

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

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ABSTRACT

Chronic Kidney Disease (CKD) 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 CKD patients, accounting for this association. However, factors unique to these patients, such as uraemia, oxidative stress, 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 CKD, 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 preventative and therapeutic interventions for stroke in the general population. In this review, we will explore the complexities and challenges of these interventions in the renal population.

Key words: Chronic Kidney Disease; Stroke; Dialysis; Primary Prevention; Secondary prevention

INTRODUCTION

Chronic kidney disease (CKD) is an increasing global health burden with an estimated prevalence worldwide of 11-13%.¹ CKD is associated with an eight- to ten-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 about 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 clustering of shared vascular risk factors including hypertension, diabetes mellitus, and atrial fibrillation but ‘non-traditional’ risk factors such as anaemia, 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 stroke⁸ but there is a lack of clinical trials of prevention and treatment of stroke in the renal population with most of evidence to support use of existing treatments derived from posthoc subgroup analyses.^{9, 10} In this review, we will 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*.

PRIMARY PREVENTION OF STROKE IN CKD

Antiplatelets

Among high-risk patients with prior vascular disease or some other predisposing condition, anti-platelet therapy has been associated with a 25 percent relative risk reduction in nonfatal stroke compared with placebo.¹¹ 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.¹² Clinical practice guidelines are ambiguous about their use in CKD patients, because those with moderate to severe CKD were systematically excluded from most clinical trials evaluating efficacy and safety.¹³

In a large Cochrane review of 50 RCTs (27,139 participants) of antiplatelet treatment for the prevention of cardiovascular outcomes in CKD, antiplatelet agents reduced the risk of myocardial infarction (RR=0.87, 95% CI 0.76-0.99), but not all-cause mortality (RR=0.93, 0.8-1.06), cardiovascular mortality (RR=0.89, 0.70-1.12) or stroke (RR=1.00, 0.58-1.72).¹⁴ Antiplatelet agents increased the risk of major (RR=1.33, 1.10- 1.65) and minor bleeding (RR=1.49, 1.12-1.97). Though few studies were available for direct comparison, meta-regression analysis indicated no differences in the relative benefit 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 in primary prevention in CKD were available only

from a post-hoc subgroup analysis of a single study, the Hypertension Optimal Treatment (HOT) Trial.¹⁵ In this trial, the relative risk of major cardiovascular events were reduced by 9% (95% CI -9% to 24%), 15% (-17% to 39%), and 66% (33% to 83%) for patients with baseline eGFR of ≥ 60 , 45 to 59, and < 45 mL/min/1.73m² respectively (p for trend = 0.03) but there was no significant benefit for stroke as an individual endpoint and a near doubling in the risk of major bleeding (RR=2.04, 1.05 to 3.96).

In a more recent meta-analysis that focused only on primary prevention studies in CKD, 3 trials (HOT, Heart and Renal Protection [HARP], Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes [JPAD] trial) were identified providing data for 4468 participants.¹⁶ Overall, there was no statistically significant reduction in major cardiovascular events including stroke (RR=0.92, 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 one trial (HARP) was CKD-specific.

The Aspirin To Target Arterial events in Chronic Kidney Disease (ATTACK) trial (NCT03796156) is an open-label, multi-centre 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 the bleeding concerns, there are reports of high rates of antiplatelet hyporesponsiveness in patients with CKD that may partially explain poorer

outcomes.¹⁷ CKD and ESKD are independent risk factors for clopidogrel resistance; 50-80% of patients with ESKD have high on-treatment residual platelet reactivity (resistance) when treated with clopidogrel¹⁸. However, it has been suggested that the high burden of co-morbidities in CKD patients may account for this observation rather than CKD itself.¹⁹

Overall, the current guideline recommendations to generally avoid primary prevention with aspirin in CKD patients are reasonable in the context of recent randomized trials (ASpirin in Reducing Events in the Elderly study [ASPREE], Aspirin to Reduce Risk of Initial Vascular Events [ARRIVE], A Study of Cardiovascular Events in Diabetes [ASCEND])²⁰⁻²² 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

Anti-coagulation 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.^{23, 24} However, there is considerable recognition of the underuse of oral anticoagulation for stroke prevention in atrial fibrillation (AF) in renal disease, and their use is often complicated by high bleeding rates and uncertain benefit²⁵. In particular, there are concerns regarding warfarin use given the association

with vascular calcification due to inhibition of the enzyme matrix gamma-carboxyglutamate Gla protein that scavenges calcium phosphate in tissues.²⁶

