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Medical Therapy for Carotid Artery Stenosis

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Patients with carotid atherosclerotic disease are at an increased risk for stroke. This chapter reviews the risk factors associated with carotid artery stenosis and the medical interventions that decrease the cardiovascular risk from carotid atherosclerotic disease.

Key Words: Angiotensin-converting enzyme inhibitor, antiplatelet therapy, antithrombotic therapy, cardiovascular risk factors, carotid artery stenosis, statin.

INTRODUCTION

Patients with carotid atherosclerotic disease are at an increased risk for stroke. The focus of the rest of this book is on carotid arterial revascularization, which in certain patient subsets has been shown to decrease the future risk of stroke and death (1–4). This chapter focuses on medical interventions that decrease the risk from carotid atherosclerotic disease.

TRADITIONAL CARDIOVASCULAR RISK FACTORS AND CAROTID STENOSIS

Traditional cardiovascular risk factors correlate with carotid artery stenosis. In the Framingham Heart Study, the odds ratio of moderate carotid stenosis ($\geq 25\%$) in men was 2.11 (95% confidence interval [CI] 1.51–2.97) for an increase of 20 mmHg in systolic blood pressure (SBP), 1.10 (95% CI 1.03–1.16) for an increase of 10 mg/dL of total cholesterol, and 1.08 (95% CI 1.03–1.13) for an increase of 5 pack-years of smoking, with similar findings in women (5). In a study of 3998 people in Osaka, Japan, the number of major coronary risk factors was associated with a higher likelihood of severe

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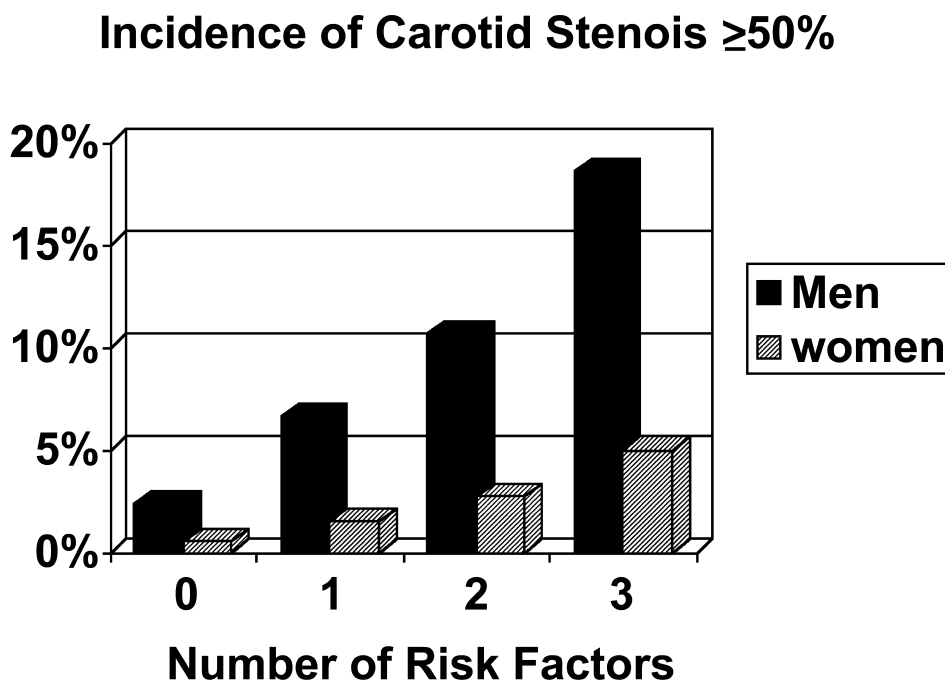


Fig. 1. Correlation between cardiac risk factors (hypertension, dyslipidemia, and tobacco abuse) and incidence of significant carotid stenosis ($\geq 50\%$). A linear relationship exists between the number of risk factors and the likelihood of significant carotid stenosis. This relationship was stronger in men than in women. (Adapted from ref. 6.)

($\geq 50\%$) carotid stenosis (Fig. 1). Major coronary risk factors in this study were hypertension (SBP ≥ 140 , diastolic blood pressure [DBP] ≥ 90 , or on medication), hyperlipidemia (total cholesterol >220 mg/dL or on medication), or tobacco abuse (current smoker). The mean carotid arterial intimal–medial thickness (IMT) was also increased with increasing numbers of coronary risk factors (6). Another study found that patients with carotid stenosis had higher SBP and DBP, and higher plasma cholesterol and triglyceride concentrations than the control groups. They had, as well, a far greater likelihood of being cigarette smokers and a greater likelihood of having diabetes mellitus and previous evidence of coronary and peripheral arterial disease. Patients with carotid stenosis were also more likely to have two or more of these common risk factors of atherosclerosis than were the control subjects (7). Other studies have suggested diabetes mellitus, family history of stroke, low high-density lipoprotein (HDL) levels, coronary artery disease (CAD), and peripheral arterial disease as associated risk factors (7–12). Overall, approx 40% of the incidence of carotid stenosis can be accounted for by traditional risk factors (10).

Thus, the focus of medical therapy for carotid atherosclerotic disease typically concentrates on treatment of these risk factors: hypertension, dyslipidemia, diabetes mellitus, and tobacco use. Importantly, disease in the carotid arteries suggests that atherosclerotic disease may exist elsewhere in other arterial beds. The National Cholesterol Education Program and ATP III guidelines consider the presence of carotid disease equivalent to the presence of CAD for calculating cardiovascular risk (13).

What are Useful End Points or Outcomes to Measure?

The major carotid surgical revascularization studies utilized ipsilateral stroke, all-stroke, fatal stroke, and/or all-cause mortality as end points (1–4). The SAPHIRE (Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy) trial comparing carotid stenting to carotid endarterectomy used a composite including death, stroke, and myocardial infarction (MI) to better reflect the totality of the risk of revascularization (14).

Unfortunately, for the purposes of our discussion, nearly all clinical trials addressing medical therapies have not focused on patients with carotid stenosis. Major trials of medical therapy have focused on patients with prior cardiovascular events, known atherosclerotic disease, or with multiple cardiovascular risk factors. Trials specifically evaluating patients with carotid stenosis are lacking and generally have been underpowered and have enrolled small numbers of patients. All-cause mortality, cardiac death, MI, coronary revascularization, and/or stroke have all been used as end points in these trials. From a global perspective for the patient, these combination end points best reflect the “real world.” The goal is to prevent any or all cardiovascular complications. To better determine the effect on carotid atherosclerotic disease, however, a more limited end point of ischemic ipsilateral stroke would be preferable. Unfortunately, most trials did not report the proportion of patients with carotid disease, the severity of carotid disease, or the subtype of strokes in the outcomes. Therefore, for the most part, the reduction in stroke risk specifically attributable to treated carotid disease cannot be separated from the overall reduction in stroke risk for a given therapy.

Hypertension

Hypertension is a well recognized risk factor for cardiovascular disease, and is perhaps the most important modifiable risk factor for stroke. Most evidence about the effects of blood pressure (BP) on the risk of cardiovascular complications is obtained from two types of data: prospective nonrandomized observational studies correlating the relationship between BP and the incidence of stroke and other adverse outcomes, and randomized trials of antihypertensive drug therapy.

