Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines

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Chronic kidney disease is strongly associated with an increased risk of stroke, small vessel disease, and vascular dementia. Common vascular factors for stroke, such as hypertension, diabetes, and atrial fibrillation, are more prevalent in patients with chronic kidney disease, accounting for this association. However, factors unique to these patients, such as uremia, oxidative stress, and mineral and bone abnormalities, as well as dialysis-related factors are also believed to contribute to risk. Despite improvements in stroke treatment and survival in the general population, the rate of improvement in patients with chronic kidney disease, especially those who are dialysis dependent, has lagged behind. There is a lack of or conflicting evidence that those with renal disease, particularly when advanced or older, consistently derive benefit from currently available preventive and therapeutic interventions for stroke in the general population. In this review, we explore the complexities and challenges of these interventions in the population with renal disease.

Kidney International (2020) **97,** 266–278; https://doi.org/10.1016/j.kint.2019.09.024

KEYWORDS: chronic kidney disease; dialysis; primary prevention; secondary prevention; stroke

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Received 30 June 2019; revised 6 September 2019; accepted 26 September 2019; published online 18 October 2019

Chronic kidney disease (CKD) is an increasing global health burden with an estimated prevalence of 11% to 13% worldwide.[1] CKD is associated with an 8- to 10-fold increase in cardiovascular mortality, equivalent to that in patients with diabetes or prior myocardial infarction,[2,3] and even mild reductions in glomerular filtration rate (GFR) are associated with substantial increases in cardiovascular risk.[4] There is a particularly strong association between CKD and cerebrovascular disease. Meta-analyses of cohort studies and trials indicate that reduced GFR increases the risk of stroke by 40%[5] and that proteinuria increases the risk up to 70%[6] even after adjusting for traditional cardiovascular risk factors. These associations may be attributable to a cluster of shared vascular risk factors including hypertension, diabetes mellitus, and atrial fibrillation (AF), but "nontraditional" risk factors such as anemia, hyperuricemia, and mineral bone disorders may also play a role (Figure 1).[7] CKD is a strong independent predictor of mortality and poor functional outcomes in patients with acute stroke,[8] but there is a lack of clinical trials of prevention and treatment of stroke in the population with renal disease, with most evidence to support use of existing treatments derived from *post hoc* subgroup analyses.[9,10] In this review, we explore this evidence for the primary and secondary prevention of stroke and acute treatment. Current recommendations for the primary and secondary prevention of stroke in CKD are outlined in Table 1.[11–19]

PRIMARY PREVENTION OF STROKE IN CKD

Antiplatelets

In high-risk patients with prior vascular disease or some other predisposing condition, antiplatelet therapy has been associated with a 25% relative risk (RR) reduction in nonfatal stroke compared with placebo.[20] Despite their proven benefit in the general population, major gaps exist in our understanding of the effects of antiplatelet drugs on thrombosis and bleeding in CKD, particularly in the setting of primary prevention.[21] Clinical practice guidelines are ambiguous about their use in patients with CKD, because those with moderate to severe CKD were systematically excluded from most clinical trials evaluating efficacy and safety.[11]

In a large Cochrane review of 50 randomized controlled trials (RCTs) (27,139 participants) of antiplatelet treatment for the prevention of cardiovascular outcomes in CKD,

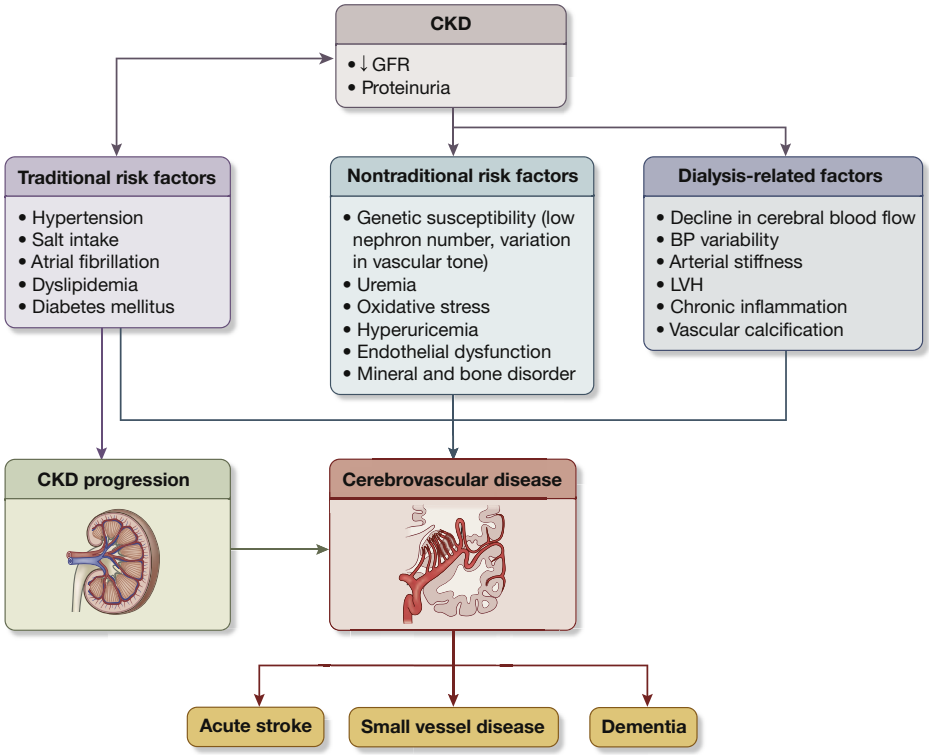

Figure 1 | Traditional and nontraditional risk factors for cerebrovascular diseases in patients with chronic kidney disease (CKD). BP, blood pressure; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy.

antiplatelet agents reduced the risk of myocardial infarction (RR, 0.87; 95% confidence interval [CI], 0.76–0.99), but not all-cause mortality (RR, 0.93; 95% CI, 0.8–1.06), cardiovascular mortality (RR, 0.89; 95% CI, 0.70–1.12), or stroke (RR, 1.00; 95% CI, 0.58–1.72).[22] Antiplatelet agents increased the risk of major (RR, 1.33; 95% CI, 1.10–1.65) and minor (RR, 1.49; 95% CI, 1.12–1.97) bleeding. Although few studies were available for direct comparison, meta-regression analysis indicated no differences in the relative benefits or harms of treatment by type of antiplatelet agent. They concluded that there is currently insufficient evidence to support the role of antiplatelets in primary prevention, particularly in those with early stages of CKD who do not have clinically evident occlusive cardiovascular disease. However, data on the effects of antiplatelet agents on primary prevention in CKD were available only from a *post hoc* subgroup analysis of a single study, the Hypertension Optimal Treatment trial.[23] In this trial, the RR of major cardiovascular events were reduced by 9% (95% CI, −9% to 24%), 15% (95% CI, −17% to 39%), and 66% (95% CI, 33%–83%) for patients with a baseline estimated glomerular filtration rate (eGFR) of ≥60, 45 to 59, and <45 ml/min per 1.73 m^2, respectively ($P = 0.03$ for trend), but there was no significant benefit for stroke as an individual end point and a near doubling of the risk of major bleeding (RR, 2.04; 95% CI, 1.05–3.96).

