Stroke in Chronic Kidney Disease: Prevention and Management

Raymond R. Townsend

Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania


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Faculty:
George L. Bakris, MD, Hypertensive Diseases Unit, Section of Endocrinology, Diabetes and Metabolism, Pritzker School of Medicine, University of Chicago, Chicago, Illinois
Stuart L. Linas, MD, Department of Internal Medicine, Division of Renal Diseases and Hypertension, University of Colorado Health Sciences Center, Denver, Colorado
Raymond R. Townsend, MD, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

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Learning Objectives:
1. To examine the epidemiology and pathophysiology of stroke and cardiovascular disease in the chronic kidney disease population
2. To evaluate the efficacy of current therapies for the treatment of cardiovascular risk in patients with renal disease
3. To apply new clinical insights for the identification and treatment of cardiovascular risk to improve outcomes for patients with chronic kidney disease

Target audience: Physicians in internal medicine, nephrology, endocrinology, and other health care providers who are interested in the treatment of hypertension and kidney disease.

Categories: Stroke prevention, angiotensin receptor blocker, angiotensin-converting enzyme inhibitor, kidney disease

The incidence of stroke is elevated among individuals with kidney disease. Traditional risk factors seem to account for much but not all of this excess risk. Blood pressure control is the most important aspect of stroke prevention. Multiple classes of antihypertensive agents, including diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers, have reduced stroke risk. Some physiologic and clinical evidence suggests that angiotensin II receptor blockers may offer superior benefit to that of angiotensin-converting enzyme inhibitors for the same level of blood pressure control; however, few head-to-head trials have compared these two agent classes directly using stroke as an outcome.

High BP and kidney disease have been associated with increased incidence of stroke (1). BP control is crucial to stroke prevention (2). Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), among other antihypertensive agents, have demonstrated effectiveness in reducing stroke risk (3). This article reviews stroke prevention as well as acute stroke management in patients with kidney disease.

Assessing Stroke Risk in Individuals with Renal Disease

In another article in this supplement, Bakris et al. summarize epidemiologic data documenting an association between kidney function and stroke risk (1,4,5). Evaluating stroke risk in individuals with kidney disease involves much the same process as in other populations because the same risk factors apply (Table 1) (2,6). Patients should be assessed for the presence of risk factors listed in Table 1, as well as for type of renal disease and estimated GFR.

Traditional risk factors account for much but not all of the excess stroke risk in chronic kidney disease (CKD). Epidemiologic studies report an elevated stroke risk in kidney disease after adjustment for such factors (where kidney function is usually stated as an estimated GFR <60 ml/min per 1.73 m² or a serum creatinine >1.3 mg/dl) (4,5,7,8). Physiologic evidence also suggests that renal impairment itself in some way increases susceptibility to stroke. The proportionate contribution of tra-
Table 1. Risk factors for stroke

<table>
<thead>
<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Alcohol consumption (especially ≥300 g/wk)</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Autosomal-dominant polycystic kidney disease</td>
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<tr>
<td>Body fat distribution</td>
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<tr>
<td>Carotid stenosis</td>
</tr>
<tr>
<td>Cigarette smoke exposure</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Dietary factors†</td>
</tr>
<tr>
<td>Dyslipidemia†</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Postmenopausal hormone therapy</td>
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<tr>
<td>Sickle cell disease</td>
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</tbody>
</table>

†From Goldstein et al. (2) and Ruigrok et al. (6).
	For subarachnoid hemorrhage.
	High sodium intake, low potassium intake.
	For ischemic stroke.

ditional risk factors and the CKD milieu to stroke risk is unclear. Modifiable risk factors should be identified and addressed.

Those at elevated risk for intracranial aneurysm can be evaluated through noninvasive imaging. Counseling patients in advance about the implications of detection on driver’s licensing, life insurance, and other issues is advisable (9).

Preventing Stroke

Several approaches to primary and secondary stroke prevention have been explored in the literature, including the treatment of dyslipidemia and anemia, BP control, and the use of ARB outside of BP control. The current evidence and the merit of these approaches are discussed here in the context of stroke and cardiovascular disease (CVD) risk and prevention.

