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Net clinical benefit of rivaroxaban compared with warfarin in atrial fibrillation: Results from ROCKET AF

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ABSTRACT

Aims: The aim of this study was to determine the net clinical benefit (NCB) of rivaroxaban compared with warfarin in patients with atrial fibrillation.
Methods: This was a retrospective analysis of 14,236 patients included in ROCKET AF who received at least one dose of study drug. We analyzed NCB using four different methods: (1) composite of death, stroke, systemic embolism, myocardial infarction, and major bleeding; (2) method 1 with fatal or critical organ bleeding substituted for major bleeding; (3) difference between the rate of ischemic stroke or systemic embolism minus 1.5 times the difference between the rate of intracranial hemorrhage; and (4) weighted sum of differences between rates of death, ischemic stroke or systemic embolism, intracranial hemorrhage, and major bleeding.
Results: Rivaroxaban was associated with a lower risk of the composite outcome of death, myocardial infarction, stroke, or systemic embolism (rate difference per 10,000 patient-years [RD] = −86.8 [95% CI −143.6 to −30.0]) and fatal or critical organ bleeding (−41.3 [−68 to −14.7]). However, rivaroxaban was associated with a higher risk of major bleeding other than fatal or critical organ bleeding (55.9 [14.7 to 97.2]). Method 1 showed no difference between treatments (−35.5 [−108.4 to 37.3]). Methods 2–4 favored treatment with rivaroxaban (2: −96.8 [−157.0 to −36.8]; 3: −65.2 [−112.3 to −17.8]; 4: −54.8 [−96.0 to −10.2]).
Conclusions: Rivaroxaban was associated with favorable NCB compared with warfarin. The NCB was attributable to lower rates of ischemic events and fatal or critical organ bleeding.

1. Introduction

Current professional society guidelines recommend treatment with an oral anticoagulant in patients with atrial fibrillation (AF) who are at increased risk of thromboembolism [1–3]. However, anticoagulation is inherently associated with an increased risk of bleeding, and the benefits of anticoagulation must be weighed against the risks. Thus, for patients with AF, the reduced risk of ischemic stroke and systemic thromboembolism (SSE) must be weighed against the increased risk of bleeding when considering antithrombotic therapy. The concept of

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net clinical benefit (NCB) has been proposed as a method to estimate the overall relative benefits of different antithrombotic agents, taking into account both thromboembolic and bleeding risk [4,5]. NCB is typically calculated as a composite of thromboembolic and bleeding events, often with numerical weights applied to different outcomes to account for their clinical severity; [4] a therapy that lowers the risk of thromboembolism more than it increases the risk of bleeding would therefore have a favorable NCB.

Rivaroxaban is an oral direct factor Xa inhibitor that is noninferior to warfarin for the prevention of stroke in patients with AF [6]. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, rivaroxaban had a similar risk of overall major bleeding. However, within the subcategories of major bleeding, a differential effect was seen. Rivaroxaban was associated with a lower rate of fatal bleeding and intracranial hemorrhage (ICH) but a higher rate of less impactful major bleeding requiring transfusion. Data regarding the NCB of rivaroxaban compared with warfarin, taking into account both ischemic and bleeding risks, are limited to a single publication that employed only one descriptive method using overall event rates [7]. The goal of this post-hoc analysis was to estimate the NCB of rivaroxaban compared with warfarin using several different methods in a patient-level analysis. In addition, we sought to identify patient characteristics that were associated with an NCB with one agent compared with the other.

2. Methods

The design and main results of the ROCKET AF study have been published previously [6,8]. Briefly, ROCKET AF was a multicenter, international, double-blind, double-dummy, randomized trial comparing fixed-dose rivaroxaban (20 mg once daily, or 15 mg once daily in patients with a creatinine clearance of 30–49 mL/min) with adjusted-dose warfarin (target international normalized ratio 2.0–3.0) for the prevention of stroke (ischemic or hemorrhagic) or systemic embolism. To maintain blinding, point-of-care testing was used to determine real international normalized ratios (in patients taking warfarin) or generate sham values (in patients taking rivaroxaban and receiving placebo warfarin). The doses of warfarin and matching placebo tablets were adjusted based on these values.

All appropriate national regulatory authorities and the ethics/institutional review boards at all participating centers approved the study. All patients provided written informed consent.

2.1. Patient population

Complete inclusion and exclusion criteria for ROCKET AF have been published [8]. Briefly, patients with electrocardiographically documented nonvalvular AF at moderate to high risk of stroke were recruited at 1178 participating sites in 45 countries. Elevated stroke risk was indicated by a history of stroke, transient ischemic attack, or systemic embolism, or at least two of the following risk factors: heart failure or left ventricular ejection fraction ≤35%, hypertension, age ≥ 75 years, or diabetes mellitus (i.e., $CHADS_2$ score ≥ 2). Those with a high risk for bleeding (including previous intracranial bleeding, surgical trauma within 30 days, and gastrointestinal bleeding within 6 months) were excluded.

The present study included all patients who received at least one dose of study drug (on-treatment population N = 14,236). In a sensitivity analysis, we repeated the study with all patients who were randomized (intention-to-treat population, N = 14,264).

2.2. Outcomes

The efficacy endpoints included in this analysis were all-cause death, stroke (including both ischemic and hemorrhagic events), myocardial infarction, systemic embolism, and the composite of these four endpoints. The safety endpoints included were fatal or critical organ bleeding, bleeding requiring transfusion of ≥2 units of whole blood or packed red blood cells or causing a drop in hemoglobin ≥2 g/dL, and a composite of these two endpoints (defined as major bleeding). Critical organ bleeding was defined as bleeding in any of the following anatomic locations: intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome. Outcomes were assessed as time-to-first-event from the first dose of the study drug to 2 days following permanent study drug discontinuation (first dose to last dose +2 days). Patient outcomes were censored after the first event.

