

Hawkins, N. M. et al. (2016) Severity of renal impairment in patients with heart failure and atrial fibrillation: implications for non-vitamin K antagonist oral anticoagulant dose adjustment. *European Journal of Heart Failure*, 18(9), pp. 1162-1171. (doi:<u>10.1002/ejhf.614</u>)

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Deposited on: 13 July 2016

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Severity of renal impairment in patients with heart failure and atrial fibrillation: implications for non-vitamin K antagonist oral anticoagulant dose adjustment.

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Short title: Renal impairment in HF and AF: implications for NOACs Word Count: 3496

Abstract

Aims. The non-vitamin K antagonist oral anticoagulants (NOACs) have varying degrees of renal elimination which may be challenging in patients with heart failure (HF) and atrial fibrillation (AF). We examined the severity and variation in renal impairment, and the proportion of patients requiring NOAC cessation or dose reduction.

Methods and results. Retrospective analysis of patients with HF and AF in the Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity program. Trends in renal impairment over 26 months were defined using Cockcroft-Gault (CG), simplified Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) equations. Mean eGFR was worse at every time point in patients with AF compared to those without AF, the difference being approximately 11 ml/min (CG), 9 ml/min (CKD-EPI) and 7 ml/min (MDRD). As renal function declined, CG classified a greater proportion of patients as having moderate or severe CKD and agreement with MDRD/CKD-EPI declined. At least moderate renal impairment was present in one quarter of patients with AF at baseline, one third by study completion, and approaching one half at least once during follow-up. The projected need for NOAC dose reduction was accordingly high, though varied between individual NOACs due to different criteria for adjustment.

Conclusions. Renal impairment in patients with HF and AF is common, fluctuates, progresses, and frequently mandates NOAC dose reduction, though the need for cessation is rare. Baseline renal function, the method of estimating GFR, and intensity of monitoring should be considered when commencing oral anticoagulation.

Keywords: heart failure; atrial fibrillation; renal insufficiency; non-vitamin K antagonist oral anticoagulants

Abbreviations

- ACEI angiotensin enzyme converting inhibitor
- AF atrial fibrillation
- AF-CHF Atrial Fibrillation and Congestive Heart Failure
- ARISTOTLE Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial
- Fibrillation
- BSA body surface area
- CG Cockcroft-Gault
- CKD chronic kidney disease
- CKD-EPI Chronic Kidney Disease Epidemiology Collaborative
- eGFR estimated glomerular filtration rate
- EMA European Medicines Agency
- ENGAGE AF Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation
- LVEF left ventricular ejection fraction
- HF heart failure
- NYHA New York Heart Association
- MDRD Modification of Diet in Renal Disease
- NOACs non-vitamin K antagonist oral anticoagulant drugs
- RELY Randomized Evaluation of Long-Term Anticoagulation Therapy
- 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

Introduction

Heart failure (HF), atrial fibrillation (AF) and chronic kidney disease (CKD) form a complex and dangerous triad. Their incidence, prevalence and severity are all interrelated, through shared pathophysiological mechanisms and risk factors such as diabetes and hypertension. Each is a powerful independent and additive predictor of mortality and hospitalisations.^{1,2} The confluence of all three also engenders a thrombotic-haemorrhagic paradox: CKD and HF increase both the risk of stroke and the risk of haemorrhage in patients with AF.³⁻⁶ The balance between the benefit and risk of anticoagulation in AF patients with significant CKD is uncertain, which is a particular concern in HF where the combination of CKD and AF is especially common. In the EuroHeart Surveys for HF and AF, a history of renal insufficiency was present in 13% and 10% of patients with concurrent AF and HF respectively.^{7, 8} This prevalence doubled to 20% in patients hospitalized with HF in the Get With The Guidelines registry.⁹ However, over half of patients admitted to a Spanish hospital with decompensated HF had significant renal impairment when defined using eGFR < 60 ml/min.¹⁰

Although the pivotal trials of non-vitamin K antagonist oral anticoagulant drugs (NOACs) included patients with HF (approximately one third of patients in ARISTOTLE and RELY, over one half in ENGAGE AF, and two thirds in ROCKET-AF),¹¹⁻¹⁴ individuals with severe CKD (creatinine clearance < 25 or 30 ml/min) were excluded as NOACs exhibit varying degrees of renal excretion. In patients with lesser degrees of renal dysfunction NOAC dose adjustment is recommended.¹⁵ Use of NOACs in patients with HF may therefore be complicated by concomitant CKD, not just at the time of initiation but also subsequently given that renal dysfunction tends to decline over time in HF. To better understand this potential problem, we examined the proportion of patients with moderate or severe renal impairment that would prompt NOAC dose adjustment at baseline and adjustment or discontinuation over follow up in the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) programme.

Methods

The rationale, methods, eligibility criteria and outcomes of the CHARM programme have been published previously.^{16, 17} Key exclusion criteria included serum creatinine e 3 mg/dL (265 ¼mol/L), serum potassium e 5.5 mmol/L, known bilateral renal artery stenosis, symptomatic hypotension, and critical valve disease. Eligible consented patients with symptomatic heart failure (New York Heart Association [NYHA] class II-IV) were enrolled into one of three parallel clinical trials according to left ventricular ejection fraction (LVEF) and angiotensin converting enzyme inhibitor (ACEI) treatment: LVEF \leq 40% and not receiving an ACEI due to previous intolerance (CHARM-Alternative, n=2028); LVEF \leq 40% receiving ACEI treatment (CHARM-Added, n=2548); and LVEF > 40% (CHARM-Preserved, n=3023). There were 7599 patients randomised, 3803 receiving candesartan and 3796 placebo. Patients enrolled in North America underwent central laboratory measurement of creatinine at baseline, 6 weeks, 14 months and 26 months (Visits 1, 4, 7 and 10). There were 2673 patients with a valid creatinine after exclusion of 2 patients with baseline serum creatinine concentration recorded > 10 mg/dL.

