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REVIEW

Prescription of DOACs in Patients with Atrial Fibrillation at Different Stages of Renal Insufficiency

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ABSTRACT

Atrial fibrillation (AF) and renal insufficiency often coexist and are increasingly prevalent with advancing age. Both the risk of thromboembolic events and bleeding propensity are higher in patients with AF and impaired renal function versus those with good renal health. Direct oral anticoagulants (DOACs) are being increasingly preferred over vitamin K antagonists (VKAs) in the treatment of patients with AF and impaired renal function as VKAs may accelerate progression of chronic kidney disease. DOACs, however, are eliminated by the kidneys to varying degrees, and their dosages must be adapted in accordance with renal function. Since creatinine clearance (CrCl) monitoring is recommended in patients with AF receiving DOAC therapy, CrCl must be routinely monitored in patients at the start and during the course of anticoagulation to avoid deviation from Summary of Product Characteristics dosage specifications. This review article provides an overview of current knowledge on the selection and dose of DOACs including apixaban, dabigatran, edoxaban and rivaroxaban in AF patients at different stages of renal insufficiency, with a special focus on elderly patients with comorbidities and receiving multiple medications. The groups discussed in this review include patients with varying levels of CrCl including hyperfiltration or CrCl > 90 ml/min, CrCl < 90–50 ml/min, CrCl < 50–30 ml/min, CrCl < 30–15 ml/min and end-stage renal disease or on dialysis.

Keywords: Atrial fibrillation; Creatinine clearance; Glomerular filtration; Direct oral anticoagulant; Oral anticoagulant; Renal function; Renal insufficiency

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Key Summary Points

Both atrial fibrillation (AF) and renal insufficiency are diseases of the elderly patient, and their prevalence increases with advancing age.

Direct oral anticoagulants (DOACs) (including apixaban, dabigatran, edoxaban and rivaroxaban) are preferred over vitamin K antagonists in patients with AF who are eligible for anticoagulation.

Guidelines for DOAC dose reduction are based on calculation of creatinine clearance (CrCl) using the Cockcroft-Gault (CG) equation.

Since DOACs are eliminated by the kidneys to varying degrees, their dosages must be adapted in accordance with renal function.

Therefore, CrCl-CG monitoring is recommended in patients with AF receiving DOAC therapy, particularly elderly patients with comorbidities and receiving multiple medications (and therefore at a special risk of over- or under-dosing).

INTRODUCTION

The co-existence of atrial fibrillation (AF) and renal insufficiency is a complex phenomenon that affects many patients. Registry data, meta-analyses and observational studies show that approximately 30–60% of all patients with AF also have mild-to-moderate renal insufficiency (estimated glomerular filtration rate [eGFR] 30–89 ml/min) [1–3]. Approximately an additional 3% of AF patients have severe renal insufficiency (eGFR < 30 ml/min) [1–3].

Both AF and renal insufficiency, in particular, are diseases of the elderly patient. The prevalence of renal dysfunction increases markedly after the age of 60 and continues to increase with age, reaching approximately 34% in the 70–79 age group [4]. Indeed, the incidence and prevalence of AF also correlate with age [5, 6]. Data from the GARFIELD-AF study demonstrated that patients with moderate-to-severe chronic kidney disease (CKD) at the time of AF diagnosis were older compared with those with mild or no CKD [7].

The risk of a thromboembolic event in patients with AF is higher in those with impaired renal function versus good renal health [8]. This is because renal insufficiency contributes to increased levels of procoagulant activity and thrombogenicity [9]. Thus, an eGFR < 60 ml/min/1.73 m^2 increases the risk of stroke by 43%. and for every 10 ml/min/1.73 m^2 decrease in GFR, the risk of stroke increases by 7% [10, 11].

Bleeding propensity is also markedly higher in patients with renal failure because of uraemic platelet dysfunction and coagulation disorders [8, 12], thereby making it difficult to provide necessary anticoagulation in these patients. To make matters worse, vitamin K antagonists (VKAs) have been suggested to accelerate progression of chronic kidney disease (CKD) because VKAs contribute to atherosclerotic plaque formation and calcification of vessels and soft tissues through their mechanism of action [13–16]. These problems do not exist with direct oral anticoagulants (DOACs), although these substances are also eliminated by the kidneys to varying degrees and their dosages must be adapted in accordance with renal function [17–20]. Therefore, it is essential that renal function is determined not only at therapy initiation, but also repeatedly during the course of anticoagulation [21].

Guidelines for the dose reduction of DOACs are based on renal function calculations of creatinine clearance (CrCl) using the Cockcroft-Gault (CG) equation (Fig. 1) [21–23]. However, in everyday clinical practice, renal function is more frequently evaluated by eGFR, calculated using patients' serum creatinine concentration via either the Modification of Diet in Renal Disease Study (MDRD) or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Fig. 1) [24–27]. CrCl is defined as the

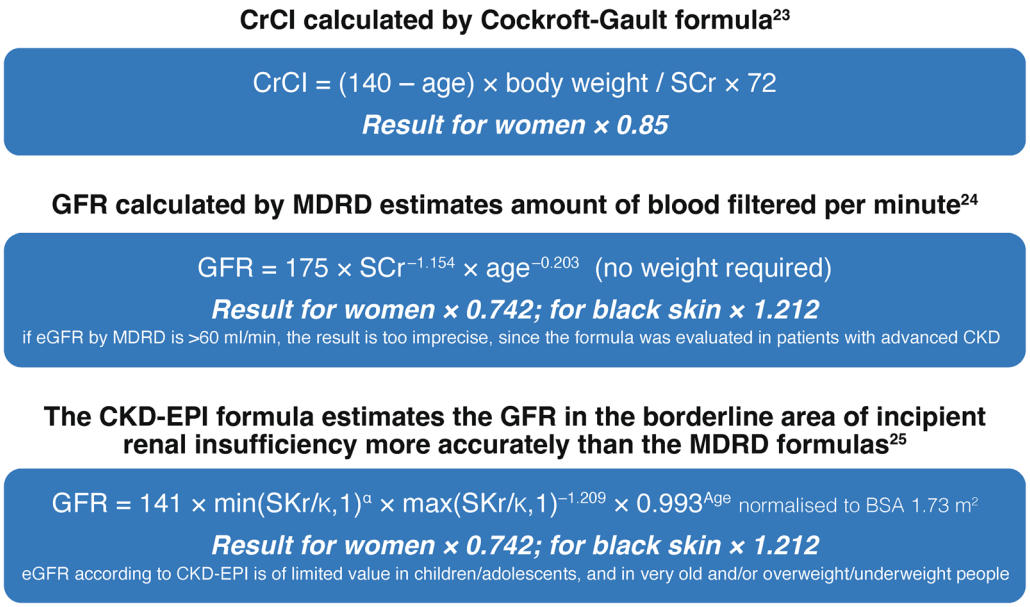

Fig. 1 Kidney function determines the DOAC dose–the difference between CrCl and GFR. Figure adapted from a German CME article published via the interdisciplinary doctors portal 'der niedergelassene Arzt' [98]. SCr = serum creatinine [mg/dl]; gender dependent factor κ = 0.7 (women) or 0.9 (men); gender dependent factor α = − 0.329 (women) or − 0.411 (men); min = minimum of SCr/κ and 1; max = maximum of SCr/κ and 1; age = age [years]. BSA, bovine serum albumin; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

volume of blood plasma cleared of creatinine per unit of time and includes both glomerular and tubular excretion [28]. In contrast, GFR estimates the volume of blood filtered by the glomeruli per minute. In patients with normal-to-moderate renal function, calculations of GFR with the MDRD and CKD-EPI formulae can underestimate actual renal function, which can lead to inadequate anticoagulation by under-dosing [29]. Conversely, in those with severe renal impairment, CrCl-CG overestimates actual filtration capacity, since CrCl includes tubular secretion in addition to GFR [28–30]. This can lead to the 'over-treatment' of patients [29].

