

Approaches to prevention of a first stroke

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Summary

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Stroke is one of the leading causes of mortality and morbidity worldwide. Despite recent important advances in therapeutic approaches, only a very small proportion of patients receive treatment and treatment is still far from satisfactory. Several conditions and life-style factors have been identified as risk factors for stroke, and strategies aimed at modifying these are the best way to reduce the burden imposed by the disease. We review the available data on the effectiveness of modifying risk factors by means of life-style changes, drugs, and surgery in the primary prevention of stroke. Identification of new risk factors and of markers for individuals at high risk is essential for more efficacious prevention.

Keywords: cerebrovascular disorders; prevention; risk factors

Résumé

L'accident cérébrovasculaire ischémique est une des principales causes de mortalité et morbidité dans le monde. Malgré les développements récents dans la thérapeutique, seul un petit nombre de patients vont bénéficier de cela et son efficacité est encore loin d'être satisfaisante. Plusieurs conditions morbides et styles de vie ont été identifiés comme facteurs de risque pour l'accident vasculaire cérébral, et des différentes stratégies adressées à les modifier sont le meilleur moyen pour diminuer l'impact de la maladie. Nous revoyons

dans cet article, les données de la littérature visées à modifier les facteurs de risque à travers des changements de style de vie, des médicaments, et de la chirurgie à fin de prévenir de façon primaire la maladie. Pour avoir une prévention plus efficace, l'identification des facteurs de risque et des marqueurs pour les malades à haut risque est essentiel.

Mots clés: maladies cérébrovasculaires; prévention; facteurs de risque

Stroke epidemiology

Stroke is the third leading cause of death worldwide [1], and the leading cause of disability in developed countries [2]. Although Switzerland has one of the lowest stroke death rates in the world at 38–47 per 100 000 per year, much lower, for example, than in eastern European countries with rates of 176–249 per 100 000 per year, stroke still imposes an enormous burden on the health system [3]. Stroke accounts for 10% of deaths in the developing world, and, worldwide, was responsible for 4.4 million (9%) of 50.5 million deaths in 1990 [1]. However, it is more disabling than lethal, with at least 30% of the survivors making an incomplete recovery and a further 20% requiring assistance for activities of daily living [4], and the suffering of stroke survivors and their families and carers must also be taken into account.

During recent decades, there has been a decline in the incidence of stroke, but recent studies suggest that it is no longer falling [5] and may, in fact, be increasing. Moreover, ageing of the population may soon result in an increase in the absolute number of strokes. In addition, although important advances in therapeutic approaches, such as thrombolysis, have been made, treatment for stroke is still far from satisfactory. In fact, only a small proportion (1.7%) of ischaemic strokes are treated with thrombolytic agents in some community hospitals [6]. Thus, it is clear that major efforts should be made in stroke prevention.

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Type of evidence

The purpose of this paper is to review evidence for the effectiveness of different approaches to the primary prevention of stroke (table 1). Large randomised controlled trials are generally considered the gold standard in evaluating the efficacy of clinical intervention. The great strength of these studies is that, since patients are randomly assigned to either the putative casual or some alternative experience (another agent or no exposure at all), the study groups are similar not only in terms of already known determinants of outcome, but also in terms of currently unknown determinants [7]. However, in the case of some risk factors (e.g. smoking), it would be not ethical to randomly assign patients to be exposed or nonexposed. In some situations, therefore, a cohort study, in which the investigator identifies exposed and nonexposed groups of patients and follows them to monitor the outcome, may provide the best level of evidence, particularly when the information comes from a large database and statistical techniques are used to allow for imbalances due to confounding variables [7]. Nevertheless, an important imbalance, which is either not measured or is unknown to the investigators, may influence the outcome. When the outcome of interest is very rare or takes a long time to develop, case-control studies may be used. In these, patients who have developed the outcome of interest (cases) are compared with persons who do not have this outcome (controls), but who are otherwise similar to the cases with respect to important determinants of outcome, such as age and sex. Limitations of case-control studies are that a condition may change after the outcome (e.g. see homocysteine and *Chlamydia pneumoniae*), a recall bias may influence the results, and, as in cohort studies, unmeasured confounding variables may be responsible for differences. Meta-analysis can provide an objective summary of all the available evidence, but whether meta-analysis is better than large randomised controlled trials is a matter of contention [8].

Limitations

It is often difficult to draw conclusions from stroke epidemiological studies [9]. Stroke is a heterogeneous disorder that includes ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage, each of which has many subtypes, and studies on stroke have been limited by their inadequate classification. Moreover, the various

studies differ in terms of methodology (case-controlled or prospective cohort), study population (Japanese, American, or Nordic), and drug posology. Sometimes, the results are conflicting. Thus, the recommendations made in the present presentation should be balanced, for each individual, against the risk and cost. In addition, results of stroke prevention trials are coming out so fast that, by the time this review is published, new risk factors may already have emerged.

Risk factors

Modifiable risk factors for stroke include hypertension, diabetes mellitus, hypercholesterolaemia, cigarette smoking, alcohol abuse, and oral contraceptives. Age, sex, race, and family history of stroke are not modifiable and will not be addressed here. New potential risk factors, such as inflammation and infection, are discussed.

