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Evaluation of the Influence of Etiological Factors on the Economic Burden of Ischemic Stroke in Younger Patients in China Using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) Classification

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Manuscript Preparation E
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Background: Worldwide, stroke results in healthcare costs and economic costs, particularly in patients aged <45 years. This study aimed to evaluate the factors influencing the economic burden of ischemic stroke in younger patients in China based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiological classification.





Material/Methods: Retrospective review of the medical records of 961 patients aged between 18–45 years, diagnosed with acute ischemic stroke, was performed to identify healthcare costs for one year. Stroke severity was assessed using the modified Rankin Scale (mRS) score and the National Institutes of Health Stroke Scale (NIHSS) score. Stroke was categorized according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification as being due to large artery atherosclerosis (LAA), cardioembolism (CE), small artery occlusion (SAO), other determined causes (OC), and undetermined etiology (UND).

Results: Total direct medical costs at one-year follow-up were US\$10,954.14, including inpatient cost of US\$5,958.44, and outpatient cost of US\$3,397.60. Inpatient and total costs at one year were significantly increased in the CE subtype ($P < 0.001$), and were significantly less in the UND subtype ($P < 0.001$). Multivariable logistic regression analysis showed that mRS score, TOAST category, NIHSS score, and the presence of atrial fibrillation were the significant factors influencing cost at one-year follow-up and total cost in younger patients with ischemic stroke. Overall, patient costs in China were less than those in high-income countries.

Conclusions: In the younger patient population in China, etiological factors influenced the economic burden of ischemic stroke.

MeSH Keywords: **Cost of Illness • Stroke • Young Adult**

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Background

Worldwide, ischemic stroke affects quality of life and is associated with patient morbidity, disability, and mortality. In China, the incidence of ischemic stroke is increasing, particularly in the younger age group under 45 years, and imposes a heavy burden on families, national health services, social services, and the economy [1–3]. The increasing trend for ischemic stroke in younger patients, rather than the elderly population, imposes a heavier social and economic burden, and younger patients experience ischemic stroke from different causes, and have different risk factors, and clinical manifestations. It has previously been reported that in the population in China aged between 15–45 years, the incidence of stroke is between 18–142 per 100,000 for men and between 23–95 per 100,000 for women, and between 9.77–13.44% of all stroke patients in China are under 45 years of age [4]. Therefore, more relevant measures are required in this country to reduce the prevalence of ischemic stroke in the younger population, and to evaluate the cost-benefit of stroke prevention in terms of the cause so that appropriate healthcare policy is developed. These public health improvements require an evaluation of total healthcare costs associated with ischemic stroke in China.

There have been few previously published studies on the healthcare costs in younger stroke patients, particularly in China [5]. Jennum et al. reported the findings from a controlled national study evaluating the healthcare costs of stroke in Denmark and showed that the attributable cost of direct net healthcare following stroke were €10,720, €8,205, and €7,377 for patients, and €989, €1,544 and €1.645 for their partners, for hemorrhagic, ischemic, and unspecified cause of stroke, respectively [6]. Sonig et al. reported that the mean cost of hospitalization and treatment was \$70,325.11, and \$97,546.92 for stroke patients who required transfer between facilities in the US [7]. Wang et al. showed that the average out-of-pocket per capita cost of treatment for stroke was RMB 3028.4 (\$484.80) in 2008 in China [8]. Currently, there have been few published studies in the English language on healthcare costs for younger patients with ischemic stroke in China, which make it difficult to compare costs worldwide. Also, previous studies have mainly provided findings on the factors that affect the cost of initial diagnosis and treatment, without combined long-term cost and outcome. Hamilton et al. showed that there was a positive relationship between cost and prognosis in pediatric patients with ischemic stroke and reported that poorer quality of life resulted in higher healthcare costs, which were also associated with etiology [9].

Therefore, the main aim of this retrospective study was to evaluate the factors influencing the economic burden of ischemic stroke in younger patients in China based on the Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiological classification [10]. The study also aimed to identify other factors

that might be associated with cost, and also to provide data that might form the basis for future studies to support healthcare policy for younger patients with ischemic stroke in China.

