ESC European Society of Cardiology

European Heart Journal (2019) **40**, 1492–1500
doi:10.1093/eurheartj/ehy802

Efficacy and safety of reduced-dose non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: a meta-analysis of randomized controlled trials

Kang-Ling Wang[1,2], Renato D. Lopes[3], Manesh R. Patel[3], Harry R. Büller[4], Doreen Su-Yin Tan[5], Chern-En Chiang[1,2], and Robert P. Giugliano[6]*

[1]General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan; [2]School of Medicine, National Yang-Ming University, Taipei, Taiwan; [3]Duke Clinical Research Institute, Duke University School of Medicine, 2400 Pratt Street, Durham, NC 27710, USA; [4]Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; [5]Department of Pharmacy, Khoo Teck Puat Hospital, Singapore, Singapore; and [6]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Received 29 March 2018; revised 14 August 2018; editorial decision 5 October 2018; accepted 26 November 2018; online publish-ahead-of-print 22 December 2018

See page 1501 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz014)

Aims Non-vitamin K antagonist oral anticoagulants (NOACs) require dose reductions according to patient or clinical factors for patients with atrial fibrillation (AF). In this meta-analysis, we aimed to assess outcomes with reduced-dose NOACs when given as pre-specified in pivotal trials.

Methods and results Aggregated data abstracted from Phase III trials comparing NOACs with warfarin in patients with AF were assessed by treatment using risk ratios (RRs) and 95% confidence intervals (CIs) stratified by patient eligibility for NOAC dose reduction. Irrespective of treatments, annualized rates of stroke or systemic embolism and major bleeding were higher in patients eligible for reduced-dose NOACs than in those eligible for full-dose NOACs (2.70% vs. 1.60% and 4.35% vs. 2.87%, respectively). Effects of reduced-dose NOACs compared with warfarin in patients eligible for reduced-dose NOACs on stroke or systemic embolism [RR 0.84 (95% CI 0.69–1.03)] and on major bleeding [RR 0.70 (95% CI 0.50–0.97)] were consistent with those of full-dose NOACs relative to warfarin in those eligible for full-dose NOACs [RR 0.86 (95% CI 0.77–0.96) for stroke or systemic embolism and RR 0.87 (95% CI 0.70–1.08) for major bleeding; interaction *P*, 0.89 and 0.26, respectively]. In addition, NOACs were associated with reduced risks of haemorrhagic stroke, intracranial haemorrhage, fatal bleeding, and death regardless of patient eligibility for NOAC dose reduction (interaction $P > 0.05$ for each).

Conclusions Patients eligible for reduced-dose NOACs were at elevated risk of thromboembolic and haemorrhagic complications when treated with anticoagulants. NOACs, when appropriately dose-adjusted, had an improved benefit-harm profile compared with warfarin. Our findings highlight the importance of prescribing reduced-dose NOACs for indicated patient populations.

Keywords Anticoagulants • Atrial fibrillation • Outcomes

Introduction

Warfarin effectively reduces risks of stroke and mortality in patients with atrial fibrillation (AF).[1] However, advanced age, low body weight, and renal impairment are factors that increase the risk of major bleeding and that influence decisions regarding anticoagulant prescriptions.[2,3] Gauging the risk of bleeding against the risk of stroke is more complex in vulnerable patients. Therefore, they are more often denied effective anticoagulants.[4]

Because non-vitamin K antagonist oral anticoagulants (NOACs) have fewer drug interactions and require no need for regular

* Corresponding author. Tel: +1-617-278-0181, Fax: +1-617-264-5130, Email: rgiugliano@bwh.harvard.edu

monitoring, the uptake of these agents has been rapid.[5] An important message from landmark randomized controlled trials (RCTs) in patients with AF is that NOACs have a favourable benefit-harm profile across a wide range of patients,[6,7] including vulnerable populations.[8,9] Therefore, they represent an attractive therapeutic option among those who are at increased risk of bleeding.[10,11] Although NOACs are pharmacologically more predictable, and therefore safer, than warfarin, factors pertinent to patient characteristics or clinical settings still influence their pharmacokinetics. In Phase III RCTs in patients with AF, reduced-dose rivaroxaban, apixaban, and edoxaban were prospectively studied in patients at risk of increased drug levels.[12–14] Efficacy and safety of reduced-dose rivaroxaban and edoxaban have been reported,[15,16] whereas detailed information regarding reduced-dose apixaban is not yet published.

Patients enrolled in Phase III RCTs in whom reduced-dose NOACs by study criteria were evaluated accounted for a relatively modest fraction of entire populations being studied [≈21%, ≈5%, and ≈25% of Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) patient populations at baseline, respectively].[12–14] Nevertheless, they represented an important subgroup that might be more susceptible to not only overexposure but also underexposure to treatments in clinical practice. In this meta-analysis, we aimed: (i) to assess efficacy and safety of reduced-dose NOACs relative to warfarin in patients with AF who met NOAC dose-reduction criteria and who were enrolled in Phase III RCTs; and (ii) to further explore whether relative effects of NOACs compared with warfarin differed between patients eligible for reduced-dose NOACs and those eligible for full-dose NOACs.

