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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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 ≤ 40% and not receiving an ACEI due to previous intolerance (CHARM-Alternative, n=2028); LVEF ≤ 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] × 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 m^2.[24, 25] BSA was calculated with the Dubois and Dubois formula as used to develop the MDRD and CKD EPI formula,[23] where BSA(m^2) = 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 × (Scr μmol/L)$^{-1.154}$ × (age)$^{-0.203}$ × 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/1.73m^2. The CKD-EPI single equation is eGFR = 141 × min(Scr/^{o}, 1)$^{\pm}$ × max(Scr/^{o}, 1)$^{-1.209}$ × (0.993)^{Age} × 1.018 [female] × 1.159 [if black], where Scr is serum creatinine, ^{o} 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/^{o} or 1, and max indicates the maximum of Scr/^{o} or 1.[31]

Statistical analysis and renal impairment classification

Unadjusted (ml/min) and body surface area adjusted (ml/min/1.73m^2) 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 ± 18.4 versus -0.4 ± 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 $CHADS_2$ 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 de-normalised 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.

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Conflicts of Interest

Conflicts of Interest: none declared.

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

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

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 (± 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 (± 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**
14 months (n)	419	1657	419	1657	419	1657
Mean (± SD)	*70.6 (37.1)*	*82.1 (43.6)*	*66.0 (27.5)*	*74.0 (32.7)*	*67.2 (28.8)*	*75.8 (31.8)*
Normal (> 80) (%)	32.0	43.8	28.4	37.5	31.7	41.4
Mild (50 – 80) (%)	32.7	33.9	38.4	39.2	35.6	35.9
Moderate (30 – 49) (%)	27.2	17.0	25.5	17.7	25.1	16.8
Severe (< 30) (%)	8.1	4.9	7.6	5.7	7.6	5.9
At least moderate (%)	**35.3**	**22.4**	**33.2**	**23.4**	**32.7**	**22.7**
26 months (n)	347	1386	347	1386	347	1386
Mean (± SD)	*73.6 (43.0)*	*83.8 (43.6)*	*68.3 (31.0)*	*75.2 (32.8)*	*69.2 (30.3)*	*77.3 (31.8)*
Normal (> 80) (%)	33.7	45.7	28.0	40.2	30.3	44.5
Mild (50 – 80) (%)	32.3	32.6	42.4	37.2	40.3	33.7
Moderate (30 – 49) (%)	28.5	17.1	23.6	17.5	23.1	16.4
Severe (< 30) (%)	5.5	4.5	6.1	5.2	6.3	5.4
At least moderate (%)	**34.0**	**21.6**	**29.7**	**22.7**	**29.4**	**21.8**

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).

