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Stroke: background, epidemiology, etiology and avoiding recurrence

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Epidemiology

The impact of stroke

In both the developing and developed countries, the burden of stroke is enormous. Stroke was responsible for 1 in every 15 deaths in the USA in 2001 and, on average, every three minutes someone dies from a stroke (American Heart Association, 2004). Stroke is the second leading cause of death worldwide and the third in developed countries (Murray and Lopez, 1997; Sarti *et al.*, 2000). In 2002, there were more than 5.47 million deaths from cerebrovascular disease worldwide (World Health Organization [WHO], 2003a).

However, stroke is more disabling than lethal, with at least 30% of the survivors making a incomplete recovery and a further 20% requiring assistance for activities of daily living (Bonita *et al.*, 1997). Cerebrovascular diseases are the first cause of serious long-term disability in the USA (American Heart Association, 2004) and the second worldwide in individuals more than 60 years of age (WHO, 2003a). In addition, the psychosocial burden of caregiving should be mentioned. The long-term caregivers of people with stroke more frequently complain of restraints in social life, uncertainty about care needs, constant worries, and feelings of heavy responsibility. A lower quality of life, as well as an increased prevalence of depression, was also found among stroke caregivers (Morimoto *et al.*, 2003).

Finally, because stroke is a leading cause of lost years and disability, it has a very high economic cost. Although the cost may vary according to the type (Bergman *et al.*, 1995; Taylor *et al.*, 1996; Payne *et al.*, 2002) (e.g. hemorrhagic vs. ischemic) and severity of stroke (Caro *et al.*, 2000), the mean lifetime cost for ischemic stroke (IS) including inpatient care, rehabilitation and follow-up is expected to be at

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US$ 140, 048, and the estimated direct and indirect cost of stroke in the USA for 2004 is US$ 53.6 billion (Taylor *et al.*, 1996; American Heart Association, 2004).

Secular trends in stroke mortality

The mortality from stroke has been clearly changing over time. In the USA, it is estimated that between 1915 and 1968 stroke mortality has decreased approximately 1.5% per year, probably as a result of improvements in general public health and nutritional status of the citizens (Wolf and D'Agostino, 1998). Between 1950 and 1968, although mortality from coronary heart disease (CHD) increased about 10%, stroke continued to decrease (National Institutes of Health [NIH], 2002) and there is evidence that it is still declining (Howard *et al.*, 2001). Nevertheless, since the population is aging, the actual number of deaths is rising; consequently, even though the death rate fell approximately 3.4% between 1991 and 2001, the actual number of deaths rose 7.7% in the USA (American Heart Association, 2004).

In most of the other developed countries, mortality rates have also fallen since the early 1990s, especially in Japan and Western Europe (Sarti *et al.*, 2000; Feigin *et al.*, 2003; Truelsen *et al.*, 2003). In the WHO MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project (2003b), the average stroke mortality in Turku-Loimaa, Finland fell from 82 per 100 000 in 1983–1985 to 60 per 100 000 in 1990–1992 (Tuomilehto *et al.*, 1996) (Fig. 1.1). Conversely, the mortality from countries in Eastern Europe has increased in recent years (Truelsen