Methods

Our report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Data source and search

We searched PubMed, CENTRAL, CINAHL, and EMBASE databases for Phase III RCTs (from database inception through June 2018). To ensure a comprehensive literature search, reference lists of published meta-analyses and reviews were reviewed. Furthermore, websites of the Food and Drug Administration (www.accessdata.fda.gov/scripts/cder/drugsatfda) and the European Medicines Agency (www.ema.europa.eu) were searched for information of approved NOACs.

Eligibility criteria

We only included RCTs comparing an approved NOAC that had a pre-specified dose-reduction scheme with warfarin (targeting an international normalized ratio between 2.0 and 3.0) in patients with AF and 1-year or longer follow-up duration. Phase II studies, observational data, and RCTs in the setting of interventions (e.g. catheter ablation, cardioversion, or coronary interventions) were not eligible.

Data extraction and quality assessment

Two authors (K.-L.W. and C.-E.C.) independently evaluated studies for possible inclusion and non-relevant studies were excluded after reviewing titles and abstracts. For potentially eligible studies, full-text papers were retrieved and assessed independently. Data by treatment were extracted independently by the same authors using a standardized form and were stratified by patient eligibility for NOAC dose reduction. If outcome data were reported in multiple publications, the following hierarchy of data sources was used: the first report of the intention-to-treat population in peer-reviewed papers then public reports from regulatory agencies. Unpublished patient characteristics at baseline in ARISTOTLE were obtained by the second author (R.D.L.). Unpublished subgroup data in ENGAGE AF-TIMI 48 were obtained by the senior author (R.P.G.). Risks of bias were assessed independently using the Risk of Bias Tool developed by the Cochrane Collaboration. Disagreements between two authors were resolved by consensus.

Definition of dosing regimens

Reduced-dose NOACs were defined per pre-specified criteria pertinent to individual RCTs: rivaroxaban 15 mg once daily in patients with creatinine clearance 30–49 mL/min; apixaban 2.5 mg twice daily in patients with two or more of following criteria: age ≥80 years, body weight ≤60 kg, and the serum creatinine level ≥1.5 mg/dL; and edoxaban 30 mg once daily in patients with creatinine clearance 30–50 mL/min, body weight ≤60 kg, or concomitant medications with potent P-glycoprotein interactions.

Data synthesis and analysis

Results for efficacy and safety of reduced-dose NOACs compared with warfarin were not universally reported in published literature. Therefore, primary outcomes of interest in this study were limited to stroke or systemic embolism and major bleeding. Other outcomes, including ischaemic stroke, systemic embolism, gastrointestinal bleeding, haemorrhagic stroke, intracranial haemorrhage, fatal bleeding, and death, were explored whenever available. Study definitions for all outcomes that have been reported in main trial papers and/or in supplemental appendices were accepted. Data sources are reported in Supplementary material online, *Table S1*.

Outcome rates were pooled in the inverse-variance weighted model, in which the standard error of the given incidence rate by treatment and by patient eligibility for NOAC dose reduction was estimated by dividing the square root of the event number by exposure. Dichotomous data by study were compared by the risk ratio (RR) using the DerSimonian and Laird random-effects model. Considering that different meta-analytic methods and data sources could influence results, two sets of sensitivity analyses were performed: (i) the Knapp–Hartung method was used, accounting for the uncertainty associated with statistical heterogeneity that might not be accurately incorporated by the DerSimonian and Laird method when only a small number of trials were involved[17]; and (ii) the effect size for each outcome was estimated using summary statistics [reported unadjusted hazard ratios and corresponding 95% confidence intervals (CIs)] that were logarithmically transformed, weighted for the inverse of variance, and pooled in a random-effect model accounting for follow-up duration. Since the European label and guidelines recommend dose adjustments for dabigatran in patients at risk of overexposure,[18] additional sensitivity analyses included summary statistics from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) European label simulation analysis that reported efficacy and safety of dabigatran when adjusted according to the European label.[19] Heterogeneity between trials was assessed using the I^2 test and interactions between subgroup differences were examined by the Cochran Q statistic. Tests for heterogeneity or interactions were not adjusted for

multiplicity because these assessed whether there was any evidence of a difference in the treatment effect between subgroups.[20] Because all included RCTs were individually powered to evaluate efficacy of the studied NOAC on prevention of stroke or systemic embolism *a priori*, the pooled analysis of NOACs compared with warfarin on stroke or systemic embolism was not accounted for multiple comparisons. All other pooled analyses and subgroup analyses were adjusted using the Bonferroni correction and among which subgroup analyses on stroke or systemic embolism were adjusted separately from other outcomes.

Statistical analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat Inc., New Jersey, USA) and the p.adjust function and the metafor package in R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified three RCTs (Supplementary material online, *Figure S1*), including 7351 patients eligible for reduced-dose NOACs from a total population of 46 426 patients for the analysis on stroke or systemic embolism. All trials were judged to be at low risk of bias (Supplementary material online, *Figure S2*). Patients eligible for reduced-dose NOACs were older and more likely to be women, and therefore had lower creatinine clearance, than those eligible for full-dose NOACs. The risk of ischaemic stroke (assessed by the $CHADS_2$ score) was consistently higher in patients eligible for reduced-dose NOACs in whom warfarin management (by time in therapeutic range) was more challenging (*Table 1*). *Table 2* reports patient distributions per eligibility criterion for reduced-dose NOACs.

