Stroke

SPECIAL REPORT

Chronic Kidney Disease and Cerebrovascular Disease

Consensus and Guidance From a KDIGO Controversies Conference

Dearbhla M. Kelly, MBBChBAO, MSc, DPhil, MRCPI; Zanfina Ademi, MPH, PhD; Wolfram Doehner, MD, PhD; Gregory Y.H. Lip, MD; Patrick Mark, MB ChB, PhD; Kazunori Toyoda, MD, PhD; Christopher X. Wong, MBBS, MSc, MPH, PhD; Mark Sarnak, MD, MS; Michael Cheung, MD; Charles A. Herzog, MD; Kirsten L. Johansen, MD; Holger Reinecke, MD, PhD; Manish M. Sood, MD, MSc

ABSTRACT: The global health burden of chronic kidney disease is rapidly rising, and chronic kidney disease is an important risk factor for cerebrovascular disease. Proposed underlying mechanisms for this relationship include shared traditional risk factors such as hypertension and diabetes, uremia-related nontraditional risk factors, such as oxidative stress and abnormal calcium-phosphorus metabolism, and dialysis-specific factors such as cerebral hypoperfusion and changes in cardiac structure. Chronic kidney disease frequently complicates routine stroke risk prediction, diagnosis, management, and prevention. It is also associated with worse stroke severity, outcomes and a high burden of silent cerebrovascular disease, and vascular cognitive impairment. Here, we present a summary of the epidemiology, pathophysiology, diagnosis, and treatment of cerebrovascular disease in chronic kidney disease from the Kidney Disease: Improving Global Outcomes Controversies Conference on central and peripheral arterial disease with a focus on knowledge gaps, areas of controversy, and priorities for research.

Key Words: atrial fibrillation ■ diagnosis ■ dialysis ■ epidemiology ■ uremia

In February 2020, an international and interdisciplinary Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference was held in Dublin, Ireland to discuss central and peripheral arterial disease in chronic kidney disease (CKD). Here we report on the natural history of cerebrovascular disease in CKD, specifically key issues in the epidemiology, pathophysiology, evaluation, treatment/prevention, and complications of stroke in CKD (full conference agenda, scope of work, and discussion questions are available at https://kdigo.org/conferences/central-peripheral-arterial-disease/). Of note, the specific relationship between CKD and hemorrhagic stroke was beyond the remit of this conference and as such is not discussed in this article.

EPIDEMIOLOGY OF STROKE IN CKD

From a global perspective, the burden of CKD is on the rise with a prevalence estimate of 9.1% (8.5–9.8) for all CKD stages.[1] It is well established that impaired kidney function is an independent risk factor, above and beyond traditional risk factors, for cardiovascular disease. Kidney function, as determined by the estimated glomerular filtration rate (eGFR), demonstrates an inverse step-wise relationship with incident stroke risk increasing by 3-, 4.1-, 5.4-, and 7.1-fold for CKD stage 3 to 5 and dialysis compared with the general population.[2] Proteinuria itself is an under-recognized risk factor for stroke, independent of blood pressure and diabetes, and coupled with declines in kidney function, substantively elevates stroke

Correspondence to: Dearbhla M. Kelly, MBBChBAO, MSc, MRCPI, Wolfson Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom. Email dearbhla.kelly@ndcn.ox.ac.uk

The Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.029680.

For Sources of Funding and Disclosures, see page e341.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ATTACK	Aspirin to Target Arterial Events in Chronic Kidney Disease
CANVAS	Canagliflozin Cardiovascular Assessment Study
CKD	chronic kidney disease
CREST-2	Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial
CSPPT	China Stroke Primary Prevention Trial
CT	computed tomography
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
HR	hazard ratio
ICH	intracerebral hemorrhage
KDIGO	Kidney Disease: Improving Global Outcomes
LDL-C	low-density lipoprotein cholesterol
NASCET	North American Symptomatic Carotid Endarterectomy Trial
OR	odds ratio
PCSK9	proprotein convertase subtilisin/kexin type 9
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
REGARDS	Reasons for Geographic and Racial Differences in Stroke
RR	relative risk
SBP	systolic blood pressure
SCI	silent cerebral infarction
SGLT-2	sodium-glucose cotransporter 2
SHARP	Study of Heart and Renal Protection
SPRINT	Systolic Blood Pressure Intervention Trial
SPS3	Secondary Prevention of Small Subcortical Strokes
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TRACK	Treatment of Cardiovascular Disease With Low Dose Rivaroxaban in Advanced Chronic Kidney Disease

risk.[3] Further, there is a dose-response with higher levels of proteinuria conferring an elevated risk (macroalbuminuria versus microalbuminuria: adjusted relative risk [RR], 2.65 [95% CI, 2.25–3.14] versus RR, 1.58 [95% CI, 1.39–1.80]).[4]

Atrial fibrillation (AF) is common in the CKD population and enhances the risk of stroke.[5] In hemo- and peritoneal dialysis patients, there are 1.5-fold and 1.3-fold reported increases in the risk of AF relative to the general population.[6,7] Furthermore, the prevalence of AF in dialysis patients is rising, with a 3-fold increase from 1992 to 2006 in the United States, coinciding with the rising age and comorbidity burden of dialysis patients.[8,9]

Important temporal relationships regarding the timing of dialysis and stroke risk exist. An ischemic stroke in advanced CKD (stage 4 or 5) is associated with an exceedingly high 30-day risk of kidney failure (CKD stage 4: 6.8%, stage 5: 25.7%) or death (CKD stage 4: 22.4%, stage 5: 21.2%).[10] The time of dialysis initiation is a particularly vulnerable period for acute stroke as the 30-day period before and after dialysis initiation is associated with a 3-fold increase in stroke, transient ischemic attack, or recurrent stroke risk.[11] The day after the long interdialytic gap is also associated with greater risk than other days.[12] With regard to dialysis modality, hemodialysis patients appear to be at higher stroke risk compared with peritoneal and kidney transplant patients, although the contribution of inherent differences among patients on each modality cannot be fully accounted for (ie, confounding by treatment indication).[13] Unfortunately, patients with a functioning kidney transplant retain a high incidence of stroke at 5.96/1000 patient-years and a 1-year mortality rate of 42.3% poststroke.[14]

Stroke subtype is intricately linked to mechanism, prognosis, prevention, and risk of recurrence and as such, represents a basic requisite to further improve stroke care. The risk of all classic stroke subtypes (ischemic [large vessel, cardioembolic, small vessel] and hemorrhagic) are universally reported to be elevated in CKD and dialysis.[15] However, epidemiologically, the relative contribution of each stroke subtype across CKD stages and receipt of dialysis remain largely unknown, apart from cardioembolic events which may occur more frequently in CKD.[5] A recent population-based study of 3178 stroke events classified by the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria, reported no significant difference between stroke subtypes in early (median eGFR, 47 mL/min) CKD.[16] Whether stroke subtype is altered with more advanced CKD remains unknown.

PATHOPHYSIOLOGY

An overview of proposed pathophysiology pathways to stroke in CKD is outlined in Figure 1. Essentially, it is acknowledged that cerebrovascular disease in this setting is attributable to a combination of synergistic traditional and nontraditional mechanisms.[17] Shared traditional risk factors or mechanisms include hypertension, diabetes, AF, carotid artery disease, heart failure,[18] obesity, and dyslipidemia—all of which are frequently comorbid with CKD and accentuated in its presence. Hypertension, in particular, is present in 67% to 92% of patients with CKD[19] and has recently been shown to markedly confound the association between CKD and stroke when long-term premorbid blood pressure

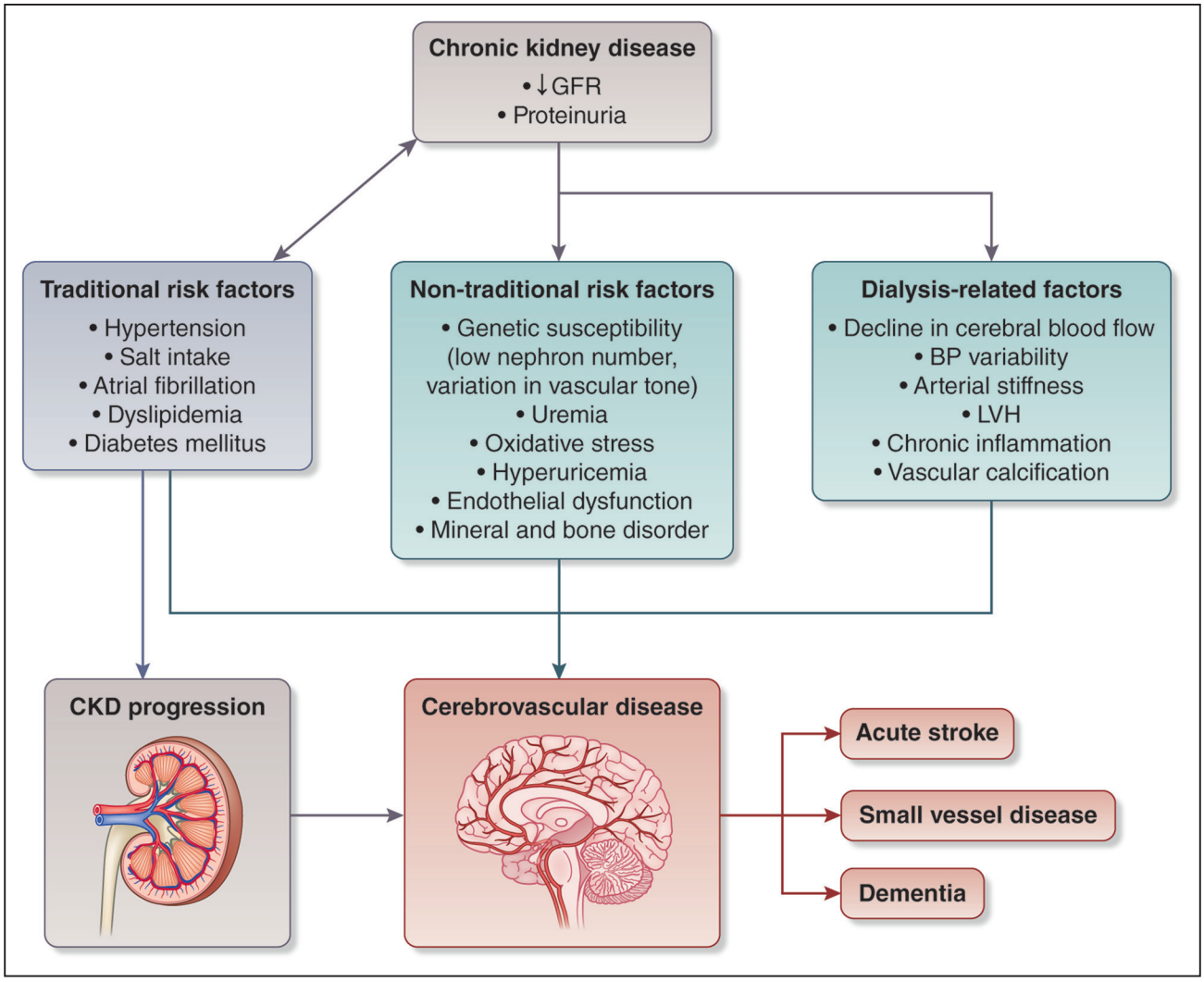

Figure 1. The interplay of traditional, nontraditional, and dialysis-specific risk factors in the cause stroke in chronic kidney disease (CKD).

BP indicates blood pressure; GFR, glomerular filtration rate; and LVH, left ventricular hypertrophy.

is adjusted for.[20] The current evidence suggests that CKD is associated with a greater propensity to thrombosis, but the clot formed in CKD is structurally and functionally different to clot formed where renal function is normal; this may explain why patients with CKD are at higher risk of thrombosis, but are paradoxically, too, at higher risk of bleeding.[21]

Nontraditional CKD-related risk factors such as chronic inflammation, uremic toxins, reactive oxygen radicals, anemia, and mineral-bone disorder are proposed to contribute to risk by triggering vascular injury and endothelial dysfunction.[17] Uremia can cause protein carbamylation which has proatherosclerotic effects via enhanced dyslpidemia.[22] It can also impair platelet adhesiveness and platelet endothelial interaction, increasing the risk of hemorrhagic stroke.[23] Hyperphosphatemia, arising from CKD-related mineral-bone disorder, causes arterial medial calcification by inducing an osteogenic phenotype change of vascular smooth muscle cells.[24] The role and relative contribution of nontraditional risk factors above and beyond traditional risk factors for cerebrovascular disease in CKD remains unclear. CKD may in itself be associated with stroke, but it should also be considered as a marker of severity and control of underlying risk factors such as hypertension and diabetes, especially when epidemiological studies do not track A1C, left ventricular hypertrophy, other markers of disease severity over time.

There are also hemodialysis-specific risk factors that appear to influence stroke risk including cerebral hypoperfusion, enhanced arterial stiffness and wide blood pressure variability. Cerebral arterial mean flow velocity has been shown to decline significantly during dialysis[25] and this intradialytic hemodynamic instability causes transient cerebral stunning, leading to cumulative ischemic white matter changes over time.[26] Greater arterial stiffness and blood pressure variability are also predictive of cardiovascular events in hemodialysis patients.[27,28]

Stroke. 2021;52:e328–e346. DOI: 10.1161/STROKEAHA.120.029680

RISK PREDICTION TOOLS

A number of well-known risk prediction tools exist to quantify stroke risk in individuals with AF in the general population including $CHADS_2$ and CHA_2DS_2-VASc.[29,30] The accuracy of these tools or modified versions that incorporate a measure of renal function have been examined in the CKD and dialysis population (see Table 1).