Outcomes reported with warfarin use in both 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 (HR=0.76; 95% CI, 0.64 to 0.91; P=0.003) and among patients requiring renal-replacement therapy (HR=0.44, 0.26-0.74; p=0.002), but with a non-significantly decreased risk among patients with non-end-stage CKD (HR=0.84, 0.69-1.01).²⁷ There was an increasing risk of bleeding among all warfarin users with renal disease (HR=1.33, 1.16 to 1.53; P<0.001). This contrasts with the results of Swedish registry data (SWEDHEART) that showed a lower risk of stroke in both groups without a higher risk of bleeding.²⁸ However, the latter cohort were a higher risk group post recent myocardial infarction and included fewer dialysis patients, 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 risks of ischemic stroke/thromboembolism, major bleeding, and mortality.²⁹ In patients with AF and non-end-stage CKD, warfarin use was associated with a lower risk of ischemic stroke/thromboembolism (HR=0.70, 0.54-0.89; P = 0.004) and mortality (HR=0.65, 0.59-0.72; P < 0.00001), but had no effect on major bleeding (HR=1.15; 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 end-stage kidney disease (ESKD), warfarin had no apparent effect on the risks of stroke (HR=1.12, 0.69-1.82; P=0.65) and mortality (HR=0.96, 0.81-1.13; P=0.60), but increased the risks of major bleeding (HR=1.30, 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 ESKD patients with AF. Similarly in a 2017 meta-analysis of only dialysis patients, warfarin was not associated with a significant reduction in ischemic stroke (HR=0.77, 0.55-1.07), but possibly increased intracranial hemorrhage (HR=1.93, 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).³⁰

These analyses suggest that warfarin is not associated with a clear benefit but likely increased harm among dialysis patients with AF. 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 dialysis patients with AF. It should be reserved for the highest-risk patients in this group such as those with a history of prior stroke or a documented cardiac thrombus. The results of the ongoing trial (AVKDIAL

[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 (NOAC) appear to have at least an equivalent, if not more favourable safety and efficacy profile when compared to vitamin K antagonists in CKD. Most of the randomized trials of NOACs (RE-LY, ARISTOTLE, ROCKET-AF) have included non-valvular AF patients with an eGFR ≥ 30 mL/min/1.73 m² and therefore, the best evidence for their use is in CKD patients with an eGFR of 30-59 mL/min/1.73m².³¹⁻³³ In a systematic review and meta-analysis of eight RCTs (9693 participants) that compared NOACs to 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 to 1.04]), recurrent thromboembolism or thromboembolism-related death (RR=0.97, 0.43 to 2.15]), or bleeding events (RR=0.89, 0.68 to 1.16]) between NOACs versus vitamin K antagonists.³⁴ However, although not statistically significant, there was clearly a trend towards 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, 0.66 to 0.93[]), hemorrhagic stroke (RR=0.48, 0.30 to 0.76]), and all-cause death (RR=0.88, 0.78 to 0.99)].³⁵ However, the reduction

in major bleeding (RR=0.80, 0.61 to 1.04]) was non-significant when compared to warfarin. This meta-analysis was again limited only to patients with a creatinine clearance >25 mL/min as there was no data available for patients with more advanced CKD including dialysis-dependent ESKD.

However, NOAC use in dialysis patients appears promising from observational data so far. A comparison of warfarin versus apixaban in dialysis patients was performed using a retrospective cohort study of 25 523 patients included in the United States Renal Data System (USRDS).³⁶ In matched cohorts, there was no difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR=0.88, 0.69-1.12; P=0.29), but apixaban was associated with a significantly lower risk of major bleeding (HR=0.72, 0.59-0.87; P<0.001). In sensitivity analyses, standard-dose apixaban was superior to both reduced-dose apixaban and warfarin with lower risks of stroke/systemic embolism and death.