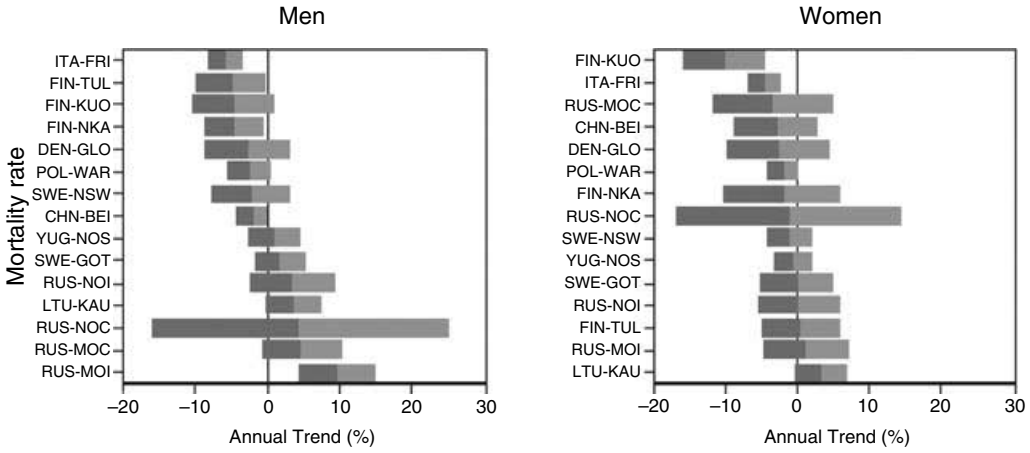

Fig. 1.1 Mortality trends in the MONICA project (WHO, 2003b). Horizontal bars in the mortality rate show the 95% confidence intervals around the estimated annual trend. Note that stroke mortality has lowered in countries from Western Europe, China and Poland whereas the opposite has happened to countries in most of the populations studied in Eastern Europe. ITA, Italy; FIN, Finland; DEN, Denmark; POL, Poland; SWE, Sweden; CHN, China; YUG, Yugoslavia; RUS, Russia; LTU, Lithuania.

et al., 2003; WHO, 2003a). Data from the WHO indicate that in Russia between 1985 and 1994 mortality rates increased by 2.19% per year for men aged 35–74 years (Sarti *et al.*, 2000).

There are few studies concerning mortality trends in developing countries making it, difficulty to draw conclusions. Except for some places such as Mauritius (which has not shown an evident variation in time), in most countries mortality rates have also been declining (Sarti *et al.*, 2000; de Padua Mansur *et al.*, 2003), especially for the population aged 35–74 years.

The determinants of stroke mortality: incidence and case-fatality

Stroke mortality is a function of the incidence (new cases per year) and the case-fatality (proportion of those who die). It varies widely in different regions of the world (Fig. 1.2) and depends on factors such as local environmental, cultural, socioeconomic and genetic variables. Incidence can only be drawn from population-based stroke studies. Most of the studies capable of providing such information show that incidence of stroke declined during the 1970s and 1980s, but between the 1980s and 1990s this decline slowed, reaching a plateau or even increasing in some populations, such as in Söderhamn, Sweden or in Auckland, New Zealand (Bonita *et al.*, 1993; Feigin *et al.*, 1995, 2003; Brown *et al.*, 1996; Numminen *et al.*, 1996; Morikawa *et al.*, 2000; Pessah-Rasmussen *et al.*, 2003; Terént, 2003). Nonetheless, there are other populations, such as in Turku, Finland

