Preventing Stroke in Patients With Chronic Kidney Disease and Atrial Fibrillation
Benefit and Risks of Old and New Oral Anticoagulants

Holger Reinecke, MD; Christiane Engelbertz, PhD; Wolf-Rüdiger Schäbitz, MD

Epidemiology of Chronic Kidney Disease

Chronic kidney disease (CKD) is a major global health problem. It is defined by decreased kidney function (characterized by a reduced estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m^2) and kidney damage characterized by albuminuria or proteinuria.[1] To standardize definitions and facilitate risk stratification, 5 different stages of severity have been defined by the National Kidney Foundation in 2002: CKD stage 1 with a normal eGFR ≥90 mL/min per 1.73m^2 but proven proteinuria, CKD stage 2 with eGFR 60 to 89 mL/min per 1.73 m^2, CKD stage 3 with eGFR 30 to 59 mL/min per 1.73 m^2, CKD stage 4 with eGFR 15 to 29 mL/min per 1.73 m^2, and CKD stage 5 with eGFR <15 mL/min per 1.73 m^2.[1]

The incidence and prevalence of CKD vary among different regions, which may be explained by both different surveillance programs and differences in underlying diseases.[2] The median worldwide prevalence is estimated to be ≈7.2% in people aged ≥30 years.[3] In the US population, prevalence was estimated to be ≈13%.[4] Prevalences in European or Asian populations are similar, ranging ≤20% in Japan.[3,5] In general, the prevalence increases with age, although the prevalence in the US population is only 0.7% in the age group 20 to 39 years (CKD stages 3 and 4), it rises ≤37.8% in people aged ≥70 years.[4] One recent study reported a higher prevalence of CKD in women compared with men, regardless of age categories and ethnicity.[3]

CKD and Atrial Fibrillation

Atrial fibrillation (AF) is the most frequent arrhythmia in general and a key factor determining morbidity and mortality in patients with CKD primarily because of the occurrence of thromboembolic events, especially ischemic strokes. In the general population, the prevalence of AF increases from <0.5% in patients aged <50 years to 15% in patients aged 80 years.[6] In patients with renal insufficiency, the risk of AF is even more elevated. An association between CKD and incident AF was reported by several studies.[7–9] All found increasing hazard ratios (HR) for new-onset AF with decreasing kidney function, even in multivariate analysis. Another study described vice versa an association between incident AF and the development of dialysis-dependent CKD (adjusted HR, 1.67; 95% confidence interval [CI], 1.46–1.91).[10] The Chronic Renal Insufficiency Cohort (CRIC) study reported a prevalence of 16.0% for AF in patients with eGFR ≥45 mL/min and 20.4% in patients with eGFR <45 mL/min. In patients with impaired kidney function and ≥70 years of age, the prevalence rate was 25.5%.[11] Other studies also found increasing prevalence of AF with decreasing renal function.[12,13] In dialysis-dependent patients with CKD stage 5, the prevalence of AF was estimated to range between 3.5% and 27%, depending on AF type.[14]

Morbidity and Mortality in CKD Patients With AF

CKD, as well as AF, is associated with an increased mortality risk.[15,16] This applies even more to patients with both conditions. In a retrospective cohort study of >1 million Medicare patients (5.1% with CKD) with incident AF, the unadjusted 1-year mortality rate was 35.6% in patients with CKD stages 3 to 5 and 20.7% in patients without CKD. The adjusted HR for death in patients with CKD and incident AF was 1.14 (95% CI, 1.00–1.30) for CKD stages 1+2 and 1.27 (95% CI, 1.20–1.35) for CKD stages 3 to 5 compared with patients without CKD. Interestingly, the association of CKD stage and risk of death after incident AF diminished with increasing age, although the association was highest in the group 66 to 69 years of age (CKD 1+2: HR, 1.69; CKD 3–5: HR, 1.80 versus no CKD), the HR was 0.90 (CKD stage 1+2) respective 0.89 (CKD stage 3–5) in the group ≥85 years of age.[9] In another recently published study of 387 patients with AF, both eGFR and CHADS$_2$ score were strong independent predictors of all-cause (HR, 3.57; respective 3.16) and cardiovascular mortality (HR, 3.33; respective 5.53) in multivariate analysis.[17] For hemodialysis patients with AF, HRs for death between 1.16 and 2.32 compared with patients without AF were estimated.[14,18–20] Another study found a 4-year mortality rate of 81% in patients with dialysis-dependent CKD and AF.[21]

