefore, stroke patients need to be transported to

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CLINICAL PERSPECTIVE

What Is New?

- Reperfusion therapy, including intravenous recombinant tissue plasminogen activator and endovascular thrombectomy, is effective in reducing the risk of disability or death after ischemic stroke.
- However, in the administration of intravenous recombinant tissue plasminogen activator and endovascular thrombectomy for acute ischemic stroke, regional disparities in reperfusion therapy have emerged as an imminent global public health problem.
- The present study highlights the issue of regional disparity in the quality of stroke care in Japan as well as patient outcomes after acute ischemic stroke.

What Are the Clinical Implications?

- Our analysis revealed that regional disparity was present in the use of reperfusion therapy and post-reperfusion mortality in different aspects with regard to intravenous recombinant tissue plasminogen activator monotherapy and endovascular thrombectomy in Japan.
- Systematic and repeated analyses of geographical disparities in stroke care are crucial to facilitating continued efforts to ensure widespread implementation of reperfusion therapy.
- We identified regional factors that potentially hinder or facilitate the use of reperfusion therapy; data-driven improvements in stroke systems of care are needed to eliminate regional disparities in therapy and reduce the burden of stroke in the entire population.

Nonstandard Abbreviations and Acronyms

EVT	endovascular thrombectomy
IV rt-PA	intravenous recombinant tissue plasminogen activator
NDB	National DataBase of Health Insurance Claims and Specific Health Checkups

appropriate hospitals as early as possible to receive reperfusion therapy.[8–13]

Stroke systems of care have been reorganized to increase the rate of reperfusion therapy at various levels such as hospital, local, regional, and national. During the dissemination of reperfusion therapy, issues of regional disparity for the provision of such therapy have been highlighted. Stroke patients may still lose an opportunity to receive reperfusion therapy depending on their residential areas even though they potentially have indications for therapy. Nevertheless, there remains a paucity of data about the disparities in the provision of IV rt-PA and/or EVT to stroke patients across Japan. In addition, there has been scant study of which regional factors may potentially cause variability in the usage of reperfusion therapy across different regions.

In this study, we aimed to determine whether regional disparity exists in the usage of reperfusion therapy and 30-day in-hospital mortality after the therapy, and which regional factors are associated with usage of the therapy in each region of Japan. To this end, we retrospectively investigated the nationwide claims data on all patients with acute ischemic stroke who were hospitalized and treated with reperfusion therapy during recent years using the National DataBase, one of the world's largest health care databases covering the entire population of Japan.

METHODS

Study Design, Study Setting, and Data Source

We performed a retrospective analysis of data from patients with acute ischemic stroke who received reperfusion therapy in Japan using the National DataBase of Health Insurance Claims and Specific Health Checkups (NDB). The NDB is a large-scale nationwide database of health insurance claims data covering almost all of the population (125–126 million people) of Japan. After proposing our research plan to the Ministry of Health, Labour and Welfare of Japan, a government advisory committee reviewed our proposal and recommended that the Ministry grants us permission to use the data and perform the study (No. 0326-26). Claims data required for the present study were then provided to us for public health research in accordance with the Act on Assurance of Medical Care for Elderly People. This study was approved by the Institutional Review Board of Kyushu University (No. 28–70). The need for informed consent was waived, as all data were anonymized before being received by the authors. The data are stored in the secure system at the Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author. The data, methods used in the analysis, and materials used to conduct the research will be available to qualified researchers for purposes of reproducing the results or replicating the procedures, with committee and Ministry approval to access the required data, upon request submitted to the corresponding author.

Regional Factors

To elucidate which regional factors were associated with usage of reperfusion therapy, we investigated the following characteristics in each prefecture: density of hospitals with 3 stroke care levels (stroke centers: high level of stroke care; tertiary hospitals except stroke centers: middle level of stroke care; and hospitals of other types: low level of stroke care); density of neuroendovascular specialists; market concentration of hospitals performing reperfusion therapy; population density; proportion of rural residents; annual wage level; and rate of delayed ambulance transport. The definitions of these variables are described in Data S1.

Regional Disparity

Regional inequality was assessed using the data of 47 prefectures, which are administrative regions in Japan. A Gini coefficient was used to quantify the inequality according to prefectures. The Gini coefficient is generally used to measure income inequality but is also applied to health care variables such as health care access, treatment usage, and clinical outcomes.[14–17]

The Gini coefficient was calculated using the following formula:

$$G = 1 - \sum_{k=1}^{n} \left(H_k - H_{k-1}\right)\left(U_k + U_{k-1}\right)$$

where H_k is a cumulated portion of the 47 prefectures, and U_k is a cumulated portion of age- and sex-adjusted utilization or the age- and sex-standardized mortality ratio by the respective prefectures. The Gini coefficient ranges from 0 (perfect equality) to 1 (perfect inequality) and is categorized as low (<0.2), moderate (≥0.2, <0.3), high (≥0.3, <0.4), or extreme inequality (≥0.4).[15,16]

Usage of Reperfusion Therapy

Claims data of patients who had stroke in the NDB were extracted with diagnostic codes associated with stroke, corresponding to the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes I60 to I69. Thereafter, we investigated data from patients with acute ischemic stroke who were hospitalized and treated with IV rt-PA and/or EVT from April 2010 to March 2016. IV rt-PA was defined as use of rt-PA (alteplase) for acute ischemic stroke. EVT was defined as percutaneous thrombectomy (Japanese medical service code: K178-4) or the use of any type of thrombectomy catheter. Four types of percutaneous thrombectomy device became available for acute ischemic stroke during the study period. These included the Merci Retrieval System (Concentric Medical, Mountain View, CA, USA), Penumbra System (Penumbra, Alameda, CA, USA), Solitaire FR (Covidien, Mansfield, MA, USA), and Trevo ProVue (Stryker Neurovascular, Fremont, CA, USA).

Usage of reperfusion therapy was evaluated by age- and sex-adjusted number of use of IV rt-PA alone, EVT, or IV rt-PA and/or EVT per 100 000 people in each prefecture. Because the NDB does not include data on the date of stroke onset, we could not discriminate patients who had acute ischemic stroke from those with a history of ischemic stroke but who were treated for other diseases and had a recorded *ICD-10* diagnosis code for ischemic stroke (I63). Therefore, we used the size of the general population as the denominator to avoid inclusion of a large number of patients with previous stroke in the denominator. To minimize the influence of regional differences in the incidence rates of ischemic stroke, age and sex were standardized to the total population on October 1 in Japan, which were estimated by the results of Population Estimates from Statistics Bureau of Japan.

Post-Reperfusion 30-Day Mortality

We defined post-reperfusion 30-day mortality as in-hospital death from any cause within 30 days after reperfusion therapy for the index stroke (Data S1). For comparison of 30-day mortality after the therapy among regions, we calculated the age- and sex-standardized death ratio in each prefecture, which was obtained by dividing the observed number of deaths in each region by the expected number of deaths standardized to the population in Japan on October 1.