There are currently two RCTs underway that are examining the safety and efficacy of NOACs compared to warfarin in the dialysis population. In the US-based Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation (RENAL-AF) (NCT02942407), patients are randomized to standard dose apixaban versus warfarin with a lower apixaban dose used in select patients. In the second German multi-centre trial, AXADIA (Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease) (NCT02933697), chronic haemodialysis patients are randomized to receive either apixaban 2.5 mg

twice daily or the Vitamin-K antagonist, phenprocoumon.³⁷ These trials are anticipated to be completed in September 2019 and July 2022, respectively. 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 those of the earlier observational USRDS data³⁶, that standard dose apixaban is associated with a lower risk of stroke, major bleeding and mortality when compared with warfarin in haemodialysis patients. However, with low enrolment numbers, there are concerns that the trials will be under-powered to evaluate the important intracerebral haemorrhage 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 15-50 ml/min in the latest American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines and they have also recommended consideration of either warfarin or apixaban use in ESKD (Grade IIb; moderate quality evidence) (*Table 1*).³⁸ NOAC use in those with a GFR of 30-50 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 < 30 ml/min, a group who are at 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 in 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 dialysis patients 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% or greater 10-year risk of developing cardiovascular disease, or the patient is over 40 years old in the setting of diabetes mellitus.^{39, 40} In patients with prior unstable angina or myocardial infarction, statin use appears to reduce the risk of subsequent stroke by 50%.⁴¹ As a coronary artery disease equivalent in terms of vascular risk⁴², 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 MI limited to studies in which pre-existing 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 to 0.79; $I^2 = 59\%$), death (3 studies, 7215 participants): RR=0.63, 0.44 to 0.90; $I^2 = 38\%$), and MI (4 studies, 7519 participants; RR=0.54, 0.38 to 0.76; $I^2 = 0\%$) but uncertain effects on cardiovascular mortality (1 study, 304 participants): RR 0.37, 0.01 to 8.90).⁴³ Although data for treatment effects on cardiovascular events were

predominantly derived from post-hoc subgroup analyses, there wasn't substantial heterogeneity. The best evidence to support the role of statin therapy in primary prevention for CKD patients comes from the Study of Heart and Renal Protection (SHARP) trial, in which 9270 patients with CKD (including 6247 non-dialysis patients) and without pre-existing vascular disease were randomly assigned to placebo or to the combination of simvastatin 20 mg daily plus ezetimibe 10 mg daily, confirmed benefit for CKD patients with a 25% reduction in non-haemorrhagic stroke in the treatment arm.⁴⁴

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*).^{13, 39, 45} According to Kidney Disease Improving Global Outcomes (KDIGO),⁴⁵ CKD patients over 50 years of age are considered at sufficiently high risk of a cardiovascular event ($\geq 10\%$ risk of manifest coronary heart disease over 10 years) to justify statin therapy without the need for applying 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 reductions in LDL cholesterol obtained in more advanced CKD.⁴⁶ The dialysis subgroup analysis of the SHARP (Study of Heart and Renal Protection) trial⁴⁴ and other randomized trials investigating statins for primary prevention of cardiovascular events in end-stage kidney disease (ESKD), such as the 4D study (Die Deutsche Diabetes Dialyse Studie)⁴⁷ and

AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events)⁴⁸, found no benefit of statin therapy in the dialysis population. Suggested reasons for this “statin resistance” include the poor association of LDL cholesterol with cardiovascular risk in this population, owing to the predomination of nontraditional risk factors (e.g., mineral and bone abnormalities, uraemia)⁴⁹, lipid abnormalities (e.g., lipoproteins rendered highly atherogenic by oxidation or carbamylation), intracellular cholesterol synthesis activated by inflammatory stress⁵⁰, and its pro-calcifying effects.⁵¹ Both the 2014 KDIGO Lipid Work Group and 2018 AHA/ACC 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*).^{39, 52}

In practice, given the excess baseline cardiovascular risk in this group, we would recommend a low threshold for starting statin therapy for the purpose of primary prevention for patients with non-dialysis CKD over the age of 40, particularly in the presence of an unfavourable lipid profile or an additional risk factor (e.g. hypertension, smoking).

Anti-hypertensive agents

A collaborative prospective meta-analysis of randomised 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 <60 mL/min/1.73 m²⁵³. Compared with placebo, BP lowering regimens reduced the risk

of major cardiovascular events by about 16% per 5 mm Hg reduction in systolic blood pressure (SBP) in individuals with (HR=0.83, 0.76-0.90) and without reduced eGFR (0.83, 0.79-0.88). Nor was there any evidence that the effects of different drug classes on major cardiovascular events varied between patients with different eGFR (all $P>0.60$ for homogeneity). The major limitation of this meta-analysis is that most participants with CKD were in stage 3a (45-60 mL/min/m²), and few participants (0.4%) had eGFR ≤ 30 mL/min/1.73 m², limiting the generalizability of these results to people with more advanced CKD.