A meta-analysis of 61 prospective observational studies including approx 1 million adults found that each 20 mmHg SBP or 10 mmHg DBP difference was associated with a more than twofold increase in the stroke or death rate. Men and women had similar findings, and hypertension was found to be associated with both fatal hemorrhagic and ischemic stroke. The risk remained elevated until the BP reached a low of 115 mmHg systolic and 75 mmHg diastolic (12). An analysis of 18 studies on Chinese and Japanese patients found a significant association between DBP and both hemorrhagic and nonhemorrhagic stroke. Each 5 mmHg reduction in DBP was associated with a reduced odds ratio (OR) of nonhemorrhagic stroke [OR = 0.61 (95% CI 0.57–0.66)] and hemorrhagic stroke [OR = 0.54 (95% CI 0.50–0.58)] (15).

In the Systolic Hypertension in the Elderly Program (SHEP) study, 4736 patients ≥ 60 yr of age with isolated systolic hypertension were enrolled. The average SBP was 155 mmHg in control patients compared to 143 mmHg in treated patients, resulting in a 36% relative risk reduction in total stroke ($p = 0.0003$). Nonfatal and fatal MI were reduced 27%, with a 32% reduction in cardiovascular events (16). In a meta-analysis of 37,000 patients, antihypertensive therapy resulted in a 5–6 mmHg decrease in the DBP, which was associated with a 42% reduction in stroke (95% CI 35–50%, $p < 0.0001$) and a 14% reduction in cardiovascular events (95% CI 4–22%, $p < 0.01$) with follow-up over 2–5 yr (17).

In patients with a history of stroke or transient ischemic attack (TIA), BP continues to be an important risk factor. However, concerns exist about the safety of BP reduction in this patient cohort, especially in the presence of cerebrovascular disease. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial studied the effect of BP reduction in 6105 patients with a history of stroke or TIA within 5 yr. Patients were treated with either perindopril or placebo. Physicians had the option of adding indapamide (a diuretic) to perindopril at their discretion. The treatment arm reduced BP (systolic/diastolic) by 9/4 mmHg. Notably, combination therapy reduced the BP by 12/5 mmHg vs 5/3 mmHg with perindopril alone. Over 4 yr of follow-up, treatment was associated with a 28% reduction in stroke (10% vs 14%, $p < 0.0001$) and a 26% reduction in major vascular events. Combination therapy reduced the stroke rate by 43% whereas single-agent therapy did not produce a significant reduction in stroke rate (18).

COMPARATIVE TRIALS

The choice of antihypertensive agent depends on the clinical presentation and other comorbidities. While numerous trials have been performed attempting to determine which antihypertensive agent is preferable as first-line treatment, the majority of patients will likely need more than one agent, making this discussion less relevant. However, these trials (ALLHAT, HOPE, EUROPA, PEACE, VALUE, and CAMELOT) do have useful insights into which patient cohorts benefit from antihypertensive therapy, the magnitude of the treatment effect, and the utility of specific medications.

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) enrolled 33,357 patients ≥ 55 yr of age with hypertension and ≥ 1 cardiovascular risk factor to therapy with an angiotensin-converting enzyme inhibitor (ACE inhibitor), a calcium channel blocker, or a diuretic with mean follow-up of 4.9 yr. The α -blocker treatment arm was stopped prematurely because of an increased adverse event rate with doxazosin compared to diuretic therapy. The primary end point, combined fatal coronary heart disease or nonfatal MI, and all-cause mortality were not significantly different between treatment groups. SBP was increased in the amlodipine-treated group (0.8 mmHg, $p = 0.03$) and in the lisinopril-treated group (2 mmHg, $p < 0.001$), compared to the chlorthalidone-treated group. Treatment with amlodipine was associated with an increased rate of heart failure (10.2% vs 7.7%, RR 1.38, 95% CI 1.25–1.52), while treatment with lisinopril was associated with an increased rate of stroke (6.3% vs 5.6%, RR 1.15, 95% CI 1.02–1.30) (Fig. 2). The rate of combined cerebrovascular disease and heart failure was also higher with lisinopril (19). The difference in stroke rates between lisinopril and chlorthalidone may be attributed to the BP differences achieved between the two therapies. However, thiazide-type diuretics should be preferred as first-line therapy in patients who do not have a specific indication for another agent (e.g., ACE inhibitors or β -blockers in left ventricular dysfunction, β -blockers after MI, etc.).

CARDIOPROTECTIVE EFFECT OF ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKER (ARBs)?

The Heart Outcomes Prevention Evaluation (HOPE) study randomized >9000 high-risk patients to treatment with ramipril or placebo. Patients were deemed high risk if they had evidence of cardiovascular disease including coronary disease, prior MI, stroke, or peripheral arterial disease, or if they had diabetes mellitus and ≥ 1 cardiovascular risk factor (dyslipidemia, hypertension, microalbuminuria, or tobacco abuse).

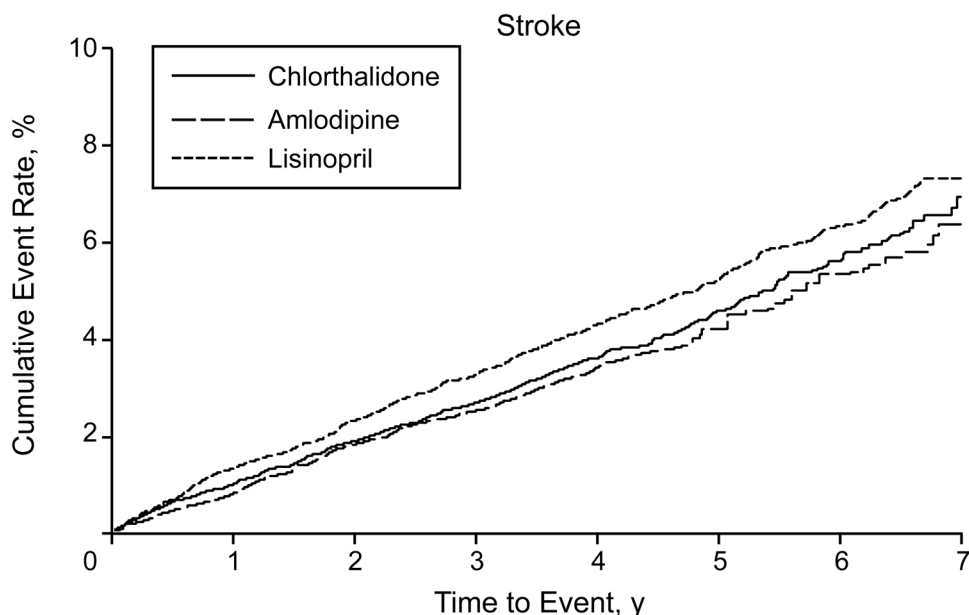


Fig. 2. Cumulative risk of stroke in patients treated with different antihypertensive medications (lisinopril, amlodipine, chlorthalidone) in the ALLHAT trial. Lisinopril therapy was associated with an increase in stroke rate compared to chlorthalidone therapy at 6 yr (6.3% vs 5.6%, RR 1.15; 95% CI 1.02–1.30). (Reproduced with permission from the ALLHAT study [19].)

