Stroke Treatment and Prevention

Stroke is the third most common cause of death in the world, and a major source of a disability. This invaluable reference will provide clinicians caring for stroke patients with ready access to the optimal evidence for best practice in acute stroke treatment and secondary prevention. The author, who is a Member of the Editorial Board of the Cochrane Stroke Review Group, describes all available treatments for acute stroke and secondary prevention, the rationale for using them, and, where available, the highest-level evidence (level 1) for their safety and effectiveness.

Where level 1 evidence is not available, he offers advice on reasonable practice and information about current research. The evidence for each treatment is followed by the author's interpretations, and the implications of the evidence in the care of stroke patients.

This is therefore an essential resource for clinicians, translating into practice advances that have been made in the treatment and prevention of stroke, and suggesting the most appropriate interventions.

Stroke Treatment and Prevention

An Evidence-Based Approach

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This book is dedicated to my wonderful and
loving parents (Jean and John)
and
daughters (Genevieve and Michelle)

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Preface

Stroke is an enormous public health problem. It is the third most common cause of death (causing 4.4 million deaths worldwide in 1990) and the most important cause of disability among adults (with an estimated prevalence of 0.6% population) in the world. It also imposes an enormous cost on the community, accounting for about 5% of all health service costs.

During the past decade, several promising treatments for stroke have been evaluated by means of the most reliable methods – the randomised-controlled trial (RCT) and the systematic review and meta-analysis of RCTs – providing a reasonably reliable body of evidence for the efficacy and safety of several treatments for stroke. In order for these advances to make an important difference to patient outcome and the health of nations, they need to be translated into practice. One way to facilitate this is by increasing the access to best evidence for stroke care practitioners and consumers. At present, these data are available at several sites including the *Cochrane Library*, MEDLINE, and Evidence-Based Medicine publications and web sites such as Clinical Evidence http://www.clinicalevidence.org/, EBM Guidelines http://www.ebm-guidelines.com/ and the Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/guidelines/index.html. Furthermore, they are regularly updated to incorporate new evidence as it arises. However, none are dedicated in a single corpus specifically for clinicians who manage stroke patients and their families.

The aim of this book is to provide stroke clinicians (and their patients and families), with ready access to the optimal evidence to guide best practice in acute stroke treatment and (secondary) prevention of recurrent serious vascular events. Where available, I have quoted the highest level of evidence (level 1) to guide practice – RCTs and systematic reviews and meta-analyses of RCTs – and have predominantly sourced the *Cochrane Library*, to whom I am grateful for allowing me to reproduce their work. Of course, by the time you read this book, there will have been further updates in the *Cochrane Library* every quarter, with new reviews and updated earlier reviews, which I would encourage you to 'visit'. After each section describing the evidence, I have made a comment about my interpretation of the

evidence, and the implications of the evidence for clinical practice and research. As level 1 evidence is not (yet) available for many areas of stroke management, I have tried to define which areas are 'evidence-poor' and even 'evidence-free', what might be reasonable practice under these circumstances (acknowledging that absence of evidence of effectiveness does not necessarily mean evidence of absence of effectiveness (Alderson, 2004)), and what research is ongoing and needed.

Ultimately, in order to translate evidence into practice, clinicians must be aware of, and prescribe, the most appropriate interventions for their patients based on effectiveness, safety, affordability and patient preferences. And patients must be adequately informed and consent to comply with the prescription. Since most strokes are first-ever strokes and sudden in onset, it is commonly a shock for previously healthy people with a first-ever stroke or transient ischaemic attack (TIA) to be suddenly impaired neurologically, to be asked to consider sometimes risky and costly investigations and treatments (e.g. catheter angiography, thrombolysis, decompressive neurosurgery, carotid surgery or stenting), and prescribed at least three drugs (e.g. antithrombotic, statin and antihypertensive) for life. Consequently, all the options must be presented sensitively, simply and repeatedly by clinicians who know the risks (large and small) and benefits (large and small) of the treatments. And this must be done quickly, on the day of presentation or as soon as possible thereafter, because of the high risk of early recurrent stroke. Perhaps the drugs should be introduced one at a time so that any early adverse effects can be correctly attributed. Stroke medicine therefore remains an art as well as a science. It cannot be undertaken solely by 'robots' according to a 'cook-book' or protocol; the results of RCTs and meta-analyses have to be interpreted accurately, and coupled with clinical experience, acumen and common sense, in order to be applied optimally to individual patients (Warlow *et al.*, 2003).

