

Drug / BRAND	Vitamin K Antagonist	DOACs			
	Warfarin COUMADIN, g	Thrombin Inhibitor	Factor Xa Inhibitors		
		Dabigatran PRADAXA, g	Rivaroxaban XARELTO	Apixaban ELIQUIS	Edoxaban LIXIANA; SAVAYSA
Landmark AF RCTs Comparing to Warfarin non-inferiority analysis; superiority if appropriate	Active comparator; efficacy / safety demonstrated in multiple RCTs (e.g. ACTIVE-W) & meta-analyses.	RE-LY ¹ N=18,113 randomized 1:1:1 dabi 110mg or 150mg BID vs warf (TTR 64%) ITT; open-label RCT Note: 75mg dose not studied	ROCKET-AF ² N=14,264 riva 20mg* daily vs warf (TTR 55%) ITT; double-blind, RCT *20% (n=1474) on riva had CrCl 30-49mL/min → 15mg daily	ARISTOTLE ³ N=18,201 apix 5mg* BID vs warf (TTR 62%) ITT; double-blind RCT *4.7% (n=428) on apix had ≥2: ≥80yr, ≤60kg, SCr ≥133 umol/L → 2.5mg BID	ENGAGE-AF ⁴ N=21,105 randomized 1:1:1 edox 30mg* or 60mg daily vs warf (TTR 65%) ITT; double-blind RCT *edox 30mg if CrCl 30-50mL/min, or ≤60kg, or on verapamil or quinidine
↓ Stroke / Systemic Embolism	✓ absolute differences minimal when TTR≥65%	✓✓? NNT=88/2yrs 2.2% dabi 150mg vs 3.4% warf; dabi 110mg vs warf NS	✓? riva vs warf NS only per-protocol met non-inferiority, not ITT	✓✓? NNT=167/1.8yrs 2.3% apix vs 2.9% warf	✓✓? NNT=141/2.8yrs 2.6% edox 60mg vs 3.3% warf ITT non-infer, mITT superior; edox 30mg vs warf NS
Intracranial Hemorrhage	✗ low incidence but ↑ rates in RCTs vs DOACs	✓ ↓ rate vs warfarin NNT=116/2yrs 0.6% dabi 150mg vs 1.5% warf	✓ ↓ rate vs warfarin NNT=250/1.6yrs 0.8% riva vs 1.2% warf	✓ ↓ rate vs warfarin NNT=128/1.8yrs 0.6% apix vs 1.4% warf	✓ ↓ rate vs warfarin NNT=99/2.8yrs 0.9% edox 60mg vs 1.9% warf
Major GI Bleed	✓	✗ NNH=100/2yrs 3.1% dabi 150mg vs 2.1% warf; dabi 110mg vs warf NNT=77 / 2yrs (but less benefit)	✗ NNH=100/1.6yrs 3.2% riva vs 2.2% warf	✓ no difference vs warfarin 1.2% apix vs 1.3% warf	✗ NNH=166/2.8yrs 3.3% edox 60mg vs 2.7% warf; edox 30mg vs warf NNT=67 / 2.8yrs (but less benefit)
Major Bleed	✓	✓ no difference vs warfarin 6.6% dabi 150mg vs 7% warf	✓ no difference vs warfarin 5.6% riva vs 5.4% warf	✓✓ ↓ bleeds vs warfarin NNT=67/1.8yrs 3.6% apix vs 5.1% warf	✓✓ ↓ bleeds vs warfarin NNT=67/2.8yrs 6% edox 60mg vs 7.5% warf
Bleed Management	✓ Vitamin K, PCC	✓ idarucizumab PRAXBIND	✗ FDA'18 antidote: andexanet alfa ANDEXXA		
Discontinuation Rates	–	✗ NNH=25/2yrs 21% dabi vs 17% warf	– no difference vs warfarin	✓ NNT=45/1.8yrs 25% apix vs 28% warf	– no difference vs warfarin
Renal function (CrCl <30mL/min)	RCTs ongoing. Observational data conflicting, benefit may not outweigh harm	✗ Contraindicated <30mL/min	very limited data avoid <15mL/min	very limited data avoid <15mL/min	very limited data avoid <15mL/min
Half-life Pros/Cons	Half-life of DOACs is shorter than warf. Con: nonadherence (missed doses) will result in earlier loss of anticoagulation status vs warfarin. Pro: anticoagulation is achieved faster after starting, & when managing bleeds coagulation status returns to normal faster after stopping.				
Other	INR monitoring ✓ tailor dose re: stroke vs bleed risk ✗ ? inconvenient	✗ ? ↑ MI see RxFiles Q&A ✗ ↑ Dyspepsia NNH=18/2yrs vs warf		↓ All-Cause Mortality NNT=132/1.8yrs 6.6% apix vs 7.4% warf	
Drug Interactions	Warfarin has ↑↑ drug interactions. However, (1) very few interactions with warfarin are absolutely contraindicated - warfarin dose can be adjusted in response to INR; (2) management on DOACs interactions (esp. 3A4 inducers/inhibitors, P-gp) has expanded over the years.				
Cost per month	✓✓ \$15	✗ (\$98 g ✗ ▼) - \$120	✗ \$105	✓ \$37 g (brand=\$118)	✗ \$107
Indirect costs with warfarin include INR monitoring and time/travel to the patient.					

