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Original Article

Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: A retrospective population-based cohort study

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ABSTRACT

Backgound: Randomized controlled trials (RCTs) have shown that dabigatran, rivaroxaban and warfarin cause similar bleeding rates.
Methods: We performed a retrospective population-based cohort study to determine the incidence of bleeding in patients with atrial fibrillation (AF) beginning dabigatran, rivaroxaban or warfarin. Consecutive patients initiating anticoagulation for AF during a 3 year period were identified using a computerized database. Patients who bled and required hospitalization underwent chart review. Bleeding incidences were calculated per 100 patient-years of treatment.
Results: 18,249 patients were included: 9564 (52.4%) received warfarin, 5976 (32.7%) dabigatran, and 2709 (14.8%) rivaroxaban. Bleeding incidences were 3.9 (95% CI, 3.6–4.4) in warfarin-treated patients, 4.2 (95% CI, 3.7–4.7) in dabigatran patients, and 4.1 (95% CI, 3.0–5.3) in rivaroxaban patients. Intracranial hemorrhage (ICH) rates were 0.71 (95% CI, 0.56–0.90) for warfarin, 0.4 (95% CI, 0.18–0.87) for dabigatran, and 0.27 (95%CI, 0.10–0.80) for rivaroxaban. GI hemorrhage rates were 1.88 (95%CI, 1.62–2.20) for warfarin, 2.98 (95% CI, 2.4–3.5) for dabigatran and 2.39 (95%CI, 1.6–3.5) for rivaroxaban.
Conclusions: We demonstrate similar bleeding rates with both dabigatran 150 mg and 110 mg and rivaroxaban compared to warfarin.

1. Introduction

Warfarin reduces the risk of ischemic stroke and systemic embolism in patients with atrial fibrillation (AF) but is inconvenient to use [1,2]. Recently direct oral anticoagulants (DOACs) have received regulatory approval in many countries for stroke prevention in AF: dabigatran (110 mg twice daily and 150 mg twice daily), rivaroxaban, and apixaban, all given in fixed doses without regular laboratory monitoring. They are at least as effective and safe as VKAs for stroke prevention in AF are all associated with fewer intracranial hemorrhages, whereas dabigatran and rivaroxaban were associated with more gastrointestinal (GI) bleeding than warfarin [3].

Because patients in randomized clinical trials (RCTs) are selected and might not be representative of non-study AF patients seen in usual clinical practice, there is a need to determine whether the outcome rates are comparable. This is of interest because there have been reports of excessive bleeding with dabigatran and rivaroxaban resulting in litigation and concern on the part of physicians and their patients about the safety of dabigatran (and other DOACs) when used in routine care [4,5]. In this study, we report the incidence of hemorrhage in a large cohort of consecutive AF patients seen in routine practice initiating treatment with rivaroxaban, dabigatran, or warfarin. At the time that this study was conducted apixaban, a third DOAC was not available in Israel.

2. Methods

This retrospective population-based cohort study used the computerized database of the Israeli Clalit Health Services healthcare organization, which has 4.3 million members representing all ethnic and income groups in Israel, to identify patients who were prescribed warfarin,

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dabigatran (110 mg or 150 mg twice daily) or rivaroxaban for the first time, and for a minimum of 3 consecutive months. All patients initiating their anticoagulant between January 1, 2011 and December 1, 2013 were eligible and were followed until February 28, 2014, a bleeding episode or death, whichever occurred first. The sub-group with a diagnosis of AF (ICD-9 codes 4273 and 43,731,) was identified and comprised the study population. Demographic and clinical data, including age, sex, $CHADS_2$ score, serum creatinine and concomitant medications for each consecutive patient were extracted. The HAS-BLED score could not be reliably caclulated because data regarding blood pressure measurements were not available.

Patients admitted to hospital with hemorrhage defined by the ICD-9 codes (Appendix 1) as the primary diagnosis were identified. Manual review of each electronic hospital discharge report was undertaken by one of us (TN) and details regarding the site of hemorrhage, and mortality within 30 days of the hemorrhage were recorded.

Anticoagulation was with: 1) warfarin, target INR of 2.0–3.0, 2) rivaroxaban, 20 mg once daily, and 3) dabigatran, either 150 mg twice daily or 110 mg twice daily. Dabigatran was approved for stroke prevention in AF in Israel in January 2011, and rivaroxaban in January 2012.

Bleeding incidences were calculated as the rates of bleeding per 100 patient years of treatment and 95% confidence intervals (CIs), for overall bleeding and for subgroups of patients with intracranial hemorrhage (ICH) and GI bleeding. Patients with DOAC-related bleeding were compared with patients warfarin-related bleeding.

2.1. Statistical methods

Data are presented as numbers or percentage for discrete variables and median and range for continuous variables. Differences between patient groups were analyzed using the Chi square test for discrete variables and the student's t-test or ANOVA for continuous variables. Hazard ratios (HRs) and 95% CIs were calculated and compared by Cox regression analysis. Analyses were performed using SPSS-21 software. A p value of <0.05 was statistically significant.

2.2. Ethics committee approval

Approval was obtained from the Institutional Review Boards of the Meir Medical Center and Clalit Health Services.