I am grateful to Professors Charles Warlow and Peter Sandercock (Edinburgh, Scotland) and Jan van Gijn (Utrecht, The Netherlands) for introducing me to evidence-based stroke medicine, and to John Wiley and Sons Limited for granting me permission to reproduce many of the figures in this book from the *Cochrane Library*.

Graeme Hankey

1

The size of the problem of stroke

Stroke is an enormous and serious public health problem. It is the third most common cause of death in the world, after ischaemic heart disease and all types of cancer combined. Stroke caused 4.4 million deaths in 1990, and two thirds of these occurred in less developed countries (Murray and Lopez, 1996, 1997). Stroke is also the most important cause of disability among adults. The estimated prevalence of stroke-related disability is more than 0.6% of the population of the world, which represented 3% of the world's disability burden in 1990 (Murray and Lopez, 1996, 1997; Lopez and Murray, 1998).

In the USA in 1994, stroke was the second most common cause of death, the fourth greatest cause of disability-adjusted life years, the fifth highest consumer of days in hospital, the fifth most prevalent major disorder and the eighth most commonly occurring disorder (incidence) (Gross *et al.*, 1999).

Stroke is therefore costly (and becoming increasingly costly) to health care systems. It is estimated that stroke accounts for 4–6% of health care budgets, excluding the costs of social services and carers. Stroke accounts for almost 6% of total health care costs in Finland, 5% in the UK and over 3% in the Netherlands (Isaard and Forbes, 1992; Taylor *et al.*, 1996; Evers *et al.*, 1997; Dewey *et al.*, 2001; Payne *et al.*, 2002; Levy *et al.*, 2003; Evers *et al.*, 2004; Martinez-Vila and Irimia, 2004). However, stroke attracts far less research funding than heart disease or cancer (Rothwell, 2001; Pendlebury *et al.*, 2004).

Incidence

The incidence of new cases of first-ever stroke, standardised for age and sex, is about 200 per 100,000 per year (i.e. 0.2% of the population (and 0.4% of people aged <45 years)) in the few white populations studied in Europe, the USA and Australia, and non-white populations in development countries (Fig. 1.1) (Sudlow and Warlow, 1997; Feigin *et al.*, 2003; Warlow *et al.*, 2003; Feigin, 2005, Lavados *et al.*, 2005). However, the incidence of stroke may be higher, and up to twice as common in Siberia, Eastern Europe and China, and lower in some parts of France, such as Dijon, which has the lowest incidence.

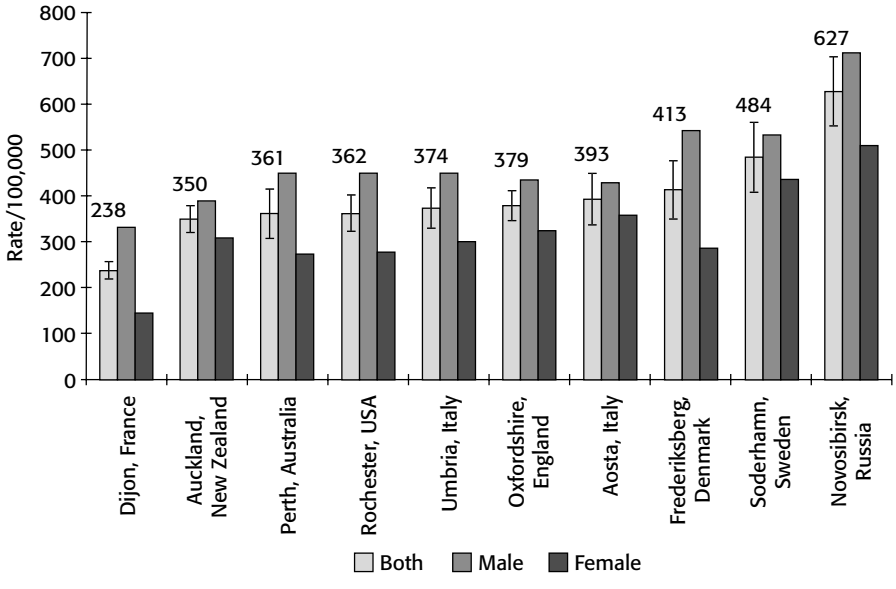

Figure 1.1 Incidence of stroke (ischaemic and haemorrhagic combined) amongst 10 different communities according to age groups 45 years and older. Reproduced from Sudlow and Warlow (1997), with permission form the authors and Lippincott Williams & Wilkins.

