

US Cost Burden of Ischemic Stroke: A Systematic Literature Review

Bart M. Demaerschalk, MD, MSc, FRCP(C); Ha-Mill Hwang, PharmD;
and Grace Leung, MPH

Stroke is one of the most significant health problems in the United States. In 2005, the prevalence of stroke was 5.8 million among adults age 20 years and older.¹ Given that the majority of strokes occur in the elderly (age >65 years), the prevalence of stroke is expected to increase dramatically with the lengthening of life expectancy and advancing age of our population. Approximately 780,000 strokes occur each year and of these, 600,000 are first attacks.¹ Stroke is the third leading cause of death behind heart disease and cancer and the leading cause of serious long-term disability.¹ In 2004, stroke accounted for approximately 1 of every 16 deaths.¹ Among all strokes, 87% are ischemic, 10% are intracerebral hemorrhage, and 3% are subarachnoid hemorrhage.¹ Stroke imposes a significant economic burden on our healthcare system, with acute ischemic stroke accounting for the bulk of costs. Total direct and indirect cost resulting from stroke has been reported to be more than \$65 billion for 2008 alone.¹ Direct cost encompasses all expenditures from hospitalization, nursing homes, physicians and other healthcare professionals, drugs and other medical durables, and home healthcare, whereas indirect cost accounts for lost productivity due to morbidity or mortality. Stroke can be ranked among the most expensive chronic diseases such as cancer (\$219.2 billion in 2007), diabetes (\$174 billion in 2007), and depression (\$83.1 billion in 2000).^{2,4}

Despite the high financial burden, limited recent studies have focused on costs associated with stroke in the United States. Establishing total stroke-related costs is essential to evaluate and support the health economic research on stroke systems of care. The present article provides a systematic review of the literature to determine the overall costs of stroke in the United States, with a focus on ischemic stroke when costs are specified by subtype.

METHODS

Literature Search

Full-text papers were identified on the basis of a literature search in PubMed/MEDLINE and Ovid/EMBASE databases from January 1995 to July 2008. The terms used for the electronic search included [ischemic stroke and costs and cost analysis] or [ischemic stroke and economics] or [ischemic stroke and hospital charges] or [ischemic stroke and fees] or [isch-

In this article

Take-Away Points / p526

www.ajmc.com

Full text and PDF

Web exclusive

eAppendices A and B

Background: Stroke is an expensive disease from a patient, caregiver, and societal perspective. In spite of the high cost burden, only limited numbers of recent studies have focused on stroke-related costs in the United States.

Objective: To conduct a systematic literature review to determine current US costs of stroke and to assess if a gap in available information exists.

Methods: A literature search was conducted using the PubMed/MEDLINE and Ovid/EMBASE databases, within the date range of January 1995 to July 2008. The search, screening, application of eligibility criteria, appraisal, data extraction, and synthesis were completed by one investigator and then independently confirmed by a second.

Results: The literature review revealed that the majority of cost-related analyses focused on short-term in-hospital care and early critical care as the key drivers of acute ischemic stroke hospitalization costs. Moreover, long-term medical expenses resulting from nursing home and ambulatory care as well as indirect expenditure from lost earnings and informal care represent the most significant burden on lifetime costs of stroke.

Conclusions: Further studies that focus on these long-term and indirect expenditures are essential to assess the impact of new treatments on total stroke costs. Overall, the high costs associated with stroke clearly indicate there is an imperative need for effective preventive therapy, early critical care, and rehabilitation, which in turn will reduce the national expenditure for stroke-related healthcare services and improve productivity.

(*Am J Manag Care.* 2010;16(7):525-533)

**For author information and disclosures,
see end of text.**

Take-Away Points

A systematic review of the literature was done to determine the overall costs of stroke in the United States, with a focus on ischemic stroke, which accounts for the bulk of the costs.

- The majority of cost-related analyses focused on short-term in-hospital care and early critical care as the key drivers of acute ischemic stroke hospitalization costs.
- Further studies that focus on long-term and indirect expenditures are essential to assess the impact of new treatments on total stroke costs.
- There is an imperative need for effective preventive therapy, early critical care, and rehabilitation.

emic stroke and reimbursement] or [ischaemic stroke and costs and cost analysis] or [ischaemic stroke and economics] or [ischaemic stroke and hospital charges] or [ischaemic stroke and fees] or [ischaemic stroke and reimbursement] and not atrial fibrillation and not hypertension. Even though the search focused on ischemic stroke, articles that did not specify stroke type were not excluded. We limited the search to titles and abstracts of human studies conducted in the United States and published in English. Search strategy development, searching, screening, application of criteria, selection, appraisal, data extraction, and synthesis were completed by at least 2 investigators. Disagreements were resolved by consensus.

Exclusion Criteria

Title and abstract content exclusion criteria were (1) disease areas other than stroke, (2) focus on stroke prevention, (3) focus on nonadult patients, (4) focus other than cost of illness, and (5) country of origin outside the United States. Additionally, articles were excluded when the content of the publication (6) had a focus other than cost of illness or (7) lacked quantitative methods.