In a more recent meta-analysis that focused only on primary prevention studies in CKD, 3 trials—Hypertension Optimal Treatment trial, Heart and Renal Protection trial, and Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes trial—were identified, providing data for 4468 participants.[24] Overall, there was no statistically significant reduction in major cardiovascular events including stroke (RR, 0.92; 95% CI, 0.49–1.73; $P = 0.79$), but there was a high level of heterogeneity between studies ($I^2 = 71\%$; $P = 0.06$) and only 1 trial (Heart and Renal Protection study) was CKD specific.

The Aspirin To Target Arterial Events in Chronic Kidney Disease trial (ClinicalTrials.gov identifier: NCT03796156) is an open-label, multicenter primary prevention trial currently underway that is investigating whether the addition of daily aspirin to usual care will reduce the risk of major vascular events in patients with CKD (excluding those at stage 5 or dialysis dependent). The investigators intend on recruiting 25,210 patients and anticipate finishing in 2025.

In addition to bleeding concerns, there are reports of high rates of antiplatelet hyporesponsiveness in patients with CKD, which may partially explain poorer outcomes.[25] CKD and end-stage kidney disease (ESKD) are independent risk factors for clopidogrel resistance; 50% to 80% of patients with ESKD have high on-treatment residual platelet reactivity (resistance) when treated with clopidogrel.[26] However, it has been suggested that the high burden of comorbidities in patients with CKD may account for this observation rather than CKD itself.[27]

Overall, the current guideline recommendations to generally avoid primary prevention with aspirin in patients with CKD are reasonable in the context of recent randomized trials (ASPirin in Reducing Events in the Elderly study,

Table 1 | Current available guidelines for the primary or secondary prevention of CV disease in CKD

Guidelines	NICE[11]	KDIGO[12,13]	ACC/AHA/ASA[14–18]	Society for Vascular Surgery[19]
Antiplatelet therapy	• Offer only for secondary prevention, but caution about the increased risk of bleeding	• Aspirin is indicated for secondary prevention but not for primary prevention	• Aspirin may be considered for primary prevention for GFR 30–45 ml/min and should be given for secondary prevention	
BP control	• Target BP <140/90 mm Hg in general, but <130/80 mm Hg if ACR ≥70 mg/mmol or diabetic • Use preferably RAS antagonist	• Individualize targets according to age, CVD, and comorbidities • BP <140/90 mm Hg if not diabetic and UAE <30 mg/24 h	• Target BP <130/80 mm Hg • Use RAS antagonist	
Anticoagulation	• Consider apixaban in preference to warfarin if GFR 30–50 ml/min in at-risk nonvavlular AF		• Consider reduced-dose NOACs if GFR 15–50 ml/min • Consider warfarin or apixaban in ESKD	
Statins	• Give atorvastatin 20 mm Hg for primary or secondary prevention • Discuss higher doses with the renal specialist if GFR <30 ml/min	• Check a lipid profile in all new patients with CKD • If >50 yr and stage 3–5 CKD, treat with statin or statin/ezetimibe • >50-yr-old with stage 1 or 2 CKD, treat with statin • In dialysis-dependent CKD, do not initiate statins but continue if already taking	• Initiate a moderate-intensity statin and/or ezetimibe in nondialysis CKD if 40 to 75 yr of age with LDL-C concentration 70–189 mg/dl and at 10-yr ASCVD risk ≥7.5% • In dialysis-dependent CKD, do not initiate statins but continue if already taking	
Carotid interventions				• Consider if symptomatic with moderate to severe stenosis • CEA > CAS • CAS may have a role in selected patients

ACC, American College of Cardiology; ACR, albumin/creatinine ratio; AF, atrial fibrillation; AHA, American Heart Association; ASA, American Stroke Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAS, carotid artery stenting; CEA, carotid endarterectomy; CKD, chronic kidney disease; CVD, cardiovascular disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; NOAC, novel oral anticoagulant; RAS, renin-angiotensin system; UAE, urinary albumin excretion.

Aspirin to Reduce Risk of Initial Vascular Events study, and A Study of Cardiovascular Events iN Diabetes)[28–30] that did not find aspirin to be beneficial for stroke prevention in other at-risk groups (elderly, moderate cardiovascular risk, and diabetes, respectively) (Table 1).

Anticoagulants

Warfarin. Anticoagulation has been shown to reduce the risk of stroke by approximately two-thirds in the general population, and it is also associated with reduced stroke severity and lower mortality rates.[31,32] However, there is considerable recognition of the underuse of oral anticoagulation for stroke prevention in AF in renal disease, and their use is often complicated by high bleeding rates and uncertain benefit.[33] In particular, there are concerns about warfarin use given the association with vascular calcification due to the inhibition of the enzyme matrix gamma-carboxyglutamate Gla protein that scavenges calcium phosphate in tissues.[34]

Outcomes reported with warfarin use in both patients with non–end-stage CKD and dialysis-dependent patients with nonvalvular AF have been conflicting. In a Danish cohort study, warfarin treatment was associated with a significantly decreased risk of stroke or systemic thromboembolism overall (hazard ratio [HR], 0.76; 95% CI, 0.64–0.91; $P = 0.003$) and in patients requiring renal replacement therapy (HR, 0.44; 95% CI, 0.26–0.74; $P = 0.002$) but with a nonsignificantly decreased risk in patients with non–end-stage CKD (HR, 0.84; 95% CI, 0.69–1.01).[35] There was an increasing risk of bleeding in all warfarin users with renal disease (HR, 1.33; 95% CI, 1.16–1.53; $P < 0.001$). This contrasts with the results of Swedish registry data (SWEDEHEART) that showed a lower risk of stroke in both groups without a higher risk of bleeding.[36] However, the latter cohort was a higher risk group post recent myocardial infarction and included fewer patients on dialysis, limiting the generalizability of their results.

