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Safety evidence for NOACs in AF

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Contributing Specialist

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Abbreviations used in this review
AF = atrial fibrillation
GI = gastrointestinal
HR = hazard ratio
NOAC = non-vitamin K antagonist oral anticoagulant
RCT = randomised controlled trial
RR = relative risk
VKA = vitamin K antagonist

ABOUT RESEARCH REVIEW

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Publication overview

Real-world evidence that supports RCT data is an important tool in the arsenal of evidence for the therapeutic management of any condition. Head-to-head RCT data comparing NOACs (non-vitamin K antagonist oral anticoagulants also called 'new' or 'novel' oral anticoagulants, or direct oral anticoagulants) with each other are lacking. This review summarises and discusses the real-world comparative effectiveness of NOACs and warfarin for preventing stroke, bleeding and mortality in patients with non-valvular AF (atrial fibrillation), as recently described by multiple real-world evidence publications such as Graham et al. in Am J Med.[1] Supporting evidence from RCTs is also summarised. The NOACs of interest for this summary are those that are currently funded in NZ, namely dabigatran and rivaroxaban. Among patients with non-valvular AF with similar baseline characteristics, standard-dose NOACs were found to have a more favourable benefit-to-harm profile than warfarin, and among NOACs, dabigatran appears to have a more favourable benefit-to-harm profile. This article was supported by an educational grant from Boehringer Ingelheim.

Introduction

AF is the most common sustained cardiac arrhythmia, affecting ~2% of the general population in Western countries, with a strong relationship between AF prevalence and age.[2–4] AF is also associated with a ~5-fold increased risk of stroke. The overall prevalence of AF in NZ is similar to other countries, but Māori are more likely to be diagnosed with AF. Moreover, both Māori and Pacific people are diagnosed with AF ~10 years earlier than those of other ethnicities in NZ, and their associated risk of stroke is elevated at a younger age. Stroke due to AF is associated with higher mortality and an increased incidence of recurrent stroke compared with non-AF-associated stroke.[3,4]

This review will summarise data from a number of studies showing that the use of oral anticoagulants leads to a reduction in the risk of AF-associated stroke. Both European and US AF guidelines now recommend the use of NOACs over VKAs for the prevention of stroke in eligible patients with non-valvular AF.[5,6] In NZ, use of oral anticoagulation is restricted to the VKA warfarin and two funded NOACs, namely dabigatran and rivaroxaban. While warfarin and NOACs reduce the risk of stroke, NOACs do not have some of the same clinical limitations as warfarin.

RCT evidence supports use of NOACs for preventing stroke in AF

The pivotal ROCKET-AF and RE-LY RCTs compared the two NOACs funded in NZ, namely oral rivaroxaban (15mg or 20mg once daily) and oral dabigatran (110mg or 150mg twice daily), respectively, with dose-adjusted warfarin (target INR 2.0–3.0).[8,9] These trials studied the prevention of stroke and systemic embolism in patients with non-valvular AF who were at risk for stroke.

RE-LY[7]

In RE-LY, dabigatran 110mg and dabigatran 150mg were noninferior to warfarin for reducing the primary endpoint of stroke or systemic embolism (1.53% and 1.11%, respectively, vs. 1.69% per year [p<0.001 for noninferiority]), with the 150mg dose even proving to be superior to warfarin (RR 0.65 [0.52, 0.81; p<0.001]; Table 1).[7,9] Major or minor bleeding rates were lower with dabigatran, 110mg and 150mg, compared with warfarin (respective RRs 0.78 [0.74, 0.83] and 0.91 [0.86, 0.97]), but the risk with dabigatran 150mg was greater than with the 110mg dose (1.16 [1.09, 1.23]). In terms of major bleeding only, dabigatran 110mg was associated with a lower risk than warfarin (RR 0.80 [95% CI 0.70, 0.93]), while no significant difference was seen between the dabigatran 150mg vs. 110mg dose (1.16 [1.00, 1.34]) or between dabigatran 150mg and warfarin (0.93 [0.81, 1.07]).

