HANDBOOK OF COMPLEX PERCUTANEOUS CAROTID INTERVENTION
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Edited by

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DEDICATIONS

To my husband, David, and our son, Evan, and my family, who make my life endeavors worthwhile. And to my mentors in Interventional and General Cardiology (Drs. Donald Beanlands, Deepak Bhatt, Irvine Franco, John Jue, David Moliterno, Eric Topol, and Jay Yadav), for their guidance and support through my training, and for inspiring me to excel.

Jacqueline Saw, MD

To my wife, Karin, and my parents, Cristina and Emilio, with all my love and gratitude. This book would not be possible without the teachings of Dr. Jay Yadav and the remarkable Peripheral Intervention Staff at the Cleveland Clinic Foundation.

J. Emilio Exaire, MD

To Megan and my family for their love, support, and encouragement, and to the interventional cardiologists at the Cleveland Clinic (especially Drs. Yadav, Franco, Whitlow, Topol, and Bajzer) for their mentorship, friendship, time, and investment in me. I would not be who I am and where I am without you.

David S. Lee, MD

To my family for their unfailing support and understanding, and to the interventional cardiology fellows at the Cleveland Clinic for their curiosity and inspiration.

Jay S. Yadav, MD
Since the first carotid angioplasty that was performed in 1980, this technique has undergone tremendous modifications and improvements. Stents for the carotid artery were utilized in the early 1990s, and emboli protection devices were introduced about 2000. Advances in equipment (guidewires, catheters, balloons, stents, and emboli protection devices) have improved the technical success and safety of carotid stenting. With the recent SAPPHIRE publication revealing non-inferiority of carotid stenting compared with carotid endarterectomy for high-risk surgical patients, this percutaneous procedure is now considered a viable alternative to endarterectomy for these patients. In fact, the FDA has approved carotid stenting for high-risk patients using the AccuLink™ stent and AccuNet™ device (Guidant Corporation, Santa Clara, CA) in August 2004, and the Xact™ and EmboShield™ system (Abbott Vascular Devices, Redwood City, CA) in September 2005.

Increasing numbers of carotid stenting are being performed around the world, and established interventionalists and trainees alike are seeking to be instructed in performing this meticulous procedure. Unfortunately, there are insufficient well-established peripheral vascular training programs to meet this increasing demand. Only a small proportion of current trainees are enrolled in fellowship programs with dedicated carotid interventional training that perform high-volume extracranial carotid stenting; even fewer are enrolled in programs that also partake in intracranial and acute stroke interventions. In North America, this shortage of dedicated training programs leaves interested interventionalists pursuing carotid stent training through short educational courses, and often haphazard and limited “hands-on” experience in other institutions.

The purpose of our Handbook of Complex Percutaneous Carotid Intervention is to provide a learning resource to complement the “hands-on” training of established interventionalists and trainees. This handbook is intended for various disciplines participating in the management of patients with carotid and vertebral artery stenosis, including interventional cardiologists, vascular surgeons, interventional radiologists, and interventional neurologists. The focus of this handbook is on percutaneous intervention of patients with extracranial carotid artery stenosis. As interventionalists of the cerebrovasculature are often faced with stenosis involving other cerebral vessels, we complemented our handbook with sections on percutaneous interventions of intracranial stenosis, vertebral artery stenosis, and acute stroke.

We have provided a detailed introduction to the techniques of extracranial and intracranial, carotid, and vertebral interventions. We reviewed the indications, approaches, equipment, and potential complications of these percutaneous interventions. As many patients undergoing such procedures are elderly and high-risk with challenging anatomy, we also provided some useful pearls and troubleshooting of technically difficult cases. In addition, our section on challenging cases illustrates our approach to frequently encountered challenges at the Cleveland Clinic.

The Handbook of Complex Percutaneous Carotid Intervention is also meant to provide a comprehensive review of the management of carotid artery stenosis. Thus, we have
included chapters reviewing the epidemiology and significance of carotid stenosis, medical therapy, noninvasive and invasive imaging of the carotid artery, and carotid endarterectomy. In this current era of evidence-based medicine, we have also included chapters reviewing sentinel studies supporting carotid endarterectomy and carotid stenting.