A systematic review and meta-analysis of 13 observational studies (>48,500 patients) evaluated the use of warfarin in patients with AF and CKD to assess the risk of ischemic stroke/thromboembolism, major bleeding, and mortality.[37] In patients with AF and non–end-stage CKD, warfarin use was associated with a lower risk of ischemic stroke/thromboembolism (HR, 0.70; 95% CI, 0.54–0.89; $P = 0.004$) and mortality (HR, 0.65; 95% CI, 0.59–0.72; $P < 0.00001$) but had no effect on major bleeding (HR, 1.15; 95% CI, 0.88–1.49; $P =$

0.31). Most of the patients included in this analysis had stage 3 or 4 CKD, and this group appears to derive benefit from warfarin with a reasonable safety profile.

However, in patients with AF and ESKD, warfarin had no apparent effect on the risk of stroke (HR, 1.12; 95% CI, 0.69–1.82; $P = 0.65$) and mortality (HR, 0.96; 95% CI, 0.81–1.13; $P = 0.60$) but increased the risk of major bleeding (HR, 1.30; 95% CI, 1.08–1.56; $P = 0.005$). A major limitation of this meta-analysis is that it is based solely on observational cohort studies, as there are no RCTs that have addressed this question. However, the majority of studies do not support a protective effect for warfarin in patients with ESKD and AF. Similarly in a 2017 meta-analysis of only patients on dialysis, warfarin was not associated with a significant reduction in ischemic stroke (HR, 0.77; 95% CI, 0.55–1.07), but possibly increased intracranial hemorrhage (HR, 1.93; 95% CI, 0.93–4.00), although without effect on gastrointestinal bleeding (HR, 1.19; 95% CI, 0.8–1.76) or all-cause mortality (HR, 0.89; 95% CI, 0.72–1.11).[38]

These analyses suggest that warfarin is not associated with a clear benefit but likely increased harm in patients with AF on dialysis. The risk estimates may be confounded though by variable time in the therapeutic range and by the inclusion of low-risk patients not expected to benefit from anticoagulation. However, in the absence of any definitive trial data to support its efficacy or safety, we would not recommend routine use of warfarin in patients with AF on dialysis. It should be reserved for the highest-risk patients in this group, such as those with a history of stroke or a documented cardiac thrombus. The results of the ongoing AVKDIAL trial (Oral Anticoagulation in Hemodialysis Patients; ClinicalTrials.gov identifier: NCT02886962) that will compare vitamin K antagonists with no anticoagulation in dialysis-dependent patients with AF are eagerly awaited.

Non–vitamin K anticoagulants. Novel oral anticoagulant agents (NOACs) appear to have at least an equivalent, if not more favorable, safety and efficacy profile when compared with vitamin K antagonists in CKD. Most of the randomized trials of NOACs (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE], and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF]) have included patients with nonvalvular AF with an eGFR of ≥30 ml/min per 1.73 m^2, and therefore, the best evidence for NOAC use is in patients with CKD with an eGFR of 30 to 59 ml/min per 1.73 m^2.[39–41] In a systematic review and meta-analysis of 8 RCTs (9693 participants) that compared NOACs with vitamin K antagonists for stroke prevention in patients with CKD (defined as creatinine clearance of 30–50 ml/min), there was no significant difference in the risk of stroke and systemic thromboembolism (RR, 0.64; 95% CI, 0.39–1.04), recurrent thromboembolism or thromboembolism-related death (RR, 0.97; 95% CI, 0.43–2.15), or bleeding events (RR, 0.89; 95% CI, 0.68–1.16) between NOACs and vitamin K antagonists.[42] However, although not statistically significant, there was clearly a trend toward better thromboembolic and bleeding outcomes with NOAC use.

A recent larger systematic review and meta-analysis of 11 trials (16,787 participants) confirmed superiority of high-dose NOACs compared with vitamin K antagonists for stroke or systemic embolism (RR, 0.79; 95% CI, 0.66–0.93), hemorrhagic stroke (RR, 0.48; 95% CI, 0.30–0.76), and all-cause death (RR, 0.88; 95% CI, 0.78–0.99).[43] However, the reduction in major bleeding (RR, 0.80; 95% CI, 0.61–1.04) was nonsignificant when compared to warfarin. This meta-analysis was again limited only to patients with a creatinine clearance of >25 ml/min, as no data were available for patients with more advanced CKD including dialysis-dependent CKD.

However, NOAC use in patients on dialysis appears to be promising from observational data so far. A comparison of warfarin and apixaban in patients on dialysis was performed using a retrospective cohort study of 25,523 patients included in the United States Renal Data System.[44] In matched cohorts, there was no difference in the risk of stroke or systemic embolism between apixaban and warfarin (HR, 0.88; 95% CI, 0.69–1.12; $P = 0.29$) but apixaban was associated with a significantly lower risk of major bleeding (HR, 0.72; 95% CI, 0.59–0.87; $P < 0.001$). In sensitivity analyses, standard-dose apixaban was superior to both reduced-dose apixaban and warfarin with a lower risk of stroke or systemic embolism and death.

Currently 2 RCTs are underway that are examining the safety and efficacy of NOACs compared with warfarin in the population on dialysis. In the US-based Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation (RENAL-AF; ClinicalTrials.gov identifier: NCT02942407), patients are randomized to standard-dose apixaban versus warfarin, with a lower apixaban dose used in select patients. In the second German multicenter trial Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease (AXADIA; ClinicalTrials.gov identifier: NCT02933697), patients on chronic hemodialysis are randomized to receive either apixaban 2.5 mg twice daily or the vitamin K antagonist phenprocoumon.[45] RENAL-AF has recently finished and AXADIA is anticipated to be completed in July 2022. The primary outcome of both trials is the comparison of safety (major bleeding) events with secondary outcomes of stroke or systemic embolism. They also both include a pharmacokinetic substudy to determine longer-term safe dosing around dialysis. Their results may confirm the earlier observational United States Renal Data System data,[44] that standard-dose apixaban is associated with a lower risk of stroke, major bleeding, and mortality when compared with warfarin in patients on hemodialysis. However, with low enrollment numbers, there are concerns that the trials will be underpowered to evaluate the important intracerebral hemorrhage risk and to demonstrate significant superiority over vitamin K antagonists for stroke outcomes.