Estimation of GFR using the two filtration markers creatinine and cystatin C as part of the CKD-EPI formula (CKD-EPI $eGFR_{cr\text{-}cys}$) has been shown to be more accurate than equations that use creatinine or cystatin C alone [31]. However, this equation (as well as other creatinine-based formulae) includes a race coefficient, originally included to improve measurement accuracy [32]. As race is considered to be a social rather than biological construct, its inclusion in GFR estimations may be unnecessary [32]. The more recent CKD-EPI 2021 equations omit race, and the combined CKD-EPI 2021 eGFRcr-cys provided the most accurate eGFR measurements and exhibited small race-related differences between groups [32].

Since CrCl-CG is always used by pharmaceutical companies and the health authorities when determining therapeutic dose adjustments of any pharmaceutical drug, including DOACs, CrCl-CG monitoring is recommended in patients with AF receiving DOAC therapy [21, 22]. In this review article, we discuss the evidence available to guide DOAC selection and dosing in AF patients with different stages of renal insufficiency and clearance capacities (Table 1). This article is based on previously conducted studies only and does not contain

Table 1 CKD staging according to the 2021 EHRA practical guide on the use of DOACs

CKD stage	Description	GFR range, ml/min/1.73 m^2
G1	Normal or high	≥ 90
G2	Mildly decreased	60–89
G3a	Mildly to moderately decreased	45–59
G3b	Moderately to severely decreased	30–44
G4	Severely decreased	15–29
G5	Kidney failure	< 15

Adapted from 2021 EHRA practical guide on the use of DOACs [21]
CKD, chronic kidney disease; GFR, glomerular filtration rate; DOAC, direct oral anticoagulants

any new studies with human participants or animals performed by any of the authors.

HYPERFILTRATION OR CRCL > 90 ML/MIN

Several definitions for glomerular hyperfiltration are used in the literature including the aberrant elevation of whole-kidney GFR, increased filtration fraction or elevated filtration through a single nephron [33–35]. Physiologically, consumption of a high-protein meal or pregnancy can cause hyperfiltration [30]. Pathologically, glomerular hyperfiltration can be seen in the early stages of diabetes mellitus or hypertensive nephropathy, and also in obesity, resulting from a change in the vascular tone of the afferent and efferent arterioles, leading to a subsequent increase in glomerular pressure [30]. In response to a reduction in nephron numbers, single nephron filtration increases resulting in glomerular hypertension and hypertrophy and proteinuria [30, 34]. Ultimately, glomerulosclerosis develops causing progressive renal decline [30].

In the long term, hyperfiltration is detrimental to the kidney and a risk factor for cardiovascular (CV) disease and increased mortality; therefore, therapeutic mitigation or elimination is necessary [30, 34, 36]. Therapeutic intervention may involve the use of renin-angiotensin system (RAS) blockers to inhibit the vasoconstrictive effect of angiotensin II at the vas efferens or sodium-glucose co-transporter-2 (SGLT2) inhibitors, constricting the afferent arteriole, thereby reducing the burden of excessively filtered molecules in the proximal tubule (e.g., albumin, glucose and phosphate) [34].

Glomerular hyperfiltration leads to an increase in CrCl, therefore resulting in the accelerated excretion of renally eliminable drugs. Since all four DOACs are excreted renally, albeit to variable degrees, hyperfiltration advances the decline in efficacy and/or drug levels in the body, resulting in potentially subtherapeutic anticoagulation. Sub-analyses of the ROCKET-AF and ENGAGE AF-TIMI 48 trials indicated a trend towards reduced efficacy (stroke or systemic embolic events [SEE]) in patients with AF and CrCl > 95 ml/min who received rivaroxaban or edoxaban versus warfarin, respectively [37, 38]. Despite this, bleeding rates were observed to be similar or lower versus warfarin with rivaroxaban or edoxaban, respectively, and the net clinical benefit of edoxaban over warfarin was maintained [37, 38]. Nevertheless, this finding prompted an update to the European Summary of Product Characteristics (SmPC) for edoxaban highlighting the need for the careful assessment of individuals' thromboembolic and bleeding risk in those with higher CrCl values [19]. Post hoc analyses of regulatory data submitted to the Food and Drug Administration (FDA) also

showed that in patients with CrCl ≥ 80 ml/min, risk of ischaemic stroke versus warfarin was similar but slightly lower with dabigatran (hazard ratio [HR]: 0.84) and slightly higher with rivaroxaban and apixaban (HR: 1.07 and 1.35, respectively) [39]. Risk of SEE versus warfarin was lower for dabigatran, rivaroxaban and apixaban (HR: 0.71, 0.89 and 0.88, respectively) [39].

The use of different methods or formulae to determine renal function may affect the categorisation of patients at the higher end of the spectrum (> 95 ml/min). This was demonstrated using data from the ORBIT-AF registry, which included 9315 patients with AF [40]. Overall, 26% of patients had an estimated CrCl of > 95 ml/min calculated via the CG equation [40] Compared with the CrCl ≤ 95 ml/min group, these patients were more likely to be younger (median: 64 versus 78 years), male (74% versus 52%) and have a higher body weight (median: 109 versus 80 kg) [40]. Patients with CrCl > 95 ml/min also had a superior CV risk profile (i.e., with a lower prevalence of hypertension, congestive heart failure and cerebrovascular events) and lower stroke (median CHA_2DS_2-VASc score: 3 versus 4) and bleeding risk (median Anticoagulation and Risk Factors in Atrial Fibrillation [ATRIA] score: 1 versus 3) scores [40]. However, when GFR was estimated using the MDRD formula, only 12% had an eGFR > 95 ml/min/1.73 m^2; the proportion was even lower using the CKD-EPI formula at 7% [40]. Given these variable results, physicians must be conscious of the method used to estimate renal function in their clinics and be aware that the CG formula was used for three out of the four DOACs (excluding apixaban) during their clinical trial programmes and in SmPCs to guide DOAC dosing [18–20, 40].

In daily practice, glomerular hyperfiltration usually affects only a small proportion of patients (e.g., those in the initial stage of diabetic nephropathy). In most patients, renal function and filtration capacity often tend to be limited because of their age and comorbidities.

CRCL < 90–50 ML/MIN

Patients with a CrCl < 90–50 ml/min comprise the majority of the AF population and are categorised as having grade 2 or 3a CKD, signaling mildly to moderately decreased renal function [21]. Across the four DOAC trials, approximately 80% of patients enrolled had a CrCl ≥ 50 ml/min [41–44]. In these trials, the individual DOACs demonstrated either comparable or superior efficacy regarding the prevention of stroke and SEE compared with warfarin [41–43], findings that have been reaffirmed by subsequent meta-analyses [45–47]. In addition, the risk of a major bleeding event was significantly reduced with apixaban, dabigatran and edoxaban and risk of intracranial haemorrhage and fatal bleeding was significantly reduced with rivaroxaban compared with warfarin [41–44]. Together, these data informed the European Society of Cardiology (ESC) guideline recommendation for DOACs to be used in preference to VKAs in the majority of patients with AF [22]. Evidence also suggests that DOACs are associated with a reduced risk of progression in renal decline or injury versus warfarin [48–54].

