Primary prevention of stroke: blood pressure, lipids, and heart failure

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Received 7 September 2010; revised 20 October 2010; accepted 2 December 2010; online publish-ahead-of-print 1 February 2011

Stroke contributes significantly to morbidity, mortality, and disability worldwide. Despite the successes accomplished in the acute treatment and rehabilitation of stroke, the global burden of this disease can only be tackled with co-ordinated approaches for primary prevention. Stroke is a heterogeneous disease and the contribution of individual risk factors to its occurrence estimated by population attributable risk differs from coronary heart disease. Here, we review evidence to demonstrate the prominent role of elevated blood pressure (BP) and heart disease on risk of stroke, while the influence of lipids on stroke is less clear; we also demonstrate that stroke is an important complication of heart failure. Current approaches to primary preventive action emphasize the need to target the absolute risk of cardiovascular diseases rather than individual risk factors. Lifestyle interventions serve as a basis for primary prevention of cardiovascular diseases. It is estimated that 70% of strokes are potentially preventable by lifestyle modification but prospective evidence is needed to support these hypotheses derived from epidemiological studies. Different strategies for drug interventions in primary prevention are discussed, including the polypill strategy. Additional measures are needed for the primary prevention of stroke which focus on BP, chronic heart failure, and possibly lipids.

Keywords: Hypertension, Cholesterol, Heart failure, Triglycerides, Polypill, Adherence

Introduction

The global burden of stroke is substantial. Stroke is the second leading cause of death, one of the leading causes of adult acquired disability worldwide, and hence a major contributor to health-care costs.¹ For example, in the UK, the direct and indirect societal costs caused by stroke are about 8.9 billion pounds a year.² Stroke is a disease of the elderly. The median age at the onset of first stroke in Europe is 73 years.³ It is anticipated that the absolute number of stroke patients will increase substantially over the next decades. The WHO estimates that the absolute number of first-ever stroke patients in the European Union and selected European Fair Trade Association countries will increase from 1.1 million in 2000 to 1.5 million in 2025 if incidence rates remain stable.⁴

Disease condition ‘stroke’

The pathophysiology of acute coronary vascular syndromes is primarily related to plaque rupture followed by local thrombosis. In contrast, stroke is a rather heterogeneous clinical syndrome consisting of different pathophysiological and aetiological subgroups (Figure 1). Stroke is a clinical diagnosis and is classified according to the duration of clinical symptoms into transient ischaemic attack or stroke.⁵ New tissue- instead of time-based classification systems are challenging this traditional definition.⁶ The clinical entity ‘stroke’ is further subdivided based on the underlying pathology into ischaemic stroke (IS), primary intracranial haemorrhage, or subarachnoidal haemorrhage. IS can be classified according to the leading aetiological cause into large-artery atherosclerosis, cardioembolism, small-artery occlusion, other causes, and undetermined aetiology⁷ with new classification systems proposed in the light of wider availability of advanced diagnostic facilities.⁸

Risk factors for stroke

The main risk factors for ischaemic and haemorrhagic stroke, respectively, are well known and can be differentiated into non-modifiable (age, sex, genetic predisposition, ethnicity) and modifiable ones (smoking, hypertension, lifestyle factors, diabetes)⁹ with...
variations in the impact of specific risk factors between haemorrhagic stroke and IS. For example, atrial fibrillation (AF) is a risk factor for IS but not for haemorrhagic stroke.10–12 Most risk factors contribute to both coronary heart disease (CHD) and IS. However, the relative contribution of individual risk factors differs substantially between the two disease conditions.13 Defining the weight of risk factors by population attributable fractions (PAF) (i.e. the proportion of a disease that could be theoretically prevented if a risk factor would be absent) reveals hypercholesterolaemia as the main risk factor for CHD14–17 and hypertension for stroke18,19 (Figure 1). However, the estimation of PAF for a specific risk factor is not trivial, especially if diseases are caused by multiple risk factors not acting independently,20 and the estimates are dependent on the definition of the population at risk.21 The four main modifiable risk factors diabetes, smoking, hypertension, and hypercholesterolaemia explain less variance of occurrence of stroke compared with the occurrence of myocardial infarction [e.g. 55% of stroke events vs. 88% of myocardial infarction events in the European Prospective Investigation into Cancer and Nutrition (EPIC) study were attributed to these four risk factors].22

Minimizing the impact of stroke on society will thus require effective strategies for reducing its incidence in the general population. Here, we review current strategies for the main modifiable risk factors: blood pressure (BP), lipids, and heart disease.