The incidence of stroke, in white populations at least, is roughly equal in men and women, and rises steeply with age; about a quarter occur below the age of 65 years and about a half below the age of 75 years. Consequently, the absolute number of stroke patients is likely to increase in the future, because of the ageing of most populations, despite uncertainty over whether stroke incidence is rising, falling or remaining static (see below).

Among incidence studies with the highest rates of brain imaging, the distribution of the pathological types of stroke among populations is similar (about 80% ischaemic, 15% primary intracerebral haemorrhage and 5% subarachnoid haemorrhage) (Warlow *et al.*, 2003). The proportion of stroke due to primary intracerebral haemorrhage is reported be higher in Africa and Asia but this claim remains to be confirmed by well-conducted population-based studies.

Prevalence

The prevalence of stroke is probably somewhere between 5 and 12 per 1000 population (i.e. 1% of the population) but this estimate depends on the age and sex structure of the population (Bonita *et al.*, 1997). In women and men aged 65–74 years, the prevalence of stroke is 25 and 50 per 1000, respectively (Wyller *et al.*, 1994;

Table 1.1. Age-standardised stroke mortality (per 100,000 population) between 40 and 69 years of age in 27 countries in 1985 (Bonita *et al.*, 1990).

	Men		Women	
Country	Rank	Rate	Rank	Rate
Bulgaria	1	249	1	156
Hungary	2	229	2	130
Czechoslovakia	3	177	4	103
Romania	4	172	3	129
Yugoslavia	5	145	5	101
Singapore	6	136	6	92
Japan	7	107	11	60
Scotland	8	99	7	77
Finland	9	98	13	57
Poland	10	96	10	62
Hong Kong	11	94	9	64
Austria	12	90	16	48
Northern Ireland	13	84	8	67
Ireland	14	72	12	59
England and Wales	15	71	14	54
Germany	16	68	19	39
Belgium	17	64	18	41
New Zealand	18	62	15	50
France	19	60	26	28
Australia	20	60	17	45
Denmark	21	55	20	38
Norway	22	55	22	35
Sweden	23	48	24	30
The Netherlands	24	47	23	31
USA	25	45	21	35
Canada	26	39	25	28
Switzerland	27	38	27	21

Bots *et al.*, 1996; Geddes *et al.*, 1996). Stroke prevalence also depends on incidence and survival.

Mortality

The mortality rates of stroke vary widely among countries for which routine death-certificate data are available, from about 20 to 250 per 100,000 population per year (Sarti *et al.*, 2000) (Table 1.1).

Table 1.2. Factors influencing stroke mortality rates.

- The incidence of stroke and its pathological and aetiological subtypes
- The severity and case fatality of stroke
- The age and gender of the population affected by stroke
- The accuracy of death certificates

Stroke mortality varies because of many factors (Table 1.2). For example, pathological stroke subtypes with a very low case fatality (e.g. lacunar infarction) contribute little to mortality statistics whereas pathological and aetiological subtypes with a high case fatality (e.g. primary intracerebral haemorrhage, total anterior circulation infarction) do. As stroke mortality rises rapidly with age, any assessment of mortality must account for age, and any comparisons in mortality must be age standardised or, perhaps better, restricted to certain age groups where the diagnosis of stroke is most likely to be correct (age 55–64 years) or where the number of strokes is largest (age 65–74 years). However, even after adjusting for age, the age-standardised death rate attributed to stroke varies 6-fold among developed countries (Table 1.1) (Bonita *et al.*, 1990; Sarti *et al.*, 2000). In the early 1990s, stroke mortality was lowest in western Europe, the USA, Japan and Australia, and highest in Eastern Europe and countries of the former Soviet Union (Sarti *et al.*, 2000).

Very little is known about stroke mortality in the developing world, nor about the relative distribution of stroke subtype mortality among different countries anywhere in the world.

Case fatality, recurrent stroke and functional outcome

The case fatality rates after a first-ever stroke (all types combined) are about 12% at 7 days, 20% at 30 days, 30% at 1 year, 60% at 5 years and 80% at 10 years (Dennis *et al.*, 1993; Hankey *et al.*, 2000; Hardie *et al.*, 2003). The relative risk of death in stroke survivors is about twice the risk of people in the general population, and the risk persists for several years.

Death within a few hours to days after stroke is usually due to the direct effects of the brain lesion itself (usually intracerebral or subarachnoid haemorrhage, and less commonly massive brainstem infarction) or its complications (e.g. brain oedema) causing brain herniation. Later, the complications of immobility (e.g. bronchopneumonia, venous thromboembolism) and recurrent vascular events of the brain and heart are the common causes of death (Fig. 1.2).

