**Mini-CAT- Spring 2019 -Jinjin Lin**

**Clinical Question:**

Scenario: A 69 years old male with PMHx of DM, CHF and non-valvular Afib presented to follow up with cardiology in the office. Cardiology is consulted and recommend patient to continue with Rivaroxaban for Afib.

Clinical question: In adult patients with Afib, is Rivaroxaban more effective than Warfarin in management?

**PICO Question:**

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| **P** | **I** | **C** | **O** |
| Atrial fibrillation | Rivaroxaban | Warfarin | Risk of stroke |
| Elderly | Xarelto | Coumadin | Risk of systemic embolism |
|  | Novel oral anticoagulant | Vitamin K Antagonist | Risk of bleeding |
|  | Non-Vitamin K Antagonist Oral Anticoagulants |  | Adverse effects |
|  | Direct Factor Xa Inhibitor |  |  |

**Search Strategy:**

Key words used: Atrial fibrillation, Xarelto, warfarin, effectiveness, safety, risk of stroke, risk of bleeding

Database: PubMed

Results found:

Rivaroxaban Afib / limits: human, publications dates 5 years🡪 1046

Rivaroxaban vs Warfarin non-valvular Afib / limits: human, publications dates 5 years🡪 39

Database: Cochrane

Results found:

Rivaroxaban/ limits: human, publications dates 5 years🡪 10

Rivaroxaban vs Warfarin Afib / limits: publications dates 5 years🡪 1

Database: MEDLINE Complete

Results found:

Rivaroxaban Atrial fibrillation / limits: academic Journals, publications dates 5 years🡪 289

Rivaroxaban Warfarin Atrial fibrillation / limits: academic Journals, publications dates 5 years 🡪 96

Narrow down: review article, human, 5 years publication dates, systemic review, meta-analysis, RCT, retrospective cohort, large sample size, indexed for MEDLINE. Try to read through abstract quickly and include articles are most recent and higher level of evidence if possible, also intervention and control, outcome of study must match my clinical questions. For selection of articles, systemic review and meta-analysis are my first choice, however, most systemic review and meta-analysis studies are comparing all direct factor Xa inhibitors (apixaban, darexaban, edoxaban, and rivaroxaban) to warfarin, not just rivaroxaban verse warfarin. For example, there is one systemic review from Cochrane, which comparing direct factor Xa inhibitors to warfarin; and the systemic review includes only 2 studies comparing rivaroxaban to warfarin, which is my clinical question. I did not include this systemic review, even it is from 2018. The 1st systemic review is the most precise systemic review I can find that compare rivaroxaban and warfarin. I also found some RCTs, which specifically compares rivaroxaban and warfarin in Afib patients; however, the study is conducted in Asia. I did not include these RCTs, because of the sample population. I also include in 2 retrospective cohort studies, even they are not the highest level of evidence, they are based on large sample sizes, the 3rd article has 150,697 participants and the 4th article has 186,132 participants; and studies are conducted in the United States. Overall, I try to include articles that specifically for rivaroxaban and warfarin, studies done in the United States, published recently and based on large sample size.

