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ORIGINAL RESEARCH

Termination Based on Event Accrual in Per Protocol Versus Intention to Treat in the ROCKET AF Trial

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BACKGROUND: In event-driven clinical trials, study termination is based on accrual of a target number of primary efficacy events. For noninferiority trials in which superiority is conditionally examined, the ideal cohort in which to track event accrual is unclear. We used data from the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial to determine the effect of primary efficacy-event tracking in the per-protocol cohort during the on-treatment period versus the intention-to-treat (ITT) cohort during the ITT period.

METHODS AND RESULTS: ROCKET AF was terminated after accruing 429 primary efficacy events (stroke or systemic embolism) in the per-protocol cohort during the on-treatment period for noninferiority. We identified the date on which 429 events occurred in the ITT cohort during the ITT period. We performed noninferiority and superiority analyses based on hypothetical study termination on this date. ROCKET AF would have terminated 226 days earlier if events were tracked during the ITT period. Similar to the main trial findings, rivaroxaban would have met noninferiority versus warfarin for the primary efficacy end point (hazard ratio [HR], 0.77; 95% CI, 0.62–0.96; $P<0.001$). In contrast to the main trial findings, rivaroxaban would have met superiority for the primary efficacy end point (HR, 0.82; 95% CI, 0.68–0.99; $P=0.038$). In both termination scenarios, rivaroxaban was associated with a lower risk of intracranial hemorrhage and similar risk of other safety end points.

CONCLUSIONS: Clinical trial termination based on event accrual in the ITT cohort versus the per-protocol cohort may have important implications on trial results depending on rates of study drug discontinuation and event rates off treatment.

Key Words: anticoagulation ■ atrial fibrillation ■ clinical trial ■ embolic stroke ■ research methodology ■ warfarin

In randomized clinical trial design, sample size calculation involves determination of a target number of end-point events to provide ample statistical power to detect noninferiority or superiority.[1,2] Once the target number of end-point events is reached, the trial is typically terminated. Depending on the goal of the study, the populations for study analysis and study termination are considered different. Specifically, the per-protocol (PP) cohort (all randomized patients who had no protocol violations and received ≥1 dose of the study drug) with end-point event accrual tracked during the on-treatment period may be ideal for a noninferiority trial. This is to reduce bias from patients coming off the study drug and having events that would bias toward the null hypothesis (thus a determination of noninferiority). To demonstrate superiority, the intention-to treat (ITT) cohort (all randomized patients regardless of drug exposure or protocol violations) with

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CLINICAL PERSPECTIVE

What Is New?

- Tracking outcome event accrual in an intention-to-treat cohort during the intention-to-treat period, as opposed to the per-protocol cohort during the on-treatment period, may result in important differences in clinical trial duration and statistically significant differences in clinical trial findings.

What Are the Clinical Implications?

- The choice of treatment period used to track events in event-driven trials is a crucial step in clinical trial design and may have important implications in trial results and should be considered by clinical trialists early during clinical trial design.

Nonstandard Abbreviations and Acronyms

NOAC	non–vitamin K antagonist oral anticoagulant
PP	per protocol
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation

event accrual tracked in the ITT period (from randomization to end of the study regardless of drug exposure) may be ideal for study analysis. Although conservative, ITT maintains comparability of prognostic factors in the 2 groups because of randomization, preserves sample size, and minimizes systematic bias associated with nonadherence, protocol deviations, or withdrawal after randomization. In event-driven trials where noninferiority is the primary goal with conditional analysis of superiority after noninferiority is met, it is unclear whether to terminate the trial based on accrual of events in PP patients during the on-treatment period versus ITT patients during the ITT period.

The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial was an international, double-blind, double-dummy, randomized, event-driven trial that evaluated rivaroxaban versus warfarin for thromboembolism prevention in patients with atrial fibrillation.[3] The trial was terminated based on accrual of primary efficacy events in the PP cohort during the on-treatment period. We aimed to understand whether trial termination based on primary efficacy-event accrual in the ITT cohort during the ITT period would have implications for the overall study results.

METHODS

In keeping with the terms of the study contract, data from this publication will not be made publicly available.

The design and primary results of the ROCKET AF trial have previously been reported.[3,4] The ROCKET AF study protocol was reviewed and approved by the institutional review board or ethics committee at each participating site and by the coordinating center's institutional review board. In brief, ROCKET AF randomized 14 264 patients with atrial fibrillation who were at increased risk of stroke to either rivaroxaban or warfarin in 1:1 fashion. The primary efficacy end point was stroke or systemic embolism, and the primary safety end point was major or nonmajor clinically relevant bleeding. Analysis cohorts included a PP cohort, an ITT cohort, and an on-treatment (safety) cohort (defined in Table 1). For patients excluded from the PP cohort because of protocol deviation (n=103 in the rivaroxaban arm and n=78 in the warfarin arm), a breakdown of the types and numbers of protocol deviations by treatment arm can be found in Table S1. The ITT period was defined as the time from randomization until study termination, which occurred after accrual of the prespecified number of primary efficacy events. The on-treatment period was defined as the time from the first to the last dose of the study drug, plus 2 days.