The ideal BP target for cardiovascular protection in the CKD population remains elusive. There has never been a dedicated BP RCT in the renal population for the prevention of stroke and most of the existing evidence has been derived from posthoc or subgroup analysis (see *Table 2*). Earlier studies (Modification of diet in renal disease [MDRD], African American Study of Kidney Disease and Hypertension [AASK])^{54, 55} failed to demonstrate benefits of intensive BP lowering (Target mean arterial pressure [MAP] ≤ 92 vs ≤ 107 mmHg) 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, among patients with CKD and hypertension without diabetes, targeting an SBP<120 mm Hg compared with <140 mm Hg reduced rates of major cardiovascular events and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome.⁵⁶ 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, 0.57–1.70; $P = 0.96$) though the trial was stopped early

(median follow-up 3.3 years). The results of SPRINT are weighted heavily in the recent US blood pressure guidelines⁵⁷ while international guidelines have traditionally been more conservative with their BP targets, risk stratifying on the basis of proteinuria or diabetes (*Table 1*).^{13, 45}

A post hoc analysis of the China Stroke Primary Prevention Trial (CSPPT),⁵⁸ evaluated the impact of actual achieved blood pressure on first stroke among hypertensive patients with mild-to-moderate CKD. 3230 hypertensive patients with eGFR 30–60 mL/min/1.73 m² and/or proteinuria were included. Compared with participants with a time-averaged on-treatment SBP of 135 to ≤140 mmHg, the incidence of total first stroke (1.7% vs 3.3%; HR=0.51, 0.26–0.99) and ischaemic stroke (1.3% versus 2.8%; HR=0.46, 0.22–0.98) diminished significantly in patients with a time-averaged SBP of ≤135 mmHg. A time-averaged DBP of ≤80 mmHg, compared with a time-averaged DBP level of 80 to ≤90 mmHg, was significantly associated with a lower risk of haemorrhagic stroke (0.2% versus 0.9%; HR=0.18, 0.04–0.80). Therefore, their findings are supportive of more intensive BP control for cerebrovascular protection in CKD patients as per the SPRINT trial.

However, intensive blood pressure control may be deleterious for dialysis patients. A retrospective cohort study of 113,255 hemodialysis patients over a 5-year period found U-shaped associations between change in systolic blood pressure, all-cause mortality and cardiovascular mortality⁵⁹. Post-dialytic drops in systolic BP of up to 30 were associated with greater survival, but larger decreases of systolic BP and any

increase in systolic BP (over 0 mm Hg) were related to increased mortality.

Approximately 7% of participants had pre-existing 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 post-dialysis 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 incidences of white-coat hypertension and masked hypertension⁶⁰. Home BP readings, when compared to pre- or post-dialysis BP readings, have been shown to correlate more closely with ambulatory BP readings in dialysis patients. Out-of-office BP readings in patients with CKD are associated strongly 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.⁶¹ There may be mechanisms intrinsic to dialysis (such as haemodynamic instability or circulatory stress) that independently increase stroke risk and in keeping with this hypothesis, the long interdialytic gap has been associated with greater stroke event rates.⁶² The addition of convection therapy to dialysis in haemodiafiltration was associated with a significant 61% risk reduction in stroke in a multicenter, open-label, randomized controlled trial of 906 chronic haemodialysis patients.⁶³ This may be linked to higher

removal of inflammatory mediators or middle-sized molecules that may influence endothelial function, or improved haemodynamic stability. More frequent haemodialysis also appears to be associated with improved surrogate markers of stroke risk such as hypertension control and left ventricular mass.⁶⁴

Dialysate cooling may be novel approach to prevent ischaemic brain injury, mediated through its positive effects on haemodynamic stability and its reduction of circulatory stress. Higher mean arterial pressure (MAP) extrema points frequencies (indicative of greater haemodynamic instability) have been shown to correlate with brain white matter damage and worse neurocognitive test scores in haemodialysis patients.⁶⁵ In a study of dialysate cooling, 73 haemodialysis patients were randomized to dialyze with a dialysate temperature of either 37°C or 0.5°C below the core body temperature.⁶⁶ In the group randomized to a lower dialysate temperature, the MAP 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 haemodialysis-induced brain injury. However, no studies to date have examined incident stroke as an outcome for patients treated with cooled dialysate.