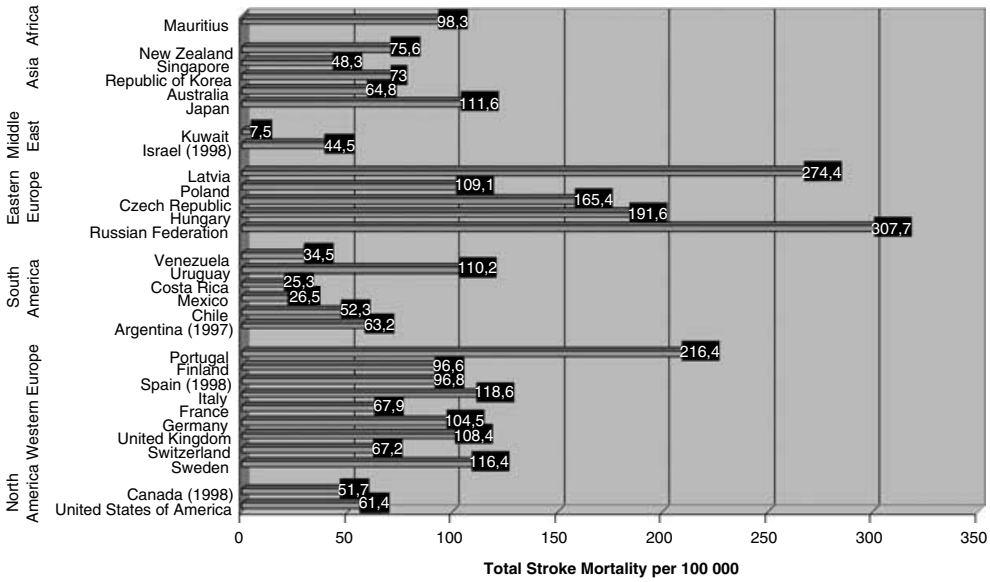

Fig. 1.2 Stroke mortality worldwide. Note the wide variation and the higher rates in countries located in Eastern Europe and Portugal. Data are from 1999 unless otherwise specified. (From WHO, 2003c.)

or in Perth, Australia, that have continued to show a decline (Jamrozik *et al.*, 1999; Immonen-Raiha *et al.*, 2003; Kubo *et al.*, 2003; Sivenius *et al.*, 2004).

Since there are many studies that report a plateau in the incidence levels of stroke over recent years, it seems that the decline in stroke mortality is mainly a consequence of lowering case-fatality rather than a lowering of the incidence rate (Asplund *et al.*, 1998; Asplund, 2001; Sarti *et al.*, 2003; Truelsen *et al.*, 2003).

There are plausible explanations for the reduction in case-fatality. The first is better acute stroke care. Although there are no new specific treatments for stroke that would lead to a clear difference in case-fatality since the early 1990s, the management of medical complications could have improved. The second possibility is a decline in stroke severity. In fact, there are many studies that indicate a reduction in the cases of intracerebral haemorrhage (ICH), a subtype of stroke with high case-fatality (Lawlor *et al.*, 2002; Kubo *et al.*, 2003; Terént, 2003), and an increase in milder strokes. In Sweden, for example, between 1975 and 2001, the incidence of ICH decreased by approximately two-thirds, whereas the incidence of milder strokes almost doubled (Terént, 2003). In Portland, USA (Barker and Mullooly, 1997), stroke severity declined between 1967 and 1985, with a reduction in the rates of people in coma or wheelchair bound. Finally, the development of newer methods for the diagnosis of stroke (such as computed tomography and magnetic resonance) have allowed easier diagnosis of strokes that are mild in nature, with minimal neurological deficits. In Rochester, USA, for example, the incidence of stroke has increased but stroke severity has decreased coincidently with the advent of computed tomography (Broderick, 1993).

Etiology

Although primary prevention interventions are outwith the scope of this chapter (Bronner *et al.*, 1995; de Freitas and Bogousslavsky, 2001), results of randomized controlled trials are reported here, since they provide the best data on clinical epidemiology. The demonstration that specific modification of a presumed risk factor in one group reduces the incidence of stroke compared with the other similar (randomized) group, which had no intervention, is one of the best ways for establishing a causal relationship.

Risk factors

Classically, stroke can be divided into IS (accounting for about 80%) and hemorrhagic stroke (20%). IS is further broadly subdivided into lacunar infarction (small artery disease), large artery disease and cardioembolic stroke; hemorrhagic stroke could be subdivided into ICH and subarachnoid haemorrhage (SAH). The

Table 1.1 Stroke risk factors

Non-modifiable	Modifiable	Emerging
Age	Hypertension	Fibrinogen
Gender	Diabetes mellitus	Hyperhomocysteine
Race	Hypercholesterolemia	Inflammation/infection
Heredity	Cigarette smoking	
	Alcohol abuse	
	Diet	
	Oral contraceptive	
	Atrial fibrillation	

classification of stroke into several types and further subtypes is of great importance. The incidence of morbidity, mortality, and recurrence of hemorrhage and infarction in the various types/subtypes is entirely different, as are their physiopathology and natural history (de Freitas and Bogousslavsky, 2003).

