ROCKET-AF: Rivaroxaban vs Warfarin in patients with Atrial Fibrillation

Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF

BOTTOM LINE

In atrial fibrillation (AF) patients with an ↑ risk of stroke (mean CHADS2 score 3.5), rivaroxaban 20mg po daily:

- Was non-inferior (i.e. no worse than) to warfarin for stroke or systemic embolism
- Had less hemorrhagic strokes, systemic embolism & bleeding (critical, fatal & intracranial) versus warfarin
- Had more drops in hemoglobin ≥20 g/L, transfusions, gastrointestinal bleeding, epistaxis & hematuria versus warfarin

At time of publication, rivaroxaban for AF is approximately $100/month; 15mg, 20mg tablets. *AFRL® Warfarin + monitoring ~$35/month.

BACKGROUND

- Vitamin K antagonists (VKA) are used to ↑ the risk of stroke in AF patients; however, these agents require frequent monitoring, interact with drugs/food, & require several days of therapy to become therapeutic/discontinuation before clearing the body.
- New oral anticoagulants (apixaban ELIQUIS, 2,3 dabigatran PRADAXA & rivaroxaban XARELTO) are alternatives to VKA, such as warfarin.
- ROCKET-AF is a new oral direct factor Xa inhibitor.
- ROCKET-AF is the first Phase III study assessing the use of rivaroxaban for stroke prevention in AF patients.

TRIAL BACKGROUND

DESIGN: randomized, multi-centre 45 countries, double-blinded, double-dummy controlled trial with concealed allocation; non-inferiority with pre-designed superiority, intention-to-treat & per-protocol analysis. Funded by Johnson & Johnson and Bayer.

INTERVENTION: rivaroxaban 20mg* po daily vs dose-adjusted warfarin (INR 2-3 measured ±1 month)

* rivaroxaban 15mg po daily in patients with CrCl 30-49 mL/min see page 2 for subgroup analysis

INCLUSION: persistent/paroxysmal AF on ≥ 2 episodes documented on ECG within 30 days of enrolment; age ≥ 18 yrs; risk of future stroke: history of stroke/TIA or systemic embolism OR ≥ 2 of the following: HF or LVEFs<35%, HTN (on BP meds ±6 months before of SBP>140 mmHg or DBP>90 mmHg), age ≥75 yr, or DM (i.e. CHADS2 score of ≥ 2). Only 10% could have a CHADS2 score of ≥ 2, with the remainder having a score of ≥ 3 or prior stroke, TIA or systemic embolism

EXCLUSION: Cardiac-related conditions or due to reversible disorders, active endocarditis, mitral stenosis, presence of atrial myoma or LV thrombus, planned cardionversion, prostatic heart valve, BP ≥ 160/100 mmHg, Hemorrhagic risk-related criteria active internal bleeding, hx of major surgical procedure or trauma within 30 days, GI bleed within 6 months, hx of intracranial/intracerebral/spinal/traumatic intracranial bleeding, chronic hemorrhagic disorder, known intracranial neoplasm, arteriogenous malformation, or aneurysm, planned invasive procedure with potential for uncontrollable bleeding, including major surgery; anemia Hgb <100g/L; any stroke within 14 days (severe within 90 days) or TIA within 3 days, indication for anticoagulant therapy for a condition other than AF (e.g. VTE); tx with ASA>100mg/d, ASA/thienopyridine or IV antplateletates within 5 days; fibrinolitics within 10 days; anticipated need for long-term tx with NSAID; systemic treatment with a strong inhibitor/inducer of CYP 450 3A4 within 4 days or planned treatment during the study; pregnancy/breastfeeding; HIV, CrCl<30mL/min, liver disease or ALT>3x ULN.

POPULATION at baseline: n=14,264 non-valvular AF patients at risk of stroke

- AF *81% persistent, *17.6% paroxysmal, 1.4% newly diagnosed/assessed; CHADS2 mean ±3, median=3, CHADS2 score ≥2% = 13%, 2% = 3, 29% =4, 13% = 5, rivaroxaban 1.7% vs warfarin 2.2% = 6 (p<0.05 for CHADS2 score of 6)
- *60% Ø; median age 73yrs 25% ≥79yrs, BMI 28 kg/m², BP 130/80 mmHg, CrCl 67mL/min
- History of stroke/TIA 55%, HF 63%, HTN 91%, DM 40%, MI 17%
- Baseline medications: β-blocker ~65%, diuretics 60%, ACE-I 55%, statins 43%, digoxin 39%, ASA 38%. Previous use of vitamin K antagonist 62%.