CKD and Stroke

Patients with AF are at increased risk for stroke, which have marked impact on quality of life and survival.[6] With decreasing eGFR, the relative risk of thromboembolism, mostly ischemic stroke, increased by 39%.[22] A Japanese community-based observational study reported an even higher risk of stroke for patients with eGFR <40 mL/min (relative hazard 3.1 compared with eGFR <70 mL/min).[23] Examining patients with eGFR <60 mL/min and an elevated stroke risk (CHADS$_2$ score ≥2) revealed an HR of 11.0 for ischemic stroke compared with patients with eGFR ≥60 mL/min and CHADS$_2$ score <2.[17]

The up-to-date largest population is from a Danish national registry of 132 372 patients with AF and CKD and showed that patients with non–end-stage CKD compared with those without had a factor 1.49 increase (95% CI, 1.38–1.59) for stroke and systemic embolism.[24] Consistently, this large population study also showed that a more severe impairment of renal function is associated with a higher stroke risk (HR for patients with renal replacement therapy, 1.83; 95% CI, 1.57–2.14). This increase in stroke rates in hemodialysis patients was already found in prior reports from the US Renal Data System (15.1% compared with 9.6% in patients with CKD without hemodialysis and 2.6% in matched patients without CKD).[25]

CKD increases not only the risk of clinically apparent cardioembolic stroke, but recent studies suggest also a relationship between deep white matter lesions and intracranial small vessel disease.[26] Similar to age and hypertension, renal dysfunction may become a risk factor for progressing white matter disease and its associated cognitive syndromes, such as mild cognitive impairment and vascular dementia.[26,27]

Oral Anticoagulation for the Prevention of Stroke in AF

During recent years, in patients with AF and an increased risk of stroke, oral anticoagulation has unequivocally turned out to be the only effective prevention. This evidence bases on numerous studies and has been implemented in all current guidelines. However, the use of oral anticoagulation in patients with CKD has only been assessed in a small number of studies. These are subsequently summarized briefly regarding the results of old or classic drugs for oral anticoagulation (warfarin, phenprocoumon) and the so-called new oral anticoagulants (apixaban, dabigatran, rivaroxaban).

Warfarin and Phenprocoumon

Warfarin and phenprocoumon are potent vitamin K antagonists with multiple, well-known limitations. The most prominent are the need for regular international normalized ratio (INR) controls because of markedly differing drug doses in each individual and numerous interactions with other drugs. Nearly all trials investigating warfarin in patients with renal impairment and AF focused on dialysis-dependent CKD. In brief, all were observational studies. Most of these were small studies with markedly diverging results, although some studies found an increased risk of ischemic stroke in dialysis patients, others described no differences in risk of stroke or even reduction of

strokes and mortality.[28] One larger retrospective cohort study with 1671 incident hemodialysis patients with pre-existing AF compared patients without anticoagulants with warfarin, aspirin, and clopidogrel. The overall stroke rate was 4.8% (95% CI, 4.0–5.7). The risk of new stroke was highest in the warfarin group (7.1%; 95% CI, 5.7–8.7), whereas the risk in the other treatment groups was between 2.7% and 3.5%. Cox regression analysis revealed a 2-fold increase in the risk of stroke in patients treated with warfarin versus nonuse (HR, 2.00; 95% CI, 1.34–2.99). The risk of stroke was greatest in warfarin users without INR monitoring versus nonusers (HR, 2.79; 95% CI, 1.65–4.70). However, the subgroups were not comparable: those with the highest risk received oral anticoagulation; therefore, the results may be biased by selection.[29]

Another report is that from a Danish publication about a 12-year registry that studied the risk reduction of stroke and systemic thromboembolism among patients without and with CKD (including dialysis dependents) and on or off anticoagulation. In patients with CKD without dialysis (n=3587), a 16% risk reduction in stroke (HR, 0.84; 95% CI, 0.69–1.01; P=0.07) was observed under warfarin therapy compared with no anticoagulation. This effect was even more pronounced with a 56% risk reduction (HR, 0.44; 95% CI, 0.26–0.74; P=0.002) by warfarin in end-stage renal disease patients (77.9% on hemodialysis, 15.4% with peritoneal dialysis, 6.7% with renal transplants). Aspirin increased the risk of stroke or systemic thromboembolism in all groups. However, warfarin increased the risk of bleeding in both CKD patients (HR, 1.36; 95% CI, 1.17–1.59; P<0.001) and dialysis-dependent patients (HR, 1.27; 95% CI, 0.91–1.77; P=0.15).[24]

