Review

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Primary Prevention of Stroke in Chronic Kidney Disease Patients: A Scientific Update

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Primary prevention · Stroke · Chronic kidney disease

Abstract
Background: Although chronic kidney disease (CKD) is an independent risk factor for stroke, official recommendations for the primary prevention of stroke in CKD are generally lacking. ***Summary:*** We searched PubMed and ISI Web of Science for randomised controlled trials, observational studies, reviews, meta-analyses and guidelines referring to measures of stroke prevention or to the treatment of stroke-associated risk factors (cardiovascular disease in general and atrial fibrillation (AF), arterial hypertension or carotid artery disease in particular) among the CKD population. The use of oral anticoagulation in AF appears safe in non-end stage CKD, but it should be individualized and preferably based on thromboembolic and bleeding stratification algorithms. Non-vitamin K antagonist oral anticoagulants with definite dose adjustment are generally preferred over vitamin K antagonists in mild and moderate CKD and their indications have started being extended to severe CKD and dialysis also. Aspirin, but not clopidogrel, has limited indications for reducing the risk for atherothrombotic events in CKD due to its increased bleeding risk. Carotid endarterectomy has shown promising results for stroke risk reduction in CKD patients with high-grade symptomatic carotid stenosis. The medical treatment of arterial hypertension in CKD often fails to efficiently lower blood pressure values, but recent data regarding the use of interventional procedures such as renal denervation, baroreflex activation therapy or renal artery stenting are encouraging. ***Key Messages:*** In the absence of clear guidelines and protocols, primary prevention of stroke in CKD patients remains a subtle art in the hands of the clinicians. Nevertheless, refraining CKD patients from standard therapies often worsens their prognosis.

Background

Chronic kidney disease (CKD) has been recognized by the American Heart Association as an independent risk factor for stroke [1]. The incidence of stroke is indeed disproportionately higher in CKD patients and especially in end-stage renal disease (ESRD): 14.9–49 per 1,000 person-years in ESRD [2, 3] compared to 0.41–2.38 per 1,000

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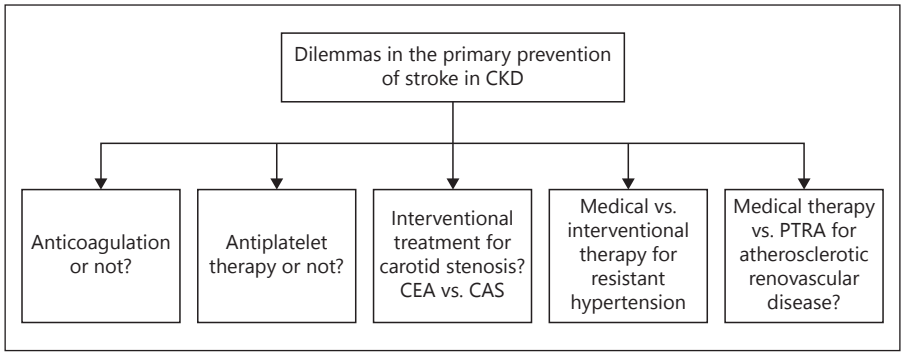

Fig. 1. Practical clinical dilemmas in the management of primary stroke prevention in chronic kidney disease. CEA, carotid endarterectomy; CAS, carotid angioplasty and stenting; PTRA, percutaneous transluminal renal angioplasty.

persons/year in the general population worldwide [4]; concurrently, stroke may cause renal impairment [5] and figures describing the 2-way "cerebro-renal" relationship are similar: CKD stage 3 or higher increases the risk for stroke by 43% [6], while post- (ischaemic) stroke kidney dysfunction occurs in up to 40% stroke survivors among the general population [5].

Nevertheless, measures for preventing a first stroke are often difficult to input in CKD due to the lack of sufficient data: guidelines are poor in giving recommendations in this population and thus clinicians frequently face significant dilemmas such as the decision to use anticoagulation or antiplatelet agents, to choose between medical and interventional management or to choose between 2 different types of interventional procedures that pose considerable risks, and so on (Fig. 1).