About two-thirds of stroke patients have well known risk factors for stroke. Risk factors can be divided into modifiable and non-modifiable, and new potential risk factors are also being studied (Table 1.1) (Sacco, 1995). Risk factors may also be specific for one stroke type or subtype.

Age

In all studies of stroke, there is a clear increase in the incidence and prevalence with age. The main reasons for this are reduction of incidence and case-fatality of stroke in the younger population; the longer time for effect of environmental risk factors; and higher prevalence of risk factors with age, such as atrial fibrillation, hypertension, diabetes, and CHD (Stolk *et al.*, 1997; Wattigney *et al.*, 2003).

Race and ethnic origin

Although the definitions of ethnicity are controversial (Shriver, 1997; Fustinoni and Biller, 2000; Saposnik *et al.*, 2003), there is an important variation in mortality among the different racial and ethnic groups studied.

In USA and Europe, the death rates from cerebrovascular disease among black people are consistently higher than other groups (Broderick *et al.*, 1998; Qureshi *et al.*, 1999; Rosamond *et al.*, 1999; Stewart *et al.*, 1999; Longstreth *et al.*, 2001; Wolfe *et al.*, 2002; Centers for Disease Control and Prevention [CDC], 2003). In the USA, between 1991 and 1998, the decline in mortality rate was about 2.0% per year in Asian and Pacific Islanders, followed by Hispanics and black people (1.4%), Alaskan Natives (1.1%) and white people (0.8%) (CDC, 2003). Possible reasons for these higher mortality rates in black people are a more stressful socioeconomic

lifestyle and less access to medical therapy, reflected in a lower probability of receiving secondary prevention therapy (Kaplan and Keil, 1993; Giles *et al.*, 1995; Gorelick, 1998; Cabrera *et al.*, 2001; Christian *et al.*, 2003). In addition, black people have higher predisposition and incidence of hypertension and diabetes mellitus compared with white people (Burt *et al.*, 1995a, b; Giles *et al.*, 1995; Baker *et al.*, 1998; Hajat *et al.*, 2001; Gupta *et al.*, 2003). Finally, there seem to be differences in IS subtypes, with black people showing a higher risk for lacunar infarction and large-artery intracranial occlusive disease, whereas white people may be more prone to cerebral embolism, transient ischemic attack (Gorelick *et al.*, 1998), and extracranial atherosclerotic disease (Gupta *et al.*, 2003). Asians have the highest frequency of hemorrhagic stroke, compared with other groups (CDC, 2003).

Family history

In a recent review of the most important studies about the relationship between stroke and family history (Floeβmann *et al.*, 2004), there seemed to be a small genetic contribution to stroke, based on twin studies, with monozygotic twins being 1.6 times more likely to be concordant for stroke compared with dizygotic twins. Moreover, the genetic factors seemed to be more linked to stroke in younger people, particularly those less than 70 years.

This genetic predisposition could be, in part, a reflection of the fact that many risk factors for cardiovascular diseases may have genetic influences, such as hypertension (Oparil *et al.*, 2003), diabetes (Florez *et al.*, 2003), hypercholesterolemia (Snieder *et al.*, 1999), CHD (Hirashiki *et al.*, 2003), carotid stenosis (Fox *et al.*, 2003), and obesity (Damcott *et al.*, 2003). In addition, some genetic mutations, such as factor V Leiden, prothrombin G20210A, methylenetetrahydrofolate reductase C677T, and the genotypes of angiotensin-converting enzyme (ACE) I/D and apolipoprotein allele e4, have been shown to augment the risk of stroke particularly in the presence of hypertension, diabetes mellitus, smoking, and drinking (Szolnoki *et al.*, 2003).