Population with atrial fibrillation

The CHARM dataset contains 3 variables referring to AF: medical history of AF (n=2084), AF on baseline ECG (n=1148);¹⁸ and new AF detected during the study (n=392).¹⁹ Overall 2527 (33.3%) of patients had AF defined by one or more of these variables. Previous CHARM analyses have examined patients with baseline ECG AF,¹⁸ or development of new AF.¹⁹ However, this does not capture a proportion of patients for whom anticoagulation is indicated with either paroxysmal AF or persistent AF restored to sinus rhythm before enrolment. Conversely, including all patients with a history of reported AF likely overestimates the population requiring anticoagulation, as

diagnoses may be inaccurate or include isolated episodes (e.g. sepsis, peri-operative) for which lifelong anticoagulation is inappropriate. We compromised by including patients with a history of AF who were also prescribed anticoagulants at baseline. The final group with AF consisted of 1666 (21.9%) patients: baseline ECG AF (n=1148) and prior AF with baseline anticoagulation (n=1348 of whom 830 with baseline ECG AF).

eGFR equations

Estimated GFR (ml/min) was calculated using three widely accepted methods,^{20, 21} the Cockcroft-Gault (CG),²² simplified Modification of Diet in Renal Disease (MDRD),²³ and Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) equations. Pharmacokinetic studies and NOAC clinical trials have used the CG method to estimate renal function, leading to adoption as the standard for drug dosing and drug labels. The equation includes weight and estimates raw creatinine clearance without normalisation to body surface area (BSA), thus being particularly relevant to drug elimination. The CG formula is recommended for drug dosing by the National Kidney Foundation and the product monograph of all four NOACs. Actual as opposed to ideal body weight was utilised as estimates based on actual weight demonstrate greater concordance with measured GFR.²⁴ CG eGFR (= $[140 - age] \times$ weight (kg) × 1.23 or 1.03 (males or females) / serum creatinine (µmol/L).

By contrast, both the MDRD and CKD-EPI equations estimate GFR adjusted for BSA $(ml/min/1.73m^2)$ using serum creatinine, age, sex and race. We de-normalised results to estimate raw GFR by multiplying by BSA divided by 1.73 m².^{24, 25} BSA was calculated with the Dubois and Dubois formula as used to develop the MDRD and CKD EPI formula,²³ where BSA(m²) = 0.007184 × height^{0.725} (cm) × weight^{0.425} (kg).²⁶ The original simplified MDRD four component equation,^{21, 23, 27, 28} was subsequently re-expressed for serum creatinine standardised to isotope dilution mass spectrometry (IDMS),^{29, 30} permitting direct comparison with the IDMS calibrated

CKD-EPI definitions. MDRD eGFR = $30849 \times (\text{Scr }\mu\text{mol/L})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ [if female] × 1.212 [if black].

The CKD-EPI formula was derived from a larger, more representative sample of the U.S. population.³¹ The principal benefit is improved accuracy compared with the MDRD formula for estimates higher than 60 ml/min/1.73m². The CKD-EPI single equation is eGFR = 141 × min(Scr/°, 1)[±] × max(Scr/°, 1)^{-1.209} × (0.993)^{Age} × 1.018 [female] × 1.159 [if black], where Scr is serum creatinine, ° is 0.7 for females and 0.9 for males, ± is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/° or 1, and max indicates the maximum of Scr/° or 1.³¹

Statistical analysis and renal impairment classification

Unadjusted (ml/min) and body surface area adjusted (ml/min/1.73m²) estimates of GFR are respectively employed to describe renal impairment for drug dosing and the extent of renal disease. Severity of both entities is classified using identical thresholds. A renal clearance drug is removed from the body proportional to absolute (unadjusted) creatinine clearance rather than the normalised version. A normalised GFR will under- and over-estimate drug removal in large and small patients respectively. We therefore present unadjusted or denormalised values.

Severity of renal impairment was graded according to eGFR (ml/min) and the European Medicines Agency (EMA) as recommended in all four NOAC product monographs (Table 1): normal (>80), mild (50 – 80), moderate (30 – 50), severe (15 – 30), very severe (<15). These differ from the National Kidney Foundation thresholds for normal and mild renal impairment (90 and 60 respectively).³² Data are reported as frequencies and percentages. Logistic regression was used to identify independent predictors of moderate and severe renal impairment according to CG equation. The following 15 baseline variables were selected as candidate predictors of worsening renal function (WRF) based on univariate association (p<0.1) (eGFR, candesartan treatment, systolic blood pressure, diuretics, age, height, weight, urea, haemoglobin) or clinical rationale combined

with results of recent meta-analysis of WRF in HF (ACEI, sex, ejection fraction, diabetes, hypertension, spironolactone).³³

Impact of candesartan treatment

In CHARM overall, candesartan titration was associated with a significant decrease in eGFR at 6 weeks relative to placebo (-5.0 \pm 18.4 versus -0.4 \pm 17.9 mL/min (p<0.001)), with no further significant treatment-time interaction beyond the titration phase. We included the 6 week time point in the primary analysis to reflect clinical practice in which neurohormonal antagonists and diuretics are regularly introduced and titrated, and because candesartan treatment was only one among a number of predictors of worsening renal function. Moreover, the associated decline in eGFR had minimal impact on the total proportion of patients with moderate or severe renal impairment during long term follow-up. A sensitivity analysis excluding measurements at the 6 week time point is presented in the online Appendix).

Results

Baseline characteristics stratified by presence of AF and severity of renal impairment are presented in Online Appendix Tables 1 and 2. Compared to patients without AF, those with AF were older, had a more frequent history of hypertension and stroke, higher virtual CHADS₂ scores (mean 2.8 (SD 1.1) vs. 2.5 (SD 1.0), p<0.001), and were more often prescribed oral anticoagulation, digoxin and amiodarone.

Mean eGFR was worse at every time point in patients with AF compared to those without AF, irrespective of the estimation method (p<0.001 for every comparison). The difference in means was approximately 11 ml/min (CG), 9 ml/min (CKD-EPI) and 7 ml/min (MDRD) (Table 2). At baseline, one quarter of patients with AF had at least moderate renal impairment (eGFR <50 ml/min) estimated using CG (27.9%), MDRD (26.5%), or CKD-EPI (26.7%) (Table 2). The

prevalence of at least moderate renal impairment in patients with AF increased over time, whether measured using either CG, MDRD or CKD-EPI: CG at baseline, 6 weeks, 14 months and 26 months respectively 27.9%, 31.5%, 35.3% and 34.0% (p=0.07); MDRD 26.5%, 29.9%, 33.2%, 29.7% (p=0.16); CKD-EPI 26.7%, 29.5%, 32.7%, 29.4% (p=0.24).

Fluctuation of CKD severity over time

Among the 2673 patients with documented baseline creatinine, 2530 had at least one additional measurement. CKD severity according to CG, MDRD and CKD-EPI remained stable or improved in around two thirds (67.7%, 64.1% and 67.7% respectively) of patients with AF and serial measurements, and declined in the remaining third (32.3%, 35.9% and 32.3% respectively) (Table 3). Considering only moderate or severe CKD, one fifth of patients with AF were stable from baseline onwards (CG 22.6%, MDRD 20.3%, CKD-EPI 20.7%). A similar proportion had worsening renal impairment of at least moderate severity across the four visits (CG 21.4%, MDRD 23.7%, CKD-EPI 22.4%). Considering all time points, nearly half (44.0%) of patients with AF had either stable or fluctuating moderate or severe renal impairment applying the Cockcroft-Gault formula and EMA classification as recommended in the product monograph. This was greater than observed in patients without AF (44.0% vs 30.4%, p<0.001). Sensitivity analysis excluding creatinine measurements at week 6 (the candesartan titration phase) yielded similar results (42.0% vs 28.5%, p<0.001) (Online Appendix Table 3).