RESULTS

median follow-up: per-protocol (PP) & safety population = 590 days; intention-to-treat (ITT) = 707 days

TABLE: EFFICACY & SAFETY

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINTS</th>
<th>NON-INFERIOR DATA</th>
<th>SUPERIORITY DATA</th>
<th>HAZARD RATIO (95% CI)</th>
<th>NNT/NNH</th>
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<tbody>
<tr>
<td>PRIMARY ENDPOINTS</td>
<td>RIVAROXABAN</td>
<td>WARFARIN</td>
<td>PRIMARY ENDPOINTS</td>
<td>RIVAROXABAN</td>
</tr>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>(n=6958)</td>
<td>(n=7081)</td>
<td>(n=269)</td>
<td>(n=241)</td>
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<tr>
<td>ITT</td>
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<tr>
<td>2.70% (n=188)</td>
<td>3.80% (n=269)</td>
<td>1.7%/yr</td>
<td>2.1%/yr</td>
<td>3.4%/yr</td>
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<tr>
<td>EFFECTIVE: Based on safety population, rivaroxaban n=7061 vs warfarin n=7082 excluding violated site &amp; those who did not receive a dose</td>
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<tr>
<th>SECONDARY ENDPOINTS</th>
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<td>PRIMARY ENDPOINTS</td>
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<td>WARFARIN</td>
<td>PRIMARY ENDPOINTS</td>
<td>RIVAROXABAN</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.41% (n=29)</td>
<td>0.26% (n=50)</td>
<td>0.71% (n=50)</td>
<td>0.44%/yr</td>
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<tr>
<td>Systemic Embolism</td>
<td>0.07% (n=5)</td>
<td>0.04%/yr</td>
<td>0.31% (n=22)</td>
<td>0.19%/yr</td>
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<tr>
<td>Myocardial Infarction</td>
<td>1.43% (n=101)</td>
<td>0.91%/yr</td>
<td>1.78% (n=126)</td>
<td>1.12%/yr</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>2.95% (n=208)</td>
<td>(1.87%/yr)</td>
<td>3.53% (n=250)</td>
<td>(2.21%/yr)</td>
</tr>
</tbody>
</table>

BLEEDING: Based on safety population, rivaroxaban n=7111 vs warfarin n=7082 excluded those who did not receive a dose

Major Bleed* 5.6% (n=395) (3.6%/yr) | 5.4% (n=386) (3.4%/yr) | NS | -
Hemoglobin ≤220g/L 4.3% (n=305) (2.8%/yr) | 3.6% (n=254) (2.3%/yr) | 1.22 | 1.03-1.44 | 143
Transfusion 2.6% (n=183) (1.6%/yr) | 2.1% (n=149) (1.3%/yr) | 1.25 | 1.01-1.55 | 200
Critical Bleeding 1.3% (n=91) (0.8%/yr) | 1.3% (n=133) (1.2%/yr) | 0.69 | 0.53-0.91 | 167
Fatal Bleeding 0.4% (n=27) (0.2%/yr) | 0.8% (n=55) (0.5%/yr) | 0.50 | 0.31-0.79 | 250
Intracranial bleed 0.8% (n=55) (0.5%/yr) | 1.2% (n=84) (0.7%/yr) | 0.67 | 0.47-0.93 | 250
Gastrointestinal Bleed† 3.3% (n=224) | 2.2% (n=154) | P<0.05 | 100
Epistaxis 1.0% (n=721) | 8.6% (n=609) | P<0.05 | 67
Hematuria 4.2% (n=296) | 3.4% (n=242) | P<0.05 | 125
Discontinuation Rates 23.7% | 22.3% | - | -

RIVAROXABAN VS WARFARIN:
- Non-inferior (i.e. no worse than) to warfarin for stroke or systemic embolism.
- ↓ hemostatic risk, systemic embolism & bleeding (critical, fatal & intracranial).

WARFARIN VS RIVAROXABAN:
- Concurrent ASA use: warfarin (36.2%) vs rivaroxaban (34.9%)
- Baseline CHADS2 score of 6: warfarin (2.2%) vs rivaroxaban (1.7%), p<0.05.
- Rivaroxaban TTR= mean 55%, median 58%. North American sites: 64%.7

OTHER COMMENTS:
- Lost to follow-up: 32
- 93 patients excluded (50 rivaroxaban & 43 warfarin) from all efficacy analyses before unblinding because of violations in Good Clinical Practice.
- Subgroup analyses: NS

* Major Bleed = Hemoglobin ≤220g/L, transfused <2units, or symptomatic bleeding critical area or organ (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome), fatal outcome or permanent disability.
† Gastrointestinal Bleed = upper, lower, rectal gastrointestinal bleeding
PUBLISHED SUBGROUP ANALYSES

Note: subgroup analyses are not powered to detect a conclusive difference between treatments groups; however, the following subgroup analyses were similar to the overall trial results with the entire patient population.