**Blood pressure**

High BP is a common phenomenon in the population. Its prevalence varies according to geography and ethnic background. At the 140/90 mmHg threshold, the prevalence of hypertension is 28% in North America and 44% in six European countries.23 In sub-Saharan Africa, although overall hypertension prevalence is up to 15%, middle-income urban dwellers can have prevalence rates as high as 32%.

**Blood pressure and stroke**

Hypertension has been identified as a major risk factor for stroke. The INTERSTROKE study, which evaluated the contribution of various risk factors to the burden of stroke worldwide, concluded that hypertension provided 34.6% of the PAF for stroke19.
In the ACCORD study, where almost 5000 participants reduce stroke incidence more than they reduce myocardial infarcts. Ezzati et al. previously attributed 70–76% of strokes occurring in 14 subregions of the world to a limited number of risk factors, with hypertension as the biggest driver of stroke risk.

More recently, it has also been recognized that hypertension is also a risk factor for reduced cognitive function. In a large observational study of a healthy population, an increase of 10 mmHg in diastolic BP (DBP) was associated with 7% higher odds of cognitive impairment. This is similar to the conclusion that a 1 mmHg rise in systolic BP (SBP) in midlife was associated with a 1% increase in risk of cognitive decline later in life. In addition to a direct association with dementia, hypertension also aggravates Alzheimer’s disease, and the presence of a single lacune at autopsy, even when asymptomatic, increased the probability of dementia by a factor of 18 in the Nun Study.

**Blood pressure lowering in primary stroke prevention**

INTERSTROKE and INTERHEART report that hypertension provided 34.6 and 17.9% of the PAF for stroke and myocardial infarction, respectively (Figure 2). This is supported by a population-based study from France showing that individuals with stroke were more likely to be hypertensive than those with myocardial infarcts. At standard doses, drugs that lower BP also reduce stroke incidence more than they reduce myocardial infarcts. In the ACCORD study, where almost 5000 participants with type 2 diabetes were assigned to target SBPs of <120 or <140 mmHg and were followed 4.7 years for vascular events, stroke was the only outcome with a significantly lower incidence in the intensive therapy group. Thus, the brain is the organ most benefited when BP is reduced.

Several authors have estimated the extent of protection that results when BP is lowered. Girerd and Giral concluded that each 2 mmHg reduction in SBP was associated with a 25% reduction in stroke events. More recently, Beckett et al. showed that in patients 80 years of age or older, treatment which lowered mean SBP and DBP by 15.0/6.1 mmHg resulted in a 39% reduction in the rate of fatal strokes at 2 years of treatment. Jones et al. estimated that a 35–44% reduction in the incidence of new strokes can be achieved by lowering BP. Finally, Sokol et al. concluded from their review of the effect of BP management on the incidence of primary and secondary strokes that prolonged reduction in DBP of 5, 7.5, and 10 mmHg would lower stroke rates by at least 34, 46, and 56%, regardless of the starting BP level.

**Conclusions: blood pressure and primary prevention of stroke**

Despite the overwhelming evidence that hypertension is a major cause of damage particularly to the brain and that the brain benefits the most from BP lowering, there are no randomized clinical trials that provide a BP target for effective prevention of first strokes. This can only be answered by a new study that attempts to define a target. The challenges of designing such a trial have recently been described. Nonetheless, the SBP Intervention Trial (SPRINT) launched recently by NIH, with a target SBP of <120 mmHg, should go a long way to filling this gap. In the meantime, it is clear that improving the management of hypertension at the population level will result in optimum brain protection. Law et al. suggest that in people aged 60–69 with a DBP of 90 mmHg, three drugs at half standard dose reduced the risk of stroke by 62%, whereas one drug at standard dose had half this effect. In addition, they advocate lowering BP in the population broadly rather than ‘measuring it in everyone and treating it in some’.

