

Comparing Non-Vitamin K Antagonist Oral Anticoagulants (NOACs) to Different Coumadins: The Win-Win Scenarios

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In addition to warfarin, the family of vitamin K antagonist (VKA) oral anticoagulants includes acenocoumarol, phenprocoumon, phenindione and fluindione.¹ These drugs alter the functionality of vitamin K-dependent coagulation factors II, VII, IX and X and anticoagulant proteins C, S and Z by inhibiting the vitamin K epoxide reductase complex subunit 1 (VKORC1), while non-vitamin K antagonist oral anticoagulants (NOACs) directly inhibit a single coagulation factor (i.e. dabigatran inhibits factor II, and rivaroxaban, apixaban and edoxaban inhibit activated factor X).² All NOACs exhibit a stable, dose-related anticoagulant effect with no food–drug and less drug–drug interactions than VKAs and are used in fixed doses without routine laboratory monitoring of anticoagulant effect or food restrictions.^{1,2} In a meta-analysis of the four landmark randomized clinical trials (RCTs) of NOACs versus warfarin in patients with atrial fibrillation (AF), NOACs were associated with a significant 19% relative risk reduction (RRR) in any stroke or systemic embolism (SSE), a significant 10% RRR in all-cause mortality and a 14% RRR in major bleeding ($p = 0.06$).³ Importantly, all NOACs consistently reduced haemorrhagic stroke or any intracranial bleeding for $> 50\%$ (both $p < 0.0001$).³

Owing to these advantages, international AF guidelines now recommend NOACs as the first-choice treatment or a viable alternative to VKAs in patients with AF at increased risk of stroke (excluding those with a mechanical heart valve or rheumatic mitral stenosis).^{4,5} With increasing use of NOACs in clinical practice,⁶ the real-world evidence (RWE) of their effectiveness and safety relative to warfarin rapidly accumulates,^{7–10} broadly confirming the results of NOAC landmark trials (see ►Table 1).¹¹

Although warfarin is the most commonly used VKA worldwide, in some countries other VKAs are more often prescribed (e.g. acenocoumarol in Spain or Germany, phenprocoumon in Germany, Austria, Denmark, Switzerland, the Netherlands and

Brazil, and fluindione in France),¹² and there are clinically relevant differences among these drugs. For example, some VKAs have a short half-life of ≤ 12 hours (i.e. phenindione 5–10 hours, acenocoumarol 8–11 hours), while others have an intermediate (warfarin 40 hours [range, 20–60], fluindione 31 hours) or a long half-life (phenprocoumon 110–130 hours). The effects of CYP2C9 polymorphisms on the stability of anticoagulant effect are less evident with phenprocoumon than warfarin or acenocoumarol, which results in a more stable anticoagulant effect of phenprocoumon, requiring less frequent laboratory monitoring and dose adjustments.¹³

How do NOACs compare with these VKAs? In this issue of *Thrombosis Haemostasis*, Hohnloser et al¹⁴ reported the first retrospective observational comparison of the effectiveness and safety of dabigatran, rivaroxaban and apixaban versus phenprocoumon in a large anticoagulant-naïve AF cohort ($n = 61,205$), and their findings were broadly consistent with results of the pivotal RCTs³ and RWE¹¹ comparing NOACs versus warfarin (see ►Table 1). Similarly, a small propensity score-matched retrospective study of VKA-naïve AF patients ($n = 766$) starting dabigatran or acenocoumarol¹⁵ and a nationwide retrospective matched-cohort study of VKA-experienced AF patients ($n = 17,410$) taking fluindione or switching to dabigatran or rivaroxaban¹⁶ provided a reassuring RWE on the NOACs performance relative to acenocoumarol and fluindione, respectively (see ►Table 1).

The study of Hohnloser et al¹⁴ also provided an insight into the effectiveness and safety of reduced NOACs doses compared with phenprocoumon. Interestingly, the use of dabigatran 110 mg or rivaroxaban 15 mg in their study was close to that in the RE-LY (51% vs. 49.7%)¹⁷ or ROCKET AF (28% vs. 20.7%)¹⁸ trial, while the use of apixaban 2.5 mg was much higher than in the ARISTOTLE trial (37% vs. 4.5%).¹⁹ Since reduced NOACs doses were preferentially prescribed to older and sicker patients who were likely good candidates for

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Table 1 The effectiveness and safety of NOACs compared with various VKAs in the real-world observational studies