1) Pre-Designed Subgroup Analysis of ROCKET-AF Patients with Moderate Renal Impairment (=CrCl 30-49 mL/min at baseline)

- Background: patients with CrCl 30-49 mL/min have a 25-30% ↑ rivaroxaban serum concentration → 25% ↓ in rivaroxaban =15mg
- N=2950 (20.7% of ROCKET-AF patient population), rivaroxaban 15mg po daily (n=1474) vs dose-adjusted warfarin (INR 2-3, n=1476)
- Population: compared to the ROCKET-AF patients with CrCl ≥50 mL/min, patients with a CrCl 30-49 mL/min:
  - ↑ age (median 79 years), CHADS score (median 3.7 ±1), history of HF ≥66%, PAD ~7.5% & MI <19%
  - ↓ BMI (median 25 kg/m²), history of stroke/TIA ~50% & DM ~32%
- Compared to the ROCKET-AF patients with CrCl ≥50 mL/min, patients with a CrCl 30-49 mL/min had an↑ risk of stroke & systemic embolism (primary endpoint) & ↑ risk of bleeding.
  - Rivaroxaban 15mg po daily vs warfarin had consistent results when compared to patients with preserved renal function.

2) Pre-Designed Subgroup Analysis of ROCKET-AF Patients with Previous Stroke or TIA

- N=7468 (52% of ROCKET-AF patient population), previous stroke (n=4907) or TIA (n=2561)
- Median time from previous stroke or TIA to randomization was 551 days (interquartile range 126-1702 days)
- Rivaroxaban (n=3754) versus warfarin (n=3714)
- Population: compared to ROCKET-AF patients without a history of stroke/TIA, patients with a history of stroke/TIA (p<0.05):
  - ↑ CrCl (median 69 mL/min), CHADS score (median 4), previous ASA (38%) or vitamin K antagonist (59%) use
  - ↓ age (median 71 years), BMI (median 27.5 kg/m²), persistent AF (80%), HTN 85%, HF 51%, DM 25%, MI 15%, PAD 5%, COPD 9%
- Regardless of study group, patients with a history of stroke/TIA had ↑ risk of stroke & systemic embolism (primary endpoint) & ↓ risk of major bleeding (compared to ROCKET-AF patients without a history of stroke/TIA):
  - Stroke & systemic embolism: without a history of stroke/TIA 1.66% vs with a history of stroke/TIA 2.87%, HR 1.7 (95% CI 1.44-2.02), p<0.0001
  - Major bleeding: without a history of stroke/TIA 3.89% versus with a history of stroke/TIA 3.18%, HR 0.81 (95% CI 0.70-0.93), p=0.0037
- The comparison of rivaroxaban versus warfarin was similar, regardless of whether the anticoagulants were used as primary or secondary stroke prevention.

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- Important clinical endpoints (e.g. stroke & bleed) • Double blind, double dummy with sham INRs
- Moderate to high risk of stroke (mean CHADS score = 3.5)
- Used both per-protocol & intention-to-treat analysis
- Similar discontinuation rates in both groups (rivaroxaban 23.7% versus warfarin 22.2%)
- Only 32 patients lost to follow-up (0.22%)

LIMITATIONS:
- Warfarin was within therapeutic range only 55% North American sites 64% of the study period ACTIVE-W 63.8%, ARISTOTLE 66%, RELY 64%
- Short study duration • One site violated Good Clinical Practice
  - ~ 35% of patients in each arm of the trial were on concomitant aspirin treatment

UNCERTAINTIES:
- Drug not yet studied in patients with CrCl<30 mL/min or in liver disease
- Drug interactions?
  - Stroke after rivaroxaban stopped 28 days later
- No antidote for reversing bleeding with rivaroxaban
- Lack long-term follow-up & real-world experience with rivaroxaban

RELATED STUDIES

J-ROCKET AF
- Japan was not included in the original ROCKET-AF trial because:
  - Pharmacokinetic data: Cmax & area under the curve for rivaroxaban 15mg po daily in Japanese patients = rivaroxaban 20mg po daily in Caucasians.
  - Japanese clinical practice guidelines recommend a target INR of 1.6 – 2.6 in patients ≥70 years of age.
- N=1280; randomized, double-blind, double-dummy, multicentre 150 sites, non-inferiority trial in Japan.
- Intervention: rivaroxaban 15mg* po daily versus dose-adjusted warfarin (INR 2-3 in patients <70 years of age & INR 1.6-2.6 in patients ≥70 years old).
- *rivaroxaban 10mg po daily in patients with CrCl 30-49 mL/min → 22% of the patient population
- Safety: rivaroxaban was non-inferior to warfarin for the composite of major & non-major bleeding; individual composite endpoints not statistically significant when separated. Differences in location of bleeds were not tested for statistical significance.
- Efficacy: not powered for efficacy stroke & systemic embolism was NS (p=0.05).
- Overall, the J-ROCKET AF study results were similar to the global ROCKET-AF study.

RxFiles RELATED LINKS

- Canadian Family Physician RxFiles: Article Oral anticoagulation in atrial fibrillation http://www.cfp.ca/content/58/8/850.full
Additional references:


6 ROCKET AF Study Investigators. Rivaroxaban – once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: Rationale and Design of the ROCKET AF study. Am Heart J 2010;159:340-7.e1


