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Effects of apixaban compared with warfarin as gain in event-free time – a novel assessment of the results of the ARISTOTLE trial

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Abstract

Background: A novel approach to determine the effect of a treatment is to calculate the delay of event, which estimates the gain of event-free time. The aim of this study was to estimate gains in event-free time for stroke or systemic embolism, death, bleeding events, and the composite of these events, in patients with atrial fibrillation randomized to either warfarin or apixaban in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE).

Design: The ARISTOTLE study was a randomized double-blind trial comparing apixaban with warfarin.

Methods: Laplace regression was used to estimate the delay in time to the outcomes between the apixaban and the warfarin group in 6, 12, 18 and 22 months of follow-up.

Results: The gain in event-free time for apixaban versus warfarin was 181 (95% confidence interval 76 to 287) days for stroke or systemic embolism and 55 (–4 to 114) days for death after 22 months of follow-up. The corresponding gains in event-free times for major and intracranial bleeding were 206 (130 to 281) and 392 (249 to 535) days, respectively. The overall gain for the composite of all these events was a gain of 116 (60 to 171) days.

Conclusions: In patients with atrial fibrillation, 22 months of treatment with apixaban, as compared with warfarin, provided gains of approximately 6 months in event-free time for stroke or systemic embolism, 7 months for major bleeding and 13 months for intracranial bleeding.

Keywords

Anticoagulation, apixaban, bleeding, gains in event-free time, stroke prevention, atrial fibrillation

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Introduction

Atrial fibrillation is the most common clinically important arrhythmia with a prevalence above 10% in those above the age of 80 years.[1] Atrial fibrillation is associated with an increased risk of stroke, heart failure and premature mortality.[2] International guidelines recommend preventive treatment with oral anticoagulation that substantially reduces the risk of stroke and mortality but simultaneously increases the risk of bleeding, including intracranial bleeding.[3,4]

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial

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(ARISTOTLE) was a randomized controlled multicentre trial that showed that apixaban, a non-vitamin K antagonist oral anticoagulant (NOAC), compared with warfarin, reduced the risk of stroke, major bleeding and death in patients with atrial fibrillation and at least one additional risk factor for stroke.[5] As is conventional, the effect of apixaban in ARISTOTLE was assessed using Cox proportional-hazards modelling, with the treatment effect expressed as a hazard ratio.[5] Although well established, this method has some limitations, and in providing an estimate of relative risk-reduction may not, alone, be sufficient for clinical decision making.[6–10] Alternative methods have been suggested to complement hazard ratios derived from proportional-hazards modelling,[11,12] one of them being the novel 'delay of event' measure, which estimates treatment effects as event-free time gained on the time scale regarding a certain outcome.[12,13]

The aim of this study was to estimate effects of apixaban versus warfarin in the ARISTOTLE trial as gains in event-free time estimated by delay of events, for stroke or systemic embolism, death and bleeding events or the composite of these events as another measure of treatment effect. Since absolute gains by treatment generally depend on the patient's initial risk, gain in event-free time was also assessed in subgroups based on age, prior stroke or systemic embolism and prior warfarin treatment, and by the quality of the medical centre's therapeutic range for warfarin treatment.

Methods

The ARISTOTLE trial design and participants

Details of the ARISTOTLE trial have been published.[5,14] Briefly, ARISTOTLE was a double-blind, double-dummy, randomized clinical trial that compared apixaban with warfarin in 18,201 patients, recruited between 2006 and 2010 at 1034 centres in 39 countries.

The patients included in the ARISTOTLE trial had atrial fibrillation and one or more additional risk factor for stroke including: age $\geq$75 years; history of prior stroke, history of transient ischaemic attack, or systemic embolism; symptomatic heart failure within 3 months or systolic dysfunction with a left ventricular ejection fraction $\leq$40%; diabetes mellitus; and hypertension requiring pharmacological treatment. Exclusion criteria were atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation, stroke within the previous seven days, required aspirin >165 mg/day or both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine level of >2.5 mg/dl or calculated creatinine clearance of <25 ml/min) among others.[14]

Patients who met the inclusion criteria were randomly assigned (1:1) to receive either apixaban (5 mg twice daily) or warfarin with a treatment target of international normalized ratio (INR) 2.0–3.0. The apixaban dose was reduced to 2.5 mg twice daily for patients with two of the three criteria older age, higher creatinine level and lower body weight. Randomization was stratified according to whether patients had received warfarin previously or not.