The mean BP at enrollment was 139/79 mmHg. Patients treated with ramipril had a 22% reduction in MI, stroke, or cardiovascular death, a 26% reduction in cardiovascular death, a 32% reduction in stroke, a 15% reduction in revascularization, and a 23% reduction in heart failure. The benefit was seen within the first year and was consistent within all subgroups. Treatment with ramipril would prevent 18 deaths per 1000 patients treated, 16 MIs, and 9 strokes (20). The magnitude of BP lowering with ramipril was 3.3/1.4 mmHg. The benefit seen initially was thought to be much greater than what could be attributed to BP lowering alone, suggesting that ACE inhibitor may have cardiovascular benefit beyond just BP reduction. A subgroup of patients with ambulatory BP monitoring, however, had much greater BP reductions than what was recorded at office visits (21).

The EUROPA (European trial on reduction of cardiac events with perindopril in stable CAD) study also treated nearly 14,000 high-risk patients with an ACE inhibitor, perindopril, or placebo. Patients were considered high risk if they had a prior MI, known CAD, coronary revascularization, or a positive stress test. The mean BP at enrollment was 137/82 mmHg. Therapy with perindopril was associated with a 5/2 mmHg decrease in BP. Patients enrolled in EUROPA were not as high risk as patients in HOPE. The cardiovascular mortality in the placebo-treated groups was 8% for HOPE and 4% for EUROPA. Perindopril treatment, however, was still associated with a 20% reduction in the combined end point of cardiovascular death, MI, or cardiac arrest. The benefit was seen at 1 yr and was consistent among subgroups (22).

The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial treated patients with stable CAD [prior MI or coronary artery bypass graft (CABG) or known angiographic CAD] with either trandolapril or placebo. The mean

baseline BP at enrollment was 133/78 mmHg. Treatment with trandolapril did not result in any significant reduction in adverse events. The incidence of cardiovascular death, nonfatal MI, or revascularization was 21.9% with trandolapril compared to 22.5% with placebo. Notably, the cardiovascular risk was not as high in this patient cohort as with patients enrolled in either HOPE or EUROPA, suggesting perhaps that the value of therapy may be proportional to the underlying risk (23).

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial compared valsartan therapy to amlodipine therapy in hypertensive patients at high risk, defined as known coronary heart disease, dyslipidemia, diabetes mellitus type 2, cerebrovascular disease, peripheral arterial disease, left ventricular hypertrophy, reduced renal function, proteinuria, or tobacco abuse. The mean BP at enrollment was 155/88 mmHg. After mean follow-up of 4.2 yr, the primary composite end point of cardiac events, MI, stroke, and death was not significantly different between the treatment arms (24).

The Comparison of amlodipine vs enalapril to limit occurrences of thrombosis (CAMELOT) trial compared treatment with either amlodipine or enalapril to placebo in patients with known angiographic coronary disease $>20\%$ and DBP <100 mmHg. Mean baseline BP was 129/78 mmHg. The primary end point was a composite of cardiovascular death, nonfatal MI, resuscitated cardiac arrest, coronary revascularization, hospitalization for either angina or congestive heart failure, fatal or nonfatal stroke, TIA, and new diagnosis of peripheral arterial disease. The incidence of the composite end point was 23.1% in the placebo group compared to 16.6% in the amlodipine-treated group and 20.2% in the enalapril-treated group. Only the amlodipine-treated arm had a statistically significant reduction in risk (HR 0.69, 95% CI 0.54–0.88, $p = 0.003$). The enalapril-treated arm had a hazard ratio of 0.85 (95% CI 0.67–1.07, $p = 0.16$). While the BP reduction was similar with both treatment arms (4.8/2.5 mmHg with amlodipine and 4.9/2.4 mmHg with enalapril), the once daily dosing of both drugs raises the possibility that BP lowering may not have been as stable with enalapril (half-life of ~ 11 h) compared to amlodipine (half-life of ~ 50 h). Moreover, amlodipine has antianginal properties, which may have reduced the need for coronary revascularization and hospitalization for angina. The reduction in the incidence of nonfatal MI, stroke, and death was similar between amlodipine and enalapril treatments, although not statistically significant for either compared to placebo (25).

Overall, these trials suggest that high-risk patients with “normotensive” blood pressures (baseline BP of 137–139/79–82 mmHg) still benefit from therapy. Moreover, it seems likely that the magnitude of BP lowering achieved by therapy may be more important than the actual agent used, although this is controversial.

GOAL OF BLOOD PRESSURE MANAGEMENT

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) issued new guidelines for the treatment of BP in 2003. The recommended target BP was $<140/90$ mmHg in patients with cardiovascular disease and $<130/80$ in patients with diabetes mellitus or chronic kidney disease with proteinuria. They concluded that most patients will require at least two BP medications to reach these goals (26). The 2003 European Society of Hypertension-European Society of Cardiology (ESH-ESC) guidelines for the management of arterial hypertension, however, recommended a goal BP $<130/85$ mmHg in high-risk patients with cardiovascular disease (27). Given the results of HOPE, EUROPA, PEACE, VALUE, and CAMELOT, several conclusions become evident.

Patients at higher risk derive greater benefit from BP reduction even if they are not “hypertensive.” Blood pressure reduction itself may be more important than the actual agent used. Certain classes of medications are of greater benefit in certain clinical situations, such as ACE inhibitors for patients with congestive heart failure, left ventricular dysfunction, or diabetes mellitus, and β -blockers for patients with angina, prior MI, or congestive heart failure. Overall, however, the recommendations of ESH-ESC may better reflect goals of therapy in high-risk patients.

CAROTID DISEASE AND BLOOD PRESSURE REDUCTION

In patients with severe carotid atherosclerotic disease, concerns exist about decreasing the BP especially in the setting of severe bilateral carotid stenosis or carotid occlusion. Cerebral perfusion has been hypothesized to be dependent on perfusion pressure, and therefore systemic BP. Decreasing the BP in this setting may result in increasing ischemia to regions of the brain that are marginally receiving sufficient blood flow at baseline. While this hypothesis has validity in the acute stroke setting, very little clinical data exists about this possibility for long-term treatment. Rothwell et al. conducted a post hoc analysis of data from three trials, two of which were carotid revascularization trials in symptomatic patients with carotid stenosis (NASCET and ECST) and one in patients with stroke or TIA with low likelihood of carotid stenosis treated with aspirin. Increased BP correlated with higher stroke risk in patients with symptomatic carotid disease, although this relationship is blunted in comparison to other patients presenting with TIA or stroke. Carotid occlusion did not affect this, but patients with bilateral $\geq 70\%$ stenosis had an increased stroke risk with decreased BP, suggesting that aggressive BP reduction may result in worse outcomes in this cohort of patients (28). However, it is important to note that this was a post hoc analysis looking at the relationship of BP at time of enrollment and subsequent stroke. This was not a trial of BP lowering, and the relatively small number of strokes in these patients with bilateral carotid disease makes the data liable to statistical variance. However, caution is still warranted in this cohort of patients.