Table 1. Efficacy and safety outcomes from the RE-LY trial of dabigatran versus warfarin for preventing stroke/systemic embolism in at-risk patients with non-valvular AF[7,9]

Endpoint	Percentage of participants per year			RRs (95% CI)	
	Dabigatran 110mg	Dabigatran 150mg	Warfarin	Dabigatran 110mg versus warfarin	Dabigatran 150mg versus warfarin
Stroke or systemic embolism (primary efficacy outcome)	1.53%	1.11%	1.69%	0.90 (0.74, 1.10; p<0.001*)	0.65 (0.52, 0.81; p<0.001*)
Ischaemic or unspecified stroke	1.34%	0.92%	1.20%	1.11 (0.89, 1.40; p=0.35)	0.76 (0.60, 0.98; p=0.03)
Major haemorrhage (primary safety outcome)	2.71%	3.11%	3.36%	0.80 (0.70, 0.93; p=0.003)	0.93 (0.81, 1.07; p=0.31)
Life-threatening haemorrhage	1.22%	1.45%	1.80%	0.68 (0.55, 0.83; p<0.001)	0.81 (0.66, 0.99; p=0.04)

*for noninferiority

ROCKET-AF[8]

In the ROCKET-AF trial, rivaroxaban was also found to be noninferior to warfarin for the proportions of participants experiencing ischaemic or haemorrhagic stroke or systemic embolism (composite primary efficacy endpoint) in both per-protocol and intent-to-treat analyses (1.7% vs. 2.2%; HR 0.79 [95% CI 0.66, 0.96] and 2.1% vs. 2.4%; 0.88 [0.75, 1.03], respectively; p<0.001 for noninferiority in both analyses).[8] The combined rate of major and nonmajor bleeding was similar between rivaroxaban and warfarin recipients (14.9% vs. 14.5% [p=0.44]).

RCT evidence lacking for dabigatran vs. rivaroxaban

Unfortunately, there have been no RCTs and only a few observational studies comparing the safety and efficacy of dabigatran with rivaroxaban. Therefore, evidence gleaned from real-world use may be useful for tailoring the use of oral anticoagulants for stroke prevention in patients with non-valvular AF. A number of real-world studies have been undertaken comparing dabigatran with rivaroxaban for preventing stroke in patients with non-valvular AF. The findings from these real-world studies have consistently reported no significant differences in efficacy between these two NOACs for reducing stroke and systemic embolism, and significantly lower bleeding risks with dabigatran than with rivaroxaban.[1,10–19]

The largest real-world study comparing dabigatran with rivaroxaban for preventing stroke in patients with non-valvular AF was commissioned by the US FDA, through an interagency agreement with the Centers for Medicare & Medicaid Services.[1] This observational study in older US Medicare beneficiaries with AF compared standard doses of each NOAC with warfarin and with each other. A number of outcomes were studied, including hospitalisation for thromboembolic stroke, intracranial haemorrhage, major extracranial bleeding and all-cause mortality.

Real-world study design (Graham *et al.*)

US Medicare beneficiaries aged ≥65 years with an inpatient or outpatient diagnosis of AF or atrial flutter (according to ICD-9 coding) who had started standard-dose dabigatran (150mg twice daily), rivaroxaban (20mg once daily), apixaban (5mg twice daily; not funded in NZ) or warfarin between October 2010 (when the US FDA approved dabigatran) and September 2015 were included in this study.[1] The study population was restricted to all eligible NOAC and warfarin users with very similar characteristics using 1:1 propensity score matching.

The patients were followed until Medicare disenrollment, anticoagulant interruption of >3 days, another anticoagulant was dispensed, kidney transplantation or initiation of dialysis, admission to a skilled nursing facility or nursing home, transfer to hospice care, end of the study period or the occurrence of a study outcome.[1]

Study outcomes

Outcomes evaluated were hospitalisation for thromboembolic stroke, intracranial haemorrhage, major extracranial bleeding (hospitalised for bleeding with the requirement that the bleeding event: i) was treated with red blood cell or whole blood transfusion; ii) involved a critical site; or iii) resulted in death) and all-cause mortality.

Study population

The study included 448,944 individuals with non-valvular AF who had started anticoagulant therapy, with 159,927 person-years of on-treatment follow-up data available for analysis; the mean duration of follow-up was 130 days.[1] The mean age of the patients was 75.4 years and 47.4% were female. Among these patients, 183,318 had started warfarin, 86,198 had started dabigatran and 106,389 had started rivaroxaban. Minor differences were seen among these cohorts for number of variables, but they were closely balanced for all covariates after adjustments.