Several issues render their use problematic in this population. First, for the purpose of stroke risk prediction, the addition of CKD as a binary variable (present/absent) is likely to be insufficient since stroke risk progressively increases with worsening renal function alongside bleeding risk.[32] Second, risk factors are dynamic, and renal dysfunction may develop later even if normal initially.[33] Third, there have been methodological flaws in the validation of some of these novel scores such as CHA_2DS_2-VAK where female sex was substituted with kidney disease.[34] In this study, there was no data on oral anticoagulant use at follow-up which would impact on event rates, no censoring of patients initiated on anticoagulation, and no time-in-therapeutic range monitoring. Fourth, attempts to validates these scores in highly selected trial cohorts have largely excluded those with more advanced kidney disease (ie, eGFR <30 mL/min per 1.73 m^2).[35] Overall, scores to predict stroke in patients with AF with CKD, with or without the addition of kidney parameters, demonstrate poor model discrimination or at least little change in their predictive value with the addition of kidney disease (Table 1).[31,35,36] This may be the case because CKD is associated with many comorbidities (ie, heart failure, diabetes and hypertension) which are already accounted for by the current CHA_2DS_2-VASc score. Furthermore, model discrimination for existing tools appears to worsen with increasing CKD severity and the need for dialysis paradoxically as both AF and stroke risk increase. This raises a number of questions regarding the role of routine use of existing risk scores in advanced CKD/dialysis. The utility of existing tools must be balanced against their inherent inaccuracy in an already high-risk population. As such, there is a need for further research to examine whether prediction improves (1) in existing tools with the addition of kidney- or dialysis-specific variables (above and beyond CKD as a binary variable), (2) in existing tools by redefining prediction factors to be more kidney-specific (eg, hypertension in dialysis patients), and (3) with the development of de novo advanced CKD/dialysis-specific tools. Finally, it is difficult to recommend novel prediction tools when therapy for those with advanced CKD who have been excluded from most of the anticoagulation trials is unclear, and a focus on better renal-specific bleeding risk prediction tools may be more useful in terms of therapeutic decision-making.

Bleeding and stroke risk are strongly correlated. A number of bleeding risk prediction tools have been proposed, and a Patient-Centered Outcomes Research Institute (PCORI)-systematic review and evidence appraisal identified the HAS-BLED score as the best validated published score to assess bleeding.[37] However, there are limited data in the dialysis population, and like stroke risk, bleeding risk is dynamic and changes with changes in risk factors.[38] The appropriate use of bleeding scores is to draw attention to modifiable bleeding risk factors and to identify patients at high bleeding risk early review and follow-up. This was tested in the mAFA-II (mobile atrial fibrillation application) cluster randomized trial,[39] where integrated care intervention that included the HAS-BLED score resulted in a lower bleeding events (due to mitigation of modifiable bleeding risk factors) and over 12 months, an increase in anticoagulation use, compared with usual care.[40]

DIAGNOSTIC CONSIDERATIONS AND CHALLENGES

There have been concerns regarding the routine use of computed tomography (CT) angiography or CT perfusion imaging in the setting of CKD due to the theoretical risk of contrast-induced nephropathy.[41] This can lead to inertia or undue delay in this time-sensitive treatment pathway for patients with kidney disease.[42] Such concerns appear to be unfounded as results of a recent meta-analysis of 14 studies (5727 CT angiography/CT perfusion imaging and 981 noncontrast CT patients) found that

Table 1. The Effects of Adding Points for CKD on the Ability of Risk Scores to Predict Ischemic Stroke in AF

	Points for CKD	C-index (95% CI)	NRI % (95% CI)	
			At 1 y	At 5 y
$CHADS_2$	0	0.72 (0.72 to 0.73)	…	…
R-$CHADS_2$	1	0.72 (0.72 to 0.72)	0.4 (0.1 to 0.8)	0.4 (0.0 to 0.7)
R_2-$CHADS_2$	2	0.72 (0.71 to 0.72)	−5.3 (−16.1 to 0.6)	0.6 (0.1 to 1.1)
CHA_2DS_2-VASc	0	0.71 (0.71 to 0.72)	…	…
R-CHA_2DS_2-VASc	1	0.71 (0.71 to 0.72)	0.5 (0.0 to 0.8)	0.4 (0.0 to 0.8)
R_2-CHA_2DS_2-VASc	2	0.71 (0.70 to 0.71)	−4.6 (−5.5 to 3.0)	0.7 (0.2 to 1.3)

AF indicates atrial fibrillation; CKD, chronic kidney disease; and NRI, net reclassification index.
Reprinted from Friberg et al[31] with permission. Copyright ©2015, Oxford University Press.

the risk of acute kidney injury was significantly lower for patients who had received contrast compared with those who did not (odds ratio [OR], 0.47 [95% CI, 0.33–0.68]; $P<0.01$).[43] Importantly, there was no significant difference in acute kidney injury risk among those without and with prior kidney disease exposed to contrast.

Concerns regarding use of gadolinium in CKD may also lead to under-utilization of brain magnetic resonance imaging. The association of gadolinium-based contrast agents and the rare but debilitating skin condition, nephrogenic systemic fibrosis, in patients with advanced kidney disease was first described in 2007.[44] Although more recent evidence suggests that the risk associated with the newer, more stable group II gadolinium-based contrast agent (gadobenate dimeglumine, gadobutrol, gadoterate meglumine, or gadoteridol) is quite low (<0.07%),[45] the key sequences of a stroke-protocol magnetic resonance imaging (diffusion weighted imaging, fluid-attenuated inversion recovery, and gradient echo) do not require its use. The potential risks of gadolinium would, therefore, likely outweigh any potential benefits in this setting. However, in general, patients with kidney disease should not be denied CT angiography/CT perfusion imaging or gadolinium-free MR imaging as they appear to be safe and allow the opportunity for detailed stroke subtyping with its implicit mechanistic and prognostic insights.[46,47]

With regard to dialysis-dependent patients, some additional challenges may exist in terms of ascertainment of diagnosis or outcomes. Since these patients have >3-fold increased risk of stroke death compared with age- and sex-matched people in the general population,[48] the cause of these events may never be fully ascertained. In addition, strokes may occur during or shortly after the hemodialysis session in over one-third of cases,[49] and this may lead to under-recognition and under-diagnosis as the presentation may be initially misdiagnosed. Despite frequent contact with health professionals, dialysis patients have been shown to present a median of 8.5 hours after the onset of symptoms.[50] In a cross-sectional analysis of 148 patients with end-stage kidney disease (ESKD) without a prior diagnosis of stroke or transient ischemic attack, 46 (36.5%) had experienced one or more stroke symptoms.[51] These unreported symptoms were then subsequently associated with a 2- to 3-fold higher odds of cognitive or functional impairment, suggesting that these may have represented clinically significant events.

MANAGEMENT OF STROKE IN CKD

Patients With CKD Receive Suboptimal Stroke Care

There is clear evidence from both United States and European data that there are inequities in stroke care for patients with CKD.[52,53] In an analysis of nearly 700 000 patients from the Get With The Guidelines–Stroke program cohort, despite higher inpatient mortality rates, each successive strata of CKD was increasingly less likely to receive evidence-based therapies compared with no CKD.[52] This included acute stroke therapies such as thrombolysis and antiplatelets, but also preventative treatment such as statin therapy and smoking cessation. Similarly, in a Scottish cohort study, dialysis patients were less frequently admitted to an acute stroke unit (64.6 versus 79.6%; $P<0.001$), less likely to receive aspirin acutely (75.3 versus 83.2%; $P=0.01$), and more likely to die (22.9 versus 14.4%; $P=0.002$) than their non-ESKD counterparts.[53] Stroke units have very clear benefits in the general population with a 28% reduction in death or dependency and a number needed to benefit of only 6.[54] The benefits appear to be maintained in the CKD population where admission to a stroke unit was associated with lower risk of death (hazard ratio [HR], 0.68 [0.55–0.84]; $P<0.001$).[53] Concerns regarding aggressive use of evidence-based therapies in CKD may be based on higher risks of adverse outcomes related to therapy, for example higher bleeding risk.[55] In addition, premorbid frailty and goals of care may also influence how treatment is started. Patients with CKD are frequently multimorbid and multimorbidity is known to have a multifaceted impact on stroke from cause to treatment and rehabilitation.[56] Further investigations specifically evaluating the net clinical benefit of stroke care and care pathways in individuals with CKD are required.

Intravenous Thrombolysis

Irrespective of age or initial stroke severity, intravenous thrombolysis administered within the first 4.5 hours after an ischemic stroke onset is associated with better functional outcomes[57] and more recently, benefits to up to 9 hours have been seen depending on adequate patient selection.[58] This is crucial for the CKD population who often represent an older cohort, prone to large infarcts due to a high prevalence of underlying AF.[59] However, this group also have a greater bleeding diathesis[60] and often, a preexisting cerebrovascular disease burden[61] that may increase the risks of treatment. Most of the randomized controlled trials of thrombolysis either excluded patients with advanced CKD or did not report CKD-specific outcomes so there is limited data on its safety and efficacy in this group.

In a meta-analysis of 7 observational studies (7168 patients), patients with CKD who were treated with intravenous thrombolysis had a higher risk of both symptomatic intracerebral hemorrhage (ICH; OR, 1.56 [1.05–2.33]) and mortality (OR, 1.70 [1.03–2.81]) compared with those treated without CKD.[62] There was no statistically significant difference in terms of functional

 Stroke. 2021;52:e328–e346. DOI: 10.1161/STROKEAHA.120.029680

outcomes at 3 months. However, this meta-analysis has several limitations including its lack of individual-participant data, dose or timing details, and high heterogeneity.

In contrast, a post hoc analysis of the ENCHANTED trial (Enhanced Control of Hypertension and Thrombolysis Stroke Study), a multicentre, randomized open-label blinded trial comparing low dose (0.6 mg/kg) to standard-dose (0.9 mg/kg) alteplase, intravenous thrombolysis-treated patients with CKD had greater risk of mortality but not disability or symptomatic ICH.[63] Compared with patients with normal renal function (>90 mL/min per 1.73 m^2), those with an eGFR <30 mL/min per 1.73 m^2 had a 2-fold increased mortality risk (4.9% versus 14.6%) and every 10 mL/min per 1.73 m^2 lower eGFR was associated with an adjusted 9% increased odds of death in intravenous thrombolysis-treated patients. There was no difference between low-dose and standard-dose alteplase. However, there was only 103 patients (out of 3310) with an eGFR <30 mL/min per 1.73 m^2, and the excess mortality in this group appeared to related to higher rates of pneumonia, sepsis, or other nonvascular causes, rather than an excess of symptomatic ICH. Similarly, higher rates of mortality but not symptomatic ICH were reported in dialysis patients treated with intravenous thrombolysis in a large US-based registry study but again, they were a significantly multi-morbid group with higher rates in-hospital complications such as pneumonia and deep vein thrombosis.[64]

Use of intravenous thrombolysis in CKD or dialysis patients is one of the key inequities in stroke care with delays to treatment[42] and under-treatment reported.[52,53] Although there is clearly a lack of evidence in this area, we would concur with the guidelines that recommend intravenous thrombolysis use in otherwise-eligible patients with CKD without restriction including in hemodialysis patients with a normal activated partial thromboplastin time (Table 2).[65]

It seems unlikely that the large benefits of an acute treatment would be completely nullified in this group and conceivable that outcomes would be worse in the absence of treatment given the high rates of stroke mortality consistently observed in the CKD and dialysis population.[53,68] The studies to date have generally only used those without CKD as the control group. In the absence of randomized controlled trial directly comparing intravenous thrombolysis versus no intravenous thrombolysis in patients with CKD, a meta-analysis of individual-level patient from the previous stroke trial data would help clarify the safety and efficacy of treatment in this group.

Endovascular and Surgical Interventions

As per the thrombolysis trials, many thrombectomy trials (eg, SWIFT-PRIME [Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke], 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[69,70] and no trial has reported outcomes according to CKD status. From the limited available observational data, there are conflicting reports on the outcomes post-thrombectomy in this group. CKD was not associated with poor functional outcome (defined as modified Rankin Scale score, 3–6; OR, 1.13 [0.99–1.28]; *P*=0.072) or ICH, but was associated with a higher risk of 90-day mortality (OR, 1.15 [1.01–1.31]; *P*=0.038) in a prospective analysis of 505 patients presenting with anterior-circulation stroke.[71] In a small study (106 patients; 20.6% CKD prevalence) of posterior-circulation stroke, CKD was associated with a higher risk of ICH post-thrombectomy but not mortality.[72] However, the benefits of mechanical thrombectomy

Table 2. Key Recommendations for the Management of Acute Stroke in CKD Based on Expert Consensus

Acute ischemic stroke	
Acute blood pressure targets	We would recommend following the AHA/ASA guidelines with regard to blood pressure targets depending on the eligibility for thrombolysis. The presence of CKD should not modify these targets.
High-dose aspirin therapy	This should be given if an ICH has been excluded, if the patient is not eligible for thrombolysis, and if there is no other contraindication present.
IV thrombolysis	A patient with CKD or who is dialysis-dependent should be treated with thrombolytic therapy provided that the aPTT is normal and that there is no other contraindication present. Dose modification for renal function is not recommended.
Mechanical thrombectomy	A patient with CKD or who is dialysis-dependent should undergo a mechanical thrombectomy for a large-vessel occlusive stroke if they are otherwise eligible for treatment.
Decompressive hemicraniectomy	Given the poor prognosis in the general population, the decision for surgical intervention for malignant hemispheric infarction should be individualized in this setting taking into account the patient's premorbid functional status.
Admission to an acute stroke unit	It is essential that a patient with an acute ischemic stroke who has CKD or who is dialysis-dependent be admitted to an acute stroke unit.
Spontaneous ICH	
Acute blood pressure targets	Early intensive blood pressure lowering (SBP <140 mm Hg in <1 h) appears to be equally safe and effective in CKD.[66]
Anticoagulation reversal	Patients with CKD or who are dialysis-dependent should receive reversal agents for vitamin K- and nonvitamin K anatagonists as per the general population. Idarucizumab is safe to use in impaired renal function.[67]
Surgical evacuation of hematoma	Patients with CKD or who are dialysis-dependent should be undergo surgical evacuation of ICH where indicated if they are otherwise eligible.
Admission to an acute stroke unit	It is essential that a patient with an acute ischemic stroke who has CKD or who is dialysis-dependent be admitted to an acute stroke unit.