Hyperlipidemia

EPIDEMIOLOGICAL PARADOX

Hyperlipidemia has been associated with carotid atherosclerotic disease. Elevated total cholesterol was associated with an increased likelihood of moderate carotid stenosis in the Framingham Study. Other studies have suggested a correlation between total cholesterol/HDL ratio and carotid stenosis and an inverse relationship between HDL and carotid stenosis (29,30). High HDL may be associated with reduced carotid plaque progression (31). Surprisingly, however, elevated lipid levels are not established as a risk factor for stroke (32). Our understanding of how dyslipidemia affects stroke risk comes from two types of data: observational studies looking at the association of plasma lipid levels and stroke and randomized controlled trials of lipid-lowering therapy and the effect on stroke risk. Unfortunately, unlike work on hypertension, a discordance is seen between the epidemiological studies and the therapeutic studies. Only a weak association between lipid levels and stroke is observed, but a significant benefit is seen with lipid-lowering therapy, primarily statins, in reducing stroke risk.

In a large analysis of 450,000 patients, no correlation between cholesterol levels and stroke could be found, except potentially in patients younger than 45 yr of age. This finding was not different after adjusting for gender, DBP, history of CAD, or ethnicity.

Unfortunately, three quarters of the stroke events in this analysis were from studies that recorded only fatal strokes. Moreover, the type of stroke was not recorded in any of the trials to allow for analysis by subtype (33). In another analysis, Iso et al. studied more than 350,000 men to determine the relationship between total cholesterol level and risk of fatal stroke. After adjustment for age, smoking, DBP, and ethnicity, there was an association between total cholesterol level and fatal nonhemorrhagic stroke ($p = 0.007$). Interestingly, however, in men with DBP >90 mmHg, a low total cholesterol (<160 mg/dL) was associated with a threefold greater risk of fatal hemorrhagic stroke ($p = 0.05$) (34). In a case control study, separating patients into quintiles based on total and HDL cholesterol values, the highest quintile of total cholesterol compared to the lowest quintile had an increased risk for nonhemorrhagic stroke (OR 1.6 [95% CI 1.3–2.0]). Atherosclerotic stroke (OR 3.2) and lacunar stroke (OR 2.4) had the strongest associations. The lowest quintile of total cholesterol had an increased risk of hemorrhagic stroke (35).

Similar findings were seen in different ethnic cohorts. The Copenhagen City Heart Study found that total cholesterol only correlated with nonhemorrhagic strokes in patients with serum total cholesterol levels of >309 mg/dL (>8 mmol/L). The risk associated with lower cholesterol levels remained fairly constant. An association between plasma triglycerides and nonhemorrhagic strokes (RR 1.12 [95% CI 1.07–1.16]) and an inverse relationship between HDL levels and nonhemorrhagic strokes were found. Notably, however, the lipid studies were performed on nonfasting samples (36). People in eastern Asia tend to have higher incidence of hemorrhagic stroke than Western populations. An analysis of 18 studies studying Chinese and Japanese patients found that total cholesterol levels were only weakly correlated with strokes. Each 0.6 mmol/L reduction in total cholesterol was associated with a trend to a reduced risk of nonhemorrhagic stroke (OR 0.77 [95% CI 0.57–1.06]), and an increased risk of hemorrhagic stroke (OR 1.27 [95% CI 0.84–1.91]) (15).

Overall, elevated cholesterol levels correlated with ischemic stroke, albeit weakly, and an association was found between low cholesterol levels and hemorrhagic stroke.

STATIN THERAPY

Amarenco et al. performed a meta-analysis on more than 90,000 patients treated with statin therapy enrolled into randomized clinical trials published before August 2003. Statin therapy was found to reduce the stroke rate significantly (risk reduction of 21% [OR 0.79 {95% CI 0.73–0.85}]) (Fig. 3). After trials for which stroke was not a specified end point were excluded, the OR was 0.80 (95% CI 0.74–0.87). A nonsignificant reduction in fatal strokes of 9% was also found (OR 0.91 [95% CI 0.76–1.10]). Statin therapy also did not affect the likelihood of hemorrhagic stroke. The pooled OR was 0.90 (95% CI 0.65–1.22). Overall, each 10% low-density lipoprotein (LDL) reduction reduced the risk of stroke by 15.6% (95% CI 6.7–23.6%). Approximately 33–80% of the stroke reduction could be attributed to the LDL reduction. Each 10% reduction in LDL also reduced the carotid IMT by 0.73% per year (95% CI 0.27–1.19%). The correlation between LDL reduction and IMT reduction was significant ($r = 0.65$, $p = 0.004$) (37).

Patients with “normal” cholesterol levels also benefit from statin therapy to reduce stroke. The Cholesterol and Recurrent Events (CARE) trial treated 4159 patients with a history of MI with average cholesterol (mean 209 mg/dL) and LDL levels (mean 139 mg/dL) with either pravastatin or placebo. The pravastatin-treated group had an

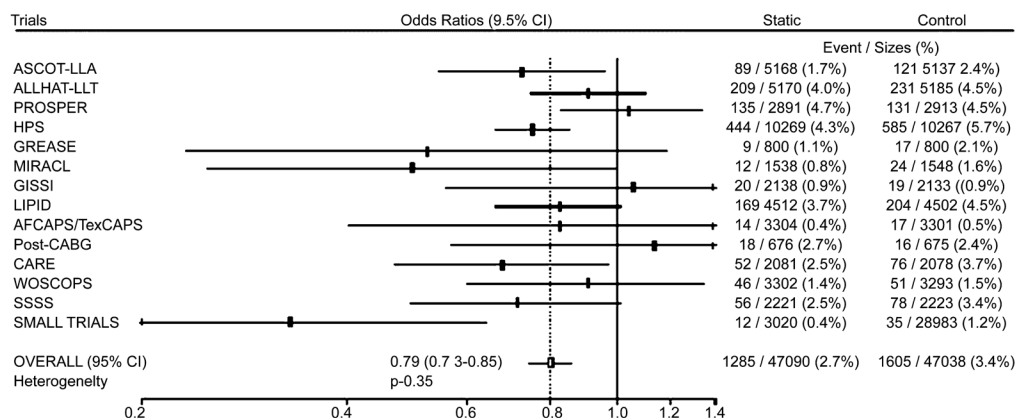


Fig. 3. Effects of statin therapy on fatal and nonfatal stroke risk from the study by Amarenco et al. Odds ratios for stroke reduction with statin therapy are shown for individual trials. The small trials included in the meta-analysis were grouped together. (Reproduced with permission from ref. 37.)

average reduction of 20% total cholesterol and 32% LDL. Patients treated with pravastatin had a 32% reduction in all-cause stroke (95% CI 4–52%, $p = 0.03$) and a 27% reduction in stroke or TIA (95% CI 4–44%, $p = 0.02$). No increase in hemorrhagic strokes was observed (38). A subgroup analysis of the Anglo-Scandinavian Cardiac Outcomes Trial focused on hypertensive patients with multiple cardiac risk factors with normal total cholesterol values (<6.5 mmol/L). Patients in this cohort treated with atorvastatin had decreased nonfatal MI and cardiac death. Fatal and nonfatal stroke was also reduced by 27% (95% CI 4–44%, $p = 0.024$). The benefit of statin therapy was observed in the first year of treatment (39).

Aggressive treatment with statin therapy also reduced the stroke risk. The Treating to New Targets (TNT) trial enrolled 10,000 patients with stable coronary disease with LDL levels <130 mg/dL and treated them with either low- (10 mg daily) or high-dose (80 mg daily) atorvastatin therapy. High-dose atorvastatin therapy significantly reduced LDL more than low-dose atorvastatin (average LDL of 77 mg/dL vs 101 mg/dL) and was associated with a significant 25% reduction in fatal and nonfatal stroke (95% CI 4–41%). Cardiovascular events were also reduced (40).