Primary prevention is aimed at reducing the risk of stroke in asymptomatic subjects; recommendations concerning patients with transient ischaemic attacks and coronary heart disease are considered here as *secondary prevention*. Changes to modifiable risk factors are known to reduce the incidence of stroke in asymptomatic subjects. The role of drugs and surgery has not been clearly determined. Primary prevention in patients with special characteristics, such as atrial fibrillation and carotid stenosis, is also discussed.

Hypertension

Hypertension is the most prevalent and modifiable risk factor for stroke and associated with ischaemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage [10–12].

Antihypertensive therapy substantially reduces the risk of stroke. A meta-analysis of 14 randomised trials showed that only a 5–6 mm Hg reduction in diastolic blood pressure resulted in a significant reduction of 42% (95% CI 33–55%) in stroke in treated patients, a value that could be achieved with less than 5 years of treatment using diuretics or beta-blockers as first-choice drugs [13].

Although there is no longer uncertainty about whether hypertension should be treated, many questions have only recently been answered. In the beginning of the 1990s, there was a reluctance to reduce high blood pressure in the elderly. The Swedish Trial in Old Patients with Hypertension (STOP Hypertension trial) showed that antihyper-

Table 1 Best evidence for the effectiveness of approaches to primary prevention of stroke.

risk factors	best evidence ¹	comments	recommendations
hypertension	randomised controlled trials, meta-analysis	Newer antihypertensive agents (ACE inhibitors and calcium antagonists) may be as effective as conventional treatment (diuretics and beta-blockers) in the reduction of stroke.	Blood pressure should be lowered to normal values by life-style changes and/or pharmacological treatment.
diabetes mellitus	cohort studies		Strict control of glucose levels in diabetes has not yet been proven to be associated with a reduced risk of stroke, but should be encouraged because of benefits in terms of micro-vascular complications.
cholesterol	randomised controlled trials, meta-analysis	Randomised controlled trials have shown that statin use, but not necessary cholesterol reduction, decreases the risk of stroke in coronary heart disease patients.	Statins should be prescribed in patients with high cholesterol levels because of the benefits for coronary heart disease [142]. The value of statins in the primary prevention of stroke is still unclear.
cigarette smoking	cohort studies, meta-analysis	Individuals who stop smoking show a marked reduction in stroke risk within 2–4 years of cessation.	Cigarette smoking should be discouraged.
alcohol consumption	cohort studies, meta-analysis	Different types of beverage (wine, beer, spirits) seem to have the same effect on stroke risk.	Alcohol use is related to serious morbidity and social problems, therefore public recommendation for stroke prevention may promote more hazards than benefits. Encouragement of high-risk subjects on an individual basis may be helpful. Excessive use of alcohol should be avoided.
oral contraceptives	cohort studies, meta-analysis	The risk of stroke associated with new oral contraceptives is very low.	There is no contraindication for oral contraceptives for women without vascular risk factors.
postmenopausal oestrogen replacement therapy	cohort studies	There seems to be no association between hormone replacement therapy and stroke.	Postmenopausal hormone use should not be discontinued, as it markedly reduces the risk of coronary heart disease.
physical activity	cohort studies	Studies show conflicting results.	Regular, moderate levels of physical activity may be part of a primary prevention strategy for stroke.
diet	cohort studies	Data are still limited and controversial.	Consumption of fruits and vegetables should be encouraged, since they are a rich source of potassium and fibres.
aspirin	randomised controlled trials, meta-analysis	Long-term aspirin increases the risk of haemorrhagic stroke.	There is no scientific support for prescribing aspirin to reduce the risk of stroke in asymptomatic patients.
carotid endarterectomy	randomised controlled trials, meta-analysis		Endarterectomy may be indicated for certain patients with 60–99% stenosis. Only patients with a low surgical risk (<3%) and with a life expectancy of at least 5 years are likely to benefit from surgery [143].
vitamin supplementation	randomised controlled trials		There is no clear evidence that multi-vitamin supplementation reduces the risk of stroke.
homocysteine	cohort studies, case-control studies	There is no agreement in the literature regarding whether this is a risk factor or an acute phase reactant.	There is no clear evidence for prescribing vitamins or folate to reduce homocysteine levels. Randomised controlled trials addressing this issue are ongoing.

¹ Best evidence provided by randomised controlled trials, cohort studies and case-control studies.

tensive treatment in people aged 70–84 was safe and conferred a 45% reduction (95% CI 14–67%) in risk of stroke compared with placebo [14]. Diuretics or beta-blockers were again the first-choice medications. Although this trial excluded subjects with isolated systolic hypertension (systolic blood pressure >160 mm Hg and diastolic blood pressure <90 mm Hg), a common condition in the elderly, this issue was addressed in another trial, the Systolic Hypertension in the Elderly Program (SHEP), the results of which were published in the same year and showed that management of isolated systolic hypertension with diuretics and beta-blockers in subjects older than 60 years reduced the total incidence of stroke by 36% (95% CI 18–50%) [15]. These results were supported by the recent Systolic Hypertension in Europe (Syst-Eur) trial, which achieved a 42% reduction (95% CI 17–60%) in the risk of stroke in subjects older than 60 years with isolated systolic hypertension, but this time using a calcium antagonist [16].