**Lipids**

**Cholesterol and stroke**

Total blood cholesterol levels are a prominent risk factor for cardiovascular disease. The association of cholesterol and stroke, however, is much less clear: surprisingly, epidemiological studies found no consistent relationship between cholesterol levels and overall stroke risk. For example, neither the Framingham Study nor the Honolulu Heart Study found an association between cholesterol levels and cerebrovascular disease. The Prospective Studies Collaboration has brought together evidence from 61 individual prospective studies and analysed the data of 55 000 vascular deaths. There was no clear relationship between blood cholesterol and stroke (except in people aged 40–60 years and with normal or high-normal BP). In many of the individual studies, no differentiation between stroke subtypes was performed. For example, many strokes were not verified by brain imaging and, hence, could not even be differentiated into haemorrhagic stroke vs. IS. Indeed, the MRFIT study in 350 000 men which examined the link between cholesterol and fatal stroke (and differentiated haemorrhagic stroke from IS) showed a J-shaped relationship between total cholesterol levels and stroke mortality (Figure 3).

This could be explained by an association of higher cholesterol with IS and, vice versa, between lower cholesterol and haemorrhagic stroke—at least in patients with co-morbid high BP. Similarly, in the Prospective Studies Collaboration in individuals with...
SBP > 145 mmHg, total cholesterol was negatively related to haemorrhagic and total stroke mortality. Another caveat of the meta-analyses is the fact that often only fatal strokes were analysed. Taken together, the relationship between cholesterol and total stroke is weak but it seems likely that cholesterol is associated with increased risk at least in the subgroup of atherothrombotic strokes.

Only few studies addressed the association of elevated LDL cholesterol levels and SBP, and they did not find consistent findings. In contrast, high HDL levels are associated with reduced stroke risk, and vice versa, low HDL is associated with increased stroke risk. Also, the ratio of total cholesterol to HDL cholesterol (or the LDL/HDL cholesterol) ratio may be more predictive. This is also supported by the INTERSTROKE study which showed that the ratio of apolipoprotein B to A1 was predictive for stroke risk. Overall, the population attributable risk of low HDL cholesterol is estimated to be 10%.

The role of triglyceride levels for stroke risk is also unclear. Some studies and meta-analyses report an association between triglyceride levels and IS, but several studies found no relationship between fasting triglyceride levels and IS risk (as was demonstrated for cardiovascular disease). In contrast, non-fasting triglyceride levels may be a better prediction for stroke (and cardiovascular risk). Recently, a cohort study also found an association of non-fasting triglyceride levels and IS in women. Triglyceride levels vary considerably, making risk prediction difficult, and the lack of standardization may explain some of the contradictory results. The ongoing Berlin Cream & Sugar Study will employ an oral triglyceride tolerance test with standardized conditions to predict the risk of further strokes.

**Lipid lowering in primary stroke prevention**

Earlier intervention trials with non-statin cholesterol-lowering drugs (including fibrates) failed to show a reduction of stroke risk, which stands in contrast to the fact that these drugs lowered cardiovascular risk (along with cholesterol levels). In contrast, results from randomized trials have demonstrated that treatment with HMG-CoA reductase inhibitors (i.e. statins), which lower total and LDL cholesterol, not only reduces the incidence of ischaemic heart disease but also of IS. As a rule of thumb, the reduction in LDL cholesterol by 1.5 mmol/L reduces IS risk by about a third. Statins were also protective in populations at high vascular risk but without documented CHD, such as in the ASCOT-LA or CARDS (primary diabetic population) cohorts.

So far, however, the protective results of statins on stroke risk are limited to patients at high risk for stroke (i.e. with CHD or other additional risk factors) and it remains unclear whether statin treatment is effective for stroke prevention in the general population without CHD. Data on the elderly, moreover, are very limited: in the PROSPER trial, pravastatin had no effect on stroke (while it reduced the combined vascular endpoint by 15%). For secondary stroke prevention, both the SPARCL trial and a subgroup of the HPS trial demonstrated a significant reduction of secondary cerebrovascular events in stroke patients even without additional CHD. Consequently, statin therapy has become a pillar of treatment in addition to aspirin and BP medication.

Of note, reduction in IS risk by statins may be associated with a small increase in haemorrhagic stroke as suggested by two secondary prevention trials, SPARCL and HPS. Statins might therefore not be indicated for patients with haemorrhagic strokes. Further studies of how exactly lipids, cholesterol, and lipoprotein particles contribute to stroke risk invite further research.