Statistical methods

The risks for these outcomes over time were illustrated in weighted Kaplan-Meier cumulative incidence plots, with single-weighted Cox proportional hazards models used to estimate HRs with 95% CIs for all NOAC-warfarin and NOAC-NOAC pairwise comparisons. Adjusted incidence rates and incidence rate differences were also estimated, and 30-day case fatality rates were determined for thromboembolic stroke, intracranial haemorrhage and major extracranial bleeding. Prespecified subgroup analyses by age, sex, antiplatelet use and bleeding risk scores (CHA_2DS_2VASc and HAS-BLED) were also performed along with a number of prespecified and *post hoc* sensitivity analyses.

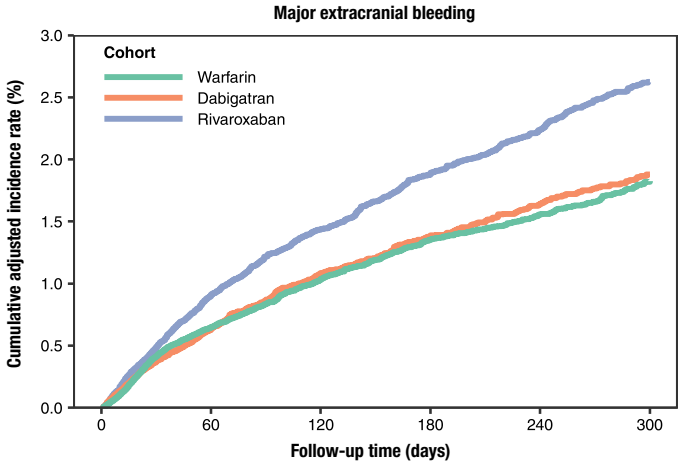
Results

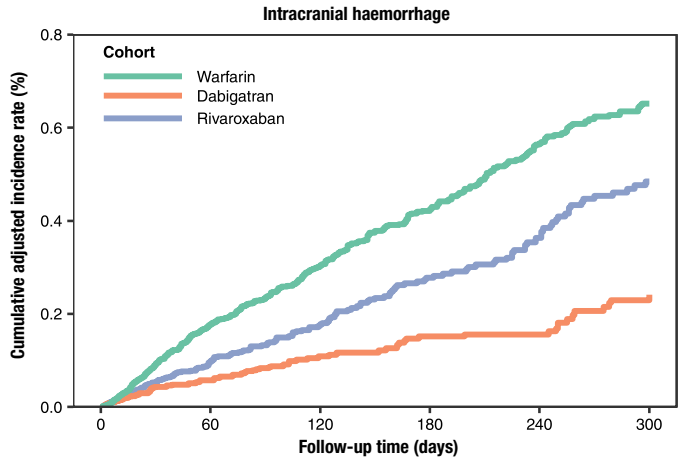
There were 11,263 outcome events recorded during follow-up.[1] Safety analyses revealed that compared with warfarin, dabigatran and rivaroxaban were both associated with lower likelihood of intracranial haemorrhage (Table 2, Figure 1). Major extracranial bleeding risk did not differ between dabigatran and warfarin, but rivaroxaban was associated with a higher risk than warfarin; both NOACs were associated with higher risks of major GI bleeding when compared with warfarin. When the two NOACs were compared with each other, the likelihood of bleeding was higher with rivaroxaban than with dabigatran.

Table 2. Adjusted HRs (95% CIs) for pairwise comparisons of dabigatran, rivaroxaban and warfarin for safety outcomes[1]

	Intracranial haemorrhage	Major extracranial bleeding
Dabigatran versus warfarin	0.38 (0.31, 0.47)	1.04 (0.96, 1.14)
Rivaroxaban versus warfarin	0.65 (0.56, 0.77)	1.38 (1.29, 1.49)
Rivaroxaban versus dabigatran	1.71 (1.35, 2.17)	1.32 (1.21, 1.45)

Figure 1. Adjusted Kaplan-Meier plots for intracranial haemorrhage and major extracranial bleeding associated with warfarin, dabigatran or rivaroxaban in patients with non-valvular AF (adapted from Graham *et al.*)[1]