Outcome summary

Pooled rates of stroke or systemic embolism and major bleeding by treatment and by patient eligibility for NOAC dose reduction are summarized in *Figure 1*. Irrespective of treatments, annualized event rates were higher in patients eligible for reduced-dose NOACs than in those eligible for full-dose NOACs for stroke or systemic embolism and for major bleeding (Supplementary material online, *Figure S3*). Among patients eligible for reduced-dose NOACs, annualized rates of stroke or systemic embolism were 3.03% (95% CI 2.47–3.59%) for warfarin and 2.39% (95% CI 1.80–2.98%) for reduced-dose NOACs, whereas annualized rates of major bleeding were comparably higher [4.98% (95% CI 4.25–5.71%) and 3.60% (95% CI 2.61–4.60%) for warfarin and for reduced-dose NOACs, respectively]. With regard to other thrombo-embolic and haemorrhagic outcomes, annualized event rates were consistently higher in patients eligible for reduced-dose NOACs than in those eligible for full-dose NOACs regardless of treatments (Supplementary material online, *Table S2*).

Efficacy and safety by non-vitamin K antagonist oral anticoagulant dose

Supplementary material online, *Table S3* summaries pooled analyses on comparative efficacy and safety of NOACs. Compared with warfarin, NOACs were associated with a lower risk of stroke or systemic embolism [RR 0.86 (95% CI 0.78–0.94)] that was driven by a large reduction in the risk of haemorrhagic stroke. There were also substantial reductions in risks of intracranial haemorrhage and fatal bleeding with NOACs despite a higher risk of gastrointestinal bleeding. Overall, there was a trend toward a lower risk of major bleeding with NOACs [RR 0.83 (95% CI 0.67–1.03)].

In line with the overall patient population, there were consistent trends in favour of reduced-dose NOACs compared with warfarin among patients eligible for reduced-dose NOACs for all efficacy and safety outcomes except gastrointestinal bleeding (*Take home figure*). Among patients eligible for full-dose NOACs, similar risk reductions were observed in stroke or systemic embolism [RR 0.86 (95% CI 0.77–0.96)] and major bleeding [RR 0.87 (95% CI 0.70–1.08)] with full-dose NOACs relative to warfarin (interaction *P*, 0.89 and 0.26, respectively) (*Figure 2*). Compared with warfarin, reduced-dose NOACs were associated with the similar risk of ischaemic stroke and a trend toward a lower risk of systemic embolism (Supplementary material online, *Figures S4 and S5*). Risks of haemorrhagic stroke, intracranial haemorrhage, and fatal bleeding were consistently lower with reduced-dose NOACs than with warfarin with summary RRs ranging between 0.43 and 0.58. In addition, comparative effects of NOACs on other safety events between patients eligible for reduced-dose NOACs and those eligible for full-dose NOACs were similar (each interaction $P > 0.05$) (Supplementary material online, *Figure S6*).

Sensitivity analysis

Sensitivity analyses using the Knapp–Hartung method were broadly consistent with base-case analyses (Supplementary material online, *Table S4*). Effect estimates using hazard ratios were statistically comparable to those derived from dichotomous data (Supplementary material online, *Figure S7*). Additional analyses incorporating data on the RE-LY European label simulation analysis showed that consistent trends in lower risks of stroke or systemic embolism and serious bleeding favoured reduced-dose NOACs, including dabigatran, in patients who met NOAC dose-reduction criteria (Supplementary material online, *Figure S8*).

Discussion

In this meta-analysis of three pivotal RCTs comparing NOACs with warfarin in patients with AF, we found that patients eligible for reduced-dose NOACs were at higher risk of thrombo-embolic and haemorrhagic complications than those eligible for full-dose NOACs when treated with anticoagulants. Compared with warfarin, the benefit-harm profile of NOACs, when dose-adjusted appropriately, were consistently better than warfarin whether patients met or did not meet NOAC dose-reduction criteria.

Balancing between risks of stroke and bleeding is necessary for the optimal use of anticoagulants in clinical practice. The greatest obstacle to the use of anticoagulants is the risk of bleeding. However, many of the same patient characteristics that are associated with excess bleeding are also associated with disabling stroke and death.[21] Our findings further confirmed that patients at high risk of increased NOAC levels were at greater risk of thromboembolism and haemorrhage when treated with warfarin. A possible mechanism accountable for this phenomenon other than inherent risks (referenced by risk scores) is that warfarin management is often more difficult in patients who are older, Asian, with lower body weight, or with renal impairment.[22–24] It is among these same patients in whom benefits of

