Direct oral anticoagulants for secondary prevention in patients with non-valvular atrial fibrillation

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ABSTRACT

The patients with non-valvular atrial fibrillation (NVAF), both permanent and paroxysmal, and history of previous transient ischemic attack (TIA) or stroke represent a category of patients at high risk of new embolic events, independently of the presence of other risk factors. In these patients, national and international guidelines recommend oral anticoagulants as first choice for antithrombotic prevention. Direct oral anticoagulants (DOACs) have been demonstrated to be not inferior to warfarin for many end points in NVAF patients in terms of efficacy and safety. The *post hoc* analysis in selected subgroups of patients enrolled in the three mega trials of phase III comparing DOACs (RE-LY, ROCKET-AF and ARISTOTLE) with warfarin help to evaluate whether superiority and non-inferiority persist in these subgroups. Here, patients with NVAF and history of previous TIA/stroke receiving DOACs as secondary prevention are compared with patients with the same characteristics receiving warfarin. An analysis of these patients has been recently published (separately for each of three DOACs). This analysis shows that DOACs maintain their non-inferiority when compared with warfarin in secondary prevention, representing a real alternative in this context of patients at high risk for ischemic and bleeding events.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population and in clinical practice.[1-4] Its presence increases 2-7-fold the risk of ischemic stroke and systemic embolism compared to patients in sinus rhythm, showing a mean incidence of new embolic events of approximately 5% *per* year.[5-8] The magnitude of AF embolic risk is influenced by the presence of additional prognostic factors: age over 65 years, congestive heart failure, blood hypertension, diabetes, history of previous transient ischemic attack (TIA) or stroke, history of vascular diseases, female sex. Their weight in predicting embolic risk has been codified in practical scales such as the $CHADS_2$ and the most recently released CHA_2DS_2-VASC. These are well known and have been extensively validated in clinical practice.[5] A history of a previous TIA or stroke is considered a par-

ticularly important predictor of recurrent embolic events since its presence gives a score of 2 in the $CHADS_2$ and it is equivalent to age over 75 years in CHA_2DS_2-VASC.[5] In both scales, the presence of a score of 2 or over is indicative of subjects at high risk of stroke or systemic embolism (>4%/year if $CHADS_2$ ≥2, >2.2%/year if CHA_2DS_2-VASC ≥2). Therefore, the history of a previous TIA or stroke itself identifies those subjects at high risk of embolism.

The most recent guidelines on the treatment and clinical management of patients with NVAF agree in recommending oral anticoagulants, either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs), as the first choice of treatment in thromboembolic prevention in patients at high or moderate risk of stroke or systemic embolism. Despite the fact that patients at high risk of cerebral or systemic embolism represent a category with increased bleeding risk too, treatment with VKAs seem to provide the most net clinical benefit in patients with $CHADS_2$ of 2 or over.[9] The most recent guidelines suggest as a possible alternative the combination acetylsalicylic acid (ASA)/clopidogrel to oral anticoagulants in patients at low bleeding risk or ASA alone in patients at high bleeding risk when oral anticoagulants are contraindicated because of limitations or when not accepted by the patient.[5-8,10] In patients at low embolic risk, no antithrombotic therapy is recommended. However, where the physicians are inclined to recommend antithrombotic prevention therapy, the guidelines suggest the use of ASA alone[5-8,10] (Figure 1).

Vitamin K antagonists reduce the relative risk of stroke and systemic embolism by 64% (95% confidence interval (95% CI): 49-74%) *versus* placebo with a number needed to treat (required number of patients treated to avoid an event, NNT) of 40 in primary prevention and 14 in secondary prevention and 39% (95% CI: 19-53%) *versus* ASA.[11] DOACs, direct thrombin inhibitors (dabigatran) and Factor Xa (rivaroxaban and apixaban) have been shown to be not inferior to warfarin in terms of efficacy and safety in the majority of the end points considered in three phase III randomized clinical trials (RCTs) (RE-LY for dabigatran, ROCKET-AF for rivaroxaban, ARISTOTLE for apixaban). In particular, in the primary efficacy (combination of *ischemic and hemorrhagic strokes and systemic embolism*) and safety end point (major bleedings or, just for rivaroxaban, combination of *major and non-major but clinically relevant bleedings*).[12-14] Higher doses of dabigatran (150 mg administered twice daily) and apixaban have also been shown to be superior to warfarin in the primary end point of efficacy, while rivaroxaban has been demonstrated to be superior only in the statistical analysis *per* protocol (on treatment) but not in the overall intention to treat analysis.[12-14] However, it should be noted that rivaroxaban shows superiority on warfarin in the intention to treat analysis during treatment (HR 0.79 (95% CI: 0.66-0.96); P for superiority=0.02), while it shows non-superiority in the intention to treat analysis after treatment discontinuation (HR 1.10 (95% CI: 0.79-1.52); P for superiority=0.58). Dabigatran at a higher dose has also been demonstrated to be superior to warfarin in reducing the risk of ischemic strokes (relative risk (RR) 0.76, 95% CI: 0.59-0.97). Overall, DOACs have shown a good safety profile, resulting non-inferior and, for many safety end points, also superior to warfarin with exception of inferiority on gastrointestinal bleedings for higher dose of dabigatran (150 mg twice/day) and rivaroxaban. However, it should be said that the post-marketing analysis by the Food and Drug Administration (FDA) has demonstrated that the risk of gastrointestinal bleeding is 3-fold lower for dabigatran in comparison to warfarin in *real life*.[15] Of utmost significance is the overall relative risk reduction (RRR) of 55% of intracranial bleedings associated with DOACs when compared to warfarin.[16-18]

The results of the three phase III RCTs on DOACs in NVAF have been described in detail and commented on in a previous article.[19] The details of these RCTs are summarized in Tables 1-3.

