Oral Anticoagulation in Chronic Kidney Disease and Atrial Fibrillation

The Use of Non-Vitamin K-Dependent Anticoagulants and Vitamin K Antagonists

Gunnar H. Heine, Vincent Brandenburg, Stephan H. Schirmer

Summary

Background: Cardiological societies recommend, in their guidelines, that patients with atrial fibrillation and an intermediate (or higher) risk of stroke and systemic embolization should be treated with oral anticoagulant drugs. For patients who do not have mitral valve stenosis or a mechanical valve prosthesis, non-vitamin-K dependent oral anticoagulants (NOAC) are preferred over vitamin K antagonists (VKA) for this purpose. It is unclear, however, whether patients with chronic kidney disease and atrial fibrillation benefit from oral anticoagulation to the same extent as those with normal kidney function. It is also unclear which of the two types of anticoagulant drug is preferable for patients with chronic kidney disease; NOAC are, in part, renally eliminated.

Methods: This review is based on pertinent publications retrieved by a selective literature search, and on international guidelines.

Results: Current evidence suggests that patients with atrial fibrillation who have chronic kidney disease with a glomerular filtration rate (GFR) above 15 mL/min/1.73 m² should be treated with an oral anticoagulant drug if they have an at least intermediate risk of embolization, as assessed with the CHA2DS2-VASc score. For patients with advanced chronic kidney disease (GFR from 15 to 29 mL/min/1.73 m²), however, this recommendation is based only on registry studies. For dialysis patients with atrial fibrillation, decisions whether to give oral anticoagulant drugs should be taken on an individual basis, in view of the elevated risk of hemorrhage and the unclear efficacy of such drugs in these patients. The subgroup analyses of the NOAC approval studies show that, for patients with atrial fibrillation and chronic kidney disease with a creatinine clearance of >25–30 mL/min, NOAC should be given in preference to VKA, as long as the patient does not have mitral valve stenosis or a mechanical valve prosthesis. For those whose creatinine clearance is less than 25 mL/min, the relative merits of NOAC versus VKA are still debated.

Conclusion: The cardiological societies’ recommendation that patients with atrial fibrillation should be given oral anticoagulant drugs applies to the majority of such patients who also have chronic kidney disease.

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The prevalence and prognostic importance of atrial fibrillation in chronic kidney disease

In the general population without overt kidney disease, the incidence and prevalence of atrial fibrillation are highly correlated with age (4, 5). In CKD patients, atrial fibrillation is notably more common, which is partly due to the fact that risk factors for this arrhythmia—such as older age, arterial hypertension, hypertensive and ischemic heart disease, or hemodynamically relevant valvular changes—accumulate particularly in this population subgroup.

The incidence of atrial fibrillation per 1000 patient years in a nationwide study of the general population in Taiwan was 5.0 events; in CKD patients not requiring dialysis it was 7.3 events; and in dialysis patients, 12.1 events (6).

In a systematic cross-sectional analysis from Austria, 26.5% of all hemodialysis patients in Vienna had prevalent atrial fibrillation (7), as did one in every five CKD patients who were not dialysis-dependent in the large US chronic renal insufficiency cohort (CRIC) (e1), whereas the prevalence in the adult general population is 3% (4, 5). Investigations of the CRIC also showed that atrial fibrillation is a prognostic marker of CKD progression (8). The prevalence of atrial fibrillation is expected to rise further over the coming decades (9).

In addition to its pathophysiological role in (systolic and diastolic) heart failure, the prognostic
importance and therapeutic relevance of atrial fibrillation follows in particular from the risk of intracardiac thrombus formation with subsequent systemic and cerebral embolisms. The latter often trigger strokes that are more severe than strokes of another pathogenesis and which in epidemiological studies have been associated with higher morbidity—for example, after adjustment, a 2.2 increase in confinement to bed in a US cohort study (10)—and case fatality. The case fatality rate at one year was 49.5% versus 27.1% in an Italian cohort study when patients with strokes of different etiologies (atrial fibrillation versus another pathogenesis) were compared (11).