While anaemia (defined as haemoglobin levels of <130 g/L for men or <120 g/L for women) has been associated with increased stroke risk in CKD patients⁶⁷, higher haemoglobin targets achieved with erythropoietin-stimulating agents (ESA) have been linked to increased stroke risk in more advanced stages. In the TREAT study (4048 patients with diabetes, CKD and moderate anaemia) using Aranesp (darbapoetin alpha), a doubling of stroke (both ischaemic and haemorrhagic) risk was

observed in the higher (130 g/L) compared with the lower (90 g/L) targeted group.⁶⁸ It is for this reason that most guidelines recommend using ESA therapy to generally target haemoglobin values ranging between 100 and 120 g/L in CKD patients, individualizing the value in this target range according to the possible comorbidities of the patients.⁶⁹

ACUTE STROKE TREATMENTS IN CKD

Thrombolysis

Intravenous thrombolysis (IVT) has become the standard of care for many patients admitted with acute ischaemic stroke with better functional outcomes and survival.⁷⁰ However, its use may be more problematic in CKD patients given their greater bleeding diathesis⁷¹ and pre-existing cerebrovascular disease burden.⁷² 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 ICH and mortality [pooled OR=1.56, 1.05-2.33 and 1.70, 1.03-2.81, respectively].⁷³ Patients with CKD also had 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.

Post-hoc analysis of the ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study) confirmed an association between CKD and increased mortality but not disability or symptomatic ICH.⁷⁴ Compared with patients with normal renal function (>90 mL/min/1.73 m²), those with an eGFR <30 mL/min/1.73 m² had increased mortality (adjusted OR=2.07, 0.89-4.82; P=0.04 for trend); every 10 mL/min/1.73 m² lower eGFR was associated with an adjusted 9% increased odds of death in IVT-treated patients; a risk which did not seem to vary between low-dose and standard-dose alteplase. However, the excess mortality in patients with advanced CKD did not seem to be explained by a greater number of ICH but was mostly attributable to higher rates of pneumonia, sepsis, or other non-vascular aetiologies, consistent with earlier reports of important confounders in the relationship between IVT-treated CKD patients and stroke outcomes.⁷⁵

Stroke guidelines continue to recommend IVT use in otherwise-eligible CKD patients without restriction including in patients with ESKD on hemodialysis and normal aPTT.⁷⁶ 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 hours⁷⁷) and the absence of a trial directly comparing IVT versus no IVT in CKD patients, where outcomes may conceivably be expected to be worse in the latter case.

Intra-arterial interventions

Since several thrombectomy trials (SWIFT-PRIME, REVASCAT) excluded patients with advanced CKD^{78, 79} and only one trial (ESCAPE) reported baseline renal function of participants⁸⁰, there are no trial data to support or caution against intra-arterial treatments in patients with CKD. However, it is clearly a very 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.⁸¹ 90-day mortality and symptomatic ICH rates did not differ between 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 included patients) did not associate with poor functional outcome (defined as mRS 3-6; OR=1.13, 0.99-1.28; $p=0.072$) or ICH.⁸² However, it was associated with a higher risk of 90-day mortality (OR=1.15, 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.⁸³ 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 multi-center study of

nearly 4000 patients, those with CKD had a 49% (95% CI 17–89) greater risk of neurological deterioration during their hospitalization, a 138% (95% CI 61–257) greater risk of in-hospital mortality, and a 25% (95% CI 5–48) greater risk of significant disability at discharge, even after adjusting for confounding variables such as age, initial stroke severity, cardio-embolic stroke subtype, and infectious complications.⁸⁴

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.⁸⁵⁻⁸⁷ In a post-hoc analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial, patients with recent ischemic stroke with a baseline eGFR <45 mL/min/1.73m² had a risk of recurrent stroke events that was 53% greater than those with eGFR of 60-74 mL/min/1.73 m² even after adjustment for traditional vascular risk factors.⁸⁷ 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.⁸⁸ In 15,778 participants, aspirin reduced the 6 week risk of recurrent ischaemic stroke by about 60% and disabling or fatal ischaemic stroke by about 70%. As we have already discussed, there are some bleeding concerns and potential anti-platelet hypo-responsiveness 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.⁸⁹ 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*).^{13, 45, 90}

Patients with CKD may not derive the same benefits from the use of dual antiplatelet therapy (DAPT) in mild stroke/TIA as those with normal renal function. In a post-hoc analysis of the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) in which these patients were randomized to clopidogrel-aspirin or aspirin-alone treatment, patients with moderate CKD (defined as eGFR <60 ml/min/1.73m²; majority stage 3) treated with combination therapy did not experience a reduction in early recurrent stroke (HR=1.00, 0.43-2.35; P=0.99).⁹¹ The CHANCE investigators later demonstrated though that carriage of the CYP2C19 loss of function allele (a genetic polymorphism for clopidogrel resistance) was associated with significantly increased risk of stroke, ischemic stroke and combined vascular events in patients on DAPT with an eGFR < 75 ml/min/1.73 m².⁹²