In the range of mild-to-moderate renal insufficiency, differences among the four DOACs most often arise from their individual potential to interact with other compounds, demanding careful consideration regarding co-medications and their metabolism or elimination. For instance, the metabolism of all DOACs is influenced by the P-glycoprotein (P-gp) pathway. In patients receiving co-medication with strong P-gp inhibitors, which increase DOAC plasma levels, guidelines vary between DOACs. Apixaban use is not recommended whereas a reduced dose of dabigatran or edoxaban is suggested with some P-gp inhibitors [17–21]. In those receiving P-gp inducers, which decrease DOAC plasma levels, DOACs must be used with caution, avoided or are fully contraindicated [17–21]. DOACs are also metabolised to variable degrees by cytochrome P (CYP) enzymes in the liver (Fig. 2) [21]. Concomitant use of strong cytochrome P (CYP) 3A4 inducers

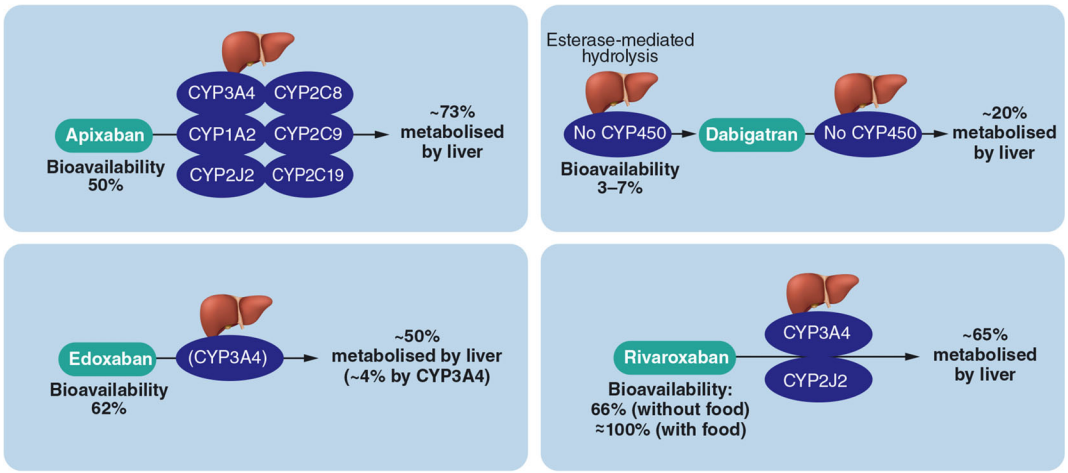

Fig. 2 Metabolism of the different DOACs in the liver by cytochrome P enzymes. CYP, cytochrome P

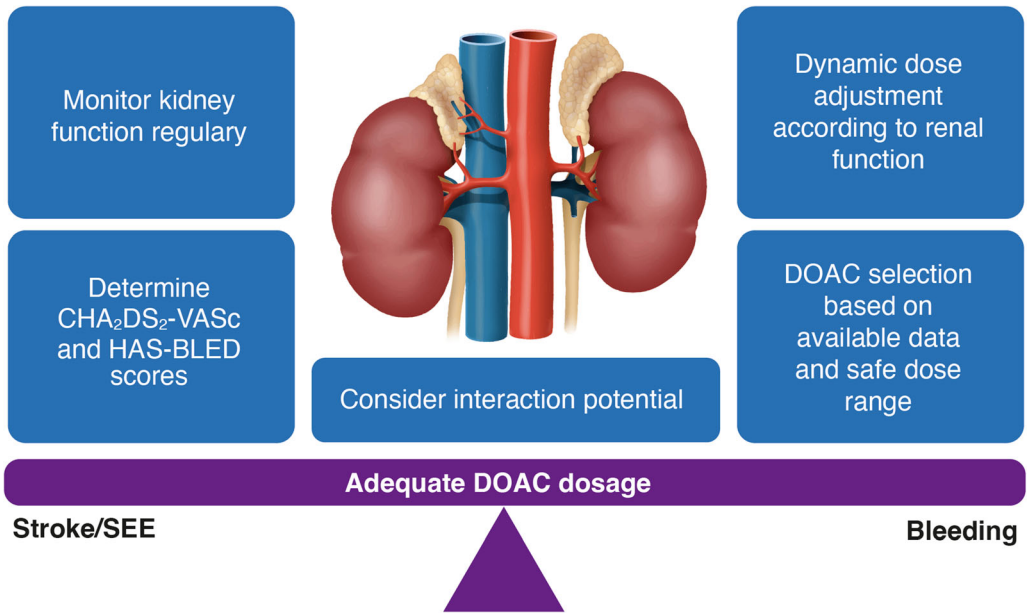

Fig. 3 Measurements and selection criteria for DOAC therapy in patients with renal insufficiency and AF. Figure adapted from a German CME article published via the interdisciplinary doctors portal 'der niedergelassene Arzt' [98]. DOAC, direct oral anticoagulant; SEE, systemic embolic event

or inhibitors is not advised with rivaroxaban and apixaban [17, 20, 21].

CRCL < 50–30 ML/MIN

In patients with renal insufficiency, adequate DOAC dosing must be carefully managed on an individualised basis to ensure that optimal efficacy and safety are achieved regarding stroke prevention in AF (Fig. 3). According to guideline recommendations, patients with AF should have their renal function monitored at least on a yearly basis [21]. When eGFR progressively decreases and approaches clearance rates of < 60 ml/min/1.73 m^2, monitoring frequency

should be increased, since these patients are edging closer to meeting DOAC dose reduction criteria thresholds [21]. However, evidence suggests that these guidelines are not strictly followed in routine clinical practice [55, 56]. For example, renal function was not evaluated in 721 of the 8518 DOAC-treated patients included in the baseline population of the ORBIT-AF II registry [55].

A reduced dose is recommended in patients receiving edoxaban or rivaroxaban when CrCl values fall to between < 50–15 ml/min and may be considered in patients receiving dabigatran with CrCl < 50–30 ml/min [18–20]. In patients receiving apixaban, eligibility for dose reduction differs, since two out of three criteria (age ≥ 80 years, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dl) must be met [17]. In elderly patients ≥ 80 years with cardio-renal syndrome and the need for continuously adapted diuretic therapy, body weight and creatinine levels often fluctuate. This complicates the long-term stable dosing of apixaban, which often leads to a prophylactic dose reduction in the presence of only a single criterion [57].

In the pivotal phase III ARISTOTLE study, patients who met two out of three dose reduction criteria, including serum creatinine of ≥ 1.5–2.5 mg/dl, received apixaban 2.5 mg twice daily (BID); those with serum creatinine > 2.5 mg/dl (CrCl < 25 ml/min) were excluded from the study [43]. Patients with moderate-to-severe renal impairment (CrCl < 50 ml/min) who received apixaban had a higher annualised bleeding rate versus those with no renal impairment (CrCl > 80 ml/min; 3.2 versus 1.5%/year); however, the rate was lower versus patients with moderate-to-severe renal impairment treated with warfarin (6.4%/year, respectively) [43]. In fact, across the different ranges of renal function, the reduction in major bleeding with apixaban versus warfarin was greatest in the CrCl < 50 ml/min subgroup (HR: 0.5; > 50–80 ml/min: 0.77; > 80 ml/min: 0.80) [58].

A substudy of the ENGAGE AF-TIMI 48 trial revealed that 2740 of the 14,071 patients who received either warfarin or the high-dose edoxaban regimen (HDER; 60 or 30 mg once daily [OD]) had a baseline CrCl between 30 and 50 ml/min [38]. Of these 2740 patients, 84% were eligible for a dose reduction at randomisation and received either edoxaban 30 mg OD or warfarin [38]. In patients receiving HDER versus warfarin with CrCl 30–50 ml/min, primary efficacy (stroke/SEE, HR [95% confidence interval, CI]: 0.87 [0.65–1.18], $p = 0.37$) and safety (major bleeding, 0.76 [0.58–0.98], $p = 0.036$) outcomes as well as net clinical benefit (stroke, SEE, major bleeding or all-cause death, 0.86 [0.75–0.98], $p = 0.027$) were consistent with the overall results obtained in the trial [38].

In the ROCKET AF trial, 20.7% of enrolled patients with AF had moderate renal insufficiency (CrCl 30–49 ml/min) and were eligible for randomisation to rivaroxaban 15 mg OD, a reduced dose regimen whose selection was guided by pharmacodynamic and pharmacokinetic studies [59]. Nevertheless, stroke/SEE and bleeding rates were higher in this subgroup versus those with CrCl ≥ 50 ml/min, irrespective of treatment type [59]. In the intention-to-treat analysis, the risk of stroke/SEE was numerically lower with rivaroxaban 15 mg OD versus warfarin (HR [95% CI]: 0.86 [0.63–1.17], $P_{\text{interaction}} = 0.85$) in patients with CrCl 30–49 ml/min, and the risk of major and clinically relevant non-major (CRNM) bleeding was similar between the groups (0.98 [0.84–1.14], $P_{\text{interaction}} = 0.45$) [59]. Overall, no significant benefit was found with rivaroxaban 15 mg OD versus warfarin in patients with moderately impaired renal function [59].