**Thromboembolic prophylaxis using oral anticoagulants**

In patients with atrial fibrillation who have healthy kidneys, the risk for stroke and systemic thromboembolism (henceforth referred to as risk of embolism) was lowered by two-thirds by giving oral anticoagulation medication, whereas thrombocyte aggregation inhibitors are notably less effective (12, 13). The indication for oral anticoagulation depends on the individual embolism risk. Consequently, patients after mechanic valve replacement or with moderate to severe mitral valve stenosis are at a very high risk of developing embolism, and oral anticoagulants are urgently indicated. In all other patients, a risk assessment should be undertaken, using CHA2DS2-VASc scores (Table 1). Oral anticoagulants are not required if the embolism risk is very low—a CHA2DS2-VASc score of 0–1 in men and 1–2 in women.

In parallel, the risk of hemorrhage in patients receiving oral anticoagulants should be estimated—for example, by using the HAS-BLED score (Table 1). In a scenario of an increased hemorrhage risk (HAS-BLED score ≥ 3 [23]), risk factors for hemorrhages should be minimized, but if possible oral anticoagulation should be continued, as risk factors for embolisms and hemorrhages overlap (14) and even patients with a raised hemorrhage risk will benefit from oral anticoagulation.

In CKD patients with atrial fibrillation, the overlapping risk of embolism and hemorrhage is particularly clear: the patients mostly have a high risk of embolism, which is already obvious from their high CHA2DS2-VASc scores. Several cohort studies showed that the CHA2DS2-VASc score allows stratification of the embolism risk even in CKD patients; the integration of renal function parameters into the CHA2DS2-VASc score does not improve its predictive value (15).

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**TABLE 1**

<table>
<thead>
<tr>
<th>CHA2DS2-VASc risk factors</th>
<th>Points</th>
<th>HAS-BLED risk factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heart failure</td>
<td>+1</td>
<td>Hypertension ≥ 160 mm Hg systolic</td>
<td>+1</td>
</tr>
<tr>
<td>Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
<td>Renal dysfunction</td>
<td>+1</td>
</tr>
<tr>
<td>Resting blood pressure &gt;140/90 mm Hg in at least two measurements or under antihypertensive therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75 years</td>
<td>+2</td>
<td>Liver injury</td>
<td>+1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>+1</td>
<td>Previous stroke</td>
<td>+1</td>
</tr>
<tr>
<td>Fasting glucose &gt;125 mg/dL or medication (oral antidiabetic drugs ± insulin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous stroke, transient ischemic attack or thromboembolism</td>
<td>+2</td>
<td>Previous hemorrhage/predisposition for hemorrhage (anemia)</td>
<td>+1</td>
</tr>
<tr>
<td>Vascular disorder</td>
<td>+1</td>
<td>Labile international normalized ratio (INR) (time period in therapeutic target area &lt;60%)</td>
<td>+1</td>
</tr>
<tr>
<td>Previous myocardial infarction, peripheral-arterial occlusive disease or aortic plaques</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>+1</td>
<td>Age &gt;65 years</td>
<td>+1</td>
</tr>
<tr>
<td>Female sex</td>
<td>+1</td>
<td>Medications (thrombocyte aggregations inhibitors, non-steroidal anti-inflammatory drugs)</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alcohol (≥ 8 drinks/week)</td>
<td>+1</td>
</tr>
</tbody>
</table>

CHA2DS2-VASc: congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes, stroke (2 points), vascular disease, age (65–74 years), sex category (female). The adjusted stroke risk dependent on the CHA2DS2-VASc Score is <1 % (0 points), 1.3% (1 point), 2.2% (2 points), 3.2% (3 points), 4.5% (4 points), 6.7% (5 points), 9.6% (6 points), 9.6% (7 points), 6.7% (8 points), and 15.2% (9 points) [23].