NOACs are preferentially recommended as first-line therapy for those with a GFR of 15 to 50 ml/min in the latest American Heart Association/American College of

Cardiology/Heart Rhythm Society guidelines, and these guidelines have also recommended consideration of either warfarin or apixaban use in ESKD (grade IIb; moderate quality evidence) (Table 1).[14] NOAC use in those with a GFR of 30 to 50 ml/min is clearly appropriate in the context of the pooled trial data that indicate superiority to vitamin K antagonists. However, there is less evidence to support their use in those with a GFR of <30 ml/min, a group who are at a higher risk of abrupt and unpredictable deterioration in their renal function, resulting in reduced NOAC clearance and increased risk of bleeding. Warfarin should potentially still be the drug of choice in these patients pending trial data, confirming their safety in this vulnerable group. Low-dose apixaban is an alternative for patients who wish to avoid or who are intolerant of warfarin, provided that they are aware of the added risk. In the absence of wider clinical experience with NOAC use in patients on dialysis and again trial evidence to support its safety, we would be reluctant to advocate for its unselect use at this time in this group, but would instead recommend careful consideration in individual situations with involvement of a stroke physician and discussion of the potential benefits and risks with the patient.

Statins

Guidelines generally recommend lipid-lowering therapy for primary prevention in the general population if the patient has a ≥10% ten-year risk of developing cardiovascular disease or the patient is 40 years and older in the setting of diabetes mellitus.[15,46] In patients with prior unstable angina or myocardial infarction, statin use appears to reduce the risk of subsequent stroke by 50%.[47] As a coronary artery disease equivalent in terms of vascular risk,[48] patients with CKD appear to derive similar benefits. A Cochrane review and meta-analysis of RCTs of statins in people with non–dialysis-dependent CKD included a sensitivity analysis for major cardiovascular events, death, and myocardial infarction limited to studies in which preexisting cardiovascular disease was an exclusion criterion at baseline. They found significant treatment effects on major cardiovascular events (5 studies, 13,766 participants: RR, 0.60; 95% CI, 0.46–0.79; $I^2 = 59\%$), death (3 studies, 7215 participants: RR, 0.63; 95% CI, 0.44–0.90; $I^2 = 38\%$), and myocardial infarction (4 studies, 7519 participants: RR, 0.54; 95% CI, 0.38–0.76; $I^2 = 0\%$) but uncertain effects on cardiovascular mortality (1 study, 304 participants: RR, 0.37; 95% CI, 0.01–8.90).[49] Although data for treatment effects on cardiovascular events were predominantly derived from *post hoc* subgroup analyses, there was no substantial heterogeneity. The best evidence to support the role of statin therapy in primary prevention for patients with CKD comes from the Study of Heart and Renal Protection (SHARP) trial, in which 9270 patients with CKD (including 6247 patients not on dialysis) and without preexisting vascular disease were randomly assigned to placebo or to the combination of simvastatin 20 mg daily plus ezetimibe 10 mg daily, confirmed benefit for patients with CKD, with a 25% reduction in nonhemorrhagic stroke in the treatment arm.[50]

The potential role of statins in the primary prevention of death and major cardiovascular events in CKD has been recognized in both US and international guidelines, though there are some differences in terms of need for additional risk stratification (Table 1).[11,12,15] According to Kidney Disease: Improving Global Outcomes,[12] patients with CKD who are 50 years and older are considered at sufficiently high risk of a cardiovascular event (≥10% risk of manifest coronary heart disease over 10 years) to justify statin therapy without the need to apply any formal risk calculation in individual patients.

However, the use of lipid-lowering therapy in patients on chronic dialysis is contentious. The relative decrease in cardiovascular risk by statins diminishes as renal function declines, even after allowing for the smaller reduction in low-density lipoprotein cholesterol (LDL-C) concentration obtained in more advanced CKD.[51] The dialysis subgroup analysis of the SHARP[50] and other randomized trials investigating statins for the primary prevention of cardiovascular events in ESKD, such as the 4D study (Die Deutsche Diabetes Dialyse Studie)[52] and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events),[53] found no benefit of statin therapy in the population on dialysis. Suggested reasons for this "statin resistance" include the poor association of LDL-C with cardiovascular risk in this population owing to the predomination of nontraditional risk factors (e.g., mineral and bone abnormalities and uremia),[54] lipid abnormalities (e.g., lipoproteins rendered highly atherogenic by oxidation or carbamylation), intracellular cholesterol synthesis activated by inflammatory stress,[55] and its pro-calcifying effects.[56] Both the 2014 Kidney Disease: Improving Global Outcomes Lipid Work Group and 2018 American Heart Association/American College of Cardiology guidelines suggest that statins should not be initiated in patients on dialysis but that statins could be continued in patients already receiving them at the time of dialysis initiation (Table 1).[15,57]

In practice, given the excess baseline cardiovascular risk in this group, we would recommend a low threshold for initiating statin therapy for the purpose of primary prevention for patients with nondialysis CKD older than 40 years, particularly in the presence of an unfavorable lipid profile or an additional risk factor (e.g., hypertension and smoking).

Antihypertensive agents

A collaborative prospective meta-analysis of randomized trials of blood pressure (BP) lowering versus control and major cardiovascular events in people with and without CKD (26 trials, 152,290 participants) included 30,295 individuals with an eGFR of <60 ml/min per 1.73 m^2.[58] Compared with placebo, BP-lowering regimens reduced the risk of major cardiovascular events by ~16% per 5-mm Hg reduction in systolic blood pressure (SBP) in individuals with (HR, 0.83; 95% CI, 0.76–0.90) and without (HR, 0.83; 95% CI, 0.79–0.88) reduced eGFR. Nor was there any evidence that the effects of different drug classes on major cardiovascular events varied between patients with different eGFR values (all