The Heart Protection Study (HPS) deserves special mention because it was the only large statin trial that included a significant number of patients with prior stroke and TIA. HPS studied 20,536 patients with known arterial occlusive disease or diabetes mellitus and treated them with either simvastatin 40 mg daily or placebo. The average LDL level at the time of enrollment was 131 mg/dL, of whom about one third had LDL levels of <116 mg/dL. The magnitude of reduction of LDL by simvastatin was 39 mg/dL. In all patients, there was a 25% relative risk reduction for stroke (95% CI 15–34%, $p < 0.0001$). The rate of ischemic strokes was decreased 28% (95% CI 19–37%, $p < 0.0001$) with no increase in hemorrhagic strokes. Moreover, the rate of TIA was decreased (2.0% vs 2.4%, $p = 0.02$) and the need for carotid revascularization was also reduced (0.4% vs 0.8%, $p = 0.0003$). Notably, the benefit was found by the end of the second year of therapy. The reduction in stroke was found in patients with CAD, diabetics, and patients with low LDL (<116 mg/dL) at enrollment (41).

Of all the patients enrolled, 3280 had a history of cerebrovascular disease defined as prior nondisabling ischemic stroke or TIA, and/or prior carotid endarterectomy or

angioplasty. In this subgroup analysis, no reduction was found in the stroke rate, although a 20% relative risk reduction was found in the rate of any vascular event (95% CI 8–29%, $p = 0.001$). Notably, patients who had a stroke within 6 mo were excluded, and on average the cerebrovascular event occurred 4.3 yr before enrollment. Stroke events were not subtyped although this was typical for most medical therapy trials. The reason for this lack of benefit in this subgroup is unclear and somewhat perplexing (41).

NONSTATIN THERAPY

Nonstatin lipid-lowering therapy has not consistently shown to decrease stroke risk. A meta-analysis of lipid-lowering therapy revealed a relative risk reduction of 17% for strokes. Statin therapy had a more pronounced effect compared to other treatments (RRR of 26%). The effect was primarily seen when the total cholesterol was reduced to <232 mg/dL (42). Another meta-analysis revealed only a benefit for statin therapy but not for other medication and lifestyle therapies for decreasing LDL. Some of the lack of benefit of these other therapies has been attributed to their relative lack of efficacy in reducing LDL compared to statin therapy. However, in the VA-HIT trial, patients with low HDL cholesterol (≤ 40 mg/dL) treated with gemfibrozil had a decreased rate of stroke compared to placebo (31% RRR [95% CI 2% to 52%, $p = 0.036$]). The rate of TIA and carotid endarterectomy were also reduced with gemfibrozil. The benefit was evident after just 6–12 mo (43).

ACUTE STROKE TREATMENT WITH STATINS

Statin therapy has multiple effects beyond just lipid lowering and may provide neuroprotective effects in the setting of acute stroke. In an occlusion–reperfusion model of stroke in mice, treatment with atorvastatin for 14 d before the stroke reduced stroke volume by 40%. This protective effect was lost when the statin therapy was stopped abruptly, with complete loss of protection after 4 d. The authors concluded in this study that the neuroprotective mechanism may be due at least in part to upregulation of endothelial nitric oxide synthase (44). In humans, a small retrospective study of 167 patients suggested that being on prior statin therapy at the time of acute ischemic stroke improved neurologic outcomes at 3 mo (using the modified Rankin score and the Barthel Index), although the initial stroke severity and risk of progression were not different than in patients not on statin therapy (45). In a slightly larger retrospective study of 650 patients, those on lipid lowering therapy at the time of an acute ischemic stroke had a reduced risk of stroke progression and a lower 90-d mortality rate than those not on therapy. More than 90% of patients on lipid-lowering therapy were on statin therapy (46). Although these findings are preliminary, they are provocative about the benefit of statins in this setting, and will hopefully lead to clinical trials assessing the value of statin therapy in acute stroke.

Diabetes Mellitus

Diabetic patients have an increased risk of cardiovascular events including ischemic stroke. The ATP III guidelines consider diabetes mellitus to be the equivalent of known coronary atherosclerotic disease for future risk, and advocates aggressive secondary prevention. Diabetic control, however, has not been as convincingly associated with reduced risk of macrovascular events including ischemic stroke. The Diabetes Control and Complications Trial (DCCT) found conclusively that aggressive diabetic control was

associated with reduced microvascular events (retinopathy, nephropathy, neuropathy). However, there was only a trend to reduction of macrovascular or cardiovascular events (3.2% vs 5.4%, $p = 0.08$) (47). This trial, however, focused on young type 1 diabetic patients, who likely did not have as high a likelihood of having ischemic events. However, in type 2 diabetic patients, the UK Prospective Diabetes Study (UKPDS) trial found no difference in cardiovascular events between intensive therapy and conventional therapy (48). A subgroup analysis suggested that there might be a reduction in MI and stroke with improved diabetic control.

Overall, diabetic control should be advocated for reduction in microvascular complications. There may be a benefit in reducing macrovascular complications, although this has not been convincingly borne out in either type 1 or 2 diabetic patients. However, aggressive control of other risk factors especially in type 2 diabetic patients including hypertension, dyslipidemia, and smoking cessation are of great importance in reducing the cardiovascular risk, including the risk of ischemic stroke. In the UK Prospective Diabetes Study 38 Trial, intensive BP control, primarily with the use of an ACE inhibitor or β -blocker, resulted in significant BP lowering. The mean BP at baseline was 160/94 and decreased to 144/82 mmHg with intensive treatment vs 154/87 mmHg with standard treatment. Improved BP control was associated with a 32% reduction in diabetes-related death (95% CI 6–51%, $p = 0.019$), 44% reduction in strokes (95% CI 11–65%, $p = 0.013$), and 37% reduction in microvascular complications (95% CI 11–56%, $p = 0.0092$) (49).

Smoking Cessation

Tobacco abuse has a known association with carotid atherosclerosis as well as adverse cardiovascular events. Smoking cessation reduces this risk eventually over time, although the risk likely does not fully normalize. One observational study in British men found that current smokers had a 3.7-fold relative risk (95% CI 2.0–6.9) for stroke compared to men who had never smoked. Men who quit had a decreased risk compared to men who were smoking, but the risk is still elevated compared to men who never smoked although not significantly (RR 1.7; 95% CI 0.9–3.3, $p = 0.11$). The reduced risk seen in men who quit smoking was seen within 5 yr. The amount of tobacco used determined the risk reduction. Light smokers (<20 cigarettes/d) had a risk similar to men who never smoked, while heavy smokers (≥ 20 cigarettes/d) were not able to eliminate the risk entirely (RR 2.2; 95% CI 1.1–4.3). Hypertensive men had a greater benefit from smoking cessation compared to normotensive men (50). Women had similar outcomes, with a 2.6-fold risk of stroke (95% CI 2.08–3.19) compared to women who had never smoked. Women who quit smoking still had an elevated risk, although not as great as current smokers (RR 1.34, 95% CI 1.04–1.73). The risk of all stroke and ischemic stroke was reduced to similar levels as women who never smoked within 2–4 yr. Unlike the study in men, the number of cigarettes smoked did not influence the reduction in risk associated with smoking cessation (51).