Carotid stenting is an exciting and burgeoning field. It is often a challenging procedure, which may expose patients to life-threatening complications. Its success as the preferred revascularization therapy of high-risk patients is contingent upon low periprocedural complications, which in turn is highly dependent on operator skills. As studies comparing carotid stenting and endarterectomy for low-risk patients are completed, we may see a further increase in the volume of carotid stenting. We hope that our *Handbook of Complex Percutaneous Carotid Intervention* will provide a useful resource to guide interventionalists through this challenging and important revascularization procedure of the 21\textsuperscript{st} century.

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*David S. Lee, MD*
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The accompanying CD ROM contains the movies associated with Part III, Challenging Case Illustrations and Pearls, and all color illustrations from the book.

The following hardware and software are the minimum required to use this CD-ROM:

- For Microsoft Windows: An Intel Pentium II with 64 MB of available RAM running Windows 98, or an Intel Pentium III with 128 MB of available RAM running Windows 2000 or Windows XP. A monitor set to 832 × 624 or higher resolution.
- For Macintosh OS X: A Power Macintosh G3 with 128 MB of available RAM running Mac OS X 10.1.5, 10.2.6 or higher. A monitor set to 832 × 624 or higher resolution.
- For Macintosh Classic: A Power Macintosh G3 with 64 MB of available RAM running System 9.2. A monitor set to 832 × 624 or higher resolution.
I

CLINICAL EXPERIENCE
Summary

Carotid artery stenosis is a prevalent disease, caused predominantly by atherosclerosis. The reported prevalence is dependent on the population screened, investigative tool used, and the criteria employed. The presence of carotid artery stenosis is associated with an increased risk of stroke and other ischemic manifestations of systemic atherosclerosis (e.g., myocardial infarctions and vascular deaths). Thus, carotid revascularization strategies for stroke prevention had been aggressively pursued over the past five decades. This chapter reviews the epidemiology and prevalence of carotid artery stenosis.

Key Words: Carotid artery stenosis, carotid artery stenting, carotid endarterectomy, epidemiology, stroke.

INTRODUCTION

Carotid artery stenosis is a prevalent disease, caused predominantly by atherosclerosis. Other causes are rare and include fibromuscular dysplasia, trauma, and carotid dissection. The reported prevalence of carotid artery stenosis is dependent on the population screened, investigative tool used, and criteria employed. In the Framingham Study cohort, the prevalence of significant carotid artery stenosis (carotid ultrasound stenosis >50%) was 7% in women and 9% in men (1). The prevalence is higher among individuals at risk for atherosclerosis (11%), those who have underlying cardiac disease (18%), and those presenting with acute stroke (60%) (2). It is clear that age and the presence of atherosclerotic risk factors increase the prevalence of disease. Not surprisingly, the presence of carotid artery stenosis is associated with an increased risk of...
stroke and other ischemic manifestations of systemic atherosclerosis (e.g., myocardial infarctions and vascular deaths). Thus, carotid revascularization strategies for stroke prevention had been aggressively pursued over the past five decades.

**STROKE**

**Prevalence of Stroke and Economic Burden**

The primary goal of revascularization of significant carotid artery stenosis is to prevent strokes. Strokes can have major impact on both the individual and the society, incurring disability and draining the healthcare system and the economy. Each year, approx 750,000 Americans and 50,000 Canadians experience a new or recurrent stroke (3). Stroke is the third leading cause of death, and the principal cause of long-term disability. Approximately one third of patients die within 30 d, and one third are left with permanent disability. The economic burden in North America is astounding, costing the healthcare system more than 50 billion dollars annually in the United States and approx 3 billion dollars annually in Canada (3).