Outcomes

This study's primary outcome was the event of stroke (ischaemic or haemorrhagic) or systemic embolism, the same as in the original ARISTOTLE trial.[5] A priori defined secondary outcomes were death from any cause and a composite of stroke, systemic embolism, death or major bleeding. Safety outcomes were major and intracranial bleeding according to International Society on Thrombosis and Haemostasis criteria.[15]

Statistical analyses

Delay of events was calculated as differences in time-to-event between the apixaban and warfarin groups at equal proportions of events occurred (percentiles).[12,13] Given a specific percentile, the delay of event expresses the treatment benefit in terms of a delayed event, that is, the event-free time that is attributed to the superior treatment on the time scale. When using this approach, the proportions of event in each group are fixed and the time period is the estimated outcome.[16] Delay of events and corresponding 95% confidence intervals (CIs) in days were estimated by fitting Laplace regression models. Laplace regression is a type of quantile regression suitable for censored data.[17] Quantile regression has advantages such as no distributional assumptions about the regression error term need to be made; its inference is invariant to monotone transformations of the outcome variable; and it permits thorough inference on the entire shape of the conditional distribution and not just the mean.[18]

Delay of events and corresponding percentiles were estimated at four time points: 6 months, 12 months, 18 months and 22 months (median length of follow-up) into the study period. At each time point the event rate in per cent (percentile) in the apixaban group was used as the base for delay of event estimations. Interaction tests were performed for treatment groups and subgroups. Results were also graphically reported over the full follow-up by plotting the delay time in the apixaban group versus the warfarin group. The analyses were performed with the Laplace package of the statistical software R.[17]

Subgroups

Analyses of delay of events due to treatment were also performed in a priori defined subgroups of patients <75 years or ≥75 years, with or without prior stroke or systemic embolism, and those having used warfarin or another vitamin K antagonist >30 consecutive days or not having received warfarin for more than 30 days previously. Each trial centre's quality of warfarin treatment was assessed using a linear mixed model as the median predicted centre's average time in therapeutic range (cTTR) in warfarin-treated patients, as previously described.[19] Based on the results, participants were then dichotomized into those treated at centres with cTTR at or below the median, or above median cTTR. For more detailed descriptions of the cTTR classification, readers are referred to previous publications.[19]

Ethical considerations and trial registration

ARISTOTLE was approved by the institutional review board/ethics committee at each investigative site and all patients gave written informed consent. ARISTOTLE is registered with ClinicalTrials.gov, number NCT00412984.

Results

Among the 18,201 patients that were enrolled in the ARISTOTLE trial, the median age was 70 years and 12,522 patients (68.8%) were younger than 75 years of age. Overall, 3523 patients (19.4%) had a history of stroke or systemic embolism, and 10,376 (57.1%) had a history of prior warfarin treatment. The median predicted cTTR for the patients in the warfarin arm was 66.0%, with an interquartile range from 60.0% to 71.2%. The median length of follow-up was 22 months (interquartile range 18–29).

Over a median of 22 months of follow-up, 212 patients (1.27% per year) in the apixaban group developed stroke or systemic embolism; the corresponding number in the warfarin group was 265 (1.60% per year). Death from any cause occurred in 603 patients (3.52% per year) in the apixaban group, and in 669 patients (3.94% per year) in the warfarin group (Table 1). Major bleeding occurred in 327 patients (2.13% per year) in the apixaban group and 462 patients (3.09% per year) in the warfarin group; intracranial bleeding occurred in 52 patients (0.33% per year) in the apixaban group and in 122 patients (0.80% per year) in the warfarin group. The composite outcome of stroke, systemic embolism, death or major bleeding occurred in 1009 patients (6.13% per year) in the apixaban group and in 1168 patients (7.20% per year) in the warfarin group.

Table 1. Overall outcome and delay of events associated with apixaban, as compared with warfarin, in the total material.