The choice of anti-platelet agent or combination may be important. In a recent systematic review and meta-analysis of 11 secondary prevention RCTs (13628 participants) of DAPT (variable combinations) in CKD, compared to the control group, there was a reduction in the risk of major adverse cardiovascular events (RR=0.87, 0.78-0.97), myocardial infarction (RR=0.76, 0.61-0.92), and stroke (RR=0.81, 0.68-0.94).⁹³ Compared to aspirin/clopidogrel, aspirin plus ticagrelor or

prasugrel reduced the risk of all-cause death (RR=0.74, 0.6-0.88) in CKD; and with no differences for major adverse cardiovascular events (RR=0.88, 0.61-1.14), or major bleeding (RR=0.93, 0.37-1.48). However, dialysis patients and those with advanced CKD (stages 4-5) were not well-represented in the included trials so although DAPT 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 on major outcomes as the subgroups without CKD (40% reduction in the risk of stroke).^{43, 94} Their impact may be greater when given as high-intensity therapy (either atorvastatin 80mg or rosuvastatin 20mg 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, 0.56 to 0.85) without a clear difference in adverse events between those with CKD and those without.⁹⁵

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.^{47, 48} Certain high-risk subgroups did appear to benefit in post-hoc analyses including those with a baseline LDL-cholesterol concentration >145 mg/dL (3.76 mmol/L)⁹⁶ and diabetic patients.⁹⁷

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may also have a role in secondary stroke prevention. The ACC recommends their addition (or ezetimibe) to maximally tolerated statin therapy in high-risk patients with atherosclerotic cardiovascular disease and CKD where less than 50% LDL-C reduction has been achieved with statins, including high-intensity statins.⁹⁸ In a pooled analysis of 8 ODYSSEY phase 3 trials (4629 participants; 10% of which had impaired renal function) that compared alirocumab with either placebo or ezetimibe (with most participants also taking statins), the mean reduction in LDL-C observed with alirocumab was ~60% in those with and without impaired renal function.⁹⁹

Antihypertensive agents

There is clear evidence to support the use of anti-hypertensive therapy, particularly with renin-angiotensin (RAS) inhibitors, in the secondary prevention of stroke in CKD patients from the Perindopril Protection against Recurrent Stroke Study (PROGRESS). The PROGRESS study enrolled 6105 participants with recently symptomatic cerebrovascular disease and randomly allocated them to perindopril-based blood pressure-lowering therapy or placebo.¹⁰⁰ In a post-hoc analysis of the PROGRESS study, compared with those with normal renal function, CKD patients (N = 1757) were at approximately 1.5-fold greater 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 among CKD patients. The absolute benefits of treatment were 1.7-fold greater for those with CKD than for those without. Perindopril prevented one stroke or other cardiovascular event among

every 11 patients with CKD treated over five years, although it was unclear what the achieved blood pressure or level of urine albumin were in either arm of the trial. However, intensive anti-hypertensive therapy (to target SBP <120 mmHg) in high-risk diabetic patients with CKD in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP) was associated with a significant reduction in stroke risk (albeit with an NNT of 89 to prevent one stroke over 5 years).¹⁰¹

The European and US guidelines are somewhat conflicting in their recommendations for CKD patients and do not stratify their blood pressure target goals according to primary or secondary prevention in CKD (*Table 1*).^{57, 102} The US guidelines are driven largely by the results of the SPRINT-CKD substudy⁵⁶ and assume that the vast majority of patients with CKD have a 10-year atherosclerotic cardiovascular disease risk greater than 10%, placing them in the high risk category that requires initiation of antihypertensive drug therapy at BP \geq 130/80 mmHg. Although these guidelines are less individualized and more prescriptive than the European¹⁰² or KDIGO⁴⁵ ones, there is a general consensus that the current body of evidence supports this target for both primary and secondary cardiovascular disease prevention in CKD patients, regardless of proteinuria or diabetic status.¹⁰³

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.¹⁰⁴ For medically treated patients with symptomatic high-grade stenosis, risk for ipsilateral stroke at 2 years was significantly higher in patients with CKD than in those with preserved renal function (31.6 versus 19.3%; $P = 0.042$).¹⁰⁵ 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 one ipsilateral stroke within 2 years was four for patients with CKD and 10 for patients without CKD. The risk for 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, among the 524 patients with CKD analyzed in this study, the mean eGFR was 49 ml/min/1.73 m² (with a minimum of 19 ml/min/1.73 m²) which limits the generalizability of these results to those with stage 4/5 CKD.

