The social and economic consequences of stroke impose a considerable burden on patients, payers, and society in terms of premature death, long-term disability, restricted social functioning, costs of care, lost productivity, and informal caregiver time. In industrialized countries stroke is the third most common cause of death and the major cause of serious long-term disability in adults. About 1 million first ischemic strokes are estimated to occur each year in the European Union (population 450 million). The burden of stroke is expected to rise even further given that the number of elderly people is expected to increase in industrialized countries over the coming decades. The combination of an aging population, declining stroke case-fatality rates, and limited success in reducing the incidence of stroke has resulted in an increase in the prevalence of stroke survivors. In England, Wales, Scotland, and the Netherlands, stroke alone accounts for 3% to 4% of the direct costs of healthcare. Besides the cost of acute hospitalization, there are direct costs related to rehabilitation, ambulatory medical treatment and long-term care of disabled stroke survivors.

Given the pressures on healthcare funding, it is essential that policymakers acquire a better understanding of the current and future burden associated with stroke. The purpose of the present cost-of-illness (COI) study, therefore, was to estimate life expectancy and costs associated with first ischemic stroke in an unselected population-based cohort of statutorily health-insured (SHI) patients in Germany. To that end, life-years lived and cost in each year poststroke were estimated. The study was undertaken as a component of the Erlangen Stroke Project.

Methods

Study Area and Source Population

All data were collected in the Erlangen Stroke Project (ESPro). The ESPro is a prospective population-based stroke registry based in...
Bavaria, Germany, covering a total study population of 102 000 residents (census 2003) in the Community of Erlangen. The unique feature of the ESPro is its continuing case ascertainment and long-term follow-up, irrespective of age, without any stop since 1994. The study population, clinical definitions, examinations performed, and methods used have been described in detail elsewhere.10,11,12,13

Case Ascertainment
All hospitalized and nonhospitalized patients in the study region with suspected cerebrovascular disease (ie, fatal or nonfatal stroke, transient ischemic attack, or cerebral vein thrombosis) are regularly examined and assessed.

Diagnostic Criteria
Stroke was diagnosed by a study neurologist according to the World Health Organization (WHO) criteria.14 First-ever-in-a-lifetime strokes were defined as strokes occurring in patients without any prior stroke event.15

Follow-Up
As demanded in the Helsingborg Declaration, the patients were followed-up at 3 months, 12 months, and then yearly.16

Study Design
The present study is a disease-specific COI study that focuses on the particularities of first ischemic stroke.37 An incidence-based, bottom-up approach was used as the study design.18 The validity of this approach is greater when the sample is unbiased, as in a strictly population-based stroke registry such as ours. All analyses were performed from the perspective of statutory health insurance (SHI), the major source of healthcare funding in Germany, covering nearly 88% of the population in 2003.19

Resources Included
Direct costs were defined as all the goods, services, and other resources that are consumed during the provision of a healthcare intervention for stroke or its sequelae. Length of stay in hospital was differentiated by department and by level of care. Hospital stays related to the initial stroke event, recurrent strokes, or complications of first or recurrent strokes were included. Following the suggestion of Evers et al, all direct costs were aggregated into 4 main categories18: inpatient costs, outpatient costs, rehabilitation costs and nursing costs.

Collection of Resource Data
Data were collected by reviewing medical records in hospitals, nursing homes, and general practitioners’ offices. In addition, trained research nurses interviewed all patients and their relatives in their homes using structured and standardized questionnaires.

Unit Costs
All costs were calculated in year 2004 euros (EUR) from the perspective of SHI.

Hospitalizations
Costs of hospitalization were calculated on the basis of length of stay and institution-specific daily tariffs. Tariffs were obtained from the health insurance fund and encompassed medical care including drugs and board and lodging (eg, laundry and catering).

Outpatient Services
Costs of outpatient treatment were calculated in accordance with the German uniform value scale (Einheitlicher Bewertungsmaßstab).20 The scale lists all outpatient services reimbursed by SHI. Services are grouped by specialty; in addition, there are 147 basic services (consultations, visits, screening).

Outpatient Prescription Medications
We recorded the number and market price of medications prescribed by office-based physicians. Only outpatient prescriptions were considered because the cost of drugs used during stays in an acute or rehabilitation hospital is covered by the institution’s tariffs.

Rehabilitation Services
The costs of inpatient and outpatient rehabilitation were calculated on the basis of the institution’s daily tariffs. These tariffs were communicated by the health insurance fund and covered medical care including drugs as well as board and lodging.