Statistical Analysis

We estimated 95% CI of the Gini coefficients by 2000-bootstrap sampling. To evaluate the association between regional factors and the use of reperfusion therapy in each region, we conducted panel data analysis using a fixed-effects model. The results by random-effects model were additionally assessed as sensitivity analysis if the random-effects model was considered appropriate by the Hausman test. The multivariable model included density of hospitals with 3 levels of stroke care (stroke centers [high level of stroke care], tertiary hospitals except stroke centers [middle level of stroke care], and hospitals of other types [low level of stroke care]), density of neuroendovascular specialists, market concentration of hospitals performing reperfusion therapy, population density, proportion of rural residents, annual wage level, rate of delayed ambulance transport, and period after extended time window of IV rt-PA. We estimated coefficients and 95% CI of age- and sex-adjusted usage of reperfusion therapy for each variable. All statistical analyses were performed using STATA 16 (StataCorp LP, College Station, TX, USA). Two-sided *P* values of <0.05 were regarded as statistically significant.

RESULTS

Usage of Reperfusion Therapy

During the study period, a total of 69 948 patients with acute ischemic stroke (mean±SD age 74.9±12.0 years, 41.4% of whom were women) received reperfusion therapy in Japan (Table 1). The temporal trends in the age- and sex-adjusted utilization according to types of reperfusion therapy between 2010 and 2015 are shown in Figure 1 (upper panels) and Table S1. The usage of IV rt-PA monotherapy appeared to slightly increase after extension of the therapeutic time window from 3.0 hours to 4.5 hours in 2012. By contrast, the usage of EVT drastically increased from 2010 to 2015. Consequently, the overall number of patients treated with IV rt-PA and/or EVT significantly increased during the study period.

The market concentration of hospitals differed according to type of reperfusion therapy between 2010 and 2015 (Figure S1). Hospitals performing IV rt-PA monotherapy were competitive during the study period. By contrast, market concentration of EVT was highly concentrated in 2010 but significantly decreased to moderately concentrated in 2015.

Next, we investigated the regional inequality in the usage of reperfusion therapy using Gini coefficients (Figure 1 [lower panels], Table S1, Figures S2 through S4). Gini coefficients for IV rt-PA monotherapy showed relatively low inequality during the study period. By contrast, Gini coefficients for EVT showed extreme inequality in 2010 but decreased to moderate inequality in 2015. Overall, IV rt-PA and/or EVT were performed under relatively low inequality.

Regional Factors Associated With Usage of Reperfusion Therapy

We investigated how regional factors were associated with reperfusion therapy (Table 2, Table S2). The Hausman test showed that the fixed-effects regression model was appropriate for patients overall (*P*<0.001) and for patients treated with EVT (*P*<0.001); however, the null hypothesis was not excluded for patients treated with IV rt-PA monotherapy (*P*=0.39). Therefore, the random-effects model was also applied as sensitivity analysis for IV rt-PA monotherapy (Table S3). However, the results were essentially unchanged, even in the random-effects model.

The results showed that density of stroke centers (high level of stroke care), density of neuroendovascular specialists, and market concentration of hospitals performing reperfusion therapy were positively associated with usage of reperfusion therapy, whereas density of hospitals of other types (low level of stroke care), proportion of rural residents, and rate of delayed ambulance transport were negatively associated with reperfusion therapy. Regarding IV rt-PA monotherapy, densities of stroke centers (high level of stroke care) and tertiary hospitals except stroke centers (middle level of stroke care) were positively associated with use of IV rt-PA monotherapy, and in the random-effects model the proportion of rural residents was additionally associated with decreased use of IV rt-PA monotherapy (Table S3). By contrast, density of neuroendovascular specialists, market concentration, and wage level were positively associated with EVT use, but density of hospitals other than stroke centers (middle or low level of stroke care), proportion of rural residents, and rate of delayed ambulance transport were negatively associated with EVT use.

Post-Reperfusion 30-Day Mortality

Finally, we evaluated the age- and sex-standardized death ratio within 30 days after reperfusion therapy (Figure 2 [upper panels] and Table S4). The standardized death ratio after IV rt-PA monotherapy was relatively constant between 2010 and 2015. However, the death ratio after EVT in each prefecture ranged widely in 2010 but converged to a narrow range in 2015. Overall, the death ratio after IV rt-PA and/or EVT varied in 2010 but thereafter trended toward a level similar to that of IV monotherapy.

Regional disability in post-reperfusion age- and sex-standardized mortality showed different trends depending on type of reperfusion therapy during the study period (Figure 2 [lower panels] and Table S4). The Gini coefficient in the standardized death ratio demonstrated low inequality (0.18–0.23) for IV rt-PA monotherapy throughout the study period. By contrast, Gini coefficients of death ratio showed extreme

Table 1. Demographics of Patients Treated With Reperfusion Therapy

	Total	2010	2011	2012	2013	2014	2015
No.	69 948	8385	9413	10 519	12 403	13 714	15 514
Age, y, mean±SD	74.9±12.0	73.8±11.9	74.2±11.9	74.6±11.7	75.1±11.8	75.2±12.1	75.6±12.1
Women, n (%)	28 931 (41.4)	3460 (41.3)	3775 (40.1)	4330 (41.2)	5111 (41.2)	5678 (41.4)	6577 (42.4)

Data represent mean±SD and number (percentage) of patients who received reperfusion therapy in each year in Japan. Each year indicates the fiscal year, 12 months from April to March.