The two main issues nowadays are to what extent blood pressure should be lowered and which medical regimen should be chosen. It has been argued that, at a certain level of reduction of blood pressure, mortality increases, resulting in the so-called J curve. However, the J curve has never been confirmed for mortality from stroke and whether it exists in coronary heart disease is a matter of controversy. The Hypertension Optimal Treatment (HOT) study demonstrated the benefits of lowering systolic and diastolic pressures, respectively, to 140 mm Hg and 85 mm Hg; efforts to lower the blood pressure further (down to 120 mm Hg systolic and 70 mm Hg diastolic) appeared to give little further benefit, but did not result in any additional risk [17].

It has been questioned whether newer antihypertensive agents (angiotensin-converting enzyme [ACE] inhibitors and calcium antagonists) give the same benefits as conventional treatment (diuretics and beta-blockers). In contrast to European guidelines [18], American guidelines [19] for the treatment of hypertension do not recommend first-line treatment with newer agents. However, the results of several randomised controlled trials addressing this issue have been published in the last two years [20–24]. In the Captopril Prevention Project (CAPPP) trial, stroke was more common in patients receiving an ACE inhibitor (captopril) than in those assigned to diuretics and beta-blockers [20], but a suboptimal dose of captopril, and therefore a higher blood pressure in the captopril group, throughout the trial may explain the stroke excess. In the Swedish Trial in Old

Patients with Hypertension 2 (STOP Hypertension-2), calcium antagonists and ACE inhibitors gave similar results to conventional treatment (beta-blockers or diuretics) in the prevention of stroke [21]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed a smaller reduction in the frequency of stroke and combined cardiovascular events with the alpha-blocker, doxazosin, than with chlorthalidone [22]. Diltiazem was more effective than a diuretic and beta-blocker regimen in lowering the rate of stroke in the Nordic Diltiazem (NORDIL) study [23]. The Intervention as a Goal in Hypertension Treatment (INSIGHT) trial reported that the calcium channel blocker, nifedipine, and the diuretic combination, co-amiloride, were equally effective in preventing stroke [24]. Overall, with the exception of alpha-blockers, the accumulated results on antihypertensive therapy suggest that ACE inhibitors and calcium antagonists are effective alternatives for lowering blood pressure.

Diabetes mellitus

Diabetes is a well-established, independent risk factor for ischaemic stroke, but not for haemorrhagic stroke. In the Honolulu Heart Program, the age-adjusted incidence rate of ischaemic stroke in diabetics was more than twofold higher than in subjects in the low-normal category of glucose tolerance (adjusted RR 2.45, 95% CI 1.73–3.47), but the incidence of haemorrhagic stroke did not differ between the groups [25]. However, it is not clear whether strict control of blood glucose is effective. In fact, in patients with type 2 diabetes, intensive sulfonylurea and/or insulin therapy ameliorated microvascular complications, but not macrovascular complications, such as stroke [26]. 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 in macrovascular complications was not significant [27, 28].

Asymptomatic hyperglycaemia was also considered to be an independent risk factor for stroke, but prospective studies yielded inconsistent results [25, 29–31]. It was found to be associated with ischaemic stroke in the Honolulu Heart Program [25] and the Whitehall Study [29]. In the latter, non-diabetic men with glucose concentrations above the 95th percentile had a stroke mortality rate higher than normoglycaemic, and even diabetic, subjects. However, a pooled analysis of the

Whitehall Study, Paris Prospective Study, and Helsinki Policemen Study failed to demonstrate this relationship [30]. The British Regional Heart Study showed that hyperglycaemic subjects had an increased risk of stroke, but that this was no longer significant when patients who developed diabetes during follow-up were excluded, and the authors suggested that the excess stroke risk in hyperglycaemic subjects might be, in part, due to inclusion of men with subclinical diabetes [31].

Obesity

Data linking obesity and stroke are limited. It is not clear whether otherwise healthy, mildly, or moderately, obese subjects are at a higher risk of stroke than healthy non-obese subjects. One study reported a lack of relationship between the body-mass index (BMI) and stroke [32], whereas another did demonstrate a relationship, but no adjustment was made for blood pressure and blood lipids [33]. Nevertheless, overall, the evidence suggests that there is a U-shaped relationship between weight and stroke, i.e. subjects at either extreme of the BMI are at highest risk [33–35]. The relative risk associated with a greater BMI declines with age, and, in older people, the risk of death and stroke is similar across a wide range of BMIs [35].

Lipids

Total cholesterol

The relationship between cholesterol levels and coronary heart disease is well established, and hypercholesterolaemia is one of the most important risk factors for this disease. Although there are strong links between coronary heart disease and cerebrovascular diseases, it remains controversial whether a high cholesterol level is a risk factor for stroke, and hundreds of articles, including prospective cohort and case-control studies, reviews, and meta-analyses, have addressed this issue.

In the Framingham Study, a negative relationship was found between high cholesterol levels and stroke in females [36]. The Multiple Risk Factor Intervention Trial (MRFIT) found that, in men with a diastolic blood pressure ≥ 90 mm Hg, the risk of intracranial haemorrhage 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 [37]. On the other hand, the risk of death from ischaemic stroke 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 haemorrhagic stroke (RR 1.27, 95% CI 0.84–1.91) and a reduction in the risk of ischaemic stroke (RR 0.77, 95% CI 0.57–1.06) with decreasing cholesterol concentrations [11]. However, the results of this last study did not support the previous suggestion that the risk of haemorrhagic stroke was higher in patients with both low cholesterol concentrations and high blood pressure. The above results on ischaemic stroke 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 of age [12]. Moreover, two “early” meta-analyses of cholesterol-lowering trials showed no significant difference in stroke risk between the treatment and control groups [38].

