Stroke and Its Prevention in Chronic Kidney Disease

Sami Khella* and Melissa B. Bleicher†
*Department of Neurology and †Division of Renal, Electrolyte and Hypertension, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

This is a review of stroke mechanisms and management. The concept of stroke and transient ischemic attack and the recently proposed revision in definitions and controversies are discussed. We also discuss the use of antiplatelet and anticoagulant drugs for stroke due to carotid and cardiac disease.

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This work is dedicated to M.C.K.

Correspondence: Dr. Sami Khella, Penn Presbyterian Medical Center, Department of Neurology, Suite 320 MOB, 39th and Market Streets, Philadelphia, PA 19104. Phone: 215-387-2052; Fax: 215-222-1856; E-mail: sami.khella@uphs.upenn.edu

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ure secondary to primary glomerulonephritides commonly experience strokes at least 36 mo after initiation of dialysis (16). This finding supports the data that perhaps CKD in combination with other cardiovascular risk factors accelerates atherosclerosis in the predialysis population, but CKD alone may be insufficient as an independent risk factor for stroke.

Dialytic support, including both hemodialysis (HD) and peritoneal dialysis, have been shown to be risk factors for stroke. In one report of an HD population, cerebrovascular disease had a prevalence rate of almost 20% (17). The RR is higher for white than black patients and higher in women than in men (6). No studies have assessed stroke risk in renal transplant recipients. Although there are some epidemiologic data for stroke in patients with CKD, there are fewer data for stroke treatment in patients with CKD.

**Mechanisms of Stroke**

**Vascular occlusion in the cerebral circulation results in ischemia of cerebral tissue that causes tissue infarction. Approximately 80% of strokes are ischemic. In between 10 and 20% of strokes, the infarcted tissue subsequently hemorrhages (18,19).**

The main pathophysiologic mechanisms of stroke seem to be thrombosis, embolism, or altered coagulation. We limit the discussion, with attention to patients with CKD, to thromboembolism as a result of atherosclerosis, inflammation, and cardioembolism, because a discussion of coagulopathies, myocardial infarction with other cardiovascular risk factors accelerates atherosclerosis in the predialysis population, but CKD alone may be insufficient as an independent risk factor for stroke.

**Large- and Medium-Sized Artery Strokes**

In the large- and medium-sized arteries of the brain or neck, atherostenosis leads to either thrombotic occlusion of the vessel or artery-to-artery embolism. The distribution of atherosclerotic plaques varies by gender and race; this literature is vast and complex. The American dialysis population has more severe atherosclerotic disease of the carotid arteries compared with those with normal renal function (6). By contrast, a 22-yr review of stroke incidence in a Japanese HD population found a marked increased incidence of strokes in the vertebrobasilar system (21). The accelerated progression of atherosclerosis in this population, which may begin during advanced CKD, can be related to a number of factors that are unique to advanced kidney disease, namely elevated calcium-phospate product, hyperhomocysteinemia, inflammation, oxidative stress, and anemia (14,22).

**Arteriolar and Capillary Strokes (Lacunar Strokes)**

Lacunes are defined, for operational purposes, as small (several millimeters), deep cerebral infarcts (23). They are common, causing approximately 20% of all ischemic strokes (24). These lacunes are most often found in the white matter, basal ganglia, thalamus, pons, and cerebellum.

Since the earliest descriptions, lacunar stroke has been considered to be due to pathology of the small penetrating arteries of the brain (25), whereas large- and medium-sized arteries are affected by atherosclerosis. It is unclear whether this process also affects the microscopic penetrating arteries of the brain, which lead to these small lacunar infarcts (25).

Initially, hypertension was thought to be the main cause of disease of the penetrating arteries of the brain and, therefore, the cause of lacunar infarcts (26), but hypertension has been shown to be no more important in the development of lacunes compared with other types of stroke (27). The paucity of autopsy material in patients with lacunar stroke has made it difficult to define a particular arteriopathy in these clinically defined syndromes (27).

The concept of lacunar stroke as a disorder that is exclusively due to terminal arteriolar vessels has been challenged (28,29). Patients with “lacunar syndromes” have been shown to have acute occlusion of medium arteries (28–30) or even cardioembolism (27,31).