Material and Methods

This retrospective study included patients diagnosed with ischemic stroke from the Key Laboratory of Ministry of Education for Cardiovascular and Cerebrovascular Diseases, Chinese Gannan Medical University, which included 9 million people, and 18 counties and cities. The medical records of younger patients, under 45 years of age, diagnosed with ischemic stroke between January 1 2012, and December 31 2015, were reviewed. Medical record and billing data were obtained for inpatient and outpatient charges. The study design and protocol were approved by the local institutional review board (IRB) and the National Research Committee, and all clinical procedures conformed to local clinical guidelines and were in accordance the 1964 Declaration of Helsinki and its revisions. Informed consent to participate in the study was obtained from the study participants.

The study inclusion criteria included patients with arterial ischemic stroke, who were aged between 18–45 years, with the diagnosis of acute ischemic stroke confirmed by neuroimaging. Exclusion criteria included patients with clinically silent infarcts, infarction caused by hypoxic-ischemic encephalopathy or cerebral sinovenous thrombosis, brain trauma, cerebral hemorrhage, subarachnoid hemorrhage (SAH), and transient ischemic attacks (TIAs). Additional exclusion criteria are shown in Figure 1. Stroke severity was assessed using the modified Rankin Scale (mRS) score and the National Institutes of Health Stroke Scale (NIHSS) score.

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) five etiological subtypes used were stroke due to large artery atherosclerosis (LAA), cardioembolism (CE), small artery occlusion (SAO), other determined causes (OC), and undetermined etiology (UND) [10]. The classification of stroke subtypes was performed by at least two experienced senior neurologists.

Cost categories and cost data

The healthcare costs for the management of younger patients within one year after the onset of ischemic stroke were obtained from the hospital billing system. Costs were divided into in-hospital and outpatient charges. The initial hospitalization costs included patient medications, care unit costs, and costs of surgery, additional tests, and imaging. The inpatient costs associated with the onset stroke were classified as stroke-related costs. For outpatient costs, the clinic category of each visit was reviewed and designated as stroke-related.

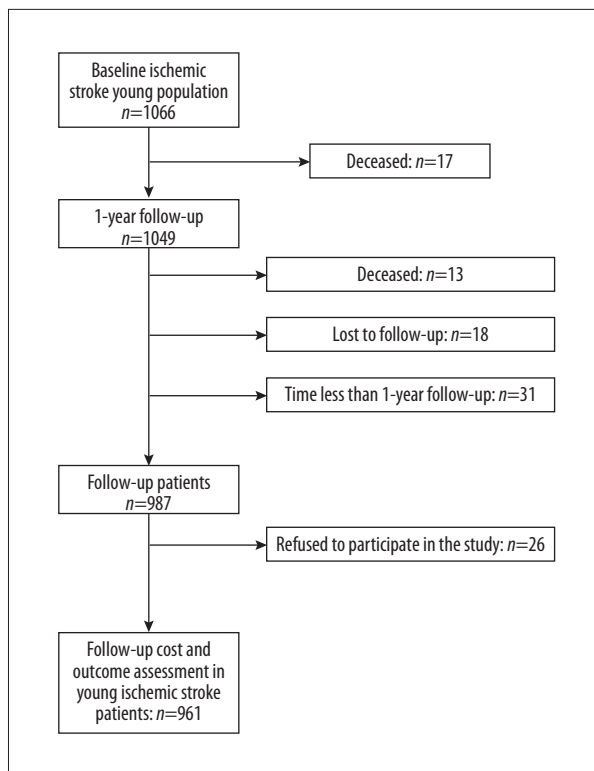


Figure 1. Flowchart of the eligible study participants.

Medications, registration, additional tests, imaging, subspecialty clinics, and rehabilitation were included as outpatient costs, which were captured by meetings with the patients or by telephone interview. The US Consumer Price Index was used for cost-to-charge ratios. The average exchange rates in 2012–2015 were 1 USD=6.22¥, according to the World Bank online website.