Quality Assessment of Publications

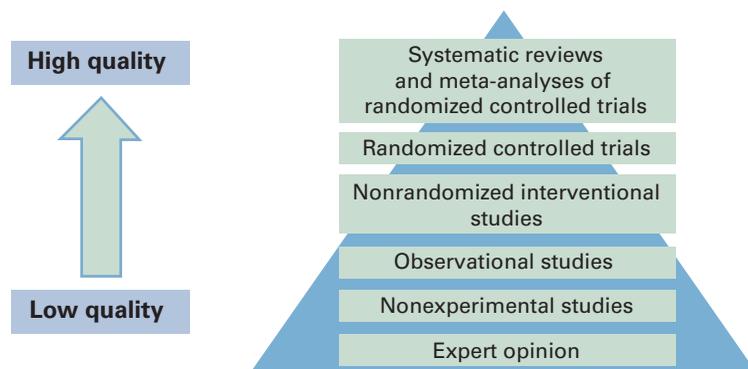
Several instruments are designed for critical appraisal of economic analyses.^{5,6} In the current literature review, the

selected publications were assessed with the SIGN grading system, which provides levels of evidence and grades of recommendation for evidence-based clinical guidelines.⁶ The study type combined with an assessment of methodologic quality determines the level of evidence.⁶ Systematic reviews, meta-analyses of randomized controlled trials, and randomized controlled trials rank above nonrandom-

ized interventional and observational studies, whereas non-experimental studies and expert opinion are ranked at the bottom (Figure 1).⁶ Based on this hierarchy, a level of evidence of 1++ applies to high-quality meta-analyses, systematic reviews of randomized controlled trials, or randomized controlled trials with a very low risk of bias, while a level of evidence of 4 applies to an expert opinion.⁶ In the final step, a grade of recommendation (A through D) is assigned to each study or recommendation based on the level of evidence as follows:

- **Grade A.** At least 1 meta-analysis, systematic review, or randomized controlled trial rated as 1++ and directly applicable to the target population, or a systematic review of randomized controlled trials or a body of evidence consisting largely of 1+ related studies directly applicable to the target population and demonstrating overall consistency of results.
- **Grade B.** A body of evidence, including 2+ rated studies directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from 1++ or 1+ rated studies.
- **Grade C.** A body of evidence, including 2+ rated studies directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from 2++ rated studies.
- **Grade D.** Evidence level 3 or 4 or extrapolated evidence from 2+ rated studies.⁶

■ **Figure 1.** Hierarchy of Study Types^a



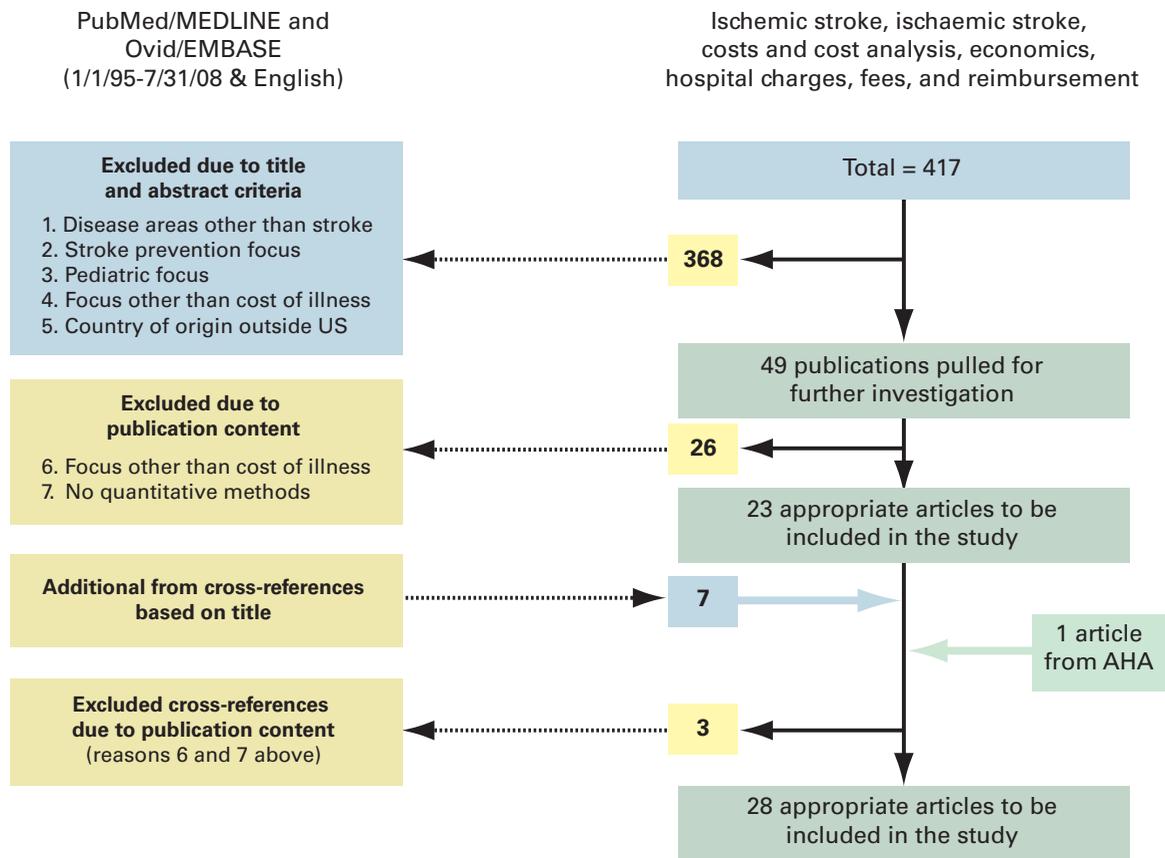
^aData from Harbour et al.⁶

RESULTS

Search Yield and Quality Assessment

A total of 417 potential abstracts were identified; 408 from MEDLINE via PubMed and 9 from EMBASE via Ovid. Of the 417 abstracts, 368 were excluded due to the aforementioned title and abstract content exclusion criteria 1-5 (Figure 2). Of the 49 publications pulled for further investigation, 26 were excluded because of publication content exclusion criteria 6 and 7. Thus, of the 417 abstracts that were initially selected from