Presently, the mechanism of stroke protection by statins is not entirely clear. Cholesterol-independent pleiotropic effects may contribute to it: statins reduce inflammation, are anti-atherogenic, lower BP, stabilize plaques, are anti-thrombotic, improve fibrinolysis, and decrease platelet activation. They also have immunomodulatory effects, increase the number of circulating endothelial progenitor cells, and improve endothelium function. In addition, statins have neuroprotective properties, reduce ischaemic lesion size in animal stroke models, and may therefore also improve stroke outcome. However, the relative contribution of LDL cholesterol lowering vs. other pleiotropic statin actions on the reduction of stroke risk cannot be easily differentiated since essentially all pleiotropic effects of statins are also dependent on HMG-CoA reductase inhibition. Thus, these effects go hand in hand with any effect on LDL cholesterol levels, are dose-dependent, and correspond with the potency of a given statin drug. In other words, LDL cholesterol may as well serve as a biomarker for pleiotropic statin effects. It is therefore not surprising that there is a linear association between reduction in LDL cholesterol concentration and stroke incidence among the major statin trials.

Recently, the JUPITER trial tested the hypothesis whether individuals with elevated inflammatory biomarkers but without hyperlipidaemia benefit from high-dose statin treatment. In fact, high-sensitivity C-reactive protein levels were demonstrated to be associated with the risk of IS, although its relevance is still unclear. Rovastatin reduced major cardiovascular events including death from cardiovascular causes in apparently healthy men and women with average LDL cholesterol and elevated high-sensitivity C-reactive protein. Stroke reduction by rosuvastatin treatment was also significant, but the absolute rate was low and the number needed to treat consequently rather high (i.e. 286). The JUPITER study has already evoked intensive debate. However, its relevance for (primary) stroke prevention is limited by the low number of stroke events and the fact that it included individuals without a specific condition placing them at risk for stroke.

**Conclusions: lipids and primary prevention of stroke**

Present guidelines recommend the regular measurement of blood cholesterol levels. The National Cholesterol Education Program III provided guidelines for the management of patients without previous cerebrovascular events with elevated non-HDL cholesterol levels and additional risk factors. It is unclear whether lowering lipids is effective in the primary prevention of stroke in the general population (without CHD or additional vascular risk...
Heart failure

Cardiac diseases including valve disease and chronic heart failure (CHF) represent a risk factor for IS64 (Table 1). Approximately 25% of all ISs are due to cardiac embolism.65 Up to 10–24% of the patients with IS have CHF, and in 9% of ISs, CHF is the likely cause.66–69 For CHF, a meta-analysis calculated that 18 per 1000 persons suffered a stroke during the first year after the diagnosis and increased to 47 at 5 years.70 The overall relative risk of stroke in CHF increases approximately two to three folds compared with patients without CHF. In addition, CHF represents an independent predictor for the severity of cerebral ischaemia and associated poor outcome.71 A recent analysis showed that the odds ratio of in-hospital mortality rate for stroke patients with CHF was more than doubled than for those without CHF.72 Stroke patients with CHF also stayed longer in the hospital.67 The stroke risk in patients with CHF increases further with age, concomitant arterial hypertension, and AF.

Recent imaging studies suggest that the incidence of silent cerebral ischaemia in CHF patients may be high (up to 40% of the CHF population).72 Silent cerebral ischaemia, losses in grey matter, and decreased cerebral perfusion may significantly contribute to cognitive impairments that are reported in many CHF patients (25–80%)73,74. A recent analysis of the Framingham study looked at 1504 participants without prior stroke or dementia showed that the cardiac index correlated with brain volume and information processing speed75 (Table 2). Further research is needed to characterize the underlying mechanism(s) for this association, which is largely unknown, and to develop strategies for specific prevention.

It seems likely that CHF-related strokes are primarily embolic. The risk of embolism correlates with the degree of left ventricular (LV) dysfunction. Specifically, an ejection fraction <30% is associated with an increased risk of embolism.76 Chronic heart failure is associated with an activation of thrombus formation likely mediated by the renin–angiotensin system, endothelial dysfunction, increased blood velocity, and dysregulation of mediators (e.g. thrombin, plasminogen, and others).77 The main cause for emboli in patients with CHF is AF.78 The prevalence of AF in CHF is 10–17% and it increases with LV dilatation and New York Heart Association (NYHA) stage.79 The degree of LV dysfunction is associated with embolic events and can be used to stratify stroke risk in patients with AF (Table 3). Chronic heart failure is therefore an important factor for the assessment of stroke risk. For example, CHF is included in the CHADS2 score to assess stroke risk in AF patients.80 An assessment of the individual co-morbidities using the CHADS2 score can help to make individual recommendations. For individuals with a CHADS2 score of 0 treatment with aspirin is sufficient, for a CHADS2 of 1 aspirin or anticoagulation can be used and all patients with a CHADS2 >1 clearly benefit from anticoagulation.