AHA indicates American Heart Association; aPTT, activated partial thromboplastin time; ASA, American Stroke Association; CKD, chronic kidney disease; ICH, intracerebral hemorrhage; IV, intravenous; and SBP, systolic blood pressure.

for unselected posterior-circulation stroke in the general population are also less certain.[73] There is not much evidence on outcomes in dialysis patients and theoretically, they may represent a more problematic group given their challenging vascular access and greater tendency to bleed. Reassuringly though, in an analysis of 915 dialysis patients treated with thrombectomy from the Nationwide Inpatient Sample (2005–2010), endovascular treatment was associated with lower in-hospital mortality (OR, 0.5 [0.2–0.9]) and moderate-to-severe disability (OR, 0.3 [0.2–0.5]) compared with the no treatment in dialysis patients.[74] Although there is a need for greater research, we would advocate for its use in an otherwise suitable patient as CKD would also be expected to be associated with worse outcomes in the absence of thrombectomy (Table 2).

With regard to surgical interventions in acute stroke (eg,decompressive hemicraniectomy for malignant cerebral hemispheric infarction and hematoma evacuation for intracerebral hemorrhage) there is no evidence specific to CKD or dialysis patients to support or caution against these interventions. However, given that CKD is present in nearly one-third of patients hospitalized with ICH and is associated with greater likelihood of institutionalization and in-hospital mortality, we would not recommend withholding surgery in an otherwise eligible patient (Table 2).

Dialysis Considerations in the Acute Phase

There are a number of potential challenges with regard to dialysis in acute brain injury such as stroke. First, an increase in brain water content with intermittent hemodialysis may lead to further increases in intracranial pressure as subclinical cerebral edema during intermittent hemodialysis has been observed even in stable patients.[75] Second, changes in osmolality during hemodialysis from the reverse osmotic shift due to urea[76] or other newly formed brain osmoles[77] may also accentuate intracranial pressure. Third, blood pressure and volume fluctuations also have the potential to extend the penumbra in patients with acute stroke as global cerebral blood flow has been shown to decline acutely by 10% during hemodialysis,[78] and intradialytic hypotension has been associated with cerebral ischaemia.[26] Lastly, systemic anticoagulation during hemodialysis may potentiate hemorrhage,[79] worsen cerebral edema, and increase the risk of cerebral herniation.[80]

Unfortunately, there is no evidence in the literature to guide best clinical practice in this scenario but rather only expert opinion-based reviews.[81,82] Our consensus suggestions are summarized in Figure 2 but decisions on modality type, timing, dose, anticoagulation, and other considerations should ultimately be individualized with input from both stroke physicians and nephrologists. These prescription modifications are most relevant to patients with larger infarcts, blood pressure dependent infarcts (eg, in the presence of high-grade intracranial or extracranial stenosis), or ICH, that is, those who are most vulnerable to neurological deterioration from stroke extension or increasing cerebral edema. In such patients, we would preferentially recommend continuous forms of renal replacement therapy as this has

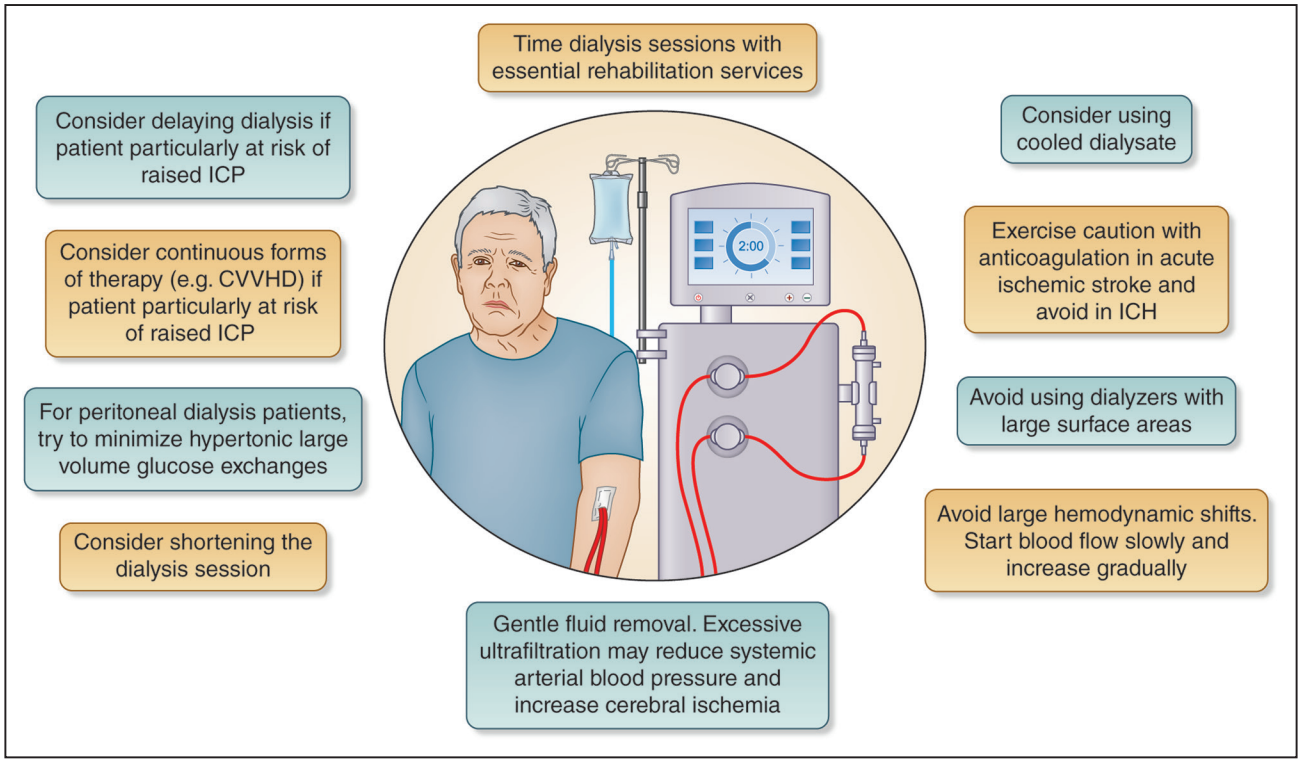

Figure 2. Suggestions for dialysis prescribing in acute stroke.
CVVHD indicates continuous venovenous hemodialysis; ICH, intracerebral hemorrhage; and ICP, intracranial pressure.

been associated with greater intracranial stability compared with standard intermittent hemodialysis and haemofiltration.[83] Changes in osmolality and urea and bicarbonate levels during continuous renal replacement therapy are much less than those during intermittent hemodialysis and hemofiltration. However, the disadvantage is that the circuit must function continuously for continuous renal replacement therapy to be successful and this requires anticoagulation. Regional anticoagulation with citrate (ie, a selective block of the whole hemostatic cascade only in the circuit and not in the patient's blood circulation[84]) is, therefore, indicated in this setting rather than system heparinization, though there is no data on use of citrate in patients with acute stroke. Where possible, delaying dialysis in patients with ICH may be advisable given the heightened risk of worsening cerebral edema and incurring herniation syndromes.[80]

For patients who are stable enough for intermittent hemodialysis, we would recommend consideration of a cooled dialysate as this has been shown to reduce intradialytic hypotension, improve cerebral perfusion, and reduce cerebral ischemia during hemodialysis.[85] Shortening the dialysis sessions may minimize fluctuations in plasma osmolality. The role of osmotherapy with additional mannitol or hypertonic saline in this setting is unclear and should be decided on a case-by-case basis. Peritoneal dialysis may be associated with better intracranial stability than intermittent hemodialysis but large volume, high glucose exchanges should be minimized.[86] In general, we would advocate discontinuing continuous therapies as soon as possible and closely coordinating intermittent hemodialysis or peritoneal dialysis schedules with the relevant therapists in the stroke unit to avoid impeding essential rehabilitation. Ultimately, these are consensus-based suggestions, and high-quality observational and randomized evidence is required.

PREVENTATIVE THERAPIES

We have outlined the consensus recommendations of the KDIGO group for the primary and secondary prevention of stroke in CKD in Table 3.

Lifestyle Modifications

Although specific data on stroke risk reduction in this group is lacking, lifestyle modifications such as salt restriction,[90] weight management,[94] regular exercise,[95] and smoking cessation[96] have been shown to improve intermediate outcomes associated with vascular risk such as blood pressure, lipid profiles, insulin resistance, and proteinuria, and are therefore, strongly encouraged in CKD.

Antiplatelet Therapies

Unfortunately, patients with moderate-to-severe CKD were excluded from most clinical trials evaluating efficacy and safety of antiplatelet agents so there is little evidence to inform guidelines in this area, particularly for primary prevention.[87] In a meta-analysis of 3 trials that studied the effect of antiplatelet therapy for primary prevention in CKD, there was no statistically significant reduction in major cardiovascular events including stroke (RR, 0.92 [0.49–1.73], *P*=0.79) or in mortality (RR, 0.74 [95% CI, 0.55–1.00], *P*=0.05).[97] However, there was an increase in major bleeding events (RR, 1.98 [95% CI, 1.11–3.52], *P*=0.02). The ATTACK (Aspirin to Target Arterial Events in Chronic Kidney Disease) trial (URL: https://www.clinicaltrials.gov; Unique identifier: NCT03796156) is an open label, multi-center primary prevention trial of aspirin in CKD currently underway that may help clarify the role (or lack thereof) of aspirin in this setting. There is somewhat better evidence to support the use of antiplatelet therapy in secondary vascular prevention in CKD. In a large Cochrane review of 50 RCTs (27 139 participants), 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 specifically stroke (RR, 1.00 [0.58–1.72]).[98] However, it is unlikely that the large benefits of aspirin as demonstrated in the general population[99] would be completely nullified in patients with CKD and the guidelines consistently recommend its use for secondary prevention in this setting.[87,88,100]

Anticoagulation

Similar to antiplatelet therapy, anticoagulation tends to be underused in the renal population owing to bleeding or vascular calcification concerns, and uncertain benefit in the dialysis population.[101] However, there is clear, consistent evidence of the efficacy of well-managed warfarin for the prevention of stroke in patients with AF and CKD albeit with a more variable effect on bleeding events.[102,103] Nonvitamin K antagonist oral anticoagulants appear to be superior to warfarin in CKD, as highlighted by a recent meta-analysis of 11 trials where nonvitamin K antagonist oral anticoagulants conferred lower risk of stroke or systemic embolism (RR, 0.79 [0.66–0.93]), hemorrhagic stroke (RR, 0.48 [0.30–0.76]), and all-cause death (RR, 0.88 [0.78–0.99]) compared with warfarin.[104] However, there was no difference in risk of extracranial bleeding and the meta-analysis was limited only to patients with a creatinine clearance >25 mL/min. Reassuringly, reversal agents such as idarucizumab appear to be safe and effective in CKD.[67]

Anticoagulation use in dialysis patients is more problematic. Multiple meta-analyses do not support a protective effect for warfarin in the prevention of ischemic stroke and suggest that it is associated with increased risk of major bleeding.[103,105] However, these have been based solely on observational cohort studies as there are no trials that have addressed this question. Furthermore,

Table 3. Recommendations for the Primary and Secondary Prevention of Stroke in CKD