The results of these phase III RCTs have already been accepted by the scientific community and DOACs are now included in the latest guidelines on clinical management of NVAF published by the most important international scientific Societies, such as the American College of Chest Physicians (ACCP) and the European Society of Cardiology (ESC). DOACs are recommended as the first choice for thromboembolic prevention in high risk (grade of recommendation and level of evidence IA) or moderate risk (IB recommendation ACCP, IIAa ESC) patients with NVAF, as are VKAs over which, however, these should be preferred.[5,8]

The combination of ASA plus clopidogrel significantly reduces the risk of thromboembolism when compared with ASA alone but it is not superior over ASA alone in reducing the all cause mortality rate or the combined end point *all cause mortality plus morbidity*, as shown by the ACTIVE-A study (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events-Aspirin). Furthermore, this combination causes a significant increase in total bleedings over ASA alone[20] with a rate of bleedings similar to that of VKAs and a reduction in terms of efficacy when compared to VKAs, as evident from the results of the ACTIVE-W study.[21] ASA is considered the fourth choice of prevention therapy in patients with NVAF at high or moderate thromboembolic risk, as it reduces (not significantly) the relative risk of stroke compared with placebo by 19% (95% CI: –1 to 35%).[5,8,11]

A practical flow chart on the most recent recommendations for antithrombotic prevention in NVAF is shown in Figure 1.[5,8]

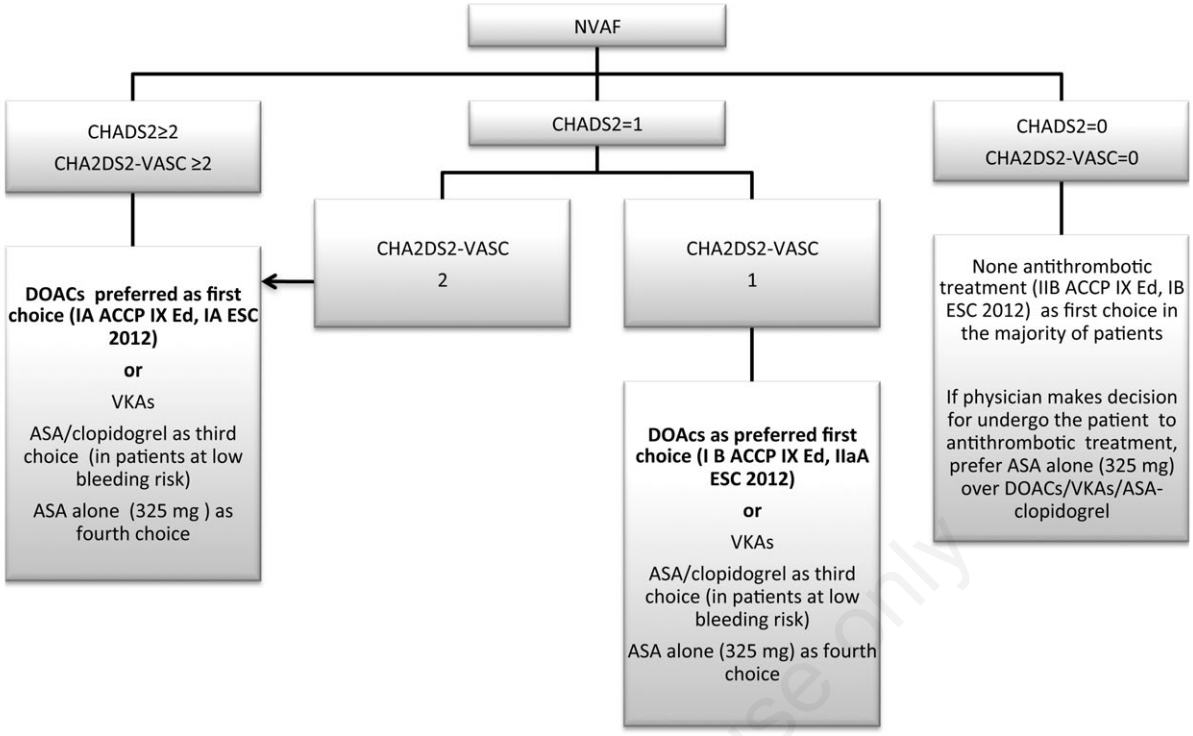


Figure 1. Summary of most recent guidelines on thromboembolic prevention in patients with non-valvular atrial fibrillation (NVAF).

DOACs in secondary prevention: findings from phase III randomized controlled trials

Post hoc analyses of selected subgroups of patients enrolled in the phase III RCTs on DOACs in NVAF have also been published. The analysis of the results related to patients with history of previous TIA/stroke enclosed in these trials (secondary prevention) is of great interest because of the related consequences in clinical practice.[16-18] Patient cohorts with previous TIA/stroke enrolled in the three RCTs numbered: 1195 for the RE-LY 110 mg, 1233 for the RE-LY 150 mg, 3754 for the ROCKET-AF, 1694 for the ARISTOTLE studies, respectively, compared with 4819 (RE-LY 110), 4843 (RE-LY 150), 3377 (ROCKET-AF), 7426 (ARISTOTLE) patients in primary prevention.[16-18] There was a difference in the percentage of patients with a history of TIA/stroke enrolled in the three RCTs in a comparison of the ROCKET-AF trial with RE-LY and ARISTOTLE.[16-18] In fact, the ROCKET-AF trial included approximately three times more patients with a history of TIA/stroke (54.9%) compared to RE-LY 110 mg (20%), 150 mg (20%) and ARISTOTLE (19%).[16-18]

Table 4 summarizes the general characteristics of the populations enrolled in the three RCTs.

Thromboembolic risk in patients with previous transient ischemic attack or stroke

Figure 2 show the rate of thromboembolic events in patients in primary and secondary prevention treated with DOACs and warfarin in the RE-LY, ROCKET-AF and ARISTOTLE studies. The incidence of ischemic events was higher in patients with a history of previous TIA/stroke than in patients without a history of previous TIA/stroke. In particular, for the primary efficacy end point and for the end point *ischemic strokes*, the three RCTs all show an increase in the incidence of thrombotic events in secondary prevention both in patients randomized to DOACs and in those randomized to warfarin.[16-18]

Bleeding risk in patients with previous transient ischemic attack or stroke

Figure 2 shows the rate of bleeding events in patients in primary and secondary prevention treated with DOACs and warfarin in the the RE-LY, ROCKET-AF and ARISTOTLE studies. For the vast majority of safety end points considered in the three RCTs, the incidence of bleeding events was higher in patients with a history of previous TIA/stroke than in patients without a history of previous TIA/stroke. In

Table 1. Enrollment criteria in phase III randomized clinical trials on DOACs in non-valvular atrial fibrillation.