Intracavitary thrombi are a source of embolism and occur in LVs impaired by myocardial infarction, valve disease, or CHF. The danger of intra-atrial thrombus formation exists particularly in patients with AF (see above). In patients with a ventricular thrombus and additional risk factors (e.g. LV dysfunction or hypertension), anticoagulation for at least 6 months is indicated.81 Intra-atrial thrombi can only be detected or excluded with sufficient diagnostic reliability by the use of transoesophageal echocardiography (TEE). In contrast, both LV function and LV thrombi (especially in the apex cordis) are better assessed by transthoracic echocardiography than by TEE.51–83 Lack of atrial thrombi does not exclude cardiogenic stroke.

Because of the increased risk of intermittent and of asymptomatic AF in CHF and the increased risk of stroke in patients with CHF in sinus rhythm, the question arises whether all patients with impaired LV function or LV aneurysms would benefit from anticoagulation. However, all published studies that tested the effect of oral anticoagulation in patients with CHF in sinus rhythm, including the WATCH trial84 were not able to demonstrate an advantage of anticoagulation with regard to mortality. Anticoagulation is effective in patients with CHF and AF, but LV dysfunction by itself does not represent an indication for anticoagulation treatment.

In addition to the causal relationship between CHF and IS, these two disease entities represent manifestations of similar underlying risk factors. In CHF patients in sinus rhythm, older age, hypertension, and diabetes are associated with increased incidence of stroke.85 Arterial hypertension is a main risk factor for stroke.
and CHF and represents one of the most important targets for prevention. Indeed, the recent Hypertension in the Very Elderly Trial (HYVET) showed that BP control in patients >80 years of age reduced both stroke and heart failure events as well as mortality.13 Blood pressure control is the basis of the prevention of CHF and stroke.13

**Primary stroke prevention**

**General principles of primary prevention**

For primary prevention of stroke, two complementary approaches can be differentiated: the population and the high-risk strategy.86,87 The population approach aims to change levels of risk factors in the entire population towards a more favourable distribution. These include environmental or lifestyle factors (such as diet, physical activity, smoking, and obesity) as well as their social and economic determinants.88 For example, the North Karelia Project aiming at risk factor level reduction by population-wide chronic disease prevention and health promotion interventions shows an 80% decline in coronary mortality over 35 years.89 In contrast, the high-risk strategy aims at identifying currently asymptomatic individuals at high risk of future vascular disease to reduce their individual risk.86 The decision to take preventive action in asymptomatic high-risk individuals should be based on ‘absolute risk rules’.13 This means that absolute levels of multiple risk factors are taken into account rather than a specific risk factor unless it is markedly increased.13,90 Risk charts are available for estimating the probability of future vascular disease (absolute risk). They contain relative risks of factors derived from cohort studies and baseline risks reflecting cultural, socio-economic, and psycho-social characteristics of a given population.90 Currently, global risk scores (e.g. SCORE91), which estimate total cardiovascular risk rather than incidence of single endpoints, are recommended for the identification of high-risk individuals.13 To provide accurate identification, these risk charts should also be adapted to the baseline risk of the population.92

**Implementing primary prevention in the population**

Lifestyle interventions serve as a basis for primary prevention. It has been proposed that 70% of stroke and over 80% of CHD might be preventable through lifestyle modifications (e.g. not smoking, healthy diet, body mass index <25 kg/m², regular physical activity, and moderate alcohol consumption).71 This estimation is in line with observations from prospective cohort studies which report that a healthy lifestyle (as defined above) is associated with an 82% decrease in CHD risk in women.94 In addition, a substantial decrease in relative risk of stroke in people with the healthiest lifestyle compared with an unhealthy lifestyle is observed in previous cohort studies95–97 (Figure 4). Until now, evidence from clinical trials is missing to confirm the data produced by these observational studies. Population strategies targeting economic and social determinants for changing lifestyle behaviour in the population require political action and need different partners at the local, national, and international levels. Examples for policy actions to put prevention into practice at the population level are provided by the recently published NICE public health guidance ‘Prevention of cardiovascular disease at population level’.98 Currently, however, it is unclear how lifestyle changes can be successfully achieved in healthy individuals.