Stroke outcomes

Stroke outcome was recorded at least one year after the onset of stroke by contacting patients and their families by telephone. The modified Rankin Scale (mRS) [11] was used to evaluate neurological functional recovery and quality of life, with six grades from 0–5, with poorer outcomes correlated with higher mRS scores. A mRS score of 0 indicated completely asymptomatic; a mRS score of 1 indicated no significant dysfunction with some symptoms, with the ability to independently perform activities of daily living; a mRS score of 2 indicated mild disability, failure to complete all pre-illness activities without assistance; a mRS score of 3 indicated moderate disability, with the need for assistance in doing activities, but not with walking; a mRS score of 4 indicated severe disability, being unable to walk alone without assistance; and a mRS score of 5 indicated severe disability that required immobility in bed, incontinence, and continuous care. Patients with a mRS score ≤ 2 were defined as having a good outcome and patients with a mRS score > 2 were defined as having a poor outcome.

Statistical analysis

Data were analyzed using SPSS version 20.0 software (IBM, Chicago, IL, USA). Demographic data were analyzed using descriptive methods, with the mean \pm standard deviation (SD) or the median. Comparison of differences in the TOAST subtypes was made using t-tests and analysis of variance (ANOVA). Spearman's rho was used to examine the correlation between cost and mRS score. Multivariable logistic regression models were used to analyze all possible confounding factors in the total cost at one-year of follow-up. A p-value < 0.05 was considered to be statistically significant.

Results

Patient demographics

This retrospective study initially identified 1,066 subjects, of whom 31 patients were excluded due to lack of one year of follow-up, 18 patients were lost to follow-up, 26 patients refused to participate in the study, and 30 patients died during the follow-up period (Figure 1). In the final study group, there were 961 patients with ischemic stroke due to arterial occlusion who were in the younger age group, 733 (76.27%) were men, and the median age was 42.12 years (± 5.72 years). The mean baseline National Institutes of Health Stroke Scale (NIHSS) score of these subjects was 7.36 (± 5.72). Among all the 961 patients, 399 (41.5%) were smokers, 499 (51.9%) had a history of hypertension, 185 (19.3%) had a history of diabetes mellitus, 452 (47.0%) had hyperlipidemia, 279 (29.0%) were diagnosed with atrial fibrillation, 340 (35.4%) had hyperhomocysteinemia, and only 103 patients (10.7%) were treated with thrombolytic therapy.

Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiological classification

Baseline characteristics from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification subtypes are shown in Table 1 [10]. The five TOAST etiological subtypes were stroke due to large artery atherosclerosis (LAA), cardioembolism (CE), small artery occlusion (SAO), other determined causes (OC), and undetermined etiology (UND) [10]. Patients in the SAO subtype had the highest association with hypertension (59.7%), hyperlipidemia (60.2%), and more were smokers (56.2%) than other subtypes. Patients in the CE subtype had the highest association with atrial fibrillation (45.8%).

Hospital and outpatient healthcare costs

Costs for hospitalization and outpatient nursing were integrated to a total charge for one year. Total costs of follow-up one year

Table 1. Baseline characteristics of young ischemic stroke with Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification subtypes.

Baseline variable	LAA (n=309)	SAO (n=201)	CE (n=277)	OC (n=76)	UND (n=98)
Age, years, (mean ±SD)	44±6	44±4	40±6	41±3	42±7
Male gender	241 (78.0)	162 (80.6)	195 (70.4)	57 (75.0)	78 (79.6)
Smoker	106 (34.3)	113 (56.2)	106 (38.3)	25 (32.9)	43 (43.9)
Hypertension	157 (50.8)	120 (59.7)	144 (52.0)	32 (42.1)	46 (46.9)
Diabetes mellitus	63 (20.4)	38 (18.9)	49 (17.7)	14 (18.4)	21 (21.4)
Hyperlipidemia	168 (54.4)	121 (60.2)	109 (39.4)	23 (30.3)	31 (31.6)
Atrial fibrillation	51 (16.5)	48 (23.9)	127 (45.8)	29 (38.2)	24 (24.5)
Hyperhomocysteinemia	152 (49.2)	65 (32.3)	61 (22.0)	33 (43.4)	29 (29.6)
NIHSS score, (mean ±SD)	10.6±4.1	6.8±3.3	13.8±5.9	8.3±4.2	6.4±2.2
Thrombolysis	23 (7.4)	8 (4.0)	36 (13.0)	11 (14.5)	25 (25.5)

UND – undetermined etiology; OC – other determined cause; CE – cardioembolism; SAO – small artery occlusion; LAA – large artery atherosclerosis; TOAST – the Trial of Org 10172 in Acute Stroke Treatment; NIHSS – National Institute of Health Stroke Scale; SD – standard deviation.