Prediction of moderate or severe CKD by baseline eGFR

Deterioration by greater than one severity class was unusual. Most patients who developed moderate renal impairment (<50 ml/min) during the study had mild baseline dysfunction (<80 ml/min). Likewise, most patients who developed severe renal impairment (<30 ml/min) had

moderate baseline dysfunction (<50 ml/min) (Figure 1). Four independent predictors of worsening moderate to severe renal impairment were identified (Table 4). Baseline eGFR (OR 1.20 [1.10 – 1.30] per 10 ml/min decrease) and allocation to candesartan treatment (OR 2.54 [1.60 – 4.05]) were the most powerful predictors, with background ACE inhibitor treatment, diuretics and systolic blood pressure exhibiting modest predictive value.

Concordance between EMA classes applying Cockcroft-Gault, MDRD and CKD-EPI formula

Among patients with AF, the concordance between EMA class according to CG and MDRD was high in the normal eGFR range (80% concordance > 80 ml/min) but declined with declining renal function (66% concordance <30 ml/min) (Figure 2A). A similar pattern was observed comparing CG against CKD-EPI (Figure 2B). With worsening renal function MDRD or CKD-EPI typically classified kidney dysfunction as less severe than did the CG equation. For example, at baseline 25% and 23% of patients with AF classified as moderate CKD by CG were reclassified as mild CKD by the MDRD and CKD-EPI estimates, respectively. However, only a minority of patients (10%) classified as having moderate CKD by the MDRD and CKD-EPI equations had a milder degree of renal function according to the CG estimate. These relationships held true for patients with and without AF (data not presented). Concordance of EMA classes based on MDRD compared with CKD-EPI was very high for all levels of severity (93% to 99%) (Figure 2C).

Incidence of recommended dose reduction or discontinuation due to renal impairment

In the US, all four licensed NOACs are contraindicated in very severe renal impairment (eGFR <15 ml/min) which was rare during follow-up (0.4%). However, edoxaban is also not recommended in patients with eGFR >95 ml/min, which precluded over one quarter of patients (23.6% at baseline and a further 5.7% during follow-up).

Apixaban dose reduction (2 of 3 criteria Table 1) was projected in 7.0% and 3.4% of patients at baseline and follow-up, respectively (Figure 3, and Online Appendix Table 4). In the US, dabigatran dose reduction is only indicated in severe renal impairment (eGFR 15 - 30 ml/min), potentially affecting a similar proportion of patients to the apixaban criteria: 6.4% at baseline and 5.4% during follow-up. By contrast, rivaroxaban and edoxaban dose reduction is recommended in moderate or severe renal impairment (eGFR 15 - 50 ml/min), affecting 27.5% of patients at baseline and a further 15.7% during follow-up.

European prescribing guidance is identical to the US for rivaroxaban, similar for apixaban, and more stringent for dabigatran and edoxaban (Table 1). In Europe at baseline and follow-up respectively, renal impairment would prohibit dabigatran in 6.8% and 5.4% of patients, with dose reduction in 14.8% and 7.5% (Figure 3). Of the 6.8% ineligible for dabigatran at baseline, 2.0% experienced sufficient improvement in renal function to become eligible during follow-up.

Discussion

In this ambulatory clinical trial heart failure population, patients with concurrent AF had significantly greater renal impairment than those without AF, which fluctuated and progressed over time. At least moderate renal impairment was present in one quarter of patients with AF at baseline, one third by study completion, and approaching one half at least once during follow-up. With worsening renal function CG classified a greater proportion of patients as having moderate or severe CKD and agreement with MDRD/CKD-EPI declined. Although severe renal impairment was uncommon, a significant proportion of patients would require NOAC dose reduction at baseline or during follow-up.

Severity and variability of renal impairment

Baseline renal dysfunction is common in both HF and AF cohorts and trial populations.^{33,35} Worsening renal function is also common, observed in 23% of patients with HF in meta-analysis.³³ In the few studies examining WRF in AF, a similar proportion of patients experienced WRF to that seen in HF trials.^{34, 35} Both HF and AF have many reasons to either cause or be associated with baseline and worsening renal impairment, many of which may interact. However, very few studies have defined renal function in patients with both conditions. In 1365 patients with systolic dysfunction and recent history of AF enrolled in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial,²⁸ the severity of renal impairment was normal, mild, moderate and severe in 9%, 44%, 43% and 3% of patients respectively. Our baseline characteristics appear discordant with these findings (33%, 41%, 21%, 6%, respectively, based upon MDRD). However, we denormalised estimates and employed EMA thresholds. Re-analysis using normalised MDRD and National Kidney Foundation thresholds returns very similar results to the AF-CHF analysis (10%, 39%, 44% and 7% respectively). This highlights the impact of varying definitions when classifying severity.

We extend the AF-CHF findings by comparing to HF 'controls' without AF, and examining renal function over time. The severity and variability of renal impairment in those with HF and AF together exceeded that in HF alone. Mean eGFR was worse at every time point utilising any estimation method. Accordingly, at least moderate renal impairment was around 50% more frequent in those with AF compared to those without (44.0% vs 30.4% over all periods using CG). A recent study found a similar proportion of renal impairment (57% with CrCl <60 mL/min) over 6 months in patients discharged following decompensated HF with concurrent AF.¹⁰

Anticoagulation dilemmas in patients with coexistent HF-AF-CKD

Patients with HF-AF have high thromboembolic risk yet low levels of appropriate anticoagulation. At best, two thirds of patients without contraindication receive oral anticoagulation: 68% of concurrent HF in the Euro Heart Survey for AF;³⁶ 65% of concurrent AF in the Get With The Guidelines HF program.³⁷ Moreover, HF is strongly associated with reduced time in therapeutic range (TTR), the single most important predictor of warfarin effectiveness and safety.³⁸ To compound matters, renal impairment is also an independent predictor of low TTR, haemorrhagic complications, and warfarin underutilisation.^{4, 5, 37, 39} Moreover, an analysis from RELY recently demonstrated greater progression of renal impairment with warfarin compared to dabigatran, possibly due to VKA effects on vascular atherosclerosis and calcification.⁴⁰ NOACs potentially address these issues through improved patient adherence and more consistent anticoagulation, yet at the same time renal impairment may increase bleeding risk and necessitate closer monitoring.