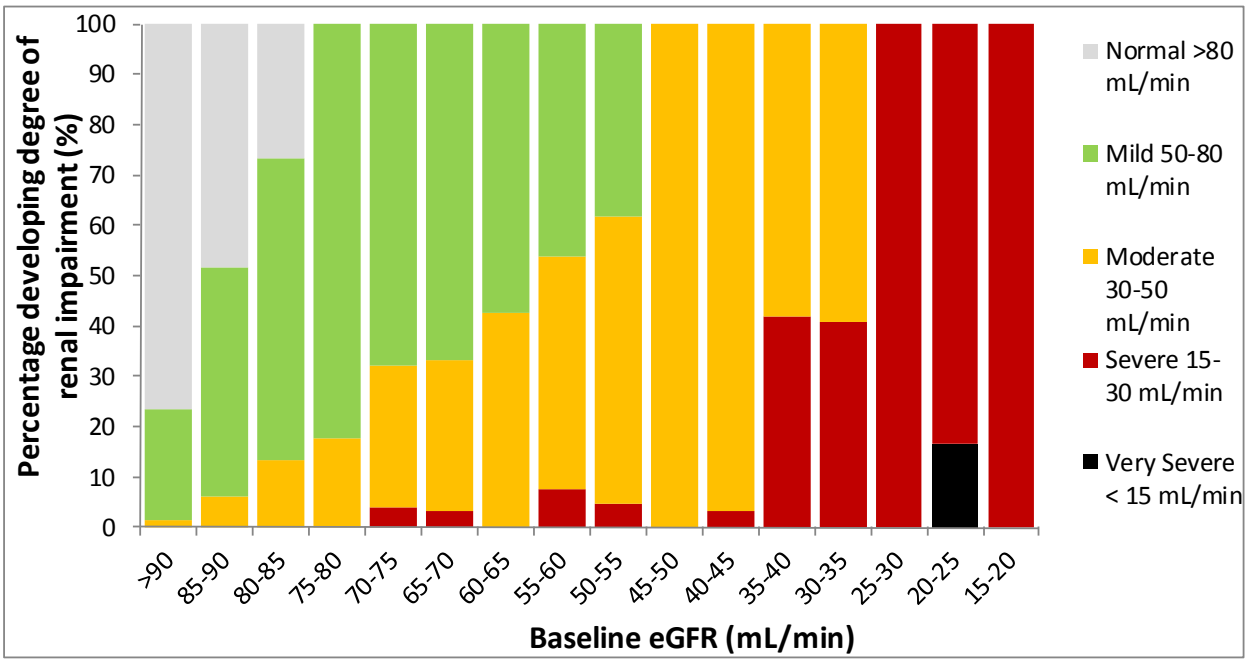


Figure 2. Percentage of patients with AF reclassified into different EMA stages at baseline when estimating GFR using Cockcroft-Gault, MDRD and CKD-EPI equations.