Recently, it was found that the gene encoding phosphodiesterase 4D was associated with IS and that it was not correlated with known risk factors (Gretarsdottir *et al.*, 2003).

Hypertension

Hypertension is the most prevalent and modifiable risk factor for stroke and is associated with IS, ICH, and SAH (Teunissen *et al.*, 1996; Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998). It is difficult to determine a relative risk for hypertension, since it interacts with other risk factors, such as age and atrial fibrillation (Whisnant, 1997). In addition, the relative risk is dependent on blood pressure. For example, in a meta-analysis, the relative risk of stroke for people in the highest quintile of diastolic blood pressure was up to 10-fold

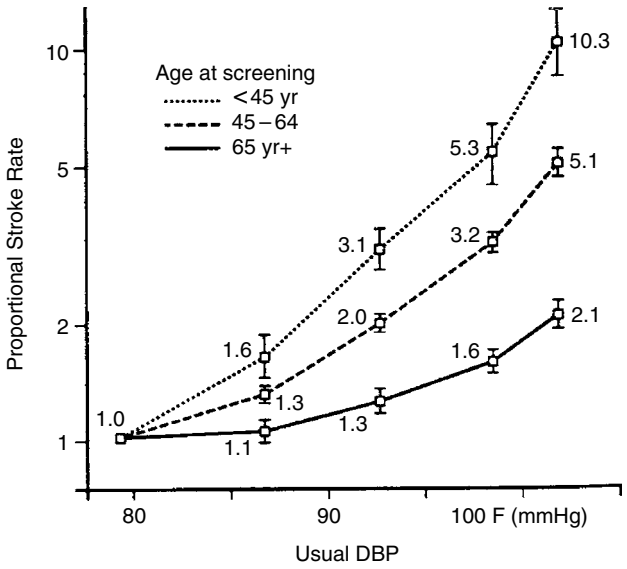

Fig. 1.3 Proportional stroke risk by age and usual diastolic blood pressure (DBP). (Data from Prospective Studies Collaboration, 1995.)

higher than for those in the lowest quintile (Prospective Studies Collaboration, 1995) Fig. 1.3).

Antihypertensive therapy substantially reduces the risk of stroke. A meta-analysis of 14 randomized trials showed that a significant reduction of 42% (95% confidence interval [CI], 33–55) in stroke in treated patients resulted from only a 5–6 mmHg reduction in diastolic blood pressure (Collins *et al.*, 1990).

Although there is no longer uncertainty about whether hypertension should be treated, many questions have only recently been answered. In the early 1990s, there was a reluctance to reduce high blood pressure in the elderly (Wolf, 1993).The Swedish Trial in Old Patients with Hypertension showed that antihypertensive treatment in people aged 70–84 years was safe and conferred a 45% reduction (95% CI, 14–67) in risk of stroke compared with placebo (Dahlöf *et al.*, 1991). Although this trial excluded persons with isolated systolic hypertension (systolic blood pressure >160 mmHg and diastolic blood pressure <90 mmHg), a common condition in the elderly, this issue was addressed in another trial, the Systolic Hypertension in the Elderly Program, which showed that management of isolated systolic hypertension in persons older than 60 years reduced the total incidence of stroke by 36% (95% CI, 18–50) (SHEP Cooperative Research Group, 1991). These results were supported by the Systolic Hypertension in Europe trial, which achieved a 42% (95% CI, 17%–60) reduction in the risk of stroke in people older than 60 years with isolated systolic hypertension (Staessen *et al.*, 1997).