Table 2. Cost differences in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification subtypes.

Cost	LAA	SAO	CE	OC	UND	P-value
Outpatient cost	3,865±1,320	3,106±1,118	3,432±1,125	3,448±1,095	1,073±927	<0.001
Inpatient cost	2,296±1,024	2,129±1,004	13,238±10,021	2,675±1,215	3,762±1,104	<0.001
One-year total cost	6,168±1,251	5,235±1,165	16,556±11,261	6,115±2,284	4,833±1,337	<0.001

UND – undetermined etiology; OC – other determined cause; CE – cardioembolism; SAO – small artery occlusion; LAA – large artery atherosclerosis; TOAST – the Trial of Org 10172 in Acute Stroke Treatment.

in this study were US\$ 10,954.14. The inpatient cost was US\$ 5,958.44, and the outpatient cost was US\$ 3,397.60. The TOAST type of ischemic stroke in young patients did influence costs, see details in Table 2. The inpatient (US \$13,238±10,021) and total costs at one year (US \$16,556±11,261) of CE subtype were the highest in all five subtypes (P< 0.001), while outpatient (US \$1,073±927) and total cost at one year (US \$4,833±1,337) of UND subtype were the least costly (P<0.001).

Costs at one-year follow-up

The distribution of modified Rankin Scale (mRS) scores at one-year follow-up in young patients with ischemic stroke with the five stroke subtypes are shown in Figure 2. There was a modest connection between etiology and quality of life, mRS scores were correlated positively with TOAST classification in young patients with ischemic stroke (r=0.77; p<0.05). Also, mRS scores were correlated positively with the total cost at one-year follow-up in young patients with following acute ischemic

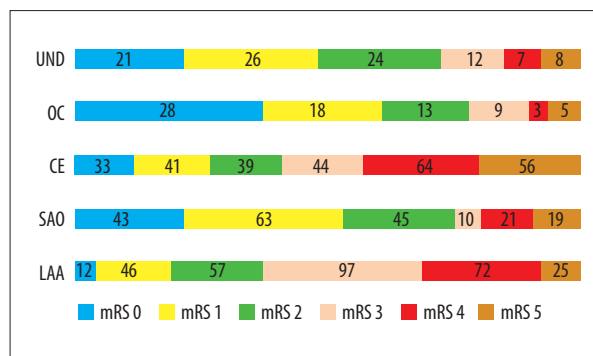


Figure 2. Modified Rankin Scale (mRS) score at one-year follow-up in younger patients with ischemic stroke and the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification subtypes. UND – undetermined etiology; OC – other determined cause; CE – cardioembolism; SAO – small artery occlusion; LAA – large artery atherosclerosis.

Table 3. Multiple variables regression analysis of influencing factors in the total costs at one-year follow-up in younger patients with ischemic stroke.

Variables	Partial regression coefficients	Standard error	OR value	95% CI	P-value
Constant	0.446	0.135			
mRS score	1.221	0.428	8.672	2.277–13.540	0.000
TOAST types	2.326	0.032	2.286	1.024–4.063	0.008
NIHSS score	1.029	0.608	1.126	1.003–3.118	0.015
Atrial fibrillation	1.135	0.322	4.663	1.332–5.826	0.039

OR – odds ratio; mRS – modified Rankin Scale; TOAST – the Trial of Org 10172 in Acute Stroke Treatment; NIHSS – National Institute of Health Stroke Scale; SD – standard deviation; CI – confidence interval.

stroke ($r=0.81$; $p<0.01$). Multivariable logistic regression analyses showed that the mRS score, TOAST subtypes, NIHSS score, and the presence of atrial fibrillation factors that influenced the total cost at one-year follow-up of younger patients with ischemic stroke. The mRS score was the most important influencing factor, followed by the TOAST subtypes, the NIHSS score, and the presence of atrial fibrillation (Table 3).