Table 2 | Trials of BP lowering in the population with CKD

Trial name	Year	Patients	Intervention	Follow-up	Results	Comments
MDRD[59,60]	1993; follow-up 2005	• N = 840 • All CKD	Target MAP ≤92 mm Hg vs. ≤ 107 mm Hg	2.2 yr (initial study); 6.2 yr follow-up	23% reduction in composite kidney failure/mortality outcome	BP not recorded during the follow-up study
HOPE[61]	2001	• *Post hoc* analysis • N = 980 with mild renal insufficiency and prior vascular disease or other risk factor (124–200 μmol/l)	Ramipril vs. placebo	4.5 yr	31% reduction in stroke risk with ramipril	
RENAAL[62]	2003	• N = 1513 • Type 2 diabetes with nephropathy	Losartan vs. placebo; target BP <140/90 mm Hg	3.4 yr	16% reduction in renal outcomes/mortality and 10% nonsignificant reduction in CV events	Patients with nondiabetic nephropathy excluded
PROGRESS[63]	2007	• *Post hoc* analysis • 1757 patients with CKD with a history of TIA/stroke	Perindopril vs. placebo	4 yr	Reduced risk of major vascular events by 30% and stroke by 35% in CKD	No data on patients with proteinuria
AASK[64,65]	2002 trial phase; 2010 cohort phase	• N = 1094 blacks with hypertensive CKD	Target MAP ≤92 mm Hg vs. ≤ 107 mm Hg	4-yr trial follow-up; 5-yr additional cohort follow-up phase	No significant differences in ESKD/mortality except in those with proteinuria	All patients had the same BP target in the cohort phase
SPRINT[66]	2017	• N = 2646 • GFR 20–59 ml/min (mean 48)	SBP <120 mm Hg vs. <140 mm Hg	3.3 yr	19% reduction in primary CV outcome, but no significant difference in stroke events	Patients with proteinuria were excluded
CSPPT[67]	2018	• N = 3230 hypertensive patients with GFR 30–60 and/or proteinuria	Enalapril/folic acid vs. enalapril alone	4.7 yr	49% reduced first stroke with a time-averaged SBP of ≤135 mm Hg (compared with SBP 135 to ≤140 mm Hg)	

AASK, African American Study of Kidney Disease and Hypertension; BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CSPPT, China Stroke Primary Prevention Trial; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; HOPE, Heart Outcomes Prevention Evaluation; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial; TIA, transient ischemic attack.

$P > 0.60$ for homogeneity). The major limitation of this meta-analysis is that most participants with CKD were in stage 3a (eGFR, 45–60 ml/min per 1.73 m^2), and few participants (0.4%) had an eGFR of ≤30 ml/min per 1.73 m^2, limiting the generalizability of these results to people with more advanced CKD.

The ideal BP target for cardiovascular protection in the population with CKD remains elusive. There has never been a dedicated BP RCT in the population with renal disease for the prevention of stroke, and most of the existing evidence has been derived from a *post hoc* or subgroup analysis (see Table 2[59–67]). Earlier studies (Modification of Diet in Renal Disease [MDRD] and African American Study of Kidney Disease and Hypertension [AASK])[64,68] failed to demonstrate benefits of intensive BP lowering (target mean arterial pressure, ≤92 mm Hg vs. ≤107 mm Hg) in this group for reducing cardiovascular morbidity and mortality but were inadequately powered for these outcomes and had short follow-up in their trial phases. From a recent prespecified Systolic Blood Pressure Intervention Trial (SPRINT) subgroup analysis, in patients with CKD and hypertension without diabetes, targeting an SBP of <120 mm Hg compared with <140 mm Hg reduced the rates of major cardiovascular events and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome.[66] However, the trial excluded people with diabetes, proteinuria >1000 mg/g, and prior stroke and the risk of stroke was similar in both treatment groups (HR, 0.99; 95% CI, 0.57–1.70; $P = 0.96$), though the trial was stopped early (median follow-up, 3.3 years). The results of the SPRINT are weighted heavily in the recent US BP guidelines,[16] whereas international guidelines have traditionally been more conservative with their BP targets, risk stratifying on the basis of proteinuria or diabetes (Table 1).[11,12]

A *post hoc* analysis of the China Stroke Primary Prevention Trial[67] evaluated the impact of the actual achieved BP on first stroke in hypertensive patients with mild to moderate CKD. A total of 3230 hypertensive patients with an eGFR of 30–60 ml/min per 1.73 m^2 and/or proteinuria were included. The incidence of total first stroke (1.7% vs. 3.3%; HR, 0.51; 95% CI, 0.26–0.99) and ischemic stroke (1.3% vs. 2.8%; HR, 0.46; 95% CI, 0.22–0.98) diminished significantly in patients with a time-averaged SBP of ≤135 mm Hg compared with participants with a time-averaged on-treatment SBP of 135 to ≤140 mm Hg. Compared with a time-averaged diastolic BP level of 80 to ≤90 mm Hg, a time-averaged diastolic BP of ≤80 mm Hg was significantly associated with a lower risk of hemorrhagic stroke (0.2% vs. 0.9%; HR, 0.18; 95% CI, 0.04–

0.80). Therefore, their findings are supportive of more intensive BP control for cerebrovascular protection in patients with CKD as per the SPRINT Trial.

However, intensive BP control may be deleterious for patients on dialysis. A retrospective cohort study of 113,255 patients on hemodialysis over a 5-year period found U-shaped associations between change in SBP, all-cause mortality, and cardiovascular mortality.[69] Post-dialytic drops in SBP of up to 30 mm Hg were associated with higher survival, but greater decreases in SBP and any increase in SBP (>0 mm Hg) were related to increased mortality. Approximately 7% of participants had preexisting cerebrovascular disease.

The method of measurement of BP may also be important in prognostication. Most clinical management of hypertension is based on office BP readings in patients with CKD and pre- and postdialysis BP readings obtained in the dialysis clinic in patients with ESKD. Compared with ambulatory BP readings, home BP monitoring in patients with CKD has been shown to be superior to office BP monitoring in diagnosing hypertension and reducing the incidence of white coat hypertension and masked hypertension.[70] Home BP readings, when compared with pre- or postdialysis BP readings, have been shown to correlate more closely with ambulatory BP readings in patients on dialysis. Out-of-office BP readings in patients with CKD are strongly associated with target organ damage.