	Primary Prevention	Secondary Prevention	Source (and strength) of recommendation
Intervention:			
Lifestyle modifications	Smoking cessation, healthy diet, weight restriction, and regular exercise should all actively encouraged.	As per primary prevention.	Expert consensus
Antiplatelet therapy	There is currently insufficient evidence to support the use of antiplatelet therapy for primary prevention.	Antiplatelet therapy for secondary prevention is uniformly recommended	NICE[87] and KDIGO[88] guidelines
Anticoagulation	In general, anticoagulation is recommended for the primary prevention of stroke with AF in this group. This is a high-risk group in which risk prediction tools such as CHA_2DS_2-VASc may have limited utility. For those with eGFR >30 mL/min per 1.73 m^2, first-line treatment should be with a NOAC. For those with eGFR 15–29 mL/min per 1.73 m^2, the choice of agent should depend on the trajectory of their renal function and should, therefore, be discussed with their nephrologist. For those with an eGFR <15 mL/min per 1.73 m^2, the decision to anticoagulate and the choice of agent should be discussed with their nephrologist.	As per primary prevention but we would advise having an even lower threshold to anticoagulate. The AHA/ACC[89] recommend using either a apixaban or warfarin in dialysis-dependent patients though long-term safety data on the former is lacking, and there is a risk of vascular calcification with the latter. Consider left atrial appendage occlusion devices in those with additional bleeding concerns as they have been shown to be safe and effective in advanced CKD after the initial periprocedural period.	AHA/ACC[89] guidelines (LOE IIb)
Dual blockade (antiplatelet+low-dose DOAC)	There may be a role for dual pathway blockade in patients with CKD (eGFR 30-59 mL/min per 1.73 m^2) who have chronic coronary artery or peripheral artery disease and who are thought to be at low risk of bleeding.	There is no evidence to support the use of dual pathway blockade for secondary prevention at this time.	Expert consensus
Blood pressure control	Tight blood pressure control to <120/80 mm Hg is essential. RAS blockers are the antihypertensive agents of choice.	As per primary prevention.	KDIGO updated 2021 blood pressure guidelines (LOE IIb)[89a]
Lipid-lowering therapy	As per KDIGO,[90] if >50 y and CKD present, treat with statin or statin/ezetimibe. In dialysis-dependent CKD, do not start statins de novo but continue if already taking.	We would recommend statin therapy for all patients with CKD who have had a stroke event. As per KDIGO guidelines,[90] statins may be continued in dialysis patients who are already taking them but should not be started unless very high LDL-C levels (3.8 mmol/L).	KDIGO[90] guidelines (LOE Ia for those >50 y and IIa-c for dialysis recommendations)
SGLT-2 inhibitors	We recommend treating all diabetic CKD patients with an eGFR > 30 mL/min per 1.73 m^2 with an SGLT-2 inhibitor.	We recommend treating all diabetic CKD patients with an eGFR >30 mL/min per 1.73 m^2 with an SGLT-2 inhibitor.	KDIGO[91] guidelines (LOE Ia)
Carotid interventions	We would not recommend carotid revascularization for patients with CKD with asymptomatic disease.	Consider carotid revascularization in nondialysis patients with CKD with symptomatic moderate-severe stenosis, and in very high-risk dialysis patients with symptomatic disease.	Society for Vascular Surgery guidelines[92]
Dialysis-related interventions	Careful attention to blood pressure and volume control when a patient is first about to start dialysis. Maintain hemoglobin values between 100 and 120 g/L.	As per primary prevention.	KDIGO[93] guidelines (LOE IIc)

AF indicates atrial fibrillation; ACC, American College of Cardiology; AHA, American Heart Association; ASA, American Stroke Association; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol; LOE, level of evidence; NICE, National Institute for Health and Clinical Excellence; NOAC, nonvitamin K oral anticoagulant; RAS, renin angiotensin; and SGLT-2, sodium-glucose cotransporter 2.

many of the included studies do not report time in the time-in-therapeutic range which may confound some of the risk estimates. In a Danish registry study of 10 423 warfarin-treated patients with AF, a time-in-therapeutic range <70% was associated with a higher risk of stroke/thromboembolism (HR, 1.39 [1.20–1.60]) and bleeding (HR, 1.22 [1.05–1.42]) among patients with eGFR of 30 to 59 mL/min per 1.73 m^2, suggesting that the quality of warfarin monitoring and management may similarly influence the efficacy and safety of warfarin in dialysis patients.[106]

Vitamin K antagonists such as warfarin have also implicated in the progression of vascular calcification in these patients due to inhibition of the enzyme matrix gamma-carboxyglutamate Gla protein that scavenges calcium phosphate in tissues.[107] A recent multi-center trial investigated the impact of vitamin K status on vascular calcification in 132 patients on hemodialysis with AF.[108] Patients were randomized to vitamin K antagonists, rivaroxaban, or rivaroxaban plus vitamin K2 supplementation. Changes in coronary artery, thoracic aorta, and cardiac valve calcium scores and pulse wave velocity, as used to measure vascular calcification progression, were not significantly different among the treatment arms. There was also no difference in all-cause death, stroke, and cardiovascular event rates between the groups. The ongoing trial AVKDIAL (Oral Anticoagulation in Haemodialysis Patients; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02886962) which will compare vitamin K antagonists with no anticoagulation in

dialysis-dependent patients with AF may help definitively answer the question of risk:benefit ratio of warfarin in ESKD.

There are some promising observational data on nonvitamin K antagonist oral anticoagulant use in advanced CKD and dialysis patients. A retrospective cohort study based on United States Renal Data System data compared warfarin versus apixaban in 25 523 dialysis patients with AF.[109] Although there was no overall difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR, 0.88 [0.69–1.12]; *P*=0.29), apixaban was associated with a lower risk of major bleeding (HR, 0.72 [0.59–0.87]; *P*<0.001). However, standard-dose apixaban was associated with lower risks of stroke/systemic embolism and death when compared with lower-dose apixaban and warfarin. The recently reported ELDERCARE-AF study (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) randomized 984 older (mean age 86) patients to low-dose edoxaban (15 mg daily) or placebo finding a significant reduction in stroke with edoxaban (2.3% versus 6.7%; HR, 0.35 [95% CI, 0.19–0.61]) and nonsignificant elevation in hemorrhage (3.3% versus 1.8%; HR, 1.87 [95% CI, 0.90–3.89]).[110] A number of individuals in the trial had advanced CKD as the mean creatinine clearance was 36.3 and 84% had an CrCl <50 mL/min. Unfortunately, data on CKD-specific subgroups was not provided in the main study results. The RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban Versus Warfarin in Atrial Fibrillation) was unfortunately terminated early due to loss of funding and therefore, only recruited 154 patients with 1-year follow-up.[111] Apixaban resulted in similar rates of bleeding and strokes as warfarin among patients with ESKD on hemodialysis. Time-in-therapeutic range with warfarin was only ≈44%. There is clearly a need for further dedicated trials of nonvitamin K antagonist oral anticoagulant versus placebo in dialysis populations.

Left atrial appendage occlusion devices, used to lower the thromboembolic risk in those with absolute or relative contraindications to long-term oral anticoagulation, appeared in one small study be equally effective and with similar procedural safety in CKD.[112] Those with an eGFR <30 mL/min per 1.73 m^2 had a lower overall survival rate but the rate of nonfatal major adverse events during follow-up (stroke, transient ischemic attack, and major bleeding) was not higher among patients with ESKD. However, an important limitation of this analysis was that it was a comparison based on expected event rates. Furthermore, no data is available on postimplantation or long-term antithrombotic regimes, which is relevant given bleeding and thrombosis risks in ESKD.

Dual Blockade of Hemostasis

A secondary analysis of the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) revealed promising results for patients with CKD.[113] The COMPASS trial was a double-blind, multicenter trial of 27 395 participants randomized to rivaroxaban (2.5 mg twice daily) plus ASA (100 mg daily), rivaroxaban alone (5 mg twice daily), or ASA alone(100 mg daily). The study, unlike many cardiovascular trials, was deliberately enriched with patients with CKD, who accounted for 6276 patients out of 27 387 in total. The primary composite outcome of cardiovascular death, myocardial infarction, or stroke was reduced with rivaroxaban plus aspirin in those with CKD (HR, 0.75 [95% CI, 0.60–0.94]). Stroke as an individual end point was particularly reduced with dual blockade therapy (HR, 0.42 [0.25–0.70]; *P*=0.0007), and there was no excess bleeding reported in those with CKD as compared with those without. However, although the RR of bleeding was similar between groups, the absolute risk for those with CKD would still be higher given their higher bleeding risk at baseline. In addition, those with an eGFR <15 mL/min per 1.73 m^2 were excluded from the trial, and there was only ≈150 people with an eGFR 15 to 29 mL/min per 1.73 m^2 which may limit some of the generalizability of these results to those with advanced CKD. Patients with a history of stroke in the preceding year were also excluded, and only 5.2% of the included patients with CKD had any prior history of cerebrovascular disease which may also limit our ability to extrapolate these results to secondary stroke prevention settings. Nonetheless, based on this trial, it may be reasonable to consider low-dose rivaroxaban and aspirin for the prevention of stroke in those with an eGFR 30 to 59 mL/min per 1.73 m^2 and a prior history of coronary artery or peripheral artery disease. The TRACK trial (Treatment of Cardiovascular Disease With Low Dose Rivaroxaban in Advanced Chronic Kidney Disease; URL: https://www.clinicaltrials.gov; Unique identifier: NCT03969953) will further examine the potential role of dual blockade as it will randomize high-risk advanced patients with CKD including those with a history of coronary artery disease, peripheral artery disease, nonhemorrhagic nonlacunar stroke, diabetes, or those ≥65 years, to low-dose rivaroxaban or placebo.

Lipid-Lowering Therapy

The efficacy of statin therapy for the primary prevention of stroke in patients with CKD was clearly demonstrated in the landmark SHARP trial (Study of Heart and Renal Protection), in which 9270 patients with CKD without preexisting vascular disease were randomly assigned to placebo or to the combination of simvastatin 20 mg daily plus ezetimibe 10 mg daily.[114] There was a 25% reduction in ischemic stroke in the treatment arm. In meta-analyses of trials of statins in patients with established cardiovascular disease, there was a ≈40% reduction in the risk of stroke in patients with CKD as per the general

population.[115,116] High-intensity therapy (eg, atorvastatin 80 mg or rosuvastatin 20 mg once daily) has also been shown to be safe and effective in this group.[117] According to KDIGO guidelines,[88] all patients with CKD over 50 years of age should therefore be started on statin plus/minus ezetimibe therapy. The American College of Cardiology has additionally recommended the addition of PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors (or ezetimibe) to maximally tolerated statin therapy in high-risk patients with atherosclerotic cardiovascular disease and CKD where <50% LDL-C (low-density lipoprotein cholesterol) reduction has been achieved with statins, including high-intensity statins.[118]

However, in a meta-analysis of individual-participant data from 28 trials, the efficacy of statins was shown to progressively deteriorate with declining renal function, with little evidence of benefit for dialysis patients in particular.[119] There are multiple proposed reasons for this statin resistance including the heightened role of nontraditional risk factors (eg, mineral and bone abnormalities, uremia), additional lipid abnormalities (eg, lipoproteins rendered highly atherogenic by oxidation or carbamylation), or intracellular cholesterol synthesis activated by inflammatory stress.[120] For this reason, KDIGO guidelines, do not recommend starting statins de novo in dialysis patients.[88]

Antihypertensive Therapy

There has not been a dedicated blood pressure trial in the CKD population for the prevention of stroke and most of the existing evidence has been derived from post hoc or subgroup analysis. The KDIGO 2021 Clinical Practice Guideline on the Management of Blood Pressure in CKD have recently been published and recommend a blood pressure of <120/80 mm Hg in CKD for both primary and secondary prevention in patients where this level can be feasibly tolerated.[89a] This recommendation has been heavily influenced by subgroup analysis of the SPRINT (Systolic Blood Pressure Intervention Trial) in which targeting a systolic blood pressure (SBP) <120 mm Hg compared with <140 mm Hg reduced rates of major cardiovascular events and all-cause death in patients with CKD.[121] The risk of stroke was similar in both treatment groups (HR, 0.99 [0.57–1.70]; *P*=0.96), but the trial was stopped early (median follow-up 3.3 years) so follow-up may have been too short to see a cerebrovascular protective effect. The generalizability of the results may also be limited as people with diabetes, proteinuria >1000 mg/g or prior stroke were excluded. However, specific stroke benefits associated with more intensive BP control have been seen in other trials such as the CSPPT (China Stroke Primary Prevention Trial).[122] In this post hoc analysis of 3230 patients with hypertension with eGFR 30 to 60 mL/min per 1.73 m^2 and proteinuria, a time-averaged SBP of ≤135 mm Hg was associated with lower risk of total first stroke compared with a time-averaged on-treatment SBP of 135 to ≤140 mm Hg, (1.7% versus 3.3%; HR, 0.51 [0.26–0.99]).

As acknowledged by another recent KDIGO controversies conference,[123] there is little evidence to guide BP target thresholds in a secondary prevention setting, and the previous 2012 BP guidelines did not specifically address this group. A posthoc analysis of the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) showed that perindopril was associated with a 35% reduction in the risk of stroke in patients with CKD with a history of recently symptomatic cerebrovascular disease.[124] Perindopril prevented one stroke or other cardiovascular event among every 11 patients with CKD treated over 5 years, although it was unclear what the achieved blood pressure or level of urine albumin were in either arm of the trial. The SPS3 study (Secondary Prevention of Small Subcortical Strokes) study, in which patients with a history of lacunar stroke were randomized to a lower (<130 mm Hg) versus higher (130–149 mm Hg) target SBP included 474 patients with CKD.[125] Intensive BP control resulted in a statistically nonsignificant reduction in the cardiovascular composite outcome in CKD but with greater risk of kidney function decline.

The ideal BP target in dialysis patients for stroke prevention is even less clear with evidence of a U-shaped associations between change in SBP, all-cause mortality and cardiovascular mortality, whereby postdialytic drops in SBP of up to 30 mm Hg are associated with greater survival, but larger decreases of SBP are associated with greater mortality.[126]

While there is clearly a need for dedicated RCTs in CKD and dialysis patients to better establish BP targets for people with and without prior stroke, the best available evidence at present supports the use of RAS inhibitors for recurrent stroke prevention.