ANTIPLATELET AND ANTITHROMBOTIC THERAPY

Antiplatelet therapy and antithrombotic therapy continue to be important weapons in the armamentarium to decrease cardiovascular death and adverse vascular events. The value of therapy depends on both the agent and the clinical situation.

Acute Stroke

For acute treatment of ischemic events, unequivocal evidence supports the use of aspirin to treat acute ST-segment elevation MI. The value of intravenous fibrinolytic therapy has also been demonstrated in these patients, although it has been displaced by primary percutaneous coronary intervention. For acute ischemic stroke, both aspirin and fibrinolytic therapy are beneficial, but to a lesser degree and with a narrower therapeutic index than for MI.

The International Stroke Trial and the Chinese Acute Stroke Trial studied the use of aspirin in acute ischemic stroke. The International Stroke Trial was a large randomized, open-label trial of 19,435 patients comparing the use of up to 14 d of treatment with either subcutaneous unfractionated heparin (5000 or 12,500 IU bid) or aspirin 300 mg daily in a factorial design. No significant difference was seen in death at 14 d with unfractionated heparin (9.0% for heparin vs 9.3% for placebo). Notably, the recurrent ischemic stroke rate was significantly lower for the heparin group (2.9% vs 3.8%) but this was offset by an increase in the risk of hemorrhagic stroke (1.2% vs 0.4%). Therefore the rate of death or nonfatal recurrent stroke at 14 d was not significantly different (11.7% vs 12.0%). Aspirin also did not significantly reduce death at 14 d (9.0% vs 9.4%). Aspirin-treated patients, however, did have a reduced rate of recurrent ischemic strokes within 14 d (2.8% vs 3.9%) with no significant increase in the rate of hemorrhagic strokes (0.9% vs 0.8%). Aspirin therapy resulted in a significantly lower rate of death or nonfatal recurrent stroke at 14 d (11.3% vs 12.4%) (52).

The Chinese Acute Stroke Trial (CAST) was a large randomized, placebo-controlled, clinical trial of 21,106 patients with acute ischemic stroke comparing aspirin 160 mg daily with placebo, started within 48 h of symptoms and continued for up to 4 wk. Aspirin-treated patients had a significant reduction in death at 4 wk (3.3% vs 3.9%, $p = 0.04$). Aspirin therapy was also associated with a decreased recurrent ischemic stroke rate (1.6% vs 2.1%, $p = 0.01$) and a nonsignificantly increased hemorrhagic stroke rate (1.1% vs 0.9%, $p > 0.1$). The composite end point of in-hospital death or nonfatal stroke at 4 wk was significantly decreased with aspirin therapy (5.3% vs 5.9%, $p = 0.03$) (53).

Overall, treatment with aspirin in acute stroke was associated with an absolute reduction of death or nonfatal stroke of 9 per 1000 treated for 3 wk. Although a small increase was seen in extracranial bleeding, the benefits of therapy clearly outweighed the risks (54). Although the benefit seems small compared to the magnitude of benefit seen from aspirin therapy in other clinical settings, it is important to note that the duration of therapy needed to achieve this benefit was 2–4 wk compared to the years of therapy needed to obtain benefit in secondary prevention.

Secondary Prevention

In patients presenting with TIA or minor stroke, low-dose aspirin has been shown to decrease the risk of stroke. The Swedish Aspirin Low-Dose Trial (SALT) enrolled 1360 patients presenting with TIA or minor stroke and randomized them to either therapy with low-dose aspirin (75 mg daily) or placebo. Treatment with aspirin was associated with an 18% reduction in stroke or death (RR 0.82; 95% CI 0.67–0.99, $p = 0.02$) with similar reductions for stroke, frequent TIA, and MI (55). Another trial compared 30 mg of aspirin daily with 283 mg daily in patients with prior TIA or minor stroke. Low-dose aspirin was just as efficacious as the higher dose in preventing vascular death, nonfatal stroke, or nonfatal MI (14.7% in the low-dose group vs 15.2% in the high-dose group)

(56). However, the United Kingdom Transient Ischaemic Attack Aspiring Trial (UK-TIA) showed discordant results. The UK-TIA was a randomized trial of 2435 patients with presumed TIA or minor ischemic stroke treated with either 1200 mg of aspirin daily, 300 mg of aspirin daily, or placebo. Only a trend to decreased risk of major stroke, MI, or vascular death was found with aspirin (OR 0.85, 95% CI 0.71–1.03). No difference was found between low-dose and high-dose aspirin (57).

In high-risk patients, a meta-analysis of six trials of low-dose aspirin (≤ 325 mg daily) found that aspirin therapy was associated with a 20% reduction in stroke, 18% reduction in death, 30% reduction in MI, and a 30% reduction in vascular events. However, aspirin use was associated with increased gastrointestinal bleeding (58). Overall, the efficacy of aspirin for preventing strokes seems to be relatively leveled from a dose of 50 mg/dL to 1500 mg/dL daily (59). The Antithrombotic Trialists' Collaboration published a meta-analysis of antiplatelet therapy in 2002. In general, in high-risk patients, antiplatelet therapy was associated with a 25% reduction in nonfatal strokes. In patients with prior TIA or stroke, antiplatelet therapy was associated with a 22% reduction in the composite end point of nonfatal stroke, nonfatal MI, or vascular death. Thirty-six events would be prevented in 2 yr for every 1000 patients treated. Aspirin was the most commonly used antiplatelet agent in this study (60).

Aspirin and Treatment for Carotid Stenosis

Few studies have assessed the benefit of aspirin therapy for secondary prevention in patients with known carotid stenosis. Most have enrolled relatively few patients and have been underpowered to assess the effect of aspirin. One such study by Cote et al. evaluated 372 patients with known carotid stenosis of $\geq 50\%$ treated with either aspirin 325 mg daily or placebo for 2 yr. Notably, these patients were asymptomatic from their carotid disease and did not undergo revascularization. No significant difference was found between treatment groups in the rate of death or significant ischemic event. The multivariate analysis found an adjusted hazard ratio for aspirin of 0.99 (95% CI 0.67–1.46, $p = 0.95$) (61). In the Antithrombotic Trialists' Collaboration analysis, there was a trend toward improved outcomes with aspirin therapy in patients with carotid stenosis, similar in magnitude to that found with aspirin for secondary prevention (60).

Patients undergoing carotid endarterectomy benefit from aspirin therapy. A small trial of 232 patients randomized to aspirin 75 mg daily or placebo starting preoperatively and continued for 6 mo after surgery found that intraoperative stroke and post-operative stroke with residual defects were lower in the aspirin-treated arm (1.7% vs 9.6%, $p = 0.01$). There was a trend toward a lower rate of any neurological event and/or death in the aspirin treated arm ($p = 0.12$). Notably, there was no significant increase in bleeding complications with aspirin therapy (62). This benefit is likely the result of decreased emboli during surgery in patients treated with aspirin. When transcranial Doppler (TCD) monitoring was performed in symptomatic patients with carotid stenosis, the absence of aspirin therapy was associated with a sevenfold increase in microembolic events found via TCD (63). Low-dose aspirin is preferred over high-dose aspirin in patients undergoing carotid endarterectomy. The ASA and Carotid Endarterectomy (ACE) Trial found that patients treated with aspirin 81 mg or 325 mg daily had a lower combined rate of stroke, MI, and death compared to 650 mg or 1300 mg daily at 3 mo (6.2% vs 8.4%, $p = 0.03$), and a trend toward benefit at 30 d (5.4% vs 7.0%, $p = 0.07$) (64).