Dialysis and related interventions

There is a higher incidence of stroke in ESKD than in earlier stages of CKD, and the rate is particularly high during the period of dialysis initiation.[71] There may be mechanisms intrinsic to dialysis (such as hemodynamic instability or circulatory stress) that independently increase stroke risk, and in keeping with this hypothesis, the long interdialytic gap has been associated with higher stroke event rates.[72] The addition of convection therapy to dialysis in hemodiafiltration was associated with a significant 61% risk reduction in stroke in a multicenter open-label RCT of 906 patients on chronic hemodialysis.[73] This may be linked to higher removal of inflammatory mediators or middle-sized molecules that may influence endothelial function or improved hemodynamic stability. More frequent hemodialysis also appears to be associated with improved surrogate markers of stroke risk, such as hypertension control and left ventricular mass.[74]

Dialysate cooling may be a novel approach to prevent ischemic brain injury, mediated through its positive effects on hemodynamic stability and its reduction in circulatory stress. Higher mean arterial pressure extrema points frequencies (indicative of greater hemodynamic instability) have been shown to correlate with brain white matter damage and worse neurocognitive test scores in patients on hemodialysis.[75] In a study of dialysate cooling, 73 patients on hemodialysis were randomized to dialyze with a dialysate temperature of either 37 °C or 0.5 °C below the core body temperature.[76] In the group randomized to a lower dialysate temperature, the mean arterial pressure extrema points frequencies and brain white matter microstructure parameters including fractional anisotropy, axial diffusivity, and radial diffusivity did not vary significantly at 12 months, indicating that dialysate cooling may be protective against chronic hemodialysis–induced brain injury. However, no studies to date have examined incident stroke as an outcome for patients treated with cooled dialysate.

Although anemia (defined as hemoglobin levels of <130 g/l for men or <120 g/l for women) has been associated with increased stroke risk in patients with CKD,[77] higher hemoglobin targets achieved with erythropoietin-stimulating agents have been linked to increased stroke risk in more advanced stages. In the TREAT study (4048 patients with diabetes, CKD, and moderate anemia) using Aranesp (darbapoetin alfa), a doubling of stroke (both ischemic and hemorrhagic) risk was observed in the higher (130 g/l) compared with the lower (90 g/l) targeted group.[78] It is for this reason that most guidelines recommend using erythropoietin-stimulating agent therapy to generally target hemoglobin values ranging between 100 and 120 g/l in patients with CKD, individualizing the value in this target range according to the possible comorbidities of patients.[79]

ACUTE STROKE TREATMENTS IN CKD

Thrombolysis

Intravenous thrombolysis (IVT) has become the standard of care for many patients admitted with acute ischemic stroke with better functional outcomes and survival.[80] However, its use may be more problematic in patients with CKD given their greater bleeding diathesis[81] and preexisting cerebrovascular disease burden.[82] Some studies have reported an increased bleeding risk in IVT-treated patients with advanced CKD compared with patients with normal renal function. In a pooled analysis of 7 observational studies (7168 patients), IVT-treated patients with CKD had a higher risk of symptomatic intracerebral hemorrhage (ICH) and mortality (pooled odds ratio [OR], 1.56; 95% CI, 1.05–2.33 and pooled OR, 1.70; 95% CI, 1.03–2.81, respectively).[83] Patients with CKD also had an increased risk of poor functional outcomes at 3 months. The interpretation of this meta-analysis is limited, however, by heterogeneity, lack of detail on the effect of IVT dose or time window, and lack of comparative data on outcomes in patients not given IVT.

A *post hoc* analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study confirmed an association between CKD and increased mortality but not disability or symptomatic ICH.[84] Compared with patients with normal renal function (eGFR, >90 ml/min per 1.73 m^2), those with an eGFR of <30 ml/min per 1.73 m^2 had increased mortality (adjusted OR, 2.07; 95% CI, 0.89–4.82; $P = 0.04$ for trend); every 10 ml/min per 1.73 m^2 lower eGFR was associated with an adjusted 9% increased odds of death in IVT-treated patients, a risk that did not seem to vary between low-dose and standard-dose alteplase. However, excess mortality in patients with advanced CKD did not seem to be

explained by a higher rate of ICH but was mostly attributable to higher rates of pneumonia, sepsis, or other nonvascular etiologies, consistent with earlier reports of important confounders in the relationship between IVT-treated patients with CKD and stroke outcomes.[85]

Stroke guidelines continue to recommend IVT use in otherwise eligible patients with CKD without restriction, including patients with ESKD on hemodialysis and normal activated partial thromboplastin time (aPTT).[86] This seems reasonable in the context of the considerable benefits derived from treatment in the general population (2.5-fold increased odds of a good outcome if treated within 3 hours[87]) and the absence of a trial directly comparing IVT and no IVT in patients with CKD, where outcomes may conceivably be expected to be worse in the latter case.

Intra-arterial interventions

Because several thrombectomy trials (SWIFT-PRIME [Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke] and REVASCAT [Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset]) excluded patients with advanced CKD[88,89] and only 1 trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE]) reported baseline renal function of participants,[90] there are no trial data to support or caution against intra-arterial treatments in patients with CKD. However, it is clearly an efficacious treatment in the general population as the number needed to treat to reduce disability with mechanical thrombectomy was 2.6 in pooled data of these trials.[91] Ninety-day mortality and symptomatic ICH rates did not differ between the intervention and control groups.

There is only limited observational evidence as to whether CKD influences the procedural risk, clinical outcomes, or mortality associated with thrombectomy. In a prospective study of 505 consecutive patients with anterior circulation stroke treated with mechanical thrombectomy, CKD (present in 20.2% of the included patients) did not associate with poor functional outcome (defined as modified Rankin Scale 3–6; OR, 1.13; 95% CI, 0.99–1.28; $P = 0.072$) or ICH.[92] However, it was associated with a higher risk of 90-day mortality (OR, 1.15; 95% CI, 1.01–1.31; $P = 0.038$). In contrast to these findings, in a smaller study (106 patients; 20.6% CKD prevalence) of vertebrobasilar stroke treated with thrombectomy, CKD was associated with a higher risk of any ICH but did not predict mortality.[93] It is difficult to interpret these conflicting results given the observational nature of these studies and their small size, but the benefits of unselected posterior circulation thrombectomies in the general population have also been less clear. It must be acknowledged though that CKD would also be expected to be associated with worse outcomes in the absence of thrombectomy. In a Japanese multicenter study of nearly 4000 patients, those with CKD had a 49% (95% CI, 17%–89%) higher risk of neurological deterioration during their hospitalization, a 138% (95% CI, 61%–257%) higher risk of in-hospital mortality, and a 25% (95% CI, 5%–48%) higher risk of significant disability at discharge, even after adjusting for confounding variables such as age, initial stroke severity, cardioembolic stroke subtype, and infectious complications.[94]

SECONDARY PREVENTION OF STROKE IN CKD

In patients with ischemic stroke, CKD has consistently been shown to be an independent risk factor for stroke recurrence.[95–97] In a *post hoc* analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial, patients with recent ischemic stroke with a baseline eGFR of <45 ml/min per 1.73 m^2 had a risk of recurrent stroke events that was 53% more than those with an eGFR of 60 to 74 ml/min per 1.73 m^2 even after adjustment for traditional vascular risk factors.[97] The magnitude of this risk emphasizes the importance of a comprehensive secondary prevention regime for these patients.

