Stroke Subtypes and their Possible Implication in Stroke Prevention Drug Strategies

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Abstract: Thrombotic strokes can affect large or small arteries in the brain. Drugs to prevent atherosclerosis complication such as thrombotic strokes, should be drugs able to prevent the accumulation of intravascular fat, reduce vascular proliferation, decease blood pressure levels with the resulting shear stress, reduce platelet aggregation, and possibly partially or totally reverse carotid plaques. Any of the commonly used antihypertensive drugs lower the incidence of stroke, with larger reductions in BP resulting in larger reductions in risk. Experimental and clinical data suggest that reducing the activity of the renin-angiotensin aldosterone system (RAAS) may have beneficial effects beyond the lowering of blood pressure to reduce stroke incidence. In clinical trials, statins consistently reduced the risk of ischemic stroke in patients with or without CHD whereas the data on the effects of other lipid modifying drugs on stroke risk are limited. Approximately 25% of strokes are recurrent. Antiplatelet therapy is indicated for the prevention of recurrent stroke in patients with a history of noncardioembolic minor stroke or transient ischemic attack (TIA). Although clinicians may choose acetylsalicylic acid (ASA) as first-line therapy for secondary prevention, clinical guidelines and evidence from trials suggest that ASA may not be the most effective strategy. A recent review discussed results from clinical trials that have compared the efficacy of ASA monotherapy versus ASA + extended release dipyridamole in secondary stroke prevention. Therefore it is difficult to extrapolate the real benefit of pharmacological prevention strategies against atherothrombotic subtype for excellence in the TOAST classification subtype that is represented by the LAAS and also with regard to lacunar subtype as an expression of lipohyalinosis process which is a further aspect of atherosclerosis.

Keywords: Atherosclerosis, atherotrombotic strokes, prevention, drugs.

INTRODUCTION

Categorization of subtypes of ischemic stroke has had considerable study, but definitions are hard to formulate and their application for diagnosis in an individual patient is often problematic.

In the past, classifications have been based primarily on risk factor profiles, clinical features of the stroke, and the findings on brain imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]). Yet, clinical and brain imaging features overlap and are not specific for any particular subtype of ischemic stroke.

Determining the cause of stroke does influence choices for management.

In 1993 Adams *et al* [1] for the Trial of Org 10172 in Acute Stroke Treatment (TOAST), a placebo-controlled, randomized, blinded study of the low-molecular-weight heparinoid given to patients within 24 hours after stroke, developed a system for diagnosis of subtype of ischemic stroke that uses components of existing diagnostic schemes.

The TOAST classification system includes five categories:

1) Large-artery atherosclerosis, 2) Cardioembolism, 3) Small-artery occlusion (lacune), 4) Stroke of other determined etiology, and 5) Stroke of undetermined etiology.

Diagnoses are based on clinical features and on data collected by tests such as brain imaging (CT/MRI), cardiac imaging (echocardiography, etc.), duplex imaging of extracranial arteries, arteriography, and laboratory assessments for a prothrombotic state.

<u>Large-artery atherosclerosis</u>. These patients have clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis.

Clinical findings include those of cerebral cortical impairment (aphasia, neglect, restricted motor involvement, etc.) or brain stem or cerebellar dysfunction. A history of intermittent claudication, transient ischemic attacks (TIAs) in the same vascular territory, a carotid bruit, or diminished pulses helps support the clinical diagnosis. Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter on CT or MRI are considered to be of potential large-artery atherosclerotic origin. Supportive evidence by duplex imaging or arteriography of a stenosis of greater than 50% of an appropriate intracranial or

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extracranial artery is needed. Diagnostic studies should exclude potential sources of cardiogenic embolism. The diagnosis of stroke secondary to largeartery atherosclerosis cannot be made if duplex or arteriographic studies are normal or show only minimal changes.

Cardioembolism: This category includes patients with arterial occlusions presumably due to an embolus arising in the heart. Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism. At least one cardiac source for an embolus must be identified for a possible or probable diagnosis of cardioembolic stroke. Clinical and brain imaging findings are similar to those described for large-artery atherosclerosis.

Small-artery occlusion (lacune): This category includes patients whose strokes are often labeled as lacunar infarcts in other classifications. The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction.

The patient should also have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated

Acute stroke of other determined etiology: This category includes patients with rare causes of stroke, such as nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders.

Diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke.

Stroke of undetermined etiology: In several instances, the cause of a stroke cannot be determined with any degree of confidence. Some patients will have no likely etiology determined despite an extensive evaluation. In others, no cause is found but the evaluation is cursory.

This category also includes patients with two or more potential causes of stroke so that the physician is unable to make a final diagnosis.

Atherosclerosis is a complex disease, and our current understanding represents a synthesis of numerous hypotheses developed over the past century and a half [2]. Currently, the pathogenesis of atherosclerosis is thought to involve a sequence of biologic events within the intima of the vessel wall which includes vascular injury, monocyte recruitment and macrophage formation, lipid deposition, platelet degranulation and thrombosis, and vascular smooth muscle cell migration, proliferation and extracellular matrix synthesis [3].

On this basis drugs to prevent atherosclerosis complication such as thrombotic strokes, should be drugs able to prevent the accumulation of intravascular fat, reduce vascular proliferation, decease blood pressure levels with the resulting shear stress, reduce platelet aggregation, and possibly partially or totally reverse carotid plaques.

Lacunes are small areas inside the brain where poor blood flow has starved a group of cells of oxygen. Lack of oxygen causes the cells to die. When this happens, it is called a *stroke* or an *infarction*. A lacunar infarct is a tiny stroke that often causes no neurologic symptoms (these are also referred to as "silent" strokes). While many healthy people have silent lacunes, some association has been shown between having lacunes and having mild problems with thinking. When a person has a lot of lacunes, or when they occur in certain key parts of the brain, dementia may develop. When the dementia is due to many small strokes, it is called *vascular dementia* ("vascular" means "related to blood vessels," and blockage of the blood vessel causes strokes. Lacunar stroke is a cerebral infarct that occurs in the territory of a single perforator artery. The mechanism that underlies lacunar infarct is presumed to be the small vessel disease [The nature of this microangiopathy includes lipohyalinosis secondary to the effects of hypertension, microatheroma of the perforator artery and, less common, emboli from heart or large vessels.

Long term data suggest that up to 25% of patients with lacunar infarcts have a second stroke within 5 years (2). A Embolism of cardiac origin accounts for about one fifth of ischaemic strokes. Strokes due to cardioembolism are in general severe and prone to early recurrence. Non-valvular atrial fibrillation is the commonest cause of cardioembolic stroke. Despite its enormous preventive potential, continuous oral anticoagulation is prescribed for less than half of patients with atrial fibrillation who have risk factors for cardioembolism and no contraindications for anticoagulation. Alternatives to oral anticoagulation in this setting include safer and easier to use antithrombotic drugs and definitive treatment of atrial fibrillation. Available evidence does not support routine immediate anticoagulation of acute cardioembolic stroke.

