CHAPTER 6

LIFETIME EFFECTS AND MEDICAL COSTS OF STROKE

6.1 SUMMARY

Introduction This chapter describes stroke occurrence in relation to its treatment. There is international consensus emerging on the contributions of trombolytic therapy, stroke units, and secondary prevention in improving stroke survival. The study presents the lifetime effects and medical costs of these interventions for the average stroke patient and identifies the optimum intervention mix.

Methods We apply the multi-state stroke model that distinguishes states after a first transient ischemic attack, a minor and a major stroke. It includes empirical utility weights for stroke disabilities and 5-year follow-up data on health care utilization and costs. It is used to compute lifetime costs and QALYs lived, by stroke state. We add pooled effectiveness and costs data for the three interventions. The table computes QALYs-lived and costs under the seven possible intervention mixes, including uncertainty distributions. A stochastic league table of the mixes presents the results in comparison to the non-intervention baseline.

Results Baseline results vary by age and sex - up to 2.7-3.7 times for QALYs lived and up to 1.4-2.0 times for cost. Stroke patients may gain a maximum of 0.5 QALYs per lifetime by the three combined interventions. Cost per QALY gained is lowest at younger ages for the stroke units and secondary prevention combined: for men about €55,000 and for women €73,000. Changes in costs and effects are small in comparison to the uncertainty ranges. All intervention mixes that include stroke units will most likely be the optimum choice.

Conclusion In spite of many uncertainties, it is shown that the development of acute stroke units deserves priority above medical therapies.
6.2. INTRODUCTION

Stroke is a major cause of disability and death in aging populations, leading to high health care costs (Murray and Lopez, 1997; Meerding et al, 1998; Holloway et al., 1999). In some countries in the late stage of the health transition, secular decline in stroke mortality appears to level off (Wolf et al., 1992; Wolf et al., 1992; Shahar et al., 1997; Barker et al., 1997; Reitsma et al., 1998). Given this possible compression of stroke mortality, it is a present challenge to reduce stroke disability (Fries, 1989; Niessen et al., 1993). Consequently, reduction of severe stroke disability may lead to a reduction of health care costs (Bonneux et al., 1998).

During the past decade, promising therapeutic options in stroke care have appeared. Consensus guidelines are already recommending widespread implementation (Adams et al., 1996; ECM, 1996; Pessin et al., 1997). Yet, there are debates. There is one on the effectiveness, feasibility and pre-requisites for trombolysis to treat patients within three hours after the onset of stroke (NINDS, 1995; Hacke et al., 1998; Wardlaw and Warlow, 1999; Jorgensen et al., 1999). Others are on the health effects and requirements of stroke units (SUTC, 1997). Options in secondary prevention are increasing and might compete in effectiveness with acetylsalicylic acid (ATC, 1994; Matchar et al., 1994; Algra et al, 1998).

Demographic changes will lead to even higher numbers of stroke patients and the new medical technologies are leading to a higher demand for stroke resources. The premise of economic analyses is that, for any given level of resources available, one wishes to maximise the total aggregate health at the population level (Weinstein et al., 1977 & 1996; Granata and Hillman, 1998). In another more standardised approach, the World Health Organisation proposes to compare health effects and costs of optional intervention mixes against a baseline disease level. Generalised comparisons of interventions provide evidence on population benefits in relation to associated costs and may lead to more informed priority setting, also in allocating for stroke care (Murray et al., 2000; Hutubessy et al., 2001).

We describe the occurrence of stroke and related costs of care from a, population-based, health care perspective. Next, we analyse changes in stroke survival and medical costs under combinations of three interventions: trombolytic therapy, acute stroke units, and secondary stroke prevention. We do this in a consistent way for the three interventions, with the remaining life span of the average stroke patient as time horizon.