During the design of ROCKET AF as an event-driven trial, it was determined that 363 primary efficacy events were needed to achieve 95% power to calculate a risk ratio noninferiority margin of 1.46 with a 1-sided α of 0.025.[3] Investigators increased the target number of events to 405 to ensure a robust statistical result. An enrollment target of 14 000 patients was deemed necessary to achieve 405 primary efficacy events. Importantly, trial termination was based on accrual of primary efficacy events in the PP cohort during the on-treatment period. At the time of trial termination, investigators were recommended to transition to open-label anticoagulation at the discretion of the site investigator or treating clinician with a vitamin K antagonist consistent with their local guidelines and best practice recommendations. Investigators were encouraged to rapidly achieve a therapeutic international normalized ratio in subjects transitioned to open-label vitamin K antagonist therapy; however, to protect the integrity of study, blinding investigators were discouraged from checking local international normalized ratio values for 3 days after study drug discontinuation. As described in the study protocol, noninferiority testing for the primary efficacy end point was performed in the PP

Table 1. ROCKET AF Analysis Cohort Definitions, Size, and Exclusions

Cohort	Definition	Cohort size	
		Rivaroxaban, n=7131	Warfarin, n=7133
Intention to treat	1. Underwent randomization 2. Followed for events from randomization until the end of the study (regardless of treatment exposure)	n=7081/7131 (99.3%) • Excluded n=50 for GCP violation*	n=7090/7133 (99.4%) • Excluded n=43 for GCP violation*
Safety (on treatment)	1. Received ≥1 dose of the study drug 2. Followed for events while on the study drug +2 days (regardless of protocol adherence)	n=7061/7131 (99.0%) • Excluded above and n=20 who never received the study drug	n=7082/7133 (99.3%) • Excluded above and n=8 who never received the study drug
Per protocol	1. Received ≥1 dose of the study drug, 2. Did not have a major protocol violation 3. Followed for events while on the study drug +2 days	n=6958/7131 (97.6%) • Excluded above and n=103 for protocol violations	n=7004/7133 (98.2%) • Excluded above and n=78 with protocol violations

GCP indicates Good Clinical Practice.
*Efficacy end points only.

cohort.[3] Once noninferiority was achieved, superiority testing for the primary efficacy end point was then performed in the ITT cohort and for the primary safety end point in the on-treatment (safety) cohort.

Statistical Analysis

To determine whether the period used to track efficacy-event accrual affected trial results, we identified the date on which ROCKET AF would have terminated if primary efficacy end point accruals were tracked in the ITT cohort during the ITT period. The percentage of efficacy events occurring in patients off the study drug both before and after this hypothetical trial termination date was calculated. Using this hypothetical termination date, we then calculated event rates for the primary efficacy end point, primary safety end point, and multiple secondary safety end points (major bleeding, intracranial hemorrhage, and death). As in the original study, noninferiority testing for the primary efficacy end point was performed in the PP cohort and superiority testing in the ITT cohort, and safety end points were analyzed in the on-treatment (safety) cohort. Cox proportional hazards models were used to compare randomized treatment arms, conducting a 1-sided test for noninferiority and a 2-sided test for superiority. These results were then qualitatively compared with the published trial results, which were based on trial termination by primary efficacy-event accrual in the PP cohort during the on-treatment period. Kaplan-Meier curves were generated illustrating event rates for randomized treatment arms and showing indicators for trial termination based on event accrual in the ITT cohort during the ITT period versus event accrual in the PP cohort during the on-treatment period. Hazard ratios (HRs) with shaded 95% CIs were plotted continuously over a range of possible trial termination dates and overlaid with a line indicating the threshold for rivaroxaban meeting superiority versus warfarin.

RESULTS

Demographics and baseline characteristics of the 14 264 patients randomized in ROCKET AF were reported in the main trial article.[4] A total of 93 patients (50 randomized to rivaroxaban, 43 randomized to warfarin) were excluded from efficacy analyses because of violations in Good Clinical Practice guidelines at one site as previously described. The number of patients excluded from the PP, ITT, and safety cohorts, as well as reasons for exclusion, are shown in Table 1.

The 405th primary efficacy event occurred in the PP cohort during the on-treatment period on April 21, 2010 (Figure 1). Because of the expected time required for data collection and cleaning, safety event reporting, event adjudication, and closure of all 1178 participating sites, an additional 24 on-treatment events occurred by the time all sites were closed, bringing the total number of observed primary efficacy events to 429. The 429th (final) primary efficacy event occurred in the PP cohort during the on-treatment period on June 3, 2010.

