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Cardiovascular Risk Factor Management in the Prevention of Stroke

Proceedings of a Satellite Symposium Held on the Occasion of the 11th European Stroke Conference, Geneva, Switzerland, May 31, 2002

Editor
Pierre Amarenco, Paris

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Introduction

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Stroke is a devastating, debilitating disease. One-third of patients die within 6 months of suffering a stroke and another third are permanently disabled. Moreover, the chance of a recurrence following stroke is exceptionally high. With a rise in the elderly population expected over the next few decades, the clinical burden and cost of stroke can only increase. It is essential, therefore, that we develop effective therapeutic strategies for the primary and secondary prevention of stroke.

The papers in this supplement are from a satellite symposium entitled *Cardiovascular Risk Factor Management in the Prevention of Stroke*, held on the occasion of the 11th European Stroke Conference in Geneva, Switzerland. The aim of this symposium was to review the compelling evidence that aggressive treatment of a patient's global risk for cardiovascular disease (CVD) can also substantially reduce the incidence of fatal and non-fatal stroke. The opening paper by Dr Peter Rothwell establishes that hypertension and hyperlipidaemia, in particular, are modifiable risk factors for both stroke and CVD.

Clinical trials of antihypertensive agents, including angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs), have clearly shown that lowering blood pressure can reduce stroke risk. Recent studies have suggested that certain CCBs might also prevent the formation and progression of carotid atheroma, independently of their blood-pressure-lowering effects. In his paper, Dr R. Preston Mason outlines the possible mechanisms that contribute to the anti-atherosclerotic benefit observed with CCBs, and speculates as to their potential impact on the prevention and treatment of stroke.

Although the benefits of vigorous antihypertensive therapy for the primary and secondary prevention of stroke are increasingly clear, a large number of important questions remain unanswered. Professor David Celermajer describes several ongoing studies that will address many of these unanswered questions, and assesses the implications of their potential answers on current clinical practice.

Several landmark studies have demonstrated that lipid lowering with statins can reduce the risk of ischaemic stroke. The benefits of statin therapy in stroke have been attributed to reductions in cholesterol and to other, non-lipid-lowering effects of statins. However, data on statins and stroke reduction are restricted primarily to patients with, or at high risk of, CVD and thus not truly representative of the overall stroke population. In his paper, Professor John Deanfield reviews a number of lipid-lowering trials in progress, such as the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study, which is designed to evaluate the benefits of aggressive lipid lowering with atorvastatin on cerebrovascular events in patients without established CVD who have experienced a previous stroke or transient ischaemic attack.

Within the past decade, our understanding of how best to reduce the risk of stroke has improved considerably. However, there is good evidence that risk factors for both stroke and CVD are currently undertreated in routine clinical practice. In the final paper, I will forward the argument that the rigorous identification and targeting of high-risk or stroke-prone individuals for blood pressure and lipid-lowering interventions should be of practical importance to all physicians, including neurologists, involved in the management of stroke.

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Incidence, Risk Factors and Prognosis of Stroke and TIA: The Need for High-Quality, Large-Scale Epidemiological Studies and Meta-Analyses

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Key Words
Stroke · Transient ischaemic attack · Cholesterol · Hypertension

Abstract
Stroke is a considerable clinical, social and economic burden. In recent clinical trials, a number of strategies have been shown to reduce the risk of stroke and transient ischaemic attack (TIA) in both primary and secondary prevention settings. Whether these treatments are leading to a significant reduction in the incidence of first and recurrent stroke in the clinic, however, remains unclear due to a paucity of high-quality epidemiological data. A similar lack of reliable epidemiological studies has undermined our understanding of the relationship between many potentially important vascular risk factors and stroke risk. Improvement in our knowledge of stroke epidemiology is a prerequisite for the planning of stroke services, the effective application of current stroke prevention strategies, the development of new strategies, and our understanding of the mechanisms of stroke. Future studies must take into account the clinical and pathological heterogeneity of TIA and stroke, and must be powered to allow subtype differences in risk factor relationships and prognosis to be determined reliably. In many cases, this will require meta-analysis of detailed individual patient data from multiple independent studies.

Introduction

Stroke is a considerable clinical, social and economic burden [1, 2]. It is likely that this burden will increase over the next few decades with the rapid rise in the elderly population. It is essential, therefore, that we develop effective strategies for stroke prevention, both at a population level and in high-risk groups, such as individuals who suffer from TIAs. This requires a detailed understanding of the epidemiology of stroke.

There are several areas of stroke epidemiology where our knowledge remains inadequate – partly because of a lack of research [3]. This review will consider the need for high-quality epidemiological studies in 2 major areas. Firstly, to improve stroke prevention, we need to know what effect our current strategies are having on the burden of stroke. Are current primary prevention strategies reducing age- and sex-specific incidence of first stroke? What effect has secondary prevention had on the risk of recurrent events after a TIA or stroke? Secondly, we still

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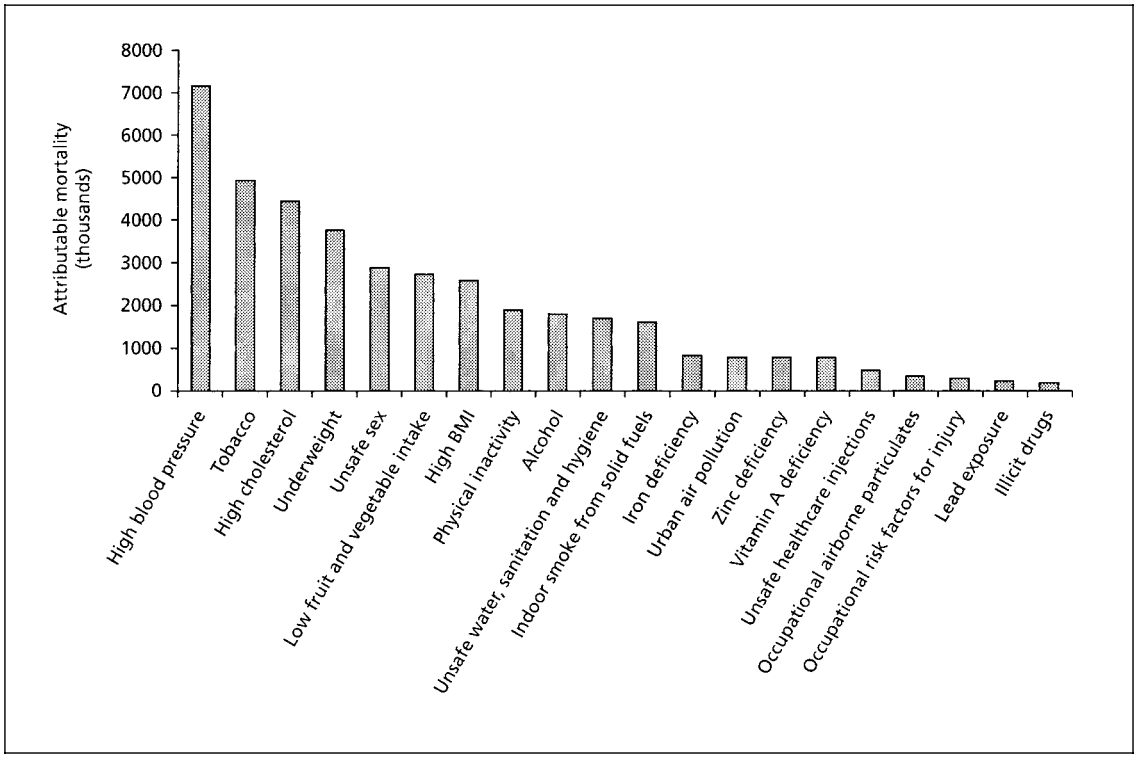

Fig. 1. World mortality due to leading global risk factors. Figures calculated by the Comparative Risk Assessment Collaborating Group for the World Health Report 2002. (Adapted from [19].)

have only a basic understanding of the relationship between many potentially important risk factors for stroke and the risk of stroke and other vascular events [4, 5]. More data are required on existing risk factors and we need to identify new, potentially modifiable, risk factors for stroke in both the primary and secondary prevention settings.

The Size of the Problem

In the UK, as in most other developed countries, stroke is the third leading cause of death after coronary heart disease (CHD) and cancer, occurring in over 150,000 people each year [2]. Stroke is also the second leading cause of mortality worldwide [6], a major cause of long-term disability in adults, and an important contributor to depression and other neuropsychiatric disorders – all at significant cost to health and community services. The majority (about 75%) of stroke cases occur in people over the age of 65 years, and approximately one-third of patients die of stroke within a year of onset [7–9]. Over half of survivors remain dependent on others for everyday activities, often with adverse effects on carers [10, 11]. Stroke accounts for more hospital and nursing home bed-days than any other condition.

Primary Prevention: Are Current Strategies Reducing Stroke Incidence?

There are a number of strategies that have been shown to reduce the risk of stroke in large randomised controlled trials and meta-analyses. Although some of these are only indicated in relatively small subgroups of patients, mainly in secondary prevention [12–14], other treatments, such as antiplatelet agents in patients at high risk of vascular events [15], blood pressure-lowering drugs [16, 17], and cholesterol-lowering drugs in high risk individuals [18], are widely used in primary prevention. Recent estimates of the contributions of individual risk factors to global all-cause mortality (fig. 1) have highlighted the importance of elevated blood pressure and cholesterol as causes of vascular disease [19]. Although not all patients in whom anti-

hypertensive and lipid-lowering therapies are indicated are treated in routine clinical practice [20, 21], the increasing use of such agents in developed countries over the last two decades should have led to a major reduction in the incidence of first stroke.

Available stroke mortality data show that, in general, the incidence of fatal stroke has indeed declined. However, this decline in mortality predates the introduction of specific treatments for stroke prevention; in many countries, stroke mortality has been falling for 50 years [22]. Moreover, the widespread use of treatments to prevent stroke has actually coincided with a deceleration in the decline in mortality [23–25]. Interpretation of trends in stroke mortality is difficult, however, because the relative contributions of changes in incidence and improved case-fatality have not been quantified adequately. For example, improved short-term survival appeared to explain the decreasing stroke mortality rates in Auckland, New Zealand, between 1981 and 1991 [9], while decreasing incidence accounted for the fall in mortality from stroke observed in Perth, Western Australia, between 1989 and 1990, and 1995 [26].

Some data are available on time trends in stroke incidence. A decline in incidence in the 1970s and 1980s was reported in the United States [27, 28], Asia [29] and Europe [30, 31], but this decline appears to have levelled off and incidence is now increasing in some areas [32–38]. Data from the World Health Organization MONItoring of trends and determinants of CArdiovascular disease (WHO MONICA) Stroke Project have shown a general tendency towards declining stroke incidence rates in people aged 35 to 64 years [39]. However, interpretation of trends in stroke incidence is difficult because of the problems involved in measuring the incidence of stroke accurately [40, 41]. Studies must be population based because a large proportion of the burden of care for stroke is borne by health services outside hospital, and because changes in patterns of referral can significantly distort longitudinal trends derived from hospital-based cases. High-quality population-based studies are challenging, however, and must satisfy strict methodological criteria [40, 41]. Studies based on mortality data, hospital-based stroke registers or incidence studies in younger age groups are much easier to perform, but do not allow reliable interpretation of geographical differences or time trends.

It remains uncertain, therefore, whether current stroke prevention strategies are leading to a significant reduction in the incidence of initial stroke. More data are required from high-quality stroke incidence studies performed over periods of several years in the same population.

Secondary Prevention: Are Current Strategies Reducing the Risk of Recurrent Stroke?

There are now several highly effective treatments for secondary prevention following a TIA or stroke, including antiplatelet agents, anticoagulation in atrial fibrillation, blood pressure lowering, lipid lowering and carotid endarterectomy. Widespread use of these treatments, along with advice on lifestyle changes, should now be leading to major reductions in the risk of recurrent stroke and other vascular events. However, changes in the risk of recurrent events are difficult to determine because of a lack of data on what the risks of recurrent events have been in the past. This is illustrated below by consideration of three simple questions about prognosis after a TIA. In each case, there has been a lack of high-quality epidemiological data on which clinical decisions could be based.

What Is the Early Risk of Recurrent Stroke after a TIA?

Approximately 15–20% of ischaemic strokes are preceded by a TIA, and guidelines highlight the need for rapid-access TIA clinics [42–44]. In spite of this, there have been few studies of the early risk of stroke after a TIA, and it is therefore uncertain how urgently patients must be seen for prevention to be effective. North American guidelines suggest that assessment and investigation should be completed within 1 week of the TIA [44], and UK guidelines recommend assessment within 2 to 4 weeks [42, 43], but there is great variation in routine practice [45]. The danger of delaying investigation and treatment after a TIA depends on the early risk of stroke. A risk of 1–2% at 7 days and 2–4% at 30 days is usually quoted [46–48]. However, a recent study of patients presenting to an emergency department, almost all of whom were enrolled within 24 h of the TIA, reported a stroke risk of 5.3% at 2 days [49]. Although this population was self-selected and the results may not therefore be generally applicable, a recent re-analysis of a population-based TIA incidence study has reported similarly high stroke risks from onset of first-ever TIA: 8.6% (95% CI = 4.8–12.4%) at 7 days and 12.0% (95% CI = 7.6–16.4%) at 30 days [50]. The risk was particularly high in patients with cerebral as opposed to ocular TIA and in patients with pre-existing hypertension (fig. 2). As such, the potential for stroke prevention if all patients with TIA seek medical attention urgently and are seen without delay is undoubtedly greater than previously thought.

