



Anticoagulation in Non-valvular ²⁶ AFib

	COUMADIN	PRADAXA	XARELTO	ELIQUIS	LIXIANA SAVAYSA USA
	Warfarin	Dabigatran _{150mg}	Rivaroxaban	Apixaban	Edoxaban
Stroke/ Systemic Embolism	✓ ¹	✓✓? ²	✓? ³	✓✓? ⁴	✓✓? ⁵
ICH	X	✓ ⁶	✓ ⁷	✓ ⁸	✓ ⁹
Major GI Bleed	✓	X ¹⁰	X ¹¹	✓ ¹²	X ¹³
Major Bleed	✓	✓ ¹⁴	✓ ¹⁵	✓✓ ¹⁶	✓✓ ¹⁷
Manage Bleed	✓ ¹⁴	✓ ¹⁸	X? ¹⁸	X? ¹⁸	X? ¹⁸
MI	✓	X? ¹⁹	-?	-?	-?
DC Rate / Dyspepsia	-	X ²⁰ /↑GI	-	✓	-
Renal function (CrCl)	✓✓ ²¹	CI <30mL/min	Avoid <15mL/min	Avoid <15mL/min Trial CI <25mL/min	Avoid <30mL/min & >95mL/min
Cost/month	✓✓ ²² \$15	X (more than \$105, except generic dabigatran only \$85)			
Half life Pros/Cons ²³	Dosing frequency, impact of missed dose, bleed management				
Monitoring ²⁴	Need for/ability to monitor INR has pros & cons.				
Certainty ^{vs} Uncertainty ²⁵ RCTs	✓✓	+/- RE-LY	+/- ROCKET-AF	+/- ARISTOTLE	+/- ENGAGE-AF

An Advantage ✓✓	✓	+/-	X	A Disadvantage X X
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Anticoagulation/Atrial Fibrillation (AFib): Notes on Outcome Comparison

Warf vs DOACs (NOACs): pros & cons for each - Loren Regier, Zack Dumont - www.RxFiles.ca – Revised Apr 2020

Note, the RE-LY trial data for Canada found warfarin had a time in therapeutic range (TTR) >70%.

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| <ol style="list-style-type: none"> 1) Stroke/Embolism: absolute differences minimal when INR control with warfarin reasonable (TTR=>65%). 2) Stroke/Embolism: Dabi 150mg BID vs Warf; NNT=88/~2yr; ITT (no difference with 110mg BID dose, but less bleeding); open label RCT. (Study pop: renal fx 30+, adherence likely better than normal conditions, etc.) 3) Stroke/Embolism: Riva 20mg daily vs Warf; non-inferiority trial design (ITT analysis favoured Riva but did not achieve superiority); double-blind RCT. (Study pop: limitations similar to RE-LY.) 4) Stroke/Embolism: Apix 5mg BID vs Warf; NNT=167/~2yrs; ITT; double-blind RCT. Also ↓ death NNT=132/~2yr. (Study pop: limitations similar to RE-LY.) 5) Stroke/Embolism: Edox 60mg daily vs Warf was noninferior (ITT analysis); superior NNT=141/~2.8yr (mITT analysis) (no difference with 30mg daily dose, but less bleeding); open label RCT. (Study pop: limitations similar to RE-LY) 6) ICH: Dabi vs Warf; NNT=116/~2yr 7) ICH: Riva vs Warf; NNT=250/~2yr 8) ICH: Apix vs Warf; NNT=128/~2yr 9) ICH: Edox 60mg vs Warf; NNT=99/~2.8yr; 30mg vs Warf; NNT=77/~2.8yr 10) GI Bleed: Dabi vs Warf; NNH=100/~2yr 11) GI Bleed: Riva vs Warf; NNH=100/~2yrs 12) GI Bleed: Apix vs Warf; no difference 13) GI Bleed: Edox 60mg vs Warf; NNH=166/~2.8yr; 30mg vs Warf; NNT=115/~2.8yr 14) Major Bleed: Dabi 150mg BID vs Warfarin; no difference; however 110mg BID had reduced major bleeding (NNT=77/~2yr) but also less benefit. 15) Major Bleed: Riva vs Warf; no difference 16) Major Bleed: Apix vs Warf; NNT=67/~2yr 17) Major Bleed: Edox 60mg daily vs Warf; NNT=67/~2.8yr; 30mg daily; NNT=26/~2.8yr (but also less benefit). | <ol style="list-style-type: none"> 18) Manage Bleeding: Warfarin - real world experience, & options include PCC & Vitamin K for reversal. New agents have less experience. Dabi has an antidote (Idarucizumab PRAXBIND CDN'16, FDA'15). Factor Xa inhibitors also have an antidote (Andexanet alfa ANDEXXA FDA'18). Shorter half life of new agents means less time until anti-coagulation status returns to normal. Life-threatening/ fatal bleed was less in dabi / riva trials. However, ISMP Jan 2013 found that bleeds with Dabi 5x more fatal than bleeds with warfarin. Peri-procedural: less experience in managing DOACs. 19) MI Risk: Dabi vs Warf; initial ↑ risk of borderline significance (p=0.048); reanalysis slightly different & non-significant (p=0.06 both doses). {↑ rates of bleeding & thrombotic AE in AFib with mechanical valves RE-ALIGN} Concerns. Controversial. [Warf considered protective.] 20) Discontinuation rates vs Warf: lower with Apix (NNT=45/~2yrs); higher with Dabi (NNH=25/~2yr); also more dyspepsia with Dabi (NNH=18/2yr). 21) All new agents lack study & experience in patients with decreased renal Fx. Dabi is contraindicated (CI) if CrCl <30ml/min. Warfarin can be used. Since AFib patients often older, impaired renal Fx an issue. Edoxaban & CrCl >95mL/min: ↑ risk of ischemic stroke^{FDA}, therefore avoid. 22) Economic review found new anticoagulants more costly than warfarin even after consideration for cost of INR monitoring was built in. However, “soft” indirect costs (e.g. time/travel to the patient) not included & may be assessed individually. Direct cost/month: Warf ~\$15, Dabi \$120 (but generic g is \$85 *ø), Riva \$105, Apix \$118. Edoxaban \$104, but is the newest in Canada. 23) Half life of new agents is shorter. “Cons” of this are that Dabi & Apix require BID dose; poor compliance (missed doses) will result in earlier loss of anticoagulation status; “Pros” are earlier achievement of anticoagulation after starting & return to normal after holding if over-coagulated. 24) INR “Con” -inconvenience factor; “Pro” -ability to assess anticoagulation status balance risk of stroke vs bleed. ? Dabi level. 25) Warfarin has 60yrs “real world” experience; new agents have about 10yrs & in limited populations. This factor will gradually change over the next few yrs. 26) If Valvular AFib: Warf OK, DOACs (NOACs) not indicated; Dabi CI |
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Note: Rate of ICH in AFib less in Canada than in trials. Gomes T, CMAJ 2012. Thus significance of this would be less in CDN context (ie. NNT would be much higher).

(This editorial synthesis based on interpretation of data from RCTs ([RELY](#), [ROCKET-AF](#), [ARISTOTLE](#), [ENGAGE-AF](#)), CADTH reports, product monographs & clinical consultation. Only direct comparisons of individual DOACs (NOACs) with warfarin have been studied. Trials designed for non-inferiority, with option for superiority analysis. Comparisons between DOACs (NOACs) have the inherent limitations of indirect comparisons. However, indirect comparisons are often required when decisions need to be made & direct comparisons are not available, nor likely to be done in the near future.)