HAS-BLED: hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile INR, elderly, drugs or alcohol (1 point each)

INR: international normalized ratio

1 Chronic dialysis dependency, renal transplantation, or serum creatinine ≥ 200 µmol/L.

2 Chronic liver disease was defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, and so forth

NB: Most studies of the epidemiology of atrial fibrillation are from the US and European countries other than Germany; In Germany, phenprocoumon, rather than warfarin is used as the vitamin K antagonist.
On the other hand, impaired renal function massively increases the risk of hemorrhage in patients taking oral anticoagulants (16), for example, owing to uremic thromboocyte function disorder and hemo-dialysis patients’ additional intermittent exposure to heparin. In contrast to the CHA²DS₂-VASc score as a predictor of embolism risk, several risk scores for hemorrhage, such as the HAS-BLED score (Table 1), include CKD as an independent risk factor.

Furthermore, vitamin K antagonists (VKA) are associated with two additional complications in CKD patients:

- VKA prevent the activation of vitamin K dependent calcification inhibitors, especially matrix-gla proteins, which at least experimentally accelerates vascular calcification (17–19). The association of VKA intake with calciphylaxis (calcific uremic arteriopathy)—a rare but life-threatening systemic disorder in dialysis patients (17, 20)—suggests the possible clinical relevance of these experiments. Currently, a randomized trial is comparing the progression of aortic valve and coronary calcification in patients taking phenprocoumon versus NOAC (NCT02066662).

- Subgroup analyses from clinical studies imply that VKA administration in dosages exceeding the therapeutic range (target international normalized ratio [INR] of 2.0–3.0) drives the progression of CKD, which may be explained with recurring subclinical bleeds into the renal tubule system and subsequent tubular necrosis (21).

For this reason, VKA do not seem to be the optimal treatment strategy for CKD patients. Additionally, a consensus protocol from the nephrological KDIGO (Kidney Disease—Improving Global Outcome) guideline group speaks out against anticoagulation of dialysis patients with atrial fibrillation for the primary prophylaxis of ischemic stroke (22). What is of note is the fact that the German licensing approval for phenprocoumon versus NOAC (NCT02066662).

The European Society of Cardiology (ESC) assumes that the German licensing approval for phenprocoumon versus NOAC (NCT02066662).

In the interdisciplinary care of CKD patients with atrial fibrillation, two central topics present themselves for discussion:

- Should people with chronic kidney disease be given oral anticoagulants in the same way as people without kidney disease, in atrial fibrillation with a moderate to high embolism risk?

- If patients with CKD and atrial fibrillation benefit from oral anticoagulation, should VKA or NOAC be the preferred option?

### Oral anticoagulants in advanced chronic kidney disease and atrial fibrillation

Randomized trials of the effectiveness of oral anticoagulation in atrial fibrillation have generally excluded patients with higher-grade CKD (Figure 1). A single one of these studies included a subgroup analysis and showed that at least persons with moderate CKD (estimated glomerular filtration rate [eGFR] of 30–59 mL/min/1.73 m²) benefit from therapeutic anticoagulation with warfarin (target INR of 2.0–3.0) and experience fewer strokes and systemic embolisms than patients

**FIGURE 1**

![Diagram showing the prevalence of atrial fibrillation and the risk of stroke and systemic embolism in patients with CKD of different stages, comparing VKA and NOAC.](image-url)

Epidemiological importance and potential therapeutic consequences of atrial fibrillation over the spectrum of chronic kidney disease

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR</th>
<th>Risk of stroke and systemic embolism (SSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKD</td>
<td>≥60</td>
<td>OAK reduces risk for SSE</td>
</tr>
<tr>
<td>CKD G 1–2</td>
<td>45–59</td>
<td>RCT</td>
</tr>
<tr>
<td>CKD G 3a</td>
<td>30–44</td>
<td>RCT</td>
</tr>
<tr>
<td>CKD G 3b</td>
<td>15–29</td>
<td>RCT</td>
</tr>
<tr>
<td>CKD G 4</td>
<td>≤15</td>
<td>NOAC are at least non-inferior to VKA and partly superior</td>
</tr>
</tbody>
</table>

In the interdisciplinary care of CKD patients with atrial fibrillation, two central topics present themselves for discussion:

- Should people with chronic kidney disease be given oral anticoagulants in the same way as people without kidney disease, in atrial fibrillation with a moderate to high embolism risk?