Nursing
Costs of stays in nursing homes and retirement homes, home nursing visits, and community services were calculated on the basis of the annual tariffs of German statutory long-term care insurance (Soziale Pflegeversicherung). This provides benefits for domiciliary, semi-inpatient, and inpatient care. The benefits vary by level of care: care category I = considerable need of care; care category II = severe need of care; care category III = extreme need of care.21 Institutionalization costs were not considered in patients already institutionalized at the time of first ischemic stroke.

Statistical Analysis
Life Expectancy
Acute and long-term mortality after stroke are driven by different forces. We found that survival within the first year after ischemic stroke was best described using nonparameterized Kaplan-Meier curves, whereas year 2 to 10 survival complied well with a Weibull parameterization. The Weibull parameterization was preferred over the exponential, the Gompertz, the lognormal, the log-logistic, and the generalized y distributions based on the Akaike information criterion22 and on graphical inspection of the Cox-Snell residuals.23 The data were consistent with hazards of dying that increased slightly in an exponential fashion in years 2 to 10 poststroke. Stata 7.0 Special Edition24 was used for analyses.

Longitudinal Cost per Stroke
Crude and discounted (3% per annum) estimates of sex-specific and overall longitudinal cost of stroke were calculated. For year 1 after first ischemic stroke we multiplied the area under the 1-year Kaplan-Meier survival curve by the mean total direct cost incurred per first-year survivor. For each subsequent year until death we multiplied the respective area under the Weibull survival projection by an estimate of mean total direct cost incurred during the respective year among those surviving it. As these cost estimates were found to be homogeneous across years 2 to 5 poststroke in both men and women, we collapsed them into a single estimate of mean total direct cost per male and female survivor per year. These 2 estimates were carried forward beyond year 5, where we had no cost data. As opposed to a 1-year-cycle Markov model, our approach thus accounted for the true curvilinear shape of the survival curve in each year poststroke. One-way sensitivity analyses were performed on the 95% confidence limits of life-expectancy poststroke in both sexes and overall.

National Stroke Cost Estimates for 2004
We estimated the financial burden imposed on the German SHI by ischemic strokes in 2004 assuming that the population was stable with respect to age and sex composition and that the age-specific incidence, prognosis, and costs of stroke were constant, in which case undiscounted lifetime costs can be interpreted as yearly (2004) costs. To this end we determined the ESPro incidence of strokes of any kind20 by sex and linear and squared age and multiplied this rate by the person-time of the population of Germany in 2004. Ischemic strokes in SHI patients accounted for 73% of the cases obtained in this way in both men and women.
National Stroke Cost Projections for 2006 to 2025
In this approach we estimated what resources the SHI would need to have included in its budgeting by the end of 2005 in order to meet the lifetime costs of all first ischemic strokes expected to occur over, for example, the following 10 years. For the purpose of this calculation, future costs were discounted at a rate of 3% per year, the annual change in the age and sex distribution of the population predicted by the Federal Statistical Office was taken into account, and the age- and sex-specific incidence of strokes and the type and unit costs of the resources used were assumed to be constant. 26 As in the previous section, estimates were made for each calendar year.

Results
A total of 1637 and 821 patients from the ESPro were available for the survival analyses and the healthcare resource utilization analyses, respectively. A cranial CT or MR scan was performed in 96% of patients. Almost every patient with ischemic stroke (98%) had been admitted to hospital for acute treatment; 55% of patients were female. Mean age at first ischemic stroke was higher in women (76.3 years) than in men (70.6 years). Overall, 52% of patients were in the age group >75 years. During 5 years of follow-up 24% of the cases (95% CI: 18 to 27) had a recurrent stroke. The male and female cohort was projected to decline according to Kaplan-Meier and Weibull as shown in the Figure. Mean undiscounted (discounted) life expectancy after first ischemic stroke was estimated at 8.6 (6.8) years in men, 6.3 (5.3) years in women, and 7.3 (5.9) years overall.

Cost per Survivor per Year
Among first-year survivors mean total direct cost was estimated at 18 517 EUR (Table 1). Rehabilitation accounted for the largest share (37%) of this. In the subsequent 4 years outpatient treatment stood out, accounting for 49% of all expenditure. Mean annual total direct cost per survivor during years 2 to 5 was 5479 EUR (Table 1).

Lifetime Cost
An overview of lifetime cost per stroke in SHI men and women is given in Table 2. First-year cost accounted for about 35% of the present value of the lifetime cost of first ischemic stroke. Mean undiscounted lifetime cost was higher in men (54 552 EUR) than in women (47 596 EUR) because ischemic stroke occurred later in life in women than in men. Overall, the lifetime cost per ischemic stroke in SHI patients was 50 507 EUR undiscounted and 43 129 EUR discounted. True discounted lifetime cost per first ischemic stroke were

Within about ±10% of the point estimates with 95% confidence considering the precision our study had with regard to life-expectancy as single factor (Table 2).