Clinical relevance of renal impairment in NOAC therapy

Maximum plasma concentrations and area under curve exposure increase with WRF, correlating with the extent of renal elimination for individual NOACs. Anticoagulant effects increase accordingly, though are typically modest. The clinical impact of pharmacodynamic changes is uncertain. In the landmark AF trials, bleeding rates were higher in moderate renal insufficiency irrespective of treatment allocation.⁴¹⁻⁴³ Overall efficacy and net clinical benefit compared to warfarin were consistent with the overall trials, with no significant heterogeneity across renal function strata. However, in RELY the relative reduction in major bleeding compared with warfarin was less in patients with eGFR <50 mL/min with either dabigatran dose.⁴³ The opposite was true in ARISTOTLE, where the relative reduction for major bleeding associated with apixaban was greatest in patients with eGFR d50 ml/min.⁴² By contrast, no such interaction was observed between renal function, treatment and major bleeding in ROCKET-AF.⁴¹ Accordingly the updated European Heart Rhythm Association Practical Guide and a recent practical review both

suggest dabigatran be second choice in patients with moderate renal impairment, with preference expressed for apixaban, or reduced dose rivaroxaban or edoxaban.^{44,45}

Clinical relevance of concordance between eGFR assessment methods

Most biochemistry laboratories provide MDRD-derived eGFR normalised for BSA. A recent cross-sectional community based study in elderly patients with AF found 15% of patients judged eligible for dabigatran applying MDRD were ineligible by CG equation.⁴⁶ We also found relative to CG that MDRD reclassified one quarter of moderate CKD as mild. Assuming CG measurements are relevant to the safety of dosing of NOACs (which is not certain), use of MDRD would result in a significant proportion of patients being over-treated or over-dosed. NOAC dose adjustment should be guided by CG estimates for many reasons: CG was employed in the pivotal NOAC trials, is recommended in the product monograph and international guidelines,⁴⁴ estimates creatinine clearance without normalisation to BSA, and is accepted practice for pharmacokinetic studies and dose adjustment.

Incidence of recommended dose reduction or discontinuation

Very few patients developed renal impairment sufficient to mandate discontinuation of any NOAC according to EU guidance. During follow-up the projected incidence of dose reduction was lowest for apixaban (7%) and highest for rivaroxaban and edoxaban (16%) due to the product labelling in relation to moderate renal impairment. Surprisingly, an additional half of patients would require dose reduction of edoxaban at baseline, due to the combination of moderate renal impairment (CrCl 15–50 ml/min) and weight criteria (d60kg).

The criteria for dabigatran diverge considerably between EU and US guidelines: the projected incidence of dose reduction or cessation was similar to apixaban using US guidance, but

approached that of rivaroxaban using the EU regulations. The discrepancy is concerning given the high renal elimination of dabigatran and the recently reported effect of plasma concentrations on major bleeding.⁴⁷

Limitations

This clinical trial population may underestimate the severity of renal impairment in real-life due to exclusion criteria, recruitment bias with younger patients and fewer comorbidities, and trial mandated close follow-up maintaining clinical stability; most pertinent of all, patients with a serum creatinine e 3 mg/dL (265 ¼mol/L) were excluded from CHARM. However, our findings reflect the minimum extent of the problem concerning NOAC use in patients with HF. Temporal changes in some determinants of estimated renal function could not be assessed e.g. diuretic dose. Severity is underestimated by survivorship i.e. patients with WRF which could precipitate excess anticoagulation and bleeding died prior to their next routine trial bloodwork. Bleeding risk could not be assessed but may influence dose reduction decisions. The CHARM trial predates the NOAC era and may not accurately represent contemporary practice. In particular, mineralocorticoid receptor antagonists are now recommended for a broader spectrum of patients and may further impact renal function and NOAC eligibility.

Conclusions

Patients with HF and AF have greater renal impairment than those without AF. Renal impairment fluctuates, progresses, and would frequently mandate NOAC dose reduction, though the need for cessation is rare. Baseline renal function, the method of estimating GFR, and intensity of monitoring should be considered when commencing oral anticoagulation. NOACs are the most commonly prescribed medication which require dose adjustment in renal impairment. Just as

warfarin required organised systems of care, so too must health systems adapt to the new challenges

of NOACs.

Funding

The authors received no financial support in preparation of the manuscript.

Conflicts of Interest

Conflicts of Interest: none declared.

	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
	ARISTOTLE	RELY	ROCKET-AF	ENGAGE AF
Drug class	Factor Xa inhibitor	Direct thrombin	Factor Xa inhibitor	Factor Xa inhibitor
-	(FXa)	inhibitor (DTI)	(FXa)	(FXa)
Renal excretion	25% renal	80% renal	30-40% renal	50% renal
Landmark trial	25-30 n=268	30 - 50 n=3374	30-50 n=1481	30-50 n=4074
population	30-50 n=2737	50 - 80 n=10697	50-80 n=3290	
stratified by eGFR	50-80 n=7587	>80 n=3880	> 80 n=2278	
	> 80 n=7518			
Recommended	Cockcroft-Gault	Cockcroft-Gault	Cockcroft-Gault	Cockcroft-Gault
method eGFR	(ml/min)	(ml/min)	(ml/min)	(ml/min)
Recommended	Annually	Annually if moderate	Annually	-
minimum renal		renal impairment		
monitoring				
EU EMA	revised 10/2015	revised 9/2015	revised 7/2015	revised 7/2015
Dose reduction	If 2 of 3:	e 80 years	CrCl 15 – 49 ml/min	CrCl 15 – 50 ml/min
	1) e 80 years	e 75 years with		or
	2) d 60 kg	additional bleeding		weight d60kg
	3) sCr e 133µmol/L	risk factor including		
	(1.5 mg/dL)	moderate impairment		
	or:	CrCl 30 – 50 ml/min		
	CrCl 15 – 29 ml/min			
Contraindication	CrCl < 15 ml/min	CrCl < 30 ml/min	CrCl < 15 ml/min	CrCl < 15 ml/min
US FDA	revised 9/2015	revised 10/2015	revised 9/2015	revised 9/2015
Dose reduction	If 2 of 3:	CrCl 15 – 30 ml/min	CrCl 15 – 50 ml/min	CrCl 15 – 50 ml/min
	1) e 80 years			
	2) d 60 kg			
	3) sCr e 133µmol/L			
	(1.5 mg/dL)			
Contraindication	CrCl < 15 ml/min	CrCl < 15 ml/min	CrCl < 15 ml/min	CrCl < 15 ml/min
				CrCl > 95 ml/min

Table 1. Summary of product monograph and renal information for the pivotal NOAC trials

Table 2. Severity of renal impairment in patients with and without atrial fibrillation, stratified by eGFR using the Cockcroft-Gault, de-normalised MDRD and CKD-EPI.

