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For people with non-valvular atrial fibrillation rivaroxaban is non-inferior to warfarin for preventing stroke or embolism, with no difference in the risk of clinically relevant bleeding

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Context

Atrial fibrillation (AF) significantly increases the risk of thromboembolism. Until recently, thromboprophylaxis in high-risk AF patients has been limited to vitamin K antagonists. Emerging, novel oral anticoagulants are more selective, targeting specific steps in the coagulation cascade. These agents include direct thrombin inhibitors such as dabigatran and Factor Xa inhibitors such as rivaroxaban, and apixaban. These medications bring the potential for decreased monitoring and improved risk profiles with regard to bleeding and drug-drug interactions.

Methods

ROCKET AF was an international, multicentre, event-driven non-inferiority trial comparing rivaroxaban versus dose-adjusted warfarin for the prevention of stroke and systemic embolism (primary efficacy endpoint). ROCKET AF enrolled 14264 patients with non-valvular AF at moderate to high risk of stroke and randomised them in a double-blind, double-dummy fashion, administering placebo pills and performing INRs, including sham INRs in the rivaroxaban patients. In addition to the primary efficacy endpoint, the primary safety endpoint was a composite of major and clinically relevant non-major bleeding events. The primary statistical analysis was an on-treatment, per-protocol analysis. Median follow-up was 707 days.

Findings

Rivaroxaban was non-inferior compared with warfarin for the prevention of stroke or systemic embolism (HR 0.79 (95% CI 0.66 to 0.96), $p < 0.001$ for non-inferiority). An intention-to-treat analysis, including all randomised patients confirmed that rivaroxaban was non-inferior to warfarin (1.7 vs 2.2 events per 100 patient years; HR 0.88 (95% CI 0.74 to 1.03), $p < 0.001$ for non-inferiority, $p = 0.12$ for superiority).

Major and non-major clinically relevant bleeding was similar between the rivaroxaban and warfarin groups (14.9 vs 14.5 events per 100 patient years; HR 1.03 (95% CI 0.96 to 1.11), $p = 0.44$). However, fatal bleeding and intracranial haemorrhage (ICH) were less frequent in the rivaroxaban group (HR for ICH 0.67 (95% CI 0.47 to 0.93), $p = 0.02$) while gastrointestinal bleeding and bleeding requiring transfusion were more frequent in the

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rivaroxaban arm. In terms of all-cause death, there were 1.9 deaths per 100 patient years in the rivaroxaban arm versus 2.2 in the warfarin arm (HR 0.85 (95% 0.70 to 1.02), $p=0.07$).

Commentary

The authors concluded that rivaroxaban was non-inferior to warfarin for the prevention of stroke and systemic embolism reduction with less intracranial bleeding. The ROCKET AF trial enrolled a previously under-studied population of patients with AF. Compared with other contemporary trials, patients in ROCKET AF had higher CHADS₂ scores. Notably, 54.8% of patients in ROCKET AF had a prior stroke, systemic embolus or TIA. The use of a double-blind, double-dummy design in a large, global AF population, allowed for a minimally biased evaluation of rivaroxaban. This population as a whole was at moderate-high risk for bleeding events given their clinical characteristics and thus, the safety evaluation of rivaroxaban proves valuable.

The primary limitation of ROCKET AF is the relatively low time in therapeutic range (TTR) in the warfarin arm (55%) as compared with other recent trials of novel anticoagulant medications (RE-LY 64% and ARISTOTLE 62%).¹² This could be explained by the higher risk population enrolled in ROCKET AF, which may have influenced the rates of complex medication interactions, hospitalisations and need for frequent warfarin titration despite variation in regional practices. The TTR in ROCKET AF may also have implications regarding the efficacy of warfarin in high-risk populations, indicating the difficulty of maintaining patients in the therapeutic range, even in a rigorous clinical trial setting.

In the RE-LY (dabigatran),¹ ROCKET AF (rivaroxaban) and ARISTOTLE (apixaban)² trials, each showed that novel anticoagulants were as effective as warfarin in preventing stroke without increased major bleeding. However, these same agents are not equivalent in other disease states such as coronary artery disease. In the RE-LY trial, patients on dabigatran had more myocardial infarctions compared with those on warfarin. In the APPRAISE trial,³ use of apixaban in addition to antiplatelet agents after acute coronary syndrome showed a concerning increase in bleeding events without a significant reduction in ischaemic events. Rivaroxaban is currently being evaluated for use in acute coronary syndromes in the ATLAS-2 TIMI 50 trial.

We soon will have several choices for thromboprophylaxis in moderate-high risk patients with AF. Rivaroxaban provides an effective, safe oral alternative to warfarin, as do dabigatran and apixaban. Rivaroxaban may be more useful in certain patient populations. More clinical trials and post-marketing surveillance data are needed to optimally define the relative advantages and disadvantages of these novel oral anticoagulants. Only time will tell how physicians will respond to these new choices and challenges.

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