Treating Dyslipidemia

Some data suggest that reduction of LDL cholesterol may be beneficial in secondary prevention of CVD, although not of stroke, among individuals with reduced kidney function. A post hoc subgroup analysis of patients with chronic renal insufficiency (creatinine clearance ≤75 ml/min) in the Cholesterol and Recurrent Events (CARE) trial indicated that pravastatin was associated with a lower incidence of the combined primary outcome (death from coronary disease or symptomatic nonfatal myocardial infarction [MI]) compared with placebo after a median follow-up of nearly 5 yr (adjusted hazard ratio [HR] 0.72; 95% confidence interval [CI] 0.55 to 0.95; P = 0.02) (10).

Patients (n = 1711) also had a history of MI and total plasma cholesterol <240 mg/dl. Reduction of stroke risk, a secondary end point, did not reach significance (adjusted HR 0.62; 95% CI 0.39 to 1.00; P = 0.051) (10). The ongoing Study of Heart and Renal Protection (SHARP), which included roughly 9,000 patients with CKD and evaluated the effects of simvastatin plus ezetimibe, should provide more information about lipid reduction and prevention of vascular events in kidney disease (11).

Addressing Anemia

Anemia has been shown to substantially increase the risk for stroke associated with CKD (7). Recombinant erythropoietin is indicated to correct this condition in individuals with CKD (12). A 2006 update of National Kidney Foundation guidelines defined target hemoglobin as ≥11.0 g/dl and advised caution when intentionally maintaining hemoglobin at >13.0 g/dl (13). A clinical trial published at the end of 2006 underscores the risk of a higher target hemoglobin level. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) investigators concluded that a hemoglobin target of 13.5 g/dl was associated with significantly greater risk for the primary composite outcome (death, MI, hospitalization for congestive heart failure without renal replacement therapy, or stroke) compared with a lower target of 11.3 g/dl (HR 1.34; 95% CI 1.03 to 1.74; P = 0.03) (14). This increased risk was associated with a lower-than-targeted hemoglobin level, as the mean achieved hemoglobin value in the higher target group was 12.6 g/dl (14). Patients in the higher target group received nearly twice the amount of epoetin α as those in the lower target group (mean 11,215 versus 6276 U/wk, respectively) (14). Quality-of-life improvements were similar in both treatment groups (14). More patients in the higher target group had at least one serious adverse event (14). It may be that the small BP increase noted with erythropoietin, the lessened bleeding tendency when hematocrit is raised (thus a greater thrombosis potential), the increase in the viscosity of blood when hematocrit is higher, and the potential oxidative stress that is induced by greater iron administration may have contributed to these findings (15). The authors therefore recommended a hemoglobin target of 11.0 to 12.0 g/dl in patients with CKD (15 to 50 ml/min per 1.73 m² in their study) (14).

BP Control

Good BP control is the most important factor in stroke prevention irrespective of the antihypertensive agent used (16). Rapid control of BP, within weeks rather than months, is an important factor in CV risk reduction, at least in hypertensive patients at high CV risk (17).

ACEI, ARB, and calcium channel blockers (CCB) have significantly reduced stroke risk in clinical trials (3). The Blood Pressure Lowering Treatment Trialists’ Collaboration’s prospective analyses of data from 29 randomized studies (n = 162,341) concluded in part that treatment with ACEI- or CCB-based regimens significantly lowered stroke risk compared with placebo and that ARB-based treatment reduced stroke risk compared with control regimens. Lower BP goals also resulted in greater decreases in stroke risk (3). Nonsignificant trends pointed to greater risk reduction with treatment based on diuretics, β blockers, and CCB compared with regimens based on ACEI (3). The investigators concluded that BP lowering is a major component of all drug classes’ effects in stroke prevention (3).