The 429th primary efficacy event in the ITT cohort during the ITT period occurred on October 20, 2009, which was 226 days earlier than the occurrence of the final event in the PP cohort in the on-treatment period. On the date that the last (429th) primary efficacy event occurred in the PP cohort during the on-treatment period (June 3, 2010), 575 primary efficacy events had occurred in the ITT cohort during the ITT period. Of the 575 primary efficacy events occurring in the ITT population through June 3, 2010, 147 (25.6%) occurred in patients off the study drug.

Results Based on Trial Termination When 429 Events Accrued in the PP Cohort During the On-Treatment Period

As reported in the main trial analysis that tracked event accrual in the PP cohort during the on-treatment period, 188 primary efficacy events were observed in

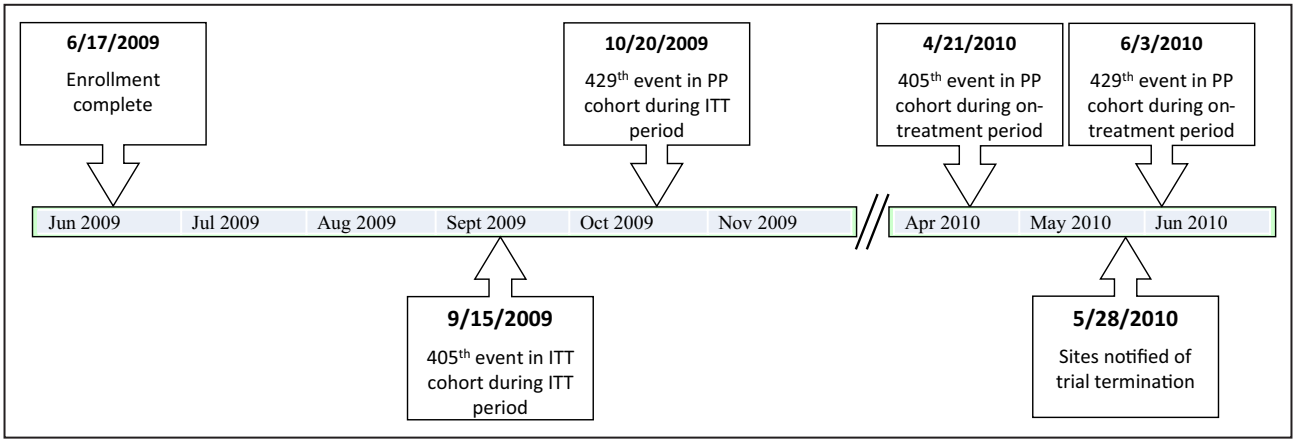

Figure 1. Timeline of events with respect to study termination and accrual of primary efficacy events in the intention-to-treat (ITT) and per-protocol (PP) cohorts.

the rivaroxaban arm, and 241 primary efficacy events were observed in the warfarin arm (1.7 and 2.2 events per 100 patient-years, respectively; HR, 0.79; 95% CI, 0.66–0.96; *P*<0.001 for noninferiority) (Table 2). In the ITT cohort, 269 primary efficacy events were observed in the rivaroxaban arm and 306 primary efficacy events in the warfarin arm (2.1 and 2.4 events per 100 patient-years, respectively; HR, 0.88; 95% CI, 0.75–1.03; *P*<0.001 for noninferiority, *P*=0.12 for superiority).

In the safety cohort, 1475 primary safety events were observed in the rivaroxaban arm and 1449 occurred in the warfarin arm (14.9 and 14.5 events per 100 patient-years, respectively; HR, 1.03; 95% CI, 0.96–1.11; *P*=0.44 for superiority). Event rates and HRs for major bleeding, intracranial hemorrhage, and death can be found in Table 2. There was no observed difference between rivaroxaban and warfarin for major bleeding or death (*P*=0.58 and *P*=0.15 for superiority,

Table 2. Trial Results Based on Trial Termination at 429 Events in the Per-Protocol (Top) Versus Intention-to-Treat (Bottom) Patient Cohorts