This review will discuss the newest evidence-based approaches for preventing a first stroke in CKD; emphasis will be made on specific conditions highly prevalent in CKD that majorly impact the risk for stroke (e.g., atrial fibrillation-AF, carotid atherosclerosis and resistant hypertension-RH) but raise great concern regarding their management. For the clarity of the scientific approach, this article is structured according to the type of stroke in general (ischaemic and haemorrhagic), in the setting of CKD. The ischaemic stroke section discusses the 2 major causes (cardioembolic and atherothrombotic), and the haemorrhagic stroke section tackles treatment-RH and bleeding on antithrombotic therapy.

Methods

We searched the electronic databases of PubMed and ISI Web of Science from inception until September 13, 2017 using the search terms "primary prevention and stroke"/"atrial fibrillation"/"resistant hypertension"/"cardiovascular disease"/"carotid"/"peripheral artery disease' and "chronic kidney disease"/"dialysis," with and without "guidelines." Randomised controlled trials (RCTs), observational studies, reviews, meta-analyses and guidelines were included if measures of stroke prevention or to the treatment of stroke-associated risk factors (cardiovascular disease [CVD] in general and AF, arterial hypertension or carotid/peripheral artery disease in particular) were first referred to in the CKD population; if highly relevant or if CKD data were very scarce or lacking, data regarding the general population was also referred to. Relevant references from the selected articles and guidelines were also searched manually afterwards.

Ischaemic Stroke

Cardioembolic Stroke: AF

CKD patients with AF (approximately a quarter of all renal patients) [7] are more prone to experiencing both stroke and bleeding, which makes the use of oral anticoagulants a subtle art in managing stroke risk in this population (Tables 1, 2) [8, 9].

Non-ESRD Patients

Anticoagulation is safe for an estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2, according to the 2016 European Society of Cardiology (ESC) guidelines for the management of AF [10].

There is currently no restriction in using vitamin K antagonists (VKA) in non-ESRD CKD [11]. The classic treatment of AF with VKA (namely warfarin) significantly reduces the risk of stroke in non-end stage CKD, without significantly impacting the risk for major bleeding [12]. VKA have a renal elimination of only 10–15% [13]; however, a creatinine clearance under 30 mL/min was shown to be an independent predictor of warfarin-associated haemorrhagic risk [14] and therefore, careful dose titration is needed in patients with advanced kidney impairment [13]. This observation is also supported by a 2017 research, which demonstrated that severe non-ESRD

Table 1. NOACs use in AF and CKD: dosage and administration according to EMA and FDA

		Dabigatran	Rivaroxaban	Apixaban	Edoxaban
eGFR ≥50 mL/min (CKD 1–3A)	EMA FDA	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily
eGFR = 15–49 mL/min (CKD 3B–4)	EMA	30–49 mL/min: 150 mg or 110 mg twice daily if high bleeding risk 15–29 mL/min: NR	15 mg once daily	30–49 mL/min: Reduce to 2.5 mg twice daily if 2 of: – Creatinine ≥1.5 mg/dL – Age ≥80 years – Body weight ≤60 kg 15–29: 2.5 mg twice daily	30 mg once daily
	FDA	30–49 mL/min: 150 mg twice daily 15–29: 75 mg twice daily		Reduce to 2.5 mg twice daily if 2 of: – Creatinine ≥1.5 mg/dL – Age ≥80 years – Body weight ≤60 kg	
eGFR <15 mL/min (CKD 5 and dialysis)	EMA FDA	NR	NR 15 mg once daily	NR Reduce to 2.5 mg twice daily if: – Age ≥80 years or – Body weight ≤60 kg	NR

Adapted from Burlacu et al. [9] and according to prescribing information for dabigatran, rivaroxaban, apixaban and edoxaban available at http://www.ema.europa.eu and www.accessdata.fda.gov.

CKD, chronic kidney disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; NOACs, non-vitamin K antagonist oral anticoagulants, NR, not recommended.

CKD patients treated with warfarin have a labile international normalized ratio with a significantly lower time-in-therapeutic range and a higher adverse events risk [15].

The novel non-vitamin K antagonist oral anticoagulants (NOACs) are associated with lower risks for stroke and major bleeding compared to warfarin in patients with mild and moderate renal impairment [16]. Nonetheless, definite dose adjustment is needed as they have variable renal elimination (Table 1) [10]. The 2016 ESC guidelines do not support the use of NOACs in CKD stages 4 and 5 due to the lack of evidence [10], but the European Medicines Agency and the Food and Drug Administration also spread the indications to CKD stage 4 based on pharmacokinetic studies (Table 1) [9].