Cockcroft			MDRD		CKD-EPI	
	AF	No AF	AF	No AF	AF	No AF
Baseline (n)	559	2114	559	2114	559	2114
$Mean (\pm SD)$	74.4 (38.7)	86.4 (44.2)	70.5 (29.6)	78.6 (32.4)	71.0 (29.1)	80.2 (31.3)
Normal (> 80) (%)	36.7	47.0	32.6	43.7	33.8	47.3
Mild (50 – 80) (%)	35.4	34.1	41.0	38.2	39.5	35.0
Moderate (30 – 49) (%)	21.1	15.3	20.8	15.0	20.2	14.5
Severe (< 30) (%)	6.8	3.6	5.7	3.0	6.4	3.3
At least moderate (%)	27.9	18.9	26.5	18.1	26.7	17.8
6 weeks (n)	501	1902	501	1902	501	1902
$Mean (\pm SD)$	73.4 (39.3)	84.4 (44.3)	68.6 (29.1)	76.5 (32.7)	69.4 (29.5)	78.1 (31.5)
Normal (> 80) (%)	34.9	45.3	31.1	40.5	32.7	44.5
Mild (50 – 80) (%)	33.5	34.3	38.9	38.3	37.7	34.8
Moderate (30 – 49) (%)	24.0	16.4	23.2	17.0	22.4	16.6
Severe (< 30) (%)	7.6	4.0	6.8	4.2	7.2	4.2
At least moderate (%)	31.5	20.3	29.9	21.2	29.5	20.8
At least moderate (%) 14 months (n)	31.5 419	20.3 1657	29.9 419	21.2 1657	29.5 419	20.8 1657
At least moderate (%) 14 months (n) Mean (±SD)	31.5 419 70.6 (37.1)	20.3 1657 82.1 (43.6)	29.9 419 66.0 (27.5)	21.2 1657 74.0 (32.7)	29.5 419 67.2 (28.8)	20.8 1657 75.8 (31.8)
At least moderate (%) 14 months (n) <i>Mean</i> (± <i>SD</i>) Normal (> 80) (%)	31.5 419 70.6 (37.1) 32.0	20.3 1657 82.1 (43.6) 43.8	29.9 419 66.0 (27.5) 28.4	21.2 1657 74.0 (32.7) 37.5	29.5 419 67.2 (28.8) 31.7	20.8 1657 75.8 (31.8) 41.4
At least moderate (%) 14 months (n) <i>Mean</i> (± <i>SD</i>) Normal (> 80) (%) Mild (50 - 80) (%)	31.5 419 70.6 (37.1) 32.0 32.7	20.3 1657 82.1 (43.6) 43.8 33.9	29.9 419 66.0 (27.5) 28.4 38.4	21.2 1657 74.0 (32.7) 37.5 39.2	29.5 419 67.2 (28.8) 31.7 35.6	20.8 1657 75.8 (31.8) 41.4 35.9
At least moderate (%) 14 months (n) $Mean (\pm SD)$ Normal (> 80) (%) Mild (50 - 80) (%) Moderate (30 - 49) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2	20.3 1657 82.1 (43.6) 43.8 33.9 17.0	29.9 419 66.0 (27.5) 28.4 38.4 25.5	21.2 1657 74.0 (32.7) 37.5 39.2 17.7	29.5 419 67.2 (28.8) 31.7 35.6 25.1	20.8 1657 75.8 (31.8) 41.4 35.9 16.8
At least moderate (%)14 months (n) $Mean (\pm SD)$ Normal (> 80) (%)Mild (50 - 80) (%)Moderate (30 - 49) (%)Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9
At least moderate (%) 14 months (n) $Mean (\pm SD)$ Normal (> 80) (%) Mild (50 - 80) (%) Moderate (30 - 49) (%) Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7
At least moderate (%) 14 months (n) Mean (±SD) Normal (> 80) (%) Mild (50 – 80) (%) Moderate (30 – 49) (%) Severe (< 30) (%) At least moderate (%) 26 months (n)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3 347	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4 1386	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2 347	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4 1386	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7 347	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7 1386
At least moderate (%)14 months (n) $Mean (\pm SD)$ Normal (> 80) (%)Mild (50 - 80) (%)Moderate (30 - 49) (%)Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3 347 73.6 (43.0)	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4 1386 83.8 (43.6)	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2 347 68.3 (31.0)	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4 1386 75.2 (32.8)	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7 347 69.2 (30.3)	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7 1386 77.3 (31.8)
At least moderate (%) 14 months (n) $Mean (\pm SD)$ Normal (> 80) (%) Mild (50 - 80) (%) Moderate (30 - 49) (%) Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3 347 73.6 (43.0) 33.7	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4 1386 83.8 (43.6) 45.7	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2 347 68.3 (31.0) 28.0	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4 1386 75.2 (32.8) 40.2	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7 347 69.2 (30.3) 30.3	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7 1386 77.3 (31.8) 44.5
At least moderate (%)14 months (n) $Mean (\pm SD)$ Normal (> 80) (%)Mild (50 - 80) (%)Moderate (30 - 49) (%)Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3 347 73.6 (43.0) 33.7 32.3	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4 1386 83.8 (43.6) 45.7 32.6	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2 347 68.3 (31.0) 28.0 42.4	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4 1386 75.2 (32.8) 40.2 37.2	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7 347 69.2 (30.3) 30.3 40.3	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7 1386 77.3 (31.8) 44.5 33.7
At least moderate (%)14 months (n) $Mean (\pm SD)$ Normal (> 80) (%)Mild (50 - 80) (%)Moderate (30 - 49) (%)Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3 347 73.6 (43.0) 33.7 32.3 28.5	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4 1386 83.8 (43.6) 45.7 32.6 17.1	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2 347 68.3 (31.0) 28.0 42.4 23.6	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4 1386 75.2 (32.8) 40.2 37.2 17.5	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7 347 69.2 (30.3) 30.3 40.3 23.1	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7 1386 77.3 (31.8) 44.5 33.7 16.4
At least moderate (%)14 months (n) $Mean (\pm SD)$ Normal (> 80) (%)Mild (50 - 80) (%)Moderate (30 - 49) (%)Severe (< 30) (%)	31.5 419 70.6 (37.1) 32.0 32.7 27.2 8.1 35.3 347 73.6 (43.0) 33.7 32.3 28.5 5.5	20.3 1657 82.1 (43.6) 43.8 33.9 17.0 4.9 22.4 1386 83.8 (43.6) 45.7 32.6 17.1 4.5	29.9 419 66.0 (27.5) 28.4 38.4 25.5 7.6 33.2 347 68.3 (31.0) 28.0 42.4 23.6 6.1	21.2 1657 74.0 (32.7) 37.5 39.2 17.7 5.7 23.4 1386 75.2 (32.8) 40.2 37.2 17.5 5.2	29.5 419 67.2 (28.8) 31.7 35.6 25.1 7.6 32.7 347 69.2 (30.3) 30.3 40.3 23.1 6.3	20.8 1657 75.8 (31.8) 41.4 35.9 16.8 5.9 22.7 1386 77.3 (31.8) 44.5 33.7 16.4 5.4

Table 3. Proportion of patients with stable versus worsening renal impairment across serial measurements stratified by atrial fibrillation, according to the European Medicines Agency classification using the Cockcroft-Gault, MDRD and CKD-EPI methods.