	INCLUSION	EXCLUSION
RE-LY (Dabigatran)	AF documented in 12-leads-ECG or in previous six months plus at least one of: previous TIA/stroke/systemic embolism, ejection fraction <40%, class NYHA ≥2 heart failure within six months before enrollment, age ≥75 years or 65-74 years when associated to at least one of diabetes, systemic blood hypertension or coronary ischemic disease	Age <18 years, severe valvular heart diseases, stroke in the previous two weeks or severe stroke (modified Rankin scale at hospital discharge 4-5), presence of high bleeding risk conditions, severe renal failure (creatinine clearance <30 mL/min), active liver disease, pregnancy
ROCKET-AF (Rivaroxaban)	AF documented at 12-leads-ECG plus at least one of: previous TIA/stroke/systemic embolism or at least two of heart failure or ejection fraction ≤35%, systemic blood hypertension, diabetes, age ≥75 years	Age <18 years, severe mitral valve tenosis, paroxysmal AF due to cause for reversal, active internal bleeding, previous severe stroke (modified Rankin scale 4-5) in the previous three months or stroke in the previous two weeks, TIA in the previous three days, history of intracranial bleeding, high bleeding risk conditions, severe renal failure (creatinine clearance <30 mL/min)
ARISTOTLE (Apixaban)	AF documented at 12-leads-ECG in two non-consecutive weeks in the previous 12 months plus at least one of: age ≥75 years, previous TIA/stroke/systemic embolism, heart failure in the previous three months or ejection fraction ≤40%, diabetes, systemic blood hypertension	Age <18 years, AF due to reversal cause, moderate-severe mitral valve stenosis, presence of conditions in which anticoagulation is necessary such as mechanical prosthetic valve, stroke in the previous week, conditions required ASA at dose >165 mg or ASA associated to clopidogrel, severe renal failure (creatine clearance <25 mL/min)

ECG, electrocardiogram; AF, atrial fibrillation; TIA, transient ischemic attack; ASA, acetylsalicylic acid.

Table 2. Summary of main efficacy and safety results found in phase III randomized clinical trials on DOACs compared with warfarin in non-valvular atrial fibrillation.

END POINTS	RE-LY 110 mg RR (95% CI) intention to treat	RE-LY 150 mg RR (95% CI) intention to treat	ROCKET-AF HR (95% CI) *per* protocol	ROCKET-AF HR (95% CI) intention to teat, on treatment	ARISTOTLE HR (95% CI) intention to treat for efficacy, *per* protocol, on treatment for safety
EFFICACY					
Ischemic strokes	1.11 (0.88-1.39)	0.76 (0.59-0.97)*	0.94 (0.75-1.17)	0.99 (0.82-1.20)	0.92 (0.74-1.13)
Combined end point *ischemic and hemorrhagic strokes or systemic embolism*	0.90 (0.74-1.10)	0.66 (0.52-0.81)*	0.79 (0.66-0.96)*	0.88 (0.75-1.03)	0.79 (0.66-0.95)*
Debilitating or fatal strokes	0.93 (0.72-1.21)	0.66 (0.50-0.87)*	nr	nr	0.71 (0.54-0.94)*
Vascular mortality	0.90 (0.77-1.06)	0.85 (0.72-0.99)*	0.89 (0.73-1.10)	0.86 (0.74-0.99)*	0.89 (0.76-1.04)
Overall mortality	0.91 (0.80-1.03)	0.88 (0.77-1.00)	0.85 (0.70-1.02)	0.85 (0.70-1.02)	0.89 (0.80-0.98)*
Myocardial infarctions	1.29 (0.96-1.75)	1.27 (0.94-1.71)	0.81 (0.63-1.06)	Nr	0.88 (0.66-1.17)
SAFETY					
Overall bleedings	0.78 (0.73-0.83)*	0.91 (0.85-0.96)*	1.03 (0.96-1.11)		0.71 (0.68-0.75)*
Major bleedings	0.80 (0.70-0.93)*	0.93 (0.81-1.07)	1.04 (0.90-1.20)		0.69 (0.60-0.80)*
Fatal bleedings	0.58 (0.35-0.97)*	0.70 (0.43-1.14)	0.50 (0.31-0.79)		nr (Apixaban risk 0.0037 *vs* warfarin risk 0.0060)
Intracranial bleedings	0.30 (0.19-0.45)*	0.41 (0.28-0.60)*	0.67 (0.47-0.93)*		0.42 (0.30-0.58)*
Gastrointestinal bleedings	1.08 (0.85-1.38)	1.48 (1.18-1.85)°	3.2% *vs* 2.2%. P<0.001°		0.89 (0.70-1.15)
NET BENEFIT					
Net benefit: vascular events, major bleedings, mortality	0.92 (0.84-1.01)	0.90 (0.82-0.99)	nr		0.85 (0.78-0.92)*

CI, confidence interval; nr, not reported. *Superiority; °inferiority; the other, no inferiority.

particular, for the end point *intracranial bleedings*, all three RCTs show higher incidence in secondary prevention both in patients randomized to DOACs and in those randomized to warfarin.[16-18]

Efficacy and safety of DOACs in secondary prevention

Tables 5 and 6 summarize the results of efficacy and safety of the DOACs compared with warfarin and analyzed according to primary and secondary prevention.

Efficacy end points

For all efficacy end points, DOACs in secondary prevention maintain the objective of non-inferiority when compared to warfarin.[16-18]

Dagibatran: the lower dose of dabigatran (110 mg twice/day), which was not inferior to warfarin in primary prevention on all efficacy end points, becomes superior to warfarin in end points regarding vascular mortality and total mortality in secondary prevention.[16] The higher dose of dabigatran (150 mg twice/day), which was superior to warfarin for all efficacy end points in primary prevention, was found to be not inferior to warfarin in secondary prevention for the same end points.

Rivaroxaban: rivaroxaban is not inferior to warfarin for the vast majority of efficacy end points in primary and secondary prevention, being superior to warfarin only on the end point *disabling or fatal stroke* in primary prevention.

Apixaban: apixaban is superior to warfarin on the end point *disabling or fatal stroke* both in primary and secondary prevention, while on all other efficacy end points apixaban is not inferior to warfarin in either context of prevention.

Figure 3 shows the RRR for total mortality with DOACs compared to warfarin.

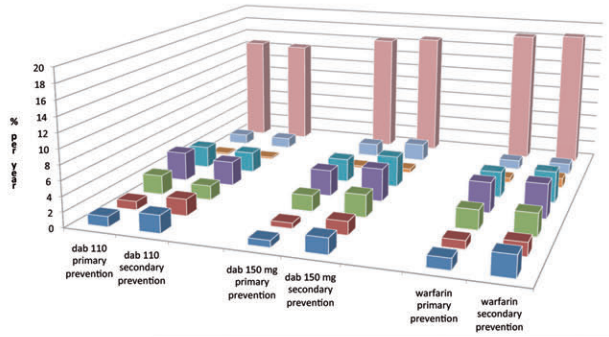
Overall, DOACs reduce the RR of ischemic and hemorrhagic strokes and systemic embolism in secondary prevention in a range between 6% for rivaroxaban (HR 0.94, 95% CI: 0·77-1·16) and 25% for dabigatran 150 mg twice/day (RR 0.75, 95% CI: 0.52-1.08) while this range is between 7% for dabigatran 110 mg twice/day

Table 3. Summary of main efficacy and safety results expressed with absolute risk reduction and number needed to treat or number needed to harm found in phase III randomized clinical trials on DOACs compared to warfarin in non-valvular atrial fibrillation.