Antiplatelets

There is strong evidence from pooled trial data that aspirin is effective at reducing recurrent stroke risk in the general population.[98] In 15,778 participants, aspirin reduced the 6-week risk of recurrent ischemic stroke by ~60% and that of disabling or fatal ischemic stroke by ~70%. As we have already discussed, there are some bleeding concerns and potential antiplatelet hyporesponsiveness that have rendered uncertain the role of aspirin in primary prevention in CKD. Furthermore, the Cochrane review, based largely on secondary prevention studies, did not reveal any significant benefits in terms of long-term stroke prevention for this population.[99] However, it is unlikely that the large benefits of acute treatment would be completely nullified in patients with CKD and the guidelines consistently recommend its use for secondary prevention in this setting (Table 1).[11,12,17]

Patients with CKD may not derive the same benefits from the use of dual antiplatelet therapy in mild stroke/TIA as those with normal renal function. In a *post hoc* analysis of the Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events (CHANCE) trial in which these patients were randomized to clopidogrel-aspirin or aspirin-alone treatment, patients with moderate CKD (defined as eGFR <60 ml/min per 1.73 m^2; majority stage 3) treated with combination therapy did not experience a reduction in early recurrent stroke (HR, 1.00; 95% CI, 0.43–2.35; $P = 0.99$).[100] The CHANCE trial investigators later demonstrated that carriage of the *CYP2C19* loss-of-function allele (a genetic polymorphism for clopidogrel resistance) was associated with a significantly increased risk of stroke, ischemic stroke, and combined vascular events in patients on dual antiplatelet therapy with an eGFR of <75 ml/min per 1.73 m^2.[101]

The choice of antiplatelet agents or combination therapy may be important. In a recent systematic review and meta-

analysis of 11 secondary prevention RCTs (13,628 participants) of dual antiplatelet therapy (variable combinations) in CKD, compared to the control group, there was a reduction in the risk of major adverse cardiovascular events (RR, 0.87; 95% CI, 0.78–0.97), myocardial infarction (RR, 0.76; 95% CI, 0.61–0.92), and stroke (RR, 0.81; 95% CI, 0.68–0.94).[102] Compared with aspirin plus clopidogrel, aspirin plus ticagrelor or prasugrel reduced the risk of all-cause death (RR, 0.74; 95% CI, 0.6–0.88) in CKD and with no differences for major adverse cardiovascular events (RR, 0.88; 95% CI, 0.61–1.14) or major bleeding (RR, 0.93; 95% CI, 0.37–1.48). However, patients on dialysis and those with advanced CKD (stages 4–5) were not well represented in the included trials, so although dual antiplatelet therapy appeared to improve outcomes in early stages of CKD, it is unclear whether those with more advanced disease would derive the same benefits.

Statins

In a meta-analysis of trials of statins in patients with established cardiovascular disease, the subgroups of patients with CKD derived the same relative benefit from statins as the subgroups without CKD (40% reduction in the risk of stroke).[49,103] Their impact may be greater when given as high-intensity therapy (either atorvastatin 80 mg or rosuvastatin 20 mg once daily). In another meta-analysis of 6 RCTs (10,993 participants), a significant decrease in stroke was observed in the high-intensity statin therapy group (RR, 0.69; 95% CI, 0.56–0.85) without a clear difference in adverse events between those with CKD and those without.[104]

However, it remains uncertain whether statins reduce specifically recurrent stroke risk in dialysis-dependent patients as the dedicated trials in this group included people with and without previous cerebrovascular events and there was no overall statistically significant benefit for all-comers.[52,53] Certain high-risk subgroups did appear to benefit in *post hoc* analyses including those with a baseline LDL-C concentration of >145 mg/dl (3.76 mmol/l)[105] and diabetic patients.[106]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may also have a role in secondary stroke prevention. The American College of Cardiology recommends their addition (or ezetimibe) to maximally tolerated statin therapy in high-risk patients with atherosclerotic cardiovascular disease and CKD where <50% LDL-C concentration reduction has been achieved with statins, including high-intensity statins.[107] In a pooled analysis of 8 Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY) phase-3 trials (4629 participants; 10% of whom had impaired renal function) that compared alirocumab with either placebo or ezetimibe (with most participants also taking statins), the mean reduction in LDL-C concentration observed with alirocumab was ∼60% in those with and without impaired renal function.[108]

Antihypertensive agents

There is clear evidence to support the use of antihypertensive therapy, particularly with renin-angiotensin system inhibitors, in the secondary prevention of stroke in patients with CKD from the Perindopril Protection Against Recurrent Stroke (PROGRESS) Study. The PROGRESS Study enrolled 6105 participants with recently symptomatic cerebrovascular disease and randomly allocated them to perindopril-based BP-lowering therapy or placebo.[63] In a *post hoc* analysis of PROGRESS, compared with patients with normal renal function, those with CKD (N = 1757) were at ∼1.5-fold higher risk of major vascular events, stroke, and coronary heart disease and were more than twice as likely to die (all $P \leq 0.002$). The use of perindopril produced a 30% reduction in the risk of major cardiovascular events and a 35% reduction in the risk of stroke in patients with CKD. The absolute benefits of treatment were 1.7-fold higher for those with CKD than for those without. Perindopril prevented 1 stroke or other cardiovascular event in every 11 patients with CKD treated over 5 years, although it was unclear what the achieved BP or urinary albumin level were in either arm of the trial. However, intensive antihypertensive therapy (to target SBP <120 mm Hg) in high-risk diabetic patients with CKD in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial (ACCORD BP) was associated with a significant reduction in stroke risk (albeit with a number needed to treat [NNT] of 89 to prevent 1 stroke over 5 years).[109]

