National Essential Medicine List Medication Review Process
Adult Hospital Level
Component: Cardiovascular

Date: 18 January 2016

Medication: Direct acting oral anticoagulants/New oral anticoagulants

Indication: To reduce the risk of ischaemic stroke in patients with atrial fibrillation.

Review question (PICO): (P) Amongst patients with atrial fibrillation are the **(I)** direct acting oral anticoagulants more efficacious than **(C)** warfarin (current standard of care, available on the National Essential Medicines List) in **(O)** preventing ischaemic stroke and/or systemic embolism?

Introduction: A motivation was received for the inclusion of novel oral anticoagulants on the National Essential Medicines List, for atrial fibrillation at secondary level of care.

Atrial fibrillation is a common condition and patients with atrial fibrillation are at risk of ischaemic stroke and systemic emboli. CHA_2DS_2-VASc Score is used to stratify risk of stroke associated with non-valvular atrial fibrillation. A score of 2 or more is generally considered to be a risk of thromboembolism, and warfarin therapy is indicated. The higher the score, the greater the risk of stroke and therefore the more compelling the use of effective anticoagulation[i].

Initial anticoagulation therapy aimed at preventing thrombo-embolic events recommended in the Adult Hospital level Standard Treatment Guideline and Essential Medicines List, 2015 is warfarin, oral 5 mg adjusted to INR. However, warfarin has a narrow therapeutic index that requires frequent INR monitoring with dose adjustments, as required[ii]; and is associated with many drug-drug and drug-food interactions. Novel oral anticoagulants (NOACs), that have recently been registered by the Medicines Control Council on the South African market, directly inhibit coagulation factors (activated thrombin by dabigatran or factor Xa by rivaroxaban) are alternatives to warfarin, and have a more predictable pharmacokinetic profile, do not require frequent monitoring with less reported drug interaction and are easier to administer compared to warfarin [iii].

A review of the available evidence follows to compare the efficacy of warfarin to the direct acting oral anticoagulants (also known as new/novel oral anticoagulants) to prevent thromboembolic events in patients with atrial fibrillation.

Search strategy: A Medline search was performed using the following search strategy:

Database: Ovid MEDLINE(R) <1946 to January Week 1 2016>

Search Strategy:

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1 exp *Hemorrhage/ or exp *Stroke/ or exp Anticoagulants/ or exp *Warfarin/ or exp *Venous Thromboembolism/ or exp *Atrial Fibrillation/ (453033)

2 exp *Rivaroxaban/ (27)

3 exp *Dabigatran/ (19)
4 exp *Warfarin/ (9298)
5 exp *Atrial Fibrillation/ (30688)
6 1 and 4 and 5 (1398)
7 limit 6 to (english language and humans and (guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or systematic reviews) and last 5 years) (155)

Selection of studies:

Inclusion criteria:
Types of studies: meta-analysis or systematic reviews of randomized controlled trials
Participants: patients with atrial fibrillation
Interventions: rivaroxaban and dabigatran
Control: warfarin
Outcomes: stroke or thromboembolic event

Results:
The Medline search identified 155 studies. Five met the inclusion criteria. However, a recent meta-analysis of RCTs[iv] that analysed all available NOACs compared to warfarin in atrial fibrillation, reviewing phase 3 RCTs from Jan 2009 to Nov 2013 and published in a high impact journal was analysed.

Furthermore, the cited primary studies for dabigatran and rivaroxaban (currently the only NOACs registered in South Africa) were retrieved for appraisal.

Cochrane collaboration database was likewise searched for relevant reviews.

Evidence synthesis:

A: Meta-analysis, 2014
Ruff et al's 2014 prespecified random-effects meta-analysis included four phase 3 trials (that reported efficacy and safety outcomes) and 71683 participants with atrial fibrillation (NOAC: n=42411 vs. warfarin: n=29272), analysed in two separate groups consisting of high dose and low dose NOACs. The article published in the Lancet mostly describes the high dose NOAC group, whilst the results of the low dose NOAC group are contained in an online appendix. It is noted that these studies were retrieved using a single database, MEDLINE, and a clinical trials register. Median follow-up of studies ranged from 1.8 to 2.8 years.

Efficacy:
High dose NOAC regimens: The study was powered to assess the primary endpoint of reduction in stroke or systemic embolic events compared to warfarin (RR 0.81, 95% CI 0.73 to 0·91; I^2=47%) with a NNT of 148. Secondary efficacy outcomes included a greater reduction in haemorrhagic stroke (RR 0.49, 95% CI 0.38 to 0.64; I^2=34%), with a NNT of 3; statistical significant reduction in all-cause mortality (RR 0.90, 95% CI 0.85 to 0.95; p=0.0003; I^2=0%), with a NNT of 220.

Low dose NOAC regimens: Reduction in stroke or systemic embolic events with low-dose regimens was comparable to warfarin (RR 1.03, 95% CI 0.84 to 1.27; p=0.74; I^2=70%); though

there was a greater reduction in haemorrhagic strokes (RR 0.33, 95% CI 0.23 to 0.46; p<0.0001; I^2 =0%), with a NNT of 144. Reduced all-cause mortality of RR 0.89, 95% CI 0.93 to 0.96; p=0.003; I^2=0, with a NNT of 92.

Safety:
High dose NOAC regimens: Secondary safety outcomes include a significantly reduction in intracranial haemorrhage (RR 0.48, 95% CI 0.39 to 0.59; p < 0.0001; I^2=32%), with a NNH of 132; but an increase in gastrointestinal bleeding (RR 1.25, 95% CI 1.01 to 1.55; p=0.043; I^2=74%), with a NNH of 185.

Low dose NOAC regimens: There was a trend towards a more favourable bleeding profile with low dose NOAC regimens vs. warfarin, with the upper limit of the 95% CI bordering on not statistically significant (RR 0.65, 95% CI 0.43 to 1.00; p=0.05; I^2=91%).

Quality:
Studies were generally heterogenous and although there was a statistical variance of the overall efficacy and safety estimates, the direction of the effects for the various NOACs was consistent (in both the high and low dose NOAC groups).

Mean age of the patients ranged from 70 to 73 years, whilst atrial fibrillation occurs in a younger population in South Africa. Majority of the patients were male (appears to be representative of the global population[v]; whilst the underlying risk of ischaemia measured using the $CHADS_2$ score differed across trials. Pooled trials had a greater proportion of high risk patients with $CHADS_2$ score of 3-6.

For the clinical subgroup analysis (gender, history of previous stroke or transient ischaemic attack, history of diabetes, renal function, $CHADS_2$ risk score, and baseline vitamin K antagonist status), there was no statistically significant major differences for stroke or systemic embolic events or safety concerns of major bleeding.

No funding was received, but details of the review process were not described and the quality and methodology of the RCTs was not assessed using a formal scoring system with the assessment of bias not being fully described. It was also unclear of how many reviewers were involved in retrieving and analysis of the data.

A later meta-analysis by Jia *et al*[vi]assessing the safety and efficacy of NOACs vs warfarin in atrial fibrillation produced similar results and reported that "The high-dose regimen had better performance than low dose in