END POINTS	RE-LY 110 mg intention to treat		RE-LY 150 mg intention to treat		ROCKET-AF *per* protocol, on treatment		ARISTOTLE intention to treat for efficacy, *per* protocol on treatment for safety	
	ARR/1000	NNT	ARR/1000	NNT	ARR/1000	NNT	ARR/1000	NNT
EFFICACY								
Combined end point *ischemic and hemorrhagic strokes or systemic embolism*	1.6	625	5.8*	172*	5.0*	200*	3.3*	303*
Ischemic strokes	–1.4	714	2.8*	357*	1.6	625	0.8	1250
Debilitating or fatal strokes	0.6	1666	3.4*	294*	4.7	212	nr*	nr*
Vascular mortality	2.6	384	3.9*	256*	3.2	312.5	nr	nr
Overall mortality	3.8	263	4.9	204	5.8	172	4.2*	238*
SAFETY								
Myocardial infarctions	–1.8	555	–1.7	588	–3.5	285	0.8*	1250*
Overall bleedings	35.3*	28*	17.3*	58*	–4	250	19.4*	51*
Major bleedings	6.5*	154*	2.5	400	–2	500	7.3*	137*
Fatal bleedings	nr*		nr		3	333	nr	nr
Intracranial bleedings	5.1*	196*	4.4*	227*	2*	500*	4.7*	212*
Gastrointestinal bleedings	–1.0	1000	–4.9°	204°	–10°	100°	1	1000
NET BENEFIT								
Net benefit: vascular events, major bleedings, mortality	5.5	181	7.3*	137*	nr	nr	9.4*	106*

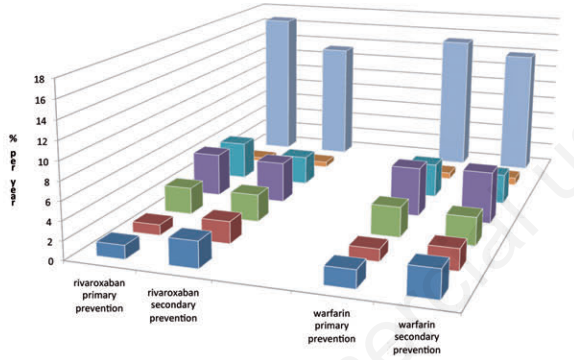
ARR, absolute risk reduction; NNT, number needed to treat. *Superiority; °inferiority; the other, no inferiority. Positive numbers are associated to NNT of DOACs on warfarin, negative numbers are associated with number needed to harm of DOACs on warfarin.

(A)



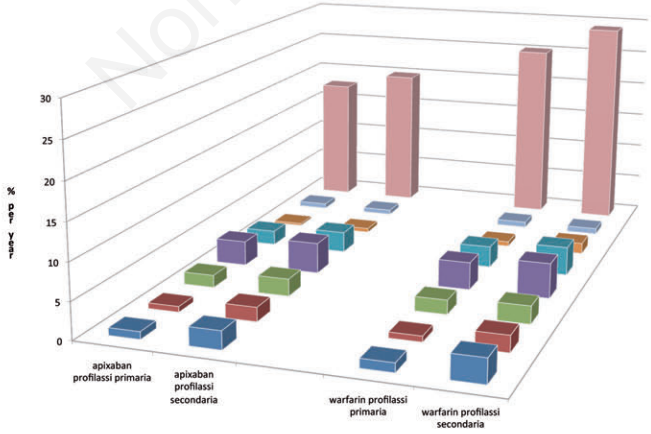
	dab 110 primary prevention	dab 110 secondary prevention		dab 150 mg primary prevention	dab 150 mg secondary prevention		warfarin primary prevention	warfarin secondary prevention
ischemic and hemorrhagic strokes and systemic embolism	1,34	2,32		0,87	2,07		1,45	2,78
ischemic strokes	1,12	2,19		0,71	1,75		1,08	1,75
vascular mortality	2,56	1,9		2,1	2,97		2,61	3
overall mortality	3,87	3,24		3,45	4,38		4,02	4,58
major bleedings	2,91	2,74		3,1	4,15		3,43	4,15
intracranial bleedings	0,22	0,25		0,27	0,53		0,63	1,28
gastrointestinal bleedings	1,35	1,39		1,73	2,32		1,23	1,41
overall bleedings	14,71	14,49		16,33	16,9		18,15	18,53

(B)



	rivaroxaban primary prevention	rivaroxaban secondary prevention		warfarin primary prevention	warfarin secondary prevention
ischemic and hemorrhagic strokes and systemic embolism	1,44	2,79		1,88	2,96
ischemic strokes	1,13	2,34		1,29	2,27
vascular mortality	2,89	2,93		3,23	3
overall mortality	4,65	4,4		5,28	5,54
major bleedings	4,1	3,13		3,69	3,22
intracranial bleedings	0,39	0,59		0,68	0,8
major and non-major clinically revelent bleedings	16,69	13,31		15,19	13,87

(C)



	apixaban profilassi primaria	apixaban profilassi secondaria		warfarin profilassi primaria	warfarin profilassi secondaria
ischemic and hemorrhagic strokes and systemic embolism	1,01	2,46		1,23	3,24
ischemic stroke	0,76	1,92		0,79	2,23
vascular mortality	1,68	2,35		1,94	2,41
overall mortality	3,37	4,22		3,75	4,77
major bleedings	1,98	2,84		2,91	3,91
intracranial bleedings	0,29	0,55		0,65	1,49
gastrointestinal bleedings	0,68	0,66		0,78	0,8
overall bleedings	17,7	19,86		25,11	29,12

Figure 2. A) Events rate in the RE-LY study; B) Events rate in the ROCKET-AF study; C) Events rate in the ARISTOTLE study.

(RR 0.93, 95% CI: 0.73-1.18) and 40% for dabigatran 150 mg twice/day (RR 0.60, 95% CI: 0.45-0.78) in primary prevention[16-18] (Figure 4).