ESRD Patients

In the absence of RCTs regarding stroke prevention in dialysis patients with AF, the decision to use oral anticoagulants should be made on an individual basis [11]. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) controversies report published in September 2017 is the first official taskforce that discusses the existing observational studies that examine warfarin use and associated stroke and bleeding risks in adults with CKD-5D and AF [17]. Strict monitoring due to the increased bleeding risk is mandatory (the KDOQI clinical practice guidelines for CVD in dialysis patients) [18].

Warfarin was reported to increase the risk of major bleeding by 30% in ESRD without having any effect on the risk of stroke [12]. Since the ESC and the European Medicines Agency do not support the use of NOACs in ESRD due to lack of sufficient data (Table 1) [9, 10] and there are no RCTs of NOACs in patients with severe CKD, warfarin still remains the only choice for oral anticoagulation [10]. Nonetheless, Food and Drug Administration supplemented the indications for apixaban and low dose of rivaroxaban usage in dialysis patients based on pharmacokinetic and pharmacodynamic studies (Table 1) [9, 19].

Ischaemic and Bleeding Risk Stratification

The use of individualized stratification models should be encouraged as refraining CKD patients from standard therapies ("therapeutic nihilism") worsens their prognosis [9, 20].

Reinecke et al. [20] have proposed a stratification algorithm for CKD patients (Fig. 2) to better identify those that would mostly benefit from anticoagulation: if [1] $CHADS_2$ score (Congestive heart failure, Hypertension, age ≥75 years, Diabetes mellitus, Stroke [double weight])

Table 2. Primary prevention of stroke in CKD: dilemmas

Atrial fibrillation	– Both high thromboembolic and bleeding risks; – Anticoagulation is generally safe for an eGFR ≥15 mL/min (ESC guidelines) [10]; – Decision to use anticoagulants should be individualized and based, preferably, on stratification algorithms (Fig. 2) [20]; – Careful monitoring of bleeding risk is mandatory [18]; NOACs: – Are generally preferred over VKAs in mild and moderate CKD [10]; – Need dose adjustment (Table 1); – Generally not suitable for CKD stage 5 [10] (apixaban and/or rivaroxaban might be considered); VKAs: – Need careful titration in advanced CKD (delayed achievement of therapeutic INR) [13];
CS	– No official firm recommendations for CKD; Aspirin: – AHA/ASA guidelines [22]: eGFR <45 mL/min, but not for CKD stages 4 and 5; – KDIGO guidelines [23]: for secondary prevention only; – Clopidogrel is not an alternative [23]; Revascularization techniques (CEA or CAS): – Higher risk for adverse events with worsening renal function [28], but reported overall stroke and death rate within the safety limits of under 3% [29]; – "May be considered in symptomatic patients with moderate to severe carotid stenosis" [25]; – CEA is generally preferred over CAS [25]; – CAS is an option in selected symptomatic high-risk patients if CEA is not suitable [25, 29, 32];
Resistant hypertension	Medical therapy: – 4th line therapy (aldosterone antagonists, centrally acting alpha-adrenergic agonists, alpha-blockers): limited use [38, 39]; Interventional approaches: – If truly resistant hypertension with systolic BP ≥160 mm Hg and failure of medical treatment [36]; Renal Denervation: – For truly resistant hypertension if eGFR ≥45 mL/min/1.73 m^2 (expert consensus of the ESC) [44]; – Consistent data in the more advanced stages of CKD are lacking [44]; – Also has renoprotective effects [41]; – BAT is becoming a promising option (also has renoprotective effects) [47, 49]; PTRA: – RCTs did not include high-risk patients with refractory hypertension and rapidly declining kidney function; – Observational studies: improves BP control and kidney function in CKD stages 4–5 [56]; – High chances of response if recent high BP (particularly over 180 mm Hg systolic) reluctant to medical therapy and prior progressive CKD [58, 59]; – Need for benefit stratification [30].

AHA/ASA, American Heart Association/American Stroke Association; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blocker; BAT, baroreflex activation therapy; BP, blood pressure; CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; CKD, chronic kidney disease; CS, carotid stenosis; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; KDIGO, Kidney Disease Improving Global Outcomes; NOAC, non-vitamin K antagonist oral anticoagulants; PTRA, percutaneous transluminal renal angioplasty; RAS, renal artery stenosis; RCTs, randomized controlled trials; VKA, vitamin K antagonist.