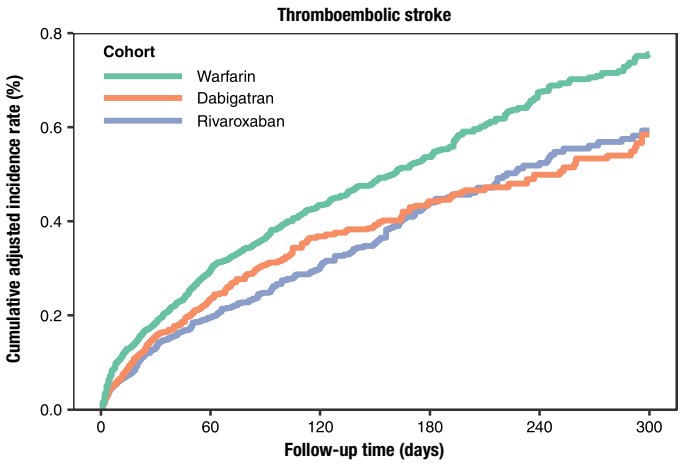
Efficacy outcomes

Efficacy analyses revealed that compared with warfarin, dabigatran and rivaroxaban were both associated with a lower likelihood of thromboembolic stroke, and there was no significant difference between the two NOACs for this outcome (Table 3, Figure 2).

Table 3. Adjusted HRs (95% CIs) for pairwise comparisons of dabigatran, rivaroxaban and warfarin for the efficacy outcome of thromboembolic stroke[1]

	Thromboembolic stroke
Dabigatran versus warfarin	0.80 (0.70, 0.93)
Rivaroxaban versus warfarin	0.72 (0.63, 0.83)
Rivaroxaban versus dabigatran	0.90 (0.76, 1.06)

Figure 2. Adjusted Kaplan-Meier plot for thromboembolic stroke associated with warfarin, dabigatran or rivaroxaban in patients with non-valvular AF (adapted from Graham *et al.*)[1]



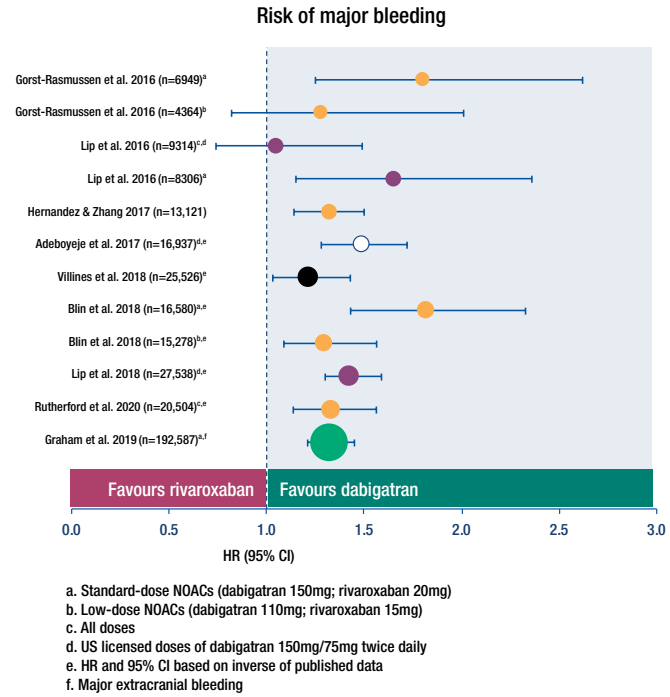
Rivaroxaban versus dabigatran

The findings of Graham *et al.* for comparisons between the two NOACs funded in NZ are supported by other studies in real-world cohorts of patients with AF, some investigating both standard and low NOAC doses.[1,10–19] These consistently report equivalence between these two NOACs for stroke/systemic embolism risk and significantly lower bleeding risks with dabigatran compared with rivaroxaban (Figure 3).