Nevertheless, most trials did not evaluated stroke according stroke subtypes and on this basis few studies exist about the role of drug prevention in lacunar stroke or cardioembolic stroke, and only more recent studies considered stroke prevention in relation of clinical subtypes of stroke classified according TOAST subtype

ATHEROTHROMBOTIC STROKE PREVENTION

Blood Pressure Reduction

Blood pressure (BP) is the most important determinant of the risk of stroke. A small reduction in BP results in a substantial reduction of both ischemic and hemorrhagic stroke. Any of the commonly used antihypertensive drugs lower the incidence of stroke, with larger reductions in BP resulting in larger reductions in risk [12]. Experimental evidence has linked the renin-angiotensin system (RAS) to the development and progression of cerebrovascular disease. Inhibition of the RAS has beneficial cerebrovascular effects and may reduce the risk of stroke in a manner possibly independent from the alterations of BP. Treatment of hypertension significantly reduces the risk of stroke; however, it is unclear whether all antihypertensive agents are equivalent in this regard. Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce the risk of cardiovascular events, including stroke. Although attenuation of the renin-angiotensin system (RAS) is often credited with the blood pressure-independent effects of this class of agents, this hypothesis has not been confirmed with regard to the end point of stroke. The Captopril Prevention Project (CAPPP) [4] found fatal or nonfatal stroke to be 1.25 times more frequent in patients randomized to captopril than in those assigned to conventional therapy with diuretics, b blockers, or both.

Diabetes mellitus is a strong risk factor for cardiovascular and renal disease. HOPE study [5] investigated whether the angiotensin-converting-enzyme (ACE) inhibitor ramipril can lower these risks in patients with diabetes. In this trial 3577 people with diabetes included in the Heart Outcomes Prevention Evaluation study, aged 55 years or older, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking ACE inhibitors, were randomly assigned ramipril (10 mg/day) or placebo, and vitamin E or placebo, according to a two-by-two factorial design. Ramipril lowered the risk of the combined primary outcome by 25% (95% CI 12-36, p=0.0004), myocardial infarction by 22% (6-36), stroke by 33% (10-50), cardiovascular death by 37% (21-51), total mortality by 24% (8-37), revascularisation by 17% (2-30), and overt nephropathy by 24% (3-40, p=0.027). After adjustment for the changes in systolic (2.4 mm Hg) and diastolic (1.0 mm Hg) blood pressures, ramipril still lowered the risk of the combined primary outcome by 25% (12-36, p=0.0004). This trial showed that ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefit was greater than that attributable to the decrease in blood pressure. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.

An ACE inhibitor was effective compared with placebo in the PROGRESS trial [6]. The perindopril protection against recurrent stroke study (PROGRESS) was designed to determine the effects of a blood-pressure-lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack. 6105 individuals from 172 centres in Asia, Australasia, and Europe were randomly assigned active treatment (n=3051) or placebo (n=3054). Over 4 years of follow up, active treatment reduced blood pressure by 9/4 mm Hg. 307 (10%) individuals assigned active treatment suffered a stroke, compared with 420 (14%) assigned placebo (relative risk reduction 28% [95% CI 17-38], p<0.0001). Active treatment also reduced the risk of total major vascular events (26% [16-34]). There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (all p<0.01). Combination therapy with perindopril plus indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43% (30-54). Single-drug therapy reduced blood pressure by 5/3 mm Hg and produced no discernable reduction in the risk of stroke.

More recently in a substudy of PROGRESS trial [7] during a mean of 3.9 years of follow-up, active treatment reduced the absolute rates of ischemic stroke from 10% to 8% (relative risk reduction [RRR], 24%; 95% confidence interval [CI], 10 to 35) and the absolute rates of intracerebral hemorrhage from 2% to 1% (RRR, 50%; 95% CI, 26 to 67). The relative risk of any stroke during follow-up was reduced by 26% (95% CI, 12 to 38) among patients whose baseline cerebrovascular event was an ischemic stroke and by 49% (95% CI, 18 to 68) among those whose baseline event was an intracerebral hemorrhage. There was no evidence that treatment effects were modified by other drug therapies (antiplatelet or other antihypertensive agents), residual neurological signs, atrial fibrillation, or the time since the last cerebrovascular event. In this trial beneficial effects of a per-

indopril-based treatment regimen were observed for all stroke types and all major clinical subgroups studied. These data suggest that effective blood pressure-lowering therapy should be routinely considered for all patients with a history of cerebrovascular events.

Thus, it would appear that ACE inhibitor therapy and -- in ACE inhibitor-intolerant patients, angiotensin receptor blocker treatment -- is warranted if primary prevention is contemplated in a high-risk patient or secondary prevention is being considered in a patient already having sustained a cerebrovascular event.

Some studies in primary prevention of stroke, acute stroke, and secondary prevention show advantages for ARBs beyond controlling BP alone. In primary prevention, the LIFE randomized trial showed a significant difference in stroke rate in favor of losartan compared with atenolol despite similar reductions in BP. In acute stroke, the role of hypertension and its treatment remains controversial. AC-CESS, however, suggested that an ARB is safe in hypertensive acute stroke patients and may offer advantages independent from BP control

Angiotensin II receptor blockers (ARBs) selectively block the angiotensin II subtype I receptor, which results in a reflexive increase in levels of angiotensin II and unopposed activation of angiotensin II subtype 2 receptors. Some clinical trials even suggest that ACE inhibitors and angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs] exert cerebroprotective effects beyond BP lowering, but the evidence is controversial. Studies on specific protective actions of antihypertensive drugs are generally hampered by the fact that any treatment-related difference in BP may play a dominant role in the prevention of stroke. There are also indications that the protective potency of ARBs might be superior to that of ACE inhibitors, due to their differential activation of angiotensin II type 2 receptors, but the clinical relevance of this mechanism is unclear. In secondary stroke prevention, there are very few antihypertensive trials. These trials show that BP lowering is at least as successful as in primary prevention, but the absolute stroke risk is much higher.

Left ventricular hypertrophy (LVH) is a strong independent indicator of risk of cardiovascular morbidity and death. LIFE study [8] is a randomised, parallel-group trial in 9193 participants aged 55-80 years with essential hypertension (sitting blood pressure 160-200/95-115 mm Hg) and LVH ascertained by electrocardiography (ECG). Authors assigned participants once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1040 patients had a primary cardiovascular event (death, myocardial infarction, or stroke). Blood pressure fell by 30.2/16.6 (SD 18.5/10.1) and 29.1/16.8 mm Hg (19.2/10.1) in the losartan and atenolol groups, respectively. The primary composite endpoint occurred in 508 losartan (23.8 per 1000 patient-years) and 588 atenolol patients (27.9 per 1000 patient-years; relative risk 0.87, 95% CI 0.77-0.98, p=0.021). 204 losartan and 234 atenolol patients died from cardiovascular disease (0.89, 0.73-1.07, p=0.206); 232 and 309, respectively, had fatal or non-fatal stroke (0.75, 0.63-0.89, p=0.001); and myocardial infarction (non-fatal and fatal) occurred in 198 and 188, respectively (1.07, 0.88-1.31,

p=0.491). Losartan seems to confer benefits beyond reduction in blood pressure

As part of the LIFE study, in a double-masked, randomised, parallel-group trial [9] researchers assigned a group of 1195 patients with diabetes, hypertension, and signs of left-ventricular hypertrophy (LVH) on electrocardiograms losartan-based or atenolol-based treatment. Mean age of patients was 67 years (SD 7) and mean blood pressure 177/96 mm Hg (14/10) after placebo run-in. We followed up patients for at least 4 years (mean 4.7 years [1.1]). We used Cox regression analysis with baseline Framingham risk score and electrocardiogram-LVH as covariates to compare the effects of the drugs on the primary composite endpoint of cardiovascular morbidity and mortality (cardiovascular death, stroke, or myocardial infarction).: Mean blood pressure fell to 146/79 mm Hg (17/11) in losartan patients and 148/79 mm Hg (19/11) in atenolol patients. The primary endpoint occurred in 103 patients assigned losartan (n=586) and 139 assigned atenolol (n=609); relative risk 0.76 (95% CI 0.58-.98), p=0.031. 38 and 61 patients in the losartan and atenolol groups, respectively, died from cardiovascular disease; 0.63 (0.42-0.95), p=0.028. Mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively; 0.61 (0.45-0.84), p=0.002. On this basis Losartan was more effective than atenolol in reducing cardiovascular morbidity and mortality as well as mortality from all causes in patients with hypertension, diabetes, and LVH. Losartan seems to have benefits beyond blood pressure reduction