**Articles Chosen** (3-5) for Inclusion (please copy and paste the abstract with link):

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| **Title** | **Rivaroxaban Versus Dabigatran or Warfarin in Real-World Studies of Stroke Prevention in Atrial Fibrillation: Systematic Review and Meta-Analysis.**  [Bai Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bai%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=28213573)1, [Deng H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Deng%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28213573)1, [Shantsila A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Shantsila%20A%5BAuthor%5D&cauthor=true&cauthor_uid=28213573)1, [Lip GY](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lip%20GY%5BAuthor%5D&cauthor=true&cauthor_uid=28213573)2. [Stroke.](https://www.ncbi.nlm.nih.gov/pubmed/28213573) 2017 Apr;48(4):970-976. doi: 10.1161/STROKEAHA.116.016275. Epub 2017 Feb 17 |
| **Abstract** | **Abstract**  **BACKGROUND AND PURPOSE:**  This study was designed to evaluate the effectiveness and safety of rivaroxaban in real-world practice compared with effectiveness and safety of dabigatran or warfarin for stroke prevention in atrial fibrillation through meta-analyzing observational studies.  **METHODS:**  Seventeen studies were included after searching in PubMed for studies reporting the comparative effectiveness and safety of rivaroxaban versus dabigatran (n=3), rivaroxaban versus Warfarin (n=11), or both (n=3) for stroke prevention in atrial fibrillation.  **RESULTS:**  Overall, the risks of stroke/systematic thromboembolism with rivaroxaban were similar when compared with those with dabigatran (stroke/thromboembolism: hazard ratio, 1.02; 95% confidence interval, 0.91-1.13; I2=70.2%, N=5), but were significantly reduced when compared with those with warfarin (hazard ratio, 0.75; 95% confidence interval, 0.64-0.85; I2=45.1%, N=9). Major bleeding risk was significantly higher with rivaroxaban than with dabigatran (hazard ratio, 1.38; 95% confidence interval, 1.27-1.49; I2=26.1%, N=5), but similar to that with warfarin (hazard ratio, 0.99; 95% confidence interval, 0.91-1.07; I2=0.0%, N=6). Rivaroxaban was associated with increased all-cause mortality and gastrointestinal bleeding, but similar risk of acute myocardial infarction and intracranial hemorrhage when compared with dabigatran. When compared with warfarin, rivaroxaban was associated with similar risk of any bleeding, mortality, and acute myocardial infarction, but a higher risk of gastrointestinal bleeding and lower risk of intracranial hemorrhage.  **CONCLUSIONS:**  In this systematic review and meta-analysis, rivaroxaban was as effective as dabigatran, but was more effective than warfarin for the prevention of stroke/thromboembolism in atrial fibrillation patients. Major bleeding risk was significantly higher with rivaroxaban than with dabigatran, as was all-cause mortality and gastrointestinal bleeding. Rivaroxaban was comparable to warfarin for major bleeding, with an increased risk in gastrointestinal bleeding and decreased risk of intracranial hemorrhage.  **©** 2017 American Heart Association, Inc.  **KEYWORDS:**  atrial fibrillation; dabigatran; real-world data; rivaroxaban; warfarin |
| **Link** | <https://www.ncbi.nlm.nih.gov/pubmed/28213573> |
| **PDF** |  |

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| **Title** | **Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.**  [Patel MR](https://www.ncbi.nlm.nih.gov/pubmed/?term=Patel%20MR%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Mahaffey KW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mahaffey%20KW%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Garg J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Garg%20J%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Pan G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pan%20G%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Singer DE](https://www.ncbi.nlm.nih.gov/pubmed/?term=Singer%20DE%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Hacke W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hacke%20W%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Breithardt G](https://www.ncbi.nlm.nih.gov/pubmed/?term=Breithardt%20G%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Halperin JL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Halperin%20JL%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Hankey GJ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hankey%20GJ%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Piccini JP](https://www.ncbi.nlm.nih.gov/pubmed/?term=Piccini%20JP%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Becker RC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Becker%20RC%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Nessel CC](https://www.ncbi.nlm.nih.gov/pubmed/?term=Nessel%20CC%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Paolini JF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Paolini%20JF%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Berkowitz SD](https://www.ncbi.nlm.nih.gov/pubmed/?term=Berkowitz%20SD%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Fox KA](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fox%20KA%5BAuthor%5D&cauthor=true&cauthor_uid=21830957), [Califf RM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Califf%20RM%5BAuthor%5D&cauthor=true&cauthor_uid=21830957). [N Engl J Med.](https://www.ncbi.nlm.nih.gov/pubmed/21830957) 2011 Sep 8;365(10):883-91. doi: 10.1056/NEJMoa1009638. Epub 2011 Aug 10. |
| **Abstract** | Abstract**BACKGROUND:** The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin. **METHODS:** In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism. **RESULTS:** In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group. **CONCLUSIONS:** In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, [NCT00403767](http://clinicaltrials.gov/show/NCT00403767).) |
| **Link** | <https://www.ncbi.nlm.nih.gov/pubmed/21830957> |
| **PDF** |  |