National Estimates
The total financial burden of first ischemic stroke to the SHI in the year 2004 was estimated at 7.1 billion EUR. The largest components were outpatient treatment (40%; 2.8 billion EUR), inpatient treatment (22%; 1.6 billion EUR), rehabilitation (21%; 1.5 billion EUR), and nursing (17%; 1.2 billion EUR). National projections for 2006 to 2025 yielded an expected direct cost at present value of 51.5 billion EUR in men, 57.1 billion in women, and 108.6 billion EUR overall (Table 3). These estimates are for lifetime treatment of newly diagnosed first ischemic strokes (2006 to 2025). They take account of ministerial figures for the expected age and sex evolution of the German resident population over this period and assume age- and sex-specific stroke rates to be constant. Attributable to the higher number of first ischemic strokes in SHI women (1.9 million) than in SHI men (1.5 million), the figures are higher for women than for men.

Discussion
This is the first incidence-based, bottom-up estimate of the overall direct lifetime cost of ischemic stroke based on follow-up 10-year survival and 5-year resource use data derived from a single population-based setting. Our findings detail stroke aftercare and cost in Germany and inform healthcare policies with regard to future fields of action and healthcare priorities.

A strength of the study is that it is designed to collect data on use of healthcare resources for several years after the incident event. It provides data from a large, unselected, community-based cohort of patients with first-ever ischemic stroke who were assessed immediately after the onset of the illness through standardized diagnostic criteria and well-validated and reliable instruments. Another major strength was the high quality of epidemiologic data used for survival projections, which provided us with accurate information on point estimates and precision of long-term survival.
TABLE 2. Direct Cost of First-Ever-in-a-Lifetime Ischemic Stroke by Time-Horizon in SHI in Germany (in year 2004 EUR)

<table>
<thead>
<tr>
<th>Horizon</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th>All</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Undiscounted</td>
<td>Discounted</td>
<td>Undiscounted</td>
<td>Discounted</td>
<td>Undiscounted</td>
<td>Discounted</td>
</tr>
<tr>
<td>1 y</td>
<td>15 566</td>
<td>15 566</td>
<td>14 799</td>
<td>14 799</td>
<td>15 140</td>
<td>15 140</td>
</tr>
<tr>
<td>5 y</td>
<td>31 405</td>
<td>30 159</td>
<td>30 817</td>
<td>29 582</td>
<td>31 077</td>
<td>29 837</td>
</tr>
<tr>
<td>10 y</td>
<td>40 905</td>
<td>37 711</td>
<td>39 097</td>
<td>36 176</td>
<td>39 921</td>
<td>36 873</td>
</tr>
<tr>
<td>Lifetime</td>
<td>54 552</td>
<td>45 549</td>
<td>47 596</td>
<td>41 304</td>
<td>50 507</td>
<td>43 129</td>
</tr>
<tr>
<td>95% CI#</td>
<td>(46 983; 63 670)</td>
<td>(40 673; 50 951)</td>
<td>(41 685; 54 568)</td>
<td>(37 127; 45 925)</td>
<td>(44 901; 56 940)</td>
<td>(39 312; 47 187)</td>
</tr>
</tbody>
</table>

#One-way sensitivity analyses on the 95% CI of life-expectancy poststroke.

TABLE 3. National Direct Ischemic Stroke Cost (in year 2004 EUR) Projections in SHI in Germany

<table>
<thead>
<tr>
<th>Horizon</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
<th>All</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Strokes</td>
<td>Cost* (Billion)</td>
<td>Strokes</td>
<td>Cost* (Billion)</td>
<td>Strokes</td>
<td>Cost* (Billion)</td>
</tr>
<tr>
<td>2006–2010</td>
<td>331 000</td>
<td>13.8</td>
<td>425 000</td>
<td>16.1</td>
<td>756 000</td>
<td>29.9</td>
</tr>
<tr>
<td>2006–2015</td>
<td>701 000</td>
<td>27.1</td>
<td>880 000</td>
<td>30.9</td>
<td>1 581 000</td>
<td>58.0</td>
</tr>
<tr>
<td>2006–2020</td>
<td>1 108 000</td>
<td>39.7</td>
<td>1 367 000</td>
<td>44.6</td>
<td>2 475 000</td>
<td>84.3</td>
</tr>
<tr>
<td>2006–2025</td>
<td>1 547 000</td>
<td>51.5</td>
<td>1 883 000</td>
<td>57.1</td>
<td>3 430 000</td>
<td>108.6</td>
</tr>
</tbody>
</table>

*Discounted (3% per annum).

Estimates take account of ministerial figures for the expected evolution of the age and sex composition of the German resident population and assume age- and sex-specific stroke rates to be constant.