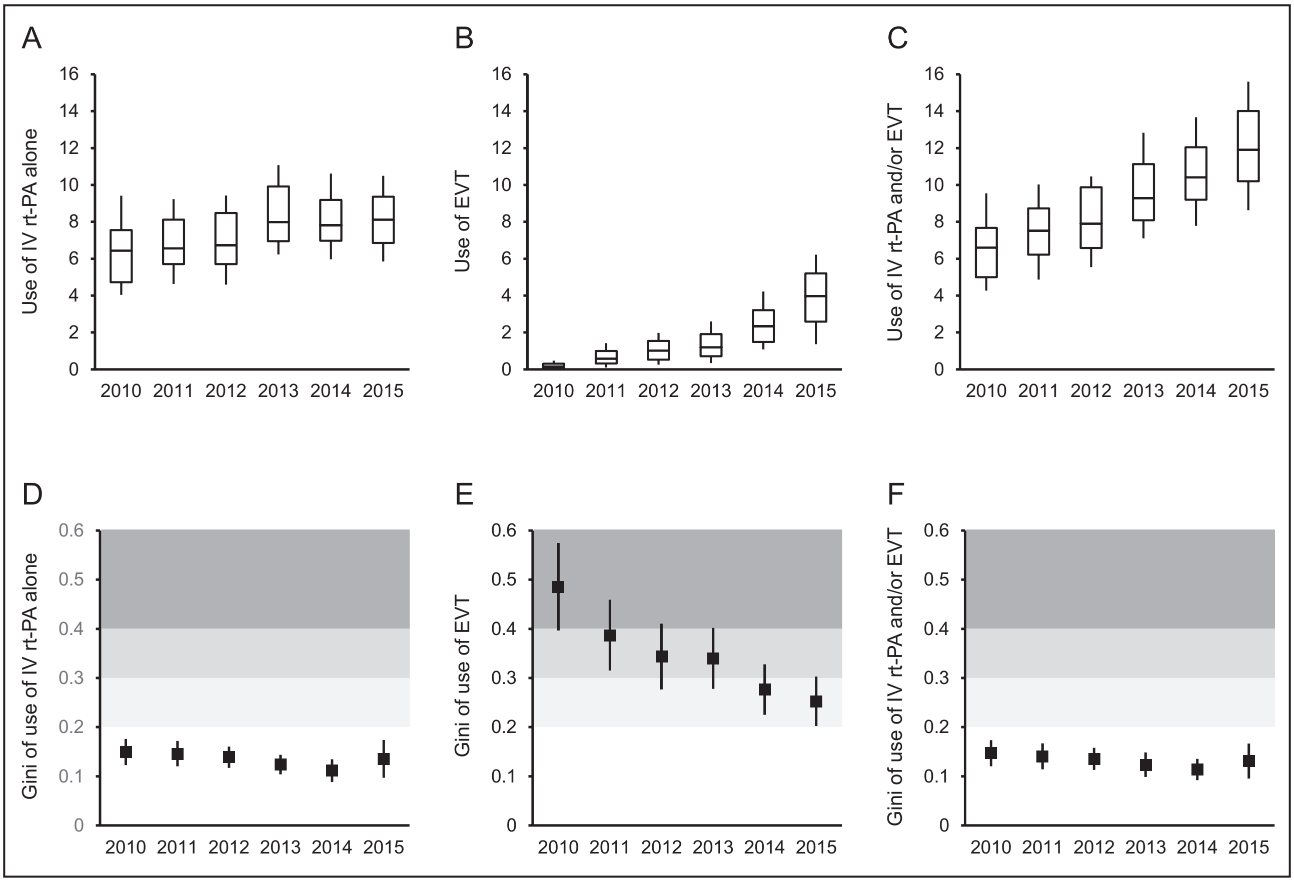

Figure 1. Usage of reperfusion therapy in each region and its regional disparity.
Usage of reperfusion therapy was assessed by age- and sex-adjusted number of uses of reperfusion therapy per 100 000 people. Upper panels show box plots of usage of intravenous recombinant tissue plasminogen activator monotherapy (**A**), endovascular thrombectomy (**B**), and intravenous recombinant tissue plasminogen activator and/or endovascular thrombectomy (**C**) in 47 prefectures. Box indicates ranges between lower quartile and upper quartile, and the horizontal line in the box represents the median. Lower and upper vertical bars indicate the 10th and 90th percentiles, respectively. Lower panels show the Gini coefficients of usage of intravenous recombinant tissue plasminogen activator monotherapy (**D**), endovascular thrombectomy (**E**), and recombinant tissue plasminogen activator and/or endovascular thrombectomy (**F**) by prefecture. Lower and upper vertical bars indicate the 95% CIs. Disparity was graded into 4 categories by Gini coefficient: low (<0.2; white), moderate (≥0.2, <0.3; light gray), high (≥0.3, <0.4; gray), or extreme inequality (≥0.4; dark gray). EVT indicates endovascular thrombectomy; and IV rt-PA, intravenous recombinant tissue plasminogen activator.

inequality (0.86) for EVT in 2010 but improved to moderate inequality (0.29) by 2015. Overall, inequality in the standardized death ratio after IV rt-PA and/or EVT appeared to be unchanged, remaining at low to moderate inequality during the study period.

DISCUSSION

Regional Disparity in Usage of Reperfusion Therapy

Geographical variation in the provision of IV rt-PA has been reported for various regions: hospitals in the United States (2005–2007),[18] hospital service areas in the United States (2007–2010),[19] rural and urban areas in the Northwest region of the United States (2008),[20] metropolitan and non-metropolitan areas in the United States (2013–2014),[21] rural and urban areas in the province of Ontario, Canada (2008–2011),[22] and regions in Korea (2008–2014).[23] In our study, inequality in IV rt-PA monotherapy was relatively low and constant between 2010 and 2015 despite the extended therapeutic time window of IV rt-PA in 2012 in Japan. By contrast, extreme inequality was found for EVT usage in 2010. Recent studies also demonstrated variations in the rates of EVT among large university hospitals in Germany (2010–2016),[24] tertiary hospitals in China (2015),[25] metropolitan areas and rural settings in the United States (2016),[26] and regions in Korea (2013 and 2014).[27] In our study, regional inequality with respect to EVT declined drastically from 2010 to 2015.

During the study period, 4 types of percutaneous thrombectomy device were approved in Japan. First,

Table 2. Association Between Regional Factors and Usage of Reperfusion Therapy

	IV rt-PA monotherapy		EVT		IV rt-PA and/or EVT	
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value
Hospital density						
Stroke centers	4.03 (1.74–6.31)	0.001	0.80 (−1.14 to 2.73)	0.42	4.82 (1.93–7.72)	0.001
Tertiary hospitals except stroke centers	1.59 (0.58–2.61)	0.002	−1.43 (−2.29 to −0.57)	0.001	0.16 (−1.12 to 1.44)	0.81
Hospitals of other types	−0.52 (−1.44 to 0.40)	0.27	−2.83 (−3.61 to −2.05)	<0.001	−3.35 (−4.52 to −2.19)	<0.001
EVT specialist density	0.58 (−0.65 to 1.81)	0.36	2.53 (1.49–3.57)	<0.001	3.11 (1.55–4.67)	<0.001
Market concentration of hospital	0.001 (−0.000 to 0.001)	0.05	0.001 (0.000–0.001)	0.046	0.001 (0.000–0.002)	0.004
Population density	0.001 (−0.004 to 0.006)	0.70	−0.001 (−0.006 to 0.003)	0.62	−0.000 (−0.007 to 0.007)	0.98
Rural population	−0.13 (−0.39 to 0.12)	0.30	−0.37 (−0.59 to −0.16)	0.001	−0.51 (−0.83 to −0.19)	0.002
Income level	0.00 (−0.26 to 0.27)	0.97	0.30 (0.08–0.52)	0.009	0.30 (−0.03 to 0.64)	0.07
Delayed ambulance transport	−0.04 (−0.23 to 0.15)	0.69	−0.36 (−0.52 to −0.20)	<0.001	−0.40 (−0.64 to −0.16)	0.001
Post-extension period	1.25 (0.93–1.57)	<0.001	0.78 (0.51–1.06)	<0.001	2.04 (1.63–2.44)	<0.001

Usage of reperfusion therapy was assessed by age- and sex-adjusted number of individuals undergoing therapy per 100 000 people in each prefecture. A fixed-effects regression model was applied. EVT indicates endovascular thrombectomy; and IV rt-PA, intravenous recombinant tissue plasminogen activator.

the Merci Retrieval System was used as a device for EVT in 2010. Then, the Penumbra System was approved in 2011 on the basis of the results of a single-arm study showing that the Penumbra System achieved safe and effective revascularization in patients with large vessel occlusive disease within 8 hours of onset.[28] As a result, the Merci Retrieval System was increasingly replaced by the Penumbra System. Subsequently, the next-generation stent retriever devices, Solitaire FR and Trevo ProVue, were developed and approved in 2014 after randomized trials demonstrated that these new devices led to better angiographic and clinical outcomes than the Merci Retriever.[29,30] Advances in these mechanical thrombectomy devices may partially contribute to a decrease in inequal EVT use during the study period.