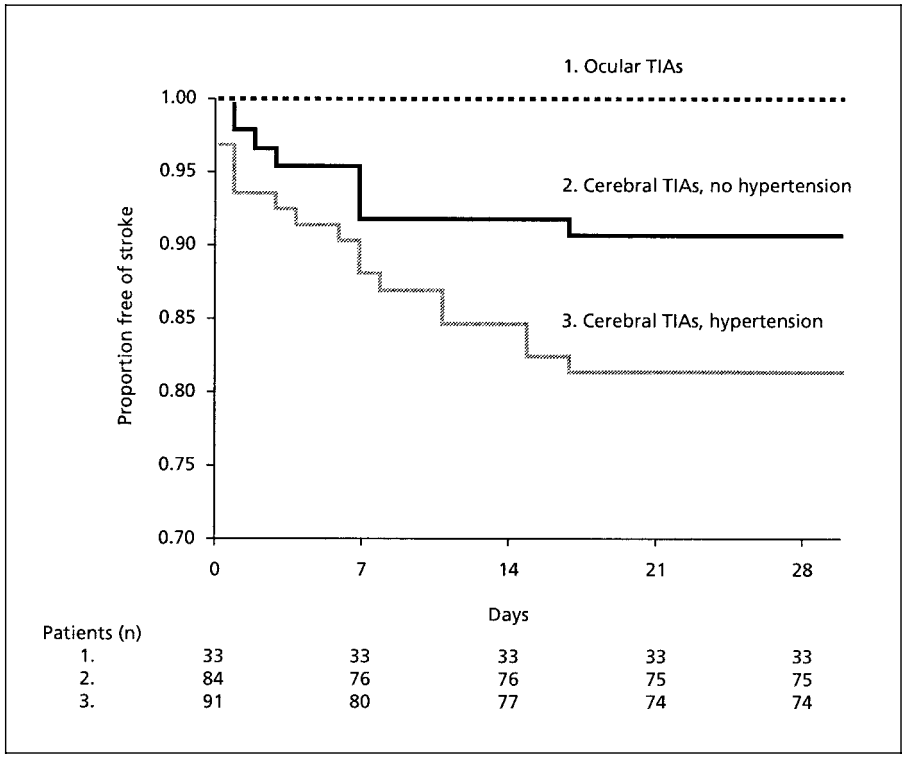

Fig. 2. Survival free of stroke from the onset of a first-ever TIA in a population-based incidence study according to the type of TIA and the presence of pre-existing hypertension. A re-analysis of data from the Oxford Community Stroke Project [52].

Table 1. The risk of stroke, 7 and 30 days after study entry, in patients presenting with a TIA in a hospital-referred case series and three randomised controlled trials [58–61]

Study	Patients	Median delay, days	Stroke risk, %	
			7 days	30 days
Oxford Hospital Series [58]	449	12	0.9	2.2
UK-TIA Aspirin Trial [59]	1,678	25	0.3	1.1
Dutch TIA Trial [60]	1,041	18	0.1	0.5
European Carotid Surgery Trial [61]	689	47	0.3	0.9

The median delay between the presenting TIA and study entry is given.

It is useful to consider how such a simple estimate as the risk of stroke following a TIA could have been so underestimated. Population-based studies of TIA are scarce, and most have not reported follow-up data [51–57]. One early population-based TIA incidence study provided some information on the risk of stroke from the date of TIA [51]. However, this analysis was based on retrospective case-note review, and some patients did not come under observation until several years after their TIA [51]. Consequently, estimates of risk have been extrapolated from hospital-based cohort studies and randomised controlled trials (table 1) [58–61]. The problem with these studies is that patients were not recruited immediately after the TIA. Rather they were derived from those patients who were referred to hospital after a TIA and had not had a major stroke by the time that they were seen. Given that the median delay from last event to study entry ranged from 12 to 47 days (table 1), the high early risk period was missed in the majority of patients. It follows that any patients who had a major stroke during this period were consequently excluded from the study.

What Is the Long-Term Vascular Risk after a TIA?

The majority of TIA patients survive event-free for a number of years after the initial TIA. It would be useful to understand the long-term risks of stroke, myocardial infarction (MI) and vascular death in this patient population in order to determine how aggressive secondary preventive treatment should be, and for how long it should be continued. It is now a requirement in the UK that all family doctors set up registers of patients with a previous TIA or stroke so that they receive appropriate preventive treatment [62]. However, clinical guidelines give no specific advice on long-term treatment, and there have only been three published studies on the long-term outcome after TIA [42–44]. Two of these studies were retrospective [63–64]; one was confined to patients less than 40 years of age [64], and the other was performed in the 1960s and early 1970s before antiplatelet agents and other preventive treatments were routinely used [63]. The only prospective study with long-term follow-up after a TIA was based on just 18 patients [65].

Described in a recent report, 290 patients who had initially been followed up after a TIA in two Oxford-based cohort studies [51, 57], and who were alive and stroke-free after a median of 3.8 years (inter-quartile range: 2.2–5.8 years), were followed up for a further 10 years [66]. The 10-year risk of stroke was 18.8% (95% CI = 13.6–23.7%, 45 events) and 114 patients had at least 1 major vascular event, giving a 10-year risk of any first stroke, MI or vascular death of 42.8% (95% CI = 36.4–48.5%) [66]. From this study it would appear that the long-term risk of major vascular events is high even in surviving TIA patients who have been stroke-free for a number of years. It follows that it is important to continue preventive treatments in this patient population.

What Is the Risk of Recurrent Stroke after a Vertebrobasilar TIA or Minor Stroke?

Not all TIAs and minor strokes have the same prognosis, and it is important that differences are determined reliably because they may influence treatment decisions. For example, amaurosis fugax and retinal infarction are consistently associated with a lower risk of subsequent stroke than carotid territory cerebral events [57, 67], and benefit from interventions such as carotid endarterectomy is consequently reduced [68, 69].

Another important subset of patients with TIA and minor stroke are those experiencing posterior circulation or vertebrobasilar (VB) territory events. Although these account for about 30% of all TIAs and minor strokes, there has been relatively little systematic research into the prognosis and risk factors for recurrent vascular events specifically in these patients. Despite this, there has been a widely held view that VB territory events have a more benign prognosis than carotid territory events. This stems from a small number of early cohort studies performed in the 1960s and 1970s [70–74], many of which do not satisfy modern methodological standards [75]. Partly as a consequence of these early studies, patients with VB events are often investigated less rigorously than patients with carotid events, and may not always receive such aggressive preventive treatment against future vascular events. However, a recent systematic review of all available published and unpublished data has shown that the risk of recurrent stroke in patients with VB events is as high as that in patients with carotid territory events, and is in fact higher if analysis is confined to population-based studies (odds ratio = 1.48, 95% CI = 1.1–2.0%) [76].

Risk Factors for Stroke

The development of effective strategies for the prevention of stroke and other vascular events has usually stemmed from an understanding of the relationship between potential risk factors and the risk of vascular events. For example, strong linear relationships between vascular risk and both blood pressure (fig. 3) [59] and cholesterol were found in prospective cohort studies in primary and secondary prevention [77–80]. These observations led to large randomised controlled trials of blood pressure lowering and cholesterol reduction. In each case, the reductions in vascular risk obtained in the treatment trials for the primary and secondary prevention of stroke were highly consistent with the risk relationships observed in the epidemiological studies [16–18].

Two particularly important issues that must be considered in interpreting studies of risk factors for stroke relate to the choice of outcomes that are reported. The first issue stems from the tendency, particularly in primary prevention cohorts, to determine risk factors for 'cardiovascular events' or 'vascular risk'. These composite outcomes (usually made up of stroke, myocardial infarction and vascular death) are generally used to increase the statistical power of analyses. However, it is often simply assumed that the effect of the risk factor on each of these separate outcomes will be qualitatively similar, and no attempt is made to determine whether there is any heterogeneity. However, there is certainly some quantitative heterogeneity in the effect of major risk factors on the risks of stroke and coronary vascular events. Blood pres-

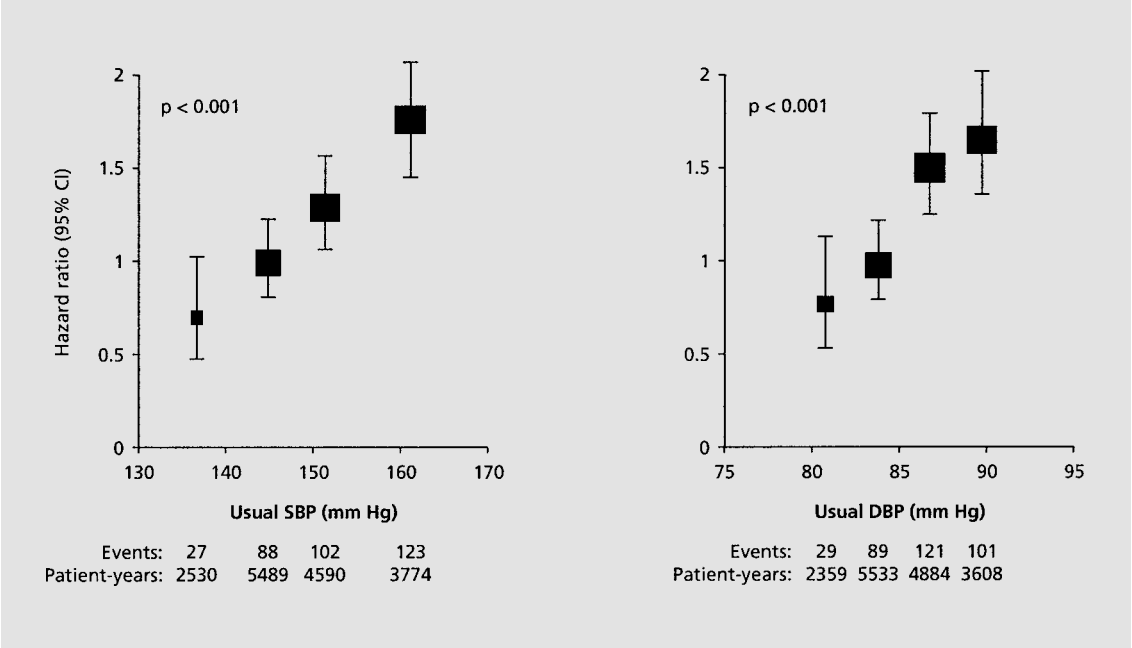

Fig. 3. The relation between the risk of stroke and usual systolic and usual diastolic blood pressure (adjusted for age and sex in a Cox proportional hazards model) in patients with a recent TIA or minor ischaemic stroke. Data derived from the UK-TIA Aspirin Trial [59].

sure is a more powerful risk factor for stroke, and cholesterol is a more powerful risk factor for coronary vascular events [77, 78]. In spite of this, blood pressure reduction is still effective in reducing the risk of coronary events, and cholesterol reduction is still effective in reducing the risk of ischaemic stroke [16–18]. Some risk factors, such as age and sex, have quite different relationships with stroke risk and coronary risk. In addition, we lack reliable data on heterogeneity of the effects of other potentially important risk factors, such as fibrinogen and particular lipid subfractions.

The second issue in relation to outcomes in studies of risk factors for stroke is that in contrast to CHD, stroke is a highly heterogeneous disorder. The vast majority of unstable angina, acute MI and sudden cardiac death are due to rupture of coronary artery plaque with subsequent thrombosis [81, 82]. Ischaemic stroke, on the other hand, is due to a variety of pathologies, including intracranial small vessel disease, cardioembolism and prothrombotic disorders, as well as large artery atherosclerosis. We need to know how risk factors differ between these different subtypes of ischaemic stroke in order to better understand the mechanisms of disease and to target preventive treatments more effectively. However, many studies of risk factors for stroke have not considered different pathological and aetiological subtypes separately, and some have often not even differentiated fully between subarachnoid haemorrhage, intracerebral haemorrhage and cerebral infarction [83–86].

Of those risk factor studies that have categorised strokes as ischaemic or haemorrhagic, most have not subdivided ischaemic stroke according to the different clinical or aetiological subtypes [87–89]. A few studies have compared the prevalence of risk factors between the different subtypes of ischaemic stroke, and have reported important differences in the frequency of established vascular risk factors [90–95]. However, most of these studies were based on hospital registers [90–94], or clinical trial populations [95], and it is possible therefore that some of the observed differences in risk factors were due to inclusion bias. Between 10% and 40% of stroke patients are not admitted to hospital [96], and the tendency to exclude very elderly patients and patients with mild or rapidly fatal strokes is a major potential bias in hospital-based studies [97]. Ideally, comparisons of risk factors between stroke subtypes should be population based in order to avoid bias.

It follows that there is currently a lack of basic epidemiological data on the effect of many potentially important risk factors for stroke, and more studies are required. A better understanding of risk factors for stroke will provide insights into pathological mechanisms, improve our ability to predict vascular risk [4, 5], help to target costly or potentially risky treatments towards patients at particularly high risk of stroke [13, 69], and aid the development of new preventive treatments.

Future studies of risk factors for stroke must be powered to determine relationships reliably. Sample sizes of many thousands are usually required to determine the relation between continuous variables and stroke risk, and meta-analyses of individual patient data from multiple studies are likely to be required. Appropriate consideration must be given to study design [76] and to statistical modelling [98, 99]. Ideally, composite outcomes, such as stroke, myocardial infarction and vascular death, should only be used when it can be shown that there is no statistically or clinically significant heterogeneity between the risk relationships for each of the separate outcomes. Similarly, analyses based only on fatal strokes should also be interpreted with caution. Whether or not a stroke is fatal depends on several factors that are usually unrelated to the severity of the stroke, such as age, nutritional status and co-morbid disease. Analyses based on fatal stroke alone (e.g., routinely collected death certificate data) will therefore be potentially confounded by these generally unmeasured factors, and can produce misleading results. Finally, as discussed above, accurate sub-classification of strokes according to the underlying aetiology and pathology is essential.

Conclusions

A detailed understanding of the epidemiology of stroke is essential for the planning of stroke services, the effective application of current stroke prevention strategies, the development of new strategies, and our understanding of the mechanisms of stroke. A lack of reliable data has undermined the effectiveness of stroke prevention in the past. Future studies must take into account the clinical and pathological heterogeneity of TIA and stroke, and must be powered to allow subtype differences in risk factor relationships and prognosis to be determined reliably. In many cases, this will require meta-analysis of detailed individual patient data from multiple independent studies.