**Emboli**

Emboli can arise from the heart, aorta, carotids, or vertebrobasilar system (32). Cardiac disorders that give rise to embolism can be grouped into six categories (33): (1) arrhythmias; (2) valvular heart disease; (3) ventricular myocardial structural abnormalities, such as aneurysms, dilated cardiomyopathies, and akinetic walls; (4) intraventricular masses, myxoma, or other tumors; (5) shunts, especially intra-atrial septal defects (patent foramen ovale alone is no longer considered a risk factor for stroke, but it is a risk factor if there is an associated atrial septal aneurysm (34); and (6) atrial lesions, such as dilated atria, thrombi, tumors, and infarcts.

**Silent Stroke**

Silent stroke is the term used to describe lesions that are found incidentally on brain imaging with computed tomography or MRI. As noted, the annual stroke incidence is approximately 700,000 (5), but the annual incidence of silent stroke is calculated to be 9,040,000 (35).

Patients with silent stroke and ischemic white matter abnormalities on MRI may be prone to depression (36) and cognitive dysfunction, which can lead to dementia and gait dysfunction (37). Perhaps most important, the risk for ischemic or hemorrhagic stroke occurs at a >10-fold annual incidence (2.79 versus 0.21%) in those with silent stroke compared with those without previous silent stroke (38). The Cardiovascular Health Cognition Study, a community-pooled study of adults who were older than 65 yr, demonstrated an inversely related relationship between kidney function and incidence of silent stroke (39). Furthermore, the prevalence of silent stroke is five times greater in HD patients compared with a healthy adult population (48.4 versus 9.6%; $\chi^2 = 22.4, P < 0.0001$) (40).

**Prevention and Treatment**

In primary and secondary prevention of stroke, it has been well established that improved outcomes occur by correcting reversible risk factors, including treating hypertension; cessation of smoking; and controlling diabetes, cardiac disease, and excessive use of alcohol. Some of the nonmodifiable risk factors are age, male gender, family history of stroke, and nonwhite race.
Hypertension
Hypertension is defined by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as systolic BP (SBP) >140 mmHg or diastolic BP >90 mmHg (41). Prehypertension is diagnosed when the SBP is 120 to 139 mmHg or diastolic BP is 80 to 90 mmHg (41).

In the general population, stroke risk doubles for every 20/10-mmHg increase in BP over 115/75, making control of hypertension imperative in stroke reduction (42). This finding has been noted in a number of long-term, placebo-controlled clinical trials for a variety of drug classes, including diuretics (43), β blockers (44), calcium antagonists, and angiotensin-converting inhibitors (45,46). The Study on Cognition and Prognosis in the Elderly (SCOPE) (47), a prospective, double-blind, randomized, parallel-group study with almost 5000 patients in 15 countries, demonstrated that patients with BP of 160 to 179/90 to 99 mmHg had a BP fall of approximately 20/10 points with a stroke reduction of 24% (95% CI -0.7 to 42.1; \( P = 0.056 \)) (48). A large body of evidence suggests that effective BP control, rather than race, ethnicity, or drug selection, is the critical factor in primary stroke prevention. Because no distinction was made to CKD in these studies, it is unclear whether this corollary can be applied to the patient with CKD (49).

One aspect of BP control that is unique to the CKD population is the recent finding of a J-shaped relationship between BP and stroke (50). In patients with stage 3 (eGFR 30 to 60 ml/min) and stage 4 (eGFR 15 to 30 ml/min) CKD, there was an increased stroke risk in those with SBP <120 mmHg compared with those with SBP between 120 and 129 mmHg (HR 2.51; 95% CI 1.30 to 4.87). This trend was similarly represented in both the presence and the absence of existing coronary artery disease. Stroke risk increased similarly in the CKD and control population with SBP >130 mmHg. Narrowing of the therapeutic target range of BP in the CKD population will, no doubt, pose a new challenge to nephrologists and primary care physicians worldwide.