■ **Figure 2.** Search Methodology and Exclusion Criteria for Stroke Cost of Illness Publications



AHA indicates American Heart Association.

the literature search using the PubMed/MEDLINE and Ovid/EMBASE databases, 23 articles met the inclusion criteria and were chosen for this study. One additional publication by the American Heart Association and 7 additional publications from cross-references based on the title were added to the list. Of the 7 additional publications, 3 were excluded because of the publication content exclusion criteria 6 and 7. Overall, a total of 28 articles were considered appropriate to be included in the present analysis. Of the 28 articles, 8 were published after 2005. A majority of the selected publications focused on direct costs, 5 of the 28 publications addressed aggregate or indirect costs, 3 addressed hospital resources, and 7 addressed medical resource use. Among the publications that focused on direct costs, there was a greater emphasis on emergency and short-term care, and less emphasis on outpatient, rehabilitation, and nursing home care.

In terms of quality assessment, 17 publications were assigned a grade B recommendation, 8 were assigned grade C, and 3 were assigned grade D, indicating an overall “moderate” rating. A high level of evidence or a grade A recommendation is typically not expected for economic studies because the

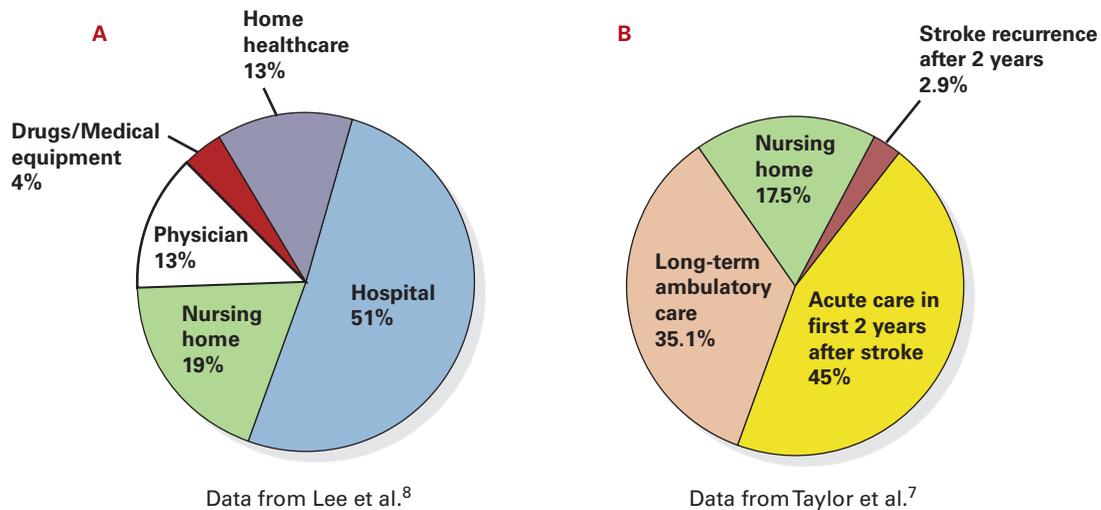
randomized controlled trial design is not always practical and these studies are more likely to be retrospective or prospective claims analyses, cohort studies, or case reports.⁶

Costs of Stroke in the United States

The total cost of stroke encompasses direct costs for providing medical care to patients as well as indirect costs associated with lost productivity.⁷ A breakdown of direct costs by type of expense as reported by Lee and colleagues and Taylor and colleagues is provided in **Figure 3**.^{7,8}

Short-Term Direct Costs. Most cost-analysis studies conducted thus far have focused on short-term, in-hospital costs of stroke (**Table 1**).⁹⁻²² The majority of these studies are retrospective analyses of different inpatient care databases, and there is considerable variation in patient numbers among these studies. For example, a study by Diringer and colleagues¹⁵ included 191 patients consecutively admitted with acute ischemic stroke at a tertiary care academic medical center in 1996, whereas Qureshi and colleagues¹⁰ analyzed data of more than a million patients from the Nationwide Inpatient Survey with stroke admissions from

■ **Figure 3.** Breakdown of Direct Costs of Stroke (Short Term and Long Term) by Type of Expense



1990 to 1991 or 2000 to 2001. When converted to 2008 dollars, the mean hospitalization costs ranged from \$8000 to \$23,000. Mean length of hospital stay ranged from 4.6 to 12.4 days.

Early critical care has been identified as a key driver of acute ischemic stroke hospitalization costs. In a report by Demaerschalk and Durocher,²³ early critical care accounted for nearly one-third of the total expenditure for the short-term inpatient stay of patients who received recombinant tissue plasminogen activator (rt-PA) therapy for ischemic stroke (eAppendix A, available at www.ajmc.com). Other major expenses were distributed as follows: 19% for medical-surgical short-term care services, 19% for radiology, 8% for rehabilitation therapies, 7% for pharmacy, and 7% for laboratory.²³ These results were in agreement with the breakdown provided by Diringier and colleagues,¹⁵ wherein 50% of hospital costs for acute ischemic stroke were attributed to room charges (34% for ward beds, 16% for intensive care unit beds), 19% for diagnostic radiology, 7% for short-term rehabilitation therapy, 5% for laboratory tests, and 5% for pharmacy.