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Atheroprotective Effects of Long-Acting Dihydropyridine-Type Calcium Channel Blockers: Evidence from Clinical Trials and Basic Scientific Research

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Key Words
Atherosclerosis · Coronary artery disease · Cerebrovascular disease · Lipid peroxidation · Calcium channel blockers · Amlodipine

Abstract
Atherosclerosis is a systemic disease that can ultimately lead to ischaemia and infarction in the heart, brain and peripheral vasculature. According to the 'response to injury' hypothesis, endothelial dysfunction is the early event that allows penetration of lipids and inflammatory cells into the arterial wall, contributing to the development of the atherosclerotic lesion. Endothelial dysfunction is causally related to a variety of risk factors for atherosclerosis, including hyperlipidaemia and hypertension. Agents that restore endothelial function and NO bioavailability have beneficial anti-atherogenic activities and can improve cardiovascular outcomes; this has been observed with angiotensin-converting enzyme (ACE) inhibitors, statins and certain dihydropyridine-type calcium channel blockers (CCBs). In the Prospective Randomised Evaluation of the Vascular Effects of Norvasc Trial (PREVENT), the CCB amlodipine provided significant clinical benefits compared with placebo, including a marked reduction in cardiovascular morbidity and a reduction in the progression of carotid atherosclerosis. As these beneficial effects of amlodipine have not been observed with other dihydropyridine-type CCBs, it has been proposed that this agent has distinct anti-atherosclerotic properties related to its strong lipophilicity and membrane location. Experimental support for this hypothesis has been obtained from various in vitro and in vivo models of atherosclerosis. These findings support a broader therapeutic role for third-generation dihydropyridine-type CCBs in the treatment of atherosclerosis.

Introduction

Atherosclerosis is a systemic inflammatory process that manifests clinically as coronary artery disease (CAD) and cerebrovascular disease, both leading causes of mortality and morbidity in the developed world. An early event in the atherosclerotic disease process is endothelial dysfunction, which promotes a constellation of processes that contribute to plaque development, including vasoconstriction, thrombosis, inflammation, oxidation and proliferation (fig. 1) [1, 2]. For example, healthy endothelial cells counter the effects of vasoconstriction through the release of locally synthesised nitric oxide (NO) [3]. In addition to vasodilation benefits, normal production of NO is associated with various anti-inflammatory benefits

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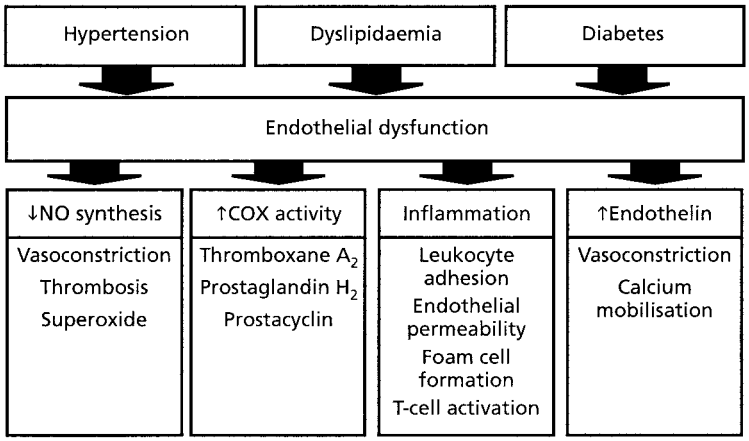

Fig. 1. Integrated cellular mechanisms of atherosclerosis [1, 2].

Table 1. Anti-atherosclerotic activities for 1,4-dihydropyridine calcium channel blockers

Reduction in vascular tone/vasospasm in coronary arteries
Inhibition of smooth muscle cell proliferation within the intima
Inhibition of smooth muscle cell migration from the media to the intima
Inhibition of lipid peroxidation
Reduction in ischaemia-induced endothelial permeability

such as: (1) scavenging of superoxide, (2) inhibition of platelet aggregation, (3) reduced hyperadhesiveness of leukocytes and (4) interference with platelet aggregation. Endothelial dysfunction, however, results in reduced NO bioavailability while increasing vessel wall permeability to atherogenic lipids and inflammatory cells such as monocytes and T lymphocytes.

Endothelial dysfunction is causally related to a variety of risk factors for cerebrovascular disease and CAD, including hypertension and hyperlipidaemia (fig. 1) [4]. Hypertension and associated metabolic disorders (diabetes mellitus) increase endothelial cell synthesis of collagen IV and fibronectin while reducing NO-dependent renal and cardiovascular relaxation [5]. Abnormally high glucose levels delay cellular replication while promoting cell death by apoptosis, in part by enhancing glycooxidation of key lipid and protein cellular constituents. Elevations in oxidised low-density lipoprotein (LDL) associated with hypercholesterolaemia also affect endothelial dysfunction and trigger inflammatory processes such as foam cell formation and increased cytokine production [2, 6]. Epidemiological evidence suggests that these risk factors have a synergistic, rather than additive, effect on stroke and CAD risk [7].

Effective and comprehensive treatment of modifiable risk factors may slow the progression of atherosclerosis while stabilising vulnerable plaques. For example, various antihypertensive and lipid-lowering agents proven to be effective in vascular diseases have been shown to contribute to restoring endothelial function and NO bioavailability. These include ACE inhibitors [8], statins [9, 10] and certain dihydropyridine-type CCBs [11–13].

Beyond their favourable effects on haemodynamics, emerging evidence has suggested dihydropyridine-type CCBs may play a broader role in the treatment of atherosclerosis. A variety of anti-atherosclerotic mechanisms for dihydropyridine-type CCBs have been proposed (table 1) [14–16]. This article will review data from clinical and scientific research that supports the hypothesis that CCBs may improve clinical outcomes in patients at risk for CAD and cerebrovascular disease by stabilising the atherosclerotic plaque.

Review of Evidence from Clinical Trials: A Potential Anti-Atherosclerotic Role for Long-Acting Dihydropyridine-Type CCBs

Studies with the shorter-acting dihydropyridine-type agents, including nifedipine (International Nifedipine Trial on Anti-atherosclerotiC Therapy [INTACT]), nicardipine (Montreal Heart Study [MHS]) and isradipine (Multicenter Isradipine/Diuretic Atherosclerosis Study [MIDAS]), have demonstrated some effects on early atherosclerotic lesions and lesions that are <20% stenotic [17–19]. Development of new lesions was inhibited in

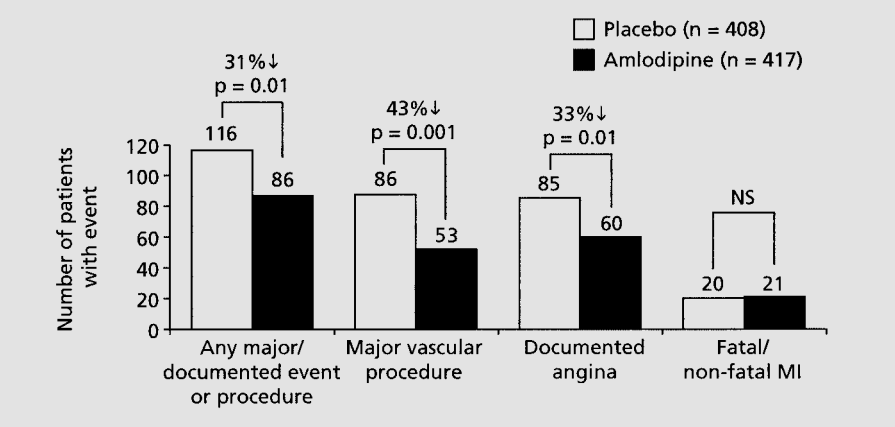

Fig. 2. The Prospective Randomised Evaluation of the Vascular Effects of Norvasc Trial (PREVENT): the dihydropyridine-type calcium channel blocker amlodipine reduces cardiovascular risk in patients with coronary artery disease [21]. MI = Myocardial infarction.

subjects receiving CCB treatment, suggesting interference with the mechanism of early plaque formation. However, these earlier dihydropyridine derivatives demonstrated no significant effect on the frequency of clinical events. In fact, in 2 of these trials, subjects assigned to the CCB group tended to have more adverse events. Nevertheless, these studies formed the basis for investigating longer-acting CCBs in an effort to more fully assess their effects on the vascular wall.

A beneficial role for vascular-selective, long-acting CCBs in reducing vascular events in patients with established CAD has been suggested in several recent clinical trials. The 3-year, placebo-controlled Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) evaluated the effects of the CCB amlodipine besylate 10 mg on the development and progression of atherosclerotic lesions in coronary and carotid arteries in 825 patients with documented CAD [20]. The results of PREVENT showed significant clinical benefits with amlodipine therapy relative to placebo in a population consisting of normotensive, or controlled hypertensive, patients (fig. 2). Treatment was also associated with significant slowing (p = 0.007) of the progression of carotid atherosclerosis (fig. 3) [21].

In terms of predefined clinical endpoints, subjects assigned to amlodipine had a 35% reduction in hospitalisations for non-fatal vascular events, including chronic heart failure (CHF) and angina (p = 0.01), compared with placebo. Major vascular procedures, such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG), were reduced by 43% with amlodipine, compared with placebo (p = 0.001). In addition, long-term treatment with amlodipine resulted in a 31% reduction in the composite endpoint of any major

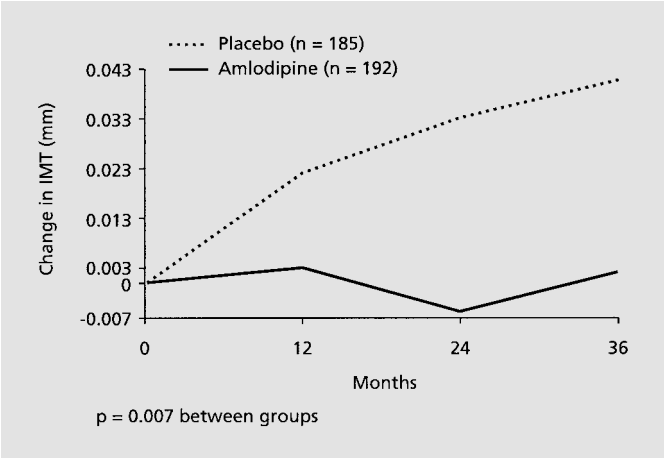

Fig. 3. The Prospective Randomised Evaluation of the Vascular Effects of Norvasc Trial (PREVENT): the dihydropyridine-type calcium channel blocker amlodipine slows the progression of carotid atherosclerosis, as measured by B-mode ultrasound [21]. IMT = Intima-media thickness.

vascular event or procedure (non-fatal vascular events, hospitalisation for CHF, unstable angina, CABG/PTCA, fatal or non-fatal myocardial infarction [MI] or stroke, and other fatal vascular events) (p = 0.01). No difference was observed between amlodipine and placebo in terms of fatal or non-fatal MI [21]. In terms of quantitative coronary angiography (QCA), no difference between amlodipine and placebo was observed in any of the coronary measurements, including the primary outcome measure of the 36-month change in mean minimum diameter of early coronary atherosclerosis segment (those with a baseline diameter stenosis of 30% or greater).

Table 2. Anti-atherosclerotic activities for amlodipine

Antioxidant activities
Remodelling of vascular smooth muscle cell membranes
Inhibition of smooth muscle cell proliferation and migration
Inhibition of endothelial apoptosis following cytokine treatment
Enhancement in endothelial nitric oxide production
Modulation of gene expression
Inhibit expression of certain matrix metalloproteinases

The findings from PREVENT are consistent with data from the recent Coronary AngioPlasty Amlodipine REStenosis (CAPARES) trial [22]. In this study, which was conducted in a similar patient population to that in PREVENT, amlodipine significantly reduced the incidence of repeat PTCA and clinical events after PTCA without a reduction in luminal loss [22]. Subjects in the treatment group showed a 50% reduction in the composite endpoint (death, MI, CABG, repeat PTCA) compared with placebo ($p = 0.007$). These clinical findings indicate an effect of amlodipine on mechanisms of atherogenesis, as manifested in changes in the vessel wall and clinical events.

In addition to clinical trials with amlodipine, the European Lacidipine Study on Atherosclerosis (ELSA) recently reported that the long-acting CCB lacidipine also slowed progression of carotid atherosclerosis [23]. The 4-year ELSA trial recruited 2,255 patients with mild to moderate hypertension. Of these, 1,868 patients had no major protocol violations and were randomised to atenolol 50–100 mg or lacidipine 4–6 mg, following a 1-month run-in period. An ultrasound scan was performed at baseline and at years 1, 2, 3 and 4 to measure the intima-media thickness (IMT), and ambulatory blood pressure was monitored over a 24-hour period. The endpoints of the study were the progression of existing plaques, the progression of IMT and the development of new lesions in previously normal carotid artery segments.

Results from the ELSA study indicated that the estimated increase in IMT in the lacidipine group was 40% less than in the atenolol group [23]. This was observed over the entire 4-year study period, as well as throughout the annual progression rate. Although blood pressure reductions were comparable between the two treatment groups throughout the study, the 24-hour mean ambulatory pressure was slightly lower in patients treated with atenolol, suggesting that the anti-atherosclerotic effect was not related to blood pressure lowering. The study was not powered to detect differences in event rate between the two treatment arms; however, the atenolol-treated patients had a slightly higher rate of serious adverse events compared with lacidipine (17.4% versus 15.8%; not significant).

Review of Evidence from Basic Science: Anti-Atherogenic Mechanisms of Action for Amlodipine

The pharmacological basis for a clinical benefit with amlodipine in CAD and cerebrovascular disease may be related to the drug's physicochemical properties, including its positive charge. Indeed, more than 90% of the amino-ethoxy function associated with the dihydropyridine ring of amlodipine is in the charged state at physiological pH. The positive charge contributes directly to strong interactions between amlodipine and phospholipids near the surface of the cell membrane, even under atherosclerotic-like conditions [24]. This model is supported by various biophysical studies including small-angle X-ray diffraction [24], differential scanning calorimetry [25] and proton nuclear magnetic resonance [26] analyses. The membrane location would place the ring structures of amlodipine near the sterol nucleus of cholesterol; in this position, the drug can reverse certain physical effects of cholesterol on membrane structure and function [24].