- If patients with CKD and atrial fibrillation benefit from oral anticoagulation, should VKA or NOAC be the preferred option?
FIGURE 2

![Atrial fibrillation flowchart]

Treatment algorithm of patients with atrial fibrillation and normal renal function or chronic kidney disease not requiring dialysis (modified from [24])

CHA₂DS₂-VASc: see Table 1; m: male patients; NOAC: non–vitamin K dependent oral anticoagulants; OAC: oral anticoagulation; VKA: vitamin K antagonists; f: female patients

The colors of the boxes indicate the evidence for oral anticoagulation (green: no indication for OAC; blue: consider OAC; red: OAC indicated)

receiving subtherapeutic (which is unusual these days) warfarin treatment (1–3 mg; mean INR 1.3) in combination with 325 mg acetylsalicylic acid (ASA) (26).

Randomized trials of the benefits of anticoagulation on patients with an eGFR <30 mL/min/1.73 m² are lacking. For this reason, recourse is often taken to cohort studies of varying quality, in which mostly retrospective data are evaluated and no stringent distinction is made between hemorrhagic and ischemic strokes. These analyses have caused certain concerns because initial registry studies in dialysis patients with atrial fibrillation who were treated by oral anticoagulation using VKA partly observed an increase rather than a decrease in strokes (27, 28). Several studies with contradictory results followed, which were recently pooled in a meta-analysis: VKA did not reduce the risk of stroke in 56 146 dialysis patients with atrial fibrillation, and hemorrhagic complications increased by 20% (29).

In patients with severe CKD and atrial fibrillation who did not require dialysis, methodologically similar retrospective studies did, however, suggest advantages for oral anticoagulants. In a large cohort study from Alberta, oral anticoagulants in patients not requiring dialysis, with an eGFR <30 mL/min/1.73 m² and incident atrial fibrillation, led to a similarly relative risk reduction for cerebral ischemia as in patients with normal or moderately impaired kidney function (30). The absolute risk of stroke and hemorrhage rose as expected with increasing renal insufficiency in the group of patients taking anticoagulants as well as in patients without anticoagulation (30).

In sum, in our opinion an indication for oral anticoagulation exists in patients with CKD G 1–G 4 (eGFR ≥ 15 mL/min/1.73 m²), as far as a sufficiently high risk of embolism exists (CHA₂DS₂-VASc score ≥ 1 in men, CHA₂DS₂-VASc score ≥ 2 in women) (Figure 2). In CKD G 5 (dialysis-dependent), the decision about oral anticoagulation (or not) will have to be made individually for each patient (Figure 3). Alternatives to oral anticoagulation that could be discussed include not using any anticoagulants at all outside the dialysis treatment, daily subcutaneous injections of low molecular weight heparin while monitoring anti-factor-Xa activity, or interventional left atrial appendage occlusion combined with time-restricted administration of thrombocyte aggregation inhibitors (24).

Although this recommendation is based on registry studies alone in patients with an eGFR <30 mL/min/1.73 m² and in such patients, sufficiently powered randomized trials are desirable, which compare the administration of oral anticoagulants with no anticoagulation at all, such studies are currently unfortunately not even in the planning stages.

**Vitamin K antagonists or non-vitamin K dependent oral anticoagulants**

The ESC guidelines prefer in almost all patients with atrial fibrillation and indication for oral anticoagulation NOAC over VKA (24). Only after mechanical valve replacement or in moderate to severe mitral valve stenosis, a compelling indication exists for VKA (24).

This preference results from registration studies in which all NOAC under investigation were at least as effective as thromboembolism prophylaxis and at least as safe as warfarin regarding the risk of hemorrhage (24), but, in particular, they halved the risk of intracerebral hemorrhage (31). These results were confirmed several times in retrospective cohort analyses after the medications had been introduced to market (32–35). In these comparison studies, warfarin (which is more commonly used in the international setting) was used rather than phenprocoumon (which is more commonly used in Germany), and meaningful randomized comparison studies between phenprocoumon and NOAC are lacking. But warfarin and phenprocoumon differ merely pharmacokinetically, not pharmacodynamically. A German cohort study comparing NOAC and phenprocoumon yielded similar results as the comparison of NOAC and warfarin (36).