The lack of established evidence for EVT may also have influenced our findings on disparities during the study period. Studies published in 2013 did not support a benefit of EVT in patients with ischemic stroke who were treated with the Merci Retriever in 3 early clinical trials.[31–33] However, during the study period, the efficacy and safety of EVT were reappraised in randomized controlled trials in which the stent retrievers were used for patients with anterior circulation large artery occlusion. In 2015, several trials and their meta-analyses published high-quality evidence that the Solitaire FR and Trevo ProVue are beneficial in improving post-stroke outcomes among patients with stroke owing to anterior circulation large vessel occlusion.[34–41] Thereafter, these newer, safer, and more effective catheters rapidly came into use across Japan. Because the final data of our study were from 1 year after the publication of these trials, the lack of evidence may have affected the rates of EVT usage during the study period. Continuous monitoring of implementation rates is required to assess the changes in regional inequality across Japan following advances in new thrombectomy devices and emerging evidence for their efficacy and safety in patients with ischemic stroke.

Regional Factors Associated With Usage of Reperfusion Therapy

Some regional factors may hinder or facilitate usage of reperfusion therapy. In our study, the proportion of rural residents was negatively associated with overall use of reperfusion therapy, suggesting that people living in rural areas may be disadvantaged in receiving reperfusion therapy. Rural-urban disparity in intravenous thrombolysis has been pointed out in the United States (2008,[20] 2000–2010,[16] 2013–2014[21]) and Canada (2008–2011).[22] However, in the Austrian Stroke Unit Registry, IV rt-PA therapy was reported to be lower in urban patients, whereas the rate of EVT use was not significantly different between groups.[42]

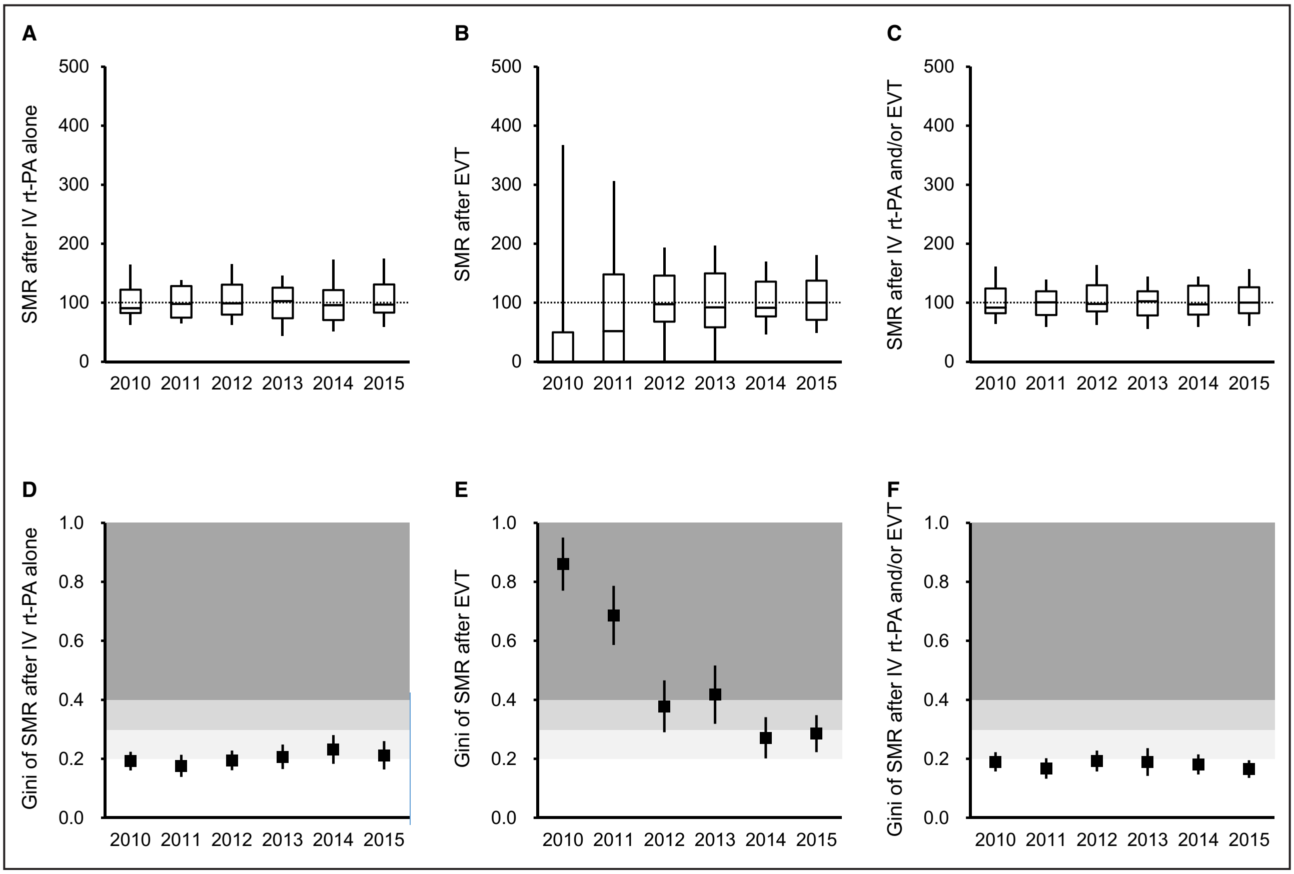

Figure 2. Standardized 30-day death ratio after reperfusion therapy and its regional disparity.
Post-reperfusion death was defined as in-hospital death from any cause within 30 days after the therapy. Standardized death ratio in each region was calculated by the ratio between the observed number of deaths and the expected number of deaths based on the age- and sex-specific rates in the general population in Japan. Upper panels show box plots of standardized 30-day death ratio after intravenous recombinant tissue plasminogen activator monotherapy (**A**), endovascular thrombectomy (**B**), and recombinant tissue plasminogen activator and/or endovascular thrombectomy (**C**) in 47 prefectures. Box indicates ranges between lower quartile and upper quartile, and the horizontal line in the box represents the median. Lower and upper vertical bars indicate the 10th and 90th percentiles, respectively. Lower panels show the Gini coefficients of standardized 30-day death ratio of intravenous recombinant tissue plasminogen activator monotherapy (**D**), endovascular thrombectomy (**E**), and recombinant tissue plasminogen activator and/or endovascular thrombectomy (**F**) by prefecture. Lower and upper vertical bars indicate the 95% CI. Disparity was graded into 4 categories by Gini coefficient: low (<0.2; white), moderate (≥0.2, <0.3; light gray), high (≥0.3, <0.4; gray), or extreme inequality (≥0.4; dark gray). EVT indicates endovascular thrombectomy; IV rt-PA, intravenous recombinant tissue plasminogen activator; and SMR, standardized mortality ratio.

Urban-rural disparity in usage of reperfusion therapy needs to be further validated in other settings.

Population density in Japan remarkably differs depending on the prefectures, from 69 people per km^2 (Hokkaido) to 6106 people per km^2 (Tokyo) in 2015. However, in our study the population density was not associated with use of reperfusion therapy. Nonetheless, the rate of delayed ambulance transport showed a negative association with use of EVT or IV rt-PA and/or EVT. Rapid transport of stroke patients to appropriate hospitals is crucial to increase the usage rate of reperfusion therapy because its administration depends on whether the onset-to-needle time is within the therapeutic time window. Previous studies, such as the FL-PR CReSD study (Florida-Puerto Rico Collaboration to Reduce Stroke Disparities, 2010–2015)[43] and the Austrian Stroke Unit Registry (2005–2016),[42] suggested that the time from onset to treatment differed by region. Worse geographic access may lead to lower rates of IV rt-PA and EVT.[44] Therefore, accessibility to stroke centers rather than the population density in each prefecture may affect the proportion of patients receiving reperfusion therapy among the overall patient population in the prefecture. A simulation study from the United States disclosed that a large proportion of the population is still unable to access comprehensive stroke centers within 60 minutes, even when primary stroke centers are selectively converted to comprehensive stroke centers.[45] Additional efforts to reduce onset-to-needle time are still required in all regions.