Observational studies may also generate new pathophysiological hypotheses about stroke occurrence. For example, individuals with acute infection99 or with increased homocysteine levels100 have a higher stroke risk and might be suitable for population-wide interventions, e.g. via immunization or vitamin supplementation, respectively. However, large primary prevention trials on the potential reduction of stroke risk are lacking and homocystein lowering with vitamins B6, B12, and folic acid failed in clinical trials in patients with a history of vascular diseases101 or stroke.102

In individuals at high risk for vascular diseases, drug intervention by health-care professionals in clinical practice is often necessary in addition to lifestyle recommendations. There are different strategies for identifying high-risk individuals. Often an opportunistic screening is undertaken for this purpose, e.g. by risk charts that are restricted to patients requesting a screening or to patients considered eligible by health practitioners. However, the use of the

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**Table 2** Change in total brain volume as a function of a 1 SD change in cardiac index

<table>
<thead>
<tr>
<th>Cardiac index</th>
<th>Total sample (n = 1504)</th>
<th>P-value</th>
<th>Without prevalent CVD (n = 1392)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>0.30 ± 0.14</td>
<td>0.03</td>
<td>0.33 ± 0.14</td>
<td>0.02</td>
</tr>
<tr>
<td>Tertile 1 (low)</td>
<td>−0.36 ± 0.17</td>
<td>0.04</td>
<td>−0.41 ± 0.17</td>
<td>0.02</td>
</tr>
<tr>
<td>Tertile 2 (mid)</td>
<td>−0.35 ± 0.17</td>
<td>0.04</td>
<td>−0.34 ± 0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>Tertile 3 (high)</td>
<td>Reference</td>
<td>—</td>
<td>Reference</td>
<td>—</td>
</tr>
</tbody>
</table>

*Cardiac index is the cardiac output divided by the body surface area.

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**Table 3** Estimation of stroke risk in patients with atrial fibrillation based on echocardiographic findings

<table>
<thead>
<tr>
<th>Finding</th>
<th>Risk/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation + normal echocardiographic finding</td>
<td>1.5%</td>
</tr>
<tr>
<td>Atrial fibrillation + enlarged left atrium</td>
<td>8.8%</td>
</tr>
<tr>
<td>Atrial fibrillation + left ventricular dysfunction</td>
<td>12.6%</td>
</tr>
<tr>
<td>Atrial fibrillation + enlarged atrium + left ventricular dysfunction</td>
<td>20.0%</td>
</tr>
</tbody>
</table>
primary prevention of stroke

charts might not be fully understood by physicians, leading to only modest changes in prescription behavior. There is also an ongoing debate about mass screening programmes for identifying high-risk individuals in whole or pre-defined populations.

Another approach was proposed by Wald and Law as a population-wide drug intervention from a given age without screening or identification of individual risk. This ‘polypill’ strategy proposes to reduce simultaneously four major cardiovascular risk factors: cholesterol, BP, homocystein/low-folate, and platelet function by drugs including a statin, three blood-lowering drugs in low dosage, folic acid, and aspirin. The authors proposed treatment for everybody older than 55 years or with a history of previous cardiovascular disease, regardless of pre-treatment risk factor levels and without monitoring of the effect. Currently, evidence from clinical trials to assess the overall benefit as well as potential adverse effects is lacking. It needs to be established whether different medications when combined in a single pill still exert their expected mechanism of action. For example, a polypill containing low doses of hydrochlorothiazide, atenolol, ramipril, simvastatin, and aspirin was compared with the individual drugs given separately in a randomized trial in primary prevention in India. This polypill was well tolerated and non-inferior to its individual components in lowering BP and heart rate. It substantially lowered LDL cholesterol and urinary 11-dehydrothromboxane B2, but to a degree that was slightly less effective than simvastatin or ASA alone. However, there is no clear consensus as to which kinds and doses of substances should be combined for optimal prevention. Drug registration of fixed combinations represents a challenge and, in the case of adverse events, it is difficult to identify the responsible component(s). Another important limitation is the reduced flexibility in choice of drug substances and individual doses. However, all currently proposed strategies for primary prevention based on modelling approaches. The cost effectiveness or real population benefits of these strategies are in debate and the outputs of clinical trials are expected.