More recently, in MOSES study [10] total of 1405 well-defined, high-risk hypertensives with cerebral event during the last 24 months (proven by cerebral computed tomography scan or nuclear magnetic resonance) were randomized to eprosartan or nitrendipine (mean follow-up 2.5 years). Primary end point was the composite of total mortality and all cardiovascular and cerebrovascular events, including all recurrent events. Blood pressure was reduced to a comparable extent without any significant differences between the 2 groups during the whole study period (150.7/84 mm Hg and 152.0/87.2 mm Hg with eprosartan and nitrendipine therapy to 137.5/80.8 mm Hg and 136.0/80.2 mm Hg, respectively, confirmed by ambulatory blood pressure monitoring). Moreover, already after 3 months, normotensive mean values were achieved, and 75.5% reached values <140/90 mm Hg with the eprosartan regimen and 77.7% with the nitrendipine regimen. During follow-up, in total, 461 primary events occurred: 206 eprosartan and 255 nitrendipine (incidence density ratio [IDR], 0.79; 95% CI, 0.66 to 0.96; P=0.014). Cardiovascular events were: 77 eprosartan and 101 nitrendipine (IDR, 0.75; 95% CI, 0.55 to 1.02; P=0.06); cerebrovascular events: 102 eprosartan and134 nitrendipine (IDR, 0.75; 95% CI, 0.58 to 0.97; P=0.03). The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) study was the first to compare an angiotensin II type 1 receptor antagonist with a calcium antagonist in secondary stroke prevention. In these high-risk hypertensive stroke patients, an early normotensive and comparable blood pressure was achieved. The combined primary end point was significantly lower in the eprosartan group. The MOSES study showed that eprosartan prevented vascular events more effectively than nitrendipine, despite similar BP-lowering effects [11,13,15].

Statins in Thrombotic Stroke Prevention

Whereas dyslipidemia is a major risk factor for coronary heart disease (CHD), its role in the pathogenesis of ischemic stroke is less clear. Epidemiological studies have provided conflicting findings regarding the association of dyslipidemia with ischemic stroke. Overall, elevated LDL-C levels appear to increase the risk of ischemic stroke. Low HDL-C levels also appear to be associated with a greater risk whereas the importance of high triglyceride levels is less clear. The discordant results of observational studies might result from the heterogeneity of stroke, since dyslipidemia is less likely to play a major role in the pathogenesis of some ischemic stroke subtypes (e.g. lacunar and cardioembolic strokes) and elevated LDL-C levels might increase the risk of hemorrhagic stroke. In clinical trials, statins consistently reduced the risk of ischemic stroke in patients with or without CHD whereas the data on the effects of other lipid modifying drugs on stroke risk are limited [16].

Over the past decade, statins have been proved to significantly decrease coronary events in the primary and secondary prevention of coronary artery disease. Recent clinical trials have indicated that statins significantly reduce stroke risk in patients with vascular disease.

Throughout the usual LDL cholesterol range in Western populations, lower blood concentrations are associated with lower cardiovascular disease risk. In such populations, therefore, reducing LDL cholesterol may reduce the development of vascular disease, largely irrespective of initial cholesterol concentrations. In MRC/BHF Heart Protection Study [17] 536 UK adults (aged 40-80 years) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo (average non-study statin use: 17%). All-cause mortality was significantly reduced (1328 [12.9%] deaths among 10,269 allocated simvastatin versus 1507 [14.7%] among 10,267 allocated placebo; p=0.0003), due to a highly significant 18% (SE 5) proportional reduction in the coronary death rate (587 [5.7%] vs 707 [6.9%]; p=0.0005), a marginally significant reduction in other vascular deaths (194 [1.9%] vs 230 [2.2%]; p=0.07), and a non-significant reduction in non-vascular deaths (547 [5.3%] vs 570 [5.6%]; p=0.4). There were highly significant reductions of about one-quarter in the first event rate for non-fatal myocardial infarction or coronary death (898 [8.7%] vs 1212 [11.8%]; p<0.0001), for non-fatal or fatal stroke (444 [4.3%] vs 585 [5.7%]; p<0.0001), and for coronary or non-coronary revascularisation (939 [9.1%] vs 1205 [11.7%]; p<0.0001). For the first occurrence of any of these major vascular events, there was a definite 24% (SE 3; 95% CI 19-28) reduction in the event rate (2033 [19.8%] vs 2585 [25.2%] affected individuals; p<0.0001). During the first year the reduction in major vascular events was not significant, but subsequently it was highly significant during each separate year. More recent studies, such as the Treat to New Target (TNT) trial, have confirmed that statins reduced the risk of first-ever stroke in patients with coronary artery disease and in other high-risk populations - mainly diabetics in the Heart Protection Study (HPS) and Collaborative Atorvastatin Diabetes Study (CARDS) trial and hypertensives in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) -

even with a normal baseline blood cholesterol level, which argues for a global cardiovascular risk-based treatment strategy [18-20].

Recently, a meta-analysis [21] reported data from 18 686 individuals with diabetes (1466 with type 1 and 17,220 with type 2) in the context of a further 71,370 without diabetes in 14 randomised trials of statin therapy. Weighted estimates were obtained of effects on clinical outcomes per 1.0 mmol/L reduction in LDL cholesterol. During a mean follow-up of 4.3 years, there were 3247 major vascular events in people with diabetes. There was a 9% proportional reduction in all-cause mortality per mmol/L reduction in LDL cholesterol in participants with diabetes (rate ratio [RR] 0.91, 99% CI 0.82-1.01; p=0.02), which was similar to the 13% reduction in those without diabetes (0.87, 0.82-0.92; p<0.0001). This finding reflected a significant reduction in vascular mortality (0.87, 0.76-1.00; p=0.008) and no effect on non-vascular mortality (0.97, 0.82-1.16; p=0.7) in participants with diabetes. There was a significant 21% proportional reduction in major vascular events per mmol/L reduction in LDL cholesterol in people with diabetes (0.79, 0.72-0.86; p<0.0001), which was similar to the effect observed in those without diabetes (0.79, 0.76-0.82; p<0.0001). In diabetic participants there were reductions in myocardial infarction or coronary death (0.78, 0.69-0.87; p<0.0001), coronary revascularisation (0.75, 0.64-0.88; p<0.0001), and stroke (0.79, 0.67-0.93; p=0.0002). Among people with diabetes the proportional effects of statin therapy were similar irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics. After 5 years, 42 (95% CI 30-55) fewer people with diabetes had major vascular events per 1000 allocated statin therapy. On this basis statin therapy should be considered for all diabetic individuals who are at sufficiently high risk of vascular events.

Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischemic attack (TIA) remains to be established. In Stroke Prevention by Aggressive Reduction in Cholesterol levels (SPARCL) study [22]. Authors randomly assigned 4731 patients who had had a stroke or TIA within one to six months before study entry, had low-density lipoprotein (LDL) cholesterol levels of 100 to 190 mg per deciliter (2.6 to 4.9 mmol per liter), and had no known coronary heart disease to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first nonfatal or fatal stroke. The mean LDL cholesterol level during the trial was 73 mg per deciliter (1.9 mmol per liter) among patients receiving atorvastatin and 129 mg per deciliter (3.3 mmol per liter) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2 percent) receiving atorvastatin and 311 patients (13.1 percent) receiving placebo had a fatal or nonfatal stroke (5-year absolute reduction in risk, 2.2 percent; adjusted hazard ratio, 0.84; 95 percent confidence interval, 0.71 to 0.99; P=0.03; unadjusted P=0.05). The atorvastatin group had 218 ischemic strokes and 55 hemorrhagic strokes, whereas the placebo group had 274 ischemic strokes and 33 hemorrhagic strokes. The five-year absolute reduction in the risk of major cardiovascular events was 3.5 percent (hazard ratio, 0.80; 95 percent confi-

dence interval, 0.69 to 0.92; P=0.002). The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group (P=0.98), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin. So In patients with recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke

Furthermore, a substudy of SPARCL study [23] tested the hypothesis that the benefit of treatment varies according to index event stroke subtype. Authors showed for subjects randomized to atorvastatin versus placebo, a primary end point occurred in 13.1% versus 18.6% of those classified as having large vessel disease (LVD, 15.8% of 4,731 participants), in 13.1% versus 15.5% of those with small vessel disease (SVD, 29.8%), in 11.2% versus 12.7% of those with ischemic stroke of unknown cause (21.5%), in 7.6% versus 8.8% of those with TIA (30.9%), and in 22.2% versus 8.3% of those with hemorrhagic stroke (HS, 2%) at baseline. There was no difference in the efficacy of treatment for either the primary end point (LVD hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.49 to 1.02, TIA HR 0.81, CI 0.57 to 1.17, SVD HR 0.85, CI 0.64 to 1.12, unknown cause HR 0.87, CI 0.61 to 1.24, HS HR 3.24, CI 1.01 to 10.4; P for heterogeneity=0.421), or MCVEs (P for heterogeneity=0.360) based on subtype of the index event. As compared to subjects with LVD strokes, those with SVD had similar MCVE rates (19.2% versus 18.5% over the course of the trial), and similar overall reductions in stroke and MCVEs. This study showed that Atorvastatin 80 mg/d is similarly efficacious in preventing strokes and other cardiovascular events, irrespective of baseline ischemic stroke subtype.

A recent review [24] considered the evidence showing that statins can prevent first or recurrent stroke or improve its outcome in subjects at moderate or high risk for cardiovascular disease (CVD). Data are reviewed according to trial design (observational or prospective) and baseline CVD risk. Two (ASCOT, CARDS) out of five primary CVD prevention statin trials showed a considerable reduction in stroke rates. In two (MIRACL and PROVE IT) out of five acute coronary syndrome trials, the prevention of first stroke was significant. Most secondary prevention trials (4S, CARE, LIPID, HPS, GREACE and TNT) showed a beneficial effect of statins in stroke prevention. Finally, SPARCL, the only secondary stroke prevention trial in subjects without overt coronary heart disease (CHD), showed a significant reduction in total and ischaemic (fatal and nonfatal) stroke rate, although a small but significant increase in nonfatal haemorrhagic stroke was noted. There was also a significant reduction in CHD-related events. The possible mechanisms responsible for statin-associated stroke prevention are discussed. The evidence suggests the need to consider early and long-term statin treatment (with substantial low-density lipoprotein cholesterol reduction) in all patients at high risk of any type of major vascular event, without discriminating CHD from stroke. Thus, statins may be beneficial to both the heart and the brain.

No study of primary prevention showed stroke reduction in patients treated with statins unless the publication of Jupiter Study [25] increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment. This study randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes

ANTIPLATELETS IN THROMBOTIC STROKE PREVENTION

The importance of antiplatelet agents for both the prevention and treatment of ischemic disease was a concept that developed as the consequence of some research that showed: (a) the contribution of platelets to both cardiac [26] and carotid disease, [27]; (b) development of reproducible assays to quantify platelet activation [28].

The recognition that all platelet stimuli share a final common pathway that is dependent on the surface glycoprotein IIb/IIIa (fibrinogen) receptor has resulted in the development of various agents which block this receptor and are currently the focus for clinical trials. The major antiplatelet therapies used for stroke prevention include aspirin, clopidogrel, and dipyridamole Clopidogrel and dipyridamole have been studied alone and in combination with aspirin, with variable results.

-Aspirin

The antiplatelet efficacy of aspirin in preventing secondary stroke was established by three studies conducted in the late 1980s and early 1990s: the Swedish Aspirin Low-dose Trial (SALT) [29]. Trials have demonstrated that aspirin—even in doses as low as 30 mg/day—reduces secondary stroke, MI, or vascular death in patients with the placebo-controlled SALT study showed that aspirin at 75 mg/day reduced the rate of recurrent stroke by 18%,7 whereas the Dutch TIA and UK-TIA studies showed that the efficacy of aspirin was similar across a dose range from 30 to 1,200 mg/day;8,9 however, higher doses were associated with increased risk for gastrointestinal and bleeding complications [30]. Two subsequent studies, the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) [31] and the Warfarin versus Aspirin in Recurrent Stroke Prevention Study (WARSS) [32] showed that aspirin was preferable to warfarin in preventing secondary stroke in patients with initial non-cardioembolic stroke.

In 2002, the Antiplatelet Trialists' Collaboration (APTC) [33] conducted a meta-analysis of 197 randomized controlled trials and 90 head-to-head comparator trials of antiplatelet agents. Results showed a 23% risk reduction in combined vascular events (MI, stroke, and vascular death) with aspirin.

-Dipyridamole

As a single agent, dipyridamole has been evaluated for prevention of stroke and other vascular events. The Antiplatelet Trialists' Collaboration APTC) demonstrated that dipyridamole showed 16% odds reduction for stroke, MI, or vascular death versus placebo in a meta-analysis of 15 trials. Additionally, aspirin plus extended-release dipyridamole demonstrated 30% odds reduction for stroke, MI, or vascular death versus placebo in a meta-analysis of 46 trials.

The Second European Stroke Prevention Study (ESPS-2) [34] is one of two studies that evaluated aspirin plus extended-release dipyridamole for secondary stroke prevention. In ESPS-2, 6,602 patients who had a recent ischemic stroke or TIA were enrolled in a multicenter, double-blind, placebo-controlled trial that randomly assigned them to one of four treatment groups: aspirin (25 mg, twice daily), extended-release dipyridamole (200 mg, twice daily), aspirin plus extended-release dipyridamole, or placebo. Both agents given as monotherapy demonstrated an independent and statistically significant reduction in recurrent stroke (18% and 16%, respectively). However, the combination of aspirin plus extended-release dipyridamole reduced stroke recurrence by 23% compared with aspirin alone and by 37% compared with placebo. Results from ESPS-2 indicate that aspirin plus extended-release dipyridamole has significant benefit over aspirin alone for prevention of second stroke.

Although 4 earlier studies using an immediate-release dipyridamole formulation did not show a benefit of combination therapy with aspirin plus dipyridamole over aspirin alone, ESPS-2 and ESPRIT provided consistent evidence of benefit with the combination. The ESPRIT Study Group included a meta-analysis of six comparative trials, including a total of 3,888 patients taking aspirin plus dipyridamole and 3,907 taking aspirin alone; this analysis demonstrated an overall RRR for combination therapy versus aspirin of 18% (95% CI, 0.74–0.91) for the composite outcome of vascular death, nonfatal stroke, or nonfatal MI.

Patients with transient ischaemic attacks (TIA) and minor ischaemic strokes are at risk of serious vascular events (death

from all vascular causes, non-fatal stroke, or non-fatal myocardial infarction). Their risk of vascular events lies between 4 and 11 percent per year. Aspirin only, in a daily dose of 30 mg or more, offers only modest protection in such patients: it reduces the incidence of major vascular events by 13 percent. In a single trial, adding dipyridamole (an alternative antiplatelet agent) to aspirin was associated with a 22 percent reduction in the risk of major vascular events compared with aspirin alone. However, a systematic review of all trials of antiplatelet agents by the Antithrombotic Trialists' Collaboration showed that, in high risk patients, there was virtually no difference between the aspirin-dipyridamole combination and aspirin alone [34].