A previous study from the United States suggested that hospital facilities were associated with the rate of IV rt-PA usage independently of geographic region and population density.[18] In the present study, densities of stroke centers and neuroendovascular specialists as well as market concentration were associated with increased use of reperfusion therapy. Detailed analysis demonstrated that density of stroke centers and density of neuroendovascular specialists were favorable to IV rt-PA monotherapy and EVT, respectively. IV rt-PA can be performed even by non-neurologist physicians via stroke telemedicine, whereas experts in endovascular techniques are prerequisite to performing EVT. A previous study showed that EVT treatment appeared to be more widespread in the United States, as more hospitals were able to perform EVT.[46] To overcome the geographic difficulties across the country, stroke centers and neuroendovascular specialists need to be optimally located to increase the usage of reperfusion therapy in individual regions.

Regional Inequality in Death Within 30 Days After Reperfusion Therapy

The present study added new findings about regional disparity in 30-day in-hospital mortality after reperfusion therapy. Gini coefficients for 30-day standardized death ratio after IV rt-PA monotherapy showed low or at most moderate inequality by region during the study period. This is possibly because IV rt-PA monotherapy had already been established as a first-line therapy for ischemic stroke in every region during the study period. By contrast, extreme inequality was found in the 30-day in-hospital death ratio after EVT in 2010, whereas this inequality rapidly diminished to moderate levels during the study period. There may be plausible explanations for this improvement in regional inequality of in-hospital mortality after EVT. First, the number of senior trainers and specialists in neuroendovascular therapy increased under certification by the Specialty Board of the Japanese Society for NeuroEndovascular Therapy. Second, advances in devices for EVT may contribute to the lowering of post-reperfusion mortality. During the study period, next-generation devices for EVT were developed to improve the efficacy and safety of the therapy since the Merci Retrieval System was first approved in 2010 in Japan.[47] Newly developed devices for EVT increased the recanalization rate and improved the balance between benefits and safety of the therapy. At the beginning of this study in 2010, high-risk procedures were performed in the limited number of tertiary or academic centers with older-generation catheters. However, because newer generation devices for EVT have achieved higher rates of success without compromising safety, their use potentially led to lower post-procedural mortality and could have partially contributed to the decline in regional inequality in the post-reperfusion 30-day death ratio. Third, during the study period, indications for EVT were standardized for patients who fulfill the inclusion criteria for the therapy.[6,48,49] EVT is currently indicated for patients who fulfill the exclusion criteria for IV rt-PA or cases where IV rt-PA therapy was unable to recanalize large vessel occlusions.[6,48,49] Further studies aimed at decreasing regional inequality in unfavorable outcomes after reperfusion therapy are warranted.

Study Limitations

This study has several limitations. First, we evaluated the age- and sex-standardized number of reperfusion therapy cases per population but not the rate of reperfusion therapy performed in patients with acute ischemic stroke owing to a lack of data on the date of stroke onset in the claims data. Consequently, the results would be affected by geographical differences in incidence rates of ischemic stroke, which could arise from geographical differences in lifestyle factors, socioeconomic factors, and cultural factors, even though age and sex were standardized. Second, the NDB does not include non-electronic claims data and claims data for patients whose medical fees were paid by public expenditure, although their proportion is estimated at <5%. Third, averaged values in each prefecture were used as explanatory variables; however, more detailed data in narrower regions would be advantageous to further elucidate the factors associated with regional disparities. Fourth, regional factors, such as EVT specialism and rural population, were not investigated annually and, therefore, the most recent data before any missing data were used instead. Fifth, although the NDB is presumed to have complete data on age, sex, and use of reperfusion therapy, these data were not collected for research purposes. Similarly, data on regional factors were publicly available but not collected for our study. Therefore, missing data and/or measurement error could be present in the variables. Finally, because we used claims data for inpatients, out-of-hospital deaths were not included in our database, which may have led to underestimation of 30-day mortality. Further studies are needed to validate the regional disparity in reperfusion therapy for patients who had stroke in other countries.

Future Perspectives

This study demonstrated regional inequality in usage of reperfusion therapy and 30-day mortality after reperfusion therapy for acute ischemic stroke in Japan.

Regional variation in usage of reperfusion therapy is probably caused by complex interplay between geographic characteristics, stroke facilities, stroke personnel, and emergency medical services in each region. Nevertheless, our study findings indicate that careful investigation of existing data sources can provide clues to addressing issues on the geographical disparities of reperfusion therapy for ischemic stroke. Factors that are advantageous to or, conversely, those that impede implementation of reperfusion therapy possibly differ depending on the region, and these can also change over time. Therefore, systematic and repeated analyses of geographical disparities in stroke care are crucial to facilitating continued efforts to ensure widespread implementation of reperfusion therapy. Based on the data, the exchange of valuable experiences from regions that have succeeded in achieving high treatment rates would be helpful to increase usage of reperfusion therapy equally throughout the country. Thus, data-driven improvements in stroke systems of care are needed to eliminate regional disparities in therapy and reduce the burden of stroke in the entire population of Japan.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

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SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Post-reperfusion 30-day mortality

To evaluate early death after reperfusion therapy, we investigated in-hospital death from any causes within 30 days after reperfusion therapy. The data were obtained by the National DataBase within 30 days after onset of index stroke. From April 2010 to March 2012, the National DataBase included information on the months, but not the exact dates. During that period, mortality within the month after reperfusion therapy was analyzed as surrogates.

Regional factors

Densities of hospitals or neuroendovascular specialists were calculated by the number per 100,000 people in each prefecture. Hospital types were categorized on the basis of stroke care levels as described below. The number of neuroendovascular specialists was obtained from the data in the survey of physicians, dentists, and pharmacists by Ministry of Health, Labour and Welfare. Senior trainers and specialists for neuroendovascular therapy were certified through a board examination and their basic ability, such as primary operator experiences, presentations at medical meetings, and publications as primary author, by the Specialty board of the Japanese Society for NeuroEndovascular Therapy. Market concentration of hospitals performing reperfusion therapy was assessed using Herfindahl-Hirschman index (HHI) as described below. Proportion of population in rural area was defined as percentage of people who do not live in densely inhabited districts: 100 − (population in densely inhabited districts/entire population). Populations in densely inhabited districts were estimated from the data of the Population Census. Wage level was defined as annual wage (US$) per person in each prefecture obtained from the data of Basic Survey on Wage Structure by the Ministry of Health, Labour and Welfare. Regarding delay in ambulance transport, the Fire and Disaster Management Agency of the Ministry of Internal Affairs and Communications in Japan collected data regarding how many inquiry calls were required for an emergency medical team to find a hospital that could accept their patient. In the survey of hospital acceptance via ambulance transport by the Agency, more than three inquiry calls were regarded as a problematic case that resulted in delayed transport to the hospital. Therefore, in this study, delayed ambulance transport was defined when patients could not be promptly transported to a hospital by ambulance within three inquiry calls to find a hospital. The rate of delayed ambulance transport was calculated as the rate of such cases to all cases transported by ambulance. In Japan, the therapeutic time window of intravenous alteplase was extended in September 2012 from 3.0 h to 4.5 h after onset, and the post-extension period was defined as the period after extension of the therapeutic time window.