Only few other trials analyzed patient populations with mild-to-moderate CKD. In an observational retrospective study of 399 patients with different stages of CKD and AF who were treated with warfarin to maintain an INR between 2.0 and 3.0 versus no warfarin, a significant reduction in the incidence of thromboembolic stroke (9% versus 26%; P<0.001) and an insignificant increase in the incidence of major bleeding (14% versus 9%) were observed. Focusing on the different degree of renal impairment, the incidence of thromboembolic stroke in patients treated with warfarin was significantly lower than in patients treated without warfarin, regardless of the CKD stage (stage 3: 10% versus 20%; P<0.05; stage 4: 5% versus 21%; P<0.05; stage 5: 10% versus 37%; P<0.001; hemodialysis patients: 10% versus 38%; P<0.005).[30]

A subgroup analysis of the Stroke Prevention in Atrial Fibrillation (SPAF) III trial, the only randomized study in this field, evaluated CKD stage 3 patients who were treated with dose-adjusted warfarin versus CKD stage 3 patients who were treated with a combination of aspirin and low-dose (1–3 mg) warfarin. Thus, a reduction in relative risk of ischemic stroke and systemic embolism of 76% under warfarin (95% CI, 42%–90%; P<0.001) was found; no difference in the incidence of major bleeding was observed.[31]

New Oral Anticoagulants

During the past years, 3 so-called new oral anticoagulant agents have been introduced. They directly intervene by inhibiting the activation of coagulation factors at the end of

the coagulation cascade. In contrary to warfarin, they are used in fixed doses, with no need for regular laboratory monitoring of INR. Because the new oral anticoagulant agents apixaban, dabigatran, and rivaroxaban are predominantly or partially excreted by the kidneys, only patients with CrCl ≥30 mL/min (dabigatran and rivaroxaban) or ≥25 mL/min (apixaban) were included in the trials.[32–35] The studies with apixaban and rivaroxaban used reduced doses for patients with CrCl <50 mL/min. Because of renal elimination, the new oral anticoagulants have a prolonged half-life in patients with CKD, resulting in enhanced antithrombotic efficacy and increased bleeding risk.

Apixaban

Apixaban is a direct oral factor Xa inhibitor with rapid absorption, a 12-hour half-life, and 25% renal excretion, which was recently approved in Europe, but not yet by the Food and Drug Administration, for the prevention of stroke and systemic embolism in patients with nonvalvular AF. Two phase 3 trials investigated the efficacy and safety of apixaban: the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial compared apixaban with aspirin in patients with AF,[32] and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial compared apixaban with warfarin.[33] In both trials, patients with an eGFR <25 mg/mL per 1.73m^2 were excluded, and patients with serum creatinine 1.5 to 2.5 mL/dL received a reduced dose of 2.5 mg apixaban BID instead of 5 mg BID. Compared with aspirin, apixaban significantly reduced the event rates of stroke and systemic embolism in patients with CKD stage 3 and with eGFR ≥ 60 mL/min per 1.73 m^2, but had no influence on major bleeding events.[32]