The two main issues at present are to what extent blood pressure should be lowered and which medical regimen should be chosen (Cutler, 1999). It has been argued that mortality increases at a certain level of reduction of blood pressure, resulting in the so-called J curve. However, the J curve has never been confirmed for mortality from stroke and whether it exists in CHD is a matter of controversy (Fletcher and Bulpitt, 1992). The Hypertension Optimal Treatment Study demonstrated the benefits of lowering systolic and diastolic pressures, respectively, to 140 and 85 mmHg, or lower (Hansson *et al.*, 1998). Efforts to lower blood pressure further (to 120 mmHg systolic and 70 mmHg diastolic) appeared to give little further benefit but did not result in any additional risk. Moreover, in the Heart Outcomes Prevention Evaluation Study (Yusuf *et al.*, 2000a), further blood pressure reduction in patients at high risk for cardiovascular events using ramipril, an ACE inhibitor, was associated with a significant 32% (95% CI, 16%–44) reduction in the rate of stroke.

It has been questioned whether newer antihypertensive agents (ACE inhibitors and calcium channel blockers [calcium antagonists]) give the same benefits as conventional treatment (diuretics and beta-blockers). According to recent guidelines (Chobanian *et al.*, 2003), there is similar cardiovascular protection from lowering blood pressure with ACE inhibitors, angiotensin-receptor blockers, and calcium antagonists as with thiazide-type diuretics and beta-blockers.

Diabetes mellitus and glucose intolerance

Diabetes is a well-established, independent risk factor for IS, but not for hemorrhagic stroke. In the Honolulu Heart Program, the age-adjusted incidence rate of IS in diabetics was more than two-fold higher than in subjects in the low–normal category of glucose tolerance (adjusted relative risk [RR], 2.45; 95% CI, 1.73–3.47) (Burchfiel *et al.*, 1995). In contrast, the incidence of hemorrhagic stroke did not differ between the groups. However, it is not clear whether strict control of blood glucose is effective. In fact, in patients with type 2 diabetes, intensive sulphonylurea and/or insulin therapy ameliorated microvascular complications but not macrovascular complications, such as stroke (UK Prospective Diabetes Study Group, 1998). Similarly, although intensive insulin therapy (given either by an external pump or by three or more daily injections) in patients with type 1 diabetes delayed the onset of microvascular complications, the reduction of macrovascular complications was not significant (Diabetes Control and Complications Trial Research Group, 1993, 1995).

Asymptomatic hyperglycemia was also considered to be an independent risk factor for stroke, but prospective studies yielded inconsistent results (Fuller *et al.*, 1983; Burchfiel *et al.*, 1995; Balkau *et al.*, 1998; Wannamethee *et al.*, 1999). In addition, it remains unclear whether the serum insulin concentration is an

independent risk factor for stroke. In the British Regional Heart Study, a J-shaped relationship was seen between serum insulin and risk of stroke, the lowest risk being seen in the second quintile of the distribution (Wannamethee *et al.*, 1999). In the Atherosclerosis Risk in Communities Study, the fasting serum insulin level was weakly associated with IS after adjusting for confounding risk factors (adjusted RR, 1.14; 95% CI, 1.01–1.3), and, again, the association was non-linear (Folsom *et al.*, 1999a).

Obesity

Data linking obesity and stroke are limited. It is not clear whether otherwise healthy mildly or moderately obese persons are at a higher risk of stroke than healthy non-obese people (Kassirer and Angell, 1998). One study reported a lack of relationship between the body mass index and stroke (Folsom *et al.*, 1999a), whereas another demonstrated a relationship but made no adjustment for blood pressure and blood lipids (Sharper *et al.*, 1997). Nevertheless, overall, the evidence suggests that there is an U-shaped relationship between weight and stroke: that is, persons at either extreme of the body mass index are at highest risk (Sharper *et al.*, 1997; Stevens *et al.*, 1998; Wassertheil-Smoller *et al.*, 2000). The RR associated with a greater body mass index declines with age, and, in older people, the risk of death and stroke is similar across a wide range of values (Stevens *et al.*, 1998).