	Apixaban group $n = 9120$	Warfarin group $n = 9081$	Hazard ratio (95% CI)	Delay of events									
				6 months		12 months		18 months		22 months			
				E (%)[b]	DoE (days) (95% CI)	E (%)[b]	DoE (days) (95% CI)	E (%)[b]	DoE (days) (95% CI)	E (%)[b]	DoE (days) (95% CI)
Stroke or systemic embolism, no. (event rate)	212 (1.27)[a]	265 (1.60)[a]	0.79 (0.66–0.95)	0.81	53 (−30 to −137)	1.35	116 (45–187)	1.86	149 (40–258)	2.30	181 (76–287)
Death from any cause, no. (event rate)	603 (3.52)[a]	669 (3.94)[a]	0.89 (0.80–0.998)	1.44	52 (17–87)	3.20	58 (8–107)	4.92	57 (−6 to 121)	6.10	55 (−4 to 114)
Major bleeding, no. (event rate)	327 (2.13)[a]	462 (3.09)[a]	0.69 (0.60–0.80)	1.20	79 (33–124)	2.20	141 (88–193)	3.10	199 (108–290)	3.80	206 (130–281)
Intracranial bleeding, no. (event rate)	52 (0.33)[a]	122 (0.80)[a]	0.42 (0.30–0.58)	0.10	51 (−4 to 105)	0.30	248 (154–342)	0.40	320 (204–436)	0.60	392 (249–535)
Stroke, systemic embolism, death or major bleeding, no. (event rate)	1009 (6.13)[a]	1168 (7.20)[a]	0.85 (0.78–0.92)	3.90	42 (14–70)	6.60	86 (43–128)	8.90	112 (53–171)	10.50	116 (60–171)

[a]Event rate in %/year.
[b]Event in per cent (percentile) reached in the apixaban group at the time point and measuring point for presented delay of event (DoE) in days.
CI: confidence interval

Estimate of gain in event-free time in the total material

The gain in event-free time for stroke or systemic embolism with apixaban, compared with warfarin, was 53 (95% CI –30 to 137) days at 6 months, 116 (45 to 187) days at 12 months, 149 (40 to 258) days at 18 months, and 181 (76 to 287) days at 22 months of follow-up (Table 1 and Figure 1(a)).

The corresponding gains in overall survival time (death from any cause) were 52 (17 to 87) days after 6 months, 58 (8 to 107) days after 12 months, 57 (–6 to 121) days after 18 months, and 55 (–4 to 114) days after 22 months of follow-up (Table 1 and Figure 1(b)).

The gain in event-free time for major bleeding was 206 (130 to 281) days and for intracranial bleeding the gain was 392 (249 to 535) days on apixaban, compared with warfarin, after 22 months (Table 1, Figure 1(c) and 1(d)).

The gain in event-free time for the composite outcome of stroke, systemic embolism, death or major bleeding was 42 (14 to 70) days after 6 months, 86 (43 to 128) days after 12 months, 112 (53 to 171) days after 18 months, and 116 (60 to 171) days after 22 months, with apixaban compared with warfarin (Table 1 and Figure 1(e)).

The continuous increase in gains in event-free time for stroke or systemic embolism, death from any cause, major and intracranial bleeding, and the composite outcome are shown in Figure 1 with the corresponding cumulative event rates for each of these outcomes. To clarify the meaning and interpretation of the delay of event measure, results on the stroke or systemic embolism outcome is highlighted with plotted lines at 12 and 22 months of follow-up in Figure 1(a).

Estimates of gain in event-free time associated with treatment in subgroups

In patients 75 years of age or older, the gain in event-free time for stroke or systemic embolism with apixaban, compared with warfarin, was 237 (95% CI 78 to 397) days after 22 months of follow-up; the corresponding number for patients below 75 years of age was 141 (–8 to 290) days (Table 2).

In patients with prior stroke, the gain in event-free time for stroke or systemic embolism with apixaban was 223 (68 to 379) days after 22 months of follow-up; the corresponding number for patients with no prior stroke was 147 (24–269) days (Table 2).

In patients previously treated with warfarin, the gain in event-free time for stroke or systemic embolism with apixaban was 205 (53 to 358) days, and for patients without previous warfarin treatment the gain was 145 (1 to 288) days, after 22 months of follow-up (Table 2).

The time gain in death from any cause by assignment to apixaban, as compared with warfarin, was similar across the subgroups after 22 months of follow-up (Table 2).

Regarding the safety outcome major bleeding, the gain in event-free time with apixaban ranged from 93 to 307 days after 22 months of follow-up (Table 3). The largest numerical difference was related to cTTR, with larger gains in centres with poorer INR control. Regarding the safety outcome intracranial bleeding, the gain in event-free time with apixaban ranged from 320 to 463 days, after 22 months of follow-up, with similar gains in all subgroups (Table 3). Generally, there were no treatment by subgroup interactions.