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| **Title** | **Comparative effectiveness of rivaroxaban versus warfarin or dabigatran for the treatment of patients with non-valvular atrial fibrillation.**  [Norby FL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Norby%20FL%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)1, [Bengtson LGS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Bengtson%20LGS%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)2, [Lutsey PL](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lutsey%20PL%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)3, [Chen LY](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20LY%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)4, [MacLehose RF](https://www.ncbi.nlm.nih.gov/pubmed/?term=MacLehose%20RF%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)3, [Chamberlain AM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chamberlain%20AM%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)5, [Rapson I](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rapson%20I%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)3, [Alonso A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Alonso%20A%5BAuthor%5D&cauthor=true&cauthor_uid=28874129)6. [BMC Cardiovasc Disord.](https://www.ncbi.nlm.nih.gov/pubmed/28874129) 2017 Sep 6;17(1):238. doi: 10.1186/s12872-017-0672-5. |
| **Abstract** | **Abstract****BACKGROUND:**Rivaroxaban is an oral anticoagulant approved in the US for prevention of stroke and systemic embolism in patientswith non-valvular atrial fibrillation (NVAF). We determined the effectiveness and associated risks of rivaroxaban versus other oral anticoagulants in a large real-world population.**METHODS:** We selected NVAF patients initiating oral anticoagulant use in 2010-2014 enrolled in MarketScan databases. Rivaroxabanusers were matched with warfarin and dabigatran users by age, sex, enrolment date, anticoagulant initiation date, and high-dimensional propensity score. Study endpoints, including ischemic stroke, intracranial bleeding (ICB), myocardial infarction (MI), and gastrointestinal (GI) bleeding, were identified from inpatient diagnostic codes. Multivariable Cox models were used to assess associations between type of anticoagulant and outcomes. **RESULTS:** The analysis included 44,340 rivaroxaban users matched to 89,400 warfarin and 16,957 dabigatran users (38% female, mean age 70) with 12 months of mean follow-up. Anticoagulant-naïve rivaroxaban initiators, but not those switching from warfarin, had lower risk of ischemic stroke [hazard ratio (HR) (95% confidence interval (CI)): 0.75 (0.62, 0.91)] and ICB [HR (95%CI): 0.55, (0.39, 0.78)] than warfarin users. In contrast, anticoagulant-experienced rivaroxaban initiators had higher risk of GI bleeding than warfarinusers [HR (95%CI): 1.55 (1.32, 1.83)]. Endpoint rates were similar when comparing anticoagulant-naïve rivaroxaban and dabigatraninitiators, with the exception of higher GI bleeding risk in rivaroxaban users [HR (95%CI) 1.28 (1.06, 1.54)]. There were no significant differences in the risk of MI among the comparison groups. **CONCLUSIONS:** In this large real-world sample of NVAF patients, effectiveness and risks of rivaroxaban versus warfarin differed by prior anticoagulant status, while effectiveness of rivaroxaban versus dabigatran differed in GI bleeding risk. |
| **Link** | <https://www.ncbi.nlm.nih.gov/pubmed/28874129> |
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| **Title** | **Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population.**  [Amin A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Amin%20A%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)1, [Keshishian A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Keshishian%20A%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)2, [Trocio J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Trocio%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)3, [Dina O](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dina%20O%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)3, [Le H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Le%20H%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)4, [Rosenblatt L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rosenblatt%20L%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)4, [Liu X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Liu%20X%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)3, [Mardekian J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Mardekian%20J%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)3, [Zhang Q](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)2, [Baser O](https://www.ncbi.nlm.nih.gov/pubmed/?term=Baser%20O%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)5,6,7, [Vo L](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vo%20L%5BAuthor%5D&cauthor=true&cauthor_uid=28635338)4. [Curr Med Res Opin.](https://www.ncbi.nlm.nih.gov/pubmed/28635338) 2017 Sep;33(9):1595-1604. doi: 10.1080/03007995.2017.1345729. Epub 2017 Jul 11. |
| **Abstract** | **Abstract**  **OBJECTIVE:**  To compare the risk and cost of stroke/systemic embolism (SE) and major bleeding between each direct oral anticoagulant (DOAC) and warfarin among non-valvular atrial fibrillation (NVAF) patients.  **METHODS:**  Patients (≥65 years) initiating warfarin or DOACs (apixaban, rivaroxaban, and dabigatran) were selected from the Medicare database from 1 January 2013 to 31 December 2014. Patients initiating each DOAC were matched 1:1 to warfarin patients using propensity score matching to balance demographics and clinical characteristics. Cox proportional hazards models were used to estimate the risks of stroke/SE and major bleeding of each DOAC vs. warfarin. Two-part models were used to compare the stroke/SE- and major-bleeding-related medical costs between matched cohorts.  **RESULTS:**  Of the 186,132 eligible patients, 20,803 apixaban-warfarin pairs, 52,476 rivaroxaban-warfarin pairs, and 16,731 dabigatran-warfarin pairs were matched. Apixaban (hazard ratio [HR] = 0.40; 95% confidence interval [CI] 0.31, 0.53) and rivaroxaban (HR = 0.72; 95% CI 0.63, 0.83) were significantly associated with lower risk of stroke/SE compared to warfarin. Apixaban (HR = 0.51; 95% CI 0.44, 0.58) and dabigatran (HR = 0.79; 95% CI 0.69, 0.91) were significantly associated with lower risk of major bleeding; rivaroxaban (HR = 1.17; 95% CI 1.10, 1.26) was significantly associated with higher risk of major bleeding compared to warfarin. Compared to warfarin, apixaban ($63 vs. $131) and rivaroxaban ($93 vs. $139) had significantly lower stroke/SE-related medical costs; apixaban ($292 vs. $529) and dabigatran ($369 vs. $450) had significantly lower major bleeding-related medical costs.  **CONCLUSIONS:**  Among the DOACs in the study, only apixaban is associated with a significantly lower risk of stroke/SE and major bleeding and lower related medical costs compared to warfarin.  **KEYWORDS:**  Warfarin; atrial fibrillation; direct oral anticoagulants; stroke |
| **Link** | <https://www.ncbi.nlm.nih.gov/pubmed/28635338> |
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| Author (Date) | Level of Evidence | Sample/Setting  (# of subjects/ studies, cohort definition etc. ) | Outcome(s) studied | Key Findings | Limitations and Biases |
| Bai Y, Deng H, Shantsila A, Lip GY(2017) | | Systematic Review | 17 studies included, with 11 studies comparing rivaroxaban versus warfarin; 897,435 participants; 6 out of 11 studies conducted in the US | Primary outcome:  -Risks of stroke and systemic thromboembolism  -Acute MI  Secondary outcomes (safety outcomes):  -Major bleeding  -Any other bleeding  -Intracerebral hemorrhage  -Gastrointestinal bleeding | -The risks of stroke and systematic thromboembolism with rivaroxaban are significantly reduced compared to patients with warfarin (hazard ratio, 0.75; 95% confidence interval, 0.64-0.85; I2=45.1%, N=9).  -Subgroup analysis with 6 observational studies evaluating ischemic stroke risk between rivaroxaban and warfarin find out that rivaroxaban is associated with lower risk of ischemic stroke (HR, 0.86; 95% CI, 0.75–0.97; I2=0.0%, N=6).  -When compared to warfarin, rivaroxaban is associated with similar risks of major bleeding (HR, 0.99; 95% CI, 0.91-1.07; I2=0.0%, N=6); acute MI (HR, 0.73; 95% CI, 0.30–1.15; I2=0.0%, N=2); mortality (HR, 1.04; 95% CI, 0.64–1.44; I2=92.7%, N=3).  -Rivaroxaban has a higher risk of gastrointestinal bleeding (HR, 1.2; 95% CI, 1.07–1.33; I2=27.5%, N=5); and lower risk of intracranial hemorrhage (HR, 0.54; 95% CI, 0.43–0.64; I2=63.6%, N=6). | -Studies were screened for this review by title and/or abstract, rather than the entire article. This may have left room for relevant articles to be excluded from the review  -Different inclusion, exclusion  criteria and follow-up periods in the included studies may lead to high heterogeneity, so it is necessary to cautiously interpret the noticeable differences in some event rates between the rivaroxaban versus warfarin comparisons  -When compare rivaroxaban to warfarin, studies only provide total participants, but not for specific numbers of participants in each group |