A published review of clinical trial results proposes the possibility of a superior benefit for ARB in stroke prevention in part because multiple trials of ACEI have demonstrated either no significant decrease or a significant increase in stroke risk.
Multiple trials of ARB have demonstrated significant reductions in stroke risk (22, 23). An exception was the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, in which valsartan-based treatments were associated with a non-significant increase in stroke rate compared with amlodipine-based regimens (17). Stroke was a secondary outcome of this trial; the primary composite outcome (cardiac morbidity and mortality) did not differ significantly between groups (HR 1.04; 95% CI 0.94 to 1.15; P = 0.49) (17).

A subsequent analysis of these findings illustrated the importance of timing as well as degree of BP reduction. BP response after the first month of treatment predicted events and survival (24). Differences in BP were significant throughout the trial but especially pronounced during this period (17). At 1 mo, mean BP in patients who were randomly assigned to amlodipine-based therapy was 4.0/2.1 mmHg lower than in those who received valsartan-based treatment. The average difference narrowed to 2.1/1.6 mmHg at 6 mo and remained at roughly that level for the rest of the study (17). From 6 mo to study end (at 72 mo), BP reduction was similar: 3.0/2.5 mmHg with amlodipine-based therapy and 3.3/2.6 mmHg with valsartan-based treatment (17). Approximately 76% of the excess strokes in the valsartan group occurred during the first year of therapy, when the difference in BP was the largest (17).

**ARB Benefits Beyond BP?**

Physiologic findings support the hypothesis that ARB may be superior to ACEI in terms of stroke prevention for the same degree of BP control (16). Experimental evidence suggests that angiotensin II (AngII) has beneficial as well as detrimental effects on CV and cerebrovascular function. The detrimental effects from increased BP stem from AngII stimulation of the AT1 receptor, which ARB block. The beneficial actions derive from AngII stimulation of the other AngII receptor type (AT2) (16). The actions of AT1 typically dominate; however, experimental evidence indicates that selective AT2 blockade enhances the cerebroprotective effects of AT2 stimulation (16). AT1 blockade leads to upregulation of AT2 receptors in endothelial cells (16). It also leaves AngII free to stimulate the AT2 receptors (16). ACEI, in contrast, interfere with the production of AngII (16).

Certain ARB offer other cerebroprotective effects unrelated to AngII (16). Losartan interferes with platelet aggregation; increased platelet aggregation has been linked to elevated stroke risk (16). The effect of serum uric acid on stroke and CV risk has been disputed (16). In an analysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, however, baseline serum uric acid was significantly associated with CV complications. Losartan’s reduction of uric acid accounted for 29% of its treatment effect on the primary composite end point (CV death, MI, or stroke) compared with atenolol (25).

The ARB telmisartan exerts beneficial effects on glucose metabolism independent of its action on the renin-angiotensin system (16). Other ARB have reduced the risk for new-onset diabetes compared with a CCB (valsartan) (17) and with a β blocker (losartan) (22). Such effects may be of interest because newly diagnosed diabetes is associated with an increased stroke risk in the first 5 yr after onset (26).

**Acute Management of BP During Ischemic Stroke**

Few data are available regarding BP management during acute ischemic stroke, making this a controversial issue (27, 28). American Stroke Association guidelines for managing BP in patients who sustain acute ischemic stroke and are ineligible for thrombolytic therapy may seem to be counterintuitive. No pharmacologic treatment should be initiated if systolic BP (SBP) is <220 or diastolic BP (DBP) is <120 mmHg unless there is end-organ involvement (e.g., acute renal failure, acute MI) (27). BP falls spontaneously in the majority of cases, and there is little scientific basis for antihypertensive therapy (27).

Further definition of what constitutes “end-organ involvement” would aid in treatment decisions. Whether consistently elevated creatinine levels (e.g., 1.8 mg/dl) can be considered an indication to administer antihypertensive therapy for patients with lower BP, for example, remains to be clarified. Determinations must be made on a case-by-case basis. Patients with SBP of >220 or DBP of 121 to 140 mmHg should receive nicardipine or labetalol. If DBP is >140 mmHg, then nitroprusside should be administered. The goal is to lower BP by 10 to 15% (27).