✓✓ An Advantage
✓
Neutral
✗
✗✗ A Disadvantage
? Unknown/Ongoing

Comments

- There is a positive correlation between warfarin's efficacy / safety and its **Time in Therapeutic Range (TTR)**. Consider local context.
- **Renal function** (also see row in table): All OAC have limited RCT data with decreased renal function (CrCl <30mL/min). Warfarin: observational data for safety & efficacy is conflicting. Dabigatran is contraindicated (CI) if CrCl <30ml/min; 80-85% renally cleared. Apixaban & rivaroxaban have limited RCT data down to CrCl 15mL/min. Apixaban & warfarin: ongoing studies in ESRD; **RENAL-AF**: apixaban vs warfarin n=154 (planned for n=760) hemodialysis patients ended early; risk of bleeding & benefit similar. Edoxaban & CrCl >95mL/min: ↑ risk of ischemic stroke; FDA recommends to avoid, but Health Canada does not. OAC not routinely recommended in Stage 5 CKD (eGFR <15mL/min). [CCS AF WR, LQ](#)
- **Valvular atrial fibrillation** (e.g. mechanical valves): warfarin is the preferred agent; dabigatran contraindicated (↑ rates of bleeding & thrombotic events in **RE-ALIGN** trial).
- **Canadian differences**: international trials with few Canadian patients; in general, most Canadian sites would be expected to have better TTR with warfarin than average,⁸ & less absolute risk of intracranial hemorrhage.⁷ These factors potentially limit DOAC advantages.
- **Importance of dose**: efficacy & bleed risk are both dependent on dose; e.g. dabigatran 110mg BID & edoxaban 30mg daily had less bleeding, but also reduced efficacy, vs dabigatran 150mg BID¹ & edoxaban 60mg daily⁴, respectively
- Life-threatening/ fatal bleed was less in dabi / riva trials.

Trials were designed as non-inferiority, with option for superiority analysis. Only direct comparisons of individual DOACs with warfarin have been studied; comparisons above are indirect & have inherent limitations; however, they are the best data available.

apix=apixaban dabi=dabigatran edox=edoxaban DOAC=direct oral anticoagulant → apix, dabi, edox, or riva PCC=prothrombin complex concentrate riva=rivaroxaban thrombin=aka Factor IIa warf=warfarin wt=weight

Anticoagulation Colour Comparison Chart

This editorial synthesis was based on interpretation of data from RCTs ([RELY](#), [ROCKET-AF](#), [ARISTOTLE](#), ENGAGE-AF), CADTH reports, product monographs & clinical consultation.

Acknowledgements: Written by Loren Regier and Zack Dumont; reformatted in 2021 by Alex Crawley. Ongoing edits provided by Lynette Kosar. Thanks to our reviewers: Lynette Kosar, Brent Jensen.

Disclosures: No conflicts of interest are reported by the authors.

Disclaimer: RxFiles Academic Detailing is part of the College of Pharmacy and Nutrition at the University of Saskatchewan. The content of this work represents the research, experience, and opinions of the authors and not those of the University of Saskatchewan. Neither the authors nor the University of Saskatchewan nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the materials will imply acknowledgment of this disclaimer and release any responsibility of the University of Saskatchewan, its employees, servants, or agents. Readers are encouraged to confirm the information contained herein with other sources.

Apixaban	22
Atrial Fibrillation	22
COUMADIN	22
Dabigatran	22
DOACs	22
Edoxaban	22
ELIQUIS	22
LIXIANA	22
PRADAXA	22
Rivaroxaban	22
Warfarin	22
XARELTO	22
Anticoagulant	22

References:

1. **RE-LY.** Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S. Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine.* 2009 Sep 17;361(12):1139-51.
2. **ROCKET-AF.** Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New England Journal of Medicine.* 2011 Sep 8;365(10):883-91.
3. **ARISTOTLE.** Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC. Apixaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine.* 2011 Sep 15;365(11):981-92.
4. **ENGAGE-AF.** Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W. Edoxaban versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine.* 2013 Nov 28;369(22):2093-104.
5. Jones M, McEwan P, Morgan CL, Peters JR, Goodfellow J, Currie CJ. Evaluation of the pattern of treatment, level of anticoagulation control, and outcome of treatment with warfarin in patients with non-valvar atrial fibrillation: a record linkage study in a large British population. *Heart.* 2005;91(4):472-477. doi:10.1136/hrt.2004.042465
6. Wells G, Coyle D, Cameron C, Steiner S, Coyle K, Kelly S, Tang A, Healey J, Hsieh SC, van Berkum J. Safety, effectiveness, and cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation.
7. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Helling C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *Cmaj.* 2013 Feb 5;185(2):E121-7.
8. Gómez-Outes A, Terleira-Fernández AI, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Direct oral anticoagulants for stroke prevention in patients with atrial fibrillation: meta-analysis by geographic region with a focus on European patients. *British journal of clinical pharmacology.* 2016 Sep;82(3):633-44. See Appendix S4: North America had among the highest rates of TTR among regions.
9. Trusler M. Well-managed warfarin is superior to NOACs. *Canadian Family Physician.* 2015 Jan 1;61(1):23-4.