Hospital types

Hospital types were categorized into 3 groups according to stroke care levels: stroke centers (high level of stroke care), tertiary hospitals except stroke centers (middle level of stroke care), and hospitals of other types (low level of stroke care). Stroke care levels were determined by the data registered in each Regional Bureau of Health and Welfare in Japan.

Stroke centers are hospitals with the capability to treat the most complex stroke cases. Stroke centers were defined as hospitals with certified Stroke Care Units or hospitals that admit stroke patients under the certified hyperacute stroke care system. A Stroke Care Unit is certified when fulfilling the following criteria: (1) dedicated stroke specialists; (2) ≥1 nurse to care for 3 stroke patients; (3) full-time physical or occupational therapists; (4) ≤30 beds per unit for stroke care; (5) stroke patients constitute ≥80% of those hospitalized in the unit; (6) appropriate facility for acute stroke care. A hyperacute stroke care system is approved if hospitals fulfill the following criteria: (1) full-time stroke specialists certified after attending a lecture on intravenous alteplase held by the Japan Stroke Society; (2) pharmacists, radiological technologists, and clinical technologists available 24 h/day, 7 days/week; (3) neurosurgical procedures capability;

(4) appropriate stroke care unit for stroke care; (5) ventilator/endotracheal intubation equipment, defibrillator, electrocardiogram, cardiopulmonary monitoring system in the care unit; (6) computed tomography/computed tomography angiography/computed tomography perfusion, magnetic resonance imaging/magnetic resonance angiography/magnetic resonance perfusion, and angiography available 24 h/day, 7 days/week.

Tertiary hospitals were defined as hospitals that are capable of certified emergency and critical care or have beds for critical care unit/intensive care unit/high care unit. Tertiary hospitals without certified stroke care units or hyperacute stroke care system were categorized into tertiary hospitals except stroke centers. Hospitals other than stroke centers and tertiary hospitals were defined as hospitals of other types.

Market concentration

Market concentration was assessed by an HHI. The HHI is generally used as an index to evaluate the market concentration of a variety of industries, including health care.[17,50,51] The HHI can be calculated by the following formula:

$$\text{HHI} = \sum_{i=1}^{n} Ci^2,$$

where Ci is rate (%) of patients treated with reperfusion therapy in each hospital and n is the number of hospitals. The HHI can be categorized as highly competitive (<100), unconcentrated and/or competitive (≥100, <1500), moderately concentrated (≥1500, <2500), and highly concentrated (≥2500). An HHI of 10,000 indicates that there is only one hospital in the prefecture.

Table S1. Utilization of reperfusion therapy and Gini coefficients between 2010 and 2015

	2010	2011	2012	2013	2014	2015
Utilization						
IV rt-PA monotherapy	6.4 (4.7–7.5)	6.6 (5.7–8.1)	6.7 (5.7–8.5)	8.0 (7.0–9.9)	7.8 (7.0–9.2)	8.1 (6.9–9.4)
EVT	0.2 (0.1–0.3)	0.6 (0.3–1.0)	1.0 (0.5–1.5)	1.2 (0.7–1.9)	2.3 (1.5–3.2)	4.0 (2.6–5.2)
IV rt-PA and/or EVT	6.6 (5.0–7.7)	7.5 (6.2–8.7)	7.9 (6.6–9.9)	9.3 (8.1–11.1)	10.4 (9.2–12.0)	11.9 (10.2–14.0)
Gini coefficient						
IV rt-PA monotherapy	0.15 (0.12–0.18)	0.15 (0.12–0.17)	0.14 (0.12–0.16)	0.12 (0.10–0.14)	0.11 (0.09–0.13)	0.14 (0.10–0.17)
EVT	0.49 (0.40–0.57)	0.39 (0.31–0.46)	0.34 (0.28–0.41)	0.34 (0.28–0.40)	0.28 (0.23–0.33)	0.25 (0.20–0.30)
IV rt-PA and/or EVT	0.15 (0.12–0.17)	0.14 (0.11–0.17)	0.14 (0.11–0.16)	0.12 (0.10–0.15)	0.11 (0.09–0.14)	0.13 (0.10–0.17)

EVT, endovascular thrombectomy; IV rt-PA, intravenous recombinant tissue plasminogen activator.
Utilization of reperfusion therapy is expressed as median (interquartile range) of data from 47 prefectures. Utilization of reperfusion therapy was assessed by age- and sex-adjusted number of cases of reperfusion therapy per 100,000 people. Gini coefficients are expressed as Gini coefficient and 95% confidence interval of use of reperfusion therapy in 47 prefectures. The bootstrap method with 2000 samples was used to estimate the 95% confidence interval of Gini coefficients. Each year indicates the fiscal year, 12 months from April to March.

Table S2. Regional factors between 2010 and 2015

	2010	2011	2012	2013	2014	2015
Hospital density, *n*/100,000 people						
Stroke centers	0.57 (0.47–0.71)	0.57 (0.47–0.77)	0.60 (0.47–0.78)	0.61 (0.50–0.78)	0.68 (0.51–0.82)	0.69 (0.51–0.83)
Tertiary hospitals except stroke centers	2.48 (1.95–2.89)	2.50 (1.96–2.90)	2.52 (2.01–2.93)	2.47 (1.92–2.99)	2.44 (1.92–2.88)	2.44 (1.82–2.91)
Hospitals of other types	1.70 (1.01–2.41)	1.58 (1.00–2.37)	1.48 (0.94–2.25)	1.45 (0.97–2.29)	1.34 (0.90–2.14)	1.28 (0.88–2.15)
EVT specialist density, *n*/100,000 people	0.40 (0.30–0.50)	–	0.50 (0.30–0.60)	–	0.50 (0.40–0.70)	–
Market concentration of hospital	1129 (683–1586)	1102 (628–1600)	1128 (650–1625)	974 (629–1575)	944 (657–1607)	1004 (646–1587)
Population density, n/km^2	280 (189–534)	279 (188–532)	278 (187–529)	277 (186–526)	270 (182–479)	270 (179–478)
Rural population, %	54 (35–61)	–	–	–	–	53 (35–62)
Wage level, $1000/year	31 (28–33)	31 (29–34)	31 (29–33)	32 (28–33)	32 (29–34)	32 (29–34)
Delayed ambulance transport, %	2.00 (0.70–4.00)	1.90 (0.80–4.70)	2.00 (0.80–4.80)	2.30 (0.80–4.40)	2.00 (0.90–4.30)	1.80 (0.90–3.50)
Extended time window of IV rt-PA	0	0	0	1	1	1

EVT, endovascular thrombectomy; IV rt-PA, intravenous recombinant tissue plasminogen activator.
Data represent median (interquartile range) of 47 prefectures. EVT specialists and rural population were not investigated annually; therefore, the most recent data prior to the missing data were used.