There are many possible explanations for the discrepancies in the results of the above studies. Firstly, 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 ischaemic stroke due to large artery disease might be counterbalanced by a negative association with haemorrhagic stroke.

The results of the first three large trials of cholesterol reduction using 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) (WOSCOP [39], 4S [40], and CARE [41]) have shaken previous concepts, and we can now divide opinion regarding cholesterol as a risk factor into two eras, the pre- and post-statin era. Six meta-analyses, including the above studies, revealed a reduction of about 25% in stroke as a result of statin use [42–47], but this information mainly comes from secondary prevention studies. Interestingly, these meta-analyses confirm that, although stroke incidence was reduced by 25%, stroke mortality was not altered by statin treatment. The reason is unclear, but these findings are in agreement with our own study, using data from the Lausanne Stroke Registry, in which patients with normal cholesterol levels had more severe ischaemic strokes than those with high cholesterol levels [48].

Of the six meta-analyses of cholesterol reduction cited above, only three have analysed primary and secondary prevention trials separately [43, 44, 47]; these revealed a non-significant 15%, 20%, and 4%¹ reduction in stroke, but none of the three

¹ Also included non-statin primary prevention trials.

included the last trial of primary prevention with 6605 randomised subjects [49]. Moreover, the trials on primary prevention were designed specifically to detect a reduction in coronary heart disease [39, 49] or in carotid intimal medial thickening [50–52]. Since cholesterol levels are strongly associated with coronary heart disease, patients with high cholesterol levels are more likely to have a cardiac event and achieve an end-point, and the population with raised plasma lipids and large-artery disease decreases with age, when strokes occur. Meta-analysis including more primary prevention trials might show a positive result, and the reduction in stroke may be mainly due to a decrease in strokes secondary to large-artery disease.

Although statin administration reduces the risk of stroke, this does not necessarily mean that its effect is mediated by a lowering of cholesterol levels per se. Indeed, in the recent LIPID study, the decreased stroke risk seen in patients with coronary heart disease using pravastatin was not related to baseline cholesterol levels [53]. Statins may also retard the progression of carotid stenosis, stabilise carotid plaques, alter vasomotor tone, and affect macrophage function, and these effects may be independent of cholesterol reduction [38]. In addition, statins may reduce embolic stroke associated with myocardial infarction, and a recent analysis of the CARE study showed that statin treatment resulted in a significant reduction in the levels of C-reactive protein (an inflammatory marker) that was not related to the magnitude of the observed lipid changes [54].

HDL cholesterol

The British Regional Heart Study [55] and the Copenhagen City Heart Study [56] reported that higher levels of HDL are associated with a decreased risk of stroke.

Triglycerides and lipoprotein (a)

There is limited and conflicting data on the association between serum triglycerides [55, 56] or lipoprotein (a) [57] and stroke.

Cigarette smoking

Studies published in the 80s clearly established cigarette smoking as a powerful risk factor for stroke, especially ischaemic stroke and subarachnoid haemorrhage [58–61]. Although, in the Hono-

lulu Heart Program, an excess of “haemorrhagic stroke” was seen among smokers, this may have resulted from the inclusion of subarachnoid haemorrhage in this group of patients [58] and it is therefore not yet clear whether a relationship exists between intracranial haemorrhage and cigarette smoking. The estimated overall relative risk of ischaemic stroke for cigarette smoking was 1.92 (95% CI 1.71–2.16), whereas the risk of subarachnoid haemorrhage was 2.93 (95% CI 2.48–3.46) [61]. The mechanism by which smoking causes subarachnoid haemorrhage is not clear, but may be due to an acute rise in blood pressure, which may predispose to arterial rupture. It appears that cigarette smoking provokes ischaemic stroke by more than one mechanism. One mechanism that is irreversible and cumulative is linked to carotid atherosclerosis progression. Indeed, the ARIC study showed that progression of carotid atherosclerosis was more rapid in current, past, and passive smokers than in non-smokers [62]. The other, and probably most important, effect of smoking on ischaemic stroke is due to short-term effects, which include increased fibrinogen levels and platelet aggregability, elevated haematocrit values, and reduced cerebral blood flow as a result of arterial vasoconstriction [63]. The importance of these short-term effects is supported by the marked reduction in stroke (ischaemic and subarachnoid haemorrhage) after ceasing smoking [58, 60–64]. Whether the risk of stroke in subjects who give up smoking reverts to that seen in subjects who have never smoked remains uncertain. Such an effect was seen in the Nurses’ Health Study within 2–4 years of cessation of smoking [60], whereas, in the British Regional Heart Study, the risk in heavier smokers (≥ 20 cigarettes per day) who stopped smoking, although considerably reduced, was still higher than in those who had never smoked [63]. Nevertheless, the early and huge risk reduction of more than 50% compared with current smokers warrants vigorous efforts to encourage subjects to stop smoking.