This study does, however, suffer from certain limitations that are commonly present in investigations of this kind. For one thing, our total cost estimates for ischemic stroke in Germany are based on patterns of resource use during the 5 years after a stroke in a population-based cohort of stroke patients living in an urban environment (the city of Erlangen). Patterns of stroke aftercare may differ in rural or remote parts of Germany, and long-term data from these regions would complement our national cost projections.

Also, we did not distinguish outpatient services occasioned by stroke from those occasioned by other pre-existing or new-onset diseases. We may, therefore, have overestimated the costs attributable to ischemic stroke itself because part of the calculated outpatient cost will also arise in an elderly population free of stroke.

The huge worldwide socioeconomic impact of stroke is attributable to the high prevalence and hospitalization rate of this condition and the frequency of long-term sequelae in survivors. Nevertheless, surprisingly few truly incidence-based, bottom-up cost-of-stroke studies have been published in the last 20 years. Nevertheless, surprisingly few truly incidence-based, bottom-up cost-of-stroke studies have been published in the last 20 years. As highlighted by Payne et al., such studies are difficult to compare because of their differences in terms of setting, resources considered, and perspective taken. Among authors that report cost after incident ischemic stroke, 2 authors used data from a hospital-based cohort of patients.

Only few investigators worldwide studied cost in an unbiased population-based setting. Persson and Norrving, reported direct costs of stroke from other pre-existing or new-onset diseases. We may, therefore, have overestimated the costs attributable to ischemic stroke itself because part of the calculated outpatient cost will also rise in an elderly population free of stroke.

The huge worldwide socioeconomic impact of stroke is attributable to the high prevalence and hospitalization rate of this condition and the frequency of long-term sequelae in survivors. Nevertheless, surprisingly few truly incidence-based, bottom-up cost-of-stroke studies have been published in the last 20 years. As highlighted by Payne et al., such studies are difficult to compare because of their differences in terms of setting, resources considered, and perspective taken. Among authors that report cost after incident ischemic stroke, 2 authors used data from a hospital-based cohort of patients.

The number of patients with status poststroke is expected to rise continuously over the next 2 decades as populations age. The increase in absolute incident stroke numbers is estimated at ~40% and 20% in men and women, respectively. Our projections of a present value of 108.6 billion EUR for first-ever ischemic strokes in Germany in the period 2006 to 2025 are based on the projected age and sex evolution of the German population and assume no changes in stroke inci-
dence, mortality, or resource consumption unrelated to age or sex. To the extent that in the future a higher proportion of patients may survive strokes in western countries, we may even have underestimated these costs.36,37

This COI study highlights the social impact of first ischemic stroke in Germany. In addition, we provide cost predictions based on the expected demographic evolution of the country. A proportion of these costs may be preventable by lifestyle changes and primary and secondary prevention programs. This possibility is of paramount importance in terms of public health because progressive aging of the population will otherwise cause an increase in patients with stroke and consequently an increase in healthcare expenditure. By laying a foundation for predicting costs of healthcare and social services, the data from this study can contribute toward the making of informed decisions on allocation of scarce resources while maintaining quality care of stroke patients.

Acknowledgments

The research work in the Erlangen Stroke Project is supported as part of the CompetenceNet Stroke by the Federal Ministry of Research (BMBF, reg. No. 01GI 0439). The registration is funded by the Federal Ministry of Health and Social Affairs (BMG, reg. No. 317-12300/17 03) and the Bavarian Ministry for Health, Nutrition & Consumer Protection (StMuVG, reg. No. 3.5/8060/10502). Data analysis was supported by an unrestricted grant from MSD Sharp & Dohme GmbH, Haar, Germany. The authors thank their fellow participants of the Erlangen Stroke Project for their help throughout this project: Universitätsklinikum Erlangen, Waldkrankenhaus St Marien, Klinikum im Europaapanal, the General Practitioners Association Erlangen and the Regional Public Health Office of Erlangen. The authors extend their thanks to their Federal Statistical Office Germany, Wiesbaden, for providing computerized national population projections 2005–2025 by continuous age and gender. Finally, the authors would like to express their gratitude to 90 general practitioners, their staff, and, not least, the patients and their family members without whose cooperation and help this study would not have been possible. The contribution of the 13 Research Nurses working in our Unit for Stroke Research & Public Health Medicine, is also gratefully acknowledged.

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Lifetime Cost of Ischemic Stroke in Germany: Results and National Projections From a Population-Based Stroke Registry: The Erlangen Stroke Project

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Stroke. 2006;37:1179-1183; originally published online March 30, 2006;
doi: 10.1161/01.STR.0000217450.21310.90

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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