Discussion

In this retrospective clinical study of patients with ischemic stroke in the younger age group, the effects of the etiology of stroke on healthcare costs was evaluated by categorizing the study population according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, which included large artery atherosclerosis (LAA), cardioembolism (CE), small artery occlusion (SAO), other determined causes (OC), and undetermined etiology (UND) [10]. Stroke severity was assessed using the modified Rankin Scale (mRS) score and the National Institutes of Health Stroke Scale (NIHSS) score. The findings of this study showed that the healthcare costs for younger patients with ischemic stroke in China differed according to the TOAST subtypes and disease severity. The inpatient cost (US \$13,238±10,021) and one-year total costs (US \$16,556±11,261) of the CE subtype were the highest in all five subtypes, while outpatient (US \$1,073±927) and one-year total cost (US \$4,833±1,337) of UND subtype were the lowest. The mRS scores were positively correlated with total one-year cost in younger patients with ischemic stroke ($r=0.81$; $p<0.01$), and these findings are consistent with those of previously published studies [12,13].

The higher patient healthcare cost in the CE subtype of ischemic stroke might be explained by the fact that patients in this subpopulation had more serious disease that required cardiac surgery. Rha et al. reported that the difference in cost was not

significant after one year, because of most medical costs were expended within the first year following stroke, including for the inpatient care, acute nursing, surgery, and rehabilitation, and after a year, the medical charges were similar [14]. The lower total cost at one year in the UND subtype was due to lower outpatient costs, but with higher inpatient cost due to the need to undertake a range of investigations to determine the etiology of the ischemic stroke.

The findings of the present study showed that the found that mRS score, TOAST etiological subtypes, NIHSS score, and the presence of atrial fibrillation were factors that influenced the total cost at one-year follow-up of younger patients with ischemic stroke. Atrial fibrillation is an important factor that affects the cost of care for stroke patients because it can result in large infarct size and requires anticoagulation treatment and cardiac treatment. However, the findings for the mRS scores showed that patients in the CE subtype had an improved mRS score 0–2 outcome when compared with the LAA subtype. The reason for this finding among the younger patients with ischemic strokes might be that some patients with the CE subtype had cardiac thrombosis and embolism due to atrial fibrillation or congenital heart disease, mainly due to patent foramen ovale (125 patients in this study). Patent foramen ovale often causes mild stroke and the prognosis is relatively good, and so patients with the CE subtype had a better mRS 0–2 outcome than the LAA subtype.

Previous studies in adult patients with ischemic strokes have shown that comorbidities can affect the treatment costs. A study from Berlin demonstrated that the direct costs for patients with ischemic stroke without the presence of atrial fibrillation were significantly lower than treatment costs for ischemic stroke caused by atrial fibrillation [15]. This previous study also reported that diabetes and high blood pressure had a significant impact on acute inpatient and total charges [15]. A further study from the U.K. showed that the etiology of

stroke played a key role in the cost of secondary care from univariate data analysis, whereas only the initial stroke severity remained significant in multivariate analysis [16]. With regard to the TOAST subtype, there have been no previously published studies on the effect on healthcare cost for the younger patient with ischemic stroke.

The outcome date from the present study conducted in China, when compared with data from other countries, showed that the healthcare costs for younger patients with ischemic stroke within one year was less than for other countries, with an average per capita cost for stroke care of \$19,118 having been identified in a literature review that included 71 studies [17]. The possible reasons for this lower cost in China might be that China has a lower gross domestic product (GDP) and available healthcare expenditure compared with other developed countries, partly due to the lack of a Chinese social medical insurance system [18]. Also, most family relatives take responsibility for post-stroke care in China, which results in less cost to the employer and healthcare providers in direct medical charges. However, direct non-medical expenses were not evaluated in the present study.