Alcohol consumption

The relationship between alcohol consumption and stroke is complex. In the Honolulu Heart Program, heavy drinkers showed a 3-fold higher risk of subarachnoid haemorrhage and intracerebral haemorrhage than non-drinkers [65]. These results are supported by those from a Finnish study, in which both binge drinking (i.e. occasional alcohol intoxication) and regular heavy drinking increased the risk of aneurysmal and non-aneurysmal sub-

arachnoid haemorrhage [66]. The effects of alcohol consumption on ischaemic stroke are still a matter of controversy. In the British Regional Heart Study, lifelong abstainers had an increased risk of stroke, but there was no convincing evidence that light or moderate drinking was beneficial for stroke risk [67]. However, a protective effect of light or moderate alcohol consumption has been suggested in several recent studies [68–70]. A recent case-control study of a multiethnic population suggested that moderate consumption (up to 2 measures of spirits, 2 cans of beer, or 2 glasses of wine per day) is associated with a reduced risk of ischaemic stroke, while heavy alcohol consumption is associated with an increased risk [68]. Although it has been suggested that certain types of beverages, particularly red wine, are more protective than others, wine, beer, and spirits had approximately the same effect [68]. Similarly, analysis of nearly 450 000 subjects included in the Cancer Prevention Study II showed that mortality from all cardiovascular causes, including stroke, was 30–40% lower in men and women who reported taking at least one drink per day than in non-drinkers [69]. Furthermore, in the recent analysis of the Physicians' Health Study, there was a significant 23% reduction in the risk of ischaemic stroke (adjusted RR 0.77, 95% CI 0.63–0.94) in men who had one, or more, drink per week, the greatest reduction being seen in men who had 1–4 drinks per week [70]. There was no significant association between alcohol consumption and haemorrhagic stroke, but heavy drinking was very rare in this population.

Alcohol has multiple effects on the body. Moderate alcohol consumption may be inversely associated with atherosclerosis. This effect may be due to a reduction in Lp (a) levels or increased HDL cholesterol levels or nitric oxide activity. Moreover, alcohol may promote changes in hemostasis by altering coagulation in a number of ways, such as reducing platelet aggregation, increasing the prostacyclin/thromboxane ratio, reducing fibrinogen levels, and reducing the aggregation and increasing the deformability of red cells [70].

Hormones

Oral contraceptives

During the 70s, the association between oral contraceptives and ischaemic stroke was established [71]. Oral contraceptives are also associated with subarachnoid haemorrhage [72] and ischaemic stroke secondary to cerebral sinus thrombosis [73].

Although the doses of oestrogen and progestagen used in oral contraceptives have since been reduced, it is only recently that the relationship between low-dose oral contraceptives and stroke has received more attention [74–77]. The WHO collaborative study and the Transnational Case Control study revealed that even low-dose oral contraceptives have a small increased risk of ischaemic [74, 76] and haemorrhagic [75] stroke. A recent meta-analysis of subarachnoid haemorrhage and oral contraceptives showed an increased risk of stroke, which, although higher with high oestrogen oral contraceptives, was also seen with low-dose oral contraceptives (adjusted RR 1.51, 95% CI 1.18–1.92, $p = 0.0009$) [72]. Although the risk of stroke was found not to be increased in current users of low-dose oral contraceptives in a pooled analysis of the Kaiser Permanent Medical Care Program of Northern California and University of Washington studies [77], a recent meta-analysis found a relative risk for ischaemic stroke of 2.75 (95% CI 2.24–3.38) among current oral contraceptives users, and of 1.93 (95% CI 1.35–2.74) among low-oestrogen preparation users [78]. Despite this discrepancy, all studies agree that the risk of stroke in young women is very low and the risk is low compared with the potential benefits of oral contraceptives. In fact, treatment of 24 000 women with low-oestrogen preparations would be expected to lead to only one additional ischaemic stroke per year [78]. However, women at high risk of subarachnoid haemorrhage or ischaemic stroke, namely those with unruptured aneurysms, a strong positive family history of subarachnoid haemorrhage [72], or a history of cigarette smoking, hypertension, or migraine, might consider alternative modes of contraception until more data are available [76, 77].

Postmenopausal oestrogen replacement therapy

Although postmenopausal hormone replacement therapy, either oestrogen alone or in combination with progestin, markedly reduces the risk of major coronary heart disease, there is no reduction in the risk of stroke [79, 80]. In an analysis based on a 16-year follow-up of 59 337 postmenopausal women participating in the Nurses' Health Study, no significant association was found between stroke and either combined hormones (adjusted RR 1.09, 95% CI 0.66–1.80) or oestrogen alone (adjusted RR 1.27, 95% CI 0.95–1.69) [79]. These findings were corroborated by a recent case-control study [80].

Physical activity

In the 90s, several studies [81–87], but not all [88], demonstrated that physical activity is inversely related to the risk of stroke. Its protective effects extend to ischaemic stroke, intracranial haemorrhage, and subarachnoid haemorrhage. However, there were important differences in the findings of these studies. The Nord-Trøndelag Health Survey only included women [87], whereas the British Regional Heart Study [81], Zutphen Elderly Study [85], Physicians' Health Study [86], and Honolulu Heart Program [82] only included men. In the last-mentioned study, no benefits of physical activity were seen in either smokers or young subjects [82], while, in the Framingham Study, no protective effects were seen in either young subjects or women [83], and, in the NHANES I study, effects of exercise were mainly seen in white women and not in black subjects [84]. Analysis of the Physicians' Health Study showed that exercise was not associated with a reduced stroke risk when adjustments were made for BMI and a history of hypertension, high cholesterol, or diabetes mellitus [86]. In the ARIC study, only a weak, non-significant association was found between physical activity and reduced risk of ischaemic stroke [88]. The negative results found in these last two studies and the differences between subgroups (e.g. women, smokers, and blacks) may be explained by imprecision in the measurement of physical activity and a lack of statistical power for identifying effects in some subgroups. Moreover, since the BMI or a history of hypertension, high cholesterol, or diabetes mellitus may be considered intermediate factors of exercise, it may be argued that adjustment for such baseline factors is not necessary.