Table S3. Association between regional factors and utilization of IV rt-PA monotherapy in sensitivity analysis

	Coefficient (95% CI)	*P*
Hospital density		
Stroke centers	3.28 (1.75–4.81)	<0.001
Tertiary hospitals except stroke centers	1.25 (0.73–1.77)	<0.001
Hospitals of other types	−0.28 (−0.72 to 0.15)	0.20
EVT specialist density	0.17 (−0.89 to 1.22)	0.76
Market concentration of hospital	0.000 (−0.000 to 0.001)	0.15
Population density	−0.000 (−0.001 to 0.000)	0.62
Rural population	−0.04 (−0.08 to −0.00)	0.03
Income level	0.00 (−0.17 to 0.17)	1.00
Delayed ambulance transport	−0.01 (−0.15 to 0.13)	0.86
Post-extension period	1.36 (1.09–1.63)	<0.001

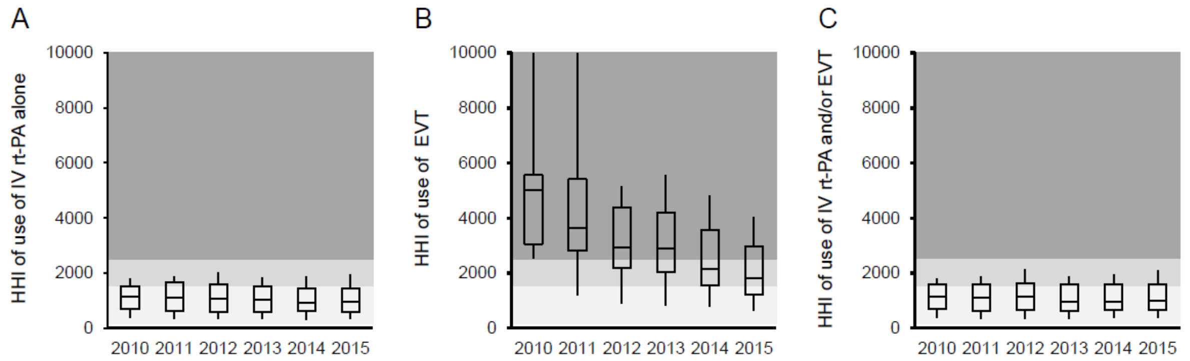
CI, confidence interval; EVT, endovascular thrombectomy; IV rt-PA, intravenous recombinant tissue plasminogen activator.
Utilization of reperfusion therapy was assessed by age- and sex-adjusted number of therapy cases per 100,000 people in each prefecture. A random-effects regression model was applied.

Table S4. Post-reperfusion 30-day death ratio and Gini coefficients between 2010 and 2015

	2010	2011	2012	2013	2014	2015
30-day death ratio						
IV rt-PA monotherapy	91 (82–122)	98 (75–128)	99 (80–131)	103 (74–126)	96 (71–121)	97 (83–131)
EVT	0 (0–50)	52 (0–148)	97 (68–146)	92 (58–150)	92 (77–136)	100 (71–138)
IV rt-PA and/or EVT	92 (82–124)	101 (79–119)	98 (85–130)	102 (79–119)	97 (80–129)	100 (82–126)
Gini coefficient						
IV rt-PA monotherapy	0.19 (0.16–0.22)	0.18 (0.14–0.21)	0.19 (0.16–0.23)	0.21 (0.17–0.25)	0.23 (0.18–0.28)	0.21 (0.16–0.26)
EVT	0.86 (0.77–0.95)	0.69 (0.59–0.79)	0.38 (0.29–0.47)	0.42 (0.32–0.52)	0.27 (0.20–0.34)	0.29 (0.22–0.35)
IV rt-PA and/or EVT	0.19 (0.16–0.22)	0.17 (0.13–0.20)	0.19 (0.16–0.23)	0.19 (0.14–0.24)	0.18 (0.15–0.21)	0.17 (0.13–0.20)

EVT, endovascular thrombectomy; IV rt-PA, intravenous recombinant tissue plasminogen activator.
Post-reperfusion 30-day death ratio is expressed as median (interquartile range) of data from 47 prefectures. The ratio of all-cause death within 30 days after reperfusion therapy was calculated by dividing the observed number of deaths in each prefecture by the expected number of deaths, standardized to the population of Japan. Gini coefficients are expressed as Gini coefficient and 95% confidence interval of standardized death ratio in 47 prefectures. The bootstrap method with 2000 samples was used to estimate the 95% confidence interval of Gini coefficients. Each year indicates the fiscal year, 12 months from April to March.

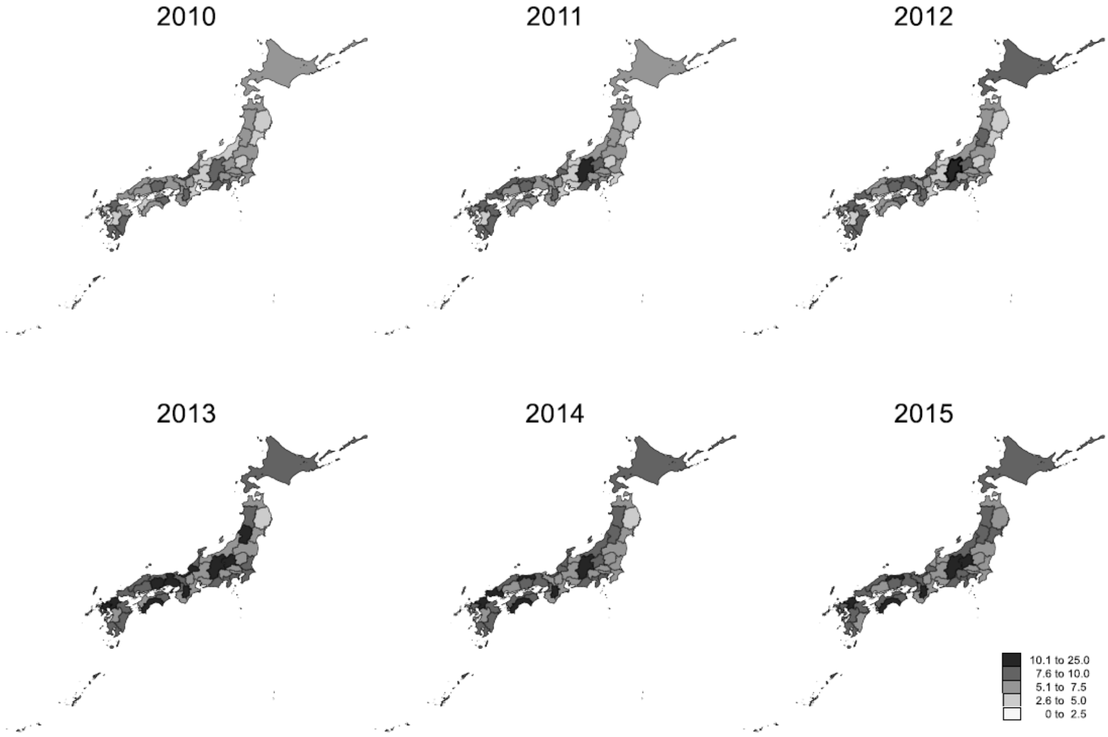
Figure S1. Market concentration of reperfusion therapy in each region



EVT indicates endovascular thrombectomy; HHI, Herfindahl-Hirschman index; and IV rt-PA, intravenous recombinant tissue plasminogen activator.