Trial results based on trial termination at 429 events in per-protocol cohort during the on-treatment period (June 3, 2010)					
Event	Rivaroxaban events per 100 patient-years (total)	Warfarin events per 100 patient-years (total)	Rivaroxaban vs warfarin HR (95% CI)	Superiority *P* value	Noninferiority *P* value
Stroke/SE, PP	1.7 (188)	2.2 (241)	0.79 (0.66, 0.96)		<0.001
Stroke/SE, ITT	2.1 (269)	2.4 (306)	0.88 (0.75, 1.03)	0.12	<0.001
Major/NMCR bleeding	14.9 (1475)	14.5 (1449)	1.03 (0.96, 1.11)	0.44	
Major bleeding	3.6 (395)	3.4 (386)	1.04 (0.90, 1.20)	0.58	
Intracranial hemorrhage	0.5 (55)	0.7 (84)	0.67 (0.47, 0.93)	0.02	
Death, ITT	4.5 (582)	4.9 (632)	0.92 (0.82, 1.03)	0.15	
Trial results based on trial termination at 429 events in the per-protocol cohort during the ITT period (October 20, 2009)					
Event	Rivaroxaban events per 100 patient-years (total)	Warfarin events per 100 patient-years (total)	Rivaroxaban vs warfarin, HR (95% CI)	Superiority *P* value	Noninferiority *P* value
Stroke/SE, PP	1.8 (137)	2.3 (181)	0.77 (0.62, 0.96)		<0.001
Stroke/SE, ITT	2.1 (193)	2.6 (236)	0.82 (0.68, 0.99)	0.038	<0.001
Major/NMCR bleeding	16.62 (1203)	16.67 (1220)	1.00 (0.92, 1.08)	0.97	
Major bleeding	3.8 (299)	3.8 (306)	0.99 (0.85, 1.17)	0.95	
Intracranial hemorrhage	0.5 (36)	0.8 (64)	0.57 (0.38, 0.86)	0.007	
Death, ITT	4.2 (388)	4.6 (417)	0.93 (0.81, 1.07)	0.31	

PP and ITT indicate the statistical analysis population, which was chosen based on whether the goal was to show noninferiority (PP) or superiority (ITT). In some cases, the analysis population appropriately differed from the period during which efficacy events were tracked.

HR indicates hazard ratio; ITT, intention to treat; NMCR, nonmajor clinically relevant; PP, per-protocol; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and SE, systemic embolism.

respectively); however, rivaroxaban was found superior to warfarin with respect to reduction in intracranial hemorrhage (HR, 0.67; 95% CI, 0.47–0.93; *P*=0.02 for superiority).

Results Based on Trial Termination When 429 Events Accrued in the ITT Cohort During the ITT Period

In a hypothetical scenario, had ROCKET AF been terminated on the date the 429th primary efficacy event occurred in the ITT cohort during the ITT period, the noninferiority analysis would have included 137 primary efficacy events in the rivaroxaban arm and 181 events in the warfarin arm (1.8 and 2.3 events per 100 patient-years, respectively; HR, 0.77; 95% CI, 0.62–0.96; *P*<0.001 for noninferiority) (Table 2). In the ITT cohort, 193 primary efficacy events would have accrued in the rivaroxaban arm and 236 in the warfarin arm (2.1 and 2.6 events per 100 patient-years, respectively; HR, 0.82; 95% CI, 0.68–0.99; *P*<0.001 for noninferiority, *P*=0.038 for superiority).

In the safety cohort, 1203 primary safety events would have been observed in the rivaroxaban arm and 1220 in the warfarin arm (16.62 and 16.67 events per 100 patient-years, respectively; HR, 1.00; 95% CI, 0.92–1.08; *P*=0.97 for superiority). Comparably estimated event rates for major bleeding, intracranial hemorrhage, and death can be found in Table 2. Analysis would have found no difference between rivaroxaban and warfarin for major bleeding or death (*P*=0.95 and *P*=0.31, respectively). Similar to the published trial results, rivaroxaban would have been found superior to warfarin with respect to reduction in intracranial hemorrhage (HR, 0.57; 95% CI, 0.38–0.86; *P*=0.007 for superiority).

Comparison Between Trial Termination Strategies and Overall Trial Results

For the primary efficacy end point, trial termination based on 429 events in the PP cohort during the on-treatment period (published results) resulted in rivaroxaban meeting the threshold for noninferiority versus warfarin (*P*<0.001), but not meeting the threshold for superiority (*P*=0.12) (Figure 2). Hypothetical trial termination based on accrual of 429 primary efficacy events in the ITT cohort during the ITT period would have resulted in rivaroxaban meeting the threshold for superiority versus warfarin (*P*=0.038). Trial termination at any time over a 5-month period (between October 12, 2009 and March 8, 2010) would have resulted in rivaroxaban meeting the threshold for superiority (Figure 3). Trial termination based on event accrual in PP patients