Summary of Evidence

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| Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM (2011) | Randomized control trial | 14,264 patients with age from 65-73 with atrial fibrillation that have mild-to-moderate risk for stroke are randomly assigned into 2 groups: rivaroxaban and warfarin | Primary outcomes:  -Risks of stroke (ischemic or hemorrhagic)  -Systemic embolism  Secondary outcomes:  -Major bleeding and nonmajor relevant bleeding events  -Risk of MI  -Mortality | -The risks of strokes and thromboembolism in warfarin group is higher than the rivaroxaban group. Stroke or systemic embolism occurred in 188 patients in the rivaroxaban group and in 241 patients in the warfarin group (Hazard ratio, 0.79; 95% CI, 0.66 to 0.96; P<0.001).  -Major and clinically relevant nonmajor bleeding are slightly higher in rivaroxaban group, with 1475 patients in the rivaroxaban and in 1449 patients in the warfarin group (HR, 1.03; 95% CI, 0.96 to 1.11; P = 0.44). In addition, GI bleeding are more common in rivaroxaban group with P<0.001.  -For rivaroxaban group, risks of MI are lower (HR, 0.81; 95% CI, 0.63 to 1.06; P = 0.12); mortality rate is lower (HR, 0.85; 95% CI, 0.70 to 1.02; P=0.07); rates of intracranial hemorrhage  are significantly lower (HR, 0.67; 95% CI, 0.47 to 0.93; P = 0.02). | -In this RCT study, about 60% of subjects are male; it does not specify any race either  -In this study, 23.7% patients in rivaroxaban group and 22.2% patients in warfarin group stop therapy, and the study does not specify the reasons of withdraw, for example, any adverse effects lead to withdraw |