Primary Prevention

The Physicians' Health Study was the largest randomized clinical trial in 22,071 men evaluating the effect of low-dose aspirin on cardiovascular mortality for primary prevention. A 44% relative risk reduction was found in the risk of MI (RR 0.56; 95% CI 0.45–0.70, $p < 0.00001$). A nonsignificant but slightly increased risk of stroke was seen, primarily of hemorrhagic stroke (RR 2.14; 95% CI 0.96–4.77, $p = 0.06$). No reduction in cardiovascular mortality was found. Subgroup analysis revealed that the benefit was predominantly in patients >50 yr of age. The risk of gastrointestinal ulceration was not significantly higher (RR 1.22, 95% CI 0.98–1.53, $p = 0.08$) (65). Although the British Doctors' Trial did not show any benefit for aspirin, a meta-analysis of five major primary prevention trials including more than 55,000 patients ($>11,000$ women) found a 32% relative risk reduction in the risk of a first MI and overall 15% relative risk reduction in vascular events, but no significant effect on nonfatal stroke or vascular death (66).

Interestingly, the Nurses' Health Study found somewhat discordant results. In this observational study of 79,319 women, low-dose aspirin use (one to six aspirin/wk) was associated with a decreased stroke risk while higher doses of aspirin (seven or more aspirin/wk) led to a slightly increased stroke risk. Multivariate analysis revealed a relative risk of 0.50 (95% CI 0.29–0.85, $p = 0.01$) for large artery ischemic stroke in woman taking low-dose aspirin compared to women not taking aspirin. Women taking 15 or more aspirin/wk had an increased risk for subarachnoid hemorrhage (RR 2.02, 95% CI 1.04–3.91, $p = 0.02$). Subgroup analysis suggested that women who were older, hypertensive, and who smoked benefited most from low-dose aspirin therapy (67). Not surprisingly, the benefit or risk of aspirin in low-risk primary prevention cohorts will depend on their underlying risk profile.

Therefore, in patients who have a 10-yr risk of $\geq 10\%$ for a coronary event, the US Preventive Services Task Force recommends the use of low-dose, long-term aspirin therapy (68). For women at increased risk of ischemic stroke, low-dose aspirin is considered beneficial.

Dipyridamole

Dipyridamole alone and in addition to aspirin has been studied extensively for secondary prevention in patients with prior stroke or TIA. Dipyridamole inhibits adenosine phosphodiesterase and adenosine deaminase, resulting in an increase and accumulation of adenosine, cyclic adenosine monophosphate (cAMP), and adenine nucleotides, with resultant platelet inhibition and vasodilation especially of the coronary circulation. The largest trial assessing the efficacy of dipyridamole was the second European Stroke Prevention Study (ESPS-2). In this study, 6602 patients with a history of stroke or TIA were randomized to 25 mg of aspirin, extended release dipyridamole 200 mg, both, or placebo, given twice daily in a factorial design. In pairwise comparisons, treatment with aspirin resulted in a 18% reduction in stroke risk ($p = 0.013$) and a 13% reduction in the risk of stroke or death ($p = 0.016$). Treatment with dipyridamole resulted in a 16% reduction in stroke risk ($p = 0.039$) and a 15% reduction in stroke or death ($p = 0.015$). More importantly, the combination of aspirin and dipyridamole was additive, leading to a 37% reduction in the stroke rate ($p < 0.001$) and a 24% reduction in stroke or death ($p < 0.001$). No significant impact on mortality was found. Similar findings were found in the rate of TIA, with a 36%

reduction for combination therapy ($p < 0.001$). Patients treated with dipyridamole had a higher incidence of headaches. All-site bleeding and gastrointestinal bleeding were significantly higher in patients treated with aspirin (69).

Prior to ESPS-2, a few studies also showed a significant reduction in stroke with the combination of aspirin and dipyridamole, compared to placebo (70). However, others comparing the addition of dipyridamole to aspirin therapy suggested no benefit, raising doubts about the value of dipyridamole (71,72). However, with the publication of ESPS-2, and a subsequent meta-analysis by Leonardi-Bee et al. (revealing a 22% reduction in recurrent stroke for the combination of dipyridamole and aspirin, compared to aspirin alone [OR 0.78, 95% CI 0.65–0.93] [73]), the combination of aspirin and dipyridamole has become accepted as first-line therapy in treating patients to prevent recurrent ischemic stroke.

Of note, dipyridamole has been used in the past as a pharmacological coronary stressor for nuclear stress tests. There has been concern about the use of dipyridamole in patients with stable angina. In fact, the American College of Cardiology has recommended against its use in this patient cohort (74). However, in the meta-analysis by Leonardi-Bee et al. combination therapy with aspirin and dipyridamole was associated with a significant reduction in the composite of nonfatal stroke, nonfatal MI, and vascular death compared to aspirin alone (OR 0.84, 95% CI 0.72–0.97) (73). In addition, a post hoc analysis of ESPS-2 did not show any increased incidence of cardiac events in patients with a history of CAD or MI treated with dipyridamole (75).

Ticlopidine

Ticlopidine has been used extensively in the past for the treatment of cardiovascular disease, after coronary stent placement, and to prevent recurrent strokes or TIA. Ticlopidine is a thienopyridine platelet antagonist that inhibits ADP-dependent platelet aggregation. Two major studies evaluated ticlopidine for secondary stroke prevention. The Canadian American Ticlopidine Study (CATS) randomized 1072 patients with recent ischemic stroke to either ticlopidine 250 mg twice daily or placebo between 1 wk and 4 mo after their index event. Treatment with ticlopidine resulted in a 30.2% relative risk reduction in stroke, MI, or vascular death (15.3% vs 10.8%, 95% CI 7.5–48.3%, $p = 0.006$). Intention-to-treat analysis found a 23.3% relative risk reduction of the combined end point ($p = 0.02$) (76). The magnitude of benefit compares favorably to aspirin therapy. The Ticlopidine Aspirin Stroke Study compared ticlopidine therapy (500 mg daily) to aspirin (1300 mg daily) in 3069 patients with recent TIA, amaurosis fugax, or stroke. The risk of nonfatal stroke or death was 17% for the ticlopidine arm and 19% for the aspirin arm at 3 yr (RRR 12%, $p = \text{NS}$). The rate of all strokes (fatal and nonfatal) at 3 yr was 10% for ticlopidine and 13% for aspirin (RRR 21%, 95% CI 4–38%, $p = 0.024$) (77). Overall, ticlopidine seems to have slightly greater efficacy compared to aspirin therapy.

Ticlopidine, however, has a significant risk profile of side effects. Patients in CATS had a 1% incidence of severe neutropenia, and 2% incidence of skin rash and diarrhea, all of which were found to be reversible after discontinuation of ticlopidine (76). In the Ticlopidine Aspirin Stroke Study, patients treated with ticlopidine had a 20% incidence of diarrhea, a 14% incidence of skin rash, and a <1% incidence of severe neutropenia (77). Given its side-effect profile in addition to its cost, ticlopidine has not been used as a first-line agent.