Lipids

Total cholesterol

The relationship between cholesterol levels and CHD is well established, and hypercholesterolemia is one of the most important risk factors for this disease. Although there are strong links between CHD and cerebrovascular diseases, the association between cholesterol levels and stroke is still debated.

In the Framingham Study, a negative relationship was found between high cholesterol levels and stroke in females (Wolf *et al.*, 1983). The Multiple Risk Factor Intervention Trial found that, in men with a diastolic blood pressure ≥ 90 mmHg, the risk of ICH was three times higher in those with low–normal cholesterol (<4.24 mmol/l or 160 mg/dl) than in those with higher cholesterol levels (Iso *et al.*, 1989). However, the risk of death from IS increased significantly with increasing serum cholesterol levels. These conclusions were recently reinforced by an overview of Japanese and Chinese studies, which revealed a trend towards an increased risk of hemorrhagic stroke (RR, 1.27; 95% CI, 0.84–1.91) and a reduction in the risk of IS (RR, 0.77; 95% CI, 0.57–1.06) with decreasing cholesterol concentrations (Eastern Stroke and Coronary Heart Disease Collaborative Research Group, 1998). However, the results of this last study did not support the earlier suggestion that the risk of hemorrhagic stroke was higher in patients with both

low cholesterol concentrations and high blood pressure. The above results on IS also contrast with those of another meta-analysis of 45 prospective cohorts, which showed no association between total cholesterol and mortality from stroke except, perhaps, in subjects under 45 years (Prospective Studies Collaboration, 1995).

There are many possible explanations for the discrepant results of the above studies. First, some studies included only fatal stroke and the results for less severe stroke may be different. Moreover, stroke subtypes were not identified, and, in studies in which no association between all strokes and cholesterol was found, a positive association with IS linked to large artery disease might be counterbalanced by a negative association with hemorrhagic stroke.

The results of the first three large trials of cholesterol reduction using 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) published in the middle 1990s (WOSCOP [Shepherd *et al.*, 1995], 4S [Scandinavian Simvastatin Survival Study Group, 1994], and CARE [Sacks *et al.*, 1996]) have challenged previous concepts, and we can now divide opinion regarding cholesterol as a risk factor into two eras; pre- and post-statin. Seven meta-analyses, including the above and newer studies, revealed a reduction of about 25% in stroke as a result of statin use (Blaw *et al.*, 1997; Crouse *et al.*, 1997, 1998; Herbert *et al.*, 1997; Bucher *et al.*, 1998; Ross *et al.*, 1999; di Mascio *et al.*, 2000; Corvol *et al.*, 2003).In the setting of primary prevention, the meta-analysis revealed a non-significant 4–20% reduction in stroke (Crouse *et al.*, 1997; Herbert *et al.*, 1997; di Mascio *et al.*, 2000; Corvol *et al.*, 2003). However, none of these analyses included recent large trials, such as the AFCAPS/TexCAPS (Downs *et al.*, 1998), Heart Protection Study (Heart Protection Study Collaborative Group, 2002a), the ALLHAT-LLT trial ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002), and the PROSPER trial (Shepherd *et al.*, 2002), which included 6605, 2629, 8880, and 3239 patients, respectively, without history of vascular disease.

High-density lipoprotein cholesterol, triglycerides, and lipoprotein (a)

The British Regional Heart Study (Wannamethee *et al.*, 2000) and the Copenhagen City Heart Study (Lindenstrom *et al.*, 1994) reported that higher levels of high density lipoprotein (HDL) were associated with a decrease in the risk of stroke, while this inverse relation was not observed in the recent analysis of the Atherosclerosis Risk in the Communities Study (Shahar *et al.*, 2003). In a study that included very old people (older than 85 years), when the relevance of lipids as determinants of cardiovascular disease risk is disputable, low HDL cholesterol, in contrast to high low density lipoprotein (LDL) cholesterol levels, was associated with mortality from stroke (Weverling-Rijnsburger *et al.*, 2003).