Discussion

We estimated the treatment effects of apixaban, compared with warfarin, on gain in event-free time for patients with atrial fibrillation. We showed that 22 months' treatment with apixaban provided gains of approximately 6 months in event-free time concerning stroke or systemic embolism, 7 months for major bleeding and 13 months for intracranial bleeding. These time-based assessments provide an alternative, clinically relevant and more comprehensible way of describing the effects of treatments,[20–24] in this case the benefits of apixaban over warfarin for stroke prevention in patients with atrial fibrillation.

The gain in event-free time with apixaban, compared with warfarin, for stroke or systemic embolism, was obtained early after treatment initiation and maintained thereafter, during the remainder of the follow-up. The gain in event-free time for major and intracranial bleeding was also continuous and almost linear, starting directly after treatment initiation and with no levelling off during follow-up. A delay of mortality occurred early after treatment start, but this effect became attenuated over time. It is worth noting that the aggregated results suggest a temporal diversity in the incremental benefits and safety of apixaban versus warfarin. For example, the primary efficacy endpoint resulted in a delay of about 6 months during 22 months of follow-up, which roughly corresponds to a relative 27% event-free time prolongation. However, 12 months of treatment were needed to let an initial effect emerge. An earlier and sustained delay was seen in terms of bleeding. The magnitude of gains in event-free time for major bleeding and, especially, intracranial bleeding was quite substantial (a relative event prolongation of about 31% and 59% respectively), given the rather short treatment period. Because the gains in time free of stroke or systemic embolism, and major or intracranial bleeding events, increased continuously during follow-up, it is possible