Hypercholesterolemia and Statins
Surprising, hypercholesterolemia has not been consistently associated with elevated stroke risk in all studies. Some prospective studies of patients with elevated serum cholesterol showed an increased stroke risk (51–53), whereas other studies failed to show such an association (5,54). Several reasons for this discrepancy have been posited (55), including lumping together of different types of stroke; the inclusion of patients who died of coronary disease before the development of stroke; the study populations were mostly of middle-aged men, whereas stroke occurs in older patients; and the interventions that were undertaken to treat patients with coronary disease reduced the risk for stroke later in life (55).

As the studies become more refined, the data are beginning to favor both cholesterol control and statin use in both primary and secondary stroke prevention in the general population. For example, in the recently published Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, the authors concluded that in “patients with a recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin per day reduced the overall incidence of strokes and of cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke” (55). Essentially the same results hold for patients with coronary disease and hypercholesterolemia, as demonstrated in several large trials. In a meta-analysis of 13 trials, there was an absolute stroke risk reduction of 31% (odds ratio 0.69; 95% CI 0.57 to 0.83) (56). The authors calculated that approximately 40 strokes could be prevented when statins were used in 10,000 patients over “a long period of time.”

Patients with CKD have been systematically excluded from most large trials that have evaluated stroke and myocardial infarction (MI), resulting in a shameful dearth of data for this population. There are data showing both safety of use and a similar lipid-lowering effect in CKD, dialysis, and renal transplant patients (United Kingdom Heart and Renal Protection [UK-HARP] and Assessment of Lescol in Renal Transplant [ALERT]) (57,58). The Pravachol Pooling Project, which combined data from three large, randomized, placebo-control trials, is the largest available data set for the use of statins in CKD (59). Its findings strongly suggest a benefit of statins in patients with stage 3 CKD and coronary heart disease on the primary end point of time to MI, coronary death, or coronary revascularization but no benefit in regard to stroke or mortality (59). The ALERT study was a multicenter, randomized, placebo-controlled trial of 2102 renal transplant patients (59). Similarly, this study found a decrease in the end point of cardiac death and nonfatal MI but no difference in the incidence of cerebrovascular events between the treatment and placebo groups (59). The 4D study evaluated the effect of atorvastatin on 1200 German HD patients with diabetes, with a primary end point of death from either MI or stroke (60). Despite an analogous impact on cholesterol reduction compared with the general population, there was no significant effect on the composite end point of all-cause mortality (RR 0.92; 95% CI 0.77 to 1.10; \( P = 0.37 \)). Once again, statin therapy reduced the rate of all combined cardiac events (RR 0.82; 95% CI 0.68 to 0.99; \( P = 0.03 \)) but did not reduce the rate of all cerebrovascular events (RR 1.12; 95% CI 0.81 to 1.55; \( P = 0.49 \)) (60). In fact, it shockingly was associated with an increased risk for fatal stroke (RR 2.03; 95% CI 1.05 to 3.93; \( P = 0.04 \)) (60). These findings raise the question of whether lipids, which were found to be a marker for cardiovascular events in the general population, serve as a surrogate in the CKD population as well. This possibility is supported by the comparable lipid-lowering effect of statins in the absence of a significant impact on end points in the previously cited studies. This is further supported by a recent analysis showing the inability of the Framingham equations to predict coronary events in patients with stages 3 and 4 CKD (61).

The data do not support initiation of treatment with a statin in the dialysis population; however, the results from a single prospective study are insufficient to implement this as the standard of care. In addition, there are no data on the benefit of continuing statin therapy on initiation of renal replacement therapy. To address these questions, two large prospective studies were designed and are under way. The Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events.
(AURORA) is a prospective, double-blind, placebo-controlled study comparing treatment with rosvustatin (10 mg/d) with placebo in preventing cardiovascular death, nonfatal MI, and nonfatal stroke in 2700 HD patients (62). The Study of Heart and Renal Protection (SHARP) is a prospective, randomized, double-blind, placebo-controlled study evaluating the efficacy of combined treatment with simvastatin (20 mg/d) and ezetimibe (10 mg/d) on subsequent vascular events in 9000 patients with CKD and without established coronary disease (63). Hopefully, these studies will clarify the standard of care on the use of statins in this population.

Antiplatelet Agents
Any discussion of stroke prevention should take into account the natural history of the disease. A brief summary of this can be found in Wilterdink and Easton’s study (64). They estimated the annual risk of stroke to be 0.6% in elderly men, 1.3% in people with asymptomatic carotid disease, and 6.1 and 9.0% in patients with a previous minor and major stroke, respectively.

