



Appendix B: Outcomes from Anticoagulant Active-Comparison, Randomized Controlled Trials (as reported)

The **absence of direct comparisons** between the new oral anticoagulants and the **heterogeneity** of the three principal randomized controlled trials (RCTs) limits reaching firm conclusions regarding differences between the new oral anticoagulants.¹⁻⁴ **Methodologic limitations** have increased relevance as sources of potential bias in non-inferiority RCTs.⁵

| | Dabigatran (RE-LY)^{6,7} | | Rivaroxaban (ROCKET AF)^{2,8,9} | Apixaban (ARISTOTLE)¹⁰ |
|--|---|---|--|---|
| | D110 versus WARF | D150 versus WARF | RIVA versus WARF | APIX versus WARF |
| Primary composite outcome | | | | |
| stroke or systemic embolismⁱ | D110 1.54% per year WARF 1.71% per year 0.90 (0.74, 1.10) | D150 1.11% per year WARF 1.71% per year 0.65 (0.52, 0.81) ↓ 0.60% per year | RIVA 2.1% per year WARF 2.4% per year 0.88 (0.75, 1.03) | APIX 1.27% per year WARF 1.60% per year 0.79 (0.66, 0.95) ↓ 0.33% per year |
| Secondary outcomesⁱⁱ | | | | |
| total mortality | D110 3.75% per year WARF 4.13% per year 0.91 (0.80, 1.03) | D150 3.64% per year WARF 4.13% per year 0.88 (0.77, 1.00) | RIVA 4.5% per year WARF 4.9% per year 0.92 (0.82, 1.03) | APIX 3.52% per year WARF 3.94% per year 0.89 (0.80, 1.00) <small>vital status missing for 380 patients</small> |
| major bleedⁱⁱⁱ | D110 2.87% per year WARF 3.57% per year 0.80 (0.70, 0.93) ↓ 0.70% per year | D150 3.32% per year WARF 3.57% per year 0.93 (0.81, 1.07) | RIVA 3.6% per year WARF 3.4% per year 1.03 (0.89, 1.19)* | APIX 2.13% per year WARF 3.09% per year 0.69 (0.60, 0.80)* ↓ 0.96% per year |
| intracranial hemorrhage^{iv} | D110 0.23% per year WARF 0.76% per year 0.30 (0.19, 0.45) ↓ 0.53% per year | D150 0.32% per year WARF 0.76% per year 0.41 (0.28, 0.60) ↓ 0.44% per year | RIVA 0.5% per year WARF 0.7% per year 0.67 (0.47, 0.93)* ↓ 0.2% per year | APIX 0.33% per year WARF 0.80% per year 0.42 (0.30, 0.58)* ↓ 0.47% per year |
| major gastrointestinal bleed | D110 1.15% per year WARF 1.07% per year 1.08 (0.85, 1.38) | D150 1.56% per year WARF 1.07% per year 1.48 (1.18, 1.85) ↑ 0.49% per year | RIVA 2.00% per year WARF 1.24% per year 1.61 (1.30, 1.99)* ↑ 0.76% per year | APIX 0.76% per year WARF 0.86% per year 0.89 (0.70, 1.15)* |

Abbreviations: D110 = dabigatran 110 mg PO BID; D150 = dabigatran 150 mg PO BID; RIVA = rivaroxaban 20 mg (15 mg) PO daily; APIX = apixaban 5 mg (2.5 mg) PO BID; WARF = adjusted-dose warfarin PO daily.

black bolded values = relative risk with 95% confidence interval; **blue bolded values** = absolute risk reduction or increase if statistically significant; *truncated follow-up: events occurring 2 days after treatment discontinuation were not counted.

Notes:

- i Includes ischemic stroke, hemorrhagic stroke, unclassified stroke, or non-CNS systemic embolism; 2013 therapeutic review judged the event definitions to be similar between the RCTs.¹
- ii Appropriate methodology for statistical significance testing of secondary outcomes in non-inferiority RCTs is uncertain.¹¹
- iii Includes decrease Hb ≥ 20 g/L, ≥ 2 unit transfusion whole blood or packed cells, bleed in a critical site, or fatal outcome; 2013 therapeutic review judged the event definitions to be similar between the RCTs; 1 2012 Ontario population-based cohort study, 125 195 adults aged ≥ 66 with atrial fibrillation prescribed warfarin, found a major bleed rate of 3.8% per person-year.¹²
- iv Includes hemorrhagic stroke and other intracranial bleeds; 2012 Ontario population-based cohort study, 125 195 adults aged ≥ 66 with atrial fibrillation prescribed warfarin, found an intracranial hemorrhage rate of 0.2% per person-year.¹²

Additional Comments:

1. Increase in stroke or systemic embolism after discontinuation of study drug: US FDA medical reviews noted excess stroke and systemic embolism in participants receiving rivaroxaban and apixaban compared with warfarin during the observation period when patients were transitioned off of assigned study drug to usual care (e.g., VKA antagonist) at the end of study.^{11,13,14}

2. Myocardial infarction: US FDA medical review noted an increased risk of myocardial infarction of 0.2% per year in participants receiving dabigatran compared with warfarin;¹⁵ 2012 meta-analysis (7 RCTs, 30 514 participants, dabigatran vs. various comparators including warfarin), dabigatran increased the risk of myocardial infarction and acute coronary syndrome (OR 1.33, 95% CI 1.03 to 1.71).¹⁶
3. Syncope: US FDA medical review noted numerically more serious syncopal events (i.e., syncope, vertigo, dizziness, presyncope) in participants receiving apixaban compared with warfarin (apixaban = 1.4%, warfarin = 1.0%).¹¹
4. Major bleed events older adults: significant treatment by age interaction for major bleeding in participants receiving dabigatran compared with warfarin (P for interaction < 0.001);¹⁷ older adults aged ≥ 75 dabigatran 110 mg vs. warfarin 1.01 (0.83, 1.23), dabigatran 150 mg vs. warfarin 1.18 (0.98, 1.42).¹⁷
5. Discontinuations due to adverse events: US FDA medical review noted participants were more likely to discontinue dabigatran due to adverse events compared with warfarin (dabigatran 110 mg = 19%, dabigatran 150 mg = 20.5%, warfarin = 15.7% over the course of the study);¹⁵ gastrointestinal disorders (e.g., dyspepsia, gastrointestinal hemorrhage) were the most common adverse events leading to dabigatran discontinuation.¹⁵

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