Based on 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 30-59ml/min/1.73m²] and 0.9% severe [eGFR <30 ml/min/1.73m²]; $P = 0.01$).¹⁰⁶ 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 procedures¹⁰⁷, 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 dialysis patients? Based on USRDS data, the perioperative and long-term outcomes after carotid endarterectomy (CEA) of 5142 dialysis patients with both symptomatic and asymptomatic diseases were studied¹⁰⁸. However, 83% of patients were asymptomatic. The 30-day stroke rate, myocardial infarction, and mortality for the asymptomatic and symptomatic groups were 2.7% vs 5.2% ($P = 0.001$), 4.6% vs 5.0% ($P = 0.69$), and 2.6% vs 2.9% ($P = 0.61$), respectively. The perioperative risks of CEA 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 CKD patients comes from the Society for Vascular Surgery who recommend carotid endarterectomy rather than stenting for symptomatic patients with moderate-severe stenosis (*Table 1*).¹⁰⁹ These patients evidently require careful perioperative assessment and management given their higher rate of short-term complications, but the long-term outcomes appear promising in non-dialysis CKD.

SGLT-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors were originally developed to treat hyperglycaemia in people with diabetes but now appear to have promising protective cardio-metabolic effects in CKD patients with (and potentially without) diabetes.¹¹⁰ They restore tubuloglomerular feedback and reduce intraglomerular pressure by increasing afferent arteriolar tone even in the presence of ambient normoglycaemia. 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.¹¹¹⁻¹¹³ In the EMPA-REG OUTCOME trial, empagliflozin 10–25 mg was shown to reduce the primary cardiovascular composite outcome (death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) by 14% compared with placebo (HR=0.86, 0.74–0.99).¹¹² This effect was driven by a 38% (HR=0.62, 0.49–0.77) reduction in cardiovascular death. These cardiovascular effects appear to be largely independent of effects on glycaemic control, BP and body weight.

The CANVAS Program randomized 10,142 participants with type 2 diabetes and eGFR >30 mL/min/1.73 m² to canagliflozin or placebo with the same primary outcome as EMPA-REG OUTCOME. The effect of canagliflozin on the primary outcome was similar in CKD patients (HR= 0.70, 0.55-0.90) and those with preserved kidney function (HR= 0.92, 0.79-1.07; P heterogeneity = 0.08).¹¹⁴ Heterogeneity was observed for the effect on fatal/nonfatal stroke, with possibly greater benefits with

declining kidney function (P heterogeneity = 0.01). These drugs are currently not approved for those with an eGFR between 30-45 ml/min/1.73m² but this eGFR-based limitation may need to be re-evaluated.

CONCLUSIONS

Stroke prevention and treatment are evidently more complex in the CKD population. 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.^{45, 57, 102}

Based often only on observational studies or on post-hoc subgroup analysis of trial data, there are clearly still gaps in the evidence for efficacy and safety for primary and secondary preventative treatments that are used routinely in the general population.

There is a need for dedicated stroke prevention trials in the CKD population, particularly in those with more advanced disease or who are dialysis-dependent.

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Figure legends

Figure 1: Traditional and non-traditional risk factors for cerebrovascular diseases in patients with CKD

Table 1: Current available guidelines for the primary or secondary prevention of cerebrovascular disease in CKD

Table 2: Trials of blood pressure lowering in the CKD population

Table 1: Current available guidelines for the primary or secondary prevention of cerebrovascular disease in CKD