The different results of DOACs in primary and secondary prevention impacts on the values of NNT and number needed to harm (required number of patients treated to cause an adverse event, NNH) (Table 6). For the majority of efficacy end points, dabigatran 110 mg twice/day significantly reduces the value of its NNTs in secondary prevention compared to primary prevention with the exception of the end point *ischemic stroke* where the NNH is 227 in secondary prevention, down from 2500 in primary prevention.[16] In contrast, dabigatran 150 mg twice/day increases its NNT values in secondary prevention.[16] In the ROCKET-AF study, rivaroxaban NNT values increase in the efficacy end points in secondary prevention, while in the ARISTOTLE study, apixaban in this context is associated with a reduction in NNTs with the exception of the end point *fatal or disabling stroke*.[17,18]

Safety end points

For all safety end points, DOACs maintain the objective of non-inferiority when compared to warfarin in secondary prevention,[16-18] with the only exception of the inferiority of higher dose of dabigatran (150 mg twice/day) on warfarin in the *gastrointestinal bleedings* end point, increasing the relative risk of 24% in secondary prevention *versus* primary prevention.[16] Data on gastrointestinal bleedings in secondary prevention for rivaraxaban, which resulted inferior to warfarin in this context, are not available.[13,17]

Dabigatran: lower dose of dabigatran (110 mg twice/day) is superior to warfarin both in primary and secondary prevention end point on major bleedings and not inferior to warfarin in the gastrointestinal bleedings end point.[16] Higher dose of dabigatran dose (150 mg twice/day) is not inferior to warfarin on major bleedings.[17] For dabigatran, data on total and fatal bleedings according to primary and secondary prevention are not reported. In the total population of RE-LY, dabigatran 110 mg resulted superior to warfarin on total and fatal bleedings, dabigatran 150 mg was not inferior to warfarin in total and fatal bleedings.[12] Dabigatran 110 mg increases the superiority on warfarin in secondary prevention with respect to major bleedings, bringing the RRR from 15% to 34%[16] (Figure 3).

Rivaroxaban: rivaroxaban is superior to warfarin in primary and secondary prevention on fatal bleedings, while it is not inferior in either context of prevention on total bleedings.[17]

Apixaban: apixaban is superior to warfarin in the major bleedings end point and not inferior on the gastrointestinal bleedings end point both in primary and secondary prevention.[18] Data on major and fatal bleedings for apixaban according to primary and secondary prevention are not available.[18]

Table 4. General characteristics of patients enrolled in RE-LY, ROCKET-AF and ARISTOTLE studies according to primary and secondary prevention.

	RE-LY 110 mg (Dabigatran)		RE-LY 150 mg (Dabigatran)		ROCKET-AF (Rivaroxaban)		ARISTOTLE (Apixaban)	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention	Primary prevention*	Secondary prevention*
Number	4819	1195	4843	1233	3377	3754	7426	1694
Age (years)	71.7±8.4 (median)	70.7±9.4 (median)	71.7±8.5	70.8±10.1	75 (median)	71	68.8±9.7	70.1±9.5
Males/females	64.3/35.7%	64.1/35.9%	63.5/36.5%	62.2/37.8%	60/40%	61/39%	65/35%	63/37%
$CHADS_2 \geq 2$	59.4%	100%	59.5%	100%	100%	100%	58%	100%
$CHADS_2 \geq 3$	18.5%	90%	17.9%	90.2%	nr°	nr°	16%	92%
ASA at moment of enrollment	40%	39.9%	38.4%	39.7%	35%	38%	31%	31%
Previous acute myocardial infarction	nr	nr	nr	nr	19%	14%	14%	17%
Systemic blood hypertension	79.2%	77%	79.3%	77.3%	96%	85%	88%	83%
Diabetes	23.7%	22.4%	22.9%	23.7%	58%	25%	25%	26%
Heart failure	nr	nr	nr	nr	76%	51%	31%	27%
Paroxysmal AF	nr	nr	nr	nr	16%	19%	nr	nr
Persistent or permanent AF	nr	nr	nr	nr	84%	81%	nr	nr

nr, not reported (exclusively patients in primary or secondary prevention). In phase III randomized clinical trials, reporting on overall patient data are expressed in detail.
*ARISTOTELE study data refer to sum of patients treated with apixaban or warfarin with previous TIA/stroke *versus* patients treated with apixaban or warfarin without previous TIA/stroke.; °ROCKET-AF study patients with CHADS2 ≥2 represent 100% and with CHADS2 ≥3.87%.

Table 5. Summary of main results found in phase III randomized clinical trials on DOACs compared to warfarin in non-valvular atrial fibrillation according to primary and secondary prevention.

END POINTS	RE-LY 110 mg RR (95% CI) intention to treat		RE-LY 150 mg RR (95% CI) intention to treat		ROCKET-AF HR (95% CI) intention to treat for efficacy end points, *per* protocol for safety end points		ARISTOTLE HR (95% CI) intention to treat for efficacy end points, *per* protocol for safety end points	
EFFICACY								
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
Ischemic strokes	1.04 (0.80-1.37)	1.26 (0.84-1.90)	0.66 (0.48-0.89)*	1.00 (0.65-1.54)	0.88 (0.64-1.21)	1.03 (0.82-1.30)	0.97 (0.74-1.26)	0.86 (0.60-1.22)
Combined end point *ischemic and hemorrhagic strokes and systemic embolism*	0.93 (0.73-1.18)	0.84 (0.58-1.20)	0.60 (0.45-0.78)*	0.75 (0.52-1.08)	0.77 (0.58-1.01)	0.94 (0.77-1.16)	0.82 (0.65-1.03)	0.76 (0.56-1.03)
Debilitating or fatal strokes	1.01 (0.73-1.39)	0.81 (0.52-1.25)	0.62 (0.43-0.89)*	0.72 (0.46-1.12)	0.58 (0.39-0.88)*	0.93 (0.70-1.23)	0.60 (0.41-0.86)*	0.87 (0.57-1.34)*
Vascular mortality	0.98 (0.82-1.17)	0.63 (0.43-0.82)*	0.80 (0.67-0.97)*	0.98 (0.70-1.36)	0.89 (0.73-1.09)	0.98 (0.80-1.19)	nr	nr
Overall mortality	0.96 (0.83-1.11)	0.70 (0.53-0.94)*	0.86 (0.74-0.99)*	0.95 (0.73-1.24)	0.88 (0.75-1.03)	0.97 (0.82-1.14)	0.90 (0.79-1.02)	0.89 (0.79-1.12)
Myocardial infarctions	nr	nr	nr	nr	0.77 (0.56-1.07)	1.13 (0.79-1.61)	nr	nr
SAFETY								
Overall bleedings	nr	nr	nr	nr	1.10 (0.99-1.21)	0.96 (0.87-1.07)	0.72 (0.68-0.76)*	0.70 (0.62-0.79)*
Major bleedings	0.85 (0.72-0.99)*	0.66 (0.48-0.90)*	0.91 (0.77-1.06)	1.01 (0.77-1.34)	1.11 (0.92-1.34)	0.97 (0.79-1.19)	nr	nr
Fatal bleedings	nr	nr	nr	nr	0.46 (0.23-0.90)*	0.54 (0.29-1.00)*	nr	nr
Intracranial bleedings	0.35 (0.21-0.57)*	0.20 (0.008-0.47)*	0.43 (0.27-0.68)*	0.41 (0.21-0.79)*	0.57 (0.34-0.97)*	0.74 (0.47-1.15)	0.44 (0.30-0.66)*	0.37(0.21-0.67)*
Gastrointestinal bleedings	1.11 (0.86-1.43)	0.99 (0.61-1.60)	1.43 (1.12-1.81)°	1.67 (1.09-2.56)°	nr	nr	0.87 (0.65-1.17)	0.83 (0.44-1.54)
NET BENEFIT								
Net benefit: vascular events, major bleedings, mortality	0.95 (0.86-1.06)	0.81 (0.66-1.00)*	0.87 (0.78-0.96)*	1.01 (0.84-1.23)	nr	nr	nr	nr