Long-Term Direct Costs. Table 2 presents a summary of studies reporting average per patient direct costs of stroke in the longer term (ie, more than 30 days poststroke).²⁴⁻²⁶ A large number of these studies were retrospective analyses of a sample of Medicare patients hospitalized for ischemic stroke. The outcomes measured varied considerably among these studies. For example, Kind and colleagues²⁴ analyzed 1-year mortality and predicted total healthcare payments for 30 to 365 days after acute stroke hospitalization; Lee and colleagues⁸ calculated costs from 1 year prior to the index event through 4 years following that event; Lipscomb and

colleagues²⁶ measured Medicare costs for each month (up to 36 months) following discharge from the index hospitalization; and Leibson and colleagues²⁰ assessed inpatient and outpatient short-term care activity for the 12 months before and after stroke.

In the study by Leibson and colleagues,²⁰ total inpatient and outpatient charges during the 12-month poststroke period were reported to be 3.4 times higher than those in the 12-month prestroke period. The analyses by Samsa and colleagues,¹⁴ Lipscomb and colleagues,²⁶ and Sloss and colleagues²⁵ have shown that the total stroke-related costs are highest during months 1 to 3 after a stroke. Taylor and colleagues⁷ reported direct cost of ischemic stroke per person during the first year in 1990 of approximately \$15,102 to \$20,574, depending on age. Fagan and colleagues¹⁶ estimated a mean cost (converted to 1996 dollars) nearing \$30,000 for year 1 and approximately \$60,000 as total cost (ie, short-term plus long-term care for the treatment of patients with acute ischemic stroke). Lee and colleagues⁸ reported an average Medicare expenditure of \$39,396 (in 1997 dollars) from the initial event through 4 years in patients identified as having acute ischemic stroke. These data emphasize the need for effective preventive and early critical care.⁸

Indirect Costs. The majority of lifetime costs for each type of stroke results from indirect costs. Indirect costs are a result of premature mortality and reduced productivity for stroke survivors.⁷ In the study by Taylor and colleagues,⁷ indirect costs accounted for 58% (\$23.6 billion) of lifetime stroke costs in the United States. Lost earnings owing to premature mortality accounted for 56% of total indirect costs, and the remainder was a result of lost earnings for stroke survivors.⁷ A cost analysis study by Brown and col-

Cost Burden of Ischemic Stroke

Table 1. Summary of Studies Reporting Average per Patient Direct Costs of Short-Term Care for Stroke (ie, In-Hospital Costs)

Study	Years of Data Collection (Dollar Years Reported)	Design	Patients	Mean Cost (Hospitalization)	Mean Cost (Adjusted to 2008 Dollars) ^a	Mean LOS
Katzan 2007 ⁹	1991-1997 (costs adjusted to 2000 dollars)	Retrospective cohort study (greater Cleveland area)	11,286 Medicare patients admitted for first stroke (635 with pneumonia)	\$6272 without pneumonia; \$21,173 with pneumonia	\$7842 without pneumonia; \$26,470 with pneumonia	7.6 days without pneumonia; 18.6 days with pneumonia (median LOS)
Qureshi 2007 ¹⁰	1990-1991 and 2000-2001 (all costs reported in 2001 dollars)	Retrospective database analysis (US all-payer inpatient care databases)	(approx)1.13 million admissions in 1990-1991; (approx)1.26 million admissions in 2000-2001 (both periods, for ischemic stroke)	1990-1991: \$13,700 2000-2001: \$16,200	1990-1991: \$16,655 2000-2001: \$19,695	1990-1991: 9.5 days 2000-2001: 5.3 days
Reed 2001 ¹¹	1998	Retrospective data for all patients admitted to 137 community hospitals	18,740 patients with ischemic cerebral infarction	\$5837	\$7710	5.9 days
Caro 2000 ¹²	1996 (costs reported in 1996 dollars)	Cost data extracted from 2 prospective 12-week international trials (1 in the United States and Canada)	593 US patients with acute ischemic stroke	\$7461	\$10,238	9 days (median)
Gillum 2001 ¹³	1997-1999	Retrospective analysis of administrative database	10,880 patients with ischemic stroke	\$18,000	ND	7.7 days
Samsa 1999 ¹⁴	1991	Retrospective analysis of Medicare claims files	49,333 Medicare patients hospitalized with cerebral infarction in 1991 (4947 with previous stroke in the past 4 years)	Initial hospital cost: \$7091 (first stroke); \$6939 (recurrent stroke)	Initial hospital cost: \$11,209 (first stroke); \$10,969 (recurrent stroke)	Initial LOS 10.9 days (first stroke); 11.6 days (recurrent stroke)
Diringer 1999 ¹⁵	1996	Prospective data collection at a tertiary care academic medical center with a stroke management team	191 patients consecutively admitted with acute ischemic stroke	\$4408 (median hospital cost per discharge)	\$6049 (median hospital cost per discharge)	6 days (median)
Fagan 1998 ¹⁶	Costs reported in 1996 dollars	Markov model estimating costs per 1000 patients treated with rt-PA vs 1000 untreated patients (NINDS rt-PA Stroke Trial)	Data at 10 days poststroke: 307 placebo and 310 rt-PA	Initial hospitalization: \$14,923 (placebo) and \$14,121 (rt-PA)	Initial hospitalization: \$20,478 (placebo) and \$19,377 (rt-PA)	12.4 days (placebo) and 10.9 days (rt-PA)
Newell 1998 ¹⁷	1995 and 1997	Retrospective analysis of medical record and financial databases in a 22-county region (northern Mississippi, Alabama, and Tennessee)	356 patients with ischemic stroke in 1995, 399 patients in 1997	1995: \$7111 1997: \$6246	1995: \$10,046 1997: \$8379	1995: 9.9 days 1997: 7.2 days