CG			MDRD		CKD-EPI	
	AF	No AF	AF	No AF	AF	No AF
n with e 2 measures	527	2003	527	2003	527	2003
Stable renal function (%)	67.7	71.2	64.1	63.9	67.7	65.9
Normal (> 80) (%)	25.4	33.8	18.0	25.9	21.4	30.1
Mild (50 – 80) (%)	19.7	23.5	25.8	25.3	25.6	23.1
Moderate $(30 - 49)$ (%)	16.7	10.9	15.6	10.0	15.2	9.7
Severe $(15 - 30)$ (%)	5.9	3.0	4.7	2.6	5.5	2.8
Stable e moderate (%)	22.6	13.9	20.3	12.6	20.7	12.6
Worse renal function (%)	32.3	28.8	35.9	36.1	32.3	34.1
Mild (>50) (%)	10.8	12.3	12.1	15.8	9.9	14.7
Moderate $(30 - 49)$ (%)	15.4	11.3	16.7	14.0	15.2	13.5
Severe $(15 - 30)$ (%)	5.7	4.7	6.5	5.8	6.6	5.5
Very Severe (< 15) (%)	0.4	0.4	0.6	0.5	0.6	0.5
Vary e moderate (%)	21.4	16.5	23.7	20.3	22.4	19.5
All e moderate (%)	44.0	30.4	44.0	33.0	43.1	32.1

Figure 1. Relative proportion of patients with AF stratified by baseline Cockcroft-Gault eGFR developing varying degrees of renal impairment during follow-up (moderate, severe or very severe).



Figure 2. Percentage of patients with AF reclassified into different EMA stages at baseline when estimating GFR using Cockcroft-Gault, MDRD and CKD-EPI equations.



	Odds Ratio (95% CI)	Wald	p value
	Multivariate Analysis	Chi	
eGFR (per 10 ml/min decrease)	1.20 (1.10 – 1.30)	14.7	< 0.001
Candesartan	2.54 (1.60 - 4.05)	15.4	< 0.001
Systolic BP (per 10 mmHg increase)	1.16 (1.04 – 1.29)	6.5	0.011
ACE inhibitor	1.68 (1.06 – 2.67)	4.8	0.029

Table 4. Independent predictors of worsening moderate to severe renal impairment.

ACEI, angiotensin enzyme converting inhibitor; eGFR, estimated glomerular filtration rate.

Figure 3. Proportion of patients requiring discontinuation or dose reduction of each novel oral anticoagulant at baseline and during follow-up, applying the EU and US product monograph guidance and Cockcroft-Gault equation.



Online Appendix Table 1. Baseline characteristics according to presence or absence of atrial fibrillation.

mean (SD) or n (%)	AF	No AF
	n=559	n=2114
Demographics		
Age (years)	69.2 (10.3)	64.2 (11.7)
Female sex	161 (28.8)	732 (34.6)
Weight (kg)	86.2 (21.5)	86.1 (21.2)
Thromboembolic risks		
Hypertension	385 (68.9)	1395 (66.0)
Age e 75	203 (36.3)	445 (21.1)
Diabetes Mellitus	196 (35.1)	800 (37.8)
Stroke	92 (16.5)	189 (8.9)
Virtual CHADS ₂ score		
Mean score	2.8 (1.1)	2.5 (1.0)
1	59 (10.6)	332 (15.7)
2	181 (32.4)	811 (38.4)
3	211 (37.7)	717 (33.9)
4	53 (9.5)	163 (7.7)
5	45 (8.1)	72 (3.4)
6	10 (1.8)	19 (0.9)
Cardiovascular History		
Myocardial Infarction	256 (45.8)	1164 (55.1)
Angina	295 (52.8)	1385 (65.5)
CABG	186 (33.3)	674 (31.9)
PCI	83 (14.8)	459 (21.7)
Heart failure		
Ejection Fraction	39.3 (16.3)	38.3 (15.7)
NYHA Class		
II	177 (31.7)	794 (37.6)
III	354 (63.3)	1275 (60.3)
IV	28 (5.0)	45 (2.1)
Heart rate (beats/min)	71.3 (11.8)	72.0 (12.0)
Systolic BP (mm Hg)	125.4 (18.4)	128.9 (18.7)
Diastolic BP (mm Hg)	72.0 (10.6)	74.1 (10.7)
Medical treatment		
ACE inhibitor	272 (48.7)	944 (44.7)
Beta-blocker	259 (46.3)	1221 (57.8)
Spironolactone	104 (18.6)	297 (14.0)
Oral anticoagulation	514 (91.9)	298 (14.1)
Digoxin	405 (72.5)	1023 (48.4)
Amiodarone	142 (25.4)	153 (7.2)
Diuretics	519 (92.8)	1790 (84.7)

BP, blood pressure; CABG, coronary artery bypass graft surgery; NYHA, New York Heart Association; SD, standard deviation

Online Appendix Table 2. Baseline characteristics stratified by severity of renal impairment according to the European Medicines Agency classification using the Cockcroft-Gault estimation