*Superiority; °inferiority; the other, no inferiority. nr, not reported.

The most important result emerged in the phase III RCTs on DOACs in NVAF is represented by the RRR of intracranial bleedings, which was overall 55%.[19] The analysis of intracranial bleeding risk within RCTs in terms of primary and secondary prevention shows that both doses of dabigatran and apixaban are superior to warfarin in both contexts whereas rivaroxaban is superior on this end point in primary prevention compared to warfarin and not inferior in secondary prevention (RR 0.74, 95% CI: 0.47-1.15).[16-18] The overall incidence of intracranial bleeding in patients on DOACs for secondary prevention was 0.90% per 100 patients treated (0.51% in primary prevention) while it was 1.84% *per* 100 patients treated with warfarin (1.14% in primary prevention), with an overall RR of 0.48 and an RRR of 52% (56% in primary prevention) (Figure 5).

Dabigatran 110 mg twice/day significantly reduces the value of its NNTs in secondary prevention compared to primary prevention, even increasing the NNH on the gastrointestinal bleedings end point (1 in every 5000 patients treated for secondary prevention develops a gastrointestinal bleeding *vs* 1 in 833 in primary prevention), while dabigatran 150 mg twice/day significantly reduces the advantages in efficacy when compared with warfarin in secondary prevention, increasing the values of its NNTs and further reducing the NNH for the end point *gastrointestinal bleeding*.[16] In the ROCKET-AF study, in secondary prevention rivaroxaban reduces its advantages on safety end points related to intracranial and fatal bleedings compared to warfarin, increasing the values of NNTs and has disadvantages for the total and major bleedings, passing from an NNT to an NNH.[17] Finally, in the ARISTOTLE study, apixaban is associated with a reduction in the values of NNTs in all safety end points in secondary prevention compared to primary prevention.[18]

Net clinical benefit

In secondary prevention, dabigatran at lower dose (110 mg twice/day) reaches superiority over warfarin in net benefit (non-inferiority on this end point compared to warfarin in primary prevention), while the higher dose (150 mg twice/day) results not inferior to warfarin (it was superior to warfarin in primary prevention) (Table 5). The net benefit of rivaroxaban and apixaban on warfarin in secondary prevention has not been reported in the *post hoc* analyses; net benefit was greater for apixaban in the overall population, while it was not reported in the ROCKET-AF study for rivaroxaban (Table 2).

Discussion

Patients with NVAF and history of previous TIA/stroke have a risk of recurrent embolism approximately three times higher compared to patients without history of TIA/stroke.[5] In this subgroup of patients, VKAs was seen to have the higher net benefit with an NNT of 14.[9] However, these patients are more complex in clinical practice compared with patients without history of TIA/stroke, presenting a higher bleeding risk.[9]

The differences emerging in secondary prevention can have important implications for clinical practice. First, DOACs are not inferior to warfarin for almost all of the efficacy and safety end points also in secondary prevention of patients with NVAF. In these patients at higher cardioembolic and hemorrhagic risk, DOACs are effective and safe alternatives, with several advantages in terms of pharmacokinetic and pharmacodynamic profile.

The analysis of phase III RCTs by dividing the patients into those with a prior history of TIA/stroke and those with no history of such events, clearly confirms that the patients in secondary prevention have an overall increased embolic and bleeding risk. In the RE-LY study, dabigatran at lower dose (110 mg twice/day), despite its association with a higher rate of ischemic and hemorrhagic stroke and systemic embolism compared to the higher dose (150 mg twice/day) both in primary and in secondary prevention, shows a superior net clinical benefit compared to warfarin due to a reduction in bleeding events.[16-18] In contrast, superiority of dabigatran at higher dose on warfarin in the net clinical benefit is lost in secondary prevention as the result of an increased rate of bleedings.[16-18] In secondary prevention, rivaroxaban and apixaban seem to lose some advantage over warfarin in terms of some benefits that had characterized them in the overall analysis of their RCTs, such as the significant reduction in intracranial bleedings and disabling or fatal strokes for rivaroxaban, and significant reduction in total mortality for apixaban. However, never losing their non-inferiority to warfarin.[17,18]

From a practical point of view, the use of DOACs is also desirable and recommended in secondary prevention, especially considering the RRR of 52% compared to warfarin with a range from 26% for rivaroxaban (HR 0.74, 95% CI: 0.47-1.15) to 80% for dabigatran 110 mg (RR 0.20, 95% CI: 0.08-0.47) for an end point of utmost importance such as *intracranial bleedings*.[16-18]

However, in clinical practice, despite the fact that to date no recommendations have been made regarding changing the dose of DOACs in secondary cardioembolic stroke prevention, it could be suggested to prefer DOACs or dosages of DOACs which have demonstrated the best efficacy/safety profile. As recently demonstrated by a meta-analysis of Rasmussen *et al.* in which DOACS were indirectly compared with each other, lower dabigatran dose (110 mg twice/day)