Various laboratories have demonstrated support for distinct anti-atherosclerotic mechanisms that may contribute to the benefit of amlodipine in CAD [11, 25, 27–30] (table 2). These cellular actions would lead to plaque stabilisation and vascular remodelling among patients with CAD and are attributed, in part, to the distinct interactions of amlodipine with membrane lipids under atherosclerotic-like conditions [31, 32], mediated by its positive chemical charge [24, 26, 31, 33]. The following is a review of 4 anti-atherogenic mechanisms that have been described for amlodipine.

Effects of Dihydropyridine-Type CCBs on Oxidative Stress Pathways

Under controlled experimental conditions, amlodipine interferes with mechanisms of lipid peroxidation, independent of calcium channel modulation [25, 34, 35]. This antioxidant activity of amlodipine is attributed to both its high lipophilicity in atherosclerotic membranes, and a chemical structure that facilitates proton-donating and resonance-stabilisation mechanisms that quench the free radical reaction [25]. If it is inserted into a location in the membrane near polyunsaturated fatty acids at relatively high concentrations, amlodipine is capable of donating

protons to lipid peroxide molecules, thereby blocking the peroxidation process. The remaining unpaired free electron associated with the amlodipine molecule can be stabilised in well-defined resonance structures associated with the dihydropyridine ring [25]. The antioxidant activity of amlodipine has also been observed in vivo using various animal models, including non-human primates, thus suggesting a distinct anti-atherogenic mechanism of action for this compound [34, 35]. In these studies, amlodipine significantly increased the resistance of lipoproteins to oxidative modification compared with placebo. Antioxidant activity has also been observed for other dihydropyridine-type agents besides amlodipine [14, 36].

Inhibition of Smooth Muscle Cell Proliferation and Migration

Smooth muscle cell proliferation and migration are early characteristics of atheroma development. Amlodipine has been shown to effectively inhibit smooth muscle cell proliferation following cholesterol enrichment [28]. This study also showed that amlodipine effectively inhibited cell proliferation at concentrations that were several orders of magnitude lower than that necessary for inhibiting calcium. Thus, amlodipine may interfere with certain adverse effects of cholesterol enrichment, resulting in loss of membrane function. In a separate study, amlodipine reduced vascular smooth muscle cell migration at sub-nanomolar concentrations following stimulation by a platelet-derived growth factor [27]. This potent effect of amlodipine could not be replicated by other CCB analogues in parallel experiments [37] and supports the hypothesis that amlodipine may interact with novel intracellular sites of action to effect changes in cell behaviour, independent of calcium flux changes.

Inhibition of Cytokine- and Free-Radical-Induced Endothelial Apoptosis

Endothelial cell dysfunction and toxicity are important early events in atherosclerosis. Tumour necrosis factor-α (TNF-α) is a cytokine that is elevated in atherosclerosis and mediates damage to the vessel wall during the inflammatory process. Cytokines such as TNF-α can activate resident macrophages that interfere with the structural integrity of the fibrous cap [38]. Disruption of the fibrous plaque reveals the underlying, highly thrombotic lipid core, leading to acute coronary syndromes in patients with CAD. In addition to its effect on plaque destabilisation, TNF-α also interferes with endothelial function, leading to the expression of proteins that mediate programmed cell death or apoptosis. Amlodipine has been shown to inhibit TNF-α-induced endothelial apoptosis in a dose-dependent manner, starting at low nanomolar levels (10.0 nM) [27]. The ability of amlodipine to inhibit excessive cell loss by apoptosis was also observed in cultured cerebellar granule cells at low nanomolar concentrations [39].

Amlodipine is also able to modulate the expression of NO from the endothelium in canine coronary microvessels by regulating its metabolism [11]. The authors of this study demonstrated that amlodipine enhanced endothelial NO production through a bradykinin-dependent pathway. This ability of amlodipine to stimulate NO synthesis was dose dependent and could not be reproduced by other CCBs (diltiazem, nifedipine), but could be replicated by the ACE inhibitor enalapril [11]. Amlodipine specifically increased the intracellular concentrations of endothelial nitric oxide synthase protein, leading to an enhanced rate of NO production.

Modulation of Vascular Cell Gene Expression and Extracellular Matrix Formation

CCBs may exhibit additional anti-atherogenic effects in patients with CAD by interfering with key molecular factors that contribute to the phenotypic conversion of vascular smooth muscle cells (SMC) from a contractile to synthetic state, leading to atheroma development. In particular, it has been demonstrated that amlodipine increases the expression of the cytokine interleukin-6 in human vascular SMC by activating its specific gene promoter. Up-regulation of interleukin-6 by amlodipine at low pharmacological concentrations leads to a potent antiproliferative effect, independent of calcium channel modulation [40]. Amlodipine was also shown to have favourable effects on the synthesis of extracellular matrix (ECM) proteins involved in atherogenesis [40].

Disruptions in ECM metabolism may contribute to vascular remodelling during the development and progression of human atherosclerotic lesions. Matrix metalloproteinases represent a family of enzymes that degrade ECM components in human atherosclerotic plaques, leading to promotion and destabilisation of the lesion [41]. In both fibroblasts and vascular SMC, CCBs have been shown to inhibit the expression of procollagens I, III and IV at nanomolar concentrations. These effects were observed following platelet-derived, growth-factor-induced and constitutive expression of collagens type I, III and IV [42]. In addition, CCB treatments that included amlodipine increased the proteolytic activity of the 72-kDa type IV collagenase, as measured by gelatin zymography, while inhibiting the transcription of the tissue

inhibitor of metalloproteinases-2 [42]. These various activities of amlodipine appear to be related to a reduction in intracellular calcium levels, leading to reduced transcription of collagen synthesis proteins.

Conclusion

As excessive cell calcium transport contributes to many cellular changes in atherogenesis, it has been proposed that pharmacological CCBs may be effective in slowing the progression of CAD. This hypothesis was recently tested in the PREVENT study, which showed significant clinical benefits with amlodipine therapy, compared with placebo, including a marked reduction in cardiovascular morbidity and significant slowing in the progression of carotid atherosclerosis. As these beneficial effects of amlodipine in CAD have not been previously observed with other dihydropyridine-type CCBs, it has been proposed that amlodipine may have distinct antiatherosclerotic properties related to its strong lipophilicity and membrane location, allowing it to modulate the atherosclerotic process via both calcium-dependent and calcium-independent pathways. Experimental data for this hypothesis have been obtained from various in vitro and in vivo models of atherosclerosis. These findings support a potentially new therapeutic role for certain third-generation dihydropyridine-type CCBs, such as amlodipine, in the treatment of atherosclerosis.

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Clinical Trials: Evidence and Unanswered Questions – Hypertension

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Key Words
Stroke · Hypertension · Calcium channel blockers · Angiotensin-converting enzyme inhibitors

Abstract
Since the pioneering publications of the Hypertension Detection and Follow-up Program (HDFP) and the Multiple Risk Factor Intervention Trial (MRFIT) in the late 1970s and early 1980s, it has become established that lowering blood pressure in high-risk patients is a highly effective form of primary prevention for stroke. Over the subsequent 25 years, over 30 large clinical trials have extended these initial observations to allow us to conclude that treatment of mild, moderate or severe hypertension, and isolated systolic hypertension in the elderly, all produce important absolute benefits. In addition, excellent specific evidence of benefit is now accumulating for certain groups of normotensive patients, including those with previous stroke, and those with established cardiovascular disease. Although the importance of vigorous antihypertensive therapy for the primary and secondary prevention of stroke is increasingly clear, a large number of unanswered questions remain. For example, while it is apparent that diuretics, β-blockers, calcium channel blockers (CCBs) and angiotensin-converting enzyme (ACE) inhibitors are all effective antihypertensive agents, the question remains as to which drug, or combination of drugs, is best for which patients. The results of several ongoing comparative trials of different drug regimens, including the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), may elucidate this further.

Introduction

Stroke ranks as the third leading cause of death, behind coronary heart disease (CHD) and cancer [1]. Each year, stroke affects nearly 20 million people worldwide and, of these, approximately 5 million people will die [2]. Of the 15 million others who survive a stroke, about a third are disabled as a result and at least 1 in 6 will suffer another stroke within 5 years. It follows that the identification of safe and effective treatments for the primary and secondary prevention of stroke is of extreme importance.

Hypertension is the most prevalent modifiable risk factor for ischaemic, haemorrhagic and lacunar stroke [3, 4]. Clinical trials evaluating the effects of blood pressure-(BP) lowering drugs in hypertensive patients have shown that both older classes of antihypertensives (diuretics and β-adrenoceptor blockers) and newer agents (ACE inhibitors, CCBs and angiotensin II receptor blockers [ARBs]) can reduce stroke risk. Despite the participation of hundreds of thousands of patients in these trials, however, a large number of important questions remain for which evidence is only just emerging (table 1). This review

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Table 1. Stroke prevention and blood pressure: unanswered questions

Primary prevention
1 Which BP measure best predicts stroke?
2 What is the optimal BP threshold for initiating therapy?
3 What is the optimal BP-lowering drug, or drug combination, and in which patients?
4 What is the optimal target for lowering BP?
5 Can non-pharmacological therapies lower BP and stroke risk?
Secondary prevention
1 How early can BP therapy be initiated after acute stroke?
2 Who should be treated with which drugs, and how aggressively?

will discuss some of these unanswered questions, and assess the implications of their potential answers on current clinical practice.

Blood Pressure Measurement and Stroke Risk – What Is the Best Predictor?

Observational studies have shown that BP levels are positively and continuously associated with the primary incidence of stroke [4, 5]. However, considerable uncertainty still exists regarding the relative importance of the various components of BP in predicting stroke risk.

A recent study examined which BP component(s) best predict CHD risk across a wide range of age groups in the Framingham Heart Study [6]. With increasing age, there was a gradual shift from diastolic BP (DBP) to systolic BP (SBP), and eventually to pulse pressure (PP), as the best predictors of CHD risk. In patients younger than 50 years of age, DBP was the strongest predictor of CHD risk. Between the ages of 50–59 there was a transition period when all 3 BP indexes were comparable predictors, and from 60 years of age onwards SBP and PP were best related to CHD risk. The finding that SBP is stronger than DBP as a predictor of CHD in middle-aged and older patients reflects the fact that the greatest burden of cardiovascular disease occurs in older subjects with isolated systolic hypertension (ISH) and a wide PP.

It is likely that aging has a similarly important role in influencing the relation of BP indices to stroke risk. The prevalence of hypertension increases with age, with ISH (SBP >160 mm Hg and DBP <90 mm Hg) becoming far more common than diastolic hypertension [7, 8]. In the National Health and Nutrition Examination Survey, for example, ISH was present in 65% of all patients older than 60 years of age, whether male or female [7]. ISH is closely associated with an increased risk of stroke [9–11]. As such, high SBP, with or without an accompanying elevation in DBP, is commonly regarded as an important predictor of stroke in the elderly [12].

In patients with combined systolic and diastolic hypertension, several studies have suggested that 24-hour mean BP and PP have different prognostic impacts on stroke and CHD. For example, Verdecchia et al [13] carried out off-therapy 24-hour ambulatory BP monitoring in 2,311 subjects (mean age 51 years) with systolic (>140 mm Hg) and/or diastolic (>90 mm Hg) hypertension. After adjusting for age, sex and diabetes, for each 10 mm Hg increase in 24-hour mean BP the risk of cerebrovascular events increased by 42% (fig. 1). In comparison, 24-hour PP was not a significant predictor of cerebrovascular events after controlling for 24-hour mean BP. Rather, PP was the dominant predictor of cardiac events in these patients; for every 10 mm Hg increase in 24-hour PP there was an independent 35% increase in the risk of cardiac events, and 24-hour mean BP did not yield significance after controlling for PP. It follows that 24-hour mean BP may be the major independent predictor of cerebrovascular events in patients with predominantly systolic and diastolic hypertension [13].

Antihypertensive Therapy and Primary Stroke Prevention – Which Drug, Which Patient?

Over the past few decades, numerous intervention studies have been conducted to determine whether BP reduction lowers the risk of initial stroke. A systematic overview of 17 controlled trials of BP-lowering drugs in hypertensive patients demonstrated that a net reduction of 5–6 mm Hg in DBP and 10–12 mm Hg in SBP was associated with a 38% reduction in the risk of fatal and non-fatal stroke (fig. 2) [14, 15]. The size of this reduction in stroke was similar in young and old individuals, and in patients with mild hypertension (DBP < 110 mm Hg) [16, 17], mild-to-moderate hypertension (DBP ≤ 115 mm Hg) [18, 19] and patients with ISH [20].

A wide variety of different antihypertensive drug regimens were examined in the above trials, including diuretics, β-adrenoceptor blockers and neurally active agents, with no large differences in benefit apparent between each class [14, 15]. In recent years, a number of newer antihypertensive agents, including ACE inhibitors and CCBs, have also been shown to reduce stroke risk by an equivalent amount to those agents studied previously.