6.3. MODEL DESCRIPTION AND SCENARIO DATA

Multi-state stroke model

We applied a multi-state life table model that has been used to describe the epidemiology of stroke in the Dutch population by age and sex (Niessen et al., 1993). Several papers have described this methodology (Niessen et al., 1993; Bonneux et al., 1998; Barendregt et al., 1997). The life table describes the disease history of stroke. It computes survival and death of patients by three linked stroke disability states: no disability, minor disability (Rankin scale score < 3) and major disability (Rankin scale score ≥ 3) (Niessen et al., 1993). It does so according by age and sex. They may enter one of the three states after a
transient ischemic attack (TIA), leading to no disability, or a stroke, leading to a minor or major disability. Death risks in all states include death from stroke, cardiovascular disease, and all other diseases. It calculates all surviving patients in each stroke disability state, in time steps of half a year, until all patients have died. Patients may change health states after the first event. The table comprises risk of disability after one month, recovery from major disability at six months and risks of recurrent events and severe disability during the first year and during all other years.

For our analyses, we multiply the patient numbers for each disability state by quality-of-life weights for minor and major stroke. Added up, this yields the total of quality-adjusted life years (QALYs) lived by all three types of stroke patients. We also multiply these patient numbers with the medical cost estimates for each state for each half a year after stroke. The cost estimates are the product of health care utilization data per patient per state for each per year, and full costs per unit per health care service. This leads to an estimate of the average lifetime costs per patient.

We re-calculated the health effects and costs attributable to the stroke interventions by adapting the stroke table risks for mortality, disability, recovery, and recurrence accordingly and adding the intervention costs. The life table recalculates the survival of patients and the number of years lived in each state and the total stroke costs. The difference with the baseline computation generates the changes in quality-adjusted years and in costs for each stroke state and for the average stroke patient.

To validate the life table for the baseline situation we have compared model-generated age and sex-specific figures on stroke events and mortality to the national empirical figures on acute hospital admissions and stroke mortality for the year 1985 (Niessen et al., 1993). We also validated computed major stroke prevalence against data from the national nursing home registry of the same period.

Input data on effectiveness of interventions In consensus meetings, we have selected effectiveness data from published meta-analyses (Table 6.1). (Limburg, 2000) We have added values from studies that allowed us to make an estimate of the effectiveness of the intervention in common practice i.e. beyond a randomized trial setting. We used the reported confidence intervals to estimate the probability distributions of the intervention effect, assuming a normal distribution (Briggs and Fenn, 1998; Briggs and Gray, 1998).

For thrombolysis, until now, only recombinant tissue plasminogen activator (r-TPA) is shown to be effective (Wardlaw and Warlow, 1999). Given within three hours after stroke it improves the outcome of acute stroke after three months (Wardlaw and Warlow, 1999; Hacke et al, 1998; NINDS, 1995). This is also the case in non-experimental settings (Chiu et al., 1998). In a meta-analysis, we pooled the data of the three randomized studies. In the control group of 284 patients 52 died, among the 294 patients in the r-TPA group 50 patients died. In the r-TPA group 184 patients had a Rankin score < 4; in the control group only 154 patients had this score (Niessen et al., 2000). The small number of patients treated leads to an odds ratio for reducing the number of patients with a Rankin score ≥ 3 with a large confidence interval. We assumed that 10% of patients are eligible for thrombolysis, although the literature reports figures between 5-8%.
**Table 6.1.** Pooled odds ratios from meta-analyses by stroke intervention and stroke survival variable. † ASA: Acetylsalicylic acid.

Stroke units lead to an improvement in stroke survival and stroke disability (SUTC, 1997; Indredavik et al., 1999; Stegmayr et al., 1999). Two long-term follow-up studies show persistent improvements of stroke survival and disability level. (Indredavik et al., 1999; Jorgensen et al., 1999). Our stroke unit care scenario includes reductions in acute fatality and in risk of a permanent severe disability, assuming a lifelong effect. In addition, we included more intensive nursing and rehabilitation in the acute stage, a length of hospital stay of 14 days and intensive rehabilitation until six months after onset (Kwakkel et al., 1999).