≥2 or [2] under 2 but age ≥75 or [3] ≥1 and age between 65 and 74 years/female sex/vascular heart disease, bleeding risk should be calculated (HAS-BLED score -Hypertension, Abnormal renal and liver function, Stroke, Bleeding Labile international normalized ratio, Elderly, Drugs or alcohol – with recurrent falls, dementia and cancer as additional factors) for the opportunity of oral anticoagulation; if the bleeding risk is low-to-intermediate (HAS-BLED = 0–2), then anticoagulation with NOAC or VKA is proposed [20].

Atherothrombotic Stroke: Carotid Stenosis

CKD patients display advanced carotid atherosclerosis with more frequently unstable or ruptured plaques due to

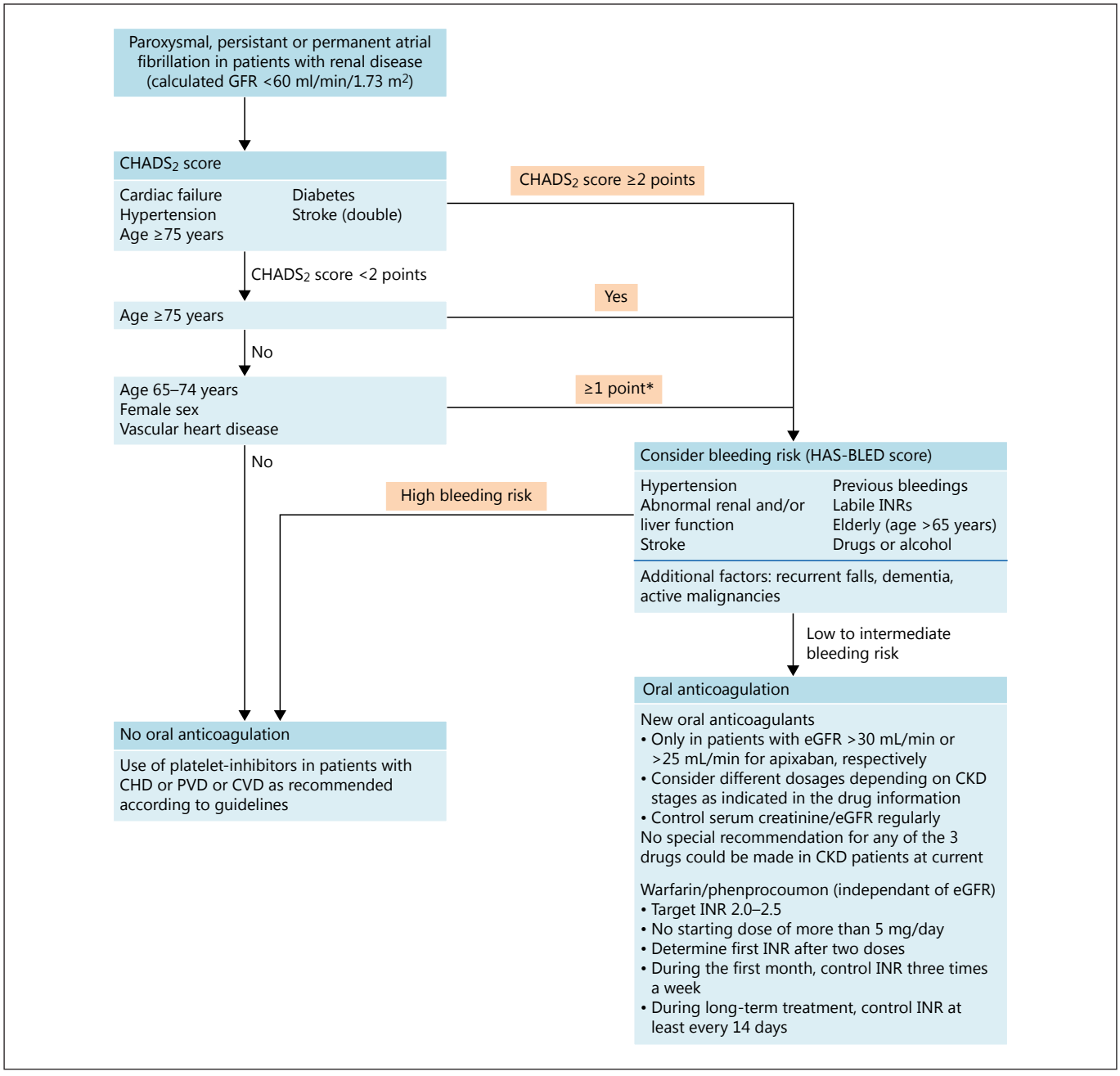

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Fig. 2. Risk stratification algorithm for anticoagulation in CKD according to Reinecke et al. [20] (reproduced with permission of the publisher. ©Stroke, Lippincott Williams and Wilkins 2013). CKD, chronic kidney disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PVD, peripheral vascular disease; NOACs, non-vitamin K antagonist oral anticoagulants; VKAs, vitamin K antagonists.

composition changes (less collagen, more calcified) and this explains the 3-fold higher prevalence of remote cerebrovascular events in these patients compared to non-CKD [21].

Specific guidelines for the medical treatment of carotid stenosis (CS) in CKD do not exist. The American Heart Association/American Stroke Association guidelines allow the use of aspirin for preventing a first stroke when eGFR is under 45 mL/min/1.73 m^2, but not for CKD stages 4 and 5 [22]; at the same time, the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines sug-

gest prescribing aspirin to CKD patients "at risk for atherosclerotic events" only for secondary prevention and if there is no increased bleeding risk [23] (Table 2). Antiplatelet drugs increase the risk for major and minor bleeding (by 33 and 49%, respectively) but do not significantly reduce the risk for stroke, all-cause and cardiovascular mortality [24]. Clopidogrel is generally not a practicable alternative to aspirin: it brings no benefits over placebo for reducing stroke risk in CKD, possibly due to an occurring clopidogrel resistance [23].