mean (SD) or n (%)	Normal	Mild	Moderate	Severe
	n=1199	n=918	n=442	n=114
Demographics				
Age (years)	58.0 (10.5)	69.2 (8.7)	73.6 (7.9)	77.3 (6.9)
Female sex	322 (26.9)	317 (34.5)	190 (43.0)	64 (56.1)
Weight (kg)	98.5 (20.9)	80.2 (15.1)	71.3 (14.2)	62.7 (11.7)
Thromboembolic risks				
Hypertension	766 (63.9)	626 (68.2)	300 (67.9)	88 (77.2)
Age e 75	65 (5.4)	276 (30.1)	228 (51.6)	79 (69.3)
Diabetes Mellitus	470 (39.2)	315 (34.3)	172 (38.9)	39 (34.2)
Stroke	100 (8.3)	108 (11.8)	52 (11.8)	21 (18.4)
CHADS ₂ score				
Mean score	2.3 (1.0)	2.6 (1.1)	2.9 (1.0)	3.2 (1.1)
1	247 (20.6)	117 (12.7)	24 (5.4)	3 (2.6)
2	482 (40.2)	341 (37.1)	146 (33.0)	23 (20.2)
3	376 (31.4)	320 (34.9)	179 (40.5)	53 (46.5)
4	59 (4.9)	75 (8.2)	61 (13.8)	21 (18.4)
5	32 (2.7)	52 (5.7)	25 (5.7)	8 (7.0)
6	3 (0.3)	13 (1.4)	7 (1.6)	6 (5.3)
Cardiovascular History				
Myocardial Infarction	573 (47.8)	516 (56.2)	266 (60.2)	65 (57.0)
Angina	729 (60.8)	589 (64.2)	288 (65.2)	74 (64.9)
CABG	327 (27.3)	325 (35.4)	166 (37.6)	42 (36.8)
PCI	259 (21.6)	185 (20.2)	83 (18.8)	15 (13.2)
Heart failure				
Ejection Fraction	39.2 (15.8)	38.3 (15.4)	37.1 (16.1)	38.8 (18.0)
NYHA Class				
Π	460 (38.4)	346 (37.7)	136 (30.8)	29 (25.4)
III	718 (59.9)	550 (59.9)	285 (64.5)	76 (66.7)
IV	21 (1.8)	22 (2.4)	21 (4.8)	9 (7.9)
Heart rate (beats/min)	72.9 (12.4)	71.1 (11.6)	71.0 (11.0)	70.8 (13.1)
Systolic BP (mm Hg)	127.7 (18.1)	128.9 (18.8)	127.3 (19.1)	130.7 (22.0)
Diastolic BP (mm Hg)	76.1 (10.5)	72.9 (10.4)	69.8 (9.9)	69.3 (11.0)
Medical treatment				
ACE inhibitor	568 (47.4)	419 (45.6)	190 (43.0)	39 (34.2)
Beta-blocker	716 (59.7)	497 (54.1)	222 (50.2)	45 (39.5)
Spironolactone	154 (12.8)	142 (15.5)	82 (18.6)	23 (20.2)
Oral anticoagulation	438 (36.5)	346 (37.7)	191 (43.2)	57 (50.0)
Digoxin	616 (51.4)	490 (53.4)	260 (58.8)	62 (54.4)
Amiodarone	97 (8.1)	99 (10.8)	70 (15.8)	29 (25.4)
Diuretics	1000 (83.4)	785 (85.5)	413 (93.4)	111 (97.4)

BP, blood pressure; CABG, coronary artery bypass graft surgery; NYHA, New York Heart Association; SD, standard deviation

Online Appendix Table 3. Sensitivity analysis excluding creatinine measurements at 6 weeks. Proportion of patients with stable versus worsening renal impairment across serial measurements stratified by atrial fibrillation, according to the European Medicines Agency classification using the Cockcroft-Gault, MDRD and CKD-EPI methods.

	CG		MDRD		CKD-EPI	
	AF	No AF	AF	No AF	AF	No AF
n with e 2 measures	440	1738	440	1738	440	1738
Stable renal function (%)	70.5	72.6	63.9	66.7	68.0	68.2
Normal (> 80) (%)	26.8	35.8	18.6	28.3	22.7	32.6
Mild (50 – 80) (%)	20.2	23.8	26.6	26.4	26.1	24.0
Moderate (30 – 49) (%)	17.3	10.5	14.1	10.0	13.6	9.3
Severe $(15 - 30)$ (%)	6.1	2.4	4.5	2.1	5.5	2.3
Stable e moderate (%)	23.4	12.9	18.6	12.0	19.1	11.6
Worse renal function (%)	29.5	27.4	36.1	33.3	32.0	31.8
Mild (>50) (%)	10.9	11.9	13.6	14.7	10.7	13.8
Moderate $(30 - 49)$ (%)	13.9	10.6	16.4	12.8	15.2	12.3
Severe $(15 - 30)$ (%)	4.5	4.4	5.9	5.2	5.9	5.2
Very Severe (< 15) (%)	0.2	0.5	0.2	0.6	0.2	0.6
Vary e moderate (%)	18.6	15.6	22.5	18.6	21.4	18.0
All e moderate (%)	42.0	28.5	41.1	30.7	40.5	29.6

Online Appendix Table 4. Proportion of patients requiring discontinuation or dose reduction of each non-VKA oral anticoagulant at baseline and during follow-up, applying the US and EU product monograph guidance and Cockcroft-Gault equation.

n=559	Baseline	Additional	Additional	Additional	Cumulative	Overall
(% relative to		6 weeks	14 months	26 months	following	including
baseline)					baseline	baseline
Europe					·	
Dose Reduction						
Apixaban	54 (9.7)	14 (2.5)	16 (2.9)	6 (1.1)	36 (6.4)	90 (16.1)
Dabigatran	83 (14.8)	10 (1.8)	17 (3.0)	15 (2.7)	42 (7.5)	125 (22.4)
Rivaroxaban	154 (27.5)	43 (7.7)	28 (5.0)	17 (3.0)	88 (15.7)	242 (43.3)
Edoxaban	284 (50.8)	42 (7.5)	26 (4.7)	17 (3.0)	85 (15.2)	369 (66.0)
Discontinuation						
Apixaban	0 (0)	1 (0.2)	1(0.2)	0 (0)	2 (0.4)	2 (0.4)
Dabigatran	38 (6.8)	14 (2.5)	13 (2.3)	3 (0.5)	30 (5.4)	68 (12.2)
Rivaroxaban	0 (0)	1 (0.2)	1(0.2)	0 (0)	2 (0.4)	2 (0.4)
Edoxaban	0 (0)	1 (0.2)	1(0.2)	0 (0)	2 (0.4)	2 (0.4)
US						
Dose Reduction						
Apixaban	39 (7.0)	6 (1.1)	6 (1.1)	7 (1.3)	19 (3.4)	58 (10.4)
Dabigatran	36 (6.4)	14 (2.5)	13 (2.3)	3 (0.5)	30 (5.4)	66 (11.8)
Rivaroxaban	154 (27.5)	43 (7.7)	28 (5.0)	17 (3.0)	88 (15.7)	242 (43.3)
Edoxaban	154 (27.5)	43 (7.7)	28 (5.0)	17 (3.0)	88 (15.7)	242 (43.3)
Discontinuation						
Apixaban	0 (0)	1 (0.2)	1(0.2)	0 (0)	2 (0.4)	2 (0.4)
Dabigatran	0 (0)	1 (0.2)	1(0.2)	0 (0)	2 (0.4)	2 (0.4)
Rivaroxaban	0 (0)	1 (0.2)	1(0.2)	0 (0)	2 (0.4)	2 (0.4)
Edoxaban	132 (23.6)	18 (3.2)	5 (0.9)	9 (1.6)	32 (5.7)	164 (29.3)