It is unclear how physical activity reduces the risk of stroke. The results of the Physicians' Health Study suggest that this association results from beneficial effects on body weight, blood pressure, serum cholesterol, and glucose tolerance, and that, apart from these effects, physical activity had no influence on stroke incidence [86]. However, in other studies, beneficial effects were seen even after controlling for these variables, suggesting that physical activity is independently associated with stroke. Other possible biological mechanisms are deceleration of the atherosclerotic process, modification of artery structure, reduced vasospasm, enhanced myocardial electric stability, and increased fibrinolysis [87].

There is no consensus on the optimal intensity and frequency of activity. In one study, vigorous exercise was seen to be of greater benefit than moderate exercise in stroke reduction [81]. How-

ever, frequent sport (vigorous activity) was associated with an increased risk of myocardial infarction, leading the authors to suggest that moderate levels of physical activity seem to be sufficient to produce a significant beneficial on stroke and coronary heart disease.

Diet

Information on the relationship between diet and stroke is limited and contradictory.

Vegetables, fruits, grains, and fibres

A protective effect of fruits, vegetables, and whole grain on stroke development has been reported [89–92]. Mechanisms proposed include the lowering of blood pressure associated with dietary fibre, reduction of serum cholesterol by dietary soluble fibre, increased potassium intake, antioxidant vitamin effects, and decreased homocysteine levels by provision of dietary folate [89, 92].

Fat

Although saturated fat intake is directly related to coronary heart disease, analysis of fat intake in middle-aged men in the Framingham cohort showed that intake of fat, saturated fat, and mono-unsaturated fat was inversely associated with ischaemic stroke [93].

Fish

The low mortality from coronary heart disease in certain populations, such as Eskimos, with a high fish consumption contributed to the hypothesis that omega-3 fatty acids in fish oil may have protective effects on vascular diseases [94]. However, cohort studies gave inconsistent results; in the Zutphen study [95], fish consumption was associated with a reduced risk of stroke, while the Physicians' Health Study [96] found no association, and the NHANES I study [97] found an association that was restricted to white women.

Vitamins

The Basel Prospective Study [98] and the recent Shibata Study [90] suggested that low vitamin levels are associated with stroke, but clinical trials

failed to show a reduction in stroke as a result of supplementation with vitamins, such as beta-carotene [99] and vitamin E [100]. Although no relationship was seen between beta-carotene or vitamin E supplementation and the risk of all strokes in a recent randomised controlled study, there was a higher incidence of subarachnoid haemorrhage, but a lower incidence of ischaemic stroke, in men taking vitamin E, and an increased incidence of intracerebral haemorrhage in the beta-carotene-supplemented group [101]; the authors stated that more data are needed to complete the relationship between vitamin E and stroke.

Cations

Since the 80s, it has been suggested that low levels of potassium are associated with stroke mortality [102]. Although it is well known that potassium intake reduces blood pressure, the apparent effect of potassium is greater than would be expected simply from this relationship. In addition, three recent large studies have supported the idea of a protective effect of potassium [103–105], mainly in hypertensive men [103, 105]. Whether potassium supplements may be broadly prescribed for hypertensive patients remains to be determined.

Calcium and magnesium intake has also been associated with reduced stroke [103, 104, 106], but further studies are necessary.

Aspirin

Over the past decades, studies have shown that aspirin can definitely reduce the recurrence of cardiovascular and cerebral vascular events. However, its effects in healthy people are not clear.

Two large clinical trials have addressed the use of aspirin in the primary prevention of vascular events [107, 108]. In a non-blind British study that analysed data from 5139 male doctors randomly allocated to receive or not receive 500 mg of aspirin daily, there was no difference in the incidence of myocardial infarction, but disabling strokes were more common in those allocated to aspirin [107]. Given the limited data regarding which of these strokes were ischaemic and which haemorrhagic, the higher incidence of strokes in the aspirin group could be due to a higher incidence of haemorrhagic stroke. The Physicians' Health Study, a randomised, double-blind, placebo-controlled trial that analysed data from 22 071 male physicians who received either 325 mg of aspirin or placebo every other day demonstrated a 44% risk

reduction in myocardial infarction and a non-significant increased risk of stroke in the aspirin group [108]. In the subgroup with haemorrhagic strokes, aspirin was associated with an increased risk of borderline statistical significance. In the Nurses' Health Study cohort, in which the incidence of stroke in women taking aspirin was recorded, those taking aspirin had a smaller relative risk (0.68) of myocardial infarction, but no change in the risk of stroke [109].

These findings are reinforced by a recent meta-analysis of trials examining the relationship between aspirin use and stroke in low-risk patients [110] which found no significant effect of aspirin on stroke in trials involving subjects with or without risk factors (RR 1.08, 95% CI 0.95–1.24), contrasting sharply with a reduction in myocardial infarction (RR 0.74, 95% CI 0.68–0.82) and a protective effect against stroke in patients with vascular disease. Moreover, long-term use of aspirin increased the risk of haemorrhagic stroke (RR 1.35, 95% CI 0.88–2.1, $p = 0.03$).