European guidelines (ESC) do not address the puzzle of carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) in CKD patients; the North American Society for Vascular Surgery Guidelines state that "among asymptomatic patients with cardiac or renal insufficiency, best medical therapy may be preferable to CAS or CEA," while "CEA or CAS may be considered among symptomatic high-risk patients with moderate to severe CS" [25].

Clinical trials investigating CEA or CAS in CKD are missing, but retrospective studies have shown that worsening renal function is generally associated with an increased risk of myocardial infarction, stroke and death after both CEA (9% for CKD vs. 2.6% for controls 30 days after CEA) [26] and CAS (hazard ratio 2.97 for CKD versus no CKD 6 months after CAS) [27], with dialysis patients being at the highest risk [28]. Despite this, Klarin et al. [29] recently reported an overall 30-day stroke and death rate of less than 3% for CEA and CAS combined across all CKD stages, which meet the criteria endorsed by the guidelines [22, 30]. Moreover, CKD stage 3 patients with symptomatic high-grade (70–99%) CS were shown to greatly benefit from CEA, with a relative stroke risk reduction of 82% compared to medical therapy [31]. CAS requires iodinated contrast and is associated with higher rates of major adverse cardiovascular and cerebrovascular events and twofold higher 30-day mortality compared to CEA in both moderate and severe CKD [29, 32]. Therefore, CAS becomes a viable option only in symptomatic patients at high-risk for CEA, especially if there is severe cardiac impairment [25] (Table 2).

Haemorrhagic Stroke

(Resistant) Hypertension

Hypertension is responsible for both ischaemic [33] and haemoragic stroke [34]. As a well-known CVD risk factor, high blood pressure (BP) is strongly correlated with the development of atherosclerosis and ischaemic stroke. However, since uncontrolled hypertension is the most common cause of spontaneous intracerebral haemorrhage [35], for scientific clarity we decided to discuss here the haemorrhagic stroke causality. In fact, the main interest in the "equation of RH" is to lower the BP values by all means.

As defined in the 2013 ESH/ESC guidelines, RH is contemplated when a therapy with 3 drugs (diuretic and 2 other antihypertensive drugs belonging to different classes at adequate doses) fails to lower BP to 140 and 90 mm Hg, respectively [36].

One third of the patients with an eGFR under 45 mL/min and almost half of patients with a urinary albumin-to-creatinine ratio >300 mg/g have RH, a major cause of haemorrhagic stroke among the CKD population [37].