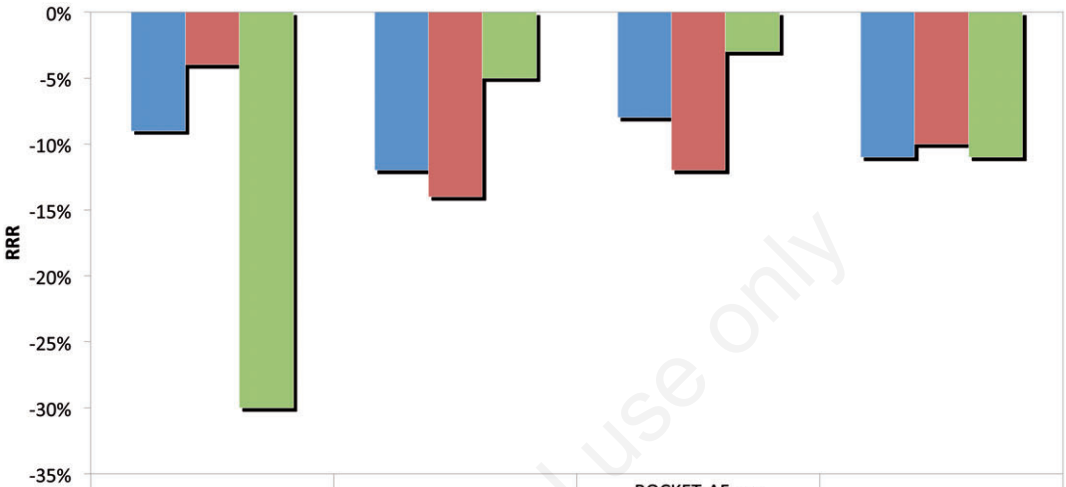
Table 6. Absolute risk reduction referred to 1000 treated patients, number needed to treat and number needed to harm found in phase III randomized clinical trials on DOACs compared to warfarin in non-valvular atrial fibrillation according to primary and secondary prevention.

	RE-LY 110 mg ARR		NNT or NNH	RE-LY 150 mg ARR		NNT or NNH	ROCKET-AF N ARR		NNT or NNH	ARISTOTLE ARR		NNT or NNH
EFFICACY												
END POINTS	**Primary prevention**	**Secondary prevention**	**Primary/secondary prevention**	**Primary prevention**	**Secondary prevention**	**Primary/secondary prevention**	**Primary prevention**	**Secondary prevention**	**Primary/secondary prevention**	**Primary prevention**	**Secondary prevention**	**Primary/econdary prevention**
Ischemic strokes	–0.4	–4.4	2500/227	3.7	0	270/infinity	1.6	–0.7	625/1428	0.3	3.2	3333/312
Combined end point *ischemic and hemorrhagic strokes or systemic embolism*	1.1	4.6	909/217	5.8	7.1	172/140	4.4	1.7	227/588	2.2	7.8	454/128
Debilitating or fatal strokes	–0.1	3.6	10,000/77	3.0	5.4	333-185	4.1	1.2	244-833	2.3	1.8	434-555
Vascular bleedings	0.5	11	2000/90	5.1	0.3	196/3333	3.4	0.7	294/1428	2.6	6	384/166
Overall mortality	1.5	13.4	666/74	5.7	1.9	175/526	6.3	1.4	158/714	3.8	5.5	263/181
SAFETY												
Overall bleedings	34.4	40.4	29/24	18.2	16.3	55/61	–15	5.6	66/178	74.1	92.6	13/10
Major bleedings	5.2	14.1	192/71	3.3	0	303/infinity	–41	9	24/111	9.3	10.7	107/93
Fatal bleedings	nr	nr		nr	nr		2.6	2.3	384/434	nr	nr	
Intracranial bleedings	4.1	10.3	244/97	3.6	7.5	277/133	2.8	0.9	357/1111	3.6	9.4	277/106
Gastrointestinal bleedings	–1.2	0.2	833/5000	–5	–9.1	200/109	nr	nr		1.0	1.4	1000/714
NET BENEFIT												
Net benefit: vascular events, major bleeding, mortality	4.2	16.1	238/62	10.2	0.3	98/3333	nr	nr		nr	nr	

ARR, absolute risk reduction; NNT, number needed to treat, NNH, number needed to harm; nr, not reported. Positive number identifies NNT of DOACs on warfarin; negative number identifies NNH of DOACs on warfarin.

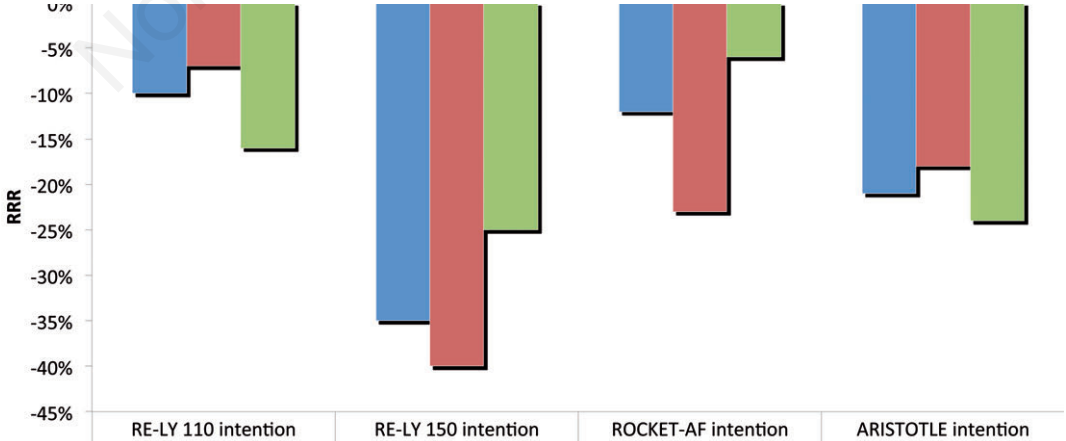
should show such a good efficacy/safety profile. However, as pointed out by the Authors, this can only be confirmed through direct comparisons.[22]

In this context, it is also interesting to refer to the recent publication of the *post hoc* analysis of the AVERROES study, a phase III RCT in which apixaban at a dose of 5 mg twice/day was compared with ASA (80-325 mg) for cardioembolic prophylaxis in patients with NVAF who are not suitable for VKAs treatment. Apixaban reduced the RR of ischemic and hemorrhagic stroke and systemic embolism by 71% compared to ASA in secondary prevention without there being any significant difference in major and intracranial bleedings.[23]