The risk of a recurrent stroke among survivors of stroke in the community is up to about 10% within 7 days, and about 18% within the first 3 months (Fig. 1.3) (Coull *et al.*, 2004; Hill *et al.*, 2004; Hankey *et al.*, 2005). The risk is 3-fold higher if the transient ischaemic attack (TIA) or ischaemic stroke is caused by large artery disease,

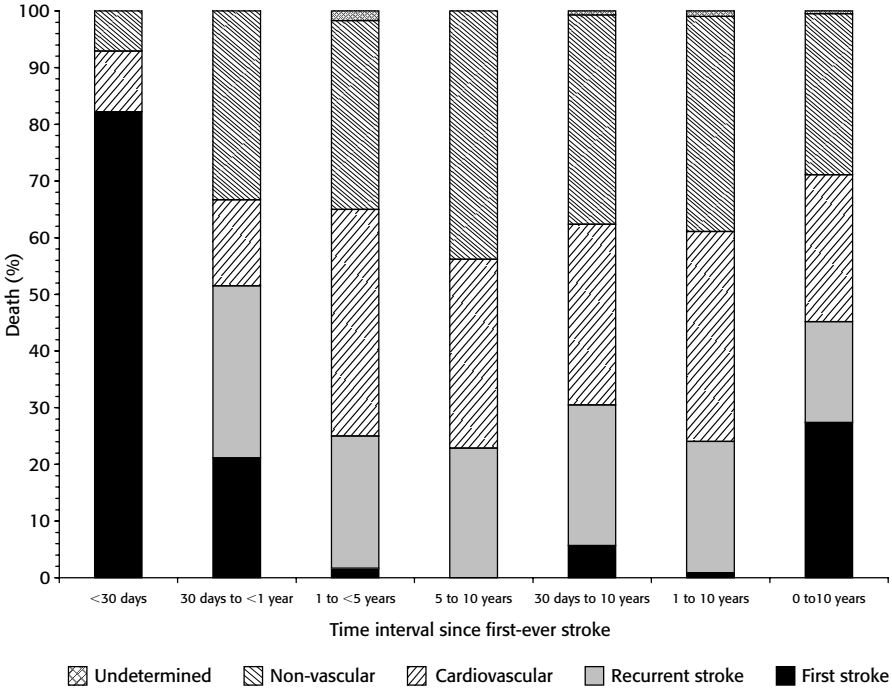

Figure 1.2 Graph showing the causes of death at different time intervals after stroke. Each column represents deaths within a defined period after stroke, and the bars within each column indicate the proportion of deaths during each period due to particular causes. Note how most deaths in the first 30 days after stroke are due to the direct effects of the stroke, whereas most deaths in subsequent years are due to cardiovascular disease and recurrent stroke. Reproduced from Hardie *et al*. (2003), with permission from the authors and Lippincott Williams & Wilkins.

and 5-fold lower if the cause is small artery disease (Lovett *et al.*, 2004). Thereafter, the risk falls to a nadir of 3 to 4% per year at 3 years, after which it gradually increases to about 7 to 8% per year at 10 years (Hankey *et al.*, 1998; Hardie *et al.*, 2004; van Wijk *et al.*, 2005). But the absolute risk varies depending on the prevalence and level of other vascular risk factors (Dippel *et al.*, 2004; van Wijk *et al.*, 2005; Rothwell *et al.*, 2005).

Among stroke survivors, neurological function begins to improve within the first few days due to resolution of the ischaemic penumbra, cerebral oedema and comordities (e.g. infection) that exacerbate the functional effects of the stroke. Thereafter, neurological and functional recovery continues, and is most rapid in the first 3 months due to neural plasticity (by which neurons adopt new functions), the acquisition of new skills through training (physiotherapy and occupational therapy) and modification of the patient's environment. Recovery continues

Table 1.3. Predictors of survival free of dependency after stroke.