(Continued)

■ **Table 1.** Summary of Studies Reporting Average per Patient Direct Costs of Short-Term Care for Stroke (ie, in-Hospital Costs) (*Continued*)

Study	Years of Data Collection (Dollar Years Reported)	Design	Patients	Mean Cost (Hospitalization)	Mean Cost (Adjusted to 2008 Dollars) ^a	Mean LOS
Holloway 1996 ¹⁸	1992	Retrospective analysis of administrative and billing data from 5 academic medical centers	908 patients with ischemic cerebral infarction	Mean cost per admission: \$9882 (median \$6824)	Mean cost per admission: \$15,165	10.8 days
Alberts 1996 ¹⁹	1993-1994 (baseline period)	Retrospective analysis of administrative data from the neurology service at a tertiary care hospital	262 stroke patients discharged from neurology service	Mean total charges per case: \$13,149 (median \$10,234)	ND	9.2 days (median 7.0 days)
Leibson 1996 ²⁰	1987-1989 (costs adjusted to 1989 dollars)	Retrospective analysis of Rochester (Minnesota) Stroke Registry	241 patients with confirmed first stroke (hospitalized)	Short-term care activity (inpatient and outpatient) in first 30 days poststroke: mean \$13,343 (median \$8619)	Short-term care activity (inpatient and outpatient) in first 30 days poststroke: mean \$23,168	Not specified
Monane 1996 ²¹	1982-1995	Observational, retrospective, consecutive case series (large tertiary care hospital in Massachusetts)	745 patients age ≥65 years admitted with ischemic stroke	Median total charges: \$8740	ND	7 days (median)
Wentworth 1996 ²²	1990-1994	Retrospective cost analysis (acute stroke unit opened in 1990)	414 Medicare patients with stroke	1990: \$14,076 1994: \$10,740	1990: \$23,187 1994: \$15,603	1990: 7 days 1994: 4.6 days

LOS indicates length of stay; ND, not determined; NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator.

^aCosts were converted to 2008 dollars using the Consumer Price Index inflation calculator (http://www.bls.gov/data/inflation_calculator.htm).

leagues²⁷ provided a projected breakdown of indirect costs (lost earnings and informal care) as well as direct costs caused by ischemic stroke (from 2005 to 2050) in non-Hispanic whites, African Americans, and Hispanics. Informal care refers to in-home assistance with activities of daily living as provided by a relative or unpaid nonrelative not associated with an organization.²⁸ The single largest contributor to overall costs in all race/ethnic groups was lost earnings (33%, 43%, and 30%, respectively), and the second largest contributor to overall costs was informal caregiving (19%, 16%, and 19%).²⁷

Aggregate Lifetime Costs. The US aggregate lifetime cost of first strokes was estimated to be \$40.6 billion by Taylor and colleagues in 1990,⁷ with ischemic stroke accounting for \$29 billion. Short-term care costs incurred in the first 2 years after a stroke (45%), long-term ambulatory

care (35%), and nursing home costs (17.5%) constituted the major expenditure groups.⁷ The mean lifetime cost of ischemic stroke was estimated at nearly \$91,000 in 1990 dollars.⁷ Lifetime cost of stroke per person was calculated as the sum of direct and indirect costs, while aggregate lifetime cost of stroke was calculated by multiplying the per person lifetime cost by the estimated incidence of first strokes in 1990.⁷ The American Heart Association estimated the direct medical and indirect expenditures attributable to stroke in 2008 as \$65.5 billion and the mean lifetime cost of ischemic stroke, which included inpatient care, rehabilitation, and follow-up care, as \$140,048 (converted to 1999 dollars).¹ Brown and colleagues²⁷ projected the US costs of ischemic stroke from 2005 to 2050 (in 2005 dollars) to be approximately \$2.2 trillion; \$1.52 trillion for non-Hispanic whites, \$313 billion for Hispanics, and \$379 billion for African Ameri-

Cost Burden of Ischemic Stroke

Table 2. Summary of Studies Reporting Average per Patient Direct Costs of Stroke in the Longer Term (More Than 30 Days Poststroke)