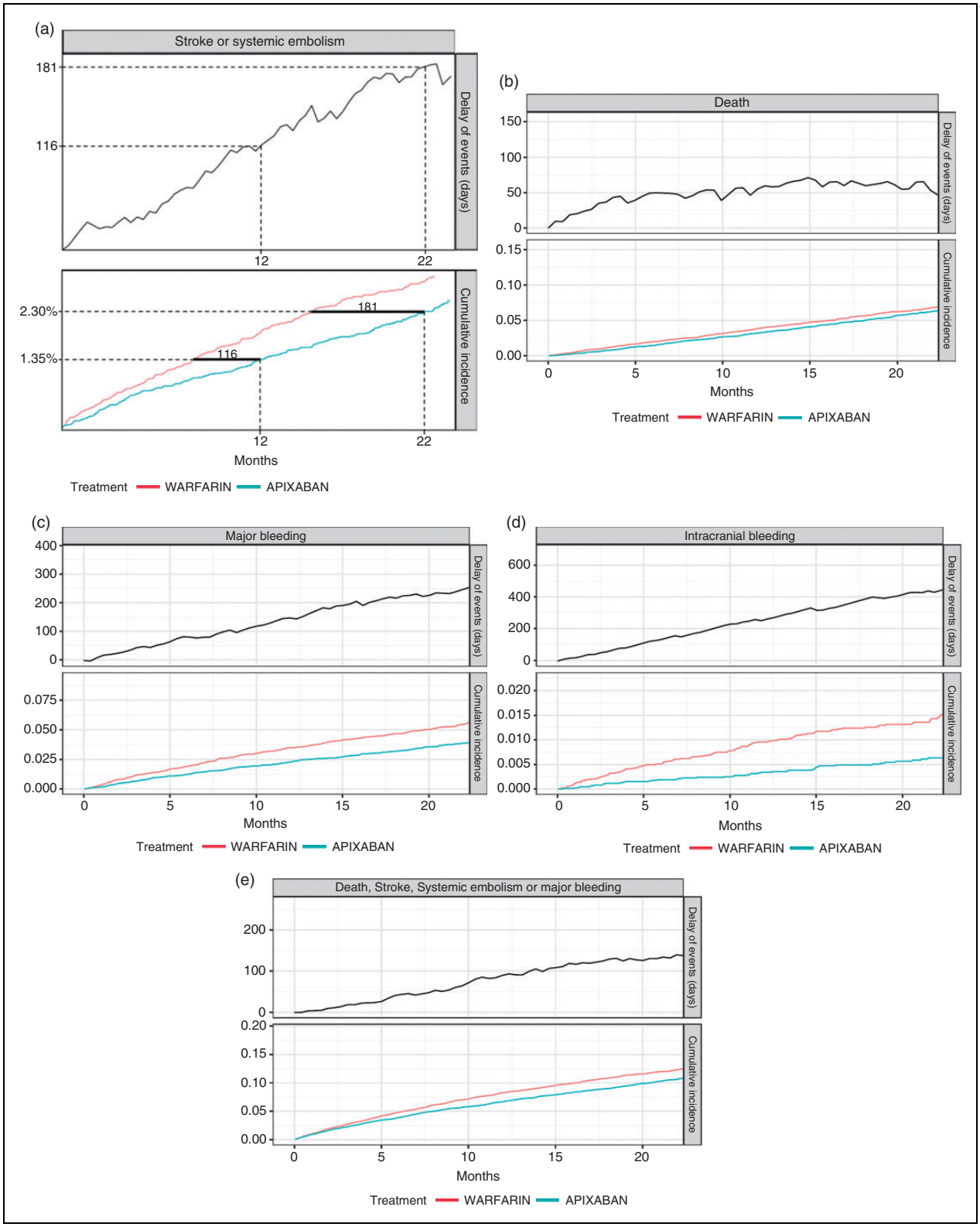

Figure 1. Cumulative incidence in apixaban and warfarin groups, and delay of events associated with apixaban use for (a) stroke or systemic embolism, (b) death from any cause, (c) major bleeding, (d) intracranial bleeding, (e) composite measure of stroke, systemic embolism, death or major bleeding.

Table 2. Delay of events associated with apixaban use, as compared with warfarin, for stroke or systemic embolism and death from any cause in subgroups.

		Stroke or systemic embolism		Death from any cause	
	Hazard ratio (95% CI)	E (%)[a]	DoE (days) (95% CI)	E (%)[a]	DoE (days) (95% CI)
Below 75 years of age	0.85 (0.67–1.10)	2.02	141 (–8 to 290)	4.75	68 (–7 to 142)
75 years of age or above	0.71 (0.53–0.95)	2.93	237 (78–397)	9.09	49 (–42 to 140)
No prior stroke or systemic embolism	0.83 (0.66–1.00)	1.80	147 (24–269)	5.85	51 (–25 to 128)
Prior stroke or systemic embolism	0.75 (0.56–1.00	4.48	223 (68–379)	7.14	69 (–45 to 183)
No prior warfarin	0.86 (0.67–1.10)	2.91	145 (1–288)	7.04	56 (–41 to 152)
Prior warfarin	0.73 (0.53–0.95)	1.84	205 (53–358)	5.39	59 (–29 to 146)
Higher cTTR	0.79 (0.59–1.10)	1.67	154 (0–308)	5.14	21 (–92 to 134)
Lower cTTR	0.79 (0.79–1.00)	2.94	203 (84–323)	7.07	71 (–5 to 147)

[a]Event in per cent (percentile) reached in the apixaban group at 22 months and measuring point for presented delay of event (DoE) in days.
CI: confidence interval; cTTR: center time in therapeutic range.

Table 3. Delay of events associated with apixaban use, as compared with warfarin, for bleeding outcomes and composite measure of stroke, systemic embolism, death or major bleeding in subgroups.

		Major bleeding		Intracranial bleeding		Stroke, systemic embolism, death or major bleeding	
	Hazard ratio (95% CI)	E (%)[a]	DoE (days) (95% CI)	E (%)[a]	DoE (days) (95% CI)	E (%)[a]	DoE (days) (95% CI)
Below 75 years of age	0.88 (0.76–1.00)	2.87	174 (46–302)	0.53	345 (149–542)	8.51	102 (23–181)
75 years of age or above	0.91 (0.77–1.10)	5.95	222 (114–330)	0.84	415 (7–823)	14.96	125 (44–207)
No prior stroke or systemic embolism	0.88 (0.70–1.10)	3.44	214 (117–310)	0.52	355 (181–528)	9.69	121 (54–187)
Prior stroke or systemic embolism	0.90 (0.80–1.00)	5.35	186 (43–328)	1.11	451 (167–735)	14.05	92 (–9 to 194)
No prior warfarin	0.91 (0.78–1.10)	3.84	229 (88–371)	0.88	320 (97–543)	11.50	121 (36–206)
Prior warfarin	0.88 (0.76–1.00)	3.76	186 (85–287)	0.45	438 (250–626)	9.77	110 (31–189)
Higher cTTR	0.79 (0.79–1.10)	4.54	93 (–11 to 197)	0.50	463 (258–668)	10.14	45 (–40 to 130)
Lower cTTR	0.87 (0.75–1.00)	3.04	307 (183–431)	0.77	324 (61–587)	10.90	178 (96–259)