- The pathological type of stroke (haemorrhage or infarction)
- The clinical syndrome and aetiological subtype of ischaemic stroke
- Age at the time of stroke
- Living alone (nobody permanently living with the patient before the stroke)
- Independent in activities of daily living before the stroke (Oxford Handicap score ⩽2 before stroke)
- Normal verbal Glasgow Coma Scale score (=5)
- Arm strength: can lift both arms to horizontal
- Able to walk without the help of another person (can use stick/Zimmer frame)

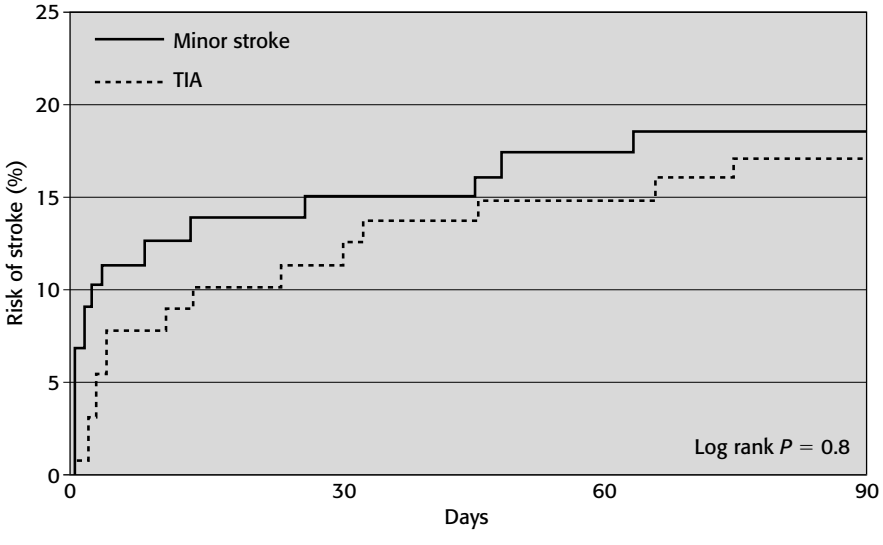

Figure 1.3 Cumulative risk of stroke in the first 90 days after a TIA or minor stroke in the Oxford Vascular Study. Reproduced with permission from the *British Medical Journal* Publishing Group and Coull *et al*. *BMJ* 2004; 328: 326–8.

more slowly over the next 6–12 months, with some gains still being realised 1–2 years after stroke (not all of which are functional adaptations).

The risk of being physically or cognitively dependent at 1 year after a stroke is about 20–30%. At 12 months after first-ever stroke, about one-third of all stroke patients have died, about 20–30% are dependent on another person for everyday activities (e.g. washing, dressing, mobilising) and 40–50% are independent (Hankey *et al.*, 2000, 2002; Warlow *et al.*, 2003; Hardie *et al.*, 2004).

The major clinical factors at the time of stroke or soon after a stroke which are predictive of being alive and independent at 6 months after a stroke are shown in Table 1.3 (Counsell *et al.*, 2002).

These factors seem to be equally predictive whether they are assessed within 48 h of stroke onset or later, whether the stroke is ischaemic or haemorrhagic in type, and whether the patient has had a previous stroke or not (Counsell *et al.*, 2002).

Trends in stroke mortality over time

Stroke mortality rates are declining in most places where it has been measured, with the exception of eastern Europe. Indeed, the decline in stroke mortality in some countries is even more rapid than in coronary heart disease mortality. However, in other countries, such as Australia, there has been a deceleration in the decline in stroke mortality (Feigin *et al.*, 2003).

The reason for the decline in stroke mortality is less clear; it may reflect a decline in the incidence of stroke (all types of stroke, or just those which are more likely to be fatal, such as haemorrhagic stroke), an improvement in case fatality (survival) after stroke (perhaps due to better medical care or reduced stroke severity) or an improvement in the accuracy of classifying stroke as a cause of death (e.g. less misclassification of sudden deaths as stroke) (Hankey, 1999).

Trends in stroke incidence over time

Recent data from the Oxford Vascular Study indicate that in Oxfordshire, UK, the incidence of stroke has declined over the past 20 years, particularly for ischaemic stroke and intracerebral haemorrhage (Rothwell *et al.*, 2004). There has also been a significant reduction in stroke mortality, but not case fatality. Similar results have been reported in Perth, Australia (Jamrozik *et al.*, 1999) but this finding is not consistent in other areas (Feigin *et al.*, 2003; Warlow *et al.*, 2003).

The Oxford Vascular Study suggests that the reduction in stroke incidence may be attributable to improved recognition and treatment of modifiable causal risk factors (such as high blood pressure, high blood cholesterol) and the increased use of other effective stroke prevention strategies (such as antiplatelet therapy) in appropriate individuals (Rothwell *et al.*, 2004). These data suggest that stroke is preventable.