The weight of the evidence to date suggests that in primary and secondary prevention of stroke from atherosclerosis, rather than cardioembolism, antiplatelet rather than anticoagulant therapy is more effective. This is true when carotid endarterectomy, which is superior to medical therapy, is not an option in a particular patient (65).

Primary Stroke Prevention
Aspirin, among the antiplatelet agents, is the oldest and most commonly used. Although there is no literature on the use of aspirin in patients with CKD HD patients for primary or secondary stroke prevention, safety of use can be extrapolated from the Cooperative Cardiovascular Project (66). The large clinical studies in which aspirin was evaluated alone in primary stroke reduction include the US Physicians’ Health Study (67) and the British Doctors’ Trial (68). Combined analysis of these two trials found a 32% (SD ±8%) reduction in sustaining a nonfatal MI and a 13% (SD ±6%) reduction in combined vascular events but a statistically NS increase for nonfatal stroke of 18% (SD ±13%) (69). One additional study (70) suggested that in low-risk patients, aspirin may actually be harmful. In that study, in which a cohort of 5011 elderly people from the Cardiovascular Health Study were followed for 4.2 yr, women had an increased risk for ischemic stroke and both men and women had an increased risk for hemorrhagic stroke. The authors raised the possibility of a confounding result from aspirin use itself as opposed to aspirin being causative. In any event, there are few, if any, good data to support the use of aspirin in primary stroke prevention and perhaps some harm in using it in people who are at low risk for a stroke. There are no data on aspirin use in primary prevention in the patient with CKD.

Secondary Stroke Prevention
For secondary prevention of stroke, one of the earliest trials compared aspirin with placebo in patients with TIA (71). The trial included almost 600 patients, 290 of whom were treated with 1300 mg. The effect was a reduction of stroke or death by 31%. Since then, a number of trials using aspirin dosages that varied from 30 to 1000 mg/d have been performed, and there is benefit from aspirin at all dosages (72).

The United Kingdom TIA (UK-TIA) aspirin trial compared 2465 patients who were taking 1200 (n = 815) or 300 mg of aspirin (n = 806) or placebo and followed for 4 yr (73). The only statistically significant reduction in disabling stroke rate (7%) was seen when the two aspirin groups were combined (73). Also, when the two aspirin groups were combined, the stroke, MI, and death rates diminished by 15% over placebo.

Swedish Aspirin Low-Dose Trial (SALT) compared 75 mg of aspirin with placebo as secondary prophylaxis after cerebrovascular ischemic events in 1360 patients who were followed for a mean of 32 mo (74,75). A statistically significant reduction (18%) was seen in either stroke or death. According to a minimeta-analysis (76) of 10 randomized trials of aspirin versus control treatment of 6171 patients after TIA or stroke, any dosage above 30 mg/d conferred some benefit (13%; 95% CI 4 to 12).

Bleeding from Aspirin
Complication rates of aspirin are difficult to estimate because of variable definitions in each trial. The common complications include gastrointestinal bleeding, epigastric pain, ulcer, or gastritis. The absolute risk for hemorrhagic stroke from aspirin at a mean dosage of 273 mg/d, according to a meta-analysis of 55,462 patients, is 12 per 10,000 (95% CI 5 to 20; P < 0.001). This translates to one extra hemorrhagic stroke for every 1000 patients who are treated for a 5-yr period (77). In the final analysis, it seems that the benefit of aspirin alone confers some benefit (13 to 22%) (78) in reducing recurrent atherosclerotic stroke, and this benefit outweighs its risks.

Antiplatelet Agents Other than Aspirin
In addition to aspirin, a number of antiplatelet drugs have been studied in stroke prevention. These include ticlopidine, clopidogrel, and dipyridamole. The studies on these antiplatelet drugs, like the aspirin literature, are confusing because of various definitions of outcomes, lengths of observations, inclusion and exclusion criteria, and many other variables. Finally, for the patient with CKD, we must extrapolate because none of this literature directly addresses those patients.