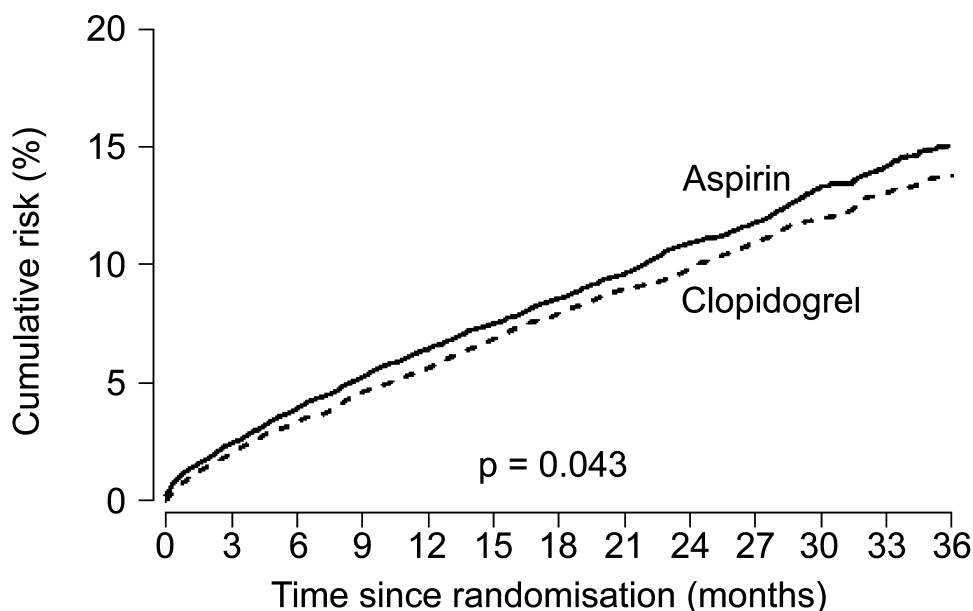


Fig. 4. Risk of adverse vascular events with clopidogrel and aspirin therapy in the CAPRIE trial. The annual rate of ischemic stroke, MI, or vascular death was reduced with clopidogrel therapy compared to aspirin therapy (5.32% vs 5.83%, RRR of 8.7%; 95% CI 0.3–16.5%, $p = 0.043$). (Reproduced with permission from ref. 78.)

Clopidogrel

Clopidogrel is also a thienopyridine platelet antagonist that inhibits ADP-mediated platelet inhibition. It has a better side-effect profile than ticlopidine, without the incidence of neutropenia. Clopidogrel has a once daily dosing, and has supplanted ticlopidine in most settings. The largest trial of clopidogrel for secondary prevention was the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, which randomized 19,185 patients to either clopidogrel 75 mg daily or aspirin 325 mg daily. These patients had a recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease. The annual rate of ischemic stroke, MI, or vascular death was 5.32% in patients treated with clopidogrel compared to 5.83% with aspirin, with a relative risk reduction of 8.7% for clopidogrel (95% CI 0.3–16.5%, $p = 0.043$) (Fig. 4). Actual treatment analysis revealed a relative reduction of 9.4% (78).

In the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study of patients presenting with acute coronary syndromes, combination therapy with aspirin and clopidogrel was shown to be more beneficial than aspirin therapy alone for reducing the number of cardiovascular events. For secondary stroke prevention, however, the benefit of combination therapy is less clear. The MATCH trial treated 7599 patients with recent ischemic stroke or TIA already on clopidogrel 75 mg daily with aspirin 75 mg daily or placebo. The primary end point was a combination of ischemic stroke, MI, vascular death, or hospitalization for acute ischemia at 18 mo. Patients treated with the combination of aspirin and clopidogrel had a nonsignificant reduction in the primary end point (6.4%, 95% CI –4.6 to 16.3%) compared to treatment with clopidogrel alone. Major and life-threatening bleeding was significantly higher in the combination therapy group, however (79). The MATCH trial has been criticized for numerous

reasons, including its entry criteria and its use of a composite end point. However, for stroke prevention, the combination of aspirin and clopidogrel has not been proven to be better than clopidogrel monotherapy. More recently, a study involving 100 patients undergoing CEA who were treated with aspirin and clopidogrel showed a 10-fold reduction in the number of patients having more than 20 emboli detected by TCD within 3 h of surgery (OR 10.23; 95% CI 1.3–83.3, $p = 0.01$) (80).

Warfarin

Antithrombotic therapy with warfarin has not been shown to be effective in preventing recurrent stroke. In the Warfarin-Aspirin Recurrent Stroke Study (WARSS), 2206 patients presenting with ischemic stroke within 30 d were randomized to either aspirin (325 mg daily) or warfarin (INR 1.4–2.8) for >2 yr. The risk of recurrent ischemic stroke or death was 17.8% in the warfarin-treated group and 16.0% in the aspirin-treated group (hazard ratio 1.13, 95% CI 0.92–1.38, $p = 0.25$). No significant differences were found in the rates of TIA, MI, or hemorrhage (2.22 major hemorrhage/100 patient-years in the warfarin group and 1.49/100 patient-years in the aspirin group). Importantly, patients with operable carotid stenosis were excluded from this trial (81). Overall, aspirin is generally preferred to warfarin for secondary prevention in patients with carotid disease. Possible exceptions are patients with thrombus in the carotid artery, critical carotid stenosis awaiting surgery, and carotid dissection in whom anticoagulation may be beneficial.

CONCLUSION

Patients with carotid artery stenosis likely have atherosclerotic disease elsewhere. Overall, the goal of therapy in these patients is not only to reduce the stroke risk attributable to the carotid stenosis, but also to decrease their global risk of cardiovascular death, MI, and stroke. To achieve this goal, therapy should focus on aggressive treatment of an individual patient's cardiovascular risk factors including hypertension, dyslipidemia, and tobacco abuse. Blood pressure reduction, even in "normotensive" patients, has a substantial impact in reducing the likelihood of stroke as well as cardiovascular death and MI. Reaching target blood pressure is likely more important than the agent used to achieve it, with notable exceptions in patients who have other indications for particular agents (e.g., ACE inhibitors in patients with congestive heart failure or diabetes mellitus). Caution should be exercised in aggressively lowering blood pressure in patients with bilateral carotid stenoses. Lipid lowering therapy, specifically statin therapy, has significant value in reducing cardiovascular risk including stroke reduction. However, the value of statin therapy in patients who have a history of cerebrovascular disease is uncertain for stroke reduction. Statin therapy should still be utilized because of its impact on overall vascular risk. Patients at high risk for vascular events will also benefit from aspirin therapy. Patients with prior stroke or TIA definitely benefit. Depending on other comorbidities, these patients may also benefit from either dipyridamole–aspirin combination therapy (patients with isolated TIAs without other significant vascular disease) or clopidogrel therapy (patients with other established vascular disease). Smoking cessation should also be advocated strongly. The value of aggressive glucose control in diabetic patients is not entirely clear for the reduction of macrovascular events. Aggressive control should still be encouraged for its favorable effect on microvascular events. In summary, although carotid revascularization is indicated for only a minority of patients with carotid atherosclerotic disease, aggressive medical therapy is indicated for all patients with carotid atherosclerotic disease.

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