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| Norby FL, Bengtson LGS, Lutsey PL, Chen LY, MacLehose RF, Chamberlain AM5, Rapson I, Alonso A. (2017) | Retrospective cohort | There are 3 comparisons: 32,495 new rivaroxaban users matched to 45,496 warfarin only users; 11,845 switchers to rivaroxaban matched to  43,904 warfarin users; and 16,957 new rivaroxaban  users matched to 16,957 new dabigatran users | Main outcome:  - Assess ischemic stroke  - intracranial bleeding  -MI  -Gastrointestinal bleeding  Control outcomes  -Hip/pelvic fracture  -Breast/prostate cancer  -Asthma | -Compared to warfarin, the reduction in stroke risk among new rivaroxaban users was larger in women compared to men (HR (95% CI) = 0.61 (0.46,  0.81) vs. 0.90 (0.70, 1.17); p for interaction = 0.02)  -Rivaroxaban initiation was associated with increased risk of GI bleeding in women but not in men (HR: 1.24 vs. 0.95, respectively; p for interaction = 0.02). New users of rivaroxaban had lower risk of hip/pelvic fractures  -Patients who switched to rivaroxaban from warfarin had a significantly higher rate of GI bleeding compared to warfarin-only users, HR (95% CI) = 1.55 (1.32–1.83). There was no significant difference in the rate of ischemic stroke, intracranial bleeding, or MI in switchers; switchers had a lower rate of hip/pelvic fractures | -For the participants, about 65% are male. Besides age and sex, the study does not inform other demographics information  -The group of switchers are older and had a higher prevalence of comorbidities and the new users are younger and have fewest comorbidities  -This study also compares risks of stroke between male and female. However, with the uneven sex study population, the results are questionable |

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| Amin A, Keshishian A, Trocio J, Dina O, Le H, Rosenblatt L, Liu X, Mardekian J, Zhang Q, Baser O, Vo L. (2017) | Retrospective cohort | 186,132 participants in total, with 52,476 patients on rivaroxaban-warfarin pairs; 20,803 apixaban-warfarin pairs; and 16,731 dabigatran-warfarin pairs | -Stroke, include ischemic and hemorrhagic stroke; and systemic embolism  -Major bleeding | -Rivaroxaban users were associated with a significantly lower risk of stroke and systemic embolism compared to warfarin (HR: 0.72; 95% CI:  0.63, 0.83; p<0.001)  -Rivaroxaban users were associated with a significantly higher risk of major bleeding compared to warfarin (HR: 1.17; 95% CI: 1.10, 1.26; p<0.001)  -Apixaban had lower risk of stroke and systemic embolism (HR 0.40; 95% CI: 0.31, 0.53; p<0.001); Dabigatran had associated with a similar risk  of stroke/SE compared to warfarin (HR: 0.94; 95% CI: 0.74–1.21; p=0.647)  -Apixaban (HR: 0.51; 95% CI: 0.44, 0.58; p<0.001) and dabigatran  (HR: 0.79; 95% CI: 0.69, 0.91; p=0.001) were associated  with a significantly lower risk of major bleeding | -The study lists partial major bleeding events, intracranial, GI, liver, splenic, and ocular hemorrhage. It does not list other bleeding sites, and for the results, they only list for overall major bleeding risks, does not specify intracranial bleeds or GI bleeds. The major bleeding results are not specific in this study  -Information bias: data are selected from Medicare databases, which are subjective to possible claims and billing errors, like missing claims and duplicated claims |

**Conclusion(s):**

Article1 (systemic review) concludes that when compared with warfarin, rivaroxaban was associated with lower risks of stroke, systematic thromboembolism, and ICH; with an increased risk of GI bleeding; and similar risks of major bleeding, any bleeding, and mortality.