Medical secondary prevention after stroke leads to reductions of both recurrent stroke and of cardiovascular mortality after a first TIA or first stroke (ATC, 1994; Matchar et al., 1994; Dippel, 1998; EAFT, 1993). We did not include disability or costs resulting from cardiovascular events. The effects of secondary prevention decrease during the years after the first stroke, possibly due to mortality selection or lack of patient compliance (ATC, 1994; Matchar et al., 1994; Dippel, 1998; EAFT, 1993). In our model, we incorporated the costs and effects of prevention during the five years after the initial stroke.

**Input data on cost estimates** Table 6.2 gives an overview of data used, published in our cost study (Bergman et al., 1995). The data include all medical costs after a first stroke related to hospital treatment, institutionalisation, rehabilitation, primary care, and home care. As the model distinguished two stroke states, we differentiated the cost data by these categories. For hospital settings, this is already known but not for the follow-up period. The same study, however, collected data on the distribution of surviving patients after a first stroke among nursing homes, rehabilitation centres, and their own homes, during a five-year follow-up. We re-analysed the data set to find a rate of institutionalisation, by initial stroke severity and by period after a first stroke (van Straaten et al., 1997; Scholte op Reimer et al, 1999). Almost no patients with a minor stroke stayed in an institution. After six months 29.1% (95% CI: 25.1-33.2) of the men with a major stroke stayed in an institution and 38.8% of the women (95% CI: 34.9-42.9). After that period...
institutionalisation stabilized among both men (16.5%; 95% CI: 12.6-20.4) and women (26.9%; 95% CI: 22.3-31.5).

Some additional estimates of the additional costs of stroke units and intensive physiotherapy needed to be collected in a separate costing study on the Rotterdam Stroke Services. (Niessen et al., 2000) Other outpatient cost estimates for medical treatment are based on official reimbursement rates (Table 6.2).

<table>
<thead>
<tr>
<th>Cost item</th>
<th>Academic hospital</th>
<th>General hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Institutional costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital admission after minor stroke</td>
<td>264</td>
<td>196</td>
</tr>
<tr>
<td>after major stroke</td>
<td>310</td>
<td>224</td>
</tr>
<tr>
<td>after fatal stroke</td>
<td>426</td>
<td>252</td>
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<tr>
<td>Home care first six months</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>after six months</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Nursing home admission</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td><strong>Additional costs of hospital interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-TPA treatment *</td>
<td>2,385</td>
<td>(1,789-2,981)</td>
</tr>
<tr>
<td>Stroke Unit * †</td>
<td>61 (44-78)</td>
<td>42 (32-53)</td>
</tr>
<tr>
<td>Intensive rehabilitation †</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Additional costs of extramural interventions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensive physiotherapy or occupational therapy †</td>
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<td></td>
</tr>
<tr>
<td>ASA powder, 38 mg; tablets 100 mg †</td>
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<td></td>
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<tr>
<td>Dipyridamol Retard caps, 400 mg †</td>
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<td></td>
</tr>
<tr>
<td>Dipyridamol + Acetylsalicylic acid, 325 mg †</td>
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<td></td>
</tr>
<tr>
<td>Pharmacy prescription charge ‡</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>General physician prescription charge #</td>
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<td></td>
</tr>
</tbody>
</table>

Table 6.2. Institutionalisation and costs of stroke care according to type of Intervention, hospital type and period after stroke onset.

* Costs of procedures and medication (uncertainty range ± 25%) (Niessen et al., 2000); Sources: † Rotterdam Stroke Service study; ‡ Insurance Council; § Royal Dutch Society of Pharmacists; #Dutch Society of Family Physicians. ASA= Acetylsalicylic acid

**Input data on utility weighing for stroke disability** We have applied utility weight distributions for minor and major stroke disability as defined by the Rankin scale (Niessen et al., 1993; Gold et al., 1998). For this, we used the EuroQol scale, shown valid in stroke patients (Dorman et al., 1997). We have assessed the disability status of 129 stroke patients (mean age 69 years) in two Rotterdam hospitals using both the Rankin scale and the five-dimensional EuroQol scale. The follow-up lasted up to six months after hospital admission. The total number of measurement pairs was 248. The measurements correlated well and are consistent during the time after stroke. Using the individual EuroQol scores, we calculated the average utility value and the average Rankin score for both minor and major stroke disabilities. The point utility value for minor stroke disability is 0.72 (SD=0.23) and for major stroke 0.47 (SD=0.31). For our analyses, accounting for uncertainty, we used the distribution of utility values from the original
EuroQol data set given the two observed point utility weight score (Dorman et al., 1997; Dolan, 1997).