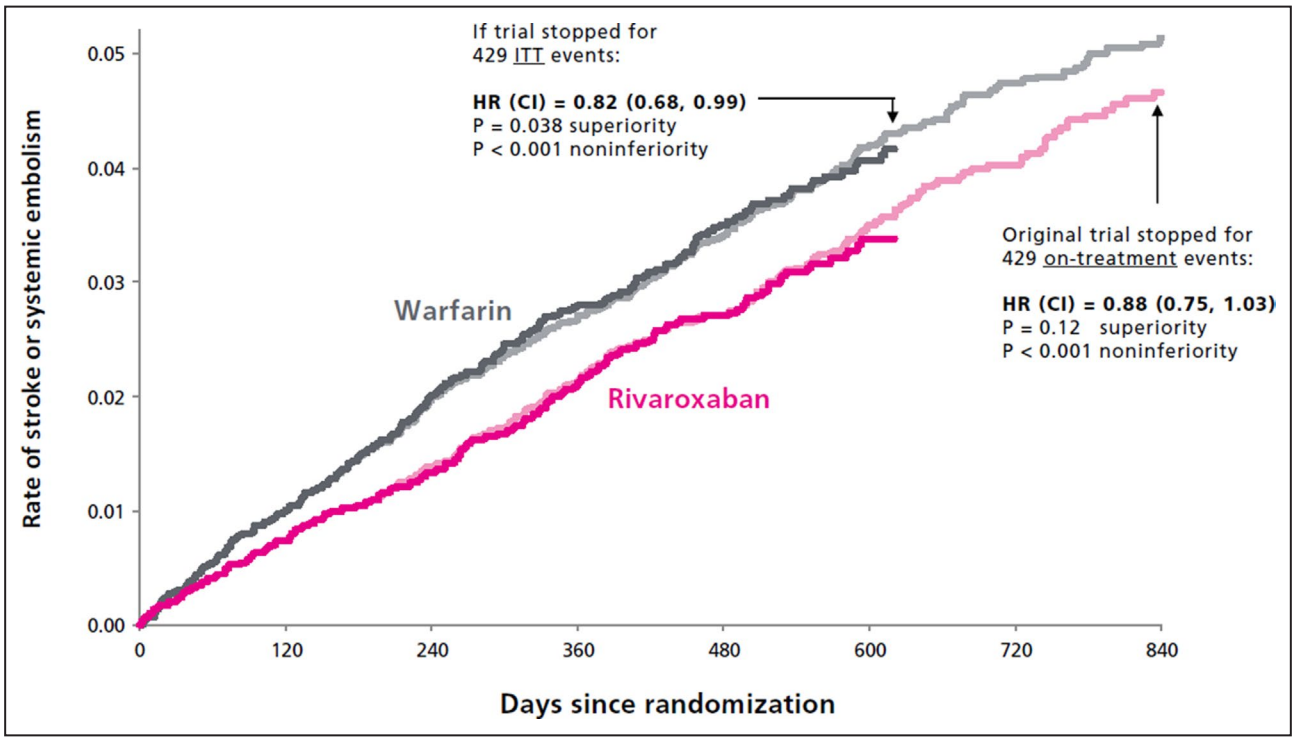

Figure 2. Kaplan-Meier curve for the primary efficacy end point (stroke or systemic embolism) with time points marked for trial termination based on events in the intention-to-treat (ITT) cohort and time period (ITT events) and the per-protocol cohort and on-treatment period (on-treatment events).
Events in the per-protocol cohort are counted during the on-treatment period and events in the ITT cohort are counted during the ITT period. Hazard ratio (HR) and *P* value were determined in ITT patients during the ITT period.