References

- 1. Fabbri G, Maggioni AP. A review of the epidemiological profile of patients with atrial fibrillation and heart failure. *Expert Rev Cardiovasc Ther*. 2012;10:1133-1140
- 2. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A metaanalysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail.* 2009;11:676-683
- 3. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G, Hankey GJ, Hacke W, Becker RC, Nessel CC, Fox KA, Califf RM, Committee RAS, Investigators. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127:224-232
- 4. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138:1093-1100
- 5. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol*. 2011;58:395-401
- 6. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, Radford MJ. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. 2006;151:713-719
- 7. Rivero-Ayerza M, Scholte Op Reimer W, Lenzen M, Theuns DA, Jordaens L, Komajda M, Follath F, Swedberg K, Cleland JG. New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. *Eur Heart J*. 2008;29:1618-1624
- 8. Nieuwlaat R, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, Lopez-Sendon JL, Meeder JG, Pinto YM, Crijns HJ. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. *Journal of the American College of Cardiology*. 2009;53:1690-1698
- 9. Mountantonakis SE, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. *Circ Heart Fail*. 2012;5:191-201
- Andreu-Cayuelas JM, Pastor-Perez FJ, Puche CM, Mateo-Martinez A, Garcia-Alberola A, Flores-Blanco PJ, Valdes M, Lip GY, Roldan V, Manzano-Fernandez S. Impact of Variations in Kidney Function on Nonvitamin K Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Recent Acute Heart Failure. *Revista espanola de cardiologia*. 2016;69:134-140

- Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139-1151
- Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883-891
- 13. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, Committees A, Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981-992
- 14. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093-2104
- 15. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, Members AATF. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071-2104
- 16. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, Pocock S. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362:759-766
- Swedberg K, Pfeffer M, Granger C, Held P, McMurray J, Ohlin G, Olofsson B, Ostergren J, Yusuf S. Candesartan in heart failure--assessment of reduction in mortality and morbidity (CHARM): rationale and design. Charm-Programme Investigators. *J Card Fail*. 1999;5:276-282
- 18. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006;47:1997-2004
- Ducharme A, Swedberg K, Pfeffer MA, Cohen-Solal A, Granger CB, Maggioni AP, Michelson EL, McMurray JJ, Olsson L, Rouleau JL, Young JB, Olofsson B, Puu M, Yusuf S. Prevention of atrial fibrillation in patients with symptomatic chronic heart failure by candesartan in the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Am Heart J*. 2006;152:86-92
- 20. Brosius FC, 3rd, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, Pennathur S, Smith GL, Wilson PW, American Heart Association K, Cardiovascular Disease C, Council on High Blood Pressure R, Council on Cardiovascular Disease in the Y, Council

on E, Prevention, Quality of C, Outcomes Research Interdisciplinary Working G. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation*. 2006;114:1083-1087

- 21. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function--measured and estimated glomerular filtration rate. *N Engl J Med.* 2006;354:2473-2483
- 22. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41
- 23. 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;130:461-470
- 24. Stevens LA, Nolin TD, Richardson MM, Feldman HI, Lewis JB, Rodby R, Townsend R, Okparavero A, Zhang YL, Schmid CH, Levey AS, Chronic Kidney Disease Epidemiology C. Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kidney Dis.* 2009;54:33-42
- 25. Jones GR. Estimating renal function for drug dosing decisions. *The Clinical biochemist. Reviews / Australian Association of Clinical Biochemists*. 2011;32:81-88
- 26. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Archives of internal medicine*. 1916;17:863-871
- 27. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation*. 2006;113:671-678
- 28. O'Meara E, Khairy P, Blanchet MC, de Denus S, Pedersen OD, Levesque S, Talajic M, Ducharme A, White M, Racine N, Rouleau JL, Tardif JC, Roy D, investigators A-C. Mineralocorticoid receptor antagonists and cardiovascular mortality in patients with atrial fibrillation and left ventricular dysfunction: insights from the Atrial Fibrillation and Congestive Heart Failure Trial. *Circ Heart Fail*. 2012;5:586-593
- 29. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology C. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem.* 2007;53:766-772
- 30. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F, Chronic Kidney Disease Epidemiology C. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006;145:247-254
- 31. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI. A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 2009;150:604-612

- Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G, National Kidney F. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137-147
- 33. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014;35:455-469
- 34. Roldan V, Marin F, Fernandez H, Manzano-Fernandez S, Gallego P, Valdes M, Vicente V, Lip GY. Renal impairment in a "real-life" cohort of anticoagulated patients with atrial fibrillation (implications for thromboembolism and bleeding). *American Journal of Cardiology*. 2013;111:1159-1164
- 35. Guo Y, Wang H, Zhao X, Zhang Y, Zhang D, Ma J, Wang Y, Lip GY. Sequential changes in renal function and the risk of stroke and death in patients with atrial fibrillation. *Int J Cardiol*. 2013;168:4678-4684
- 36. Nieuwlaat R, Capucci A, Lip GY, Olsson SB, Prins MH, Nieman FH, Lopez-Sendon J, Vardas PE, Aliot E, Santini M, Crijns HJ, Euro Heart Survey I. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. *Eur Heart J*. 2006;27:3018-3026
- 37. Piccini JP, Hernandez AF, Zhao X, Patel MR, Lewis WR, Peterson ED, Fonarow GC, Get With The Guidelines Steering C, Hospitals. Quality of care for atrial fibrillation among patients hospitalized for heart failure. *J Am Coll Cardiol*. 2009;54:1280-1289
- 38. Nelson WW, Choi JC, Vanderpoel J, Damaraju CV, Wildgoose P, Fields LE, Schein JR. Impact of co-morbidities and patient characteristics on international normalized ratio control over time in patients with nonvalvular atrial fibrillation. *Am J Cardiol.* 2013;112:509-512
- Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, Acton RT, Allon M. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J Am Soc Nephrol.* 2009;20:912-921
- 40. Bohm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, Schumacher H, Brueckmann M, Schirmer SH, Kratz MT, Yusuf S, Diener HC, Hijazi Z, Wallentin L. Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. J Am Coll Cardiol. 2015;65:2481-2493
- 41. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, Paolini JF, Hankey GJ, Mahaffey KW, Patel MR, Singer DE, Califf RM. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32:2387-2394
- 42. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33:2821-2830
- 43. Hijazi Z, Hohnloser SH, Oldgren J, Andersson U, Connolly SJ, Eikelboom JW, Ezekowitz MD, Reilly PA, Siegbahn A, Yusuf S, Wallentin L. 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;129:961-970

- 44. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467-1507
- 45. Diener HC, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, Ezekowitz MD, Granger CB, Halperin JL, Hohnloser SH, Hylek EM, Kirchhof P, Lane DA, Verheugt FW, Veltkamp R, Lip GY. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J*. 2016
- 46. Maccallum PK, Mathur R, Hull SA, Saja K, Green L, Morris JK, Ashman N. Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study. *BMJ open*. 2013;3:e003343
- 47. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L, Investigators R-L. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol.* 2014;63:321-328