With regard to the comparison with warfarin, a secondary analysis of the ARISTOTLE trial compared the efficacy and safety outcome of apixaban with warfarin in relation to renal function.[33] Three different methods were used to account for renal function: the widely applied Cockcroft–Gault formula, the chronic kidney disease epidemiology collaboration (CKD-EPI) equation, and cystatin C. Applying the Cockcroft–Gault equation, the annualized stroke rate rose from 1.05% in patients with eGFR >80 mL/min to 2.39% in patients with eGFR ≤50 mL/min, and the incidence of major bleeding events tripled from 1.65% to 4.80%. Apixaban was more effective than warfarin in preventing stroke or systemic embolism, all-cause mortality, and major bleeding, irrespective of renal impairment and the eGFR equation used (Figure 1A and 1B). Importantly, patients with eGFR ≤50 mL/min had the greatest benefit from a reduction in major bleeding with apixaban (HR, 0.50; 95% CI, 0.38–0.66; *P* value for interaction, 0.005; using Cockcroft–Gault equation for estimating GFR; similar results for CKD-EPI and cystatin C).
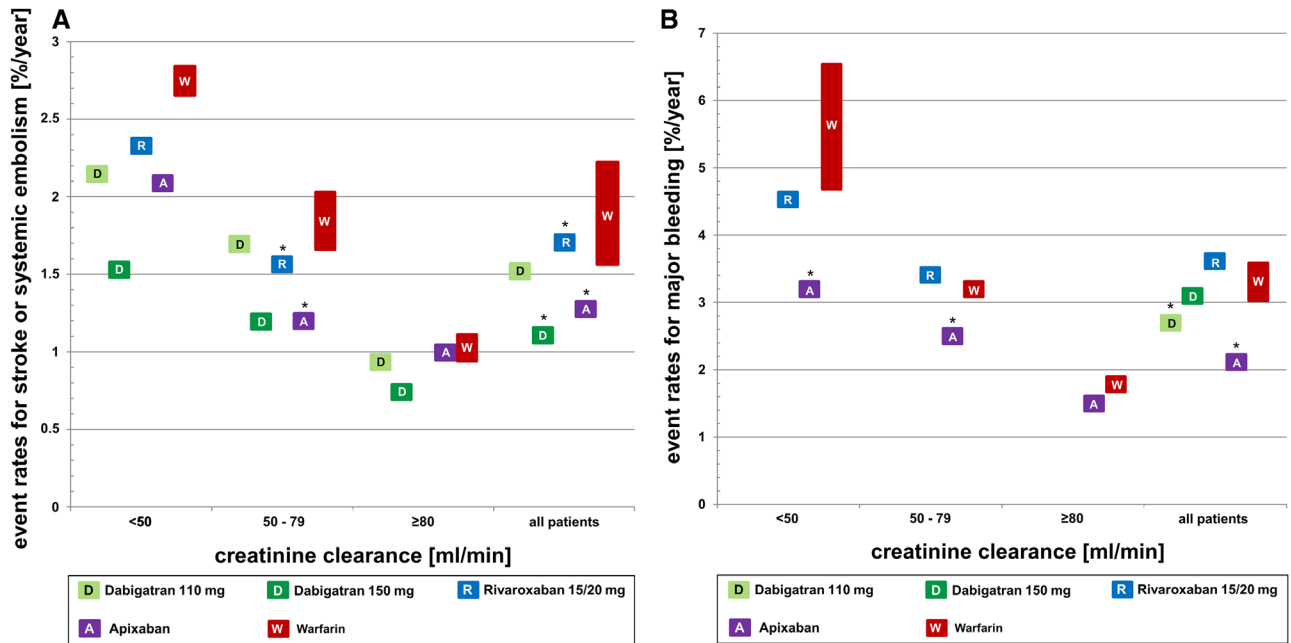
Dabigatran

Dabigatran is administered as the prodrug dabigatran etexilate that is rapidly converted by serum esterase to the direct thrombin inhibitor dabigatran. Approximately 80% of the unchanged drug is cleared renally.[36] The phase 3 Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial compared 2 fixed doses of dabigatran (110 mg and 150 mg BID) with open-label use of warfarin (INR adjusted to 2.0–3.0) in patients with AF and ≥1 risk factor for stroke. Patients with CrCl ≤30 mL/min were excluded. Overall, 150 mg dabigatran was superior to warfarin in the reduction of any stroke or systemic embolism (relative risk, 0.66; 95% CI, 0.53–0.82; *P*<0.001), as well as in the reduction of hemorrhagic (relative risk, 0.26; 95% CI, 0.14–0.49; *P*<0.001) and ischemic or unspecified stroke (relative risk, 0.76; 95% CI, 0.60–0.98; *P*=0.03; Figure 1A). Noninferiority was proven for 110 mg dabigatran versus warfarin for stroke or systemic embolism. Major bleedings were significantly reduced only at the 110 mg dosage (relative risk, 0.80; 95% CI, 0.69–0.93; *P*=0.003; Figure 1B). Subgroup analysis of patients with CrCl <50 mL/min, between 50 and 79 mL/min, and ≥80 mL/min revealed no significant treatment advantage of dabigatran compared with warfarin concerning stroke or systemic embolism.[34]