Carotid Interventions

The NASCET (North American Symptomatic Carotid Endarterectomy Trial) was the only large randomized trial of carotid interventions that reported results according to renal function.[127] Surgery was highly effective for patients with CKD with symptomatic high-grade stenosis resulting in a RR reduction of 82.3% (95% CI, 54.5%–93.1%) compared with 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 only 4 for patients with CKD. Rates of perioperative cardiac complications (myocardial infarction, congestive heart failure, and arrhythmias) were higher in the CKD group though perioperative death rates were similar between groups.

However, the majority of patients with CKD included in the NASCET analysis had CKD stage 3a with a mean eGFR of 49 mL/min per 1.73 m^2. In an analysis of the Vascular Study Group of New England database, 30-day mortality appears to increase with worsening

 Stroke. 2021;52:e328–e346. DOI: 10.1161/STROKEAHA.120.029680

renal function, from 0.4% in mild CKD to 0.9% in severe CKD (defined as an eGFR <30 mL/min per 1.73 m^2; P=0.01).[128] However, in a multi-variate regression model, CKD status did not predict 30-day stroke or death, and even in patients with severe CKD, there was an overall 5-year survival rate of 71%, contrasting with the worse outcomes for severe CKD with PVD whose 5-year survival rate was only 21% irrespective of intervention.[129] We would, therefore, agree with guidance from the Society for Vascular Surgery who recommend carotid endarterectomy for symptomatic patients with CKD with moderate-severe stenosis.[92] However, careful perioperative assessment and management is essential given their higher rate of periprocedural complications.

Unfortunately, the perioperative and long-term outcomes after carotid endarterectomy in dialysis patients appear to be quite poor. In a retrospective analysis of 5142 dialysis patients in the US Renal Disease System-Medicare-matched database, there was a high rate of 30-day complications including stroke, MI, and mortality for both asymptomatic and symptomatic patients (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).[130] The overall 3-year survival was also only 46% and 42% in the asymptomatic and symptomatic cohorts, respectively. We would, therefore, recommend carotid intervention in only a select group of high-risk, symptomatic dialysis patients. There is currently insufficient evidence to recommend stenting over carotid endarterectomy in either CKD or dialysis patients. The CREST-2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial; URL: https://www.clinicaltrials.gov; Unique identifier: NCT02089217) is an ongoing set of trials, one of which will randomize patients in a 1:1 ratio to endarterectomy versus no endarterectomy and another will randomize patients in a 1:1 ratio to carotid stenting with embolic protection versus no stenting. This will include patients with an eGFR >30 mL/min per 1.73 m^2 and may, therefore, provide further information to inform best clinical practice in this area. However, a dedicated trial of carotid interventions in symptomatic patients with high-grade stenosis who have advanced CKD or who are dialysis-dependent is clearly required.

SGLT-2 Inhibitors

SGLT-2 (sodium-glucose cotransporter 2) inhibitors appear to have promising vascular benefits in patients with CKD with type 2 diabetes as demonstrated by recent large placebo-controlled outcome trials.[131–133] However, their potential benefit for stroke prevention in the general population or this specific group is less clear. In an analysis of the CANVAS trial (Canagliflozin Cardiovascular Assessment Study) which randomly assigned 10 142 participants with type 2 diabetes and high cardiovascular risk to canagliflozin or placebo, there was no significant difference in event rates between groups (HR, 0.87 [95% CI, 0.69–1.09]), though there may have been too few events overall to detect a significant benefit.[134] However, a meta-analysis of 32 trials with 75 540 participants also did not find a class or individual effect for any of the 3 SGLT-2 inhibitors therapy for stroke prevention.[135]

Dialysis-Related Interventions

It is important for nephrologists to be aware that the period of dialysis initiation is a high-risk time for patients with a particularly high incidence of stroke.[11] The reasons for this excess risk are not entirely clear. It may relate to poor or variable BP and volume control as a similar surge of other BP-related brain pathologies have been observed during this period including posterior reversible encephalopathy syndrome.[136]

There is some evidence that dialysate cooling may be protective against chronic hemodialysis-induced brain injury by achieving better hemodynamic stability and reducing circulatory stress. In a group of 73 hemodialysis patients randomized to 0.5 °C below their core body temperature and followed-up for 1 year, they had better preservation of brain white matter microstructure parameters including fractional anisotropy, axial diffusivity, and radial diffusivity when compared with those who dialyzed 37 °C.[85] However, it is not known if regular use of cooled dialysate would impact incident stroke risk.

Finally, higher hemoglobin targets achieved with erythropoietin-stimulating agents have been associated with increased stroke risk in advanced CKD. The TREAT study (Trial to Reduce Cardiovascular Events With Aranesp Therapy) in anemic nondialysis diabetic CKD patients reported a doubling of stroke risk with erythropoietin-stimulating agent use dosed for a target hemoglobin of 130 g/L, compared with limited erythropoietin-stimulating agent use to maintain Hb ≥90 g/L.[137] Guidelines generally recommend targeting 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 the patients.[93]

MEDICAL COMPLICATIONS AFTER STROKE

There are high rates of medical complications poststroke reported in the general population including urinary tract infections, respiratory infections, pressure sores, and venous thromboembolic events.[138] Such complications appear to be accentuated in patients with kidney disease and significantly contribute to poststroke mortality.[64,139] A particular concern in this group is the development of sarcopenia poststroke which has been associated with reduced mobility, falls, and increasing mortality.[140] It seems likely that the solution to mitigate these complications

in patients with CKD, like the general population, is to encourage more widespread admission to acute stroke units. Organized stroke units specialize in managing poststroke complications and optimize patient outcomes by providing dedicated, multi-disciplinary care.[141]

FUNCTIONAL AND NEUROPSYCHIATRIC OUTCOMES AFTER STROKE

CKD is associated with a higher initial stroke severity, risk of neurological deterioration, and greater disability and likelihood of institutionalization at the time of hospital discharge (as defined by a modified Rankin Scale score ≥2).[142,143] It is also associated with both considerable short-term and long-term mortality.[68,144] These associations are consistent across different stroke subtypes,[145,146] race,[147] in populations of varying prevalence of vascular risk factors,[148,149] and even in renal transplant recipients.[14]

CKD is also associated with a significant burden of cognitive impairment and dementia that worsens with declining renal function.[150] In the REGARDS study (Reasons for Geographic and Racial Differences in Stroke), each 10 mL/min per 1.73 m^2 decrease in eGFR <60 mL/min per 1.73 m^2 was associated with an 11% increase in prevalence of cognitive dysfunction.[151] In the hemodialysis population, the prevalence of cognitive impairment may be as high as 70%.[152] Subclinical or symptomatic cerebrovascular disease is thought to play a key role in the cause of cognitive impairment in CKD as it is typically consistent with vascular cognitive impairment[153] and imaging studies in cognitively impaired patients tend to have a greater burden of white matter lesions and lacunar infarcts.[154]

SUBCLINICAL CEREBROVASCULAR DISEASE

There is a strong association between cerebral small vessel disease and CKD,[155] and this is consistent for each small vessel disease subtype including white matter lesions,[156] silent cerebral infarctions (SCI),[157] perivascular spaces,[158] and cerebral microbleeds.[159] SCI, in particular, appears to be prevalent in as many as 56.5% of clinically, asymptomatic patients with CKD or ESKD from cross-sectional analyses.[160,161] Several mechanisms for the association of small vessel disease and CKD have been proposed including their shared anatomic and physiological susceptibility to hypertensive vascular injury,[162] their shared vascular risk factors such as hypertension and diabetes,[157] or shared genetic susceptibility[163] which may explain the stronger, more independent associations observed at younger ages.[164] Regardless of their cause, as per the general population, their presence in CKD appears have implications for future stroke risk, cognition, gait, and stability. In a small study of 199 hemodialysis patients, SCI was a powerful independent predictor of cerebrovascular and all-type vascular events (HR for cerebral events, 7.33 [95% CI, 1.27–42.25]; for vascular events, 4.48 [95% CI, 1.09–18.41]).[160] From the Sefuri study, CKD with SCI was associated with vascular cognitive impairment or executive dysfunction.[165] In addition, SCI has been shown to be an independently predict kidney disease progression.[166]

How best to manage SCI in patients with CKD is, therefore, a common and important dilemma for nephrologists and stroke physicians alike. There is no official guidance that pertains specifically to patients with kidney disease, and this is essentially an evidence-free zone. However, the American Heart Association/American Stroke Association have issued a scientific statement with suggestions for the clinical care of patients with silent cerebrovascular disease in the general population.[167] Based on this, we present some modified consensus recommendations from the KDIGO group on its management in CKD in Table 4, taking into account the high prevalence of AF and the preexisting risk factor burden in this patient population. Although there have been no randomized trials of treatment for SCI, we would suggest having a low threshold for treating with antiplatelet

Table 4. Recommendations for the Management of Subclinical Cerebrovascular Disease in CKD Based on Expert Consensus

Investigations
Assess common vascular risk factors–BP, diabetes, cholesterol, smoking, obesity.
Check pulse for AF, do 12-lead ECG, and consider prolonged Holter monitoring or other extended duration devices.
Consider carotid imaging such as a carotid duplex ultrasound when there is SCI in the carotid territory.
Consider echocardiography to identify potential cardiac sources when there is an embolic-appearing pattern of silent infarction.
Consider CTA when there are large (>1.0 cm) silent hemorrhages to rule out underlying structural lesions, including arteriovenous malformations and tumors.
Management
Consider treating with aspirin and statin therapy in those with SCI if no contraindication.
Target BP control <120/80 mm Hg as per KDIGO guidelines.
It may be reasonable to factor the presence of an embolic pattern of SCI in carotid territory into clinical decision-making around carotid revascularization.
The presence of cerebral microbleeds should not necessitate de-prescribing or avoidance of prescribing antiplatelet or anticoagulant therapy, but caution should be exercised as these patients at increased future risk of both ischemic stroke and ICH. Shared decision-making with a stroke physician may be helpful.
It is reasonable to administer thrombolysis to patients with CKD with acute ischemic stroke and evidence of microbleeds if it is otherwise indicated.

AF indicates atrial fibrillation; BP, blood pressure; CKD, chronic kidney disease; CTA, computed tomography angiography; ICH, intracerebral hemorrhage; KDIGO, Kidney Disease Improving Global Outcomes; and SCI, silent cerebral infarction.

Stroke. 2021;52:e328–e346. DOI: 10.1161/STROKEAHA.120.029680

or statin therapy since their use in a secondary prevention setting in CKD is consistently recommended in guidelines.[87,88,100,168] Regarding the presence of cerebral microbleed, a recent pooled analysis of individual patient-level data has shown that in those with recent transient ischemic attack or ischemic stroke, the absolute risk of recurrent ischemic event was consistently substantially higher than that of ICH, regardless of cerebral microbleed number, distribution, and presence of anticoagulant/antiplatelet therapy.[169] However, it is not known how many, if any, patients had CKD within this meta-analysis, making it difficult to uniformly extrapolate these findings to the renal population.

CONCLUSIONS

Patients with CKD are clearly a high-risk group with a high burden of both symptomatic and asymptomatic cerebrovascular disease. Further research is needed to better understand the relative contribution of proposed pathophysiological mechanisms which may be aided by more consistent reporting of etiological stroke subtypes in CKD. The safety and efficacy of many acute treatments have not been demonstrated in the CKD population and similarly, much of the evidence that supports current preventative therapies in this group is observational or based on post hoc analyses. This evidence gap is most apparent for those with advanced CKD or dialysis dependency, who are also the group with the greatest risk. Dedicated or enriched trials are required to resolve the inequities in stroke care that are consistently observed in this population.

ARTICLE INFORMATION

Affiliations

Wolfson Center for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, United Kingdom (D.M.K.). School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia (Z.A.). Berlin Institute of Health Center for Regenerative Therapies (BCRT), and Department of Cardiology (Virchow Klinikum), German Centre for Cardiovascular Research (DZHK), Partner Site Berlin and Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin, Germany (W.D.). Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, United Kingdom (G.Y.H.L.). Institute of Cardiovascular & Medical Sciences, University of Glasgow, United Kingdom (P.M.). Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan (K.T.). Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, South Australia (C.X.W.). Division of Nephrology, Tufts Medical Center, Boston, MA (M.S.). Kidney Disease: Improving Global Outcomes, Brussels, Belgium (M.C.). Hennepin County Medical Center, Minneapolis, MN (C.A.H.). Division of Nephrology, Hennepin County Medical Center, Minneapolis, MN (K.L.J.). Department of Cardiology I, University Hospital Münster, Germany (H.R.). Ottawa Hospital Research Institute, Department of Medicine, The Ottawa Hospital, Civic Campus, ON, Canada (M.M.S.).

Sources of Funding

D.M. Kelly has received a scholarship from the Irish Nephrology Society and a Clarendon scholarship from the University of Oxford. Dr Sood is supported by the Jindal Research Chair for the Prevention of Kidney Disease. Dr Wong is supported by a Postdoctoral Fellowship from the Heart Foundation of Australia and a Mid-Career Fellowship from the Hospital Research Foundation.