Real-world evidence for NOAC outcomes

- Hernandez *et al.* 2017 – Two analyses of claims for US Medicare beneficiaries found no significant difference between dabigatran versus rivaroxaban for ischaemic stroke, systemic embolism or death or intracranial haemorrhage, but lower rates of any and GI bleeding with dabigatran (HR 0.79 [95 CI 0.69, 0.92] and 0.70 [0.55, 0.89], respectively) in one analysis and higher major bleeding risks with rivaroxaban 20mg versus dabigatran 150mg in the second (1.32 [1.17, 1.50]) and with rivaroxaban 15mg versus dabigatran 75mg (1.51 [1.25, 1.82]).[10,15]
- Lip *et al.* 2018 – Another analysis of US Medicare claims data for 27,538 dabigatran-rivaroxaban recipient pairs reported similar incidence rates of stroke/systemic embolism for dabigatran versus rivaroxaban (HR 1.15 [95% CI 0.96, 1.37]) and significantly lower rates of major bleeding (0.70 [0.63, 0.77]), GI bleeding, intracranial haemorrhage and other bleeding with dabigatran.[11]
- Adeboyeje *et al.* 2017 – Using US insurance claims data, this comparison of 8539 dabigatran recipients versus 8398 rivaroxaban recipients found that dabigatran was associated with lower risks of major and intracranial bleeding (respective HRs 0.67 [95% CI 0.58, 0.78] and 0.54 [0.43, 0.96]).[12]
- Blin *et al.* 2018 – An analysis of 27,060 dabigatran recipients and 31,388 rivaroxaban recipients found no significant difference between these two NOACs for stroke/systemic embolism (adjusted HR 0.86 [95% CI 0.67, 1.11]), but lower risks of clinically relevant and major bleeding with dabigatran (0.53 [0.43, 0.65] and 0.55 [0.39, 0.78]); results for matched pair analyses were consistent.[13]
- Gorst-Rasmussen *et al.* 2016 – A prospective cohort study of patients from Danish health registries found that recipients of rivaroxaban 20mg had a higher bleeding risk than dabigatran 110mg recipients (HR 1.81 [95% CI 1.25, 2.62]); for rivaroxaban 15mg versus dabigatran 110mg, the increased bleeding rate was not statistically significant (1.28 [0.82, 2.01]).[14]
- Lip *et al.* 2016 – Although only a *"nonsignificant difference"* for major bleeding in favour of dabigatran was reported for a real-world cohort of 4657 matched dabigatran-rivaroxaban recipient pairs, the difference reached statistical significance for new users of rivaroxaban 20mg versus matched dabigatran 150mg recipients (HR 1.65 [95% CI 1.15, 2.36]).[16]
- Norby *et al.* 2017 – This analysis of US insurance claims data found no significant difference between 16,957 rivaroxaban users and matched new dabigatran users for ischaemic stroke or intracranial haemorrhage risk, but a higher risk of GI bleeding with rivaroxaban (HR 1.28 [95% CI 1.06, 1.54]).[17]
- Rutherford *et al.* 2020 – Data from Norwegian registries for propensity score matched dabigatran and rivaroxaban recipients pairs (n=20,504) showed no significant difference for the risk of stroke or systemic embolism (HR 0.88 [95% CI 0.76, 1.02]) and a lower risk of major bleeding (0.75 [0.46, 0.88]) with dabigatran.[18]
- Villlines *et al.* 2019 – Data from the US Department of Defense Military Health System for 12,763 dabigatran recipients versus matched rivaroxaban recipients found no significant difference for stroke risk (HR 0.77 [95% CI 0.57, 1.04]) and a lower major bleeding risk with dabigatran (0.82 [0.70, 0.97]).[19]

Figure 3. Risk of major bleeding and intracranial haemorrhage with rivaroxaban versus dabigatran illustrated by HRs with 95% CIs in large (n>3000) cohorts[1,10–19]



a. Standard-dose NOACs (dabigatran 150mg; rivaroxaban 20mg)
b. Low-dose NOACs (dabigatran 110mg; rivaroxaban 15mg)
c. All doses
d. US licensed doses of dabigatran 150mg/75mg twice daily
e. HR and 95% CI based on inverse of published data
f. Major extracranial bleeding

Methodology criteria for analysis include new user design, adjusted comparisons available, propensity score matching, HRs available, adequate sample size of >3000 patients and analyses published from 2014 to 2020. Other limitations may apply.

Meta-analysed data for rivaroxaban vs. dabigatran

In meta-analyses, Bai *et al.* and Li *et al.* found similar risks of stroke/systemic embolism for rivaroxaban versus dabigatran (HRs 1.02 [95% CI 0.91, 1.13] and 1.00 [0.91, 1.10]), and both found higher major bleeding risks with rivaroxaban (1.38 [1.27, 1.49] and 1.39 [1.28, 1.50]); evidence was categorised as overall moderate- to high-quality by Bai *et al.*, and low-quality for stroke/systemic embolism and moderate-quality for major bleeding by Li *et al.*[20,21] Mitchell *et al.* have also reported a poorer safety profile for rivaroxaban compared with dabigatran.[22]

Cautious interpretation advised

It is important to bear in mind that results from these types of studies need to be interpreted with caution and should only be regarded as hypothesis-generating.[11] However, taken together, the results do seem to suggest a higher risk of major bleeding among new initiators of higher-dose rivaroxaban; differences in risk of other types of bleeding (e.g. intracranial haemorrhage) have been inconsistent. Head-to-head trials of NOACs are ongoing, and their data are expected to be released over the next few years.