Table 1 Baseline patient characteristics by study

	ROCKET AF				ARISTOTLE				ENGAGE AF-TIMI 48			
	Eligible for reduced-dose NOAC		Eligible for full-dose NOAC		Eligible for reduced-dose NOAC		Eligible for full-dose NOAC		Eligible for reduced-dose NOAC		Eligible for full-dose NOAC	
	Rivaroxaban 15 mg (*n* = 1474)	Warfarin (*n* = 1476)	Rivaroxaban 20 mg (*n* = 5637)	Warfarin (*n* = 5640)	Apixaban 2.5 mg (*n* = 428)	Warfarin (*n* = 403)	Apixaban 5 mg (*n* = 8692)	Warfarin (*n* = 8678)	Edoxaban 30 mg (*n* = 1784)	Warfarin (*n* = 1787)	Edoxaban 60 mg (*n* = 5251)	Warfarin (*n* = 5249)
Age (years)	79	79	71	71	83	83	70	69	77	77	70	70
Female sex	55	56	36	35	51	56	35	34	55	55	32	32
Body weight (kg)	NR	NR	NR	NR	58	58	83	83	65	65	86	86
CrCl (mL/min)	42	42	75	74	37	38	76	76	46	46	79	79
$CHADS_2$ score	3.7	3.7	3.4	3.4	2.8	2.8	2.1	2.1	3.0	3.0	2.8	2.8
Prior stroke or systemic embolism	50	49	56	56	19	16	12	13	32	32	27	27
Heart failure	66	65	62	62	38	34	35	35	56	56	59	58
Hypertension	92	92	90	90	85	85	87	88	90	91	95	95
Diabetes mellitus	32	33	43	41	18	16	25	25	25	27	39	39
Median TTR	NA	58	NA	58	NA	65	NA	66	NA	66	NA	69

Data are median (mean for the $CHADS_2$ score) or in %.
CrCl, creatinine clearance; NA, not applicable; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; TTR, time in therapeutic range.

Table 2 Patient distributions by dose-reduction criterion

	NOAC regimen (if reduced)	Dose-reduction criteria	Warfarin	NOAC
ROCKET AF[a]	Rivaroxaban 20 mg (15 mg) once daily	CrCl 30–49 mL/min	20.7	20.7
ARISTOTLE[a]	Apixaban 5 mg (2.5 mg) twice daily	Age ≥80 years and body weight ≤60 kg	2.5	2.7
		Age ≥80 years and the serum creatinine level ≥1.5 mg/dL	1.3	1.3
		Body weight ≤60 kg and the serum creatinine level ≥1.5 mg/dL	0.3	0.4
		Age ≥80 years, body weight ≤60 kg, and the serum creatinine level ≥1.5 mg/dL	0.1	0.1
ENGAGE AF-TIMI 48[b]	Edoxaban 60 mg (30 mg) once daily	CrCl 30–50 mL/min	19.3	19.6
		Body weight ≤60 kg	10.0	9.7
		Any concomitant potent P-gp inhibitors	3.5	3.7

Data are in %.
CrCl, creatinine clearance; NOAC, non-vitamin K antagonist oral anticoagulant; P-gp, P-glycoprotein.
[a]Safety population.
[b]Patients may have had more than one reason for reduced-dose edoxaban.

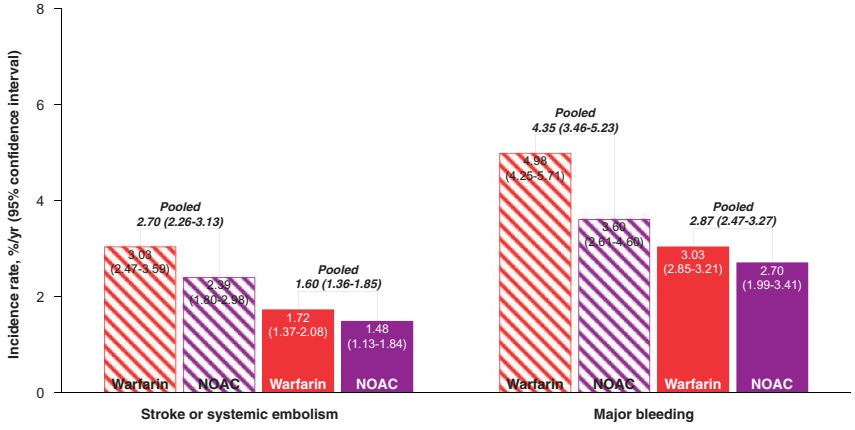
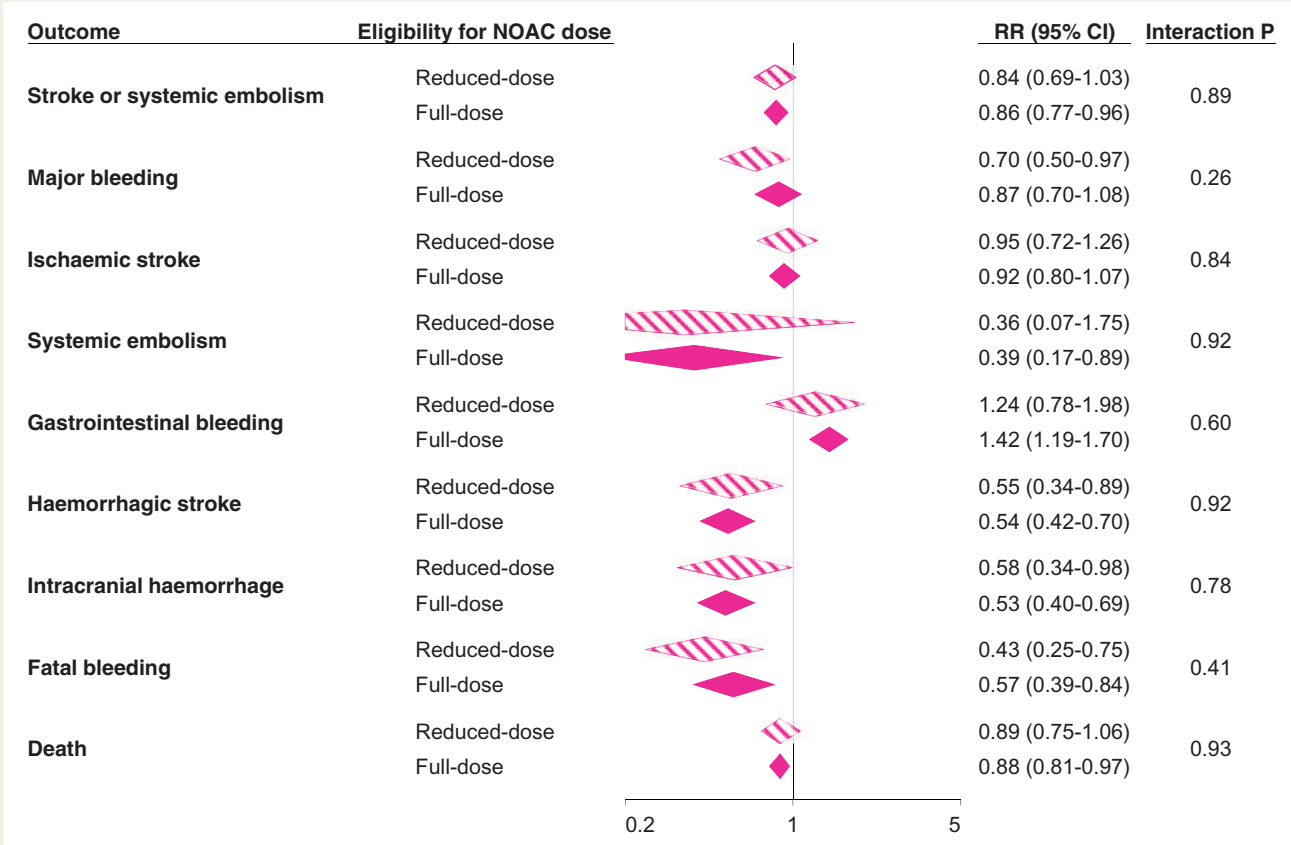