Outcome	Study setting	Dabigatran ^a HR (95% CI)	Rivaroxaban HR (95% CI)	Apixaban HR (95% CI)	Comparator
Stroke or systemic embolism	RCT ^b	0.66 (0.53–0.82) 0.91 (0.74–1.11)	0.88 (0.75–1.03)	0.79 (0.66–0.95)	Warfarin
	RWE	0.93 (0.77–1.14)	0.87 (0.71–1.07)	0.67 (0.46–0.98)	Warfarin ¹¹
		0.48 (0.32–0.72) 0.89 (0.70–1.13)	0.89 (0.77–1.02)	0.77 (0.64–0.93)	Phenprocoumon ¹⁴
		0.73 (0.21–2.55)	NR	NR	Acenocoumarol ^{15,c}
		1.10 (0.70–1.73)	0.75 (0.39–1.45)	NR	Fluindione ^{16,d}
Ischaemic stroke	RCT ^b	0.76 (0.60–0.98) 1.11 (0.89–1.40)	0.94 (0.75–1.17)	0.92 (0.74–1.13)	Warfarin
	RWE	0.96 (0.80–1.16)	0.89 (0.76–1.04)	0.95 (0.75–1.19)	Warfarin ¹¹
		0.52 (0.32–0.83) 1.05 (0.80–1.38)	0.91 (0.77–1.07)	0.82 (0.66–1.03)	Phenprocoumon ¹⁴
All-cause death	RCT ^b	0.88 (0.77–1.00) 0.91 (0.80–1.03)	0.85 (0.70–1.02)	0.89 (0.80–0.998)	Warfarin
	RWE	0.63 (0.52–0.79)	0.67 (0.35–1.30)	0.65 (0.56–0.75)	Warfarin ¹¹
		0.92 (0.84–1.01) 1.17 (1.07–1.27)	1.12 (1.04–1.21)	1.05 (0.94–1.17)	Phenprocoumon ¹⁴
Major bleeding	RCT ^b	0.93 (0.81–1.07) 0.80 (0.69–0.93)	1.04 (0.90–1.20)	0.69 (0.60–0.80)	Warfarin
	RWE	0.83 (0.65–1.05)	1.00 (0.92–1.08)	0.55 (0.48–0.63)	Warfarin ¹¹
		0.47 (0.30–0.74) 0.72 (0.55–0.94)	1.09 (0.96–1.23)	0.58 (0.48–0.71)	Phenprocoumon ¹⁴
		0.44 (0.21–0.93)	NR	NR	Acenocoumarol ^{15,c}
		0.79 (0.57–1.09)	1.11 (0.74–1.66)	NR	Fluindione ^{16,d}
ICH	RCT ^b	0.40 (0.27–0.60) 0.31 (0.20–0.47)	0.67 (0.47–0.93)	0.42 (0.30–0.58)	Warfarin
	RWE	0.42 (0.37–0.49)	0.64 (0.47–0.86)	0.45 (0.31–0.63)	Warfarin ¹¹
		0.28 (0.10–0.77) 0.66 (0.39–1.12)	0.74 (0.57–0.97)	0.39 (0.25–0.60)	Phenprocoumon ¹⁴
GI bleeding	RCT ^b	1.50 (1.19–1.89) 1.10 (0.86–1.41)	1.66 (1.34–2.05)	0.89 (0.70–1.15)	Warfarin
	RWE	1.20 (1.06–1.36)	1.24 (1.08–1.41)	0.63 (0.42–0.95)	Warfarin ¹¹
		1.26 (1.11–1.42) 1.26 (1.10–1.45)	1.35 (1.20–1.51)	0.71 (0.59–0.85)	Phenprocoumon ¹⁴

Abbreviations: AF, atrial fibrillation; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; RCT, randomized clinical trial; RWE, real-world evidence; VKA, vitamin K antagonist.

^aWhere available, data are given for dabigatran 150 mg twice a day in the upper row, and dabigatran 110 mg twice a day in the lower row.

^bThe efficacy/safety of each NOAC in the respective landmark RCT.

^cA small retrospective observational cohort of anticoagulant-naïve AF patients ($n = 766$). Patients taking dabigatran or acenocoumarol were paired using propensity score matching.

^dA nationwide, retrospective, matched-cohort observational study of VKA-experienced patients ($n = 17,410$), with 10,705 patients non-switching to a NOAC (9,688/10,705 [90%] on fluindione).

reduced NOAC doses, that could perhaps explain the comparable effectiveness and safety of reduced and standard NOACs doses relative to phenprocoumon.¹⁴ In general, the choice of NOACs dose should be determined by the patient's age, renal function and body weight or concomitant treatment with interacting drugs. Unfortunately, data on renal function were not available in the study of Hohnloser et al, and the appropriateness of NOAC dosing could not be ascertained. However,

NOACs dosing inconsistent with drug labelling has been associated with worse outcomes compared with proper dosing.²⁰

Although the observations reported by Hohnloser et al were confirmed in two pre-specified sensitivity analyses, reflecting their robustness to the various model assumptions,¹⁴ the RWE gathered from post-approval observational studies should always be interpreted with caution, taking into account their numerous limitations arising from the

study design, selection bias, cohort size, residual confounding, follow-up duration, study endpoint(s) definition and event adjudication, data completeness, statistical methods used for data analyses, etc.²¹ Nevertheless, the increasing RWE on the effectiveness and safety of NOACs in comparison to different VKAs, with reported risk ratios being very similar to those in the landmark RCTs, is generally reassuring and suggest that NOACs are performing comparably well in clinical practice as in the respective RCTs. More data are needed to optimize the use of NOACs in 'special' AF populations such as, for example, the elderly, patients on chronic dialysis or those with active malignancy.

Conflicts of interest

None declared.

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