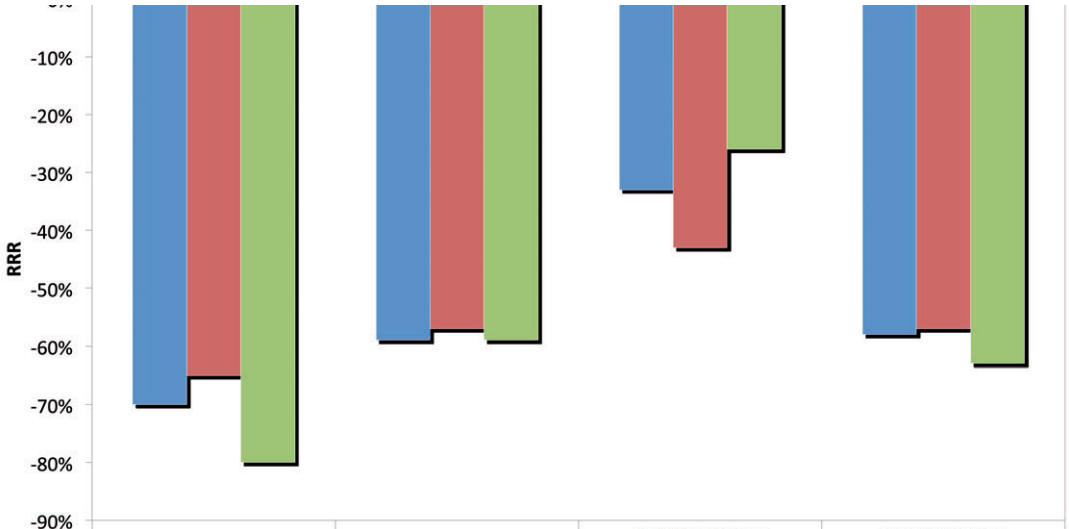
	RE-LY 110 intention to treat	RE-LY 150 intention to treat	ROCKET-AF per protocol RRR total, intention to treat RRR primary and secondary prevention	ARISTOTLE intention to treat
overall	-9%	-12%	-8%	-11%
primary prevention	-4%	-14%	-12%	-10%
secondary prevention	-30%	-5%	-3%	-11%

Figure 3. Relative risk reduction (RRR) of all causes mortality with DOACs compared to warfarin.



	RE-LY 110 intention to treat	RE-LY 150 intention to treat	ROCKET-AF intention to treat	ARISTOTLE intention to treat
overall	-10%	-35%	-12%	-21%
primary prevention	-7%	-40%	-23%	-18%
secondary prevention	-16%	-25%	-6%	-24%

Figure 4. Relative risk reduction (RRR) of strokes and systemic embolism with DOACs compared to warfarin.



	RE-LY 110 intention to treat	RE-LY 150 intention to treat	ROCKET-AF per protocol, on treatment	ARISTOTLE per protocol, on treatment
overall	-70%	-59%	-33%	-58%
primary prevention	-65%	-57%	-43%	-57%
secondary prevention	-80%	-59%	-26%	-63%

Figure 5. Relative risk reduction (RRR) of intracranial bleedings with DOACs compared to warfarin.

Concerns in secondary prevention: when to start DOACs in the acute phase of cardioembolic stroke?

The patient with cardioembolic stroke associated with NVAF should receive antithrombotic drugs for secondary prevention already from the acute phase of stroke. DOACs are not inferior (and are for many aspects superior) to warfarin for cardioembolic prevention and the most recent guidelines suggest using DOACs and not VKA for this purpose.[5,8] However, some uncertainty remains about when to start DOACs in the acute phase of a cardioembolic stroke. Although there is no uniformity on VKA management in the acute phase of a cardioembolic stroke, it is now quite clear that the optimal timing for introducing VKAs in the acute phase of stroke is represented by the period ranging from 48 h to 14 days after accurate exclusion of severe neurological deterioration, wide extension of ischemic injury and embolic cardiac comorbidity.[24] Instead, subjects with clinically severe stroke, with a large ischemic lesion and absence of cardiac conditions such as atrial or ventricular thrombosis or mechanical prosthetic valves which may be at high risk of early embolic recurrence, should start VKAs after 14 days.[24] In phase III RCTs on DOACs in NVAF, patients with recent cardioembolic stroke were excluded. With the exception of the ARISTOTLE study with apixaban, which included patients with previous stroke occurring within seven days of enrollment, the RE-LY and ROCKET-AF studies excluded patients with previous non-severe stroke occurring within 14 days and severe stroke occurring within 3-6 months of enrollement (Table 1).[12-14] It should be noted, however, that the ARISTOTLE study included only 44 patients with stroke occurring 7-14 days before enrollement of whom 23 were randomized to warfarin and 21 to apixaban.[14] Therefore, due to lack of evidence, when to start a DOACs in secondary prevention after an acute cardioembolic stroke remains a subject of debate. Very recently, recommendations for the management of DOACs in clinical practice have been made widely available.[25-29] In the context of the acute phase of cardioembolic stroke, recommendations on dabigatran suggest starting it immediately after a TIA, 3-5 days after a clinically mild stroke, after 5-7 days in patients with a stroke of moderate severity, approximately 14 days or more in patients with severe cardioembolic stroke.[25-27] Other clinical management experts have made similar suggestions for rivaroxaban. Rivaroxaban should be started immediately after a TIA, and between 48 h to 14 days after a stroke, taking into account clinical severity, lesion extension at neuroimaging, and cardiological comorbidity by echocardiography.[29]

However, there are no recommendations as to which dosage should be chosen. The acute phase of cardioembolic stroke is a well-recognized period of high risk and the incidence and risk factors of hemor-

rhagic transformation related to the use of DOACs in this phase are still not known. Therefore, the balance between risk of embolic recurrence and hemorrhagic transformation should focus on selecting the right anticoagulation and its dose, taking into account the fact that the anticoagulant effect of DOACs is almost immediate. The choice of which DOACs to use or at what dosage in the acute phase of a cardioembolic stroke should take into account its efficacy/safety profile, the risk of recurrent embolism, bleeding risk, concomitant use of drugs, or presence of comorbidity or conditions that increase the plasma concentration of the DOACs, such as renal or liver failure. Available data show that a lower dose of dabigatran (110 mg twice/day) seems to have the best benefit/risk profile and, therefore, may be the preferred choice. However, it must be said that all available data are derived from an indirect comparison of DOACs based on the results of the phase III RCTs. None of the RCTs carried out so far have made a head-to-head comparison between DOACs, and neither have there been any phase IV clinical studies aiming to widen our understanding of this issue.

Conclusions

Results of the three mega RCTs on DOACs in NVAF focused on patients with previous TIA/stroke show that new drugs maintain non-inferiority against warfarin, but also show that superiority in some end points may be lost for non-inferiority in the secondary prevention, at least for the higher dose of dabigatran (150 mg twice/day), rivaroxaban and apixaban. Instead, a lower dose of dabigatran (110 mg twice/day) seems to acquire more advantages *versus* warfarin in terms of efficacy and safety, especially in net benefit, in this context. The future use of DOACs in clinical practice should serve to confirm the different findings that have emerged in secondary compared to primary prevention.

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