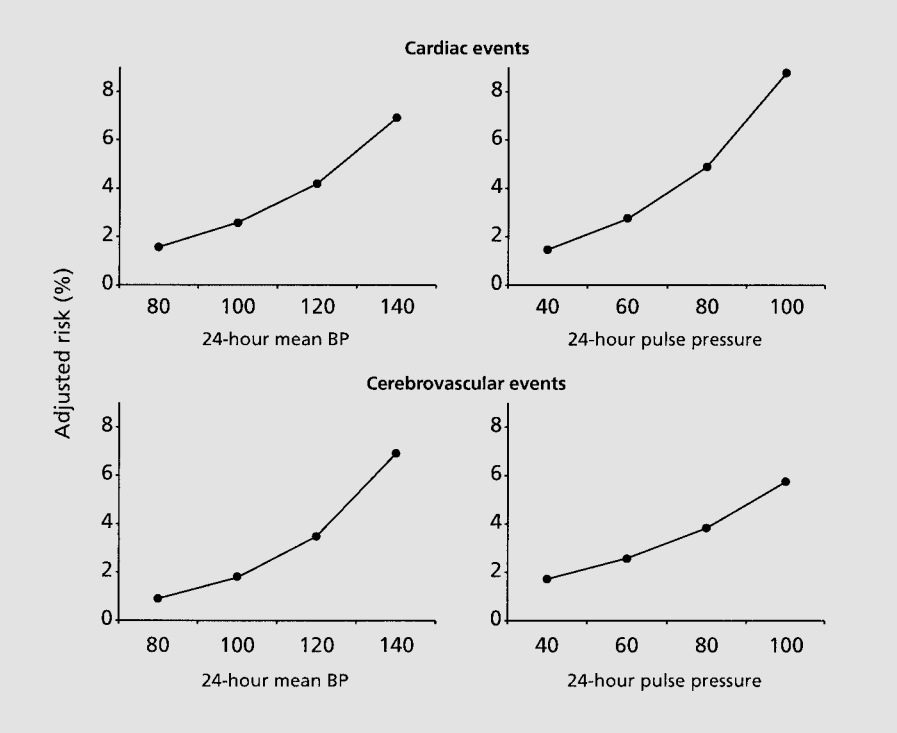

Fig. 1. Different prognostic impact of 24-hour mean blood pressure (BP) and pulse pressure on cerebrovascular and cardiac events in essential hypertension. (Adapted from [13].)

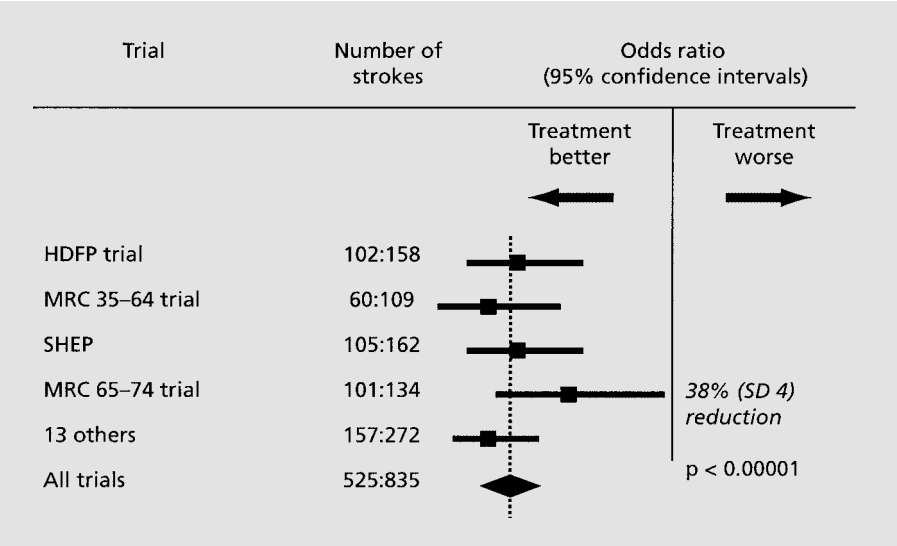

Fig. 2. Blood pressure lowering is effective in the primary prevention of stroke. A net reduction of 5–6 mm Hg DBP and 10–12 mm Hg was associated with a 38% reduction in the risk of fatal and non-fatal stroke (systematic overview of 17 controlled blood pressure lowering trials). (Adapted from [14].)

Angiotensin-Converting Enzyme Inhibitors

A number of major studies of treatment regimens based on ACE inhibitor therapy have reported substantial reductions in the incidence of initial stroke. These include the Heart Outcomes Prevention Evaluation (HOPE) study, which evaluated the clinical benefit of the ACE inhibitor ramipril in 9,297 patients at high risk for cardiovascular events, but who did not have left ventricular dysfunction or heart failure [21]. The primary outcome of the HOPE study was the composite endpoint of myocardial infarction (MI), stroke or cardiovascular death, and individual components were analysed separately. Despite the modest reduction in BP (a fall of 3.8 mm Hg SBP/2.8 mm Hg DBP), treatment with the ACE inhibitor significantly reduced the relative risk of any stroke by 32%, compared with the placebo group. The relative risk of fatal stroke

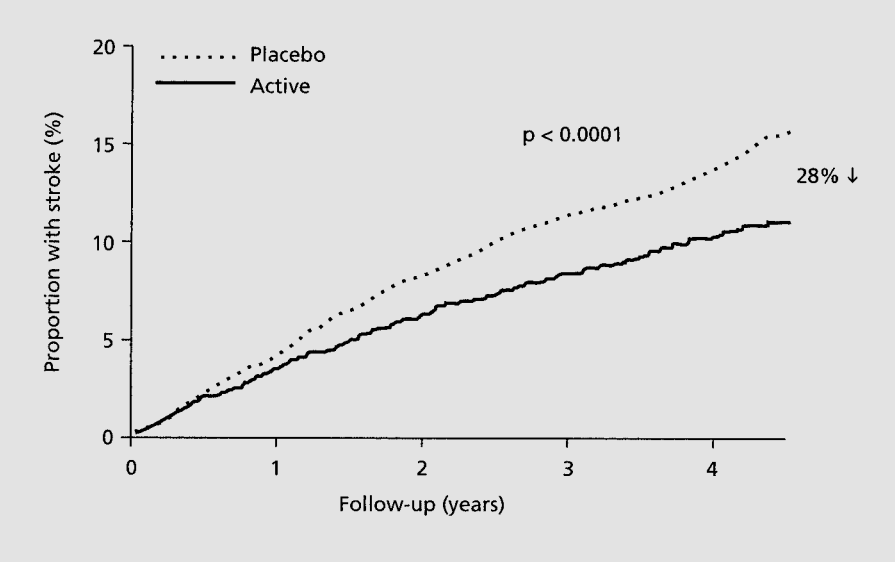

Fig. 3. Blood pressure lowering is effective in the secondary prevention of stroke – the perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS). (Reprinted with permission from [24].)

was reduced by 61%. These reductions in stroke risk could not be fully explained by the reduction in BP. Importantly, the beneficial effects of ACE inhibition were not compromised by the addition of other effective cardiovascular therapies that many patients were taking, including CCBs and statins.

Calcium Channel Blockers

Several large trials have demonstrated the benefits of CCB therapy in reducing the initial risk of stroke.

The Systolic hypertension in Europe (Syst-Eur) trial investigated whether active treatment, starting with a dihydropyridine CCB, could reduce cardiovascular complications associated with ISH [22]. Almost 4,700 older patients were randomly assigned to the CCB nitrendipine, with the possible addition of the ACE inhibitor enalapril, and hydrochlorothiazide, or matching placebos. Fatal and non-fatal stroke combined was the primary endpoint. Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1,000 patient-years (42% reduction; p = 0.003). Non-fatal stroke decreased by 44% (p = 0.007).

More recently, the Irbesartan type II Diabetic Nephropathy Trial (IDNT) assigned 1,715 hypertensive patients with diabetic nephropathy to treatment with the ARB irbesartan, the CCB amlodipine or placebo [23]. After 2.6 years, there were no significant differences between the treatment groups in the rates of death from any cause or in the cardiovascular composite endpoint (including stroke morbidity).

Antihypertensive Therapy and Secondary Stroke Prevention – Which Drug, Which Patient?

While randomised clinical trials have clearly shown that antihypertensive therapy reduces the risk of initial stroke in hypertensive patients, the perindopril PROtection aGainst REcurrent Stroke Study (PROGRESS) was the first major study to provide definitive evidence that BP lowering was effective in the secondary prevention of stroke [24]. In this trial, subjects (n = 6,105) with a history of stroke or transient ischaemic attack (TIA) were randomly assigned active treatment with the ACE inhibitor perindopril (n = 1,281), or a combination of perindopril and the diuretic indapamide (n = 1,770), or placebo (n = 3,054). The primary outcome was total stroke (fatal or non-fatal). After 4 years, active treatment reduced BP by 9 mm Hg SBP/4 mm Hg DBP, and the incidence of secondary stroke by 28% (95% CI 17–38%, p < 0.0001), compared with placebo (fig. 3).

How early should we initiate antihypertensive therapy for the secondary prevention of stroke? The recently completed Acute Candesartan Cilexetil Evaluation in Stroke Survivors (ACCESS) study was the first intervention trial to evaluate the possible benefits of antihypertensive treatment on clinical outcome in patients with acute stroke and high BP (>180/105 mm Hg). This prospective, double-blind, placebo-controlled, multicentre trial randomised 500 patients within 72 h of a stroke to the ARB candesartan, or placebo, for 7 days [Schrader et al, 1998].

ACCESS revealed that early treatment with the ARB reduced the risk for the combined endpoint of total mortality, cerebral complications and cardiovascular complications by 47.5% [25–27]. These new data may prove useful, providing guidance to physicians involved with the daily management of acute ischaemic stroke in this particularly high-risk group.

Does Antihypertensive Therapy in Normotensive Subjects Lower Stroke Risk?

Early prospective observational studies indicated that approximately three-quarters of all strokes occur in subjects with a 'usual' DBP (<95 mm Hg) and SBP (<155 mm Hg). These data suggest the potential importance of BP lowering throughout the 'normotensive' population, and not just in those patients classified as hypertensive [15].

Several trials of antihypertensive agents for primary and secondary stroke have provided excellent specific evidence that antihypertensive therapy might reduce stroke risk throughout the 'normotensive' population. For example, of the 9,297 patients with established CHD enrolled in the HOPE study, 53% did not have high BP (mean entry BP was 139/78 mm Hg) [21]. Regardless of this, benefit from ACE inhibitor therapy was seen at all BP levels, including in patients with an initial BP of less than 120 mm Hg SBP or less than 70 mm Hg DBP.

Similarly, subgroup analysis of the PROGRESS results revealed that the benefits of active treatment with the combination of perindopril and indapamide were very similar in patients classified as non-hypertensive (mean BP at entry was 136/79 mm Hg) and hypertensive (BP was >160/>90 mm Hg) [24]. The recurrence of stroke was reduced by 44% in hypertensive individuals and 42% in non-hypertensive subjects. The investigators concluded that the BP-lowering treatment reduces the risk of stroke in both hypertensive and non-hypertensive patients with a history of stroke or TIA.

It is clear that high-risk populations, including normotensive patients with previous stroke and/or established CHD, benefit significantly from vigorous antihypertensive therapy. In the clinical setting, however, most normotensives would not be considered appropriate candidates for antihypertensive medication. As such, the greatest potential for stroke prevention may be through diet and lifestyle changes that would lower BP throughout the population [28]. Since the benefits of drug therapy were established over 30 years ago, however, the use of non-drug measures to prevent stroke risk has been relatively neglected in the literature. This absence of information needs to be addressed, particularly in light of the ever-increasing burden of hypertension and stroke in the developing world.

Optimal Stroke Risk Reduction – Unanswered Questions

In the next few years, information from a number of large trials should provide some direct evidence regarding the relative effects of single and combined antihypertensive agents for the prevention of stroke. Until that time, there is little evidence that any antihypertensive regimen is more or less effective than any other in reducing the incidence of stroke [14, 15].

The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) was a randomised, parallel-group trial in 9,193 participants aged 55–80 years with essential hypertension (sitting BP 160–200/95–115 mm Hg) and left ventricular hypertrophy (LVH) [29]. Participants were assigned once-daily antihypertensive treatment with the ARB losartan, or the β-blocker atenolol, for at least 4 years and until 1,040 patients had a primary cardiovascular event (death, MI or stroke). BP fell by 30.2/16.6 mm Hg (SD 18.5/10.1) and 29.1/16.8 mm Hg (19.2/10.1) in the losartan and atenolol groups, respectively. Despite the similar reduction in BP, however, the ARB was associated with a 25% reduction in the risk of fatal and non-fatal stroke, compared with the β-blocker (0.75, 0.63–0.89, p = 0.001).

The Antihypertensive and Lipid Lowering treatment to prevent Heart Attack Trial (ALLHAT) was powered to determine whether newer antihypertensive agents are superior, similar or inferior to traditional therapy with diuretics. ALLHAT compared the effects of 3 different drugs – a CCB (amlodipine), a diuretic treatment (chlorthalidone) and an ACE inhibitor (lisinopril) – on the risk of fatal coronary events and non-fatal MI in patients with hypertension at high risk for CHD events [30]. Because of the large number of patients enrolled in ALLHAT (n = 42,448), it was also possible to examine the effect of these treatments in various subgroups, including the 23% of participants with a previous history of stroke. After an average of 4.9 years follow-up, no significant difference was observed between amlodipine and chlorthalidone for the primary outcome, or for the secondary outcomes of all-cause mortality, stroke, angina, coronary revascularization, peripheral arterial disease, cancer or end-stage

renal disease [31]. For lisinopril versus chlorthalidone, however, the lisinopril group had a 15% higher risk of stroke ($p = 0.02$); no significant difference was observed between lisinopril and chlorthalidone for the primary outcome [31]. This difference in stroke outcome may be partially accounted for by the 2 mm Hg difference in SBP between the lisinopril and chlorthalidone groups. Using an external standard of pooled results of long-term hypertension treatment trials and observational studies, MacMahon et al previously identified that a 2–3 mm Hg difference in BP might account for a 6–12% difference in stroke rates [14, 15].

It is becoming clear that monotherapy is not sufficient to attain currently recommended blood pressure targets in the majority of patients with hypertension. In the HOPE, PROGRESS and Syst-Eur trials, for example, a combination of at least 2 antihypertensive agents was often necessary to produce the largest reductions in stroke risk [21, 22, 24]. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is designed to address the question of which combination of antihypertensive drugs is most effective [32]. Having enrolled 19,342 patients with untreated SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg, or treated SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, ASCOT will compare a newer antihypertensive regimen consisting of the CCB amlodipine (with or without an ACE inhibitor) to an older antihypertensive regimen consisting of a β-blocker (with or without a diuretic) for the primary prevention of CHD. All medications are titrated until target BP is reached. For non-diabetic patients, the target is a SBP of <140 mm Hg and a DBP of <90 mm Hg; for patients with type 2 diabetes, the target is a SBP of <130 mm Hg and a DBP of <80 mm Hg. ASCOT is expected to report in 2005.