Since the approval of dabigatran, reports on adverse bleeding events in patients with reduced renal function led to a discussion about the safety of the drug. Therefore, there were several safety announcements, including 2 from the Food and Drug Administration.[37–39] A recent assessment of the risk of gastrointestinal bleeding and intracranial hemorrhage for new users of dabigatran compared with new users of warfarin showed that the bleeding rates seem not to be elevated under dabigatran compared with warfarin.[39]

Rivaroxaban

Rivaroxaban is a reversible, direct factor Xa inhibitor, with a rapid onset after oral administration. Approximately one third is eliminated by the kidney and two thirds by the liver. The phase 3 trial Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) compared rivaroxaban with warfarin in patients with nonvalvular AF with regard to moderate (CrCl, 30–49 mL/min) and mild renal insufficiency (CrCl ≥50 mL/min).[35] Event rates for stroke and systemic embolism were lower in patients treated with rivaroxaban (1.71%/y) than in the adjusted-dose warfarin group (2.16%/y; HR, 0.79; 95% CI, 0.66–0.96; *P*<0.001 for noninferiority; Figure 1A). Patients with moderate renal impairment experienced higher rates of stroke and systemic embolism than patients with mild renal dysfunction. There was a trend for reduction of stroke and systemic embolism under rivaroxaban in patients with CrCl 30 to 49 mL/min (HR, 0.84; 95% CI, 0.57–1.23) and with CrCl ≥50 mL/min (HR, 0.78; 95% CI, 0.63–0.98), although rates for ischemic stroke were slightly enhanced in patients with moderate renal insufficiency (rivaroxaban: 1.98%/y, warfarin 1.78%/y; HR, 1.11; 95% CI, 0.71–1.73; Figure 1A). Bleeding events occurred more often in patients with renal insufficiency than in patients without. Patients with renal impairment showed comparable bleeding rates under treatment of rivaroxaban versus warfarin (17.82%/y versus 18.28%/y, HR, 0.98; 95% CI, 0.84–1.14; Figure 1B), but with significant reduction of critical organ bleeding and fatal bleeding. There was no excess bleeding in patients with mild CKD under rivaroxaban or warfarin.

Figure 1. A, Annual event rate of stroke or systemic embolism at different degrees of renal impairment and in the whole study population reported by the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (dabigatran),[34] the Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial (rivaroxaban),[35] and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (apixaban).[33] **B**, Annual event rate of major bleeding events at different degrees of renal impairment and in the whole study population reported by the RE-LY trial (dabigatran),[34] the ROCKET-AF trial (rivaroxaban),[35] and the ARISTOTLE trial (apixaban).[33] Asterisks mark significant differences of the applied drug compared with warfarin. Each bar, including its height, indicates the ranges of the reported event rates for the specific drugs in these trials (**top**=upper range limit, **bottom**=lower range limit).

In a post hoc analysis of the ROCKET-AF trial, prior stroke or transient ischemic attack, as well as impaired renal function, was strong predictors of new stroke or systemic embolism during follow-up. For every decrease in CrCl of 10 mL/min, the HR increased by 12% (HR, 1.12; 95% CI, 1.07–1.16; *P*<0.0001). Thus, the authors concluded that future stroke risk stratification should also consider renal impairment (see below).[40]

CKD Stage and Oral Anticoagulation

In general, it has to be kept in mind that several methods to determine the GFR are available: measurement of the physiological GFR by 24-hour urine has been found to be unreliable, and therefore a calculated or so-called eGFR is preferred.[1] However, with the 3 most frequently used equations (Cockroft–Gault, modification of diet in renal disease, and CKD-EPI), slight to moderate differences in the eGFR may become apparent and result in a different classification of a patient into a distinct CKD stage. For instance, the above cited post hoc analysis of the ARISTOTLE trial found only a significant reduction of stroke by apixaban in the subgroup of patients with an eGFR of 25 to 50 mL/min if this was calculated by the CKD-EPI equation but not if determined by the Cockroft–Gault formula or measurement of the biomarker cystatin C. Similar differences in some, but not all, other end points (death, bleedings) were observed depending on which method was used.[33] Therefore, further studies should at least also use different GFR estimations to reveal if this has impact on the results; furthermore, future trials identifying the best equation seem to be recommended.