Disclosures

Dr Herzog reports reports grants and personal fees from Amgen, grants and personal fees from AstraZeneca, personal fees from Diamedica, personal fees from Pfizer, grants and other from Bristol Myers Squibb, other from Johnson & Johnson, other from Boston Scientific, and other from Merck during the conduct of the study; grants and personal fees from National Heart Lung and Blood Institute/National Institutes of Health (NHLBI/NIH), personal fees from Abbvie, personal fees from Corvidia, personal fees from Fibrogen, personal fees from Janssen, personal fees from NxStage, grants and personal fees from Relypsa, personal fees from Sanifit, personal fees from University of Oxford, grants from National Institute of Diabetes and Digestive and Kidney Diseases/NIH, grants from University of British Columbia, personal fees from UpToDate, other from General Electric, other from Hennepin Healthcare, and personal fees from Bayer outside the submitted work. Dr Wong reports that the University of Adelaide has received on his behalf lecture, travel and research funding from Abbott Medical, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Servier, St Jude Medical, and Vifor Pharma. Dr Lip is a consultant for Bayer/Janssen, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, Bristol Myers Squibb/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Dr Reinecke reports personal fees from Daiichi, grants and personal fees from Bristol Myers Squibb/Pfizer, personal fees from MedUpdate, personal fees from DiaPlan, personal fees from NeoVasc, grants and personal fees from Pluristem, grants from Bard, grants from Biotronik, and personal fees from Novonordisk outside the submitted work. Dr Johansen reports nonfinancial support and other from Kidney Disease: Improving Global Outcomes during the conduct of the study. Dr Toyoda reports personal fees from Daiichi-Sankyo, personal fees from Bayer Yakuhin, personal fees from Bristol Myers Squibb, personal fees from Takeda, and personal fees from Nippon Boehringer Ingelheim outside the submitted work. Dr Cheung reports personal fees from, AstraZeneca, Boehringer Ingelheim, Daiichi Sanyko, Janssen, Lilly, and Vifor Fresenium Medical Renal Pharma. Dr Sood has received speaker fees from Astrazeneca. Dr Sarnak reports personal fees from Bayer and personal fees from Cardurian outside the submitted work. Dr Mark reports personal fees and nonfinancial support from Vifor, personal fees from Astrazeneca, grants from Boehringer Ingelheim, personal fees and nonfinancial support from Pharmacosmos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from Bristol Myers Squibb, personal fees and nonfinancial support from Napp outside the submitted work. Dr Doehner reports grant support and personal fees from Aimediq, Bayer, Boehringer Ingelheim, Medtronic, Pfizer, Sanofi-Aventis, Sphingotec, Vifor Pharma. ZS Pharma, outside the submitted work. The other authors report no conflicts.

Supplemental Materials

References 101–169

REFERENCES

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the global burden of disease study 2017. *Lancet.* 2020;395:709–733. doi: 10.1016/S0140-6736(20)30045-3
2. *US Renal Data System, USRDS 2009 Annual Data Report, Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases*, Bethesda, MD, 2009.
3. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. *Nephrol Dial Transplant.* 2015;30:1162–1169. doi: 10.1093/ndt/gfv009
4. Lee M, Saver JL, Chang KH, Ovbiagele B. Level of albuminuria and risk of stroke: systematic review and meta-analysis. *Cerebrovasc Dis.* 2010;30:464–469. doi: 10.1159/000317069
5. Mace-Brickman T, Eddeen AB, Carrero JJ, Mark PB, Molnar AO, Lam NN, Zimmerman D, Harel Z, Sood MM. The risk of stroke and stroke type in patients with atrial fibrillation and chronic kidney disease. *Can J Kidney Health Dis.* 2019;6:2054358119892372. doi: 10.1177/2054358119892372
6. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, et al. Incidence and risk factors for new-onset atrial fibrillation among patients with end-stage renal disease undergoing renal replacement therapy. *Kidney Int.* 2015;87:1209–1215. doi: 10.1038/ki.2014.393
7. Shen CH, Zheng CM, Kiu KT, Chen HA, Wu CC, Lu KC, Hsu YH, Lin YF, Wang YH. Increased risk of atrial fibrillation in end-stage renal disease patients on dialysis: a nationwide, population-based study in Taiwan. *Medicine (Baltimore).* 2016;95:e3933. doi: 10.1097/MD.0000000000003933

8. van Walraven C, Manuel DG, Knoll G. Survival trends in ESRD patients compared with the general population in the United States. *Am J Kidney Dis*. 2014;63:491–499. doi: 10.1053/j.ajkd.2013.09.011
9. Winkelmayer WC, Patrick AR, Liu J, Brookhart MA, Setoguchi S. The increasing prevalence of atrial fibrillation among hemodialysis patients. *J Am Soc Nephrol*. 2011;22:349–357. doi: 10.1681/ASN.2010050459
10. Wetmore JB, Herzog CA, Sexter A, Gilbertson DT, Liu J, Kasner SE. Outcomes following ischemic stroke in older patients with CKD stages 4 and 5: a retrospective cohort study. *Am J Kidney Dis*. 2020;76:784–793.
11. Murray AM, Seliger S, Lakshminarayan K, Herzog CA, Solid CA. Incidence of stroke before and after dialysis initiation in older patients. *J Am Soc Nephrol*. 2013;24:1166–1173. doi: 10.1681/ASN.2012080841
12. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med*. 2011;365:1099–1107. doi: 10.1056/NEJMoa1103313
13. Findlay M, MacIsaac R, MacLeod MJ, Metcalfe W, Traynor JP, Dawson J, Mark PB. Renal replacement modality and stroke risk in end-stage renal disease-a national registry study. *Nephrol Dial Transplant*. 2018;33:1564–1571. doi: 10.1093/ndt/gfx291
14. Findlay MD, Thomson PC, MacIsaac R, Jardine AG, Patel RK, Stevens KK, Rutherford E, Clancy M, Geddes CC, Dawson J, et al. Risk factors and outcome of stroke in renal transplant recipients. *Clin Transplant*. 2016;30:918–924. doi: 10.1111/ctr.12765
15. Ghoshal S, Freedman BI. Mechanisms of stroke in patients with chronic kidney disease. *Am J Nephrol*. 2019;50:229–239. doi: 10.1159/000502446
16. Kelly DM, Li L, Rothwell PM; Oxford Vascular Study. Etiological subtypes of transient ischemic attack and ischemic stroke in chronic kidney disease: population-based study. *Stroke*. 2020;51:2786–2794. doi: 10.1161/STROKEAHA.120.030045
17. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014;13:823–833. doi: 10.1016/S1474-4422(14)70026-2
18. Doehner W, Ural D, Haeusler KG, Čelutkienė J, Bestetti R, Cavusoglu Y, Peña-Duque MA, Glavas D, Iacoviello M, Laufs U, et al. Heart and brain interaction in patients with heart failure: overview and proposal for a taxonomy. A position paper from the Study Group on Heart and Brain Interaction of the Heart Failure Association. *Eur J Heart Fail*. 2018;20:199–215. doi: 10.1002/ejhf.1100
19. Muntner P, Anderson A, Charleston J, Chen Z, Ford V, Makos G, O'Connor A, Perumal K, Rahman M, Steigerwalt S, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Investigators. Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) Study. *Am J Kidney Dis*. 2010;55:441–451. doi: 10.1053/j.ajkd.2009.09.014
20. Kelly DM, Rothwell PM. Does chronic kidney disease predict stroke risk independent of blood pressure?: a systematic review and meta-regression. *Stroke*. 2019;50:3085–3092. doi: 10.1161/STROKEAHA.119.025442
21. Ding WY, Gupta D, Lip GYH. Atrial fibrillation and the prothrombotic state: revisiting Virchow's triad in 2020. *Heart*. 2020;106:1463–1468.
22. Apostolov EO, Ok E, Burns S, Nawaz S, Savenka A, Shah S, Basnakian AG. Carbamylated-oxidized LDL: proatherosclerotic effects on endothelial cells and macrophages. *J Atheroscler Thromb*. 2013;20:878–892. doi: 10.5551/jat.14035
23. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. *Semin Dial*. 2006;19:317–322. doi: 10.1111/j.1525-139X.2006.00179.x
24. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*. 2000;87:E10–E17. doi: 10.1161/01.res.87.7.e10
25. Findlay MD, Dawson J, Dickie DA, Forbes KP, McGlynn D, Quinn T, Mark PB. Investigating the relationship between cerebral blood flow and cognitive function in hemodialysis patients. *J Am Soc Nephrol*. 2019;30:147–158. doi: 10.1681/ASN.2018050462
26. MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between hypotension and cerebral ischemia during hemodialysis. *J Am Soc Nephrol*. 2017;28:2511–2520. doi: 10.1681/ASN.2016060704
27. Sarafidis PA, Loutradis C, Karpetas A, Tzanis G, Piperidou A, Koutroumpas G, Raptis V, Syrgkanis C, Liakopoulos V, Efstratiadis G, et al. Ambulatory pulse wave velocity is a stronger predictor of cardiovascular events and all-cause mortality than office and ambulatory blood pressure in hemodialysis patients. *Hypertension*. 2017;70:148–157. doi: 10.1161/HYPERTENSIONAHA.117.09023
28. Chang TI, Tabada GH, Yang J, Tan TC, Go AS. Visit-to-visit variability of blood pressure and death, end-stage renal disease, and cardiovascular events in patients with chronic kidney disease. *J Hypertens*. 2016;34:244–252. doi: 10.1097/HJH.0000000000000779
29. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870. doi: 10.1001/jama.285.22.2864
30. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272. doi: 10.1378/chest.09-1584
31. Friberg L, Benson L, Lip GY. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. *Eur Heart J*. 2015;36:297–306. doi: 10.1093/eurheartj/ehu139
32. Apostolakis S, Guo Y, Lane DA, Buller H, Lip GY. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. *Eur Heart J*. 2013;34:3572–3579. doi: 10.1093/eurheartj/eht328
33. Roldán V, Marín F, Fernández H, Manzano-Fernández S, Gallego P, Valdés M, Vicente V, Lip GY. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). *Am J Cardiol*. 2013;111:1159–1164. doi: 10.1016/j.amjcard.2012.12.045
34. Cha MJ, Cho Y, Oh IY, Choi EK, Oh S. Validation of conventional thromboembolic risk factors in a korean atrial fibrillation population- suggestion for a novel scoring system, CHA2DS2-VAK. *Circ J*. 2018;82:2970–2975. doi: 10.1253/circj.CJ-18-0218
35. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G, et al; ROCKET AF Steering Committee and Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127:224–232. doi: 10.1161/CIRCULATIONAHA.112.107128
36. Banerjee A, Fauchier L, Vourc'h P, Andres CR, Taillandier S, Halimi JM, Lip GY. Renal impairment and ischemic stroke risk assessment in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project. *J Am Coll Cardiol*. 2013;61:2079–2087. doi: 10.1016/j.jacc.2013.02.035
37. Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost*. 2018;118:2171–2187. doi: 10.1055/s-0038-1675400
38. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and Delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. *Thromb Haemost*. 2018;118:768–777. doi: 10.1055/s-0038-1636534
39. Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, Wen J, Xing Y, Wu F, Xia Y, et al; mAF-App II Trial Investigators. Mobile health technology to improve care for patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75:1523–1534. doi: 10.1016/j.jacc.2020.01.052
40. Guo Y, Lane DA, Chen Y, Lip GYH. Regular bleeding risk assessment associated with reduction in bleeding outcomes: the MAFA-II randomized trial. *Am J Med*. 2020;133:1195–1202.e2.
41. Kroneberger C, Enzweiler CN, Schmidt-Lucke A, Rückert RI, Teichgräber U, Franiel T. Contrast-induced nephropathy in patients with chronic kidney disease and peripheral arterial disease. *Acta Radiol Open*. 2015;4:2058460115583034. doi: 10.1177/2058460115583034
42. Newsome BB, Warnock DG, Kiefe CI, Weissman NW, Houston TK, Centor RM, Person SD, McClellan WM, Allison JJ. Delay in time to receipt of thrombolytic medication among Medicare patients with kidney disease. *Am J Kidney Dis*. 2005;46:595–602. doi: 10.1053/j.ajkd.2005.06.008
43. Brinjikji W, Demchuk AM, Murad MH, Rabinstein AA, McDonald RJ, McDonald JS, Kallmes DF. Neurons over nephrons: systematic review and meta-analysis of contrast-induced nephropathy in patients with acute stroke. *Stroke*. 2017;48:1862–1868. doi: 10.1161/STROKEAHA.117.016771
44. Collidge TA, Thomson PC, Mark PB, Traynor JP, Jardine AG, Morris ST, Simpson K, Roditi GH. Gadolinium-enhanced MR imaging and nephrogenic systemic fibrosis: retrospective study of a renal replacement therapy cohort. *Radiology*. 2007;245:168–175. doi: 10.1148/radiol.2451070353
45. Woolen SA, Shankar PR, Gagnier JJ, MacEachern MP, Singer L, Davenport MS. Risk of nephrogenic systemic fibrosis in patients with stage 4 or 5 chronic kidney disease receiving a Group II gadolinium-based contrast agent: a systematic review and meta-analysis. *JAMA Intern Med*. 2020;180:223–230. doi: 10.1001/jamainternmed.2019.5284