**Stochastic league table methodology**

Our analysis compares the relative efficiency of each intervention sets. Given a budget level, it selects the most cost-effective option first. If there is budget left for more options, it chooses the next cost-effective options, etc, until the budget is exhausted. To allow for this, we first computed lifetime health effects and costs for the baseline and seven intervention sets for stroke at 60, 70 and 80 years of age, by sex. Combinations of the three interventions define the sets. Each of the sets includes all possible (seven), mutual exclusive, mixes of intervention options, and the baseline scenario (Table 6.3). To account for uncertainties in estimated effects and cost, we included all uncertainty ranges in the input values for effectiveness, costs, and utilities. (Tables 6.1-3 and Input data sections) The normal distributions have been truncated and entered in a random sampling procedure, using @Risk-Excel-software.

Next, the outcome distributions for QALYs and costs, generated in the multi-state life table, have been used in the stochastic league table approach. Their point estimates and standard deviations define these distributions (Table 6.3). The league table technique applies also random sampling (up to 10,000 iterations) to draw from generated distributions. Here, we made the, common, assumption that costs have a lognormal distribution and health benefits have a normal distribution. We use a software program called MCLeague, described elsewhere (Hutubessy et al., 2001). Using the results of each draw from the outcome distributions, it computes the cost-effectiveness of the intervention mix options in each set, compared to baseline. Next, it decides which combinations of mixes are to be included in the optimum package, given a budget ceiling. We treat the six sets of interventions as independent. This supposes that one can implement one without influencing the outcomes and /or costs for the other group of patients (Murray et al. 2000). This means that, if additional packages are possible, given the budget available, these are included too. The league table presents the results of our comparative CEA. It indicates the probability that a specific intervention would be included in the optimal mix of interventions given a particular level of resource availability.

### 6.4. RESULTS

Table 6.4 shows the calculated lifetime costs and QALYs lived by intervention mix as point estimates. As the standard deviations vary little between intervention mixes, we only have listed the average standard deviations in the Table 6.3. This is to simplify the presentation. In our uncertainty computations, we use the individual estimates. Outcomes by age and sex vary up to 2.7-3.7 times the number of QALYs lived and up to 1.4-2.0 times the lowest lifetime costs. At age 60, the average stroke patient gains a maximum of 0.5 QALYs per lifetime from all combined interventions (Figure 6.1). Differences in health gain between the sexes are due to differences in absolute cardiovascular risks and remaining life expectancies. The table shows that all mixes lead
either to cost savings or to low additional costs as compared to baseline and, hence, lead to more efficient stroke. Trombolysis is indicated in only a small group of patients. It adds the lowest number of QALYs: about 0.1 per average stroke lifetime. Secondary prevention is about twice as effective, preventing both strokes after transient attacks and recurrent minor strokes, still a minority of the stroke population. Stroke units, as a single intervention package, or in combinations, yield about four times as many QALYs per lifetime.

Cost differences between major and minor stroke patients (not shown) vary between 2.5 and 2.9 for men and for women between 3.8 and 4.2 (Niessen et al., 2000). These differences are largest at younger ages as patients survive for a longer period. Our results compare with previously estimated Dutch average for all strokes (Bergman et al., 1995). Institutionalization dominates lifetime costs. (Bergman et al., 1995; van Straaten et al., 1997). For comparison, in the United States the average lifetime costs of stroke are €49,000 for ischemic strokes at 65 years of age and €26,000 at 85 years, for men. For women this is €52,000 and €26,000 (Taylor et al., 1996).