Article 2 (RCT study) concludes that, risks of stroke and thromboembolism are higher in the warfarin group compared to rivaroxaban group. However, the risks of major bleeding and clinically relevant nonmajor bleeding are slightly higher in the rivaroxaban group.

Article 3 (retrospective cohort study) concludes that new rivaroxaban users have lower rate of ischemic stroke, intracranial bleeds, and hip/pelvic fractures compared to new warfarin users, but higher risk of increased GI bleeding. Switchers to rivaroxaban have higher risk of GI bleed, no significant difference in rate of ischemic stroke intracranial bleed or MI, and low rate of hip/pelvic fracture compared to warfarin users.

Article 4 (retrospective cohort study) concludes that compared to warfarin, rivaroxaban was associated with significantly lower risk of stroke and systemic embolism, but higher risk of major bleeding.

Overall, all 4 articles have the same conclusions that rivaroxaban is associated with lower risk of stroke and systemic embolism, but increased risk of GI bleeding. However, among the major bleeding events, article 1, 3 and 4 find lower risk of ICH, article 4 finds higher risk of ICH. When deciding which of these findings should be more heavily weighted, the level of evidence and sample sizes should be considered. Article 4 did not list each major bleeding events in the results, which may not count as a specific evidence for increasing risk of ICH.

**Clinical Bottom Line:**

Article 1 is a systemic review, which includes17 studies. 11 studies comparing rivaroxaban versus warfarin. And it is based on large sample size with 897,435 participants. They assess risks of stroke and systemic thromboembolism and acute MI, major bleeding, intracerebral hemorrhage, and GI bleeds by counting the numbers of adverse events, which are most important aspects in using anticoagulants. Article 2 is an RCT, and it compares the efficacy of experimental and control groups in managing Afib patients, rivaroxaban and warfarin. This article is published in 2011, not too recent, but it is conducted at 118 different sites in 45 counties and based on a large sample size with 14,262 patients. Experimental study design is a good standard for evaluating efficacy in clinical research and constitute evidence for medical treatments. Article 3 and article 4 are retrospective cohort studies that exam the efficacy of rivaroxaban and warfarin, although it is not the highest level of evidence, they are based on very large sample sizes, with total participants of 150,697 participants and 186,132 participants respectively; and also published recently, both are from 2017. The exposures (taking rivaroxaban or warfarin) are known, and multiple outcomes, risks of stroke, embolism, MI, and bleeding are examined.

In clinical practice, for outpatient long-term management of Afib, warfarin is the most popular drug to use. Warfarin is effective, but there are some downsides. Patients who are taking warfarin need to be monitored with blood work frequently to make sure the right dose is being administered. There are many potential drug interactions with warfarin that may lead to either an increase or decrease in its blood levels. All the cruciferous vegetables, like foods high in Vitamin K, such as cauliflower, cabbage and broccoli, counteract warfarin, which make dietary requirements for warfarin very important. There is a narrow therapeutic index for warfarin as well. For some patients, they may be very difficult with warfarin dosing to be in the therapeutic range without having increased risks of bleeding. Newer medications are now available as alternative to warfarin. Direct factor Xa inhibitors are most common alternatives used. They allow standard doses that may change based on an individual’s baseline kidney function. From patient’s perspective, these medications do not require any blood monitoring, which are more convenient. There also no concerning food interactions with these new medications, only limited drug interactions that need to be considered while prescribing. As with all treatment options, they are always some disadvantages. As a newer medication, rivaroxaban, is more expensive than warfarin. Rivaroxaban is not genetic, and often not completely covered by insurance plans. After researching, all articles conclude that in Afib patients, rivaroxaban is associated with lower risks of stroke/systemic embolism compared to warfarin. Regarding safety issues, all articles find higher GI bleeding rates with rivaroxaban. In addition, for intracranial hemorrhage, even though one retrospective study concludes higher risk of rivaroxaban, systemic review, RCT, and other retrospective study all conclude lower risk of ICH.

In conclusion, the clinical recommendation is based on the evidence found in the systemic, RCT and retrospective cohort, in adult patients with Afib, compared to warfarin, rivaroxaban may be better in managing Afib with less stroke/systemic embolism events. When discussing the side effects of rivaroxaban to the patients, we would inform them about increased GI bleeding risk, especially for patients with previous GI bleeds and with patient who are at high risk of GI bleeds, rivaroxaban should be used with caution.