46. Schulz UG, Rothwell PM. Differences in vascular risk factors between etiological subtypes of ischemic stroke: importance of population-based studies. *Stroke*. 2003;34:2050–2059. doi: 10.1161/01.STR.0000079818.08343.8C
47. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology*. 2004;62:569–573. doi: 10.1212/01.wnl.0000110311.09970.83
48. De La Mata NL, Masson P, Al-Shahi Salman R, Kelly PJ, Webster AC. Death from stroke in end-stage kidney disease. *Stroke*. 2019;50:487–490.
49. Toyoda K, Fujii K, Fujimi S, Kumai Y, Tsuchimochi H, Ibayashi S, Iida M. Stroke in patients on maintenance hemodialysis: a 22-year single-center study. *Am J Kidney Dis*. 2005;45:1058–1066. doi: 10.1053/j.ajkd.2005.02.028
50. Sozio SM, Armstrong PA, Coresh J, Jaar BG, Fink NE, Plantinga LC, Powe NR, Parekh RS. Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. *Am J Kidney Dis*. 2009;54:468–477. doi: 10.1053/j.ajkd.2009.01.261
51. Kurella Tamura M, Meyer JB, Saxena AB, Huh JW, Wadley VG, Schiller B. Prevalence and significance of stroke symptoms among patients receiving maintenance dialysis. *Neurology*. 2012;79:981–987. doi: 10.1212/WNL.0b013e31826845e9
52. Ovbiagele B, Schwamm LH, Smith EE, Grau-Sepulveda MV, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Patterns of care quality and prognosis among hospitalized ischemic stroke patients with chronic kidney disease. *J Am Heart Assoc*. 2014;3:e000905. doi: 10.1161/JAHA.114.000905
53. Findlay MD, Dawson J, MacIsaac R, Jardine AG, MacLeod MJ, Metcalfe W, Traynor JP, Mark PB. Inequality in care and differences in outcome following stroke in people with ESRD. *Kidney Int Rep*. 2018;3:1064–1076. doi: 10.1016/j.ekir.2018.04.011
54. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. Stroke unit trialists' collaboration. *BMJ*. 1997;314:1151–1159.
55. Molnar AO, Bota SE, Garg AX, Harel Z, Lam N, McArthur E, Nesrallah G, Perl J, Sood MM. The risk of major hemorrhage with CKD. *J Am Soc Nephrol*. 2016;27:2825–2832. doi: 10.1681/ASN.2015050535
56. Kelly DM, Rothwell PM. Impact of multimorbidity on risk and outcome of stroke: lessons from chronic kidney disease [published online November 27, 2020]. *Int J Stroke*. doi: 10.1177/1747493020975250
57. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5
58. Ma H, Campbell BCV, Parsons MW, Churilov L, Levi CR, Hsu C, Kleinig TJ, Wijeratne T, Curtze S, Dewey HM, et al; EXTEND Investigators. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med*. 2019;380:1795–1803. doi: 10.1056/NEJMoa1813046
59. Carrero JJ, Trevisan M, Sood MM, Bárány P, Xu H, Evans M, Friberg L, Szummer K. Incident atrial fibrillation and the risk of stroke in adults with chronic kidney disease: the Stockholm CREAtinine Measurements (SCREAM) Project. *Clin J Am Soc Nephrol*. 2018;13:1314–1320. doi: 10.2215/CJN.04060318
60. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. *Semin Thromb Hemost*. 2010;36:34–40. doi: 10.1055/s-0030-1248722
61. Liu Y, Lv P, Jin H, Cui W, Niu C, Zhao M, Fan C, Teng Y, Pan B, Peng Q, et al. Association between low estimated glomerular filtration rate and risk of cerebral small-vessel diseases: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2016;25:710–716. doi: 10.1016/j.jstrokecerebrovasdis.2015.11.016
62. Jung JM, Kim HJ, Ahn H, Ahn IM, Do Y, Choi JY, Seo WK, Oh K, Cho KH, Yu S. Chronic kidney disease and intravenous thrombolysis in acute stroke: a systematic review and meta-analysis. *J Neurol Sci*. 2015;358:345–350. doi: 10.1016/j.jns.2015.09.353
63. Carr SJ, Wang X, Olavarria VV, Lavados PM, Rodriguez JA, Kim JS, Lee TH, Lindley RI, Pontes-Neto OM, Ricci S, et al; ENCHANTED Investigators. Influence of renal impairment on outcome for thrombolysis-treated acute ischemic stroke: ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) Post Hoc Analysis. *Stroke*. 2017;48:2605–2609. doi: 10.1161/STROKEAHA.117.017808
64. Tariq N, Adil MM, Saeed F, Chaudhry SA, Qureshi AI. Outcomes of thrombolytic treatment for acute ischemic stroke in dialysis-dependent patients in the United States. *J Stroke Cerebrovasc Dis*. 2013;22:e354–e359. doi: 10.1016/j.jstrokecerebrovasdis.2013.03.016
65. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, et al; American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46–e110. doi: 10.1161/STR.0000000000000158
66. Zheng D, Sato S, Arima H, Heeley E, Delcourt C, Cao Y, Chalmers J, Anderson CS; INTERACT2 Investigators. Estimated GFR and the effect of intensive blood pressure lowering after acute intracerebral hemorrhage. *Am J Kidney Dis*. 2016;68:94–102. doi: 10.1053/j.ajkd.2016.01.020
67. Glund S, Stangier J, van Ryn J, Schmohl M, Moschetti V, Haazen W, De Smet M, Gansser D, Norris S, Lang B, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover Phase Ib Study. *Clin Pharmacokinet*. 2017;56:41–54. doi: 10.1007/s40262-016-0417-0
68. El Husseini N, Fonarow GC, Smith EE, Ju C, Sheng S, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Association of kidney function with 30-day and 1-year poststroke mortality and hospital readmission. *Stroke*. 2018;49:2896–2903. doi: 10.1161/STROKEAHA.118.022011
69. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
70. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
71. Laible M, Möhlenbruch MA, Pfaff J, Jenetzky E, Ringleb PA, Bendszus M, Rizos T. Influence of renal function on treatment results after stroke thrombectomy. *Cerebrovasc Dis*. 2017;44:351–358. doi: 10.1159/000481147
72. Laible M, Jenetzky E, Möhlenbruch MA, Neuberger U, Bendszus M, Ringleb PA, Rizos T. Renal impairment is associated with intracerebral hemorrhage after mechanical thrombectomy in vertebrobasilar stroke. *Cerebrovasc Dis*. 2019;47:48–56. doi: 10.1159/000497070
73. Lindsberg PJ, Mattle HP. Therapy of basilar artery occlusion: a systematic analysis comparing intra-arterial and intravenous thrombolysis. *Stroke*. 2006;37:922–928. doi: 10.1161/01.STR.0000202582.29510.6b
74. Saeed F, Adil MM, Piracha BH, Qureshi AI. Outcomes of endovascular versus intravenous thrombolytic treatment for acute ischemic stroke in dialysis patients. *Int J Artif Organs*. 2014;37:727–733. doi: 10.5301/ijao.5000349
75. Winney RJ, Kean DM, Best JJ, Smith MA. Changes in brain water with haemodialysis. *Lancet*. 1986;2:1107–1108. doi: 10.1016/s0140-6736(86)90516-7
76. Galons JP, Trouard T, Gmitro AF, Lien YH. Hemodialysis increases apparent diffusion coefficient of brain water in nephrectomized rats measured by isotropic diffusion-weighted magnetic resonance imaging. *J Clin Invest*. 1996;98:750–755. doi: 10.1172/JCI118847
77. Silver SM, Sterns RH, Halperin ML. Brain swelling after dialysis: old urea or new osmoles? *Am J Kidney Dis*. 1996;28:1–13. doi: 10.1016/s0272-6386(96)90124-9
78. Polinder-Bos HA, García DV, Kuipers J, Elting JWJ, Aries MJH, Krijnen WP, Groen H, Willemsen ATM, van Laar PJ, Strijkert F, et al. Hemodialysis induces an acute decline in cerebral blood flow in elderly patients. *J Am Soc Nephrol*. 2018;29:1317–1325. doi: 10.1681/ASN.2017101088
79. Onoyama K, Ibayashi S, Nanishi F, Okuda S, Oh Y, Hirakata H, Nishimura Y, Fujishima M. Cerebral hemorrhage in patients on maintenance hemodialysis. CT analysis of 25 cases. *Eur Neurol*. 1987;26:171–175. doi: 10.1159/000116330
80. Kumar A, Cage A, Dhar R. Dialysis-induced worsening of cerebral edema in intracranial hemorrhage: a case series and clinical perspective. *Neurocrit Care*. 2015;22:283–287. doi: 10.1007/s12028-014-0063-z
81. Davenport A. Practical guidance for dialyzing a hemodialysis patient following acute brain injury. *Hemodial Int*. 2008;12:307–312. doi: 10.1111/j.1542-4758.2008.00271.x
82. Davenport A. Changing the hemodialysis prescription for hemodialysis patients with subdural and intracranial hemorrhage. *Hemodial Int*. 2013;17(suppl 1):S22–S27. doi: 10.1111/hdi.12085
83. Davenport A, Will EJ, Davison AM. Early changes in intracranial pressure during haemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. *Nephrol Dial Transplant*. 1990;5:192–198. doi: 10.1093/ndt/5.3.192
84. Morabito S, Pistolesi V, Tritapepe L, Fiaccadori E. Regional citrate anticoagulation for RRTs in critically ill patients with AKI. *Clin J Am Soc Nephrol*. 2014;9:2173–2188. doi: 10.2215/CJN.01280214
85. Eldehni MT, Odudu A, McIntyre CW. Randomized clinical trial of dialysate cooling and effects on brain white matter. *J Am Soc Nephrol*. 2015;26:957–965. doi: 10.1681/ASN.2013101086

86. Krane NK. Intracranial pressure measurement in a patient undergoing hemodialysis and peritoneal dialysis. *Am J Kidney Dis*. 1989;13:336–339. doi: 10.1016/s0272-6386(89)80042-3
87. National Collaborating Centre for Chronic Conditions. *Chronic Kidney Disease: National Clinical Guideline for Early Identification and Management in Adults in Primary and Secondary Care*. Royal College of Physicians. 2008
88. Stevens PE, Levin A; Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group Members. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825–830. doi: 10.7326/0003-4819-158-11-201306040-00007
89. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation*. 2019;140:e125–e151.
89a. Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int*. 2021;99(suppl):S1–S87. doi: 10.1016/j.kint.2020.11.003
90. Wanner C, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. *Kidney Int*. 2014;85:1303–1309. doi: 10.1038/ki.2014.31
91. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98:S1–S115.
92. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54:e1–31. doi: 10.1016/j.jvs.2011.07.031
93. Locatelli F, Bárány P, Covic A, De Francisco A, Del Vecchio L, Goldsmith D, Hörl W, London G, Vanholder R, Van Biesen W; ERA-EDTA ERBP Advisory Board. Kidney Disease: improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. *Nephrol Dial Transplant*. 2013;28:1346–1359. doi: 10.1093/ndt/gft033
94. Bolignano D, Zoccali C. Effects of weight loss on renal function in obese CKD patients: a systematic review. *Nephrol Dial Transplant*. 2013;28(Suppl 4):iv82–98.
95. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2014;64:383–393. doi: 10.1053/j.ajkd.2014.03.020
96. Chase HP, Garg SK, Marshall G, Berg CL, Harris S, Jackson WE, Hamman RE. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA*. 1991;265:614–617.
97. Major RW, Oozeerally I, Dawson S, Riddleston H, Gray LJ, Brunskill NJ. Aspirin and cardiovascular primary prevention in non-endstage chronic kidney disease: a meta-analysis. *Atherosclerosis*. 2016;251:177–182. doi: 10.1016/j.atherosclerosis.2016.06.013
98. Palmer SC, Di Micco L, Razavian M, Craig JC, Perkovic V, Pellegrini F, Jardine MJ, Webster AC, Zoungas S, Strippoli GF. Antiplatelet agents for chronic kidney disease. *Cochrane Database Syst Rev*. 2013:Cd008834.
99. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. *Lancet*. 2016;388:365–375. doi: 10.1016/S0140-6736(16)30468-8
100. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024
101. Buckley LF, Rybak E, Aldemerdash A, Cheng JW, Fanikos J. Direct oral anticoagulants in patients with atrial fibrillation and renal impairment, extremes in weight, or advanced age. *Clin Cardiol*. 2017;40:46–52.
102. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625–635.
103. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease: a meta-analysis of observational studies. *Chest*. 2016;149:951–959.
104. Ha JT, Neuen BL, Cheng LP, Jun M, Toyama T, Gallagher MP, Jardine MJ, Sood MM, Garg AX, Palmer SC, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2019;171:181–189.
105. Harel Z, Chertow GM, Shah PS, Harel S, Dorian P, Yan AT, Saposnik G, Sood MM, Molnar AO, Perl J et al. Warfarin and the risk of stroke and bleeding in patients with atrial fibrillation receiving dialysis: a systematic review and meta-analysis. *Can J Cardiol*. 2017;33:737–746.
106. Bonde AN, Lip GYH, Kamper AL, Staerk L, Torp-Pedersen C, Gislason G, Olesen JB. Renal function, time in therapeutic range and outcomes in warfarin-treated atrial fibrillation patients: a retrospective analysis of nationwide registries. *Thromb Haemost*. 2017;117:2291–2299.
107. Poterucha TJ, Goldhaber SZ. Warfarin and vascular calcification. *Am J Med*. 2016;129:635.e631–634.
108. De Vriese AS, Caluwe R, Pyfferoen L, De Bacquer D, De Boeck K, Delanote J, De Surgeloose D, Van Hoenacker P, Van Vlem B, Verbeke F. Multicenter randomized controlled trial of vitamin K antagonist replacement by rivaroxaban with or without vitamin K2 in hemodialysis patients with atrial fibrillation: the Valkyrie study. *J Am Soc Nephrol*. 2020;31:186–196.
109. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, Tilea A, Stack AG, Balkrishnan R, Yao X et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. *Circulation*. 2018;138:1519–1529.
110. Okumura K, Akao M, Yoshida T, Kawata M, Okazaki O, Akashi S, Eshima K, Tanizawa K, Fukuzawa M, Hayashi T, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation. *N Engl J Med*. 2020;383:1735–1745.
111. Pokorney SD. Renal hemodialysis patients allocated apixaban versus warfarin in atrial fibrillation - RENAL-AF. *American Heart Association Annual Scientific Sessions (AHA 2019)*. 2019.
112. Kefer J, Tzikas A, Freixa X, Shakir S, Gafoor S, Nielsen-Kudsk JE, Berti S, Santoro G, Aminian A, Landmesser U, et al. Impact of chronic kidney disease on left atrial appendage occlusion for stroke prevention in patients with atrial fibrillation. *Int J Cardiol*. 2016;207:335–340.
113. Fox KAA, Eikelboom JW, Shestakovska O, Connolly SJ, Metsarinne KP, Yusuf S. Rivaroxaban plus aspirin in patients with vascular disease and renal dysfunction: from the COMPASS trial. *J Am Coll Cardiol*. 2019;73:2243–2250.
114. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
115. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:263–275.
116. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Perkovic V, Hegbrant J, Strippoli GF. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014:Cd007784.
117. Yan YL, Qiu B, Wang J, Deng SB, Wu L, Jing XD, Du JL, Liu YJ, She Q. High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. *BMJ Open*. 2015;5:e006886.
118. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD, Jr., DePalma SM, Minissian MB, Orringer CE, Smith SC Jr. 2017 focused update of the 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology task force on expert consensus decision pathways. *J Am Coll Cardiol*. 2017;70:1785–1822.
119. Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, Solbu MD, Mark PB, Fellström B, Jardine AG, Wanner C, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. *Lancet Diabetes Endocrinol*. 2016;4:829–839.
120. Chen Y, Ku H, Zhao L, Wheeler DC, Li LC, Li Q, Varghese Z, Moorhead JF, Powis SH, Huang A, et al. Inflammatory stress induces statin resistance by disrupting 3-hydroxy-3-methylglutaryl-CoA reductase feedback regulation. *Arterioscler Thromb Vasc Biol*. 2014;34:365–376.
121. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, Cushman WC, Hawfield AT, Johnson KC, Lewis CE, et al. Effects of intensive BP control in CKD. *J Am Soc Nephrol*. 2017;28:2812–2823.
122. Li Y, Liang M, Jiang C, Wang G, Li J, Zhang Y, Fan F, Sun N, Cui Y, He M, et al. Impact of achieved blood pressure on renal function decline and first