Conclusions

Given our current state of knowledge, it is clear that lowering BP is effective for the primary, and secondary, prevention of stroke, regardless of the antihypertensive agent employed. Significant benefits are available to elderly as well as younger patients, and for cases of mild, moderate and severe hypertension. In addition, excellent specific evidence is now accumulating in certain groups of normotensive patients, including those with previous stroke and those with established cardiovascular disease. Recognising the limitations of our current state of knowledge, however, will be important in optimising stroke prevention in both the developing and the developed world.

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Clinical Trials: Evidence and Unanswered Questions – Hyperlipidaemia

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Key Words
Stroke · Hyperlipidaemia · Statin therapy · Low-density lipoprotein cholesterol

Abstract
It is now clear that the management of hypercholesterolaemia is important for the reduction of morbidity and mortality caused by cerebrovascular and coronary events. The landmark Scandinavian Simvastatin Survival Study was the first to show conclusively that lipid-lowering therapy with statins reduces the incidence of stroke. Subsequent trials, undertaken in a variety of different patient populations, have confirmed that statin therapy reduces the incidence of stroke by approximately one-third. This important benefit has been observed in men and women, the young and the elderly, and also in subjects with diabetes mellitus. In the recent Heart Protection Study, which recruited 'high-risk' vascular subjects, stroke risk reduction was demonstrated even among those subjects considered to have 'low' low-density lipoprotein (LDL) cholesterol levels. The benefits of statin therapy in stroke have been attributed to reductions in cholesterol and to other non-lipid-lowering effects of statins. Ongoing clinical trials such as TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid lowering) will test the 'lower is better' hypothesis. Using statins to lower LDL cholesterol to levels that are below current guidelines will provide additional benefits in stroke risk reduction. Most of the data on cholesterol reduction and cerebrovascular events have been derived from studies of patients with documented coronary heart disease (CHD). The ongoing SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial will examine the benefits of LDL cholesterol lowering in patients with previous stroke or transient ischaemic attack (TIA), but no history of coronary problems.

Introduction

Hyperlipidaemia is recognised as one of the most important modifiable risk factors for coronary heart disease (CHD). Several studies, including the Framingham study and the Multiple Risk Factor Intervention Trial (MRFIT), have described a causal relationship between the level of lipids and lipoproteins and the risk of CHD [1, 2]. In addition, landmark lipid-lowering trials have shown that lowering low-density lipoprotein (LDL) cholesterol with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduces coronary mortality and morbidity in subjects with, and without, established CHD [3–5]. On the basis of these data, current guidelines for patients with vascular disease recommend statins as the

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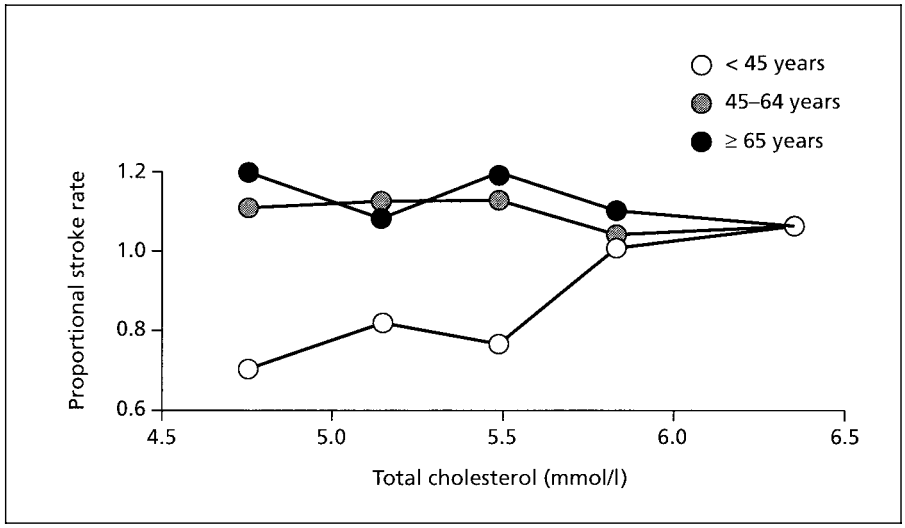

Fig. 1. The complex relationship between stroke risk and cholesterol levels – a review of 45 prospective observational studies (450,000 patients, 13,397 strokes, 5–30 years follow-up). (Reprinted with permission [7].)

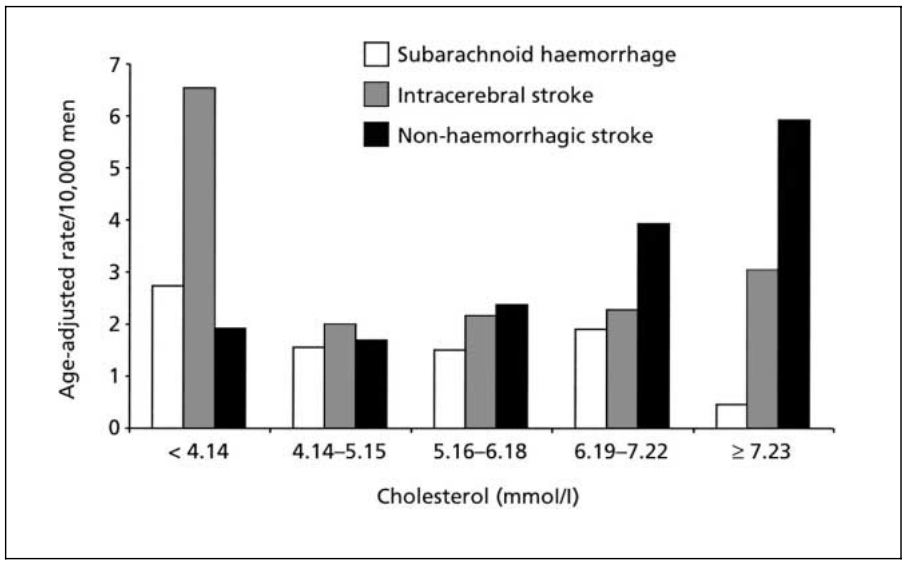

Fig. 2. The positive association between total cholesterol levels and ischaemic stroke risk, and the negative association between cholesterol level and haemorrhagic stroke (a 6-year follow-up of 350,977 men screened for MRFIT) [8].

first choice for lowering LDL cholesterol, with an optimal LDL cholesterol goal of 100 mg/dl (<2.6 mmol/l) [6].

While lipid modification has revolutionised our approach to the management of CHD, the relationship between stroke risk and lipid levels has remained unclear. For example, a review of 45 prospective observational cohorts found no clear association between serum cholesterol levels and stroke risk [7] (fig. 1). This finding may be partially explained by a failure to distinguish between stroke types. For example, a 6-year follow-up of 350,977 men screened for MRFIT revealed a positive association between total cholesterol levels and ischaemic stroke risk, and a negative association between cholesterol level and haemorrhagic stroke (fig. 2) [8].

Statin Therapy Reduces the Risk of Stroke

The landmark Scandinavian Simvastatin Survival Study (4S) was the first to show conclusively that lipid-lowering therapy with statins reduces the incidence of stroke in patients with established CHD [3, 9]. Patients (n = 4,444) with angina pectoris or previous myocardial infarction (MI) and serum cholesterol 210–310 mg/dl (5.5–8.0 mmol/l) on a lipid-lowering diet were randomised to double-blind treatment with simvastatin or placebo. Statin therapy reduced the incidence of cerebrovascular events by 30%.

Subsequently, several studies with stroke as a prespecified outcome have demonstrated that statins are effec-

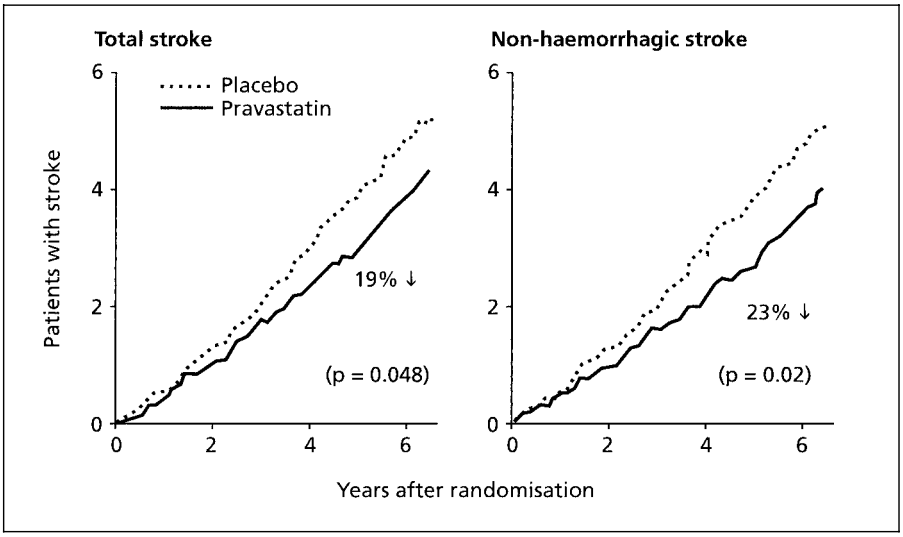

Fig. 3. Statin therapy reduces the risk of total stroke and non-haemorrhagic stroke in the LIPID trial. (Adapted from [5].)

tive in reducing stroke rates. These include the Cholesterol And Recurrent Events (CARE) trial [4] and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial [5].

The CARE trial was the first large-scale secondary prevention trial of cholesterol reduction with an HMG-CoA reductase inhibitor after MI in which stroke was a prespecified endpoint. The study included 4,159 men and women aged 21–75 years with average cholesterol levels (mean total cholesterol of 209 mg/dl (5.4 mmol/l) and LDL cholesterol of 139 mg/dl (3.6 mmol/l), and a MI 3–20 months before randomisation [4]. Following a mean period of 4.8 years, the primary endpoint of the study, coronary-artery-disease-related death or non-fatal MI, was reduced by 24% in pravastatin-treated patients compared with those on placebo. In addition, investigators reported stroke incidence declined by 31% (p = 0.03) in pravastatin-treated patients.

To elucidate further the relationship between pravastatin treatment and cerebrovascular outcome in this population, the CARE Endpoints Committee subsequently performed a detailed review of all reported cerebrovascular events [10]. A total of 128 strokes (52 on pravastatin, 76 on placebo) and 216 strokes or TIAs (92 on pravastatin, 124 on placebo) were observed, representing a 32% reduction (95% CI = 4–52%, p = 0.03) in all-cause stroke and 27% reduction in stroke or TIA (95% CI = 4–44%, p = 0.02). All categories of stroke were reduced and treatment effect was similar when adjusted for age, sex, history of hypertension, cigarette smoking, diabetes, left ventricular ejection fraction and baseline total HDL and LDL cholesterol and triglyceride levels.

A comparison of the effects of pravastatin on stroke and coronary event reduction in CARE revealed a possible predictive value of baseline LDL cholesterol on treatment effect. Pravastatin treatment of patients with LDL cholesterol levels in the lowest quintile (<125 mg/dl [3.2 mmol/l]) did not show an effect on combined fatal coronary events, non-fatal myocardial infarction and revascularisation procedures (p = 0.85) [4]. However, a non-significant 14% reduction in stroke or TIA incidence (p = 0.631) was noted in patients with these baseline lipid levels. In contrast, baseline LDL cholesterol levels in the upper quintile (>150 mg/dl [3.9 mmol/l]) were associated with risk reductions of 35% (p = 0.008) for the combined coronary outcomes and 54% for stroke or TIA (p = 0.0009).

The LIPID trial compared the effects of pravastatin on mortality due to CHD (the primary endpoint) with the effects of placebo in 9,014 men and women aged 31–75 years with a history of MI or unstable angina and a total cholesterol level of 155–271 mg/dl (4.0–7.0 mmol/l) (fig. 3). Over a follow-up period of 6.1 years, there were 419 strokes among 373 patients; 309 strokes were classified as ischaemic, 31 as haemorrhagic and 79 as of unknown type. Compared with placebo, statin therapy reduced the risk of total stroke by 19% (95% CI = 0–35%, p = 0.048) and the risk of non-haemorrhagic stroke by 23% (95 CI = 5–38%, p = 0.02). Pravastatin had no effect on haemorrhagic stroke [5]. An extended follow-up of

LIPID found that the benefits of the first 6 years of statin therapy on stroke risk continue to accumulate for at least a further 2 years [11]. The continued lower rates of stroke among those subjects originally assigned pravastatin emphasised the importance of long-term statin treatment for almost all patients with established CHD.

Recently, the Prospective Pravastatin Pooling (PPP) Project investigated the effect of pravastatin on stroke events in a prospectively defined pooled analysis of 19,768 patients from CARE, LIPID and the West Of Scotland COronary Prevention Study (WOSCOPS) [12]. When the 13,173 patients from CARE and LIPID were combined, there was a 22% reduction in total strokes (95% CI = 7–35%, p = 0.01) and a 25% reduction in non-fatal stroke (95% CI = 10–38%). The beneficial effect of statin therapy on total stroke was observed in all subgroups of patients and across a wide range of lipid values.

Based on evidence from the prevention trials, it is clear that statin therapy reduces the incidence of stroke by approximately one-third in patients with documented CHD. Data from several of these trials indicate that these effects primarily reflect a reduction in strokes of non-haemorrhagic (mostly ischaemic) origin. Importantly, this benefit has not only been observed in subgroups of the cohort studied but also in men and women, the young and the elderly.