-Aspirin+dipyridamole

Approximately 25% of strokes are recurrent. Antiplatelet therapy is indicated for the prevention of recurrent stroke in patients with a history of noncardioembolic minor stroke or transient ischemic attack (TIA). Although clinicians may choose acetylsalicylic acid (ASA) as first-line therapy for secondary prevention, clinical guidelines and evidence from trials suggest that ASA may not be the most effective strategy. A recent review discussed [35] results from clinical trials that have compared the efficacy of ASA monotherapy versus ASA + extended release dipyridamole in secondary stroke prevention. Relevant randomized experimental and clinical studies in patients with a history of minor stroke or TIA of non-cardioembolic etiology were identified using a search of the US National Library of Medicine database, with no limits on publication dates. The primary search terms used were secondary stroke prevention, antiplatelet therapy, acetylsalicylic acid, ASA, aspirin, aspirin + extended-release dipyridamole, and combination therapy. Early trials of dipyridamole monotherapy or ASA + dipyridamole involved small numbers of patients and found no significant treatment differences. Two major trials that compared ASA monotherapy, dipyridamole monotherapy, and ASA + dipyridamole were identified: the Second European Stroke Prevention Study (ESPS-2) and the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT). Efficacy measurements in ESPS-2 found that stroke relative risk reductions were 18% (P = 0.013), 16% (P = 0.039), and 37% (P < 0.001), respectively, compared with placebo for a relative risk reduction of 23.1% (P = 0.006) favoring the combination over ASA monotherapy. In ESPRIT, patients who received ASA + dipyridamole had a 20% relative risk reduction versus ASA monotherapy for the composite end point of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction, or major bleeding complications. In ESPS-2, headache was 5% more common with dual therapy compared with ASA monotherapy. ESPRIT found that combination treatment was not associated with a higher complication rate than ASA monotherapy, but that the rate of withdrawal due to adverse events was higher in the group that received the combination. Based on the results from these 2 large, randomized trials, ASA + dipyridamole was more effective than ASA monotherapy as first-line therapy for secondary stroke prevention in these patients with a history of minor stroke or TIA of noncardioembolic etiology.

- Clopidogrel

Clopidogrel has been evaluated as monotherapy and in combination with aspirin with regard to its efficacy in preventing secondary stroke. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study [36] three groups with a recent history of symptomatic cardiovascular disease (stroke, MI, or peripheral arterial disease were randomized to clopidogrel 75 mg/day or aspirin 325 mg/day to evaluate the composite outcome of ischemic stroke, MI, or vascular death as well as the relative safety of each drug. Clopidogrel was slightly more effective than aspirin in reducing cumulative risk of stroke, MI, or vascular death in patients with symptomatic atherosclerotic vascular disease (8.7% RRR; p = 0.043). However, clopidogrel did not demonstrate superiority versus aspirin in preventing recurrent stroke among patients with a history of stroke (8% RRR; p = 0.28), although the study was powered only to demonstrate significant differences in the overall population (n = 19,185). No major safety differences were observed between clopidogrel and aspirin, although the rate of serious hemorrhage was slightly higher in the aspirin group (1.55 versus 1.38%).1

In the Match Study [36] on the basis of previous trial results (including CAPRIE) in patients with cardiac and cerebrovascular disease, investigators sought to determine whether the addition of aspirin to clopidogrel would further reduce the risk of recurrent ischemic attacks in high-risk patients after recent ischemic stroke or TIA. Patients were included if they had a stroke or TIA within the previous 3 months and 1 or more of 5 additional high-risk factors within the previous 3 years: previous stroke, previous MI, angina, diabetes, or symptomatic PAD. The results of MATCH showed no significant difference between clopidogrel alone and clopidogrel plus aspirin in reducing risk of vascular events after stroke or TIA. Although there was an absolute risk reduction of 1% and a relative risk reduction of 6.4% favoring clopidogrel plus aspirin, the between-group differences were not statistically significant.

Furthermore in the CHARISMA Study (37) a prospective, multicenter, randomized, double-blind, placebo-controlled study, 15,603 patients were randomized to receive clopidogrel 75 mg/day plus lowdose aspirin (75–162 mg/day) or placebo plus low-dose aspirin, with median follow-up of 28 months. All patients were 45 years of age or older and had either multiple atherothrombotic risk factors or a history of documented coronary disease, cerebrovascular disease, or symptomatic PAD. Among all patients enrolled in CHARISMA, there was no statistically significant difference between treatment groups in the rates of occurrence of the primary efficacy endpoint (clopidogrel plus aspirin 6.8%, aspirin alone 7.3%; RR 0.93, 95% CI 0.83–1.05; p = 0.22). Patients with multiple risk factors but no clearly established vascular disease (primary prevention cohort) did not benefit from the addition of clopidogrel to aspirin; instead, adjunctive clopidogrel was associated with a nonsignificant 20% relative increase in the rate of primary events, as well as an excess in cardiovascular mortality (3.9 versus 2.2%, p = 0.01). In patients with established cardiovascular disease (the secondary prevention cohort), the addition of clopidogrel resulted in a marginally significant clinical benefit regarding

the primary endpoint (6.9 versus 7.9% with placebo; RR 0.88; 95% CI, 0.77–0.998; p = 0.046). Results of the safety analysis showed a nonsignificant increase in the primary safety endpoint of severe bleeding with clopidogrel; the rate of moderate bleeding (that required transfusion) was 2.1% in the clopidogrel group and 1.3% in the placebo group (RR, 1.62; 95% CI, 1.27–2.08; p<0.001).

Previous analyses have shown sex-based differences in response to several antiplatelet medications. Little is known about the efficacy and safety of clopidogrel in women and men. A study [41] (performed a meta-analysis of all blinded randomized clinical trials comparing clopidogrel and placebo (CURE [Clopidogrel in Unstable Angina to Prevent Recurrent Events], CREDO [Clopidogrel for the Reduction of Events During Observation], CLARITY-TIMI 28 [Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction COMMIT [Clopidogrel and Metoprolol in Myocardial Infarction Trial], and CHARISMA [Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance] trials), involving a total of 79,613 patients, of whom 30% were women. The relative efficacy and safety of clopidogrel at reducing cardiovascular events (cardiovascular death, myocardial infarction [MI], or stroke) in women and men was estimated using random-effects modeling [38,39]. Overall, clopidogrel was associated with a highly significant 14% proportional reduction in the risk of cardiovascular events (odds ratio [OR]: 0.86; 95% confidence interval [CI]: 0.80 to 0.93), with no significant differences in treatment effect between women and men. Among the 23,533 women enrolled, there were fewer cardiovascular events in the clopidogrel group compared with the placebo group (11.0% vs. 11.8%; OR: 0.93; 95% CI: 0.86 to 1.01). In women the risk reduction with clopidogrel seemed to be greatest for MI (OR: 0.81; 95% CI: 0.70 to 0.93), with the effects on stroke (OR: 0.91; 95% CI: 0.69 to 1.21) or total death (OR: 0.99; 95% CI: 0.90 to 1.08) not statistically significant. Among the 56,091 men enrolled, there were fewer cardiovascular events in those receiving clopidogrel compared with placebo (7.8% vs. 9.0%; OR: 0.84; 95% CI: 0.78 to 0.91), and the risk reduction was significant for MI (OR: 0.83; 95% CI: 0.76 to 0.92), stroke (OR: 0.83; 95% CI: 0.71 to 0.96), and total death (OR: 0.91; 95% CI: 0.84 to 0.97). Clopidogrel increased the risk of major bleeding in both women (OR: 1.43; 95% CI: 1.15 to 1.79) and men (OR: 1.22; 95% CI: 1.05 to 1.42).