In the RE-LY trial, the efficacy and safety of two dosing regimens of dabigatran (150 and 110 mg BID) with no option for dose reduction for impaired renal function were compared with warfarin [41]. In patients with a CrCl of < 50 ml/min, there was a trend towards dabigatran 110 mg BID being more effective versus warfarin (HR [95% CI]: 0.85 [0.59–1.24]), but less effective versus dabigatran 150 mg BID (150 mg versus 110 mg BID: 0.66 [0.43–1.01]) [60]. The major bleeding risk with 110 mg BID was similar versus warfarin (1.02 [0.78–1.33]) and 150 mg BID (1.20 [0.93–1.54]) [60]. The SmPC for dabigatran states that patients with a CrCl between 30 and 50 ml/min should receive 150 mg BID, except for those with a high

bleeding risk, who should receive 110 mg BID [18].

Furthermore, routine clinical data based on 4873 patients with AF from the GLORIA-AF registry who received dabigatran indicated that stroke and major bleeding rates were low across all renal function groups, including CrCl 30–49 ml/min (n = 476; 0.33/100 patient-years [95% CI 0.06–1.11] and 1.26 [0.66–1.97], respectively), although it should be noted that bleeding event rates numerically increased in line with declining renal function [61].

A meta-analysis of the four pivotal DOAC trials showed that patients with AF and moderate renal insufficiency (CrCl < 50 ml/min) had a reduced risk of stroke/SEE (risk ratio [95% CI]: 0.79 [0.66; 0.94]) and major bleeding (0.80 [0.70; 091]) with DOACs versus warfarin [62]. Nielsen et al. performed a meta-regression analysis on data from five studies which indirectly compared efficacy and safety across the four DOACs. Edoxaban 30 mg had the most favourable safety profile in patients with CrCl 25–49 compared with other DOACs, with only dabigatran 150 mg having a more favourable efficacy profile in this subgroup of patients [63].

Although SmPCs for three out of the four DOACs precisely outline the dose reduction criteria, multiple analyses have highlighted frequent dosing errors during routine clinical practice and unwarranted dosing reductions have been associated with serious consequences [55, 64–66]. Data from the ORBIT-AF II registry showed that only 43% of the 1289 patients who received a reduced DOAC dose met the criteria for dose reduction [64]. Furthermore, patients who received an inappropriate lower DOAC dose had a higher risk of experiencing a thromboembolic event (HR [95% CI]: 1.56 [0.92–2.67] versus appropriately dosed patients) and of death (2.61 [1.86–3.67]) [64].

The reasons for deviating from SmPC dosage specifications are not always clear. Renal function can be misestimated if alternative methods for calculating CrCl, other than the CG equation specified in DOAC SmPCs, are used [29]. Data from the PREFER-in-AF registry indicated that in patients with AF and CKD who had an indication for a dose reduction of dabigatran, edoxaban or rivaroxaban defined as CrCl-CG ≤ 50 ml/min, almost one fifth would be reclassified to a higher dose and nearly one quarter to receive a lower dose should the MDRD or CKD-EPI formulae be used [67]. In other cases, a misconception of the individual patient's risk for thromboembolic events or bleeding may lead to "off-label" dosing [55].

However, it does not appear to be exclusively more cardiovascularly compromised patients in whom DOAC dosing is inappropriately changed. In a retrospective analysis of prospective registry data collected on 2272 patients (mean age ± standard deviation: 72 ± 10 years) over 2 years, 21.6% (490/2272) of patients with AF who were receiving DOAC therapy were inappropriately underdosed and 1.3% (29/2272) were inappropriately overdosed [68]. Interestingly, the analysis indicated that compared with appropriately dosed patients, those who received an inappropriate low dose were younger, had higher body weights and had higher CrCl values (i.e., these patients had better renal function). The independent determinants for prescribing inappropriately low doses differed between the DOACs: HAS-BLED score for apixaban; age for dabigatran and edoxaban; and age, CrCl, HAS-BLED and $CHADS_2$ score and additional antiplatelet therapy for rivaroxaban [68]. A study conducted by Yao et al., including almost 15,000 patients with AF receiving apixaban, dabigatran or rivaroxaban during routine clinical practice, highlighted the potential consequence of inappropriately prescribing an incorrect low dose in apixaban-treated patients without a renal indication for dose reduction [69]. Among patients who received a reduced dose of apixaban with no renal indication for dose reduction, the risk of stroke or SEE increased almost fivefold versus those receiving the standard dose (HR [95% CI]: 4.87 [1.30–18.26], p = 0.02) while the risk of bleeding remained unchanged (1.29 [0.48–3.42], p = 0.61) [69].

Of all the DOACs, apixaban appears to be most frequently inappropriately dose reduced, potentially owing to its complex dosing requirements. In a study of 556 patients with AF who received apixaban upon hospitalisation in the USA, 12.2% of patients were found to receive an inappropriate low dose [70]. Of these,

the majority met only one (instead of two) dose reduction criterion, which was most often age ≥ 80 years [70]. A history of or perceived risk of bleeding was cited as the reason for giving an inappropriately low dose in approximately one third of cases [70].

Indeed, in elderly patients ≥ 80 years with AF, the dose adjustment of apixaban is problematic, since the pharmacokinetics and pharmacodynamics of apixaban seem to be altered in this patient group. Smrithi Sukumar et al. performed a study in 110 elderly patients with AF (mean age of 80.4 years), which examined the blood concentration of apixaban with differing dosing regimens (appropriate standard dose or reduced dose, or inappropriate reduced dose) [71]. Apixaban concentrations in patients who received an inappropriate reduced dose (n = 42) fell largely within the expected concentration range and did not significantly differ to the standard dose [71]. In those who received an appropriately reduced dose (n = 20), 7 had peak concentrations that were higher than the expected range seen in ARISTOTLE, and 17 had an apixaban blood concentration above the median peak concentration reported in the study [71]. The authors concluded that apixaban concentrations should be monitored in patients whose characteristics differ from those included in the randomised clinical trials (RCTs) as well as in patients who receive 'off label' doses [71].

Overall, DOACs required to meet only a single criterion to be eligible for renal impairment-related dose adjustment (e.g., CrCl < 50–15 ml/min) appear easier to use effectively. However, in patients where this criterion frequently fluctuates, risk of stroke/SEE or major bleeding could be assessed on an individual basis via CHA_2DS_2-VASC or HAS-BLED scores, which may help inform decision making regarding whether a standard dose of DOAC is necessary to prevent stroke/SEE or if a reduced dose should be prescribed because of a higher risk of bleeding. It should be noted that in the elderly, edoxaban has demonstrated sufficient efficacy and a significantly reduced risk of bleeding, even at reduced doses [72].

While the fear of bleeding appears to be the main reason for inappropriate dose reductions, incorrect dosing of DOACs may also occur unintentionally. In patients with cardio-renal syndrome, who retain fluid and rapidly gain weight during cardiac decompensation and subsequently lose weight rapidly when treated with diuretics, estimated CrCl will fluctuate frequently; therefore, kidney function must be monitored closely to avoid missing the shift in eligibility for dose adjustment.

CRCL < 30–15 ML/MIN

In the CrCl range of 50–30 ml/min, patients are eligible for the reduced dose of apixaban, edoxaban and rivaroxaban (Fig. 4), analogous to corresponding RCT data [17, 19, 20]. The extension of the approval of all reduced dose Factor Xa (FXa) inhibitors to a CrCl as low as 15 ml/min was surprising, since in the RCTs, patients with a CrCl < 30 ml/min for rivaroxaban and edoxaban or < 25 ml/min for apixaban were excluded [42–44]. The ESC guidelines and 2021 European Heart Rhythm Association (EHRA) practical guide acknowledge that FXa inhibitor use in patients with severe renal impairment (29–15 ml/min) must be approached cautiously (Fig. 4) [21, 22].