When the addition of the "fourth line" medical therapies (e.g., aldosterone antagonists, centrally acting alpha-adrenergic agonists, alpha blockers) recommended by the CKD dedicated guidelines (Kidney Disease Improving Global Outcomes, KDOQI) [38, 39] fails to efficiently lower BP, invasive procedures such as renal denervation (RD) or baroreceptor stimulation represent an alternative [36] (Table 2). Revascularization of the renal artery in patients with RH secondary to atherosclerotic renovascular disease is also an option (Table 2).

Renal Denervation

Even though there is limited evidence that RD controls the BP (and could have renoprotective effects: eGFR stabilization/increase and/or lower albuminuria) [40, 41], 2 major 2017 reviews [42, 43] questioned the benefits of RD on renal function and major cardiovascular events. According to the expert consensus of the ESC, RD may be performed truly for RH if eGFR ≥45 mL/min/1.73 m^2 (consistent data in the more advanced stages of CKD are lacking) [44]. However, renal arteries with stenosis are not eligible for RD [44] and prophylaxis of contrast-induced nephropathy is necessary [45].

Baroreflex Activation Therapy

Even if there are not yet important studies and clear protocols, baroreflex activation therapy (BAT) could become a promising option [46] in the treatment of RH. Particularly interesting for CKD patients is that BAT was not only shown to decrease office BP values in small prospective trials on CKD non-dialysis and dialysis patients [47, 48], but also to have renoprotective effects by significantly reducing proteinuria and improving eGFR [47]. BAT would be an option when RD is not possible or inef-

ficient [49]. A prospective randomized controlled trial comparing the safety and efficacy of the Barostim neo BAT device versus medical therapy is currently ongoing [50].

Renal Artery Stenting

When declining kidney function impairs the efficacy of medical treatment in controlling BP or limits the use of ACEi or ARBs in atherosclerotic renovascular disease, percutaneous transluminal renal angioplasty with stenting is usually proposed as the alternative method of choice [51].

Data from RCTs failed to demonstrate a clear benefit of stenting regarding BP, renal function and cardiovascular morbidity and mortality outcomes [52–55] and therefore, renal revascularization is not endorsed by the 2017 ESC guidelines for the management of renovascular hypertension (with few specific exceptions) [30].

However, relevant gaps in evidence are represented by RCTs not addressing high-risk patients with refractory hypertension and rapidly declining kidney function. Revascularization was shown in observational studies to improve BP control and kidney function in CKD stages 4–5 and to have a major impact upon survival [56, 57]. The 2017 ESC guidelines draw the attention towards the need for stratification of patients based on the estimated benefits of renal revascularization [30]. As such, percutaneous transluminal renal angioplasty with stenting seems to be most beneficial in those patients with recent high BP (particularly over 180 mm Hg systolic) that is reluctant to medical therapy and prior progressive kidney function impairment [30, 58, 59] (Table 2).

Cerebral Bleeding in Antithrombotics Overdosing

The risk of major bleeding in advanced CKD patients without anticoagulant treatment is twice as high as in the general population [60]. Even when thrombotic and haemorrhagic risks are estimated according to the guidelines, the indication of antithrombotic treatment is solid, and the drugs are chosen and dosed accordingly; anticoagulation therapy in CKD patients can promote bleeding episodes, as these substances can accumulate or directly interfere with an already changed haemostatic system [61, 62]. For primary prevention of cerebral haemorrhage in NOACs overdosing, there are new recommendations in the ESC guidelines for antithrombotic therapy and very good local anticoagulant reversal protocols (e.g., idarucizumab administration in dabigatran reversal [63]).

Conclusions

While CKD patients face a significantly higher risk of developing a stroke compared to the general population, the primary prevention of a cerebrovascular event in this population has significant caveats: anticoagulation is problematic especially in the late stages of CKD, antiplatelet agents have very limited indications due to the higher bleeding risk, carotid revascularization techniques are promising but are associated with higher procedural risks in CKD patients and the medical treatment of resistant hypertension is frequently inefficient or limited by side-effects, drawing the attention towards the need for interventional procedures. Official recommendations for the CKD population are very scarce and therefore, the treatment of various comorbidities associated with stroke in CKD patients is to be done on an individualized basis. Although caution is needed when managing renal patients, refraining them from standard therapies also leaves them exposed to a considerable morbidity and mortality risk.

Disclosure Statement

The authors have no conflicts of interest to declare.

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