Further advantages of NOAC include more stable pharmacokinetics. For this reason, the coagulation status does not have to be checked regularly in order
to adjust the dose when NOAC are used, in contrast to VKA. The much shorter half-life of NOAC allows for rapid onset and attenuation of coagulation inhibition; in contrast to VKA, initial and peri-interventional heparin bridging is obsolete. For dabigatran, a specific safe and rapidly effective antagonist is available in the shape of idarucizumab; market approval of an antagonist to rivaroxaban, apixaban, and edoxaban can probably be expected in 2018. As idarucizumab—like dabigatran—is eliminated by the kidneys to a relevant degree, impaired renal function does not affect the effect of idarucizumab. Dosage adjustments of idarucizumab are therefore not recommended in impaired renal function. By contrast, the effect of VKA can be counteracted with a delay by administering vitamin K or rapidly by giving clotting factors.

The disadvantage of NOAC is their greater cost and, especially in multimorbid CKD patients, potential interactions with other medications.

Subgroup analyses of the registration studies imply that patients with moderate CKD (G 3 a–b; GFR 30–59 mL/min/1.73 m²) can be treated at least equally effectively and safely by using NOAC as patients without renal disease (37).

The effectiveness and safety of NOAC in patients with CKD G 4 (eGFR 15–29 mL/min/1.73 m²) is the subject of rather more controversial discussion; occasionally, their use is advised against if the eGFR is <30 mL/min/1.73 m² (38). The central argument is that the randomized trials excluded patients with a creatinine clearance <25–30 mL/min.

However, this overlooks the fact that this exclusion criterion was checked at the start of the study. CKD is a progressive condition, with a median annual drop in the eGFR of −2.5 mL/min/1.73 m² (39, 40), which means that in many patients with a creatinine clearance scarcely above the threshold of 25–30 mL/min at the start of the study, renal function fell below this threshold over several years in the study. Unfortunately, no subgroup analyses of such patients have been published to date.

Furthermore, eGFR and creatinine clearance should not be considered identical (Table 2). The large registration studies of NOAC and the licensing authorities used creatinine clearance as estimated by the Cockcroft–Gault formula, whereas for the purposes of categorizing the stages of CKD, the eGFR is estimated by using the CKD-EPI_Creatinine equation (epidemiology collaboration, EPI). While the CKD-EPI_Creatinine equation allows for precise estimation of the real GFR, creatinine clearance as estimated by using the Cockcroft–Gault formula often notably exceeds the actual GFR (37). Finally, the CKD-EPI_Creatinine equation—different to the Cockcroft–Gault formula—provides a body-weight adjusted estimate of kidney function. The results of both formulas are therefore reported using different units (mL/min/1.73 m² versus mL/min). The clinical consequence of these methodological considerations is that some patients with CKD G 4 (eGFR 15–29 mL/min/1.73 m²) have a creatinine clearance of >25–30 mL/min. This means that for these patients from the subgroup analyses of the registration studies (37)—as discussed—evidence exists for the effectiveness and safety of NOAC compared with VKA. A further consequence is that NOAC dosages have to be adjusted to the creatinine clearance, not the eGFR. Whenever creatinine is measured, many laboratories report, however, the eGFR, rather than the creatinine clearance, because the eGFR can be calculated without knowing a patient’s body weight. If NOAC are the medication of choice, the treating physician will therefore have to calculate the estimated creatinine clearance—for example, by using online programs, such as www.uks.eu/home. If a doctor wrongly relies on the eGFR, dosage errors of prognostic relevance may ensue (e2, e3).

If NOAC in advanced CKD are rejected because of lacking randomized trials, the use of VKA should logically also be questioned, since their benefits and risks in advanced CKD have not been studied in randomized trials either. On this background, rivaroxaban, apixaban, and edoxaban were licensed in Europe in patients with a creatinine clearance of 15–30 mL/min at adjusted dosages; in the US, rivaroxaban and apixaban are even licensed for use in dialysis patients. This licensing approval was granted on the basis of small pharmacokinetic studies (e4–e6).