Study	Years of Data Collection	Design	Patients	Stroke Type	Mean Cost (Time Frame Covered)
Kind 2008 ²⁴	2000	Retrospective analysis of administrative data (southern and eastern United States)	9463 Medicare patients (≥65 years) with 0 bounce-backs to hospital within 30 days of stroke	Acute ischemic stroke	30-365 days poststroke 50th percentile: \$9767 10th and 90th percentiles: \$1667–\$35,854
Lee 2007 ⁸	1997	National random sample of Medicare beneficiaries	9131 Medicare patients	Ischemic stroke	\$39,396 (from initial event through 4 years)
Sloss 2004 ²⁵	1995-1998	Claims data from US managed care organizations	108 patients with commercial insurance and 113 patients with Medicare experiencing secondary stroke	Ischemic stroke	\$10,267 for commercial insurance or \$16,280 for Medicare (180-day attributable costs: 70% to 80% of costs were incurred in first 30 days)
Samsa 1999 ¹⁴	1991	Retrospective analysis of Medicare claims files	49,333 Medicare patients hospitalized with cerebral infarction in 1991 (4947 with previous stroke in past 4 years)	Ischemic stroke	Costs per patient-month: First strokes (recurrent strokes): months 1–3, \$3368 (\$3315) months 4–12, \$1361 (\$1700) months 13–24, \$1168 (\$1580)
Fagan 1998 ¹⁶	Costs reported in 1996 dollars	Markov model estimating costs per 1000 patients treated with rt-PA vs 1000 untreated patients (NINDS rt-PA Stroke Trial)	Data at 1 year poststroke: 294 placebo and 298 rt-PA	Acute ischemic stroke	Cost at 1 year: \$29,810 (placebo) and \$29,207 (rt-PA) Total cost (short-term plus long-term care): \$62,716 (placebo) and \$58,461 (rt-PA)
Lipscomb 1998 ²⁶	1991-1993	Analysis of data from a national sample of Medicare patients hospitalized for ischemic stroke	21,546 Medicare patients	Ischemic stroke	Mean Medicare costs following discharge from index hospitalization: 1 month: \$4207 36 months: \$694
Leibson 1996 ²⁰	1987-1989	Retrospective analysis of Rochester (Minnesota) Stroke Registry	292 patients with confirmed first stroke	All types (ischemic and hemorrhagic)	Total inpatient and outpatient charges in 12 months poststroke: 3.4 times higher than for 12 months preceding stroke
Taylor 1996 ⁷	1990 (estimates in 1990 dollars)	Computer-simulation model	NA	Ischemic stroke	Year 1 annual direct cost: \$20,574 (age <65 years) \$15,102 (age ≥85 years) Year 2 annual direct cost: \$7825 (age <65 years) \$4629 (age ≥85 years) Mean lifetime cost per person: \$90,981

NA indicates not available; NINDS, National Institute of Neurological Disorders and Stroke; rt-PA, recombinant tissue plasminogen activator.

cans. The projected proportion of indirect and direct costs of ischemic stroke by ethnic group is presented the [eAppendix B](#), available at www.ajmc.com.²⁷ The proposed figures likely underestimate the true burden of stroke, because the

estimates do not take into account the rise in salaries and treatment costs, growth among minority populations, and the increase in risk factors for stroke such as obesity, diabetes, and heart disease.

DISCUSSION

It should be noted that the SIGN grading system was used in this literature review to rank economic studies, although it was designed to grade levels of evidence and evidence-based clinical studies and as such may not be a reliable instrument for assessing economic studies. Nonetheless, stroke presents a substantial burden on the healthcare system as well as on patients, family, and society.⁷ The majority of the literature addressing stroke-related costs focuses on short-term, in-hospital expenditures, with costs ranging from approximately \$8000 to \$23,000 (adjusted to 2008 dollars), depending on the length of hospital stay. Also, the literature search did not identify studies that determined the cost of stroke rehabilitation care. In contrast, there is a relative scarcity of quality studies focusing on the long-term components of direct stroke-related medical expenses, which are substantial. For example, in the study by Taylor and colleagues,⁷ long-term ambulatory care accounted for 35% and nursing home costs accounted for 17.5% of total direct costs of stroke. In 1990 alone, there were more than 100,000 stroke-related nursing home admissions with a mean length of stay of 432 days,⁷ and in 1993 the annual cost for nursing home care based on a study of long-term care US insurers was \$20,000 to \$50,000.¹⁶ These data emphasize the need for further studies that would examine the long-term components of stroke-related medical costs. Additionally, almost all of the studies citing short-term and long-term costs were from the 1990s, highlighting the need for more current data on the costs of stroke.

Those long-term expenses are estimated to be substantial. Assuming 3% yearly inflation from 2008, total direct and indirect costs of stroke in the United States would be \$108 billion in 2025,¹ and per the cost-analysis study by Brown and colleagues,²⁷ the total cost of stroke from 2005 to 2050 is projected to be \$2.2 trillion. These cost projections for stroke are comparable to those for other high-impact chronic diseases such as cancer and cardiovascular disease. The annual productivity loss from cancer mortality is projected to be \$308 billion in 2020, while the cost associated with cancer-related deaths is expected to be \$1.47 trillion in 2020.^{29,30} The total cost of heart disease is projected to be \$149 billion in 2025.³¹

Direct and indirect costs associated with stroke can be reduced by wider utilization of improved strategies for stroke care. rt-PA (Activase), approved in 1996 by the US Food and Drug Administration (FDA), has remained the only FDA-approved drug that is indicated for improving neurologic recovery and reducing the incidence of disability in adults with acute ischemic stroke.³² Additionally, there

have been numerous cost-effectiveness studies of rt-PA, including that by Fagan and colleagues,¹⁶ which showed a decrease in rehabilitation costs of \$1.4 million and nursing home costs of \$4.8 million per 1000 eligible rt-PA-treated patients. More recently, other improved treatment strategies include the establishment of primary stroke centers and stroke center matrices that encompass multidisciplinary specialized stroke teams,³³⁻³⁵ stroke telemedicine via state-of-the-art video telecommunications and Internet-based consultative modalities for healthcare professionals and patients mainly in underserved urban and rural areas,³⁶⁻³⁹ and expansion of the rt-PA treatment time window.⁴⁰ However, further studies are required to quantify the cost-effectiveness or cost savings of these interventions independently, and when combined in regional strategies and community networks of stroke care.