stroke in hypertensive patients with chronic kidney disease. *Nephrol Dial Transplant*. 2018;33:409–417.
123. Cheung AK, Chang TI, Cushman WC, Furth SL, Ix JH, Pecoits-Filho R, Perkovic V, Sarnak MJ, Tobe SW, Tomson CRV, et al. Blood pressure in chronic kidney disease: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int*. 2019;95:1027–1036.
124. Perkovic V, Ninomiya T, Arima H, Gallagher M, Jardine M, Cass A, Neal B, Macmahon S, Chalmers J. Chronic kidney disease, cardiovascular events, and the effects of perindopril-based blood pressure lowering: data from the PROGRESS study. *J Am Soc Nephrol*. 2007;18:2766–2772.
125. Peralta CA, McClure LA, Scherzer R, Odden MC, White CL, Shlipak M, Benavente O, Pergola P. Effect of intensive versus usual blood pressure control on kidney function among individuals with prior lacunar stroke: a post hoc analysis of the secondary prevention of small subcortical strokes (SPS3) randomized trial. *Circulation*. 2016;133:584–591.
126. Park J, Rhee CM, Sim JJ, Kim YL, Ricks J, Streja E, Vashistha T, Tolouian R, Kovesdy CP, Kalantar-Zadeh K, et al. A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival. *Kidney Int*. 2013;84:795–802.
127. Mathew A, Eliasziw M, Devereaux PJ, Merino JG, Barnett HJ, Garg AX. Carotid endarterectomy benefits patients with CKD and symptomatic high-grade stenosis. *J Am Soc Nephrol*. 2010;21:145–152.
128. Klarin D, Lancaster RT, Ergul E, Bertges D, Goodney P, Schermerhorn ML, Cambria RP, Patel VI; Vascular Study Group of New England. Perioperative and long-term impact of chronic kidney disease on carotid artery interventions. *J Vasc Surg*. 2016;64:1295–1302. doi: 10.1016/j.jvs.2016.04.038
129. Fallon JM, Goodney PP, Stone DH, Patel VI, Nolan BW, Kalish JA, Zhao Y, Hamdan AD; Vascular Study Group of New England. Outcomes of lower extremity revascularization among the hemodialysis-dependent. *J Vasc Surg*. 2015;62:1183–1191.e1. doi: 10.1016/j.jvs.2015.06.203
130. Cooper M, Arhuidese IJ, Obeid T, Hicks CW, Canner J, Malas MB. Perioperative and long-term outcomes after carotid endarterectomy in hemodialysis patients. *JAMA Surg*. 2016;151:947–952.
131. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Edwards R, Agarwal R, Bakris G, Bull S, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644–657.
132. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Januzzi J, Verma S, Tsutsui H, Brueckmann M, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128.
133. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295–2306.
134. Zhou Z, Lindley RI, Radholm K, Jenkins B, Watson J, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Shaw W, et al. Canagliflozin and stroke in type 2 diabetes mellitus. *Stroke*. 2019;50:396–404.
135. Guo M, Ding J, Li J, Wang J, Zhang T, Liu C, Huang W, Long Y, Gao C, Xu Y. SGLT2 inhibitors and risk of stroke in patients with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2018;20:1977–1982.
136. Canney M, Kelly D, Clarkson M. Posterior reversible encephalopathy syndrome in end-stage kidney disease: not strictly posterior or reversible. *Am J Nephrol*. 2015;41:177–182.
137. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019–2032.
138. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. *Lancet Neurol*. 2010;9:105–118.
139. Ovbiagele B, Smith EE, Schwamm LH, Grau-Sepulveda MV, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Chronic kidney disease and bleeding complications after intravenous thrombolytic therapy for acute ischemic stroke. *Circ Cardiovasc Qual Outcomes*. 2014;7:929–935.
140. Moorthi RN, Avin KG. Clinical relevance of sarcopenia in chronic kidney disease. *Curr Opin Nephrol Hypertens*. 2017;26:219–228.
141. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2013:Cd000197.
142. Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J, Nakane H, Sugimori H, Kitazono T; FSR Investigators. Proteinuria and clinical outcomes after ischemic stroke. *Neurology*. 2012;78:1909–1915. doi: 10.1212/WNL.0b013e318259e110
143. El Husseini N, Fonarow GC, Smith EE, Ju C, Schwamm LH, Hernandez AF, Schulte PJ, Xian Y, Goldstein LB. Renal dysfunction is associated with poststroke discharge disposition and in-hospital mortality: findings from Get with the Guidelines-stroke. *Stroke*. 2017;48:327–334.
144. Wang IK, Liu CH, Yen TH, Jeng JS, Sung SF, Huang PH, Li JY, Sun Y, Wei CY, Lien LM, et al. Renal function is associated with 1-month and 1-year mortality in patients with ischemic stroke. *Atherosclerosis*. 2018;269:288–293.
145. Hayden D, McCarthy C, Akijian L, Callaly E, Ni Chroinin D, Horgan G, Kyne L, Duggan J, Dolan E, O' Rourke K, et al. Renal dysfunction and chronic kidney disease in ischemic stroke and transient ischemic attack: a population-based study. *Int J Stroke*. 2017;12:761–769.
146. Molshatzki N, Orion D, Tsabari R, Schwammenthal Y, Merzeliak O, Toashi M, Tanne D. Chronic kidney disease in patients with acute intracerebral hemorrhage: association with large hematoma volume and poor outcome. *Cerebrovasc Dis*. 2011;31:271–277.
147. Wang X, Wang Y, Wang C, Zhao X, Xian Y, Wang D, Liu L, Luo Y, Liu G, Wang Y. Association between estimated glomerular filtration rate and clinical outcomes in patients with acute ischaemic stroke: results from China national stroke registry. *Age Ageing*. 2014;43:839–845.
148. Wang X, Wang Y, Patel UD, Barnhart HX, Li Z, Li H, Wang C, Zhao X, Liu L, Wang Y, et al. Comparison of associations of reduced estimated glomerular filtration rate with stroke outcomes between hypertension and no hypertension. *Stroke*. 2017;48:1691–1694.
149. Luo Y, Wang X, Matsushita K, Wang C, Zhao X, Hu B, Liu L, Li H, Liu G, Jia Q, et al. Associations between estimated glomerular filtration rate and stroke outcomes in diabetic versus nondiabetic patients. *Stroke*. 2014;45:2887–2893.
150. Harhay MN, Xie D, Zhang X, Hsu CY, Vittinghoff E, Go AS, Sozio SM, Blumenthal J, Seliger S, Chen J, et al. Cognitive impairment in non-dialysis-dependent CKD and the transition to dialysis: findings from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis*. 2018;72:499–508.
151. Kurella Tamura M, Wadley V, Yaffe K, McClure LA, Howard G, Go R, Allman RM, Warnock DG, McClellan W. Kidney function and cognitive impairment in US adults: the reasons for geographic and racial differences in stroke (REGARDS) study. *Am J Kidney Dis*. 2008;52:227–234.
152. Murray AM, Tupper DE, Knopman DS, Gilbertson DT, Pederson SL, Li S, Smith GE, Hochhalter AK, Collins AJ, Kane RL. Cognitive impairment in hemodialysis patients is common. *Neurology*. 2006;67:216–223.
153. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, Bowler JV, Ballard C, DeCarli C, Gorelick PB, et al. Vascular cognitive impairment. *Lancet Neurol*. 2003;2:89–98.
154. Pi HC, Xu YF, Xu R, Yang ZK, Qu Z, Chen YQ, Liu GL, Dong J. Cognitive impairment and structural neuroimaging abnormalities among patients with chronic kidney disease. *Kidney Blood Press Res*. 2016;41:986–996.
155. Toyoda K. Cerebral small vessel disease and chronic kidney disease. *J Stroke*. 2015;17:31–37.
156. Zong L, Yao M, Ni J, Zhou L, Yuan J, Peng B, Zhu YC, Cui L. Kidney function is associated with severity of white matter hyperintensity in patients with acute ischemic stroke/TIA. *BMC Neurol*. 2016;16:193.
157. Makin SD, Cook FA, Dennis MS, Wardlaw JM. Cerebral small vessel disease and renal function: systematic review and meta-analysis. *Cerebrovasc Dis*. 2015;39:39–52.
158. Xiao L, Lan W, Sun W, Dai Q, Xiong Y, Li L, Zhou Y, Zheng P, Fan W, Ma N, et al. Chronic kidney disease in patients with lacunar stroke: association with enlarged perivascular spaces and total magnetic resonance imaging burden of cerebral small vessel disease. *Stroke*. 2015;46:2081–2086.
159. Peng Q, Sun W, Liu W, Liu R, Huang Y. Longitudinal relationship between chronic kidney disease and distribution of cerebral microbleeds in patients with ischemic stroke. *J Neurol Sci*. 2016;362:1–6.
160. Naganuma T, Uchida J, Tsuchida K, Takemoto Y, Tatsumi S, Sugimura K, Nakatani T. Silent cerebral infarction predicts vascular events in hemodialysis patients. *Kidney Int*. 2005;67:2434–2439.
161. Kobayashi M, Hirawa N, Yatsu K, Kobayashi Y, Yamamoto Y, Saka S, Andoh D, Toya Y, Yasuda G, Umemura S. Relationship between silent brain infarction and chronic kidney disease. *Nephrol Dial Transplant*. 2009;24:201–207.
162. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. *Hypertens Res*. 2009;32:115–121.
163. Holliday EG, Traylor M, Malik R, Bevan S, Maguire J, Koblar SA, Sturm J, Hankey GJ, Oldmeadow C, McEvoy M, et al. Polygenic overlap between kidney function and large artery atherosclerotic stroke. *Stroke*. 2014;45:3508–3513.

164. Liu B, Lau KK, Li L, Lovelock C, Liu M, Kuker W, Rothwell PM. Age-specific associations of renal impairment with magnetic resonance imaging markers of cerebral small vessel disease in transient ischemic attack and stroke. *Stroke*. 2018;49:899–904.
165. Yao H, Araki Y, Takashima Y, Uchino A, Yuzuriha T, Hashimoto M. Chronic kidney disease and subclinical brain infarction increase the risk of vascular cognitive impairment: the Sefuri study. *J Stroke Cerebrovasc Dis*. 2017;26:420–424 8.
166. Kobayashi M, Hirawa N, Morita S, Yatsu K, Kobayashi Y, Yamamoto Y, Saka S, Toya Y, Yasuda G, Umemura S. Silent brain infarction and rapid decline of kidney function in patients with CKD: a prospective cohort study. *Am J Kidney Dis*. 2010;56:468–476.
167. Smith EE, Saposnik G, Biessels GJ, Doubal FN, Fornage M, Gorelick PB, Greenberg SM, Higashida RT, Kasner SE, Seshadri S et al. Prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e44–e71.
168. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APJA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:3168–3209.
169. Wilson D, Ambler G, Lee KJ, Lim JS, Shiozawa M, Koga M, Li L, Lovelock C, Chabriat H, Hennerici M, et al. Cerebral microbleeds and stroke risk after ischaemic stroke or transient ischaemic attack: a pooled analysis of individual patient data from cohort studies. *Lancet Neurol*. 2019;18:653–665.