Apart from these methodological aspects, available data indicate that patients without need for dialysis (CKD stages 1–4) should receive oral anticoagulation for prevention of stroke. This has been shown for vitamin K antagonists as well as for all new oral anticoagulants. In general, current guidelines clearly favor the new oral anticoagulants (class I recommendation) in all patients who have difficulties to meet the therapeutic INR range of 2 to 3. New oral anticoagulants should be the preferred choice of treatment in patients with nonvalvular AF (class IIa). Importantly, the benefits of the new anticoagulants seem to be larger in more advanced CKD stages (Figure 1A and 1B). Because head-to-head comparisons of the new oral anticoagulants regarding their efficacy in preventing stroke are lacking, a recommendation for a preferred use of any of the new drugs can currently not be made.[41]

For patients on chronic dialysis (CKD stage 5), data are conflicting and difficult to interpret: although some trials reported a markedly worse outcome with oral anticoagulation,[20,29] others suggested a clear benefit[24,42] or found at least no harm.[28] A straightforward recommendation for oral anticoagulation in hemodialysis patients can, therefore, not be given. But one has to be aware: Withholding standard therapies in patients with CKD may be one major reason for worse outcome and poor prognosis.[43,44] A reasonable solution for this dilemma could be an individualized algorithm that takes both the stroke and the bleeding risk into concern.

Stratification

It has to be kept in mind that all current risk scores and stratification algorithms have been evaluated in patients without

Paroxysmal, persistant or permanent atrial fibrillation in patients with renal disease (calculated GFR < 60 ml/min/1.73m²)

CHADS₂ score

Cardiac failure	Diabetes
Hypertension	Stroke (double)
Age ≥ 75 years	

CHADS₂ score ≥ 2 points

CHADS₂ score < 2 points

Age ≥ 75 years

yes

no

**Age 65 - 74 years
Female sex
Vascular heart disease**

≥ 1 point *

no

Consider bleeding risk (HAS-BLED score)

Hypertension	Previous bleedings
Abnormal renal and/or liver function	Labile INRs
	Elderly (age > 65 yrs)
Stroke	Drugs or alcohol

Additional factors: Recurrent falls, dementia, active malignancies

High bleeding risk

Low to intermediate bleeding risk

No oral anticoagulation

Use of platelet-inhibitors in patients with CHD or PVD or CVD as recommended according to guidelines.

Oral anticoagulation

New Oral Anticoagulants
- only in patients with eGFR >30 ml/min or >25 ml/min for apixaban, respectively
- consider different dosages depending on CKD stages as indicated in the drug information
- control serum creatinine/eGFR regularly

No special recommendation for any of the 3 drugs could be made in CKD patients at current.

Warfarin/Phenprocoumon (independant of eGFR)
- target INR 2.0-2.5
- no starting dose of more than 5 mg/day
- determine first INR after two doses
- during the first month, control INR three times a week
- during long-term treatment, control INR at least every 14 days

Figure 2. Stratification algorithm for oral anticoagulation in patients with renal disease and persistent, paroxysmal, or permanent atrial fibrillation. *For patients with 1 risk score point, the current guidelines recommend either oral anticoagulants (stating that this is preferred) or 75 to 325 mg aspirin daily. This has to be outlined in this context, because all the patients included here have also renal failure and thereby present with 1 additional important risk factor, which is currently not implemented in the guidelines. CHD indicates coronary heart disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; and PVD, peripheral vascular disease.

CKD or without concern of CKD. As described above, there is, however, clear evidence that reduced renal function is an independent and important risk factor for thromboembolism.[22–24,44] Recently, for the first time a large database from a randomized trial (ROCKET-AF) was retrospectively used to establish a score that also includes renal failure.[40] It found that implementing additional risk points into the CHADS₂ score markedly increased the predictive value for ischemic stroke. However, this so-called R₂CHADS₂ score should be evaluated prospectively to determine whether it correctly identifies high-risk patients. The problem associated with the R₂CHADS₂ score is that it accounts only for eGFR rates <60 mL/min, but not <30 mL/min or if the patient depends on dialysis.