Although the most widely studied and prescribed antiplatelet agent for the prevention of stroke and other serious vascular events among high vascular risk patients is aspirin. Aspirin inhibits platelet activation by inhibiting platelet cyclooxygenase and thromboxane production, and reduces the odds of a serious vascular event by about a quarter. The thienopyridines (ticlopidine and clopidogrel) inhibit platelet activation by a different mechanism to aspirin (blocking the ADP receptor on platelets), and so may be more effective than aspirin. A very recent review [40] was to determine the effectiveness and safety of thienopyridine derivatives (ticlopidine and clopidogrel) versus aspirin for the prevention of serious vascular events (stroke, myocardial infarction (MI) or vascular death) in patients at high risk of such events, and specifically in patients with a previous TIA or ischaemic stroke. Authors earched the Cochrane Stroke

Group trials register (most recent search: March 1999) and the Antithrombotic Trialists' database. All unconfounded, double blind, randomised trials directly comparing ticlopidine or clopidogrel with aspirin in high vascular risk patients. Four trials involving a total of 22,656 high vascular risk patients were included. The trials were of high quality and comparable. Aspirin was compared with ticlopidine in three trials (3471 patients) and with clopidogrel in one trial (19,185 patients). Allocation to a thienopyridine was associated with a modest, yet statistically significant, reduction in the odds of a serious vascular event (12. 0% vs 13.0%; OR: 0.91, 95% CI: 0.84 to 0.98; 2p = 0.01), corresponding to the avoidance of 11 (95% CI: 2 to 19) serious vascular events per 1000 patients treated for about two years. There was also a reduction in stroke (5.7% vs 6.4%; OR: 0.88, 95% CI: 0.79 to 0.98; 7 [95% CI: 1 to 13] strokes avoided per 1000 patients treated for two years). Compared with aspirin, thienopyridines produced a significant reduction in the odds of gastrointestinal haemorrhage and other upper gastrointestinal upset, but a significant increase in the odds of skin rash and of diarrhoea. However, the increased odds of skin rash and diarrhoea were greater for ticlopidine than for clopidogrel. Allocation to ticlopidine, but not clopidogrel, was associated with a significant increase in the odds of neutropenia (2.3% vs 0.8%; OR: 2.7, 95% CI: 1.5 to 4.8). In the subset of patients with TIA/ischaemic stroke, the results were similar to those for all patients combined. However, since these patients are at particularly high risk of stroke, allocation to a thienopyridine was associated with a larger absolute reduction in stroke (10.4% vs 12.0%; OR: 0.86, 95% CI: 0.75 to 0.97; 16 [95% CI: 3 to 28] strokes avoided per 1000 patients treated for two years). On this basis the available randomised evidence shows that the thienopyridine derivatives are modestly but significantly more effective than aspirin in preventing serious vascular events in patients at high risk (and specifically in TIA/ischaemic stroke patients), but there is uncertainty about the size of the additional benefit.

LACUNAR STROKE PREVENTION

Lacunar strokes can be defined as strokes in which a small branch of a larger blood vessel causes the stroke. Because of the way blood vessels divide in the brain, lacunar strokes tend to occur in areas located away from the surface of the brain, where many of the smaller branches of large blood vessels are located.

As most brain areas perform a limited set of brain functions, the collection of symptoms of a given lacunar stroke usually falls within one of five categories of symptoms known to be caused by damage in these areas.

Lacunar strokes can be defined as strokes of any cause, in which the blood vessel that causes the stroke is a small branch of a larger blood vessel. Lacunar strokes are typically located in "deep areas" of the brain (i.e., away from the surface of the brain), where many of the smaller branches of large blood vessels are located. Lacunar infarcts are small (0.2 to 15 mm3) noncortical infarcts caused by occlusion of a single penetrating branch of a large cerebral artery. These branches arise at acute angles from the large arteries of the circle of Willis, stem of the middle cerebral artery (MCA), or the basilar artery.

Causes of Lacunar Stroke Diabetes mellitus is well recognized as a risk factor for development of small vessel disease throughout the body, including the penetrating arteries.

Lacunes are caused by occlusion of a single deep penetrating artery. The deep penetrating arteries are small nonbranching end arteries (usually smaller than 500 micrometers in diameter), which arise directly from much larger arteries (eg, the middle cerebral artery, anterior choroidal artery, anterior cerebral artery, posterior cerebral artery, posterior communicating artery, cerebellar arteries, basilar artery).

The accumulation of blood from a cerebral hemorrhage can also press on parts of the brain and cause damage. A subarachnoid hemorrhage is caused by the rupture of a blood vessel that is usually located between the outside of the brain and the inside of the skull. The blood vessel at the point of rupture is often previously abnormal, such as from an aneurysm (an abnormal ballooning out of the wall of the vessel).

Initially, lipohyalinosis was thought to be the predominant small vessel pathology of lacunes; however, microatheroma now is thought to be the most common mechanism of arterial occlusion (or stenosis). Occasionally, atheroma in the parent artery blocks the orifice of the penetrating artery (luminal atheroma), or atheroma involves the origin of the penetrating artery (junctional atheroma

Nevertheless, The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial is the largest secondary stroke prevention study compared extended-release dipyridamole plus aspirin (eDYP-ASA) versus clopidogrel and telmisartan versus antihypertensive regimens excluding angiotensin receptor blockers (ARBs). No statistical differences were found in either arm for the primary outcome of fatal or nonfatal stroke or prespecified secondary end points. eDYP-ASA also was associated with increases in major hemorrhagic events but not with statistical increases in combined rates of stroke recurrence or hemorrhage. The resulting interpretation that eDYP-ASA is "not noninferior" has raised questions about how to interpret noninferiority analyses

Most studies addressed to stroke prevention not evaluated stroke subtypes and on this basis they give informations mainly about atherosclerotic stroke prevention

Profess Study [42] compared the efficacy and safety of two antiplatelet regimens--aspirin plus extended-release dipyridamole (ASA-ERDP) versus clopidogrel.

In this double-blind, 2-by-2 factorial trial, we randomly assigned patients to receive 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily or to receive 75 mg of clopidogrel daily. The primary outcome was first recurrence of stroke. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. In this trial stroke subtype was classified according TOAST Classification in five subtypes: LAAS, lacunar, CEI, ODE and UDE.

A total of 20,332 patients were followed for a mean of 2.5 years. Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio, 1.01; 95% confidence interval [CI], 0.92 to 1.11). The secondary outcome occurred in 1333 patients (13.1%) in each group (hazard ratio for ASA-ERDP,

0.99; 95% CI, 0.92 to 1.07). There were more major hemorrhagic events among ASA-ERDP recipients (419 [4.1%]) than among clopidogrel recipients (365 [3.6%]) (hazard ratio, 1.15; 95% CI, 1.00 to 1.32), including intracranial hemorrhage (hazard ratio, 1.42; 95% CI, 1.11 to 1.83). The net risk of recurrent stroke or major hemorrhagic event was similar in the two groups (1194 ASA-ERDP recipients [11.7%], vs. 1156 clopidogrel recipients [11.4%]; hazard ratio, 1.03; 95% CI, 0.95 to 1.11). The trial did not meet the predefined criteria for noninferiority but showed similar rates of recurrent stroke with ASA-ERDP and with clopidogrel. There is no evidence that either of the two treatments was superior to the other in the prevention of recurrent stroke.