Figure 1 Pooled rates of stroke or systemic embolism and major bleeding. In patients eligible for reduced-dose NOACs (hatched bars), higher rates of stroke or systemic embolism and higher rates of major bleeding were observed with both treatments compared to those eligible for full-dose NOACs (solid bars). NOAC, non-vitamin K antagonist oral anticoagulant.

NOACs relative to warfarin appear most promising.[25–27] Moreover, even with high-quality warfarin management, NOACs were still associated with fewer bleeding events, including intracranial haemorrhage and fatal bleeding.[14,28]

NOACs have been comprehensively studied in their clinical development programs and knowledge learned from pharmacodynamic and pharmacokinetic studies has improved dosing schemes of three factor Xa inhibitors, thereby helping to avoid excess bleeding. Patients at risk of overexposure, despite being studied prospectively in Phase III RCTs, were relatively under-represented. Reduced-dose regimens might decrease the risk of bleeding at the cost of an elevated risk of stroke due to underexposure. In our study, reduced-dose NOACs were safer than warfarin while achieving efficacy that was at least as good as warfarin in patients who met NOAC dose-reduction criteria. It is reassuring that reducing NOAC doses appropriately does not increase untoward thromboembolism relative to warfarin.

Since NOACs provide a more predictable anticoagulation response than warfarin, they are given in fixed doses. In addition to full-dose regimens, a lower-dose version of each NOAC (rivaroxaban 15 mg, apixaban 2.5 mg, and edoxaban 30 mg) is marketed for dose reductions. In clinical practice, no difference in efficacy and safety was reported between reduced-dose NOACs and full-dose NOACs when given according to labels.[29] However, the frequent use of doses outside labels or guidelines recommendations in clinical practice is alarming and is associated with an increase in harm.[30–32] This may be



Take home figure Comparative performance between reduced-dose non-vitamin K antagonist oral anticoagulants and full-dose non-vitamin K antagonist oral anticoagulants relative to warfarin. CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; RR, risk ratio.

attributed in part to the higher complexity of patients seen in clinical practice among whom the risk of bleeding is often overestimated.[33] Although lower-dose NOACs are commonly used with the aim to reduce patient's exposure to anticoagulation, thereby reducing the risk of bleeding, it is worth noting that in RE-LY and ENGAGE AF-TIMI 48 that prospectively studied low-dose dabigatran (110 mg) and edoxaban (30 mg, reduced to 15 mg per protocol), respectively,[14,34] these low-dose regimens resulted in less bleeding but reduced efficacy compared with standard-dose regimens.[35] Clinical experience with under-dosing of NOACs suggests that, compared with appropriate NOAC dosing, rates of major bleeding and hospitalization due to bleeding were not reduced while rates of thromboembolism and cardiovascular hospitalization were increased.[31,32] Furthermore, even in patients at increased risk of falling due to frailty, an appropriately dosed NOAC is generally as efficacious as and safer than well-managed warfarin.[11,36]