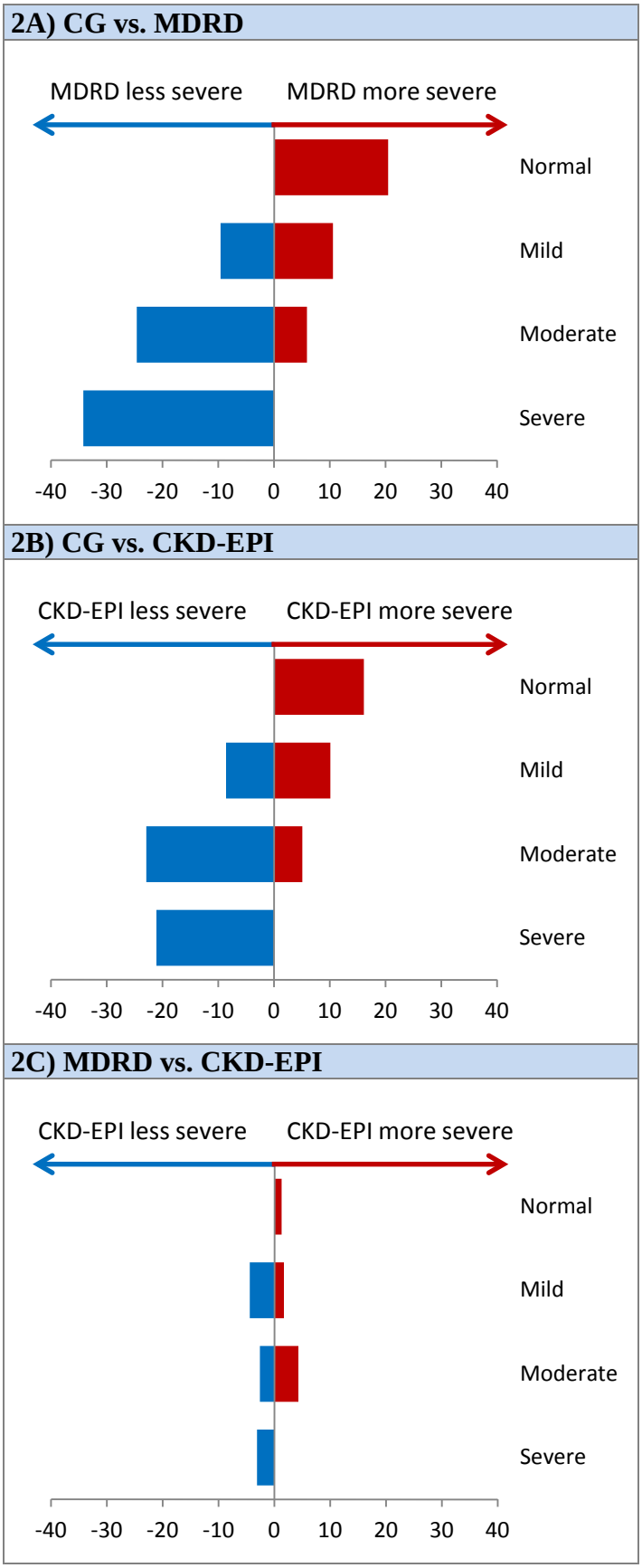


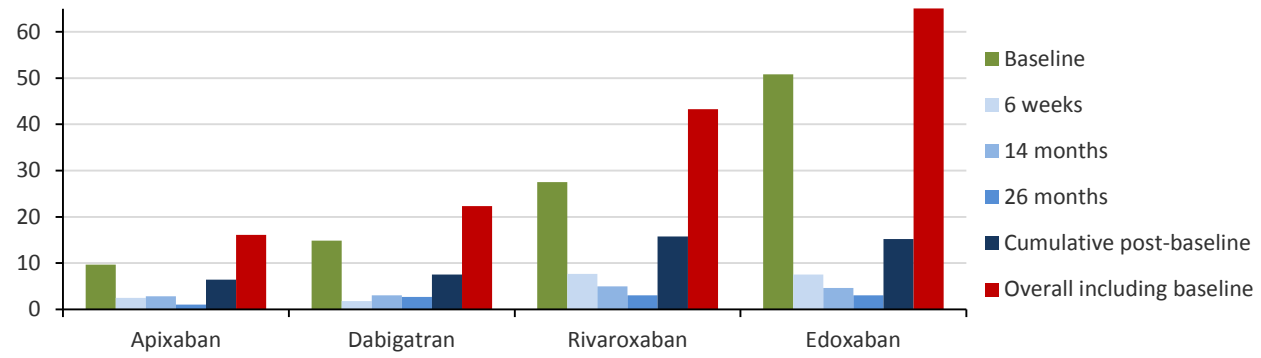
Table 4. Independent predictors of worsening moderate to severe renal impairment.

	Odds Ratio (95% CI) Multivariate Analysis	Wald Chi	p value
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

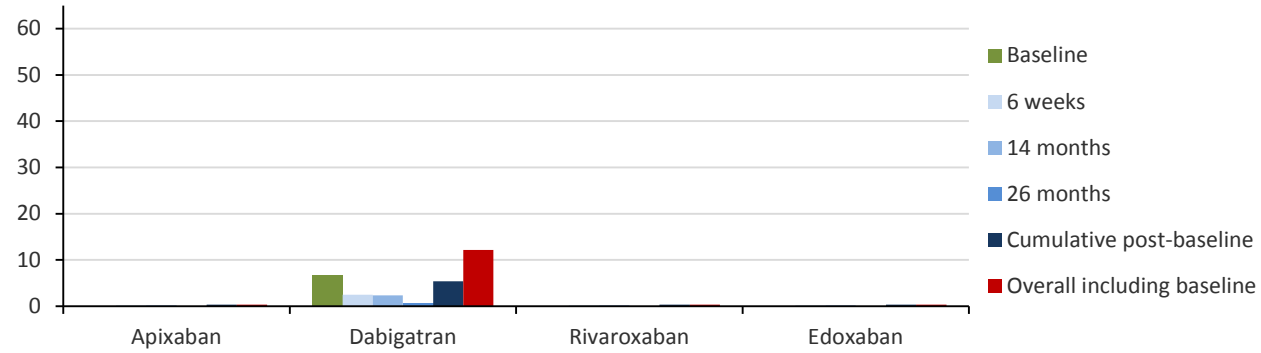
ACEI, angiotensin enzyme converting inhibitor; eGFR, estimated glomerular filtration rate.