**Prevention of Recurrent Stroke**

History of stroke confers a 20% risk for recurrent stroke within 5 yrs (29). Treatment with the ACEI perindopril and the diuretic indapamide added at the physician’s discretion reduced recurrent stroke risk over 4 yrs by 28% compared with placebo (95% CI 17 to 38%; P = 0.0001; n = 6,105) (30). The risk reduction remained significant irrespective of the presence of hypertension; roughly half of patients were hypertensive (30). In the subset of patients who received combination therapy (n = 3,544, 58% of total), the risk for recurrent stroke was reduced by 43% (95% CI 30 to 54%; P < 0.001) compared with placebo (30). The effect of perindopril alone did not differ significantly from that of placebo (30). Investigators attributed this difference to the greater BP-lowering effect achieved with combination therapy (12/5 versus 5/3 mmHg) (30).

The ARB eprosartan also has significantly reduced the risk for recurrent stroke compared with nitrendipine during a median follow-up of 2.5 yrs. Outcome was calculated by including recurrent rather than only first events. The primary end point was a composite of all-cause mortality and CV and cerebrovascular events (intracerebral hemorrhage, stroke recurrence, or transient ischemic attack/prolonged reversible ischemic neurologic deficit) (31). All patients (n = 1,405) were hypertensive (31). Approximately two thirds required multiple agents for BP control; diuretics and β blockers were the most common choices (31). The eprosartan group experienced a lower incidence density per 100 patient-years of the primary outcome (13.25 versus 16.71; incidence density rate 0.79; P = 0.014). The risk for cerebrovascular events also was reduced significantly.
Table 2. Effect of ACEI and ARB therapy on stroke risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Subjects</th>
<th>Follow-up (yrs)</th>
<th>Treatment Comparison</th>
<th>Effect of ACEI or ARB on Stroke Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT(^b) (18); post hoc subgroup analysis of randomized trial</td>
<td>(n = 31,897; \geq 55) yrs of age, HTN + (\geq 1) other CHD risk factor</td>
<td>6(^c)</td>
<td>Lisinopril versus chlorthalidone</td>
<td>15% increase unadjusted: HR 1.15; 95% CI 1.02 to 1.30</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>GFR (\geq 90) ml/min per 1.73 m(^2)</td>
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</tr>
<tr>
<td></td>
<td>GFR &lt;90 ml/min per 1.73 m(^2)</td>
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<tr>
<td>CAPPP(^b) (19); prospective, randomized</td>
<td>(n = 10,985; 25) to 66 yrs of age, HTN</td>
<td>6.1</td>
<td>Captopril versus conventional therapies (diuretics, (\beta) blockers)</td>
<td>25% increase: RR 1.25; 95% CI 1.01 to 1.55</td>
<td>0.044</td>
</tr>
<tr>
<td>ANBP(^d) (20); prospective, randomized</td>
<td>(n = 6,083; 65) to 84 yrs of age, HTN</td>
<td>4.1</td>
<td>ACEI versus diuretic</td>
<td>Total stroke, NS effect</td>
<td>0.91</td>
</tr>
<tr>
<td>HOPE (21); prospective, randomized</td>
<td>(n = 9,297; \geq 55) yrs of age, mostly normotensive, high CV risk(^e)</td>
<td>5</td>
<td>Ramipril versus placebo</td>
<td>32% decrease: RR 0.68; 95% CI 0.56 to 0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>LIFE (22); randomized</td>
<td>(n = 9,193; 55) to 80 yrs of age, HTN, LVH</td>
<td>4.8</td>
<td>Losartan versus atenolol</td>
<td>25% decrease: RR 0.75; 95% CI 0.63 to 0.89</td>
<td>0.001</td>
</tr>
<tr>
<td>SCOPE(^f,g) (23); prospective, randomized</td>
<td>(n = 4,964; 70) to 89 yrs of age, HTN</td>
<td>3.7</td>
<td>Candesartan versus placebo/active therapies</td>
<td>27.8% decrease: 95% CI 1.3 to 47.2 (nonfatal stroke)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>23.6% decrease: 95% CI (-0.7) to 42.1 (all stroke)</td>
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<tr>
<td>VALUE(^f) (17)</td>
<td>(n = 15,245; \geq 50) yrs of age with HTN and various combinations of CV risk factors or disease</td>
<td>4.2</td>
<td>Valsartan versus amlodipine</td>
<td>15% increase: HR 1.15; 95% CI 0.98 to 1.35</td>
<td>0.08</td>
</tr>
</tbody>
</table>