The European and US guidelines are somewhat conflicting in their recommendations for patients with CKD and do not stratify their BP target goals according to primary or secondary prevention in CKD (Table 1).[16,110] The US guidelines are largely driven by the results of the SPRINT-CKD substudy[66] and assume that the vast majority of patients with CKD have a 10-year atherosclerotic cardiovascular disease risk >10%, placing them in the high risk category that requires initiation of antihypertensive drug therapy at BP ≥130/80 mm Hg. Although these guidelines are less individualized and more prescriptive than the European[110] or Kidney Disease: Improving Global Outcomes[12] ones, there is a general consensus that the current body of evidence supports this target for both primary and secondary cardiovascular disease prevention in patients with CKD, regardless of proteinuria or diabetic status.[111]

Carotid interventions

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was the only large randomized trial of carotid endarterectomy in which renal function was assessed in trial participants.[112] For medically treated patients with symptomatic high-grade stenosis, the risk of ipsilateral stroke at 2 years was significantly higher in patients with CKD than in those with preserved renal function (31.6% vs. 19.3%; $P = 0.042$).[113] With surgery, there was a statistically significant RR reduction of 82.3% (95% CI, 54.5%–93.1%) in stroke risk for patients with CKD and 50.8% (95% CI, 12.6%–72.3%) for patients without CKD. The number needed to treat by

surgery to prevent 1 ipsilateral stroke within 2 years was 4 for patients with CKD and 10 for patients without CKD. The risk of perioperative death was similar between groups; however, rates of perioperative cardiac complications (myocardial infarction, congestive heart failure, and arrhythmias) were higher in the CKD group. However, in the 524 patients with CKD analyzed in this study, the mean eGFR was 49 ml/min per 1.73 m^2 (with a minimum of 19 ml/min per 1.73 m^2), which limits the generalizability of these results to those with stage 4 or 5 CKD.

Based on the observational data from the Vascular Study Group of New England database, the 30-day mortality post carotid intervention appeared to increase with worsening renal function (0.4% mild vs. 0.9% moderate [eGFR, 30–59 ml/min per 1.73 m^2] and 0.9% severe [eGFR, <30 ml/min per 1.73 m^2]; $P = 0.01$).[114] However, in a multivariate regression model, CKD status did not predict 30-day stroke or death. Although the 1-, 5-, and 10-year survival rates also decreased with worsening renal function, patients with severe CKD maintained a 71% survival at 5 years. In contrast to patients with peripheral arterial occlusive disease, for whom severe CKD reduces the 5-year survival rate to 21% irrespective of revascularization procedures,[115] patients with CKD and carotid interventions appear to do much better. Carotid revascularization may therefore have utility in carefully selected patients with moderate and severe CKD, particularly in symptomatic disease.

However, do the risks outweigh the benefits in patients on dialysis? Based on United States Renal Data System data, the perioperative and long-term outcomes after carotid endarterectomy of 5142 patients with both symptomatic and asymptomatic diseases on dialysis were studied.[116] However, 83% of patients were asymptomatic. The 30-day stroke rate, myocardial infarction, and mortality for the asymptomatic and symptomatic groups were 2.7% versus 5.2% ($P = 0.001$), 4.6% versus 5.0% ($P = 0.69$), and 2.6% versus 2.9% ($P = 0.61$), respectively. The perioperative risks of carotid endarterectomy are therefore clearly high, even for asymptomatic patients. The overall long-term (3-year) survival was also poor at 46% and 42% in the asymptomatic and symptomatic cohorts, respectively. The authors therefore conclude that surgery should only be considered in judiciously selected very high risk symptomatic patients.

The only official guidance on the management of carotid disease in patients with CKD comes from the Society for Vascular Surgery, which recommends carotid endarterectomy rather than stenting for symptomatic patients with moderate to severe stenosis (Table 1).[19] These patients evidently require careful perioperative assessment and management given their higher rate of short-term complications, but the long-term outcomes appear to be promising in nondialysis CKD.

Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter-2 inhibitors were originally developed to treat hyperglycemia in people with diabetes but now appear to have promising protective cardiometabolic effects in patients with CKD with (and potentially without) diabetes.[117] They restore tubuloglomerular feedback and reduce intraglomerular pressure by increasing afferent arteriolar tone even in the presence of ambient normoglycemia. Recent large placebo-controlled outcome trials have shown that empagliflozin and canagliflozin reduce the risk of cardiovascular disease in high-risk people with type 2 diabetes mellitus.[118–120] In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin 10 to 25 mg was shown to reduce the primary cardiovascular composite outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) by 14% compared with placebo (HR, 0.86; 95% CI, 0.74–0.99).[119] This effect was driven by a 38% (HR, 0.62; 95% CI, 0.49–0.77) reduction in cardiovascular death. These cardiovascular effects appear to be largely independent of effects on glycemic control, BP, and body weight.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) randomized 10,142 participants with type 2 diabetes and an eGFR of >30 ml/min per 1.73 m^2 to canagliflozin or placebo with the same primary outcome as that of EMPA-REG OUTCOME. The effect of canagliflozin on the primary outcome was similar in patients with CKD (HR, 0.70; 95% CI, 0.55–0.90) and those with preserved kidney function (HR, 0.92; 95% CI, 0.79–1.07) ($P = 0.08$ for heterogeneity).[121] Heterogeneity was observed for the effect on fatal/nonfatal stroke, with possibly greater benefits with declining kidney function ($P = 0.01$ for heterogeneity). These drugs are currently not approved for those with eGFR between 30 and 45 ml/min per 1.73 m^2, but this eGFR-based limitation may need to be reevaluated.

CONCLUSIONS

Stroke prevention and treatment are evidently more complex in the population with CKD. Current controversies within existing guidelines are whether there should be stratification in treatment strategies depending on age, frailty, CKD stage, diabetes status, presence of proteinuria, transplant status, or dialysis requirement.[12,16,110] Based often only on observational studies or on a *post hoc* subgroup analysis of trial data, clearly there are still gaps in the evidence for the efficacy and safety of primary and secondary preventive treatments that are used routinely in the general population. There is a need for dedicated stroke prevention trials in the population with CKD, particularly in those with more advanced disease or who are dialysis dependent.

DISCLOSURE

PMR has received funding from the Wellcome Trust, the Wolfson Foundation, the British Heart Foundation, the National Institute for Health Research, and the National Institute for Health Research Oxford Biomedical Research Centre. DMK has received a scholarship from the Irish Nephrology Society.

ACKNOWLEDGMENTS

We are grateful to Eoin Kelleher who kindly illustrated Figure 1 for this article.

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