[a]Event in per cent (percentile) reached in the apixaban group at 22 months and measuring point for presented delay of event (DoE) in days.
CI: confidence interval; cTTR: center time in therapeutic range.

that even larger benefits might be observed with longer duration treatment. The results in this study are contrasted by previous studies assessing effects as postponements of events. The effect of the antiplatelet treatment ticagrelor over clopidogrel in persons with acute coronary syndrome, with or without ST-segment elevation, was demonstrated as delays of the evaluated outcomes ranging from 83 to 98 days over 400-day follow-up, also with positive, although non-significant, curve trends for total bleeding and non-coronary artery bypass grafting-related major bleedings.[25] And the long-term follow-up of FRISC-II, a prospective randomized multicentre trial investigating the effect of early revascularization compared with a non-invasive strategy in patients with non-ST-elevation acute coronary syndrome, revealed average postponement, calculated as the area between mean cumulative count-of-events curves, of the occurrence of death or next myocardial infarction by an average of about 18 months.[26]

This present study also investigated outcomes in subgroups. For stroke or systemic embolism, the gains in event-free time were numerically larger for subgroups with a higher risk of stroke, that is, patients older than 75 years, patients with a history of prior stroke or prior warfarin treatment and for patients treated at clinic with poorer cTTR.

It is worth noting that gains in event-free time are expected to differ for different outcomes.

Outcomes such as stroke or systemic embolism and major bleeding might be avoided by a more effective and safer treatment; however, this is not the case for the outcomes that are chronically progressive despite treatment and which cannot be avoided in the long term, such as death from any cause.[27,28] In this study, the increase in delay regarding mortality levelled off over the follow-up, and the gains in overall survival time with apixaban were seen mainly during the first half of the follow-up period. For example, in the one third of patients aged 75 years or older, mortality was higher than in the younger patients and the gain in survival time shorter, likely because of the competing risk of causes of death not modifiable by apixaban.

Another difference between estimating effects using proportional hazards models and the delay of event approach used in this study is that hazard ratios are ratios of failure rates between compared groups, which in essence are a proportional comparison. The delay of event, on the other hand, is a comparison of the timing of events in the groups of interest, given equal event proportions, providing an estimate of the magnitude of the effect. Importantly, the delay is conditional on the event, meaning that the effect applies only to those who will develop the event during a time period without the superior treatment. This is a limitation of the delay of event measure, as it does not present a measure that directly applies to the whole study population, rather only those that would have the event (if treated with the control therapy). On the other hand, any preventive treatment could in a given time period have an effect only in individuals who, if untreated, would develop an event. Thus, the delay of event is a complementary estimate of a preventive effect, depicting the magnitude of effect, using a time-based measure, in those who benefit during the follow-up.

In addition, the individual interpretation of the delay of event measure is conditional on having experienced the event at a specific time point, if not treated with a more effective drug. In this case the individual interpretation of the results would be that the occurrence of an eventual stroke or a systematic embolism may be delayed up to approximately 181 days, and major bleeding delayed up to approximately 206 days, during treatment with apixaban for 22 months, compared with warfarin. For clinical decision making we suggest that delay of event be complemented with other risk information, such as estimates of an individual's absolute risk of developing the event of interest. Guidelines emphasize the importance of adherence for prescribed NOAC regimens.[4,29] Presenting treatment effects as gains in event-free times and delay of events might be more understandable for lay people, patients and clinicians,[20–24] such that these measures may have an educational role in supporting adherence to treatment. The potential use of the delay of event measure in decision making remains to be further investigated.

Conclusion

In patients with atrial fibrillation, 22 months of treatment with apixaban, as compared with warfarin, provided gains of approximately 6 months in event-free time for stroke or systemic embolism, 7 months for major bleeding and 13 months for intracranial bleeding. These alternative and innovative time-based assessments quantify the magnitude of the benefits of apixaban over warfarin used to prevent stroke and bleeding events in patients with atrial fibrillation.

Author contribution

EB, PL, LW, JO and HR contributed to the conception of the work and interpretation of the data. HR performed the statistical analysis. EB and PL wrote the manuscript, and LW and JO critically revised the first draft. JHA, CBG, SHH, EMH, RDL and JJVM critically revised the manuscript. LW, JO, JHA, CBG, SHH, EMH, RDL and JJVM contributed to the design of the clinical study. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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