In a substudy of this trial [42] patients who had had an ischaemic stroke were randomly assigned in a two by two factorial design to receive either 25 mg aspirin (ASA) and 200 mg extended-release dipyridamole (ER-DP) twice a day or 75 mg clopidogrel once a day, and either 80 mg telmisartan or placebo once per day. The predefined endpoints for this substudy were disability after a recurrent stroke, assessed with the modified Rankin scale (mRS) and Barthel index at 3 months, and cognitive function, assessed with the mini-mental state examination (MMSE) score at 4 weeks after randomisation and at the penultimate visit. Analysis was by intention to treat. 20,332 patients (mean age 66 years) were randomised and followed-up for a median of 2.4 years. Recurrent strokes occurred in 916 (9%) patients randomly assigned to ASA with ER-DP and 898 (9%) patients randomly assigned to clopidogrel; 880 (9%) patients randomly assigned to telmisartan and 934 (9%) patients given placebo had recurrent strokes. mRS scores were not statistically different in patients with recurrent stroke who were treated with ASA and ER-DP versus clopidogrel (p=0.38), or with telmisartan versus placebo (p=0.61). There was no significant difference in the proportion of patients with recurrent stroke with a good outcome, as measured with the Barthel index, across all treatment groups. Additionally, there was no significant difference in the median MMSE scores, the percentage of patients with an MMSE score of 24 points or less, the percentage of patients with a drop in MMSE score of 3 points or more between 1 month and the penultimate visit, and the number of patients with dementia among the treatment groups. There were no significant differences in the proportion of patients with cognitive impairment or dementia among the treatment groups. Disability due to recurrent stroke and cognitive decline in patients with ischaemic stroke were not different between the two antiplatelet regimens and were not affected by the preventive use of telmisartan

The PRoFESS trial showed that, among patients with a noncardioembolic ischemic stroke, the risks of recurrent stroke or the composite of stroke, myocardial infarction, or death from vascular causes are similar with aspirin plus extendedrelease dipyridamole and with clopidogrel. Despite the increased risk of hemorrhagic strokes with aspirin plus extended-release dipyridamole as compared with clopidogrel, the net benefit with regard to the risk of recurrent stroke or major hemorrhagic event was similar in the two groups. Furthermore, there was no significant difference between the two treatments in the risk of fatal or disabling strokes

Martin-Sanchez *et al* [43] conducted an observational study using data from the Stroke Unit Data Bank from con-

secutive patients with cerebral infarction. Variables analyzed: demographic data, cardiovascular risk factors, treatment with statins at stroke onset, stroke severity, stroke subtype, in-hospital complications, length of stay, and functional status at discharge (modified Rankin Scale).

A total of 2742 patients were included, 1539 were men. Mean age was 69.17 years (SD 12.19). Of these, 281 patients (10.2%) were receiving statins when admitted. The logistic regression analyses showed that previous treatment with statins was an independent predictor for better outcome at discharge among all strokes (OR, 2.08; 95% CI, 1.39 to 3.1) as well as for the atherothrombotic (OR, 2.79; 95% CI, 1.33 to 5.84) and lacunar strokes (OR, 2.28; 95% CI, 1.15 to 4.52) after adjustment for demographic data, risk factors, previous treatments, stroke subtypes, stroke severity, in-hospital complications and length of stay. This benefit was not observed either in cardioembolic or in other etiology strokes. On this basis authors concluded that previous treatment with statins is an independent factor associated with good outcomes in patients with ischaemic stroke. Atherothrombotic and small vessel strokes show the greatest benefit

The SPARCL study [23] included patients without differentiating stroke subtype, including a high proportion of lacunar strokes, whereas the greatest benefit is obtained in atherothrombotic strokes. In addition, this study included patients with intracerebral hemorrhage, in which the effects of statins are controversial. Current recommendations include the administration of statins in patients with stroke or TIA with high cholesterol levels reaching levels of LDL-cholesterol <100 mg/dL (or <70 mg/dL in those with high risk) and in patients with atherothrombotic stroke or TIA with normal cholesterol levels

CARDIOEMBOLIC STROKE PREVENTION

Cardioembolic stroke accounts for approximately 15% of all strokes and is thought to be one of the more preventable types of strokes. Features that have been reported to support cardioembolism as a mechanism for ischemic stroke have included documented cardiac source of embolism, maximal neurologic deficit at onset, multiple cerebrovascular territories involved, enhanced tendency toward hemorrhagic transformation, enhanced risk of syncope or seizure associated with presentation, and lower likelihood of premonitory transient ischemic attacks. Features that tend to make cardioembolic stroke less likely include significant cerebral atherosclerosis, stepwise progression of the neurologic deficit within a finite period of time, vascular distribution such as entire internal carotid artery territory with combined middle cerebral artery and anterior cerebral artery involvement or watershed distribution, and premonitory transient ischemic attacks. A number of cardiac conditions can promote thromboembolism, and there is risk stratification reflective of the specific condition or coexistent conditions. Anticoagulant therapy generally has been found to be the most effective means of preventing cardiogenic brain embolism, but the intensity of anticoagulation needs to be optimized to reflect the risk-to-benefit ratio for the particular patient.

Embolic stroke implies a clot originating from one site that then promotes occlusive cerebral artery disease. The most common sources of cerebral embolism include the ca-

rotid arteries, specific cardiac disease, and atheromata of the aortic arch. It is reported that cardioembolic stroke accounts for approximately 15% of all strokes [44].

In Patients with AF, stroke is the most serious and life threatening complication [45,46]. There is a fivefold increased risk of stroke and thromboembolism with AF when compared to sinus rhythm [46] Furthermore, AF accounts for up to one fourth of all cerebrovascular events and AF-related strokes are more frequently associated with persistent and severe disabilities compared to ischemic events attributable to vascular disease [47,48].

Treatment with vitamin K-antagonists (VKA) substantially reduces the long-term complications associated with cardioembolism [49,50] but despite its proved efficiacy, this option continues to be underused, even in eligible and particulary

The risk of stroke varies considerably among the group of patients with AF. Prior stroke/TIA, hypertension, advancing age, and diabetes are consistent independent predictors of stroke in patients with atrial fibrillation.

There are many ways of classifying stroke risk: In a recent comparison of 12 stroke risk stratification schemes in patients with nonvalvular AF, the Stroke Risk in Atrial Fibrillation Working Group [51] identified 7 schemes that were based directly on eventrate analyses (largely been identified from non-OAC arms of clinical trials, and occasionally from cohort studies), whereas 5 resulted from expert panel consensus.

The most frequently included features were prior stroke/TIA (in 100% of schemes), patient age, hypertension and diabetes mellitus. Two useful resources stand out in clinical practice: the Framingham risk score, derived by Wang and colleagues [52], and the CHADS2 score published by Gage *et al* [53]. Both use a five step calculation to predict the risk for stroke in patients with AF: the former considers age, gender, systolic blood pressure, diabetes, and prior stroke or TIA, each category assigned with different gradings, and predicts a 5-year stroke risk in the absence of anticoagulation. Concerning the latter, the *C* stands for recent congestive heart failure, the *H* for hypertension, the *A* for age 75 or older, the *D* for diabetes, and the *S* for prior stroke or TIA. Each category is assigned one point except stroke or TIA, which gets two due to its high association with subsequent stroke. A high score on this index correlates with a raised annual stroke rate.