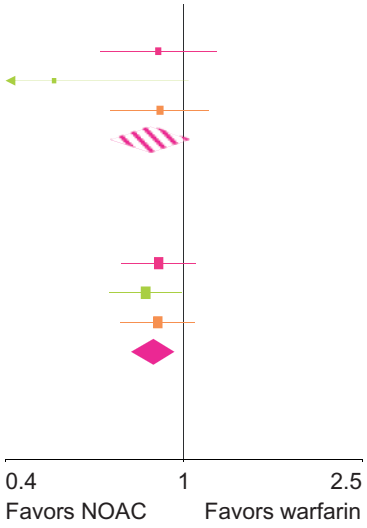
Finally, there is no universal rule for determining dose reductions. By study design, rivaroxaban 15 mg once daily was used in patients with creatinine clearance 30–49 mL/min, whereas edoxaban 30 mg once daily was used in patients with creatinine clearance 30–50 mL/min, body weight ≤60 kg, or concomitant medications with potent P-glycoprotein inhibition. Since patients with isolated advanced age (≥80 years), low body weight (≤60 kg), or renal impairment (the serum creatinine level ≥1.5 mg/dL) consistently benefited from apixaban 5 mg twice daily,[37] apixaban 2.5 mg twice daily should only be given when two or more of those conditions coexist, which was an infrequent occurrence in ARISTOTLE (only ≈5% of patients).

Limitations

First, our study was based on aggregate data abstracted from papers and regulatory agencies where not all outcomes were retrievable. Subgroup analyses from RCTs are often underpowered and meta-analyses by subgroup might not be as valid as analyses on individual patient-level data, since there was heterogeneity in studied populations and study conduct across trials. Since we used unadjusted hazard ratios as effect estimates in the inverse-variance weighted model to account for variations in follow-up duration, outcomes were independently adjudicated, and, in particular, primary outcomes of interest of our study had homogeneous definitions across three trials, we believe our findings are valid. Second, significant between-trial heterogeneity found in the analysis on major bleeding may affect the robustness of our result. However, there was little heterogeneity in efficacy outcomes and, more importantly, in serious bleeding, including haemorrhagic stroke, intracranial haemorrhage, and fatal bleeding. Third, we did not assess efficacy and safety of NOACs in patients with creatinine clearance 15–30 mL/min in whom reduced-dose rivaroxaban and edoxaban are still recommended by US and European labels.

A Stroke or systemic embolism

	NOAC n/N	Warfarin n/N	RR (95% CI)
Eligible for reduced-dose NOAC			
ROCKET AF	77/1490	86/1459	0.88 (0.65-1.18)
ARISTOTLE	12/428	22/403	0.51 (0.26-1.02)
ENGAGE AF-TIMI 48	106/1784	120/1787	0.88 (0.69-1.14)
Subtotal	**190/3702**	**228/3649**	**0.84 (0.69-1.03)**
I^2= 8%			
Adjusted P= 0.19			
Eligible for full-dose NOAC			
ROCKET AF	191/5583	219/5622	0.88 (0.73-1.06)
ARISTOTLE	200/8692	243/8678	0.82 (0.68-0.99)
ENGAGE AF-TIMI 48	190/5251	217/5249	0.88 (0.72-1.06)
Subtotal	**581/19526**	**679/19549**	**0.86 (0.77-0.96)**
I^2= 0%			
Adjusted P= 0.011			
Interaction P= 0.89			



B Major bleeding

	NOAC n/N	Warfarin n/N	RR (95% CI)
Eligible for reduced-dose NOAC			
ROCKET AF	93/1474	100/1476	0.93 (0.71-1.22)
ARISTOTLE	20/424	37/402	0.51 (0.30-0.87)
ENGAGE AF-TIMI 48	104/1776	166/1780	0.63 (0.50-0.80)
Subtotal	**217/3674**	**303/3658**	**0.70 (0.50-0.97)**
I^2= 68%			
Adjusted P= 0.50			
Eligible for full-dose NOAC			
ROCKET AF	302/5637	286/5640	1.06 (0.90-1.24)
ARISTOTLE	307/8664	425/8650	0.72 (0.62-0.83)
ENGAGE AF-TIMI 48	314/5236	358/5232	0.88 (0.76-1.01)
Subtotal	**923/19537**	**1069/19522**	**0.87 (0.70-1.08)**
I^2= 84%			
Adjusted P>0.99			
Interaction P= 0.26			

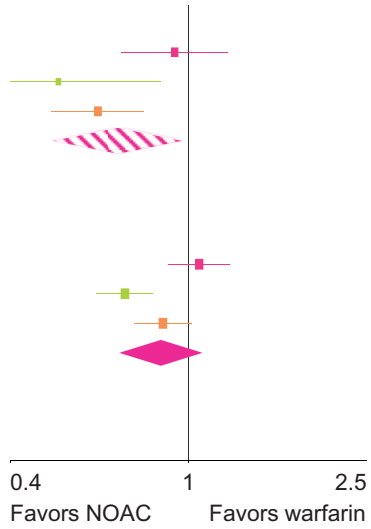


Figure 2 Risks of stroke or systemic embolism (*A*) and major bleeding (*B*) by patient eligibility for non-vitamin K antagonist oral anticoagulant dose reduction. *P-values for stroke or systemic embolism were adjusted separately. CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; RR, risk ratio.