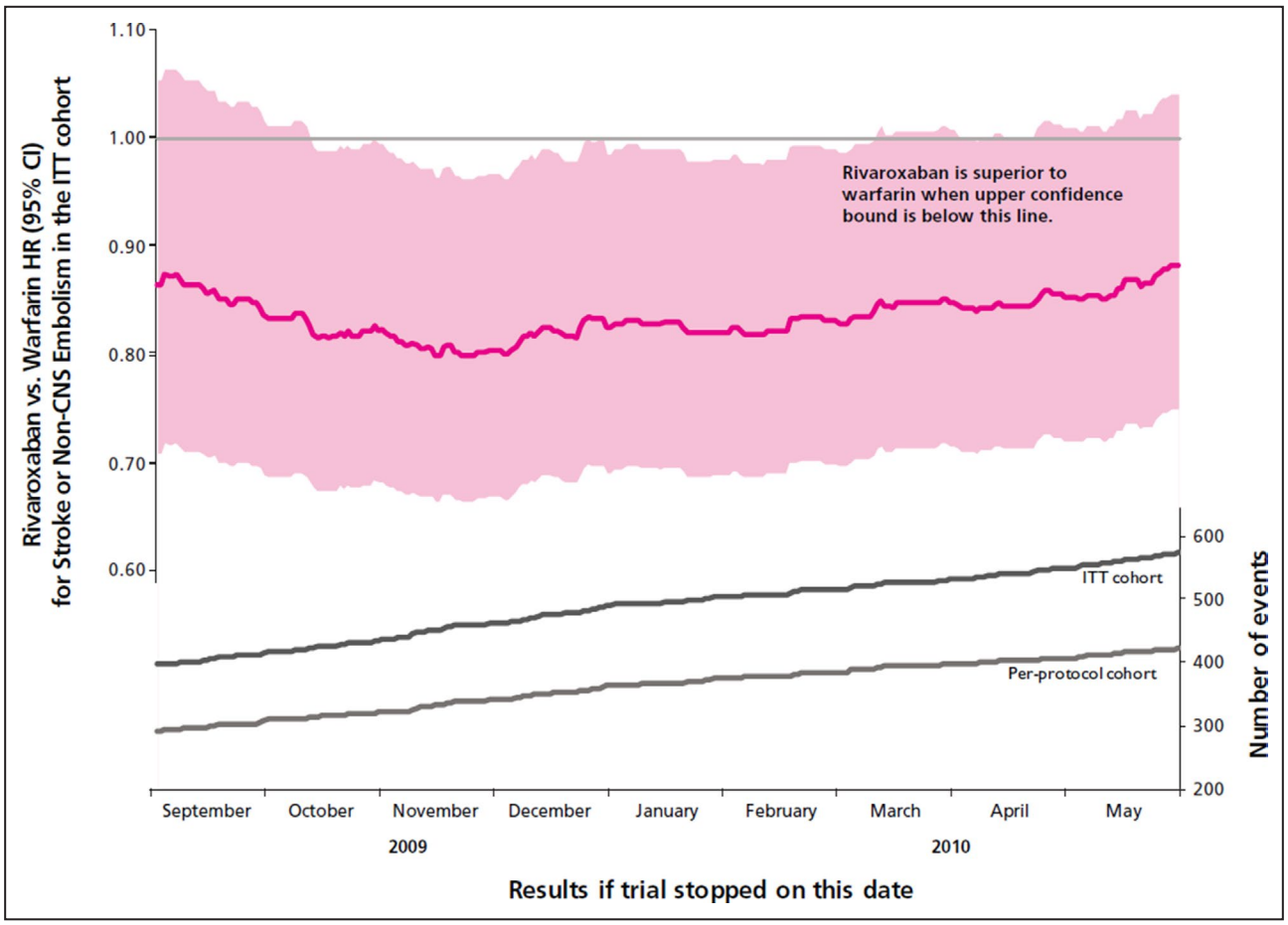

Figure 3. Hazard ratio (HR) (purple line) and 95% CI (shaded area) for the primary efficacy end point over time according to trial end date (bottom).
Events in the per-protocol cohort are counted during the on-treatment period, and events in the intention-to-treat (ITT) cohort are counted during the ITT period. CNS indicates central nervous system.

during the on-treatment period or ITT patients during the ITT period would both have produced the same conclusions on comparison of safety end points, including the primary safety end point (Figure 4), major bleeding, intracranial hemorrhage, or death.

DISCUSSION

In this post hoc exploratory analysis using data from ROCKET AF, trial termination would have occurred 226 days earlier had primary efficacy-events accrual been based on events occurring in the ITT cohort during the ITT period, as opposed to the PP cohort during the on-treatment period. Approximately one-quarter of primary efficacy events throughout the duration of the trial occurred in patients off the study drug, with no difference in off-treatment event rates before or after hypothetical trial termination based on efficacy events accrued during the ITT period. If ROCKET AF had been terminated based on event accrual in ITT patients during the ITT period, rivaroxaban would have been found superior to warfarin with respect to the primary efficacy end point of stroke or systemic embolism. For the primary safety end point and secondary safety end points major bleeding, intracranial hemorrhage, and death, trial termination based on event accrual in ITT patients during the ITT period would not have changed the published results.

Our findings imply that the use of the on-treatment period in the PP cohort in ROCKET AF to track primary efficacy-event accrual was a key factor that influenced the ultimate interpretation of the trial's pre-specified primary superiority analysis. Although it is reasonable and common methodology to track primary efficacy events in the PP cohort given that ROCKET AF was designed primarily to test noninferiority of rivaroxaban versus warfarin, the ideal time period for event tracking has not been studied, and no clear guidance on this issue has been offered by regulatory agencies[5] or accepted approach from the scientific community. In 3 other noninferiority trials of non–vitamin K antagonist