Other drugs

The recent Heart Outcomes Prevention Evaluation (HOPE) study assessed the role of ramipril, an ACE inhibitor, in patients at high risk for cardiovascular events and found that ramipril treatment was associated with a significant 32% reduction (95% CI 16–44%) in stroke [111]. It was suggested that ACE inhibitors exert additional direct effects on the vasculature, including antagonising the direct effects of angiotensin II on vasoconstriction, vascular smooth muscle cell proliferation, and plaque rupture, improving vascular endothelial function, and enhancing fibrinolysis.

Cardiac disease

Atrial fibrillation

Atrial fibrillation is associated with a high rate of ischaemic stroke. A recent review reported an average stroke rate of 5% per year in patients included in primary prevention trials, with wide clinically important variation between subpopulations of atrial fibrillation patients (0.5–12% per year) [112]. *Oral coagulation* markedly reduces the risk of stroke in patients with atrial fibrillation. This statement is based on the consistent results of six randomised trials (AFASAK [113], BAATAF [114], SPAF [115], CAFA [116], SPINAF [117],

and EAFT² [118]), aggregate analysis of which showed that anticoagulation with the oral vitamin K antagonist, warfarin, reduced the rate of ischaemic stroke by 70% compared with untreated patients. Assessment of the optimal intensity of anticoagulation in the EAFT study [119] showed that anticoagulant therapy resulting in an INR between 2.0 and 2.9 reduced the combined incidence rate for ischaemic and haemorrhagic events by 80% compared to patients with an INR below 2.0, while an INR between 3.0 and 3.9 reduced the combined rate by 40%; in contrast, an INR above 5.0 resulted in an unacceptable risk of bleeding complications and an INR below 2.0 resulted in no significant reduction in thromboembolic events.

The use of *aspirin* was assessed in four randomised trials (EAFT, AFASAK, ESPS2² [120], and SPAF) and was shown to result in a pooled risk reduction of 21% compared to placebo. In one of these trials (SPAF), aspirin was significantly less effective than warfarin. In the SPAF III low-risk study, when patients with atrial fibrillation and a low risk of stroke (absence of the four risk factors of recent congestive heart failure or left ventricular shortening $\leq 25\%$, previous thromboembolism, systolic blood pressure >160 mm Hg, or women older than 75 years) were placed on aspirin (325 mg daily) and followed in a nonrandomised cohort study, the incidence of primary events (ischaemic stroke and systemic emboli) was 2.2% per year, that of ischaemic stroke 2.0% per year, and that of disabling stroke (modified Rankin score of II or worse) 0.8% [121]. The investigators concluded that low-risk patients should be treated with aspirin, since the risk of ischaemic stroke is so low that warfarin only minimally reduces the absolute incidence of stroke.

Again in the SPAF III high-risk study, when atrial fibrillation patients with at least one of the four risk factors described above were randomised to receive either a combination of a *low fixed-dose of warfarin* (0.4–3.0 mg per day to raise the INR to between 1.2 and 1.5) plus aspirin (325 mg per day) or an adjusted-dose of warfarin (to raise the INR between 2.0 and 3.0), the trial was stopped because the incidence of primary events (7.9%) in the combination therapy group was significantly higher than in the adjusted-dose warfarin group (1.9%) [122]. Because of the SPAF III results, the AFASAK2 trial [123], which examined the efficacy of adjusted-dose warfarin, combined fixed minidose warfarin and aspirin, fixed minidose warfarin alone, and aspirin alone, was also terminated prematurely; although the differences be-

tween the four treatments did not reach statistical significance, there was a trend toward a lower stroke rate in patients receiving adjusted-dose warfarin.

As the annual rate of stroke among people with atrial fibrillation is very wide, risk stratification should separate aetiologic subtypes who should receive different treatments. Although the risk stratification schemes published by the Atrial Fibrillation Investigators and SPAF are not exactly the same, they are consistent with each other.

Patients with atrial fibrillation and at least one of the risk factors of previous stroke, transient ischaemic attacks, or systemic embolism, over 75 years of age, hypertension, or poor left ventricular function are at high risk of stroke and should be offered *anticoagulation* (target INR of 2.5, range 2.0–3.0) unless their risk of bleeding is high. Patients with atrial fibrillation and no cardiovascular disease (“lone AF”) aged less than 65 years are at such a low risk that they should either *be treated with aspirin* or *not treated*. Patients over 65 years of age without other risk factors may be considered as at moderate risk and therapy could include *warfarin* or *aspirin*. The dose of aspirin should be 300 mg a day [124], which has been shown to be effective in patients with atrial fibrillation.

For patients over 75 years of age, a lower target INR of 2.0 (1.6–2.5) may be sensible in order to minimise bleeding. However, this lower warfarin level has not been established, and many authorities disregard age and accept a higher INR target of 2.5 [125].

For some patients, aspirin might be preferred to warfarin because of situations that may increase the risk of bleeding, namely increased age (over 80–85 years), poor drug or clinical compliance, uncontrolled hypertension, alcohol excess, liver disease, bleeding lesions (peptic ulcer or previous cerebral haemorrhage), or a tendency to bleeding (including coagulation defects and thrombocytopenia) [126].