Putative Mechanisms of Statin Action on Cerebrovascular Outcome

Carotid atherosclerosis is a marker of the risks of stroke and ischaemic cerebrovascular disease [13, 14]. The finding that statins reduce the risk of stroke suggests that such treatment might be expected to have an anti-atherogenic effect in the carotid arteries. This hypothesis was recently examined in a substudy of LIPID [15]. In this study, 522 patients with a history of MI or unstable angina were randomised to treatment with a low-fat diet plus pravastatin, or to a low-fat diet plus placebo. Carotid atherosclerosis was assessed from B-mode ultrasound measurements of the common carotid artery. Statin treatment prevented any detectable increase in carotid wall thickening. After 4 years, mean carotid wall thickness had increased by 0.048 mm (SE = 0.01) in the placebo group and declined by 0.014 mm in the pravastatin-treated group (SE = 0.01) ($p < 0.0001$). Given that these positive results were obtained in patients with an average or below-average serum LDL cholesterol level, it is likely that the observed benefits of statin therapy in stroke prevention result from improvements in the vascular biology of atherosclerotic arteries, some of which are independent of their lipid-lowering properties.

Rupture of an unstable atherosclerotic plaque (as characterised by a large necrotic lipid core, a thin fibrous cap and inflammation) has been identified as the basis of most non-haemorrhagic strokes [16]. The restoration of endothelial function, and the reduction of vascular inflammation, thrombosis and cellular proliferation, will all positively affect plaque stability and progression, as well as blood flow regulation and coagulation. This concept is supported by observations of the relationship between inflammatory markers such as C-reactive protein (CRP) and vascular complications. For example, Rost et al. recently identified that elevated plasma CRP levels significantly predict the incidence of first ischaemic stroke or TIA in the Framingham Study original cohort, independently of other cardiovascular risk factors [17].

There is growing evidence to suggest that statins may improve plaque stability by a number of mechanisms not necessarily involving LDL lowering [18]. Macrophages secrete matrix metalloproteinases (MMPs) that may weaken the fibrous cap of the atherosclerotic plaque, predisposing its fissuration. Statin concentrations as low as 5 μmol/l have been shown to inhibit MMP-9, which is found in atherosclerotic tissues, by approximately 30% in cultured human macrophages [19]. In addition, statin therapy has been found to produce a dose-dependent reduction in macrophage growth and an increase in collagen content in experimental models of atheromas [20]. Histochemical analysis of atherosclerotic lesions indicate that arteries from statin-treated monkeys had significantly fewer macrophages in the intima and media, less calcification, and less neovascularisation in the intima ($p < 0.05$) compared to non-statin-treated animals [21]. Statins have also been shown to decrease smooth muscle cell migration and proliferation [22], and to restore endothelial function by directly up-regulating endothelial NO synthase (eNOS) activity [23].

Clinical trial evidence that supports a role for statins in atherosclerotic plaque stabilisation and/or restoration of endothelial function comes from the results of the Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial [24]. The MIRACL study demonstrated that intensive treatment with atorvastatin 80 mg/day, initiated 24–96 h after an acute coronary syndrome (unstable angina or non-Q-wave acute MI), significantly reduced the risk of recurrent ischaemic events after just 16 weeks of therapy, including the time to the first occurrence of death, resuscitated cardiac arrest, non-

fatal MI or angina pectoris with evidence of MI requiring rehospitalisation (p = 0.048). Atorvastatin also produced a significant 50% reduction in the incidence of fatal or non-fatal stroke (p = 0.045) in this highly unstable and high-risk population [25]. The results of MIRACL suggest that patients with acute coronary syndromes should begin to receive statin treatment before leaving hospital in order to expedite the stabilisation process.

Targeting Statin Therapy for Stroke Prevention

The majority of the landmark statin trials have been conducted in patients with or at high risk for coronary artery disease, who are not truly representative of the overall stroke population. This situation has been redressed by the recent publication of the Heart Protection Study (HPS) [26], which assessed the impact of statin therapy with simvastatin in a large cohort of relatively low-risk patients with various prior disease histories for whom the benefit and safety of LDL cholesterol lowering remained unclear. Statin therapy resulted in a constant decrease in LDL cholesterol levels, regardless of baseline level. Consistent with this, the risk of cardiovascular events decreased significantly in all subgroups, irrespective of baseline LDL cholesterol levels. The stroke findings were particularly impressive, with statin therapy lowering the risk of subsequent stroke by almost 30%. In the HPS, the benefit from statin therapy in terms of coronary event or stroke reduction was independent of the starting level of LDL cholesterol, approximately 53% of patients having LDL cholesterol levels at study entry that were below the current recommended guidelines for treatment. The HPS therefore reaffirms the importance of treating global risk rather than individual risk factors.

Indeed, from a lipid point of view, it may not be just levels of LDL cholesterol that are important in stroke risk reduction. A recent study that followed over 11,000 patients with documented CHD who were screened for, but not included in, the Bezafibrate Infarction Prevention study, and had no history of stroke or TIA, looked at the relationship between stroke and TIA according to the quintiles of triglycerides [27]. In this study, high triglycerides constituted an independent risk factor for ischaemic stroke/TIA across subgroups of age, sex, patient characteristics and cholesterol fractions. Patients experiencing an ischaemic stroke/TIA had higher mean levels of triglycerides, higher mean levels of LDL cholesterol and lower levels of HDL cholesterol. This risk factor profile is consistent with patients who have the metabolic syndrome – a population at very high risk of CHD. The fact that patients with the metabolic syndrome, as well as those with LDL cholesterol, are amenable to lipid-lowering therapy is supported by the Veterans Affairs HDL Intervention Trial (VA-HIT) and Diabetes Atorvastatin Lipid Intervention (DALI) studies with gemfibrozil and atorvastatin, respectively, both of which enrolled patients with high triglyceride and low HDL cholesterol levels [28, 29].

Unanswered Questions

A number of questions remain in terms of the relationship between lipids and clinical benefit from cardiovascular and cerebrovascular events. For example, how low should we be targeting our risk factor profile in order to get the optimum clinical benefit? The results of the landmark statin trials strongly support guidelines that advocate adjusting the intensity of cholesterol reduction to absolute risk, and a number of ongoing trials have been designed to address this issue. In the Treating to New Targets (TNT) trial, patients will be randomised to double-blind therapy with either atorvastatin 10 mg/day (target LDL cholesterol 100 mg/dl [2.6 mmol/l]) or atorvastatin 80 mg/day (target LDL cholesterol 75 mg/dl [1.9 mmol/l]). The study will test directly whether LDL cholesterol reductions below 100 mg/dl (2.6 mmol/l) do indeed confer additional benefit.

The Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL) study will also examine whether aggressive lipid lowering with atorvastatin can provide additional coronary benefit beyond that shown with other therapies. The trial has randomised approximately 8,600 patients with coronary artery disease to either atorvastatin 80 mg/day or simvastatin 20 mg/day. Patients receiving simvastatin will be titrated to the 40 mg/day dose if total cholesterol levels remain >193 mg/dl (5 mmol/l). As with the TNT trial, primary endpoints are the incidence of non-fatal MI and fatal coronary artery disease (CAD).

How early should we start lipid-lowering therapy? Autopsy studies have demonstrated that the atherosclerotic process begins during adolescence with the appearance of fatty streaks and fibrous plaques in the aorta, coronary arteries and cervical carotid arteries [30]. These early changes are correlated with cardiovascular risk factors in young adults, and the severity of the atherosclerosis increases with the number of risk factors present. Measurement of intima-media thickness (IMT) can detect

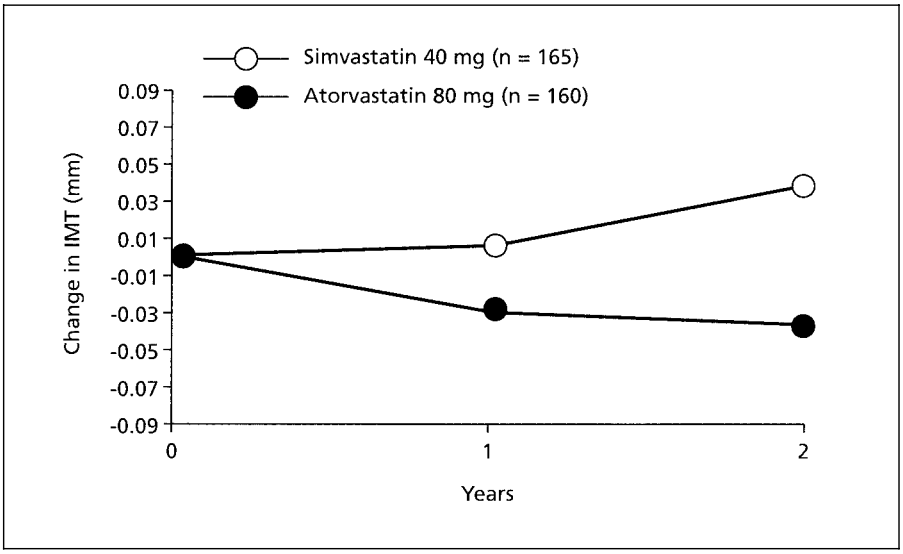

Fig. 4. The effect of aggressive lipid lowering versus moderate lipid lowering on the progression of atherosclerosis – the Atorvastatin and Simvastatin on Atherosclerosis Progression (ASAP) trial. (Reprinted with permission from [31].)

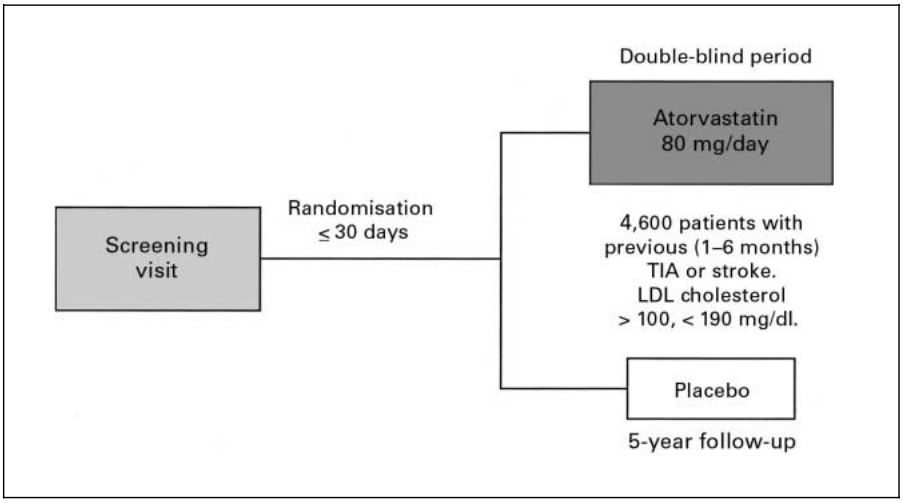

Fig. 5. The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial.

these early subclinical atherosclerotic changes non-invasively.

Increases in the carotid IMT are directly associated with an increased risk of MI and stroke in older adults. The Atorvastatin and Simvastatin on Atherosclerosis Progression (ASAP) trial was designed to assess the effect of aggressive lipid lowering versus moderate lipid lowering on the progression of atherosclerosis. LDL cholesterol lowering with atorvastatin 80 mg/day was accompanied by significant regression in carotid IMT in patients with familial hypercholesterolaemia, whereas moderate lipid lowering with simvastatin 40 mg was not [31] (fig. 4). The ASAP trial is important as the regression in carotid IMT associated with aggressive atorvastatin therapy may result in a significant reduction in cardiovascular events, and in younger adults may ameliorate the atherosclerotic process before the development of symptomatic disease.

To date, statin studies have only been conducted in patients with or at high risk for CAD. These patients are not wholly representative of the overall stroke population. To address this, the ongoing Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial has been designed to prospectively evaluate the benefits of aggressive lipid-lowering therapy with atorvastatin compared with placebo on cerebrovascular events in patients who have had a previous stroke or TIA, but who have no prior history of CAD (fig. 5). The SPARCL trial has enrolled approximately 4,600 patients and results are expected in 2004.

Conclusions

Despite the observed benefit of statin therapy in stroke prevention, a large number of important questions remain unanswered. In particular, the optimal age at which statin therapy should be started in order to maximise a subject's lifespan without cerebrovascular or cardiac events remains to be defined. It is likely that early 'investment' in vascular management will amplify clinical benefits at a later age. It is also becoming increasingly clear that optimal management of vascular disease requires a 'global' approach to risk factor management, and in particular the use of agents that will favourably modify dysfunctional arterial biology. Screening and more active medical therapy offers the exciting prospect of improved outcome, both for patients with existing vascular disease and preclinical subjects considered to be at high risk.

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Blood Pressure and Lipid Lowering in the Prevention of Stroke: A Note to Neurologists

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Key Words
Stroke · Hypertension · Hypercholesterolaemia · Statin therapy · Angiotensin-converting enzyme inhibitors

Abstract
Stroke is the leading cause of adult disability and dependency in western society. Despite the determined efforts of basic science and clinical investigators, neuroprotective therapies for acute stroke have yet to be realised. Stroke prevention, therefore, remains the key route for reducing morbidity and mortality. Hypertension and hypercholesterolaemia are the most important modifiable risk factors for stroke. Several recent landmark studies have shown that lipid lowering with statins can reduce the risk of ischaemic stroke, as well as coronary heart disease. In addition, clinical trials evaluating the effects of blood pressure lowering have shown that antihypertensive agents such as angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs) and angiotensin II receptor antagonists can reduce stroke risk. Accumulating evidence suggests certain antihypertensive agents such as CCBs might also prevent the formation and progression of carotid atheroma, independently of their blood-pressure-lowering effects. It follows that rigorous identification and targeting of high-risk or stroke-prone individuals for blood pressure and lipid-lowering interventions should be of practical importance to all physicians involved in the management of stroke.

Introduction

Neurologists are typically involved in the secondary prevention of stroke, i.e., after a transient ischaemic attack (TIA) or stroke has occurred. However, as physicians with the most knowledge about and concern for the brain, neurologists have an important role to play in informing their primary care colleagues about stroke prevention.

Epidemiology

Stroke is the third main cause of death after heart disease and cancer [1]. One third of fatal strokes occur before age 65 years, and mortality is in the region of 40–60% at 5 years. Furthermore, after major stroke the risk of subsequent myocardial infarction (MI) is increased 2–3 times above baseline [2]. Stroke is also the leading cause of neurological disability and dependency in western society [3].