\(^a\)ACEI, angiotensin-converting enzyme inhibitor; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP, Australian National Blood Pressure Study Group; ARB, angiotensin II receptor blocker; CAPPP, Captopril Prevention Project; CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HOPE, Heart Outcomes Prevention Evaluation Study; HR, hazard ratio; HTN, hypertension; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; LVH, left ventricular hypertrophy; RR, relative risk; SCOPE, Study on Cognition and Prognosis in the Elderly; TIA, transient ischemic attack; VALUE, Valsartan Antihypertensive Long-Term Use Evaluation.

\(^b\)Cerebrovascular events/stroke were a component of the primary end point.

\(^c\)Results reported as 6-yr event rates.

\(^d\)Stroke was a subcategory of cerebrovascular events, which was a subcategory of the primary composite outcome (20).

\(^e\)Vascular disease or diabetes plus \(\geq 1\) other CV risk factor.

\(^f\)Stroke was a secondary outcome.

\(^g\)Stroke was a component of the primary outcome.
Kidney disease has been associated with increased stroke risk. Prevention of stroke requires aggressive management of traditional risk factors, including hypertension. Some of the excess stroke risk in individuals with renal disease seems to derive from consequences of renal impairment.

Multiple classes of antihypertensive agents reduce stroke risk. Physiologic evidence points to a basis for stroke risk reduction with ARB beyond that attributable to BP lowering. Both ACEI- and ARB-based therapies have demonstrated efficacy in reducing the risk for recurrent stroke. Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study are \( \text{versus} \) amol (aspirin plus extended-release dipyridamole \( \text{versus} \) clopidogrel). Patients in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study are \( \geq 50 \) yrs of age, present within 120 d of ischemic stroke, and stable when randomly assigned (33).

Additional information will come from the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). This large (\( n = 25,620 \)) trial is comparing the impact of ramipril, telmisartan, and the combination on a composite end point of CV mortality, MI, stroke, or heart failure hospitalization. Patients are \( \geq 55 \) yrs of age with a history of coronary artery disease, peripheral vascular disease, cerebrovascular disease, or diabetes with end-organ damage (34). Participants will be followed for 3.5 to 5 yrs (34).

A similarly designed trial (Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease [TRANSCEnd]) compares the effect of telmisartan and placebo on the same primary end point and in patients with the same profile as those in ONTARGET except for their intolerance of ACEI (\( n = 6,000 \)) (34). Results of both trials are expected in 2008.

Conclusions

Prevention of stroke requires aggressive management of traditional risk factors, including hypertension. Some of the excess stroke risk in individuals with renal disease seems to derive from consequences of renal impairment.

Multiple classes of antihypertensive agents reduce stroke risk. Physiologic evidence points to a basis for stroke risk reduction with ARB beyond that attributable to BP lowering. Both ACEI- and ARB-based therapies have demonstrated efficacy in reducing the risk for recurrent stroke. Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) will yield additional information about the most effective regimens for preventing recurrent stroke. The findings of ONTARGET and TRANSCEnd should further clarify the role of ACEI, ARB, and the combination in risk reduction.

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References

14. Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolf-


30. PROGRESS Collaborative Group: Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 358: 1033–1041, 2001


32. Bjerre LM, Le Lorier J: Expressing the magnitude of adverse effects in case-control studies: The number of patients needed to be treated for one additional patient to be harmed. BMJ 320: 503–506, 2000

33. Diener HC, Sacco R, Yusuf S, Steering Committee, for the PRoFESS Study Group: Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: The Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS). Cerebrovasc Dis 23: 368–380, 2007