Other cardioembolic strokes

Oral anticoagulation therapy should be considered for the many well-established causes of embolism. Although evidence from randomised trials is lacking, long-term anticoagulants are routinely used in patients with mechanical prosthetic valves. In this situation, a higher target INR of between 3.0 and 4.0 is recommended [127]. Long-term anticoagulation of patients with rheumatic valvular

² EAFT and ESPS2 are secondary prevention studies.

heart disease, myocardial infarction, heart failure, cardiomyopathy, or arrhythmia may also be indicated [128].

Endarterectomy

The results of trials assessing endarterectomy in asymptomatic patients are still a matter of controversy. The largest of these trials, the Asymptomatic Carotid Atherosclerosis Study (ACAS), reported that patients with asymptomatic carotid stenosis above 60% had a 53% reduction in the 5-year relative risk of ipsilateral stroke if endarterectomy was performed [129]. However, the absolute risk reduction was small (5.9% in 5 years), as was the rate of ipsilateral stroke in the medically treated group (11.0% in 5 years, or 2.3% annually). Moreover, these results were obtained with a peri-operative rate of complications (stroke or death) of only 2.3% which is difficult to achieve in practice. In addition, in certain subgroups of patients, namely those with contralateral carotid occlusion, the risk of stroke with medical treatment is so low that surgery may be harmful [130].

A meta-analysis of five trials of endarterectomy for asymptomatic carotid stenosis concluded that, although surgery reduced the incidence of ipsilateral stroke, the absolute benefit of endarterectomy was small, as the incidence of stroke in medically treated patients was low [131]. The authors suggested that, until high-risk subgroups have been identified, medical management remains the sensible alternative for many patients with asymptomatic carotid stenosis.

Carotid angioplasty

The main problem with carotid angioplasty is that long-term follow-up data and a direct comparison with endarterectomy are not yet available. It is hoped that the ongoing Carotid and Vertebral Artery Transluminal Angioplasty Trial (CAVATAS), comparing carotid angioplasty with endarterectomy in both symptomatic and asymptomatic patients, will help to clarify the optimal indications for each procedure.

Emerging risk factors

Homocysteine

Results from cross-sectional and case-control studies support an association between elevated

homocysteine levels and stroke [132]. Results from prospective studies, however, tend to indicate either a weak association or a lack of association [132]. This suggests that homocysteine may be an acute phase reactant, rather than a risk factor. The results of the Women's Antioxidant Cardiovascular study, Vitamin Intervention for Stroke Prevention (VISP) study, and Vitamins to Prevent Stroke (VITATOPS) study, which are testing supplementation with a combination of folic acid and B vitamins, will provide important information on this issue.

Fibrinogen and other markers of hemostatic function

Few data are available relating plasma fibrinogen and stroke. A Swedish study [133] and the Edinburgh Artery Study [134] showed that, after adjustment for confounding variables, fibrinogen levels were found to be associated with stroke. However, no such relationship was found in a recent analysis of the ARIC cohort [135].

It has been suggested that high levels of tissue plasminogen activator, fibrin D-dimer [134], von Willebrand factor, and factor VIIIc [135] are associated with ischaemic stroke, but further studies are necessary.

Inflammation: C-reactive protein and other markers

In a recent analysis of the Women's Health Study, including 28 263 women, four markers of inflammation, C-reactive protein (CRP), serum amyloid A, interleukin-6, and soluble intercellular adhesion molecule type 1 (sICAM-1), were found to be independent predictors of future cardiovascular events, the most significant being CRP (adjusted RR 1.4, 95% CI 1.1–1.9, $p = 0.02$) [136].

Infection

There is growing evidence that chronic infections may be associated with atherosclerosis and, therefore, with cardiovascular diseases. *Chlamydia pneumoniae* is one of the most studied pathogens, but there is no agreement whether serologic evidence for *C. pneumoniae* is associated with stroke; this may be due to the different methodologies adopted in the different studies, such as blood collection for serologic analysis before, or after, stroke [57, 137].

Prevention in the future

Since primary prevention requires the treatment of large numbers of individuals to avoid a single event and since some therapies are associated with more hazards than benefit, it is important to be as selective as possible when using potential harmful strategies. Therefore, better identification of individuals at high risk of stroke will be a cornerstone in stroke prevention in the near future.

Advances in the genetics of stroke may result in the discovery of stroke genes and the molecular determination of individual risk patterns [138]. Surrogate markers of cerebrovascular diseases will allow shorter, less expensive clinical trials. For example, the carotid artery intima-media thickness, which is strongly associated with stroke in general [139] and with ischaemic stroke subtypes [140], may be a more powerful predictor than current risk factors and is a good candidate for measuring the endpoint for stroke due to large-artery disease. Novel serum inflammatory markers, such as CRP, may help in identifying asymptomatic subjects at high risk; an illustrative example is the recent analysis of the Physicians' Health Study, in which aspirin was found to have the greatest effect in those men with the highest CRP levels, its effects decreasing with decreasing concentrations of this inflammatory marker [141]. These new markers may provide a means of recognising subjects for whom drugs should be prescribed.

Obviously, all these advances will not reduce the burden imposed by stroke if large mass harm-free approaches to prevention, aimed at modifying life-style factors, are not implemented.

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