Apixaban is the least renally excreted DOAC, with 27% of the absorbed substance cleared by the kidneys [21]. Available pharmacokinetic data for the relatively small proportion of patients who enrolled in ARISTOTLE with CrCl 25–30 ml/min and received apixaban 5 mg (n = 12) or 2.5 mg (n = 19) BID indicated that median (range) exposure to apixaban (5512 [1956–7342] ng/ml/h and 2780 [2056–4155], respectively) for both doses was within the range observed in those who received apixaban 5 mg with CrCl > 30 ml/min (n = 3406 [568–9069] ng/ml/h) [73]. The study further demonstrated that in patients with CrCl 25–30 ml, risk of major bleeding (HR [95% CI]: 0.34 [0.14–0.80]) and major or CRNM bleeding (0.35 [0.17–0.72]) was lower than warfarin [73]. Data obtained from routine clinical practice suggest that the safety profile of apixaban 5 or 2.5 mg BID is consistent across the spectrum of

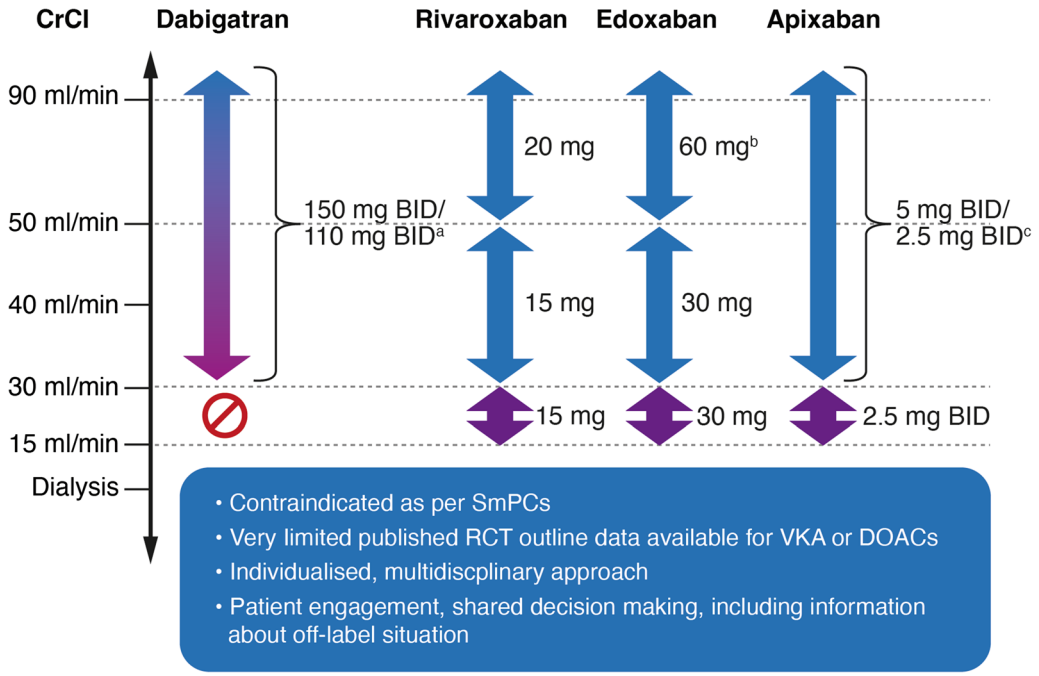

Fig. 4 DOAC dosing according to renal function. Figure adapted from 2021 EHRA Practical Guide on the use of DOACs [21]. Purple arrows indicate cautionary use. [a]110 mg BID in patients at high risk of bleeding (per SmPC). [b]Other dose reduction criteria may apply (weight ≤ 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA, SmPC edoxaban should be used in 'high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk'. [c]2 × 2.5 mg only if at least two out of three fulfilled: age ≥ 80 years, body weight ≤ 60 kg, creatinine ≥ 1.5 mg/dl (133 µmol/l). BID, twice daily; CrCl, creatinine clearance; EMA, European Medicines Agency; DOAC, direct oral anticoagulant; RCT, randomised clinical trial; SmPC, Summary of Product Characteristics; VKA, vitamin K antagonist

renal function. Jones et al. performed a retrospective cohort analysis of 340 patients with non-valvular AF who received apixaban 5 or 2.5 mg BID and were categorised according to renal function: CrCl < 25 ml/min versus ≥ 25 ml/min [74]. The analysis demonstrated no significant difference in the incidence of major bleeding events with either apixaban dose across the two renal function categories [74].

In patients receiving edoxaban, 50% of the drug is eliminated by the kidneys [21]. Using data from the Italian Registry of Drugs, Fazio et al. conducted a small, explorative, retrospective analysis of 46 patients with AF and a CrCl between 15 and 29 ml/min who received edoxaban 30 mg [75]. Promisingly, after an average of approximately 9 months of follow-up, no occurrences of stroke, SEE, major bleeding or CV death were reported. Observed events included five minor haemorrhages and one non-CV related death. Furthermore, a short, 12-week phase III Japanese study including patients with AF and CrCl ≥ 15–30 ml/min who were treated with edoxaban 15 mg OD demonstrated similar short-term safety and comparable plasma concentrations of edoxaban among those receiving edoxaban 30 or 60 mg OD with CrCl ≥ 50 ml/min [76].

Two thirds of rivaroxaban is metabolised via CYP450 (3A4 and 2J2) and CYP-independent mechanisms in the liver. The remaining one third is unmetabolised and directly eliminated by the kidneys. Rivaroxaban plasma concentrations have been shown to be elevated in renally impaired subjects and associated with more potent pharmacodynamic effects of the drug, greater FXa inhibition and prolonged prothrombin time [77]. The XARENO registry conducted in six European countries evaluated

the effectiveness and safety of rivaroxaban (n = 766; dosed according to the relevant countries' guidelines) versus warfarin (n = 695) in patients with AF and advanced kidney disease (eGFR 15–49 ml/min per 1.73 m^2) followed up for 12 months. Overall, rivaroxaban treatment had a greater net clinical benefit versus VKA, with net-clinical benefit event rates of 12.9% (51/397) and 18.3% (75/410) observed in the rivaroxaban and VKA groups, respectively (incidence rate ratio [95% CI]: 0.68 [0.47–0.96], p = 0.03) [78].

Of all the DOACs, renal excretion is highest with dabigatran (80% clearance). Dabigatran exposure was shown to be approximately six-fold higher in a small group of volunteers with CrCl > 10–30 ml/min versus no renal impairment [79] Dabigatran 150 mg BID is therefore contraindicated in such patients with AF in Europe [18]. Additional pharmacokinetic studies led to the FDA approval of dabigatran 75 mg BID in patients with CrCl 15–30 ml/min in the USA [80–84].

To summarise, it must be stated that despite individual DOAC studies in patients with severely impaired renal function (CrCl < 25–30 ml/min), evidence is currently insufficient to allow DOACs to be used effectively and safely in this patient population. Despite limited RCT data, DOAC SmPCs include guidance on the use of DOACs in AF patients with CrCl as low as 15 ml/min [21].

DOACS IN DIALYSIS-DEPENDENT PATIENTS WITH AF

DOACs are not recommended in patients with end-stage renal disease (ESRD) or on dialysis, as per the relevant SmPCs [17–20]. To date, there have been no RCTs evaluating the efficacy and safety of DOACs in dialysis-dependent patients with AF [22]. Indeed, based on data in the literature, it is unclear whether this patient group may benefit from oral anticoagulation at all (DOAC or warfarin). Two meta-analyses of patients who received VKA treatment and had AF and ESRD (n = 10,445) or who were on dialysis (n = 24,335) demonstrated no benefit to patients regarding incidence of ischaemic stroke and mortality, but the risk of haemorrhagic stroke was significantly higher [85, 86]. Thus, the ESC guidelines make no recommendations regarding the use of oral anticoagulant (OAC) treatment in patients with AF and ESRD, or on dialysis [22].