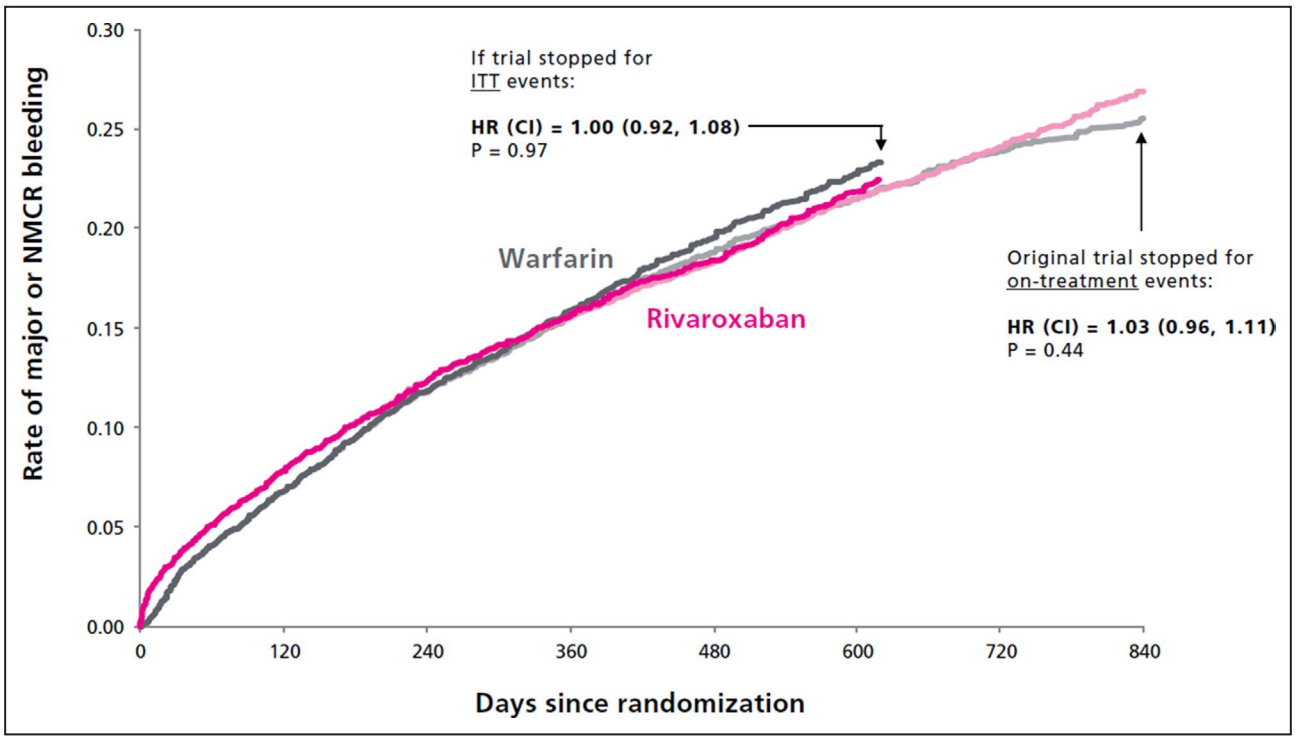

Figure 4. Kaplan-Meier curve for the primary safety end point (major or nonmajor clinically relevant [NMCR] bleeding) with time points marked for trial termination based on events in the intention-to-treat (ITT) cohort and time period (ITT events) and the per-protocol cohort and on-treatment period (on-treatment events).
Events in the per-protocol cohort are counted during the on-treatment period and events in the intention-to-treat (ITT) cohort are counted during the ITT period. Hazard ratio (HR) and *P* value are determined in safety patients during the on-treatment period.

oral anticoagulants (NOACs) versus warfarin in patients with atrial fibrillation, either an ITT or a modified ITT period (defined as ITT while on treatment) was used to track accrual of primary efficacy events.[6–8] In the 2 blinded NOAC studies that terminated based on event accrual in the more expansive ITT period, the investigational study drug reached statistical significance in the respective superiority analyses.[9,10] However, these trials were conducted and published after the ROCKET AF trial. During the design phase of ROCKET AF there was therefore no historical precedent in place or prior body of work in oral anticoagulation for atrial fibrillation to reference. It is unknown whether efficacy-event tracking in the PP cohorts would have affected the results with respect to efficacy or safety end points.

In addition to a potential change in the interpretation and nominal *P* value of the superiority analysis from ROCKET AF, the effect of efficacy-event tracking during the ITT period may have also led to a substantial cost savings. Our data demonstrate that the ROCKET AF trial would have been terminated 226 days sooner if efficacy events were tracked during the ITT period. The cost of investigational drug development is high, with estimates showing average out-of-pocket cost per approved new compound exceeding $1 billion.[11] A substantial portion of this cost is incurred in the conduct of large, phase III, randomized controlled clinical trials. The complexities of clinical trial conduct make it difficult to estimate the incremental cost associated with extending the duration of follow-up in event-driven clinical trials; however, given the high costs associated with research and development of new pharmaceuticals, this expense is surely not trivial. Identifying avenues to shorten clinical trials and reduce the cost of drug development while maintaining confidence in the safety and efficacy profile observed would have far-reaching implications in healthcare economics. This opportunity is particularly relevant to large trials with high-risk study populations and thus expected high event rates, as was the case in ROCKET AF.