Acknowledgments

We gratefully acknowledge Shilpa Lalchandani, PhD, Embryon, for assistance with the revisions and further development of the manuscript based on critical comments and direction from all authors; Susan Hogan, PhD, Embryon, for reviewing the manuscript for scientific accuracy; and Vicki Blasberg, Embryon, for managing the coordination of manuscript development and submission.

Author Affiliations: From the Department of Neurology (BMD), Mayo Clinic Hospital, Phoenix, AZ; and Genentech, Inc (HMH, GL), South San Francisco, CA.

Funding Source: Genentech, Inc, South San Francisco, CA, provided funding for editorial assistance to Embryon for editing, proofreading, and reference verification.

Author Disclosure: Dr Demaerschalk is the principal investigator (PI) for STRoKE DOC AZ TIME (Arizona Department of Health Service [ADHS]) and Stroke Telemedicine for Arizona Rural Residents (ADHS); the site PI for Interventional Management of Stroke III (IMS III; National Institutes of Health [NIH]), Stenting and Aggressive Medical Management for Preventing Recurrent Stroke (SAMMPRIS; NIH), Secondary Prevention of Small Subcortical Strokes (SPS3; NIH), Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST; NIH), Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT; AGA Medical Corporation), V10153 Acute Stroke Thrombolysis Trial (VASTT; Vernalis), Ancrod Stroke Program (ASP, Neurobiological Technology), and MP-124-A07 Trial (Mitsubishi Pharma); a co-investigator for ALbumin In Acute Stroke (ALIAS; NIH), CHOICE (Abbott), and ACT I (Abbott); a steering committee member for SPS3, ASP, and VASTT; a Data Safety Monitoring Board member for IN-STEP (Vernalis); medical monitor for Neuralieve; and an event adjudicator for Axio Research. He reports no other consultancies, honoraria, speaker bureau memberships, employment relationships, or stocks. Ms Leung is an employee of Genentech, the company that funded this work. Dr Hwang was an employee of Genentech at the time this study was developed. She is now with the University of California San Francisco, San Francisco, CA.

The opinions expressed in the current article are those of the authors. The authors received no honoraria or other form of financial support related to the development of this manuscript.

Authorship Information: Concept and design (BMD, HMH, GL); acquisition of data (BMD, HMH, GL); analysis and interpretation of data (BMD, HMH, GL); drafting of the manuscript (BMD, GL); and critical revision of the manuscript for important intellectual content (BMD, HMH, GL).

Address correspondence to: Bart M. Demaerschalk, MD, MSc, FRCP(C), Department of Neurology, Mayo Clinic Hospital, 5777 E Mayo Blvd, Phoenix, AZ 85054. E-mail: demaerschalk.bart@mayo.edu.