Changes in costs and effects are small in comparison to the computed uncertainty ranges (Table 6.3). The next section deals with selecting the optimum stroke package, given these uncertainties.

### 6.5. STOCHASTIC LEAGUE TABLE FOR STROKE CARE

*Figure 6.1* shows the same point estimates in a so-called cost-effectiveness plane, by intervention mix. For each mix, both average health gain and average costs are higher in younger age groups and are higher among the women. *Figure 6.1* clearly shows that stroke units give more benefit at slightly higher costs. It is most effective at younger ages. Here, cost per QALY gained is lowest for the mix including stroke units and secondary prevention: for men about €55,000 and for women €73,000. The plane demonstrates that trombolysis leads to relatively little average benefit at high average cost (the cost of institutionalisation of those not indicated for treatment). The same holds for secondary prevention as a single intervention. Here, cost-effectiveness ratios are over €100,000 per QALY gained. Their combination leads to as much health gain as stroke unit care at older ages.

Trombolysis and stroke units give immediate health benefits to the patient. When the age of stroke onset rises, there are fewer years without disability to gain and, consequently, cost-effectiveness of these treatments decreases with age. Optimum packages at lower budget levels would exclude these interventions at older ages.
Table 6.3. Lifetime mean quality-adjusted life years lived and medical costs after a first stroke by stroke intervention mix. Bottom line shows standard deviations. ‘SP’= Secondary Prevention; ‘rTPA’ = thrombolysis; ‘SU’= Stroke unit care; ‘SD’= standard deviation. Costs are in 1996 Euros. Discount rate for costs 3%.
Secondary prevention has delayed effects and yields more health benefits at higher ages, as the risks of recurrent stroke are higher. Hence, also due to its low costs, its cost-effectiveness increases with age and leads to cost savings. Here, optimum packages at low budget would exclude younger ages.

Figure 6.1. Lifetime health gain and total medical costs as compared to baseline by intervention mix (by age and sex; same markers; see Table 6.3. for values). ‘SP’= Secondary Prevention; ‘rTPA’ = trombolysis; ‘SU’= Stroke unit care; ‘SD’= standard deviation. Discount rate costs 3%.

Figure 6.2 gives the probability of each intervention mix to be included in the optimum stroke package by age and sex, using the stochastic life table approach. At the higher budget range (€150,000), interventions at all age and sex groups are relevant. Here, also the less cost-effective options can be included and the probabilities for each option, in each set, stabilise. At the high budget level, one can observe that any intervention mix that includes stroke units is most likely the optimum choice. Adding trombolysis or secondary prevention, actually, would not make a big difference, given uncertainties. At lower budget levels, younger age groups are, indeed, included in the optimum stroke package. One can also observe an interaction effect between trombolysis and stroke unit care: the combined effect is less that the added effect of the two options. If patients improve more because of one intervention, on average, there is less to gain from the second.
### Figure 6.2

Probability to be the optimal mix for the various stroke intervention options by available budget level. Stochastic league table analysis (MCLeague, Hurubessy et al., 2001). ‘SP’ = Secondary Prevention; ‘tTPA’ = thrombolysis; ‘SU’ = Stroke unit care.
6.6. DISCUSSION

We conclude that stroke units and medical therapies after stroke are cost saving or are cost-effective as compared to a non-intervention situation. The medical therapies are effective for small patient groups only. Costs per QALY gained are higher in stroke units than for medical therapies, yet stroke units yield higher population benefits. The organization of specialized stroke unit care deserves more priority than until now is given. Our conclusion stands, even considering all relevant uncertainties.