This study had several limitations. This was a retrospective study in a single center that relied on the accuracy of patient medical records. The patient population came from a small southern city in China with a lower level of population income, which may not have been nationally representative. However, the study sample was large, and the clinical diagnoses were

made and the treatments were implemented in accordance with current Chinese clinical guidelines, including investigations, treatment, follow-up, and secondary prevention strategies. Therefore, the study findings reflected the economic level of a whole city and possibly an economic microcosm of the whole of China. A further limitation of the study was that direct nonmedical costs and indirect medical costs were not reported although an initial attempt was made to evaluate these costs. However, it was difficult to obtain this cost data within one year after the onset of stroke, patients or their families could not provide accurate details of these costs.

Conclusions

To our knowledge, this study was the first to provide healthcare cost data for younger patients with ischemic stroke in China and to evaluate the effects of the cause of stroke on these costs using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) etiological classification. The findings of this study showed that in the younger patient population in China, etiological factors influenced the economic burden of ischemic stroke, and highlight the need to integrate cost-benefit with etiology classification in this patient population.

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References:

- Donnan GA: Navigating 2018, a year in stroke. *Int J Stroke*, 2018; 13: 5
- Feigin VL, Roth GA, Naghavi M et al: Global burden of stroke and risk factors in 188 countries, during 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet Neurol*, 2016; 15(9): 913–24
- Lekander I, Willers C, von Euler M et al: Relationship between functional disability and costs one and two years post-stroke. *PLoS One*, 2017; 12: e0174861
- Wang W, Jiang B, Sun H et al: Prevalence, incidence, and mortality of stroke in China: Results from a nationwide population-based survey of 480 687 adults. *Circulation*, 2017; 135: 759–71
- Feigin VL, Norrving B, Mensah GA: Global burden of stroke. *Circ Res*, 2017; 120: 439–48
- Jennum P, Iversen HK, Ibsen R, Kjellberg J: Cost of stroke: A controlled national study evaluating societal effects on patients and their partners. *BMC Health Serv Res*, 2015; 15: 466
- Sonig A, Lin N, Krishna C et al: Impact of transfer status on hospitalization cost and discharge disposition for acute ischemic stroke across the US. *J Neurosurg*, 2016; 124: 1228–37
- Wang Q, Liu H, Lu ZX et al: Role of the new rural cooperative medical system in alleviating catastrophic medical payments for hypertension, stroke and coronary heart disease in poor rural areas of China. *BMC Public Health*, 2014; 14: 907
- Hamilton W, Huang H, Seiber E, Lo W: Cost and outcome in pediatric ischemic stroke. *J Child Neurol*, 2015; 30: 1483–88
- Adams HP Jr, Bendixen BH, Kappelle LJ et al: Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, 1993; 24: 35–41
- Bamford JM, Sandercock PA, Warlow CP, Slattery J: Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*, 1989; 20: 828
- Ng CS, Toh MP, Ng J, Ko Y: Direct medical cost of stroke in Singapore. *Int J Stroke*, 2015; 10(Suppl. A100): 75–82
- Chevreul K, Durand-Zaleski I, Gouepo A et al: Cost of stroke in France. *Eur J Neurol*, 2013; 20: 1094–100
- Rha JH, Koo J, Cho KH et al: Two-year direct medical costs of stroke in Korea: A multi-centre incidence-based study from hospital perspectives. *Int J Stroke*, 2013; 8: 186–92
- Brüggenjürgen B, Rossnagel K, Roll S et al: The Impact of atrial fibrillation on the cost of stroke: The Berlin acute stroke study. *Value Health*, 2007; 10: 137–43
- Luengo-Fernandez R, Gray AM, Rothwell PM: Population-based study of determinants of initial secondary care costs of acute stroke in the United Kingdom. *Stroke*, 2006; 37(10): 2579–87
- Luengo-Fernandez R, Gray AM, Rothwell PM: Costs of stroke using patient-level data: a critical review of the literature. *Stroke*, 2009; 40: e18–23
- Organization for Economic Cooperation and Development (OECD) Health Data, 2010. Available at <http://www.oecd.org/health>