A retrospective cohort study of dialysis-dependent Medicare patients with AF in the US found that patients treated with apixaban 5 mg BID had a lower risk of stroke/SEE versus warfarin; however, no difference was seen with apixaban 2.5 mg BID versus warfarin [87]. Significantly fewer major bleeding events were reported with both apixaban 5 and 2.5 mg BID versus warfarin, although there were no differences in the rates of intracranial or gastrointestinal bleeding between the groups [87]. It should be noted however that the absolute rates of major bleeding for apixaban (19.7%) and warfarin (22.9%) were very high in both groups and the discontinuation rate of both agents was also high (median time on apixaban 105 days, on warfarin 157 days) [87].

Despite the paucity of evidence and contrary to SmPC recommendations, in some instances DOACs have been used in an off-label capacity in individuals with AF on dialysis. An observational analysis of the Fresenius Medical Care North America ESRD database indicated that the risk of major bleeding-related hospitalisation or death was significantly higher in dialysis-dependent AF patients who received dabigatran (150 mg or 75 mg BID) or rivaroxaban (20 mg or 15 mg OD) compared with warfarin [88].

A handful of small pharmacokinetic studies (including 7–18 patients per study) have suggested that haemodialysis has a moderate-to-limited effect on the plasma concentrations and renal clearance of apixaban, edoxaban or rivaroxaban [89–92]. For example, a phase I, open-label, crossover study in ten dialysis patients examined the pharmacokinetic profile of edoxaban [92]. The study concluded that in dialysis-dependent patients, who received a single dose of edoxaban 15 mg 2 h prior to dialysis, a further dose of edoxaban was not needed since only approximately 25% of edoxaban was eliminated by dialysis [92]. It should

be noted however that frequency of bleeding events was not investigated in these studies.

Ultimately, from a nephrological perspective, the prescription of OACs (VKA or DOACs) in dialysis-dependent patients with AF in the absence of an evidence-based, approved indication is not recommended. The recently published results of the investigator-initiated, prospective, randomised, open-label, blinded outcome assessment AXADIA trial (EudraCT number: 2015-005503-84, clinicaltrial.gov identifier: NCT02933697) warrant the need for additional interventions to reduce the risk of thromboembolic and bleeding events in patients with AF on haemodialysis. AXADIA randomised patients with AF on chronic haemodialysis to either apixaban 2.5 mg BID or the VKA phenprocoumon (international normalised ratio: 2.0–3.0) [93]. The composite primary safety outcome was defined as a first event of major bleeding, CRNM bleeding or all-cause death. The primary efficacy outcome was a composite of ischaemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis and/or pulmonary embolism. Only 97 patients were enrolled in the study (48 assigned to apixaban, mean follow-up 429 days and 49 to VKA, mean follow-up 506 days) and the trial was designed to show non-inferiority of apixaban to VKA. Over this long follow-up period, the investigators observed no differences in safety or efficacy outcomes between the two treatments. The study nevertheless confirmed the fact that even on OACs, patients with AF on haemodialysis remain at high risk of CV events. The similar SAFE-D (NCT03987711) pilot trial is ongoing; however, the RENAL-AF trial (NCT02942407) was prematurely terminated and produced inconclusive results [94]. Thus, more RCTs with larger sample sizes are needed to determine the optimal anticoagulation regimen for patients with AF on haemodialysis.

FURTHER SELECTION CRITERIA FOR DOACS IN PATIENTS WITH RENAL INSUFFICIENCY

In addition to evaluating the efficacy and safety of individual DOACs, several other factors also warrant consideration when selecting the appropriate DOAC for treating a patient with AF and impaired renal function.

Patients with chronic renal failure often take multiple medications to manage their condition (antihypertensives, cystathionine γ-lyase inhibitors, diuretics, phosphate binders, calcidiol/calcitriol, xanthine oxidase inhibitors, antidiabetics, etc.) and may require treatments for additional comorbidities. As the number of medications a patient takes increases, the potential for drug-drug interactions also increases. The choice of DOAC can also impact treatment efficacy. Substances with a low interaction potential such as edoxaban could be a suitable option for these patients; however, clinical evidence is currently lacking in this area.

Furthermore, a high tablet load also reduces patient compliance and adherence. A real-world study by Andrade et al. found that an estimated one third of AF patients who were on a BID dosing regimen took only one daily dose. These patients were less adherent than patients with an OD dosing regimen [95]. In this respect, OD administration of DOACs might be considered by physicians when selecting the most appropriate treatment.

The availability of real-life data on the treatment safety and efficacy profile can help the prescribing physician but also the patient in deciding which DOAC would be most suitable. Data from the worldwide ETNA-AF registry confirmed low rates of major bleeding, haemorrhagic and systemic thromboembolic events in > 25,000 aging patients with AF and comorbidities, including chronic renal failure treated with edoxaban after 1-year follow-up [96]. In the European regional study forming a part of ETNA-AF-Global, analysis of the 13,092 unselected patients, with a mean age of 73.6 years and mean CHA_2DS_2-VASc score of 3.1 ± 1.4, showed an incidence of 1.05%/year for major bleeding and only 0.24% for intracranial hemorrhage. Strokes or SEE occurred at an incidence of 0.82%/year [97].

CONCLUSIONS

Therapy with DOACs does not simply mean "prescribe and forget" but requires an individualised risk-adapted selection of the correct substance at an adequate dosage for the suitable patient. This includes, in particular, regular monitoring of renal function using the correct formula (CrCl-CG), as well as appropriate dose adjustment. This applies in particular to elderly patients with comorbidities under polypharmacy and the special risk of over- or underdosing.

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REFERENCES

1. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational,

prospective GARFIELD registry. PLoS ONE. 2013;8(5): e63479.

2. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol CJASN. 2011;6(11):2599–604.

3. Boriani G, Laroche C, Diemberger I, Popescu MI, Rasmussen LH, Petrescu L, et al. Glomerular filtration rate in patients with atrial fibrillation and 1-year outcomes. Sci Rep. 2016;6:30271.

4. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. PLoS ONE. 2016;11(7): e0158765.

5. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213–20.

6. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. Int J Stroke. 2021;16(2):217–21.

7. Goto S, Angchaisuksiri P, Bassand JP, Camm AJ, Dominguez H, Illingworth L, et al. Management and 1-year outcomes of patients with newly diagnosed atrial fibrillation and chronic kidney disease: results from the prospective GARFIELD—AF Registry. J Am Heart Assoc. 2019;8(3): e010510.

8. Olesen JB, Lip GY, Kamper AL, Hommel K, Kober L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367(7):625–35.

9. Vio R, Proietti R, Rigato M, Calò LA. Clinical evidence for the choice of the direct oral anticoagulant in patients with atrial fibrillation according to creatinine clearance. Pharmaceuticals (Basel, Switzerland). 2021;14(3):279.

10. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ. 2010;341: c4249.

11. Masson P, Webster AC, Hong M, Turner R, Lindley RI, Craig JC. Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis. Nephrol Dialysis Transplant. 2015;30(7):1162–9.

12. Jun M, James MT, Manns BJ, Quinn RR, Ravani P, Tonelli M, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. BMJ. 2015;350: h246.

13. Heine GH, Brandenburg V, Schirmer SH. Oral anticoagulation in chronic kidney disease and atrial fibrillation. Dtsch Arztebl Int. 2018;115(17): 287–94.

14. Peeters F, Dudink E, Kimenai DM, Weijs B, Altintas S, Heckman LIB, et al. Vitamin K antagonists, non-vitamin K antagonist oral anticoagulants, and vascular calcification in patients with atrial fibrillation. TH Open Companion J Thromb Haemostasis. 2018;2(4):e391–8.

15. Dannenberg L, Zako S, Mourikis P, Veulemans V, Kelm M, Zeus T, et al. Oral Anticoagulation therapy and progression of calcific aortic valve stenosis: factor Xa versus Factor IIa inhibition? Pharmacology. 2019;104(3–4):212–4.