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Table 1. Modifiable risk factors for stroke

Hypertension
Hypercholesterolaemia
Smoking
Diabetes mellitus
Diet: high salt and fats, low potassium and vitamins
Excess alcohol intake
Morbid obesity
Little physical exercise
Low temperature

For those who survive a stroke, 90% will have some functional deficit, and one-third of patients will have some form of dementia at 4 years [4, 5]. Stroke is clearly a very important disease in terms of public health. The direct and indirect costs for stroke in the USA in 2001 were estimated to be in the region of $50 billion [6].

Pathogenesis

Ischaemic strokes, caused by occlusion of an artery, account for 80–85% of cerebrovascular events, whereas haemorrhagic strokes, caused by a ruptured artery, account for 15–20% [7]. There are three main causes of ischaemic stroke: atherosclerotic disease of large extracranial and intracranial vessels; occlusion of intracranial vessels by emboli from a cardiac source (cardioembolic stroke) and small vessel intracranial occlusive disease resulting from hypertension and diabetes. The heterogeneity of stroke pathogenesis and difference between stroke subtypes may hamper diagnosis and management, but the neurological findings usually help to identify the location of lesions and to predict the stroke mechanism, which is fundamental for determining the initial investigations and treatment [8].

Risk Factors

Beyond the clinical events, it is necessary to manage the underlying pathology and associated risk factors. After the first 30 days, stroke survivors are more likely to die from a cardiac event than a cerebrovascular event [9]. There are two main groups of cardiovascular/cerebrovascular risk factors. The first group of risk factors is unmodifiable and is genetically determined or related to natural body functions, e.g., age, sex, race, family history and previous TIA or stroke. Age is the most powerful risk factor. Indeed, the risk of stroke doubles with every decade after 50 years of age [10]. The second group is the result of lifestyle and can be modified. Aggressive treatment of atherosclerotic risk factors can substantially reduce stroke risk in patients with a history of stroke or TIA. The risk factors may interact more than just by summation, however, so that the risk of stroke markedly increases as the number of risk factors increases. Secondary prevention therefore involves management of all the modifiable risk factors for stroke (table 1), in addition to treating the causes of the initial episode.

Hypertension

Hypertension is the major risk factor for both ischaemic stroke (cerebral infarction) and haemorrhagic stroke (intracerebral haemorrhage) [11]. It is thought to be associated with 60% of all strokes. Antihypertensive therapy reduces the risk of stroke in all age groups, both sexes and in patients with diabetes [12–14]. This applies to severe hypertension as well as mild to moderate hypertension and to isolated systolic hypertension as well as to raised levels of diastolic pressure [15].

Clinical trials in elderly patients have demonstrated unequivocally that effective blood pressure reduction in hypertensive patients up to the age of 85 years significantly reduces the mortality and morbidity associated with cardiovascular diseases (CVD). The Medical Research Council Trial of Treatment of Hypertension in Older Adults and the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) demonstrated significant reductions in the risk of stroke for patients on active treatment, 31% and 42%, respectively [12, 16]. Elevated systolic blood pressure, with or without an accompanying elevation in diastolic pressure, is the major modifiable cardiovascular risk factor in the elderly, affecting 8–15% of all subjects older than 60 years (systolic blood pressure >160 mm Hg and diastolic blood pressure <90 mm Hg) [17, 18]. Three placebo-controlled outcome trials that were specifically designed to evaluate antihypertensive treatment in patients with isolated systolic hypertension were the Systolic Hypertension in the Elderly Program (SHEP) in the United States, the Systolic Hypertension in Europe (Syst-Eur) trial and the Systolic Hypertension in China (Syst-China) trial, which published their main findings in 1991, 1997 and 1998, respectively [19–21]. When the results of these trials are pooled, active treatment compared with placebo reduced all-cause mortality by 17%, cardiovascular mortality by 25%, all cardiovascular end-

points by 32%, MI, including sudden death, by 25%, and total stroke death, by 25%, and total stroke by 37% [22]. These results provide strong evidence that antihypertensive drug treatment should be prescribed if systolic blood pressure is 160 mm Hg or higher on repeated measurement.

In the past few years a number of trials have shown that the benefits of blood-pressure-lowering drugs on stroke risk are not limited to regimens based on diuretics or β-blockers. Reductions of approximately 30% in the incidence of initial stroke have been reported with angiotensin-converting enzyme (ACE) inhibitor-based regimens [23], in particular with the Heart Outcomes Prevention Evaluation (HOPE) study, which demonstrated a 32% risk reduction for stroke [24]. In addition, reductions of approximately 39% have been reported with calcium channel blockers (CCBs) [23], a result dominated by the Syst-Eur trial [20].

The HOPE trial demonstrated a role of the ACE inhibitor, ramipril, which may not be fully explained by blood pressure reduction [24]. The 32% risk reduction in stroke was observed regardless of the baseline blood pressure; the significant difference between the ramipril and placebo treatment groups was observed with the same magnitude in each strata (≤79 mm Hg, 80–89 mm Hg, or ≥90 mm Hg) for diastolic blood pressure and (≤129 mm Hg, 130–139 mm Hg, or ≥140 mm Hg) for systolic blood pressure. The between-group difference in blood pressure reduction in the HOPE study was small – 3.1/1.7 mm Hg [25]. This may suggest that beyond blood pressure reduction, ramipril may have other pleiotropic effects. However, Cook et al recently noted that a similarly small reduction of 2 mm Hg in diastolic blood pressure could account for a 15% reduction in the stroke risk [26]. It is possible, therefore, that the small reduction in blood pressure observed in the HOPE trial may account for the risk reduction in stroke without the intervention of pleiotropic effects.

The results of the placebo-controlled HOPE trial have recently been extended in the Losartan Intervention For Endpoint reduction (LIFE) study, which compared the efficacy of the angiotensin II receptor antagonist losartan with the β-blocker atenolol in preventing cardiovascular morbidity and mortality [27]. Despite similar reductions in blood pressure, significantly fewer patients in the losartan group had fatal or non-fatal stroke, 232 compared with 309 patients, respectively.

With the exception of the HOPE trial, which was a secondary prevention trial, the studies discussed above provide evidence that blood pressure lowering reduces the risk of primary stroke. Among patients with a history of stroke or TIA, blood pressure is also associated with the risk of stroke. However, until recently, the few randomised trials that had been conducted in this patient group were promising but equivocal. Analysis of the data from the United Kingdom Transient Ischaemic Attack (UK-TIA) Collaborative Group indicated that among 2,435 patients with a history of TIA, there was a strong relationship between the levels of both systolic (fig. 1) and diastolic pressures and the risk of stroke [28].

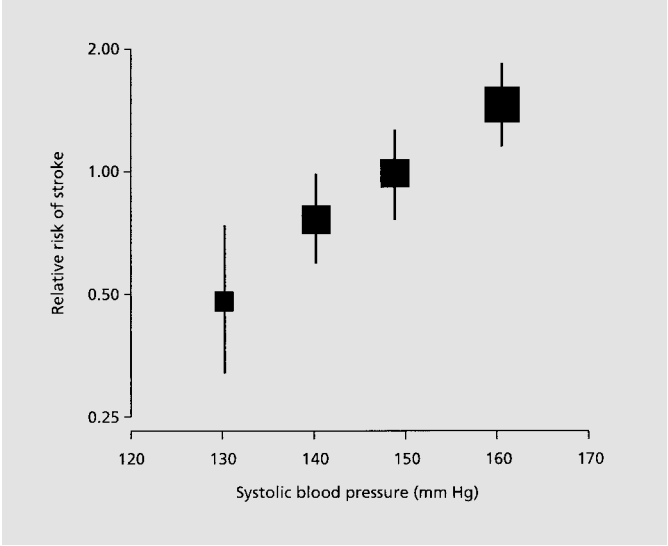

Fig. 1. Relationship between stroke risk and systolic blood pressure. (Adapted from [28].)

The Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) evaluated the effects of an ACE-inhibitor-based, blood-pressure-lowering regimen in both hypertensive and non-hypertensive patients with a history of stroke or TIA [29]. Patients were randomly assigned to active treatment with perindopril 4 mg daily (n = 1,281), or a combination of perindopril 4 mg and indapamide 2.0 to 2.5 mg (n = 1,770), or to placebo (n = 3,054). The primary outcome was total stroke (fatal or non-fatal). After 4 years, the risk of stroke was reduced in all patients on active treatment by 28% ($p < 0.0001$). Subgroup analysis of the PROGRESS results revealed that stroke risk and major vascular risk were reduced similarly in patients classified as non-hypertensive (mean blood pressure at entry was 136/79 mm Hg) and hypertensive (blood pressure was >160/90 mm Hg). The investigators concluded that the blood-pressure-lowering treatment reduced the risk of stroke in both hypertensive and non-hypertensive patients with a history of stroke or TIA.

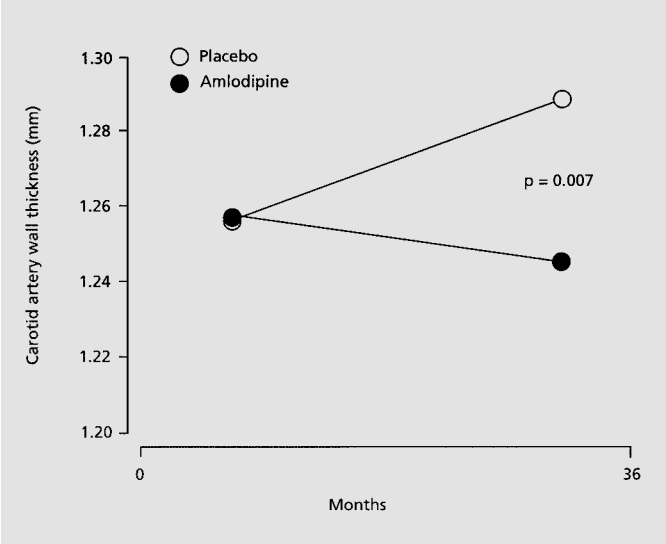

Fig. 2. The calcium channel blocker, amlodipine, slows the progression of carotid atherosclerosis. The Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) [32].

Recent trials have suggested that some antihypertensive agents may have anti-atherosclerotic effects in the carotid artery that are independent of blood pressure lowering. An increased common carotid intima-media thickness (IMT) is associated with future cerebrovascular and cardiovascular events [30]. The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), a substudy of the HOPE trial, is one such study [31]. Atherosclerosis progression was evaluated by B-mode carotid ultrasound and was significantly decreased compared with placebo in the ramipril 10 mg group. The reduction in atherosclerotic progression observed with ramipril remained significant after adjusting for systolic and diastolic blood pressure changes, and is the first demonstration of an effect of ACE inhibition on atherosclerotic progression.

The Prospective Randomised Evaluation of the Vascular Effects of Norvasc Trial (PREVENT) was designed to test whether amlodipine would slow the progression of early coronary atherosclerosis in patients with angiographically documented coronary artery disease (CAD) [32]. Amlodipine was found to have a significant effect in slowing the 36-month progression of carotid artery atherosclerosis (fig. 2). The placebo group experienced a 0.033-mm increase in IMT, whereas there was a 0.0126-mm decrease in the amlodipine group ($p = 0.007$). Further studies are now needed to determine whether these reductions in carotid artery atherosclerosis will translate into a reduction in clinical events.

Hypercholesterolaemia

The relationship between serum cholesterol levels and stroke is complex. Clinical trials in the 1990s, using HMG-CoA reductase inhibitors (statins), showed that cholesterol-lowering treatment significantly reduced cardiovascular events, including strokes, in the secondary prevention of MI [33, 34]. However, conflicting evidence from a series of epidemiological studies [5, 18, 35] and a suggestion that lowering serum cholesterol increased the risk for haemorrhagic stroke [36] has, until recently, prevented a link between serum cholesterol level and the incidence of stroke becoming fully established. However, the statin trials present a strong argument for a reappraisal of the link between cholesterol and stroke. Indeed, a meta-analysis reported an average reduction of about 30% in the incidence of cerebrovascular disease for patients on statin therapy [37]. It is now generally accepted that lipid-lowering treatment should be considered in all stroke patients with a history of coronary heart disease, even when serum cholesterol level is in the normal range. In patients with ischaemic stroke with no past history of a coronary event, who constitute 80% of the stroke population, no clear recommendation can be made, as, to date, statin studies have only been conducted in patients with, or at high risk for, CAD, who are not truly representative of the overall stroke population. To address this, the ongoing Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial has been designed to prospectively evaluate the benefits of aggressive lipid-lowering therapy with atorvastatin compared with placebo on cerebrovascular events in patients who have had a previous stroke or TIA, but who have no prior history of CAD. The SPARCL trial has enrolled approximately 4,600 patients and results are expected in 2004.

The reasons for the benefits of statin therapy in stroke prevention are unclear since, paradoxically, the link between serum cholesterol level and stroke has never been fully established. Furthermore, the positive results of statins trials were mainly obtained in patients with an average or low serum cholesterol level. This suggests non-hyperlipidaemic effects of these drugs, which promote atherosclerotic plaque stability, may also play a role. Whatever the mechanisms involved, aggressively controlling stroke risk factors should benefit public health.

Conclusion

After CVD and cancer, stroke is the third leading cause of death in many industrialised countries and the most important cause of morbidity and long-term disability. This results in substantial demands on healthcare resources in addition to the high personal toll on the individual and their family. Major efforts should therefore be focused on stroke prevention.

There is clearly considerable scope for preventing a first stroke. Aggressive treatment of atherosclerotic risk factors can substantially reduce stroke risk in patients with a history of stroke or TIA. There is also considerable overlap between the modifiable risk factors for stroke and for other cardiovascular diseases, such as coronary heart disease, and therefore aggressive management of risk factors should be encouraged because of benefits in terms of other diseases. Tools and strategies available for stroke prevention and management have grown impressively during the past decade. The benefits of blood pressure lowering for both primary and secondary prevention of stroke are clearly established. In coronary patients, statin treatment clearly reduces the risk of stroke. Ongoing trials are evaluating whether this benefit extends to patients with stroke and no past history of a coronary event.

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