### Table 2

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>eGFR (mL/min)</th>
<th>Creatinine Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G 1</td>
<td>&gt;90</td>
<td>&gt;100</td>
</tr>
<tr>
<td>G 2</td>
<td>60–89</td>
<td>3–5</td>
</tr>
<tr>
<td>G 3 a-b</td>
<td>30–59</td>
<td>2–3</td>
</tr>
<tr>
<td>G 4</td>
<td>15–29</td>
<td>1–2</td>
</tr>
<tr>
<td>G 5</td>
<td>&lt;15</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>NOAC*</th>
<th>VKA</th>
<th>Mechanical valve/moderate or severe mitral stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OAC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk assessment (CHA2DS2-VASc)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low molecular weight heparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left atrial appendage occlusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No therapy</td>
</tr>
</tbody>
</table>

* Further details on selection and dosage of NOAC are in Table 2.
Currently ongoing randomized trials are investigating the effectiveness and safety of NOAC in patients with advanced CKD and atrial fibrillation (NCT02933697; NCT02942407).

In sum, on the basis of these data we recommend for patients with CKD G 3a–b—who in almost all cases have a creatinine clearance of >25–30 mL/min—and for patients with CKD G 4 and a creatinine clearance of >25–30 mL/min the preferential use of NOAC in atrial fibrillation. Rivaroxaban, apixaban, and edoxaban seem superior to dabigatran because of their lesser accumulation in CKD (Table 2). For patients with CKD G 4 and a creatinine clearance of <25 mL/min and for dialysis patients, we regard the use of NOAC—which entails a residual risk of embolism and hemorrhage—as possible alternatives, where the indication for oral anticoagulation exists. Closing the gap in the evidence for patients with CKD G 4 with a creatinine clearance <25–30 mL/min and for dialysis patients is our joint responsibility.
Conflict of interest statement

Prof. Heine has received lecture honoraria from Daiichi Sankyo and honoraria for consultancy services and conference delegate fees from Bristol-Myers Squibb.

Prof. Brandenburg has received honoraria for consultancy services from Daiichi Sankyo. His travel and accommodation expenses were reimbursed by Pfizer. He has received lecture honoraria and honoraria for preparing a conference from Pfizer and Bayer. He has received funding for clinical and preclinical studies from Bayer, Pfizer, and Daiichi Sankyo.

Dr. Schirmer has received honoraria for consultancy services from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, and Bayer. He has received lecture honoraria and honoraria for preparing a conference from Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, and Daiichi Sankyo. He has received funding for conducting clinical studies from Daiichi Sankyo, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer.

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References


Key messages

- Vielleicht besser: Atrial fibrillation is more common in patients with impaired kidney function than in persons with normal kidney function.
- Compared to persons with atrial fibrillation and normal kidney function, atrial fibrillation patients with impaired kidney function who take oral anticoagulants have a higher risk of ischemic stroke and systemic embolism on the one hand as well as an increased risk for hemorrhage on the other hand.
- The indication for oral anticoagulation in atrial fibrillation in patients with moderate chronic kidney disease (glomerular filtration rate ≥ 30 mL/min/1.73 m²) does not differ from persons with normal kidney function.
- In patients with severe chronic kidney disease (glomerular filtration rate <30 mL/min/1.73 m²), no evidence-based data from randomized trials are available on the indication for oral coagulation. Cohort studies suggest an advantage for oral anticoagulation in patients with severe chronic kidney disease only as long as they are not dialysis-dependent.
- Patients with atrial fibrillation and moderate to severe mitral valve stenosis or mechanical heart valve replacement require vitamin K antagonists for the purpose of anticoagulation. For all other patients who require anticoagulation, non-vitamin K dependent oral anticoagulants should be the preferred treatment if their creatinine clearance is >25–30 mL/min.
Pulmonary Bullae as an Indicator of an Elevated Risk of Renal Carcinoma