Fourth, we only included factor Xa inhibitors in primary analyses because the design of RE-LY was different (e.g. no dose-reduction criteria).[38] The *post hoc* modelling from the RE-LY database was included in our sensitivity analysis, which demonstrated consistent findings with our primary analysis in the other three RCTs. Although this meta-analysis only included RCTs that had strict selection criteria and pre-specified protocols that limit the generalizability of our results, we, nevertheless, note that our findings are qualitatively similar to results reported from large observational registries.[31,32]

Conclusion

When treated with anticoagulants, rates of stroke or systemic embolism and major bleeding were higher in patients with AF who met NOAC dose-reduction criteria than in patients who did not satisfy these criteria. There was no differential effect on efficacy or safety of NOACs between patients eligible for reduced-dose NOACs and those eligible for full-dose NOACs. Thus, our findings highlight the importance of prescribing reduced-dose NOACs for right patient populations per approved clinical criteria.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Acknowledgements

We thank Ms Deborah Gurski for editorial support and Mr Yuan-Chia Chu and Ms Chun-Yi Lin for assistances in R programming.

Funding

This work was supported by the grant from the Ministry of Health and Welfare (MOHW107-TDU-B-211-123001) and the grant from the Ministry of Science and Technology (MOST104-2314-B-075-028) (both from Taiwan).

Conflict of interest: K.-L.W. has received honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Orient EuroPharm, Novartis, and Tanabe. R.D.L reports research support from Bristol-Myers Squibb, GlaxoSmithKline, Medtronic, and Pfizer, and consulting fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline, Medtronic, Merck, Pfizer, and Portola. M.R.P. reports research grants from AstraZeneca, Bayer, Jansen, Heartflow, and the National Heart, Lung, and Blood Institute, and is a consultant for AstraZeneca, Bayer, and Jansen. H.R.B has received research support and consulted for Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Ionis, Novartis, Pfizer, Roche, Sanofi, and Thrombogenics. D.S.-Y.T. has none to disclose. C.-E.C. has been on the speaker bureau for AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Merck Sharp & Dohme, Novartis, Pfizer, Sanofi, and Servier. R.P.G. reports research support to his institution from Daiichi-Sankyo and Merck, and personal honoraria for CME lectures from Daiichi-Sankyo and Merck, and is a consultant for American College of Cardiology, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Janssen, Merck, Pfizer, and Portola.

References

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
2. O'Brien EC, Holmes DN, Ansell JE, Allen LA, Hylek E, Kowey PR, Gersh BJ, Fonarow GC, Koller CR, Ezekowitz MD, Mahaffey KW, Chang P, Peterson ED, Piccini JP, Singer DE. Physician practices regarding contraindications to oral anticoagulation in atrial fibrillation: findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Am Heart J* 2014;**167**:601–609 e1.
3. Huisman MV, Ma CS, Diener HC, Dubner SJ, Halperin JL, Rothman KJ, Teutsch C, Schoof N, Kleine E, Bartels DB, Lip GY; GLORIA-AF Investigators. Antithrombotic therapy use in patients with atrial fibrillation before the era of non-vitamin K antagonist oral anticoagulants: the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) Phase I cohort. *Europace* 2016;**18**:1308–1318.
4. Gamra H, Murin J, Chiang CE, Naditch-Brule L, Brette S, Steg PG; RealiseAF investigators. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. *Arch Cardiovasc Dis* 2014;**107**:77–87.
5. Camm AJ, Accetta G, Ambrosio G, Atar D, Bassand JP, Berge E, Cools F, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Kayani G, Koretsune Y, Mantovani LG, Misselwitz F, Oh S, Turpie AG, Verheugt FW, Kakkar AK; GARFIELD-AF Investigators. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart* 2017;**103**:307–314.
6. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–962.
7. Wang KL, Büller HR, Goto S, Lin CY, Lai EY, Chiu CC, Chiang CE, Giugliano RP. Extracranial arterial and venous thromboembolism in patients with atrial fibrillation: a meta-analysis of randomized controlled trials. *Heart Rhythm* 2017;**14**:599–605.
8. Savarese G, Giugliano RP, Rosano GM, McMurray J, Magnani G, Filippatos G, Dellegrottaglie S, Lund LH, Trimarco B, Perrone-Filardi P. Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure: a meta-analysis. *JACC Heart Fail* 2016;**4**:870–880.
9. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol* 2017;**69**:1363–1371.
10. 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.
11. Steffel J, Giugliano RP, Braunwald E, Murphy SA, Mercuri M, Choi Y, Aylward P, White H, Zamorano JL, Antman EM, Ruff CT. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF-TIMI 48 analysis. *J Am Coll Cardiol* 2016;**68**:1169–1178.
12. 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; ROCKET AF Investigators. 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; ARISTOTLE Committees and 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; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
15. 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.
16. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, Deenadayalu N, Jarolim P, Betcher J, Shi M, Brown K, Patel I, Mercuri M, Antman EM. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;**385**:2288–2295.
17. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, Goodman SN. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med* 2014;**160**:267–270.
18. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H, Lip GYH, Weitz J, Fauchier L, Lane D, Boriani G, Goette A, Keegan R, MacFadyen R, Chiang C-E, Joung B, Shimizu W. Group ESCSD. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–1393.
19. Lip GY, Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S. Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database. *Thromb Haemost* 2014;**111**:933–942.
20. Bender R, Bunce C, Clarke M, Gates S, Lange S, Pace NL, Thorlund K. Attention should be given to multiplicity issues in systematic reviews. *J Clin Epidemiol* 2008;**61**:857–865.
21. Fanola CL, Giugliano RP, Ruff CT, Trevisan M, Nordio F, Mercuri MF, Antman EM, Braunwald E. A novel risk prediction score in atrial fibrillation for a net clinical outcome from the ENGAGE AF-TIMI 48 randomized clinical trial. *Eur Heart J* 2017;**38**:888–896.
22. Wang KL, Lip GY, Lin SJ, Chiang CE. Non-vitamin K antagonist oral anticoagulants for stroke prevention in asian patients with nonvalvular atrial fibrillation: meta-analysis. *Stroke* 2015;**46**:2555–2561.
23. Pokorney SD, Simon DN, Thomas L, Fonarow GC, Kowey PR, Chang P, Singer DE, Ansell J, Blanco RG, Gersh B, Mahaffey KW, Hylek EM, Go AS, Piccini JP,