NOACs versus warfarin

Other large cohort studies of real-world patients with non-valvular AF have reported lower likelihoods of stroke, death and intracranial haemorrhage with dabigatran and rivaroxaban versus warfarin.[10,11] The lower risk of major bleeding with dabigatran versus warfarin has also been reported in another large cohort study of real-world new oral anticoagulant users with non-valvular AF,[12] and another has reported a similar risk of any bleeding event.[10]

The results of several meta-analyses of real-world data are in agreement with the findings of the study by Graham *et al.* These have consistently shown that compared with VKAs, rivaroxaban and dabigatran are associated with significantly lower risks of stroke/systemic embolism and all-cause mortality, and a lower risk of intracranial haemorrhage with dabigatran.[20, 22–25] Data on the intracranial haemorrhage risk with rivaroxaban in comparison with warfarin are inconsistent, with Hirschl *et al.* reporting a lower risk and Vinogradova *et al.* reporting no significant difference.

Limitations

The limitations of the real-world study by Graham *et al.* include those inherent to observational studies and the relatively short duration of continuous anticoagulant use (<5 months).[1] Nonetheless, the number of patients still on treatment at 8 months was relatively high compared with other studies that have compared NOACs with each other. Another limitation was the restriction of the study population to first-time elderly anticoagulant users, as this represents >80% of patients with AF, but outcomes for younger patients could differ. Only standard doses were compared in this study, and other doses could yield different results. Because the warfarin users included in the analysis were propensity matched to NOAC users, the study excluded warfarin users who were less likely to be treated with a NOAC. However, the results of a *post hoc* analysis that included all warfarin users were consistent with the primary analyses, suggesting that the findings should be applicable to all warfarin users. Finally, only first-time NOAC users were included – results could be different for patients switching from warfarin to a NOAC. There are no head-to-head RCTs comparing NOACs. Real-world evidence studies may have heterogenous study populations, data analysis with known or unknown confounding errors, data bias and residual channelling effects.

Conclusions

Based on RCT and real-world data, both of the NOACs funded in NZ (dabigatran and rivaroxaban) were similarly superior to warfarin for preventing stroke in patients with non-valvular AF. Data for head-to-head comparisons of the two NOACs are not yet available, but a number of real-world studies of observational cohorts consistently suggest that both appear to be equally effective for preventing stroke/systemic embolism. However, dabigatran appears to have a more favourable benefit-to-harm profile due to more reported major bleeding events with rivaroxaban, particularly among new initiators of higher doses.

SPECIALIST COMMENTARY

In NZ, we have the choice of two different doses of both dabigatran (110mg and 150mg) and rivaroxaban (15mg and 20mg). The use of the lower doses will be associated with a lower risk of bleeding and may be associated with lower efficacy for reduction of stroke and systemic embolism. With dabigatran, the RE-LY study demonstrated the efficacy of dabigatran 110mg in patients regardless of renal function. There are no similar data from ROCKET-AF for the lower dose of rivaroxaban in patients with normal renal function.

The real-world data provide reassurance that the NOACs are both safe and efficacious in comparison with warfarin, with dabigatran associated with a lower risk of major bleeding. In addition to evidence from RCTs and real-world observational studies, the choice of oral anticoagulant is based on individual patient factors and preferences.

Rivaroxaban may be preferred in certain patient groups (e.g. known history of dyspepsia, preference for once-daily dosing), whereas dabigatran may be the first choice in patients at highest risk of bleeding and also those at highest risk of stroke and systemic embolism. Some patients and doctors also prefer dabigatran due to the availability of a fast-acting, efficacious reversal agent.