This 46-year-old woman had sustained spontaneous pneumothoraces on four separate occasions since the age of 19 because of multiple pulmonary bullae. Conditions considered in the differential diagnosis included lymphangioleiomyomatosis and histiocytosis X. Independently of this problem, she consulted a dermatologist because she had noted increasing numbers of whitish “millet seeds,” 1-2 millimeters in diameter, on her face over the past 10 years. Histological examination revealed these to be fibrofolliculomata, which, in combination with the pulmonary bullae and spontaneous pneumothoraces, led to the suspected diagnosis of Birt-Hogg-Dubé syndrome (BHDS), a condition of autosomal dominant inheritance. The diagnosis was confirmed by the demonstration of a typical FLCN mutation (c.1285dupC). BHDS patients have a 15–20% lifetime risk of renal cancer; screening every six months is recommended, with MRI in alternation with ultrasonography.

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Conflict of interest statement: The authors state that no conflict of interest exists.

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Supplementary material to:

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eReferences


### eTABLE 1

#### Definition and stages of chronic kidney disease (CKD)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD G 1</td>
<td>GFR ≥ 90 mL/min/1.73 m² + structural or functional renal abnormalities</td>
</tr>
<tr>
<td>CKD G 2</td>
<td>GFR 60–89 mL/min/1.73 m² + structural or functional renal abnormalities</td>
</tr>
<tr>
<td>CKD G 3a</td>
<td>GFR 45–59 mL/min/1.73 m²</td>
</tr>
<tr>
<td>CKD G 3b</td>
<td>GFR 30–44 mL/min/1.73 m²</td>
</tr>
<tr>
<td>CKD G 4</td>
<td>GFR 15–29 mL/min/1.73 m²</td>
</tr>
<tr>
<td>CKD G 5</td>
<td>GFR &lt;15 mL/min/1.73 m²</td>
</tr>
</tbody>
</table>

Definition of chronic kidney disease:
– Reduction in glomerular filtration rate (GFR) to below 60 mL/min/1.73 m² or
– Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased GFR, over more than three months, respectively.

### eTABLE 2

#### Cockcroft-Gault formula and CKD-EPI_{Creatinine} equation for estimating renal function

<table>
<thead>
<tr>
<th>Cockcroft-Gault formula</th>
<th>CKD-EPI_{Creatinine} equation</th>
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<tbody>
<tr>
<td>Formula for the purpose of estimating creatinine clearance</td>
<td>Formula for the purpose of estimating the glomerular filtration rate</td>
</tr>
<tr>
<td>Estimated value not adjusted for body weight (unit mL/min)</td>
<td>Estimated value adjusted for body weight (unit mL/min/1.73 m²)</td>
</tr>
<tr>
<td>Used in particular for dosage adjustments of pharmaceuticals</td>
<td>Used in particular for defining and categorizing chronic kidney disease</td>
</tr>
<tr>
<td>$(140–\text{age}) \times \text{BW}/(72 \times \text{crea}) \times 0.85$ (if female)</td>
<td>$141 \times \min(\text{crea}/c, 1)^{\alpha} \times \max(\text{crea}/c, 1)^{-1.209} \times 0.993^{0.018} \times 1.018$ (if female) $\times 1.159$ (if African-American) $c = 0.7$ in women; $c = 0.9$ in men $\alpha = -0.329$ in women; $\alpha = -0.411$ in men</td>
</tr>
<tr>
<td>First described in 1973/76</td>
<td>First described in 2009</td>
</tr>
<tr>
<td>Reference creatinine clearance at 24 hours</td>
<td>Reference on the basis of iothalamate measured glomerular filtration rate</td>
</tr>
<tr>
<td>Four variables (age, body weight, sex, plasma creatinine)</td>
<td>Four variables (age, sex, ethnicity, plasma creatinine)</td>
</tr>
<tr>
<td>Measurements of plasma creatinine in development cohort not standardized</td>
<td>Measurements of plasma creatinine in development cohort standardized</td>
</tr>
</tbody>
</table>

CKD-EPI: chronic kidney disease epidemiology collaboration; BW: body weight (in kg); crea: creatinine (mg/dL); min: minimum of crea/c or 1; max: maximum of crea/c or 1