Peterson ED. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation I. Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: results from ORBIT-AF registry. *Am Heart J* 2015;**170**: 141–148, 148 e1.
24. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, Braunwald E. Impact of renal function on outcomes with edoxaban in the ENGAGE AF-TIMI 48 trial. *Circulation* 2016;**134**:24–36.
25. Wang KL, Chiu CC, Su-Yin Tan D, Lin CY, Lai EY, Goto S, Giugliano RP, Chiang CE. Once- or twice-daily non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: a meta-analysis of randomized controlled trials. *J Formos Med Assoc* 2017;**116**:591–598.
26. Carmo J, Ferreira J, Costa F, Carmo P, Cavaco D, Carvalho S, Morgado F, Adragao P, Mendes M. Non-vitamin K antagonist oral anticoagulants compared with warfarin at different levels of INR control in atrial fibrillation: a meta-analysis of randomized trials. *International Journal of Cardiology* 2017;**244**: 196–201.
27. Chao TF, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ, Lip GYH, Chen SA. Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study. *Circulation* 2018;**138**: 37–47.
28. Sjalander S, Sjogren V, Renlund H, Norrving B, Sjalander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thrombosis Research* 2018;**167**:113–118.
29. Staerk L, Fosbol EL, Lip GYH, Lamberts M, Bonde AN, Torp-Pedersen C, Ozenne B, Gerds TA, Gislason GH, Olesen JB. Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J* 2017; **38**:907–915.
30. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, van Eickels M, Turpie AG; XANTUS Investigators. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *Eur Heart J* 2016;**37**:1145–1153.
31. Steinberg BA, Shrader P, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli G, Reiffel J, Singer DE, Peterson ED, Piccini JP; ORBIT-AF Investigators and Patients. Off-label dosing of non-vitamin K antagonist oral anticoagulants and adverse outcomes. *The ORBIT-AF II, Registry J. Am Coll Cardiol* 2016;**68**:2597–2604.
32. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol* 2017;**69**:2779–2790.
33. Steinberg BA, Kim S, Thomas L, Fonarow GC, Hylek E, Ansell J, Go AS, Chang P, Kowey P, Gersh BJ, Mahaffey KW, Singer DE, Piccini JP, Peterson ED. Outcomes Registry for Better Informed Treatment of Atrial Fibrillation I, Patients. Lack of concordance between empirical scores and physician assessments of stroke and bleeding risk in atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Circulation* 2014;**129**:2005–2012.
34. 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; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
35. Wang KL, Giugliano RP, Goto S, Chiu CC, Lin CY, Lai EY, Chiang CE. Standard dose versus low dose non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation: a meta-analysis of contemporary randomized controlled trials. *Heart Rhythm* 2016;**13**:2340–2347.
36. Rao MP, Vinereanu D, Wojdyla DM, Alexander JH, Atar D, Hylek EM, Hanna M, Wallentin L, Lopes RD, Gersh BJ, Granger CB; Apixaban for Reduction in Stroke Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Clinical outcomes and history of fall in patients with atrial fibrillation treated with oral anticoagulation: insights from the ARISTOTLE trial. *Am J Med* 2018; **131**:269–275 e2.
37. Alexander JH, Andersson U, Lopes RD, Hijazi Z, Hohnloser SH, Ezekowitz JA, Halvorsen S, Hanna M, Commerford P, Ruzyllo W, Huber K, Al-Khatib SM, Granger CB, Wallentin L; Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation (ARISTOTLE) Investigators. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. *JAMA Cardiol* 2016;**1**:673–681.
38. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, Ezekowitz MD, Nehmiz G, Wang S, Wallentin L; RE-LY Investigators. 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.