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.

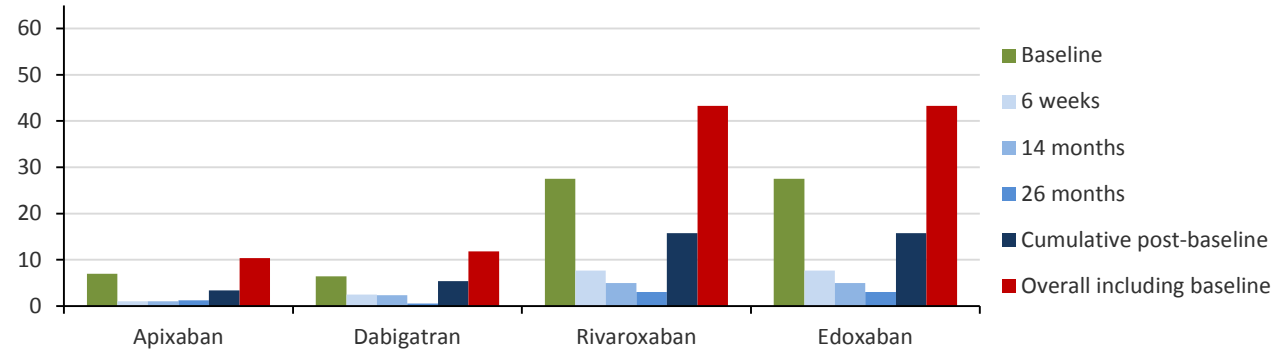
EU guidance. Percentage of patients requiring dose reduction at baseline or during follow-up.



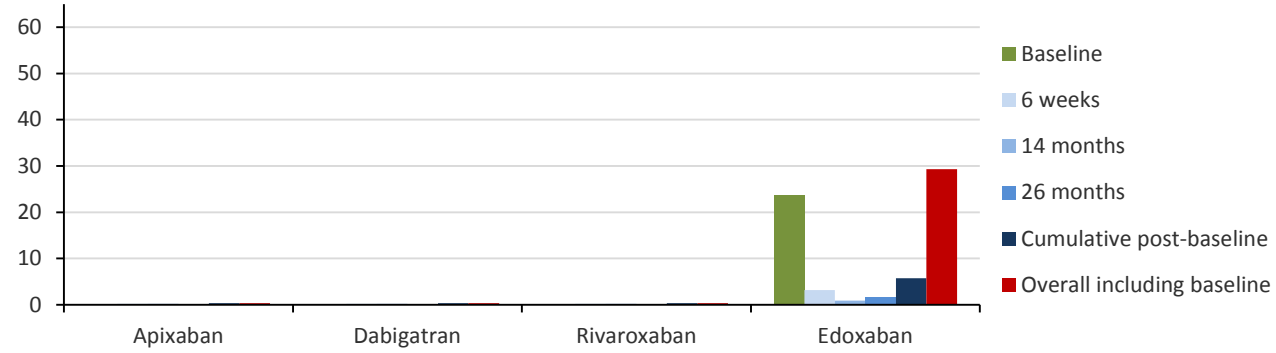
EU guidance. Percentage of patients requiring discontinuation at baseline or during follow-up.



US guidance. Percentage of patients requiring dose reduction at baseline or during follow-up.



US guidance. Percentage of patients requiring discontinuation at baseline or during follow-up.



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

mean (SD) or n (%)	AF n=559	No AF 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 n=1199	Mild n=918	Moderate n=442	Severe 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				
II	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 (% relative to baseline)	Baseline	Additional 6 weeks	Additional 14 months	Additional 26 months	Cumulative following baseline	Overall including 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)

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