High rates of study drug discontinuation in ROCKET AF played an important role in the findings from our analysis. A total of 4895 out of 14 264 (34.3%) patients in ROCKET AF prematurely and permanently discontinued the study drug, with reasons for discontinuation including adverse events (13.4%), withdrawal of consent (9.4%), investigator suspicion of a primary end point (4.4%), and investigator discretion (2.5%).[12] Patients from ROCKET AF had a higher rate of premature permanent study drug discontinuation of the 4 trials of NOACs versus warfarin in atrial fibrillation (premature permanent discontinuation rates ranging

from 18%–34%),[13] potentially because ROCKET AF enrolled patients at high risk for thromboembolic and bleeding events with the highest median $CHADS_2$ scores among the trials. Approximately one-quarter of primary efficacy events accrued in the ROCKET AF trial occurred in patients off the study drug (ie, patients either on open-label warfarin or on no anticoagulation). Notably, <50% of patients with premature permanent discontinuation of the study drug were started on an open-label oral anticoagulant, and only 5% were treated with aspirin.[12] This is an important factor that contributed to our findings. A longer duration of follow-up will inevitably result in accrual of more events occurring in patients off the study-drug, thus biasing results of a superiority analysis using an ITT cohort toward the null. Clinical trialists are thus tasked with identifying an equilibrium in trial duration that provides sufficient event rates and follow-up duration to test for investigational agent superiority without allowing for unduly long follow-up that may distort important treatment effects.

The issues described above are particularly well highlighted in trials of NOACs versus warfarin. Given the short elimination half-lives of all 4 NOACs approved by the US Food and Drug Administration for prevention of thromboembolism in patients with atrial fibrillation (ranging from 5–17 hours in patients with normal renal function),[14] anticoagulation intensity may become subtherapeutic after discontinuation. When transitioning off the study drug and onto open-label warfarin therapy in ROCKET AF, patients who were randomized to rivaroxaban had a longer period of time during which anticoagulation was subtherapeutic than those in the active control arm who continued anticoagulation with warfarin, putting patients in the rivaroxaban group at higher risk of stroke during the transitional period. Patients in ROCKET AF randomized to rivaroxaban had a 3-fold higher risk of stroke when transitioning to open-label warfarin compared with patients transitioning from blinded to open-label warfarin.[12] Only 48.8% of patients randomized to rivaroxaban had a therapeutic international normalized ratio (2.0–3.0) 30 days after transition to open-label warfarin, compared with 81.3% of those initially randomized to warfarin. For these reasons, tracking efficacy-event accrual during the on-treatment period, which results in a greater number of days of follow-up compared with event tracking during the ITT period, may not be ideal in trials of oral anticoagulants.

For study designs in which a single trial is testing both noninferiority and superiority, as was the case in ROCKET AF, trial design characteristics such as sample size determination, hierarchy of hypothesis testing, choosing analysis cohorts, and choosing the optimal treatment period to track event accrual are crucial to minimizing bias. The timing of trial termination based on prespecified event thresholds is even more important in trials enrolling patients with chronic disease conditions with accumulating time off the assigned treatment. These factors may affect the interpretation of trial findings. Future trials should consider the potential impact of time off therapy in choosing treatment periods for event accrual that will eventually determine trial termination in event-driven noninferiority trials. Alternatively, trials with a primary aim of testing noninferiority and a conditional aim of testing superiority may consider event tracking in the PP cohort for the noninferiority analysis and in the ITT cohort for the superiority analysis.

Limitations

Our results reflect that of an exploratory analysis using previously published data, and thus should be considered hypothesis generating. Furthermore, results from our analysis should solely be viewed as a case example of the implications that different event-tracking periods may have on clinical trial results. These findings should not usurp the original ROCKET AF findings or any of the secondary analyses originating from ROCKET AF data. As demonstrated in our methods, termination of an international, randomized placebo-controlled clinical trial is challenging to achieve with precision on a specific number of events or on a specific date.

CONCLUSIONS

In the ROCKET AF trial, tracking primary efficacy-event accrual in the ITT cohort during the ITT period, as opposed to the PP cohort during the on-treatment period, would have resulted in earlier trial termination and a statistically significant finding of superiority for rivaroxaban over warfarin with respect to the primary efficacy end point of stroke or systemic embolism, without any change in comparative findings for safety outcomes. The choice of treatment period used to track events in event-driven trials is a crucial step in clinical trial design and may have important implications in trial results.

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Protocol violations by treatment arm.

	Rivaroxaban (113 deviations in n=103 patients)	Warfarin (83 deviations in n=78 patients)
Received the wrong treatment or incorrect dose	74	56
Entered the study but entry criteria not met	16	14
Developed withdrawal criteria but not withdrawn	17	8
Received excluded concomitant treatment	5	4
Other	1	1

Reasons sum to more than n's because 10 patients in the rivaroxaban arm and 5 patients in the warfarin arm had 2 deviations each