Future trends in burden of stroke

The burden of stroke is likely to remain substantial for the foreseeable future, if not increase. If the incidence of stroke does not fall by at least 2% per year, every year, then the absolute number of incident stroke cases is likely to increase, given the ageing of the population (Bonita *et al.*, 2004). In developed countries, any increasing burden is likely to fall more on the acute hospital services than on rehabilitation

facilities, because strokes are more likely to be fatal in very elderly and disabled people than in younger and fitter patients (Malmgren *et al.*, 1989).

Strategies to reduce the future burden of stroke

There are two main strategies to reduce the burden of stroke:

1 Prevention of first-ever and recurrent stroke by means of the population (mass) and high-risk approaches (Rose, 1992).
2 Treatment of acute stroke to optimise survival free of complications of stroke, recurrent stroke (and coronary events – the major cause of death in long-term survivors of stroke) and handicap.

This book focuses on the second strategy.

2

Understanding evidence

One of the challenges in finding effective treatments for stroke is that stroke is not a single entity. Stroke has a broad spectrum of clinical features, pathologies, aetiologies and prognoses. Consequently, there is wide variation in the types of treatments for stroke and in the response of patients to effective treatments. This means that there is a low likelihood that there will ever be a single 'magic bullet' to treat all types of stroke. A similar analogy can be seen with infectious diseases and cancers. They also have a broad spectrum of clinical features, pathologies, causes and outcomes. As a result, there are a range of antibiotic and antineoplastic treatments targeting different aetiologies and mechanisms of cellular injury and, even in targeted patients, their effectiveness is variable. This is because the response of patients is also determined by other genetic and acquired factors.

Given that there are likely to be different treatments for different causes and sequelae of stroke, and different responses in different patients, stroke researchers need to ideally aim to evaluate the effects of treatments for particular pathological and aetiological subtypes and sequelae of stroke, and stroke clinicians need to ideally strive to target effective treatments to appropriate patients who are likely to respond favourably.

Stroke clinicians therefore need to know which treatments for patients with particular types and sequelae of stroke are effective (and ineffective), and their respective risks and costs. Theory alone is insufficient for guiding practice; treatments should have been tested appropriately and thoroughly in clinical practice (Doust and Del Mar, 2004). Although appropriate evaluation usually requires enormous efforts and resources, this is several-fold less than the costs of misplaced enthusiasm which leads to the introduction of, and perseverence with, ineffective and dangerous treatments. Indeed, if the extracranial–intracranial bypass trial had not been undertaken and reported (showing no overall effectiveness), this costly and risky procedure would still be practised widely today as a plausible, relatively safe and effective procedure (EC–IC Bypass Study Group, 1985). It can only be hoped that the future will not judge us as irresponsible when we choose to not evaluate

Table 2.1. Common treatments used in neuroscience today which are (sadly) lacking evidence of effectiveness and safety from RCTs.

- Thrombolysis for thrombosis of the basilar artery
- Anticoagulants for intracranial venous thrombosis
- Early surgery for ruptured intracranial aneurysms
- Surgery for intracerebral haemorrhage
- Surgery for cervical spondylotic myelopathy
- Surgery for syringomyelia
- Thymectomy for myasthenia gravis
- Radiation therapy for glioma
- Dopamine agonists for Parkinson's disease (different preparations, timing)

Table 2.2. Reasons for using ineffective or harmful treatments.

- Lack of reliable evidence of safety and effectiveness
- Over-reliance on surrogate outcomes
- Anecdotal clinical experience (i.e. historical controls)
- Theoretical benefit (e.g. love of the pathophysiological model, which is incorrect)
- Natural history of the disease (e.g. poor prognosis)
- Patients' expectations (real or assumed)
- A desire to 'do something'
- Ritual
- No questions asked

established procedures in the same way, on the (in my opinion undefensible) grounds that it is 'unethical' (Table 2.1) (van Gijn, 2004, 2005).

Indeed, a primary reason for the wide variation in stroke management among different clinics, cities, regions and countries, and use of ineffective and harmful treatments, is continuing uncertainty about the safety and effectiveness of many of the available treatments due to the lack of reliable evidence of efficacy and safety (Table 2.2) (Chalmers, 2004; Doust and Del Mar, 2004).

In the presence of uncertainty about the relative intrinsic merits of different treatments, clinicians cannot be certain about those merits in any given use of one of them – as in treating an individual patient. Therefore, it seems irrational and unethical to insist one way or another before the completion of a suitable evaluation/trial of the different treatments. So, the best treatment for the patient is to participate in a relevant trial. Although this is experimentation, it is simply choice under uncertainty, coupled with data collection. The choice is random, and constructive doubt