2.3. Calculation of net clinical benefit

We chose to use four different methods to estimate NCB given the multitude of approaches previously published and the lack of a widely accepted standardized approach. In Method 1, NCB was defined as the unweighted composite of all-cause death, stroke, myocardial infarction, systemic embolism, or major bleeding, with each event type weighted equally and counted to the composite only once. In Method 2, we modified the composite endpoint in Method 1 by substituting fatal or critical organ bleeding for major bleeding. This was done to exclude less-impactful, non-fatal extracranial hemorrhage events, which typically do not lead to "irreversible harm." Therefore in Method 2, NCB was defined as the unweighted composite of all-cause death, stroke, myocardial infarction, systemic embolism, fatal bleeding, or critical organ bleeding. This approach of focusing on events that are fatal or cause irreversible harm is similar to the approach the U.S. Food and Drug Administration has described for its approval of other anticoagulants [9,10].

In Method 3, NCB was calculated using an approach based on a previous study by Singer et al., which compared warfarin versus no anticoagulation in patients with AF [4]. In this method, NCB was defined as the difference between the annualized rate of SSE minus 1.5 times the difference between the annualized rate of ICH. Thus, NCB was defined as: $(SSE_{rivaroxaban} - SSE_{warfarin}) + 1.5 \times (ICH_{rivaroxaban} - ICH_{warfarin})$. The weighting factor of 1.5 reflects the greater relative impact in terms of death and disability of an ICH relative to an ischemic stroke. A numerically negative result indicates that treatment with rivaroxaban is favored compared with warfarin.

In Method 4, NCB was defined as the sum of the rate differences of SSE, ICH, major bleeding (MB) excluding ICH, and all-cause death (DE) in the two treatment groups, with each rate difference multiple by a weighting factor. This formula was based on a previous study of left atrial appendage closure by Gangireddy et al. [11] The weight assigned to each rate difference reflects the relative impact of that event type in terms of death and disability. Death is assigned the highest weight (1.00), and SSE is given a reference weight of 0.20. The weights of ICH and MB are based on an analysis of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) trials [12]. In this analysis, the hazard ratio (HR) for death after ICH was 3.08 compared with SSE, and the HR for DE after MB was 0.67 compared with SSE. Therefore, ICH is assigned a weight of 0.6 and MB a weight of 0.1. Therefore, NCB was calculated as: $1 \times (DE_{rivaroxaban} - DE_{warfarin}) + 0.2 \times (SSE_{rivaroxaban} - SSE_{warfarin}) + 0.6 \times (ICH_{rivaroxaban} - ICH_{warfarin}) + 0.1 \times (MB_{rivaroxaban} - MB_{warfarin})$. We also conducted additional sensitivity analyses using weights of 0.1 and 0.3 for SSE, 0.3 and 0.9 for ICH, and 0.05 and 0.15 for MB. For methods 1, 2, and 4, ICH was not counted within MB to avoid "double counting" of this endpoint in both stroke and major bleeding.

2.4. Statistical analysis

Baseline characteristics were summarized as counts (percentages) for categorical variables and as median values with 25th and 75th percentiles for continuous variables. Event rates were calculated as the number of events per 100 patient-years. The rate difference for each endpoint was calculated by subtracting the event rate per 100 patient-years of the warfarin group from the event rate of the rivaroxaban group (rivaroxaban minus warfarin). Thus, a negative rate difference indicates a lower event rate in the rivaroxaban group. The rate difference was multiplied by a factor of 100 and expressed as the number of additional events per 10,000 patient-years, to enable easier interpretation of the small rate differences as natural frequencies. The 95% confidence interval (CI) of the rate difference was calculated using empirical bootstrap resampling with 1000 replicates.

Kaplan-Meier (K-M) cumulative event rates throughout the duration of the ROCKET AF follow-up period were calculated according to randomized treatment. The cumulative K-M rates were converted to cumulative rate differences by subtracting the K-M estimates for each treatment. The excess number of events (per 10,000 patients) between treatments over time was visualized by plotting the cumulative rate differences.

3. Results

From December 18, 2006, through June 17, 2009, a total of 14,264 patients underwent randomization (intention-to-treat population) and a total of 14,236 patients received at least one dose of a study drug (on-treatment population). The median duration of treatment exposure was 590 days, and the median follow-up period was 707 days. The proportion of patients who stopped their assigned therapy before an endpoint event and before the termination date was 23.7% in the rivaroxaban group and 22.2% in the warfarin group. A total of 32 patients were lost to follow-up. Because of violations in Good Clinical Practice guidelines at one site that made the data unreliable, 93 patients (50 in the rivaroxaban group and 43 in the warfarin group) were excluded from all efficacy analyses.

The key clinical characteristics of the patients included in the analysis (on-treatment population) are shown in Table 1. The median age was 73 years, and 39.7% of patients were female. Comorbid conditions were prevalent: 90.5% of patients had hypertension, 62.5% had heart failure, 39.9% had diabetes mellitus, and 54.7% of patients had a previous SSE or transient ischemic attack. The mean and median $CHADS_2$ scores were 3.5 and 3.0, respectively, indicating a high-risk population. Previous use of vitamin K antagonists was reported by 62.4% of patients.