Drug adherence

Another important aspect in ensuring effectiveness of drug treatment in primary prevention is drug adherence. Increasing numbers of elderly patients require polypharmacy for chronic diseases. Non-adherence to medication is common and is associated with adverse treatment outcome. Reduced adherence is an indicator of higher morbidity, adverse events, and costs. Adherence to medical therapy correlates with reduced morbidity and survival. Average non-adherence rates are between 20 and 50% in patients with chronic diseases. Adherence to medication can be effectively improved by specific measures such as counselling of patient and care-giver, reduction of the number of single daily doses, and provision of supporting medication management such as blister packs. An important factor for medication adherence is the number of pills taken daily. Increasing numbers of single doses are directly associated with dramatically decreasing adherence. Fixed combinations, e.g. in the treatment of hypertension, can contribute to the reduction of the number of single doses and therefore also improve drug adherence. The polypill concept introduced above offers the different drug substances in a single formulation. In an analysis of > 11 900 patients on fixed-dose combination, the relative risk of non-adherence was reduced by 26% compared with patients on free-drug component regimens. Adherence can be improved using a single pill in comparison with the drugs being taken separately; however, other ways of providing combination therapy, e.g. in unit doses, may maintain the freedom of treatment. Speculation is justified that the impact of implementing comprehensive measures to improve adherence such as continuous counselling and individualized multidose adherence aids may be more important than our current focus on the development of new drugs. However, clinical trials in primary prevention are needed to test the effects of measures to improve adherence on clinical endpoints in high-risk individuals.

Implications for future management

A substantial portion of the risk factors for stroke and CHD is identical (albeit with different contributions). Thus,
recommendations for primary prevention of vascular diseases in general should also serve as a basis for the primary prevention of stroke. For example, the existing European guidelines for cardiovascular disease prevention in clinical practice commissioned by the Joint Task Force, including, for example, representatives from the European Society of Cardiology and the European Stroke Initiative, shifted from recommendations for primary prevention of stroke or CHD towards general preventive recommendations for all cardiovascular disease.

The question arises as to what additional implications for primary prevention of stroke are needed. On the basis of the research questions outlined above, a number of areas can be identified that need to be addressed in future clinical studies. For example, subjects with rare disease conditions but with particular high risk of stroke need to be identified and might require more aggressive primary preventive treatment (e.g. patients with CHF and intracavitary thrombi). Stroke-specific risk factors such as AF or carotid stenosis require specific action for stroke prevention, and tailor-made guidance is necessary. The effects of aggressive LDL-cholesterol lowering in primary stroke prevention needs to be established and it is necessary to test whether HDL-raising drugs may be beneficial (in addition to statins and lifestyle factor interventions in high-risk individuals). The role of triglycerides in primary stroke prevention needs to be established and further research is needed to address the aspect of risk prediction and potential treatment. It is currently unclear whether individuals at high absolute vascular risk but with ‘normal’ BP levels will benefit from BP lowering medication. Because of the utmost importance of BP levels for the brain, it needs to be established whether a specific BP target for effective prevention of first strokes should also apply to existing recommendations for primary prevention of cardiovascular diseases.

Funding
This work was supported by the European Union’s Seventh Framework Programme grant agreement no. 202213 (European Stroke Network, M.E. and U.L.) and no. 223153 (EIS, P.U.H), the German Ministry of Research and Education (Center for Stroke Research Berlin grant number 01 EO 0801, M.E. and P.U.H), the Volkswagen Foundation, and the Deutsche Forschungsgemeinschaft (M.E.).

Conflict of interest: M.E. has received grant support from Astra-Zeneca and Sanofi-aventis, has participated in advisory board meetings of Boehringer Ingelheim and Sanofi-aventis, and has received honoraria from Novartis, Pfizer, Bayer, Astra-Zeneca, Boehringer Ingelheim, Sanofi-aventis, Trommsdorff, Berlin-Chemie, GlaxoSmithKline, and Bristol–Myers-Squibb. P.U.H. received an unrestricted research grant from the German Stroke Foundation. U.L. has received honoraria from Astra-Zeneca, Boehringer Ingelheim, Daiichi-Sankyo, Essex, MSD, Roche, Sanofi-aventis, Servier, Takeda, and Trommsdorff.

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