16. Posch F, Ay C, Stöger H, Kreutz R, Beyer-Westendorf J. Exposure to vitamin k antagonists and kidney function decline in patients with atrial fibrillation and chronic kidney disease. Res Pract Thromb Haemost. 2019;3(2):207–16.

17. Bristol-Myers Squibb Company. Apixaban 5 mg Summary of Product Characteristics. 2021. https://www.medicines.org.uk/emc/product/2878/smpc#gref. Accessed 10 Dec 2021.

18. Boehringer Ingelheim Pharmaceuticals Inc. Dabigatran etexilate Summary of Product Characteristics. 2021. https://www.medicines.org.uk/emc/product/4703/smpc#gref. Accessed 12 Dec 2021.

19. Daiichi Sankyo Europe GmbH. Edoxaban 60 mg Summary of Product Characteristics. 2021. https://www.medicines.org.uk/emc/product/6905/smpc#gref. Accessed 19 Nov 2021.

20. Janssen Pharmaceuticals Inc. Rivaroxaban 20 mg Summary of Product Characteristics. 2021. https://www.medicines.org.uk/emc/product/2793/smpc. Accessed 12 Dec 2021.

21. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Europace. 2021;23(10):1612–76.

22. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2021;42(5):373–498.

23. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

24. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130(6):461–70.

25. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4): 247–54.

26. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.

27. Fernandez-Prado R, Castillo-Rodriguez E, Velez-Arribas FJ, Gracia-Iguacel C, Ortiz A. Creatinine clearance is not equal to glomerular filtration rate and Cockcroft-Gault equation is not equal to CKD-EPI collaboration equation. Am J Med. 2016;129(12):1259–63.

28. Kampmann JP, Hansen JM. Glomerular filtration rate and creatinine clearance. Br J Clin Pharmacol. 1981;12(1):7–14.

29. Andrade JG, Hawkins NM, Fordyce CB, Deyell MW, Er L, Djurdjev O, et al. Variability in non-vitamin K antagonist oral anticoagulants dose adjustment in atrial fibrillation patients with renal dysfunction: the influence of renal function estimation formulae. Can J Cardiol. 2018;34(8):1010–8.

30. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, Schrier RW. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol. 2012;8(5):293–300.

31. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20–9.

32. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-Based equations to estimate GFR without Race. N Engl J Med. 2021;385(19):1737–49.

33. Hostetter TH. Hyperfiltration and glomerulosclerosis. Semin Nephrol. 2003;23(2):194–9.

34. Kanbay M, Ertuglu LA, Afsar B, Ozdogan E, Kucuksumer ZS, Ortiz A, et al. Renal hyperfiltration defined by high estimated glomerular filtration rate: a risk factor for cardiovascular disease and mortality. Diabetes Obes Metab. 2019;21(11): 2368–83.

35. Huang SH, Sharma AP, Yasin A, Lindsay RM, Clark WF, Filler G. Hyperfiltration affects accuracy of creatinine eGFR measurement. Clin J Am Soc Nephrol CJASN. 2011;6(2):274–80.

36. Park M, Yoon E, Lim YH, Kim H, Choi J, Yoon HJ. Renal hyperfiltration as a novel marker of all-cause mortality. J Am Soc Nephrol. 2015;26(6):1426–33.

37. Lindner SM, Fordyce CB, Hellkamp AS, Lokhnygina Y, Piccini JP, Breithardt G, et al. Treatment consistency across levels of baseline renal function with rivaroxaban or warfarin: a ROCKET AF (Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) analysis. Circulation. 2017;135(10): 1001–3.

38. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, et al. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. Circulation. 2016;134(1):24–36.

39. Fanikos J, Burnett AE, Mahan CE, Dobesh PP. Renal function considerations for stroke prevention in atrial fibrillation. Am J Med. 2017;130(9):1015–23.

40. Pokorney SD, Shrader P, Thomas L, Fonarow GC, Kowey PR, Singer DE, et al. Influence of kidney function estimation methods on eligibility for edoxaban population impact of the US Food and Drug Administration's Approach for Its Product Labeling. Circulation. 2016;134(15):1122–4.

41. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139–51.

42. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883–91.

43. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981–92.

44. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369(22):2093–104.

45. Cameron C, Coyle D, Richter T, Kelly S, Gauthier K, Steiner S, et al. Systematic review and network meta-analysis comparing antithrombotic agents for

the prevention of stroke and major bleeding in patients with atrial fibrillation. BMJ Open. 2014;4(6): e004301.

46. Fu W, Guo H, Guo J, Lin K, Wang H, Zhang Y, et al. Relative efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation by network meta-analysis. J Cardiovasc Med (Hagerstown). 2014;15(12):873–9.

47. Verdecchia P, Angeli F, Bartolini C, De Filippo V, Aita A, Di Giacomo L, et al. Safety and efficacy of non-vitamin K oral anticoagulants in non-valvular atrial fibrillation: a Bayesian meta-analysis approach. Expert Opin Drug Saf. 2015;14(1):7–20.

48. Böhm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. J Am Coll Cardiol. 2015;65(23):2481–93.

49. Chan YH, Yeh YH, See LC, Wang CL, Chang SH, Lee HF, et al. Acute kidney injury in Asians with atrial fibrillation treated with dabigatran or warfarin. J Am Coll Cardiol. 2016;68(21):2272–83.

50. Chantrarat T, Hauythan S. The change of renal functions after nonvitamin K oral anticoagulants in patients with atrial fibrillation. Int J Cardiol Heart Vasculature. 2021;35: 100844.

51. Coleman CI, Kreutz R, Sood N, Bunz TJ, Meinecke AK, Eriksson D, et al. Rivaroxaban's impact on renal decline in patients with nonvalvular atrial fibrillation: a US MarketScan Claims Database Analysis. Clin Appl Thromb Hemostasis. 2019;25: 1076029619868535.

52. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol. 2017;70(21):2621–32.

53. Pastori D, Ettorre E, Lip GYH, Sciacqua A, Perticone F, Melillo F, et al. Association of different oral anticoagulants use with renal function worsening in patients with atrial fibrillation: a multicentre cohort study. Br J Clin Pharmacol. 2020;86(12): 2455–63.

54. Zhang C, Gu ZC, Ding Z, Shen L, Pan MM, Zheng YL, et al. Decreased risk of renal impairment in atrial fibrillation patients receiving non-vitamin K antagonist oral anticoagulants: a pooled analysis of randomized controlled trials and real-world studies. Thromb Res. 2019;174:16–23.

55. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes: the ORBIT-AF II Registry. J Am Coll Cardiol. 2016;68(24):2597–604.

56. Andreu Cayuelas JM, Caro Martínez C, Flores Blanco PJ, Elvira Ruiz G, Albendin Iglesias H, Cerezo Manchado JJ, et al. Kidney function monitoring and nonvitamin K oral anticoagulant dosage in atrial fibrillation. Eur J Clin Invest. 2018;48(6): e12907.

57. Alexander JH, Andersson U, Lopes RD, Hijazi Z, Hohnloser SH, Ezekowitz JA, et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. JAMA Cardiol. 2016;1(6): 673–81.

58. 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(22): 2821–30.

59. 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(19):2387–94.

60. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014;129(9):961–70.

61. van der Wall SJ, Teutsch C, Dubner SJ, Diener HC, Halperin JL, Ma CS, et al. Anticoagulation Prescription and Outcomes in Relation to Renal Function in Patients with Atrial Fibrillation: Results from GLORIA-AF. TH Open Companion J Thromb Haemostasis. 2021;5(1):e35–42.

62. Del-Carpio Munoz F, Yao X, Abraham NS, Bellolio MF, Rabinstein AA, Asirvatham SJ, et al. Dabigatran versus warfarin in relation to renal function in patients with atrial fibrillation. J Am Coll Cardiol. 2016;68(1):129–31.

63. Nielsen PB, Lane DA, Rasmussen LH, Lip GY, Larsen TB. Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis. Clin Res Cardiol. 2015;104(5):418–29.