The introduction of a stroke unit is a complex intervention. Most effectiveness research from Europe shows an improvement in stroke survival and handicap, and institutionalisation rate (SUTC, 1997; Indredavik et al., 1998; Jorgensen et al., 1999). This improvement does not depend on age (Falconer et al., 1994; Kalra, 1994). The few existing long-term follow-up studies after stroke unit care show a persistent improvement of stroke survival and disability (Indredavik et al., 1999; Jorgensen et al., 1999). In the United States, little evaluation research is available (Pessin et al., 1997; Lincoln et al., 1996; Lee et al., 1996). This has been less systematic (Asplund, 1997) and clinical trials show a large design effect (Ottenbacher and Jannell, 1993). Stroke unit care deserves to be a priority also in this country (Gresham et al., 1997).

One other relevant intervention, primary prevention of the major risk factor, hypertension, might yield more effective and even more cost-effective results, especially when co-existing risk factors like diabetes are treated as well. We did not include treatment of hypertension in our analysis, as there is a lack of consistent data.

Costs of stroke

In comparison to previous studies (Bergman et al., 1995; Taylor et al., 1996), we have shown that lifetime costs of stroke by age of onset and sex differ according to initial severity. In cost-effectiveness calculations of stroke interventions, one has to account for these differences.

The results of our study and a previous one for the Dutch situation are consistent. Our league table estimates are rather robust to changes in probability of nursing home admissions. For comparison, in the United States the average lifetime costs of stroke are $49,000 for ischemic strokes at 65 years of age and $26,000 at 85 years, for men. For women this is $52,000 and $26,000 (Taylor et al., 1996). The average direct costs for a Medicare stroke patient lies in the similar range of magnitude as ours. We contribute this consistency to similar distributions of patients by sex and by residence. In Rochester among 218 patients admitted to nursing homes for the first time, 24% had been admitted for 91-365 days and 21% for 1-5 years after the stroke, as measured in residence days (Brown et al., 1999). In the UK, after a 4.9 years follow-up, the distribution of patients is comparable with 29% of the survivors severely or moderately disabled, 37% were mildly disabled, and 34% were functionally independent (Wilkinson et al., 1997).

For the same reason, including productivity costs to communities would not influence the relative cost-effectiveness values. On the other hand, early discharge from stroke units with professional support might increase the burden for kith and kin (Scholte op Reimer, 1999). We did not use a human capital approach, (Taylor et al., 1996), which leads to, in our opinion, unrealistically high indirect cost estimates.
**Cost-effectiveness methodology**

Cost-effectiveness analyses of single stroke interventions are common and increasing. Outcomes are difficult to compare because of lack of standardisation and different referent populations. The population perspective and the use of a baseline make our approach consistent and allows for comparisons of different stroke interventions in different subgroups.

We compare the interventions against a baseline situation and choose the year 1985 as our reference situation. The assumption is that the studied interventions have become, or will become fully, effective in the Netherlands after this year. This is probably true for the medical therapies. Specialised stroke care probably started, gradually and earlier on an unknown scale. In our calculations, however, we consider the additional effort to be made (Limburg, 2000) For other countries, health gains as well as the additional costs of stroke units will most likely be bigger.

We used public utility values for minor and major disabilities. In another study, many patients at risk for stroke considered major stroke worse than death, i.e., a utility value lower than 0 (Samsa et al., 1999). The average utility value for major stroke in this study was 0.23 with a large spread of values. The utilities depended on how one rates one’s presence status and how one rates living with severe disability. At older ages, utility values influence cost-effectiveness results more than at younger ages. As stroke units become less cost-effectiveness with at older ages, it becomes important to consider patients’ preferences (Gold et al., 1998). In our analysis, lower utility values for major stroke would influence all our results in the same way and would not alter our conclusions.

**Conclusion**

We have compared the (combined) effects of three types of treatment after stroke on lifetime stroke disability and lifetime costs of stroke. The selected treatments reduce disability, and may be cost saving or cost-effective for the analysed patient groups. Uncertainties in our outcomes exist on intervention effectiveness and costs, institutionalisation rate, indirect costs and disability weighing. They affect the analyses in the same way and do not affect the population benefit ranking of the interventions. Our main conclusion - intensive care for stroke patients deserves priority - remains valid in spite of the large number of inherent uncertainties that we have shown.
REFERENCES