**Stroke Etiology**

More than 80% of all strokes are ischemic in origin (Fig. 1), while 20% are due to intracerebral hemorrhage (Fig. 2). Three quarters of ischemic strokes involve the anterior circulation, and one quarter involve the posterior vertebrobasilar system (4). Overall, 20–30% of all strokes are accounted for by extracranial carotid artery stenosis (5), whereas intracranial atherosclerosis account for roughly 5–10% of strokes (6,7). However, most of these data are based on a predominantly Caucasian population, and epidemiologic studies have also shown ethnicity to affect stroke etiology. For instance, in the Northern Manhattan Stroke study, intracranial atherosclerosis was shown to account for 6–10% of ischemic strokes of white patients, but up to 29% among African Americans and Hispanics (8). Among patients with lacunar infarcts, the prevalence of extracranial carotid artery disease (>50% stenosis) is approx 10% (which is likely an incidental finding). Whereas among patients with nonlacunar hemispheric stroke, 41% had ipsilateral carotid artery disease (>50% stenosis) (9).

**CAROTID ARTERY STENOSIS**

**Location of Carotid Artery Stenosis**

Atherosclerotic plaques tend to accumulate at branch ostia and bifurcations due to the disturbance of laminar flow. Thus, in the carotid circulation, there is a predilection of plaque accumulation at the carotid bifurcation into the internal carotid artery (ICA) and external carotid artery (ECA). The ostium of the ICA is most often affected, involving the outer posterior wall of the carotid sinus, and often extending into the distal common carotid artery (CCA). Atherosclerosis of the intracranial ICA and its branches is much less common (described in Chapter 13).

**Prevalence of Concomitant Intracranial Atherosclerosis**

Although uncommon, a small proportion of patients with extracranial carotid stenosis have concomitant intracranial involvement. In a series of 100 consecutive patients with severe extracranial carotid disease being considered for carotid endarterectomy, cerebral angiography showed significant intracranial disease in 15% of patients (10). In
Fig. 1. Schematic diagram illustrating frequent causes of ischemic strokes.
the NASCET (North American Symptomatic Carotid Endarterectomy) study of symptomatic patients with extracranial carotid disease, mild intracranial disease was found in 33% patients. However, by protocol design, patients with severe intracranial disease were excluded (11).

**Significance of Carotid Bruit**

Carotid disease may be discovered as patients are worked up for carotid bruit. However, the presence of carotid bruit is poorly specific for carotid stenosis. In fact, the prevalence of significant carotid stenosis in patients with asymptomatic carotid bruit is only 10–20% (12,13). Patients with carotid bruit and documented carotid stenosis on duplex ultrasound do have higher risk of cerebral events (14). Indeed, patients with carotid bruit have been shown to have a two to fourfold higher risk of subsequent strokes when compared to controls (12,13).

**Carotid Intimal–Medial Thickness**

There is a strong association between cerebrovascular atherosclerosis and adverse vascular events. Measurement of the intimal–medial thickness (IMT) on carotid ultrasound has evolved to be a reliable method to evaluate early carotid atherosclerosis (15). Many studies have documented the link between increased IMT and future adverse vascular events. In a prospective study by O’Leary et al. involving more than 4400 elderly subjects without clinical evidence of cardiovascular disease, approx 25% of patients in the fifth IMT quintile had experienced myocardial infarction or stroke at 7 yr follow-up, compared with <5% for the first quintile (Fig. 3) (16).

**Concomitant Coronary Artery Disease and Peripheral Arterial Disease**

Presence of severe atherosclerosis in one vascular bed may trigger screening for concomitant silent cerebrovascular disease. Among patients with severe coronary disease
being considered for cardiac surgery, 17–22% have >50% carotid stenosis, and 6–12% have >80% carotid stenosis \(^\text{(17)}\). Among patients with peripheral arterial disease, 14–34% had carotid stenosis >50% by duplex ultrasound \(^\text{(18,19)}\), and 5% have carotid occlusion \(^\text{(19)}\).