64. Steinberg BA, Shrader P, Pieper K, Thomas L, Allen LA, Ansell J, et al. Frequency and outcomes of

reduced dose non-vitamin K antagonist anticoagulants: results From ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). J Am Heart Assoc. 2018. https://doi.org/10.1161/JAHA.117.007633.

65. Ruiz Ortiz M, Muniz J, Rana Miguez P, Roldan I, Marin F, Asuncion Esteve-Pastor M, et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. Europace. 2018;20(10):1577–83.

66. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of dose-reduced direct oral anticoagulant therapy. Am J Med. 2016;129(11):1198–204.

67. Rohla M, Pecen L, Cemin R, Patti G, Siller-Matula JM, Schnabel RB, et al. Reclassification, thromboembolic, and major bleeding outcomes using different estimates of renal function in anticoagulated patients with atrial fibrillation: insights from the PREFER-in-AF and PREFER-in-AF prolongation registries. Circ Cardiovasc Qual Outcomes. 2021;14(6): e006852.

68. Sato T, Aizawa Y, Fuse K, Fujita S, Ikeda Y, Kitazawa H, et al. The comparison of inappropriate-low-doses use among 4 direct oral anticoagulants in patients with atrial fibrillation: from the database of a single-center registry. J Stroke Cerebrovasc Dis. 2018;27(11):3280–8.

69. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. J Am Coll Cardiol. 2017;69(23):2779–90.

70. Gibson CM, Smith CB, Davis S, Scalese MJ. Assessment of apixaban prescribing patterns for nonvalvular atrial fibrillation in hospitalized patients. Ann Pharmacother. 2018;52(1):54–9.

71. Sukumar S, Gulilat M, Linton B, Gryn SE, Dresser GK, Alfonsi JE, et al. Apixaban concentrations with lower than recommended dosing in older adults with atrial fibrillation. J Am Geriatr Soc. 2019;67(9): 1902–6.

72. Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, et al. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 trial. J Am Heart Assoc. 2016. https://doi.org/10.1161/JAHA.116.003432.

73. Stanifer JW, Pokorney SD, Chertow GM, Hohnloser SH, Wojdyla DM, Garonzik S, et al. Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. Circulation. 2020;141(17):1384–92.

74. Jones MJ, Eudaley ST, Moye RA, Hodge TA, Nesbit RM, Franks AS. Safety outcomes of apixaban in patients with nonvalvular atrial fibrillation and severe renal impairment. J Thromb Thrombolysis. 2020;50(2):330–6.

75. Fazio G, Dentamaro I, Gambacurta R, Alcamo P, Colonna P. Safety of edoxaban 30 mg in elderly patients with severe renal impairment. Clin Drug Investig. 2018;38(11):1023–30.

76. Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-term safety and plasma concentrations of edoxaban in Japanese patients with non-valvular atrial fibrillation and severe renal impairment. Circ J. 2015;79(7):1486–95.

77. Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol. 2010;70(5):703–12.

78. Kreutz RH, Deray G, Floege J, Gwechenberger M, Hahn K, Luft A, et al. A real-word, prospective observational study to compare rivaroxaban versus vitamin K antagonist treatment in patients with non-valvular atrial fibrillation and advanced chronic kidney disease. J Am Coll Cardiol. 2022;79(9; Suppl A):201.

79. Stangier J, Rathgen K, Stähle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate. Clin Pharmacokinet. 2010;49(4):259–68.

80. Martin JL, Esmaeili H, Manuel RC, Petrini M, Wiebe S, Maas H. Pharmacokinetics/pharmacodynamics of dabigatran 75 mg twice daily in patients with nonvalvular atrial fibrillation and severely impaired renal function. J Cardiovasc Pharmacol Ther. 2018;23(5):399–406.

81. Hariharan S, Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. J Clin Pharmacol. 2012;52(1 Suppl):119s-s125.

82. Lehr T, Haertter S, Liesenfeld KH, Staab A, Clemens A, Reilly PA, et al. Dabigatran etexilate in atrial fibrillation patients with severe renal impairment: dose identification using pharmacokinetic modeling and simulation. J Clin Pharmacol. 2012;52(9): 1373–8.

83. Kooiman J, van der Hulle T, Maas H, Wiebe S, Formella S, Clemens A, et al. Pharmacokinetics and pharmacodynamics of dabigatran 75 mg b.i.d in patients with severe chronic kidney disease. J Am Coll Cardiol. 2016;67(20):2442–4.

84. Boehringer Ingelheim Pharmaceuticals Inc. Dabigatran etexilate Product Information. 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s028lbl.pdf. Accessed 21 Mar 2022.

85. Wong CX, Odutayo A, Emdin CA, Kinnear NJ, Sun MT. Meta-analysis of anticoagulation use, stroke, thromboembolism, bleeding, and mortality in patients with atrial fibrillation on dialysis. Am J Cardiol. 2016;117(12):1934–41.

86. Randhawa MS, Vishwanath R, Rai MP, Wang L, Randhawa AK, Abela G, et al. Association between use of warfarin for atrial fibrillation and outcomes among patients with end-stage renal disease: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(4): e202175.

87. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, et al. Outcomes associated with apixaban use in patients with end-stage kidney disease and atrial fibrillation in the United States. Circulation. 2018;138(15):1519–29.

88. Chan KE, Edelman ER, Wenger JB, Thadhani RI, Maddux FW. Dabigatran and rivaroxaban use in atrial fibrillation patients on hemodialysis. Circulation. 2015;131(11):972–9.

89. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. J Am Soc Nephrol. 2017;28(7):2241–8.

90. Wang X, Tirucherai G, Marbury TC, Wang J, Chang M, Zhang D, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. J Clin Pharmacol. 2016;56(5):628–36.

91. De Vriese AS, Caluwe R, Bailleul E, De Bacquer D, Borrey D, Van Vlem B, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis. 2015;66(1):91–8.

92. Parasrampuria DA, Marbury T, Matsushima N, Chen S, Wickremasingha PK, He L, et al. Pharmacokinetics, safety, and tolerability of edoxaban in end-stage renal disease subjects undergoing haemodialysis. Thromb Haemost. 2015;113(4):719–27.

93. Reinecke H, Jürgensmeyer S, Engelbertz C, Gerss J, Kirchhof P, Breithardt G, et al. Design and rationale of a randomised controlled trial comparing apixaban to phenprocoumon in patients with atrial fibrillation on chronic haemodialysis: the AXADIA-AFNET 8 study. BMJ Open. 2018;8(9): e022690.

94. Pokorney SD. Renal hemodialysis patients allocated apixaban versus warfarin in atrial fibrillation—RENAL-AF. Presented at the American Heart Association Annual Scientific Sessions; November 16, 2019; Philadelphia, PA.

95. Andrade JG, Krahn AD, Skanes AC, Purdham D, Ciaccia A, Connors S. Values and preferences of physicians and patients with nonvalvular atrial fibrillation who receive oral anticoagulation therapy for stroke prevention. Can J Cardiol. 2016;32(6):747–53.

96. De Caterina R, Kim Y-H, Koretsune Y, Wang C-C, Yamashita T, Chen C, et al. Safety and effectiveness of edoxaban in atrial fibrillation patients in routine clinical practice: one-year follow-up from the global noninterventional ETNA-AF program. J Clin Med. 2021;10(4):573.

97. de Groot JR, Weiss TW, Kelly P, Monteiro P, Deharo JC, de Asmundis C, et al. Edoxaban for stroke prevention in atrial fibrillation in routine clinical care: 1-year follow-up of the prospective observational ETNA-AF-Europe study. Eur Heart J Cardiovasc Pharmacother. 2020;7(FI1):f30–9.

98. Hahn K, Kröger K. NOAK-Verordnung in verschiedenen Stadien der Niereninsuffizienz. der niedergelassene Arzt. 2021;Issue 02/2021:57–62. https://www.der-niedergelassene-arzt.de/publikationen/zeitschriften/der-niedergelassene-arzt/ausgaben-2021.