The absence of a regular contraction of the fibrillating atria leads to an increase of atrial pressure and dilatation, which together with hemoconcentration [54,55], endothelial dysfunction, and a prothrombotic state is the prerequisite for thrombus formation [56]. Echocardiography and autopsy studies have shown that more than 90% of all thrombi in patients with AF originating in the left atrium, form in the left atrial appendage (LAA) [57-60]. The pathogenesis of LAA thrombus formation has not been fully elucidated, but the precondition is likely to result from a hypercoagulable state explained by Virchow's triad of thrombogenesis – ie, abnormal changes of the vessel wall, blood flow, and blood constituents [61,62]. Nowadays, this is translated as follows: "Abnormal blood flow" means reduced flow up to stasis due

to the lack of contraction in combination with the increase of volume and size of the LAA, "abnormal blood constituents" are represented by activated coagulation factors and platelets, and "abnormal vessel wall" in this case means structural and functional changes of endothelial or endocardial cells

Treatment of stroke depends on the etiology of the original infarct. Evidence is strong that the optimal prevention therapy for cardioembolic stroke is anticoagulation with warfarin. The European Atrial Fibrillation Trial found that warfarin reduces the risk for second strokes in patients with atrial fibrillation by two-thirds and is superior to antiplatelet agents for preventing cardioembolic strokes [62]. Warfarin increases the risk of extracranial bleeding, but not severely enough to negate the benefit of reducing stroke death and disability. The target international normalized ratio (INR) for non-valvular atrial fibrillation is generally two to three, although this may be higher for certain prosthetic valves.

The use of adjusted-dose warfarin for stroke patients with atrial fibrillation who do not have significant bleeding risk has been advocated in several professional guidelines, [63-65] and the benefit has been demonstrated in clinical practice. However, not all strokes in patients with atrial fibrillation are cardioembolic in origin [66,67] and some evidence suggests that warfarin may not prevent noncardioembolic strokes [68].

In 2001 Evans *et al* [69] conducted a prospective cohort study was to determine whether the subtype of the presenting stroke influenced the effectiveness of long-term anticoagulation in preventing recurrence. In relationship of Secondary Strokes by Initial Stroke Subtype, Anticoagulation was most effective in reducing recurrent stroke in patients assigned a cardioembolic stroke initially (10.7% for aspirin versus 3.3% for warfarin, *P*_0.01). This was almost entirely due to a reduction in cardioembolic recurrences (8.4% versus 1.9%, *P*_0.01), with no differences in the rate of recurrence resulting from other causes. Patients whose initial stroke was classified as undetermined or lacunar showed no significant differences between groups in the rate of stroke recurrence, either overall or between subtypes of second stroke. However, patients presenting with lacunar stroke were more likely to have a lacunar recurrence than those in whom the first stroke was cardioembolic, regardless of treatment regimen. This prospective cohort study confirms the superiority of warfarin over aspirin in preventing cardioembolic recurrence in stroke patients with atrial fibrillation comparable to that seen in randomized controlled trials. However, long-term anticoagulation did not reduce stroke recurrence in patients presenting with lacunar strokes despite being in atrial fibrillation. prevalence of both atrial fibrillation16 and small-vessel disease increases with age and because there is a risk that some patients may be exposed to the risks of anticoagulation and intracerebral hemorrhage without necessarily benefiting from the treatment. Although it is widely recognized that stroke is a heterogeneous condition with diverse origin, little attention has been paid to stroke subtyping until recently. The importance of stroke subtype and targeting of secondary prevention to the individual who has had a relevant stroke rather than any stroke has been recognized in patients with carotid stenosis

A series of clinical trials have shown the remarkable efficacy of anticoagulation with warfarin compared to placebo in reducing stroke risk in patients with AF (Copenhagen Atrial Fibrillation Aspirin and Anticoagulation, AFASAK [70]; Stroke Prevention in Atrial Fibrillation, SPAF [Stroke 71]; Boston Area Anticoagulation Trial for Atrial Fibrillation, BAATAF [72]; Canadian Atrial Fibrillation Anticoagulation, CAFA [73]; and Stroke Prevention in Nonrheumatic Atrial Fibrillation, SPINAF [74]. In 2007, Hart and colleagues published a meta analysis [75] of the afore mentioned 5 primary prevention trials plus one study of secondary prevention [76] and demonstrated a 62% relative risk reduction for stroke in patients anticoagulated with vitamin K-antagonists (warfarin).

DISCUSSION

Stroke is the most common life-threatening neurological disorder. Based on limited acute therapies, clinicians have opted to focus on preventive strategies to limit its recurrence. Targets for prevention include modifiable risk factors such as hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, obesity, alcohol use, and physical inactivity among others. Most of these prevention strategies may appear to be directed mainly towards the prevention of thrombotic stroke,

Ischemic stroke prevention has been shown to be effective in several scenarios: primary prevention, prevention after a transient ischemic attack (TIA), and secondary prevention. Dietary, lifestyle, and risk factor modification; use of aspirin, ticlopidine, clopidogrel, and warfarin; and carotid endarterectomy all have a role in stroke prevention in selected persons. Annual risk assessment, screening, and intervention should be part of a concerted national effort to reduce the incidence of the third leading cause of death and the number one cause of adult disability in the United States.

Medical treatments with clear evidence of benefit in terms of stroke prevention include:

- Lowering blood pressure (BP) after all types of stroke or TIA

- Lowering blood cholesterol with a statin after ischaemic stroke or TIA

- Antiplatelet treatment after ischaemic stroke or TIA

Secondary stroke prevention after transient ischemic stroke (TIA) or minor stroke is of major importance in order to avoid recurrent cerebrovascular events and decrease morbidity and mortality. Systematically review of recently published, high-quality studies emphasizing the need for emergency assessment and treatment of patients with TIA and minor stroke and to give a comprehensive and distinct overview over medical secondary stroke prevention trials performed in these patients. Evaluation and implementation of preventive stroke therapy has to be immediate in patients with TIA and stroke. For patients with non-cardioembolic stroke (thrombotic strokes), antiplatelet agents are the treatment of choice. Aspirin plus extended-release dipyridamole and clopidogrel are more effective than aspirin and should be used in patients with a high risk of recurrent stroke. Treatment of risk factors such as arterial hypertension and high cholesterol is even more important in secondary stroke prevention than in primary prevention.

Stroke prevails as a common and devastating disease. Epidemiological studies have advanced our understanding of stroke risk factors and clinical trials have demonstrated effective interventions to decrease stroke risk by modifying risk factors. Stroke risk factors are classified as traditional and novel and may be further divided into modifiable and non-modifiable. Ongoing research is exploring further interventions in the management of traditional risk factors. Future research will expand our knowledge about the contribution of genetic factors to stroke, their interaction with environmental factors and open exciting avenues for the development of new therapies. Twenty percent of the United States population will have 80% of all strokes; this estimate is based on five established, major risk factors for stroke: hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, and heart disease. Therefore, stroke is not random but is generally predictable. It is an ideal target for effective prevention strategies that are simple and inexpensive.

Although several intervention trials with ACE-.inhibitors, ARBs, other antihypertensives, statins have been shown, sometimes in primary prevention and mostly in a secondary prevention setting, a significant reduction of stroke incidence, yet few studies, with the exception of some study such as PROFESS and a SPARCL subtype, used a TOAST subtype oriented analysis. Therefore it is difficult to extrapolate the real benefit of pharmacological prevention strategies against atherothrombotic subtype for excellence in the TOAST classification subtype that is represented by the LAAS and also with regard of lacunar subtype as an expression of lipohyalinosis process which is a further aspect of atherosclerosis. More frequently stroke classification in clinical trials concerns prognosis with terms such as fatal or non fatal that are less likely to reveal thrombotic or embolic pathogenesis of brain ischemia.

Future studies will be addressed to better tailor preventive strategies on clinical subtypes of stroke so to optimize drugs adaptation to real thrombotic ischemic events. Furthermore each ischemic stroke subtype as reported by some studies is related to inflammation [77-80] and arterial stiffness [81, 82] in a peculiar way and to date no study had addressed the effects of secondary prevention with cardiovascular active drugs on these markers in relationship of TOAST subtype, so this topic could represent a possible future research line.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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