**CONSEQUENCE OF CAROTID ARTERY STENOSIS**

**Disease Progression**

Similar to other vascular beds, atherosclerotic carotid disease is a dynamic process. In a prospective study of patients with asymptomatic carotid bruit and mild carotid stenosis, serial ultrasound studies showed that the annual rate of disease progression to >50% stenosis was 8\% \(^\text{(12)}\). In a recent series, among patients with moderate asymptomatic carotid disease (50–79% stenosis) followed for a mean of 38 mo, 17\% had evidence of disease progression documented on serial ultrasound examinations, with an estimated annual rate of progression of 4.9\% \(^\text{(20)}\).

**Risk of Stroke**

The risk of stroke is highly dependent on the severity of stenosis and symptom status. Patients with known carotid artery stenosis who presented with a neurologic event within the last 6 mo are more likely to have a future stroke event. For example, in the NASCET study, the risks of ipsilateral strokes at 5 yr for patients with mild (<50\%) stenosis on angiography were 18.7\% and 7.8\% for those with and without symptoms, respectively. For those with more severe (75–94\%) stenosis, the rates were higher, 27.1\% and 18.5\% for symptomatic and asymptomatic patients, respectively (Fig. 4) \(^\text{(21)}\).

Among patients studied in the asymptomatic carotid endarterectomy trials with carotid stenosis >60\%, the incidence of ipsilateral stroke at 5 yr was 11.5\% in ACAS.
Other Predictors of Stroke

Aside from symptom status and stenosis severity, plaque characteristics could also affect subsequent stroke risk. For example, hypoechoic plaques as detected by high-resolution ultrasound are associated with higher stroke risk. Presumably these plaques have high lipid content and are more prone to rupture, with subsequent thrombosis and embolization (25–27). Ulcerated plaques are also known to be more unstable and at
higher risk for neurologic event. For example, in the medical arm of NASCET, the 2-yr stroke rate among patients without an ulcer was 21.3% irrespective of stenosis severity. However, among those with an ulcer on angiography, the 2-yr stroke event increased incrementally from 26.3% to 73.2%, as the stenosis severity increased from 75% to 95% (28).

**Risks of Coronary Artery Disease**

It should be noted that patients with cerebrovascular disease have a high prevalence of silent coronary artery disease. Hertzer et al. performed coronary angiography on 200 asymptomatic patients (most of whom had carotid bruit). Eighty patients (40%) were found to have severe coronary artery disease (defined as >70% stenosis of ≥1 coronary artery), and 93 patients (46%) had mild or moderate disease. Only 27 patients (14%) had normal coronary arteries. In terms of extent of disease, 22% were considered to have severe but compensated coronary artery disease, 16% had severe but surgically correctable disease, and 2% had inoperable disease (29).

**Risk of Stroke with Coronary Artery Bypass Surgery**

High-grade carotid artery stenosis (>80%) occur in roughly 8–12% of patients scheduled for coronary artery bypass grafting, and was responsible for up to 30% of hemispheric strokes that occur early after surgery. The incidence of perioperative stroke is dependent on stenosis severity, being <2% when carotid stenosis is mild (<50% severity), but increasing to 10% with moderate lesions (stenosis 50–80%), and to 11–19% with severe stenosis (>80%). Patients with bilateral high-grade stenosis (>80%) or occlusion have up to a 25% incidence of stroke perioperatively (30). Therefore, screening for significant carotid stenosis is important prior to cardiac surgery, and is routinely performed in most institutions. This allows surgeons to have a better estimation of perioperative stroke risk.

**CONCLUSION**

Carotid artery stenosis is an important cause of stroke. Symptomatic patients with severe carotid artery stenosis are at much higher risk for future strokes than are asymptomatic patients. Patients with significant carotid artery stenosis are also at increased risk for other vascular events, as atherosclerosis is a systemic disease. Management of these patients should thus be multifaceted, and should include aggressive risk-factor modification, medical treatment to diminish global atherothrombotic risks, and carotid revascularization to lower cerebrovascular events, as appropriate.

**REFERENCES**

1. Fung and Saw


Summary

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 (≥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...
(≥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 SAPPHIRE (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 doxazocin 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).
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 \(<140/90 \text{ mmHg} \) 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 \(<130/85 \text{ mmHg} \) 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 ≥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
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 10,001 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