Ticlopidine. Ticlopidine hydrochloride (Ticlid, Roche Laboratories, Basel, Switzerland) is a thiopnyridine. It is an adenine diphosphate receptor antagonist that inhibits adenosine diphosphate-induced fibrinogen binding to platelets; this step is needed in the platelet aggregation process. Ticlopidine has been compared with aspirin in several trials of patients with stroke or TIA (79,80). Taken together, these trials demonstrated that ticlopidine is approximately 20% better than aspirin in reducing the risk for stroke in at-risk patients.

Ticlopidine has several important adverse effects including severe neutropenia (0.9%), diarrhea and skin rash in approximately 2%. It is recommended that patients have a complete blood count at 2-wk intervals during the first 3 mo of treatment. These adverse effects have precluded the use of ticlopidine on
a routine basis. A safer molecule, clopidogrel, has taken ticlopidine’s place.

**Clopidogrel.** Clopidogrel (Plavix, Bristol-Myers Squibb, New York, NY), like ticlopidine, is a thienopyridine derivative. Its effects on stroke were evaluated in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) Study (81). This was the largest (19,185 patients) randomized, blinded trial for secondary prevention of vascular events: Stroke, MI, peripheral vascular disease, or a vascular death. There was no significant benefit over aspirin (relative risk reduction 7.3%; 95% CI 5.7 to 18.7). Unlike ticlopidine, there were no cases of neutropenia or other serious adverse effects.

The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attack trial not only showed no benefit from aspirin and clopidogrel over clopidogrel in reducing recurrent stroke but also showed an increased risk for fatal hemorrhage from the combination therapy (82). This increased hemorrhagic risk has also been noted in HD patients, especially when aspirin and clopidogrel are used together (83).

**Dipyridamole.** Dipyridamole’s (Persantine, Boehringer-Ingelheim, Ingelheim, Germany; Aggrenox [Boehringer-Ingelheim] when combined with aspirin) mechanism in inhibition of platelet aggregation is not known. It induces elevations in cAMP concentrations, which block the release of arachidonic acid from membrane phospholipids and reduce thromboxane A2 activity. It also directly stimulates the release of prostacyclin, which ultimately increases platelet cAMP activity. It is also a coronary vasodilator.

In the European Stroke Prevention Study: 2 (ESP2) (84), 6602 patients were treated with 50 mg/d aspirin alone, 50 mg of aspirin and 400 mg of extended-release dipyridamole given in two divided doses, or placebo. Risk for stroke or death was most reduced in the group that received a combination of aspirin and dipyridamole (36%; \( P < 0.001 \)) in comparison with placebo. To put this in a clinically meaningful way, 58 strokes or deaths per 1000 treated patients were avoided at the end of 2 yr (84); however, this combination treatment, in absolute terms, did not reduce death at a significantly better rate than aspirin alone (10 versus 13 deaths avoided, respectively, per 1000 patients). ESPS2 has been criticized for a number of reasons: Fraudulent data were detected at one center; among the 25% who withdrew, most were in the dipyridamole group; and no significant effect on MI and fatal stroke, which is different from other antiplatelet studies. All-site bleeding and gastrointestinal bleeding were most common in the aspirin alone group.

The European/Australian Stroke Prevention in Reversible Ischaemia Trial compared aspirin (30 to 325 mg; \( n = 1363 \)) with or without (\( n = 1376 \)) 200 mg of extended-release dipyridamole twice daily in patients who already had sustained nondisabling cerebral ischemia (85). The absolute risk reduction over all vascular mortality in favor of combination therapy was 1% per year (95% CI 0.1 to 1.8). A number of smaller dipyridamole trials in stroke did not show significant benefit (86).

In summary, antiplatelet agents are effective in secondary prevention of stroke. Treatment with a particular agent has to be individualized. The reasonable choices on the basis of the available studies can include aspirin alone because of its cheap price and single-dose administration, aspirin and dipyridamole because this seems to be the most effective regimen, and dipyridamole or clopidogrel alone in patients who are at high risk for peripheral vascular disease or who are unable to take aspirin. It should be noted, however, that the stroke risk reduction from the antiplatelet agents pales in comparison with carotid endarterectomy for symptomatic disease, which has an absolute risk reduction of 16% (87).