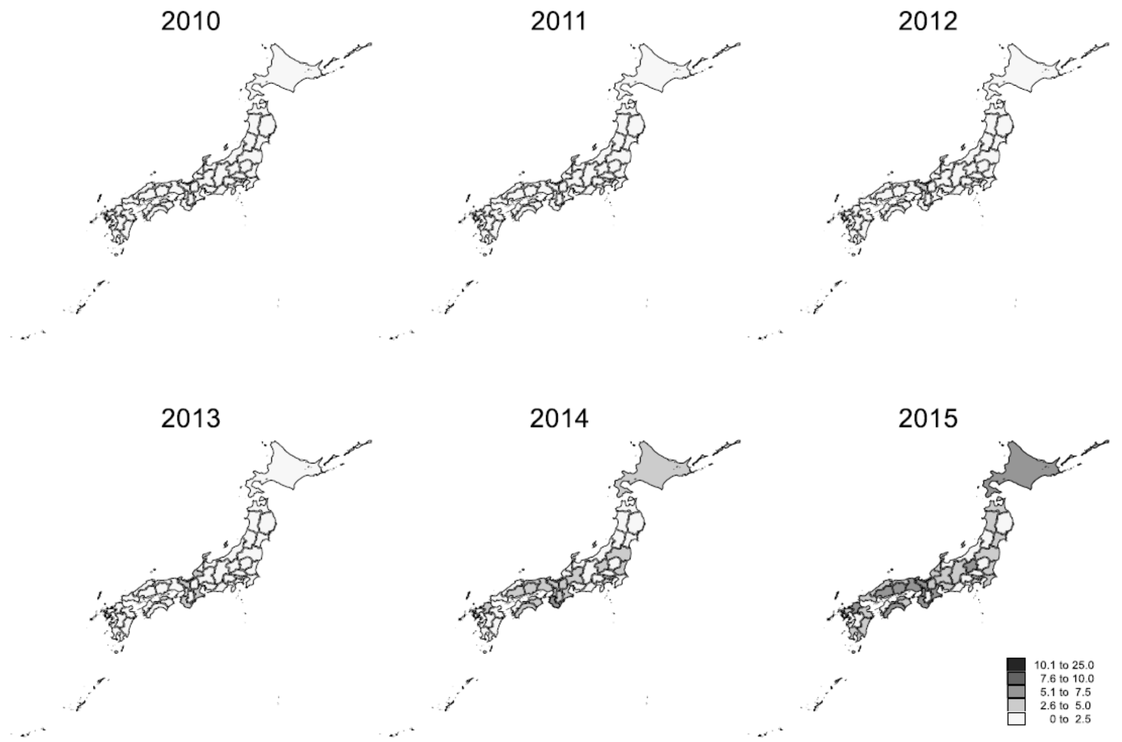
Box plots show market concentration of hospitals performing IV rt-PA monotherapy (A), EVT (B), and IV rt-PA and/or EVT (C) in 47 prefectures. Market concentration was assessed by an HHI. Box indicates ranges between lower quartile and upper quartile, and the horizontal line in the box represents the median. Lower and upper vertical bars indicate the 10th and 90th percentiles, respectively.

Figure S2. Utilization of IV rt-PA monotherapy in each region



IV rt-PA indicates intravenous recombinant tissue plasminogen activator.
Utilization of IV rt-PA monotherapy in each prefecture is shown on the map of Japan. Utilization is graded into 5 groups according to age- and sex-adjusted number of use of IV rt-PA monotherapy per 100,000 people: 0–2.5, 2.6–5.0, 5.1–7.5, 7.6–10.0, and 10.1–25.0 uses per 100,000 people in the prefecture in each year. Each year indicates the fiscal year of 12 months from April to March.

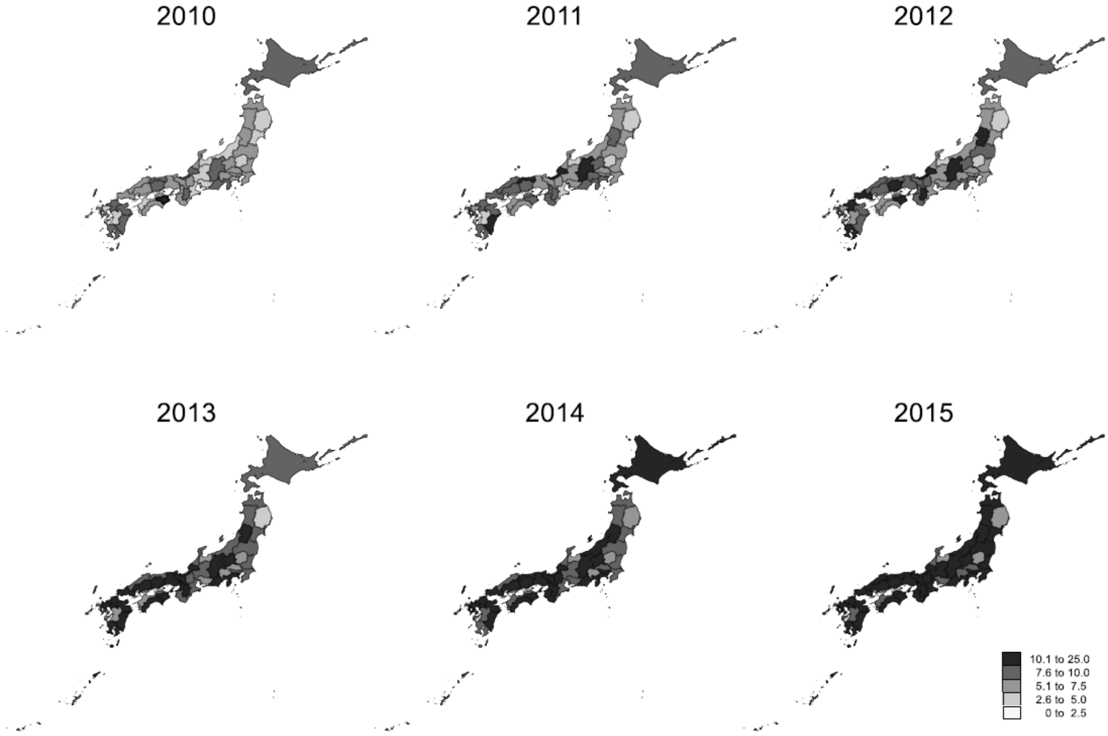
Figure S3. Utilization of EVT in each region



EVT indicates endovascular thrombectomy.

Utilization of EVT in each prefecture is shown on the map of Japan. Utilization is graded into 5 groups according to age- and sex-adjusted number of use of EVT per 100,000 people: 0–2.5, 2.6–5.0, 5.1–7.5, 7.6–10.0, and 10.1–25.0 uses per 100,000 people in the prefecture in each year. Each year indicates the fiscal year of 12 months from April to March.

Figure S4. Utilization of reperfusion therapy in each region



Utilization of reperfusion therapy in each prefecture is shown on the map of Japan. Reperfusion therapy included intravenous recombinant tissue plasminogen activator, endovascular thrombectomy, or both. Utilization is graded into 5 groups according to age- and sex-adjusted number of use of reperfusion therapy per 100,000 people: 0–2.5, 2.6–5.0, 5.1–7.5, 7.6–10.0, and 10.1–25.0 uses per 100,000 people in the prefecture in each year. Each year indicates the fiscal year of 12 months from April to March.