3. Results

18,249 patients initiated anticoagulants for AF: 9564 (52.4%) received warfarin, 5976 received dabigatran: 4170 (22.9%) received dabigatran 110 mg bid, 1806 (9.9%) received dabigatran 150 mg bid and 2709 (14.8%) received rivaroxaban (Table 1). The numbers of patients who were prescribed the different anticoagulant drugs are summarized in Fig. 1. By the end of 2013, DOACs were presicribed in about one half of patients with new onset AF. In addition, prescription

Table 1
Clinical profile of the patient cohort.

	Warfarin	Dabigatran150	Dabigatran110	Rivaroxaban
Patients (N)	9564	1806	4170	2709
Patient-years	9451	1079	3215	1086
Age (years)	79	78	82	82
Median (Range)	(27–99)	(52–89)	(55–95)	(58–91)
Women (%)	43.8	45.1	47	38.6
$CHADS_2$ score	3 (0–6)	3 (1-6)	4 (2-6)	4 (2-6)
Median (Range)				
Serum creatinine (mg/dL)	1.2 (0.3–11.6)	1.0 (0.5–4.4)	1.2 (0.5–4.1)	1.3 (0.5–3.5)
Median (Range)				
Anti platelet drug use (%)	52	50	35	55

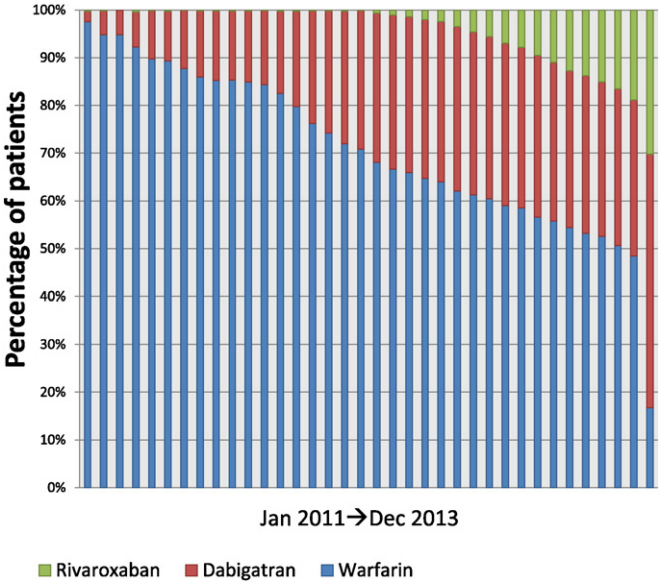

Fig. 1. Percentage of patients beginning different anticoagulant drugs each month during the study period.

of the lower dabigatran dose was chosen for more than twice as many patients as the higher dose. Consistent with this pattern of practice are the older median age, the higher serum creatinine levels, the higher proportion of women, higher incidence of anti-platelet drug use and the higher $CHADS_2$ scores of patients prescribed the lower dose.

854 patients had bleeding requiring hospital admission. At the time of hemorrhage 374 patients received warfarin, 66 received dabigatran 150 mg, 130 received dabigatran 110 mg and 44 received rivaroxaban. The bleeding rates per 100 patient-years were 3.9 (95% CI, 3.6–4.4) in warfarin-treated patients, 4.2 (95% CI, 3.7–4.7) in dabigatran-treated patients: 2.8 (95% CI, 2.0–3.9) in dabigatran 150 mg patients, 4.6 (95% CI 4.0–5.4) in dabigatran 110 mg patients and 4.1 (95% CI, 3.0–5.3) in rivaroxaban patients.

The substantial overlap of the 95% CIs of the bleeding rates among the warfarin, dabigatran, and rivaroxaban groups is consistent with the corresponding phase 3 studies and the upper borders of the 95% CIs reliably exclude a dramatic increase in the bleeding rates in any of the groups.

The HR for hemorrhage adjusted for age, sex, serum creatinine, $CHADS_2$ score and aspirin use (the significant variables by univariate analysis) for warfarin vs dabigatran 150 mg was 1.0 (95% CI = 0.7–1.3), for warfarin vs dabigatran 110 mg the adjusted HR was 1.34 (95% CI = 1.1–1.6) and for warfarin vs rivaroxaban the adjusted HR was 0.71 (95% CI = 0.53–0.95).

Compared to non-bleeding patients, patients who experienced bleeding in all NOAC groups - dabigatran overall, dabigatran 150 mg, dabigatran 110 mg and rivaroxaban had higher point estimates for known bleeding risk factors namely age, $CHADS_2$ score, serum creatinine level and anti-platelet agent use (Table 2).

3.1. Bleeding sites

The ICH rates per 100 patient-years were 0.71 (95% CI, 0.56–0.90) in warfarin-treated patients, 0.4 (95% CI, 0.18–0.87) in dabigatran patients overall: 0.37 (95% CI, 0.15–0.94) in dabigatran 150 mg patients, 0.49 (95% CI, 0.30–0.80) in dabigatran 110 mg patients and 0.27 (95%CI, 0.10–0.80) in rivaroxaban patients (Fig. 2). GI hemorrhage rates per 100 patient-years were 1.88 (95%CI, 1.62–2.20) in warfarin-treated patients, 2.98 (95% CI, 2.4–3.5) in dabigatran patients overall: 1.85 (95%CI, 1.2–2.8) in dabigatran 150 mg patients, 3.36 (95%CI, 2.8–4.0)