These conclusions must be tempered in the CKD population, which is often not included in these studies. Current literature suggests that these patients have both a high perioperative stroke or death rate from carotid endarterectomy (88,89). This literature is somewhat limited because often the studies include small numbers, are retrospective, or involve a single center; however, their warning should not be ignored, especially in the asymptomatic patient. There is virtually no literature on stenting of the carotid artery in patients with CKD.

**Anticoagulants for Stroke**

Depending on the stroke registry, various causes of embolic strokes are cited (see above, Emboli), but of the cardioembolic strokes, atrial fibrillation (A Fib) and left ventricular akinesia are among the most common (90,91). There is no literature regarding prevalence or treatment of A Fib in the CKD or renal transplant population. A Fib is far more common in the dialysis population, with prevalence reported as high as 13 to 27% (92,93); however, there is debate in the literature regarding whether A Fib is a risk factor for stroke in this unique population (94–96). It is not an uncommon transient occurrence during HD and usually resolves within 2 to 3 h without treatment (97). Nonetheless, survival is universally found to be dismal, with thromboembolic complications occurring in as many as one in three patients with chronic A Fib at 1 yr (94).

Warfarin anticoagulation therapy has been conclusively found to lower stroke risk in patients who have A Fib and are >60 yr of age and have hypertension, congestive heart failure, previous MI, or previous thromboembolism. This finding is based on six large randomized clinical trials (98–103). Best results are achieved when target international normalized ratio is 3.0 and the range is kept between 2.0 and 5.0. When the international normalized ratio is <2.0, there is no stroke protection (88), and at >5.0, most major hemorrhages occur. The lowest stroke risk is 2.0 to 3.9. Adding aspirin to low-dosage warfarin is ineffective (100). Dialysis patients who are taking warfarin have a much higher risk for hemorrhage, with the relative risk for bleeding double that of nonanticoagulated HD patients and five times that of patients without CKD (94). Counter to this hemorrhagic risk is the probability of thromboembolic complication of 34.6% per year, with one third of these events being incapacitating cerebrovascular accidents (94). In one retrospective analysis of 430 HD patients, however, use of warfarin was found to be a risk factor for stroke (95). Perhaps an even more concerning factor than bleeding risk is the mechanism of action of warfarin and the uremic milieu. Vascular calcification is regulated in a manner similar to that of bone, with the constant presence of inhibitors of calcification present.
on normal vessel walls. The activity of these inhibitors relies on vitamin K–dependent γ-carboxylation, which is limited by warfarin. Use of warfarin was associated with increased aortic calcification in patients without CKD (104). Warfarin has even been implicated as a risk factor for calcific uremic arteriopathy (105). Although this effect on vascular calcification has not been evaluated in the HD population, it does raise the possibility of exacerbating the already tremendous burden of vascular calcification. In light of these findings, a risk-benefit analysis should be done for each patient individually when considering warfarin anticoagulation for A Fib. For younger patients without additional risk factors, several studies, namely Stroke Prevention in Atrial Fibrillation II and III (100,103), found that stroke rates (2%/yr) and disabling ischemic stroke (0.8%/yr) were low and were just above the rate of major bleeding with aspirin therapy (0.5%/yr) in that study (103).

In summary, secondary stroke prevention in patients with carotid disease remains best with surgery and possibly stenting, perhaps even in the properly selected patient with CKD. When medically managed, aspirin, dipryidamole, clopidogrel, or some combination results in fair reduction of recurrent stroke. For cardioembolism, warfarin is the best choice. Hopefully, the future will bring even better options for patients with this devastating illness.

Take-Home Points
Stoke is a common and unfortunate disease among the CKD population, with tremendous morbidity and mortality.

- CKD itself is not an independent risk factor for stroke, but it becomes so when it is associated with anemia, cardiovascular disease, or macroalbuminuria.
- Stroke has a higher prevalence in the dialysis population compared with the general population.
- BP management is critical for stroke prevention.
- Initiation of a statin in dialysis patients does not seem to be of benefit, but the final word depends on the results of two ongoing studies.
- A risk-benefit assessment should be done for each patient in regard to the use of anticoagulation for prevention of cardioembolism in A Fib.

Disclosures
None.

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