TAKE-HOME POINTS

- NZ's funded NOACs were both superior to warfarin for preventing stroke in real-world non-valvular AF.
  - Intracranial haemorrhage risk is also lower, but more major bleeding with rivaroxaban.
  - Supported by RCT data.
- No head-to-head trial data on dabigatran versus rivaroxaban.
  - Real-world observational data suggest dabigatran has the more favourable benefit-to-harm profile.
    - Similar efficacy for preventing thromboembolic stroke.
    - More major bleeding with rivaroxaban has been reported.
    - Inconsistent differences in intracranial haemorrhage risk.

RESOURCES

Graham DJ et al. Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. https://www.amjmed.com/article/S0002-9343(19)30051-8/fulltext

RE-LY RCT (Connelly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation). https://www.nejm.org/doi/full/10.1056/NEJMoa0905561

ROCKET-AF RCT (Patel et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation). https://www.nejm.org/doi/full/10.1056/nejmoa1009638

Medsafe Dabigatran Data Sheet. https://www.medsafe.govt.nz/profs/Datasheet/p/Pradaxacap.pdf

Medsafe Rivaroxaban Data Sheet. https://www.medsafe.govt.nz/profs/Datasheet/x/Xareltotab.pdf

Real-world evidence comparing NOAC outcomes

Study	Statistical methods	Study limitations
Hernandez *et al.* 2017 1415 dabigatran recipients and 5139 rivaroxaban recipients[10]	Cox proportional hazard models were used to further control for differences in patient characteristics across treatment groups.	Possible confounding due to unobserved factors. Not stratified according to NOAC dose.
Hernandez *et al.* 2017 7322 dabigatran recipients and 5799 rivaroxaban recipients[15]	Two-step propensity score weighting; logistic regression and COX models. Sensitivity analyses.	No adjustment for unobserved patient characteristics. HASBLED risk score could not be calculated. Study period covered only the first 2 years after rivaroxaban entered the market. Patients who switched anticoagulation treatments or discontinued for >60 days were censored. Data on adherence to therapy were not captured.
Lip *et al.* 2018 27,538 dabigatran-rivaroxaban recipient pairs[11]	One-to-one propensity score matching based on logistic regression. Cox proportional hazard models. Subgroup and sensitivity analyses.	Inherent limitations of observational retrospective evaluations. Potential for residual confounders. Outcome measures based solely on ICD-9 codes. Reliance on prescription dispensing records.
Adeboyeje *et al.* 2017 8539 dabigatran and 8398 rivaroxaban recipients[12]	Cox proportional hazards regression models with propensity score weighting. Sensitivity analyses	Assessment of balance achieved between treatment groups was limited to the covariates measured.
Blin *et al.* 2018 27,060 dabigatran recipients and 31,388 rivaroxaban recipients[13]	High-dimensional propensity score matching.	Possible unmeasured confounding. Possibility that dabigatran was prescribed to younger, healthier patients than rivaroxaban. Possible notoriety bias.
Gorst-Rasmussen *et al.* 2016 8908 dabigatran recipients and 2405 rivaroxaban recipients[14]	Adjusted comparisons for primary endpoints. Propensity score methods used to control for baseline differences. Net clinical benefit assessed using Cox models.	Potential for residual confounding due to channelling of rivaroxaban towards elderly and less healthy patients. Risk of misclassification and ascertainment error. Limitations of comparative effectiveness studies of newly marketed drugs.
Lip *et al.* 2016 4657 matched dabigatran-rivaroxaban recipient pairs[16]	Propensity score matching pairwise comparisons with Cox proportional hazard models. Sensitivity analyses.	Inherent limitations of observational retrospective evaluations. Possible residual confounding due to unobserved confounders. Possible selection bias.
Norby *et al.* 2017 16,957 rivaroxaban recipients and matched new dabigatran recipients[17]	High-dimensional propensity scores with Cox proportional hazards models.	Possible unmeasured confounding. Outcomes and covariates ascertained from administrative data. Results may not be generalisable to the overall population. Medication adherence was not confirmed.
Rutherford *et al.* 2020 20,504 matched dabigatran-rivaroxaban pairs[18]	Propensity score matching pairwise comparisons with Cox proportional hazard models. Sensitivity analyses.	Possible unmeasured confounding. Recorded events were not adjudicated. Temporal changes in prescription patterns. Unable to identify NOAC users per label regarding dose.
Villlines *et al.* 2019 12,763 matched dabigatran and rivaroxaban recipients[19]	Propensity score matching.	Inherent limitations of retrospective database analyses. Possibility of coding errors. Possibility of residual confounding.

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