REFERENCES

1. **American Heart Association.** *Heart Disease and Stroke Statistics—2008 Update.* Dallas, TX: American Heart Association; 2008.
2. **American Cancer Society.** *Cancer Facts & Figures 2008.* Atlanta, GA: American Cancer Society, Inc; 2008.
3. **American Diabetes Association.** Economic costs of diabetes in the U.S. in 2007 [published correction appears in *Diabetes Care.* 2008;31(6):1271]. *Diabetes Care.* 2008;31(3):596-615.
4. **Greenberg PE, Kessler RC, Birnbaum HG, et al.** The economic burden of depression in the United States: how did it change between 1990 and 2000? *J Clin Psychiatry.* 2003;64(12):1465-1475.
5. **O'Brien BJ, Heyland D, Richardson WS, Levine M, Drummond MF.** Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA.* 1997;277(22):1802-1806.
6. **Harbour R, Miller J; for the Scottish Intercollegiate Guidelines Network Grading Review Group.** A new system for grading recommendations in evidence based guidelines. *BMJ.* 2001;323(7308):334-336.
7. **Taylor TN, Davis PH, Torner JC, Holmes J, Meyer JW, Jacobson MF.** Lifetime cost of stroke in the United States. *Stroke.* 1996;27(9):1459-1466.
8. **Lee WC, Christensen MC, Joshi AV, Pashos CL.** Long-term cost of stroke subtypes among Medicare beneficiaries. *Cerebrovasc Dis.* 2007;23(1):57-65.
9. **Katzen IL, Dawson NV, Thomas CL, Votruba ME, Cebul RD.** The cost of pneumonia after acute stroke. *Neurology.* 2007;68(22):1938-1943.
10. **Qureshi AI, Suri MF, Nasar A, et al.** Changes in cost and outcome among US patients with stroke hospitalized in 1990 to 1991 and those hospitalized in 2000 to 2001. *Stroke.* 2007;38(7):2180-2184.
11. **Reed SD, Cramer SC, Blough DK, Meyer K, Jarvik JG.** Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. *Stroke.* 2001;32(8):1832-1840.
12. **Caro JJ, Huybrechts KF, Duchesne I.** Management patterns and costs of acute ischemic stroke: an international study. For the Stroke Economic Analysis Group. *Stroke.* 2000;31(3):582-590.
13. **Gillum LA, Johnston SC.** Characteristics of academic medical centers and ischemic stroke outcomes. *Stroke.* 2001;32(9):2137-2142.
14. **Samsa GP, Bian J, Lipscomb J, Matchar DB.** Epidemiology of recurrent cerebral infarction: a Medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. *Stroke.* 1999;30(2):338-349.
15. **Diringer MN, Edwards DF, Mattson DT, et al.** Predictors of acute hospital costs for treatment of ischemic stroke in an academic center. *Stroke.* 1999;30(4):724-728.
16. **Fagan SC, Morgenstern LB, Petitta A, et al.** Cost-effectiveness of tissue plasminogen activator for acute ischemic stroke. NINDS rt-PA Stroke Study Group. *Neurology.* 1998;50(4):883-890.
17. **Newell SD Jr, Englert J, Box-Taylor A, Davis KM, Koch KE.** Clinical efficiency tools improve stroke management in a rural southern health system. *Stroke.* 1998;29(6):1092-1098.
18. **Holloway RG, Witter DM Jr, Lawton KB, Lipscomb J, Samsa G.** Inpatient costs of specific cerebrovascular events at five academic medical centers. *Neurology.* 1996;46(3):854-860.
19. **Alberts MJ, Bennett CA, Rutledge VR.** Hospital charges for stroke patients. *Stroke.* 1996;27(10):1825-1828.
20. **Leibson CL, Hu T, Brown RD, Hass SL, O'Fallon WM, Whisnant JP.** Utilization of acute care services in the year before and after first stroke: a population-based study. *Neurology.* 1996;46(3):861-869.
21. **Monane M, Kanter DS, Glynn RJ, Avorn J.** Variability in length of hospitalization for stroke. The role of managed care in an elderly population. *Arch Neurol.* 1996;53(9):875-880.
22. **Wentworth DA, Atkinson RP.** Implementation of an acute stroke program decreases hospitalization costs and length of stay. *Stroke.* 1996;27(6):1040-1043.
23. **Demaerschalk BM, Durocher DL.** How diagnosis-related group 559 will change the US Medicare cost reimbursement ratio for stroke centers. *Stroke.* 2007;38(4):1309-1312.
24. **Kind AJ, Smith MA, Liou JI, Pandhi N, Frytak JR, Finch MD.** The price of bouncing back: one-year mortality and payments for acute stroke patients with 30-day bounce-backs. *J Am Geriatr Soc.* 2008;56(6):999-1005.
25. **Sloss EM, Wickstrom SL, McCaffrey DF, et al.** Direct medical costs attributable to acute myocardial infarction and ischemic stroke in cohorts with atherosclerotic conditions. *Cerebrovasc Dis.* 2004;18(1):8-15.
26. **Lipscomb J, Ancukiewicz M, Parmigiani G, Hasselblad V, Samsa G, Matchar DB.** Predicting the cost of illness: a comparison of alternative models applied to stroke. *Med Decis Making.* 1998;18(2 suppl):S39-S56.
27. **Brown DL, Boden-Albala B, Langa KM, et al.** Projected costs of ischemic stroke in the United States. *Neurology.* 2006;67(8):1390-1395.
28. **Hickenbottom SL, Fendrick AM, Kutcher JS, Kabeto MU, Katz SJ, Langa KM.** A national study of the quantity and cost of informal caregiving for the elderly with stroke. *Neurology.* 2002;58(12):1754-1759.
29. **Bradley CJ, Yabroff KR, Dahman B, Feuer EJ, Mariotto A, Brown ML.** Productivity costs of cancer mortality in the United States: 2000-2020. *J Natl Cancer Inst.* 2008;100(24):1763-1770.
30. **Yabroff KR, Bradley CJ, Mariotto AB, Brown ML, Feuer EJ.** Estimates and projections of value of life lost from cancer deaths in the United States. *J Natl Cancer Inst.* 2008;100(24):1755-1762.
31. **Steinwachs DM, Collins-Nakai RL, Cohn LH, Garson A Jr, Wolk MJ.** The future of cardiology: utilization and costs of care. *J Am Coll Cardiol.* 2000;35(5 suppl B):91B-98B.
32. **Activase [prescribing information].** South San Francisco, CA: Genentech, Inc; 2005.
33. **Alberts MJ, Hademenos G, Latchaw RE, et al.** Recommendations for the establishment of primary stroke centers. The Brain Attack Coalition. *JAMA.* 2000;283(23):3102-3109.
34. **Wein TH, Hickenbottom SL, Alexandrov AV.** Thrombolysis, stroke units and other strategies for reducing acute stroke costs. *Pharmacoeconomics.* 1998;14(6):603-611.
35. **Demaerschalk BM, Bobrow BJ, Paulsen M; Phoenix Operation Stroke Executive Committee.** Development of a metropolitan matrix of primary stroke centers: the Phoenix experience. *Stroke.* 2008;39(4):1246-1253.
36. **Levine SR, Gorman M.** "Telestroke": the application of telemedicine for stroke. *Stroke.* 1999;30(2):464-469.
37. **Schwamm LH, Holloway RG, Amarenco P, et al; American Heart Association Stroke Council; Interdisciplinary Council on Peripheral Vascular Disease.** A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association. *Stroke.* 2009;40(7):2616-2634.
38. **Schwamm LH, Audebert HJ, Amarenco P, et al; American Heart Association Stroke Council; Council on Epidemiology and Prevention; Interdisciplinary Council on Peripheral Vascular Disease; Council on Cardiovascular Radiology and Intervention.** Recommendations for the implementation of telemedicine within stroke systems of care: a policy statement from the American Heart Association. *Stroke.* 2009;40(7):2635-2660.
39. **Demaerschalk BM, Miley ML, Kieman TE, et al; STARR Coinvestigators.** Stroke telemedicine [published correction appears in *Mayo Clin Proc.* 2010;85(4):400]. *Mayo Clin Proc.* 2009;84(1):53-64.
40. **del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council.** Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke.* 2009;40(8):2945-2948. ■