Guidelines	NICE ¹³	KDIGO ^{45, 115}	ACC/AHA/ASA ^{38, 39, 57, 90, 116}	Society for Vascular Surgery ¹⁰⁹
Anti-platelet therapy	<ul style="list-style-type: none"> • Offer only for secondary prevention but caution as to the increased risk of bleeding 	<ul style="list-style-type: none"> • Aspirin is indicated for secondary prevention but not for primary prevention 	<ul style="list-style-type: none"> • Aspirin may be considered for primary prevention for GFR 30-45 ml/min and should be given for secondary prevention 	
BP control	<ul style="list-style-type: none"> • Target BP <140/90 mmHg in general, but <130/80 mmHg if ACR≥70 mg/mmol or diabetic. • Use preferably RAS antagonist 	<ul style="list-style-type: none"> • Individualize targets according to age, CVD, co-morbidities. • <140/90 mmHg if not diabetic and UAE<30mg/24hr 	<ul style="list-style-type: none"> • Target <130/80 mmHg • Use RAS antagonist 	
Anticoagulation	<ul style="list-style-type: none"> • Consider apixaban in preference to warfarin if GFR 30-50 ml/min in at-risk non-valvular AF. 		<ul style="list-style-type: none"> • Consider reduced dose NOACs if GFR 15-50 ml/min. • Consider warfarin or apixaban in ESKD. 	
Statins	<ul style="list-style-type: none"> • Give atorvastatin 20 mmHg for primary or secondary prevention. • Discuss higher doses with renal specialist if GFR<30 ml/min 	<ul style="list-style-type: none"> • Check a lipid profile in all new CKD patients. • If >50 years and stage 3-5, treat with statin or statin/ezetimibe. • >50yo CKD stage 1-2, treat with statin • In dialysis-dependent CKD, don't start statins but continue if already taking 	<ul style="list-style-type: none"> • Initiate a moderate-intensity statin +/- ezetimibe in non-dialysis CKD if 40 to 75 years of age with LDL-C 70-189mg/dL and at 10-year ASCVD risk ≥ 7.5%. • In dialysis-dependent CKD, don't start statins but continue if already taking 	
Carotid interventions				<ul style="list-style-type: none"> • Consider if symptomatic with moderate-severe stenosis. • CEA > CAS • CAS may have a role in selected patients.

NICE indicates National Institute for Health and Care Excellence, KDIGO, Kidney Disease Improving Global Outcomes, ACC, American College of Cardiology, AHA, American Heart Association, ASA, American Stroke Association, BP, blood pressure, RAS, renin-angiotensin system, GFR, glomerular filtration rate, AF, atrial fibrillation, ACR, albumin:creatinine ratio, UAE, urine albumin excretion, NOAC, novel oral anti-coagulant, ESKD, end-stage kidney disease, CKD, chronic kidney disease, CEA, carotid endarterectomy, CAS, carotid artery stenting.

Table 2: Trials of blood pressure lowering in the CKD population

Trial Name	Year	Patients	Intervention	Follow-up	Results	Comments
MDRD ^{117, 118}	1993; follow-up 2005	<ul style="list-style-type: none"> • N=840 • All CKD 	Target MAP ≤92 vs ≤ 107 mmHg	2.2 years (initial study); 6.2 years follow-up	23% reduction in composite kidney failure/mortality outcome	BP not recorded during the follow-up study
HOPE ¹¹⁹	2001	<ul style="list-style-type: none"> • Post hoc analysis • N= 980 with mild renal insufficiency + prior vascular disease or other risk factor (124- 200 µmol/L) 	Ramipril vs Placebo	4.5 years	31% reduction in stroke risk with ramipril	
RENAAL ¹²⁰	2003	<ul style="list-style-type: none"> • N=1513 • Type 2 diabetes with nephropathy 	Losartan vs Placebo; target <140/90mmHg	3.4 years	16% reduction in renal outcomes/mortality and 10% non- significant reduction in CV events.	Patients with non-diabetic nephropathies excluded
PROGRESS ¹⁰⁰	2007	<ul style="list-style-type: none"> • Posthoc analysis • 1757 CKD patients with history of TIA/stroke 	Perindopril vs Placebo	4 years	Reduced risk of major vascular events by 30% and stroke by 35% in CKD.	No data on patients with proteinuria
AASK ^{55, 121}	2002 trial phase; 2010 cohort phase	<ul style="list-style-type: none"> • N=1094 black hypertensive CKD 	Target MAP ≤92 vs ≤ 107 mmHg	4 years trial follow-up; 5 years additional cohort	No significant differences in ESKD/mortality except in those with proteinuria	All patients had same BP target in cohort phase
SPRINT ⁵⁶	2017	<ul style="list-style-type: none"> • N=2646 • GFR 20-59 ml/min (mean 48) 	SBP<120 vs <140	3.3 years	19% reduction in primary CV outcome but no significant difference on stroke events	Patients with proteinuria were excluded
CSPPT ⁵⁸	2018	<ul style="list-style-type: none"> • N= 3230 hypertensive patients with GFR 30-60 +/-or proteinuria 	Enalapril/Folic acid vs Enalapril alone	4.7 years	49% reduced first stroke with time- averaged SBP of ≤135 (compared to SBP 135 - ≤140)	

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