In contrary, a recent French retrospective evaluation including 5912 patients could not find that taking concern of CKD stage improved the risk stratification by CHADS₂ or CHA₂DS₂-VASc score significantly, but there was a trend.[45]

As reported above, oral anticoagulation is the gold standard for the prevention of thromboembolism in patients with AF. Nevertheless, we know from several reports that patients with CKD receive standard therapies markedly less often than patients with normal renal function and that this is one main contributor to poor prognosis.[43,44] We, therefore, present an update of a previously presented algorithm[44] that takes these circumstances into concern, as well as some special issues about how to start and maintain oral anticoagulation in such patients, with the primary goal to improve prevention in this high-risk population (Figure 2).

For all patients with CKD, the stroke risk should be determined using the CHA₂DS₂-VASc score as recommended in current guidelines.[6] If patients have no increased risk for stroke, no oral anticoagulation is needed, and at current it would be hardly possible to give oral anticoagulation to a patient with CKD only. However, this scenario is quite unlikely because most patients with CKD have additional risk factors.

If patients turn out to have an increased risk (CHADS$_2$ score ≥2 or ≥1 of the additional listed factors), the bleeding risk should be estimated subsequently. Thus, risk factors from the HAS-BLED bleeding risk score and others as displayed should be taken into concern. However, because nearly all of these high-risk patients have a HAS-BLED score of ≥3 (age, renal failure+mostly ≥1 other), we in contrary to the AF guidelines find an exact decision threshold difficult to determine. Recent reports about the HAS-BLED score[46] and other bleeding rules[47] showed that numeric calculations of bleeding risks represent rather an illusion of quantitative correctness than the true risk of future bleedings. Therefore, risks and benefits should preferably be weighted by the physician for each patient individually.

If oral anticoagulation is not indicated, platelet inhibitors should be preserved for patients with arteriosclerotic disease, but not as an alternative for oral anticoagulation for prevention of stroke in AF because platelet inhibitors increased bleeding without preventing thromboembolism risk in AF patients with CKD.[24,29]

In general, oral anticoagulation should be recommended for the majority of patients with a high risk for stroke and with low-to-intermediate risk of bleeding. If oral anticoagulation is initiated, complication rates under oral anticoagulation have been shown to be lower if the starting dosages are given carefully with intensified controls during the first weeks.[44] Bleeding rates are highest during the first 6 to 8 weeks. If a patient is already on oral anticoagulation without complications for some months, a withdrawal of the medication in the presence of a high CHADS$_2$ score is potentially dangerous and should be monitored closely.

Disclosures

References

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1–S266.
2. Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012;379:165–180.
3. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health*. 2008;8:117.
4. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, et al. Prevalence of chronic kidney disease in the United States. *JAMA*. 2007;298:2038–2047.
5. Stevens LA, Viswanathan G, Weiner DE. Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance. *Adv Chronic Kidney Dis*. 2010;17:293–301.
6. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.
7. Horio T, Iwashima Y, Kamide K, Tokudome T, Yoshihara F, Nakamura S, et al. Chronic kidney disease as an independent risk factor for new-onset atrial fibrillation in hypertensive patients. *J Hypertens*. 2010;28:1738–1744.
8. Alonso A, Lopez FL, Matsushita K, Loehr LR, Agarwal SK, Chen LY, et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. *Circulation*. 2011;123:2946–2953.
9. Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on risk of incident atrial fibrillation and subsequent survival in medicare patients. *J Am Heart Assoc*. 2012;1:e002097.
10. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation*. 2013;127:569–574.
11. Soliman EZ, Prineas RJ, Go AS, Xie D, Lash JP, Rahman M, et al; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J*. 2010;159:1102–1107.
12. Ananthapanyasut W, Napan S, Rudolph EH, Harindhanavudhi T, Ayash H, Guglielmi KE, et al. Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. *Clin J Am Soc Nephrol*. 2010;5:173–181.
13. Baber U, Howard VJ, Halperin JL, Soliman EZ, Zhang X, McClellan W, et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Circ Arrhythm Electrophysiol*. 2011;4:26–32.
14. 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.
15. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
16. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98:946–952.
17. Nakagawa K, Hirai T, Takashima S, Fukuda N, Ohara K, Sasahara E, et al. Chronic kidney disease and CHADS(2) score independently predict cardiovascular events and mortality in patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2011;107:912–916.
18. Abbott KC, Trespalacios FC, Taylor AJ, Agodoa LY. Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality. *BMC Nephrol*. 2003;4:1.
19. Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, et al. Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. *Am J Kidney Dis*. 2008;51:255–262.
20. Wizemann V, Tong L, Satayathum S, Disney A, Akiba T, Fissell RB, et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. *Kidney Int*. 2010;77:1098–1106.
21. Vázquez E, Sánchez-Perales C, Lozano C, García-Cortés MJ, Borrego F, Guzmán M, et al. Comparison of prognostic value of atrial fibrillation versus sinus rhythm in patients on long-term hemodialysis. *Am J Cardiol*. 2003;92:868–871.
22. Go AS, Fang MC, Udaltsova N, Chang Y, Pomernacki NK, Borowsky L, et al; ATRIA Study Investigators. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2009;119:1363–1369.
23. Nakayama M, Metoki H, Terawaki H, Ohkubo T, Kikuya M, Sato T, et al. Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population–the Ohasama study. *Nephrol Dial Transplant*. 2007;22:1910–1915.
24. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367:625–635.
25. US Renal Data System. *USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes, and Digestive and Kidney Diseases, Bethesda, MD, 2006.
26. Kuriyama N, Mizuno T, Ohshima Y, Yamada K, Ozaki E, Shigeta M, et al. Intracranial deep white matter lesions (DWLs) are associated with chronic kidney disease (CKD) and cognitive impairment: a 5-year follow-up magnetic resonance imaging (MRI) study. *Arch Gerontol Geriatr*. 2013;56:55–60.
27. Wada M, Nagasawa H, Iseki C, Takahashi Y, Sato H, Arawaka S, et al. Cerebral small vessel disease and chronic kidney disease (CKD): results of a cross-sectional study in community-based Japanese elderly. *J Neurol Sci*. 2008;272:36–42.
28. Engelbertz C, Reinecke H. Atrial fibrillation and oral anticoagulation in chronic kidney disease. *JAFIB*. 2012;4:89–100.

29. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol*. 2009;20:2223–2233.

30. Lai HM, Aronow WS, Kalen P, Adapa S, Patel K, Goel A, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. *Int J Nephrol Renovasc Dis*. 2009;2:33–37.

31. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:2599–2604.

32. Eikelboom JW, Connolly SJ, Gao P, Paolasso E, De Caterina R, Husted S, et al. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. *J Stroke Cerebrovasc Dis*. 2012;21:429–435.

33. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33:2821–2830.

34. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.

35. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387–2394.

36. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J*. 2009;157:805–10, 810.e1.

37. FDA Drug Safety Communication: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate). FDA U.S. Food and Drug Administration web site. http://www.fda.gov/Drugs/DrugSafety/ucm282724.htm. Accessed March 05, 2013.

38. FDA Drug Safety Communication: update on the risk for serious bleeding events with the anticoagulant Pradaxa (dabigatran). FDA U.S. Food and Drug Administration web site. http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm. Accessed March 05, 2013.

39. Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med*. 2013;368:1272–1274.

40. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R2CHADS2 index in the ROCKET AF and ATRIA Study Cohorts. *Circulation*. 2013;127:224–232.

41. Lip GY, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. *J Am Coll Cardiol*. 2012;60:738–746.

42. Knoll F, Sturm G, Lamina C, Zitt E, Lins F, Freistätter O, et al. Coumarins and survival in incident dialysis patients. *Nephrol Dial Transplant*. 2012;27:332–337.

43. McCullough PA. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? *J Am Coll Cardiol*. 2003;41:725–728.

44. Reinecke H, Brand E, Mesters R, Schäbitz WR, Fisher M, Pavenstädt H, et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. *J Am Soc Nephrol*. 2009;20:705–711.

45. Banerjee A, Fauchier L, Vourc'h P, Andres CR, Taillandier S, Halimi JM, et al. 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.

46. Donzé J, Rodondi N, Waeber G, Monney P, Cornuz J, Aujesky D. Scores to predict major bleeding risk during oral anticoagulation therapy: a prospective validation study. *Am J Med*. 2012;125:1095–1102.

47. Dahri K, Loewen P. The risk of bleeding with warfarin: a systematic review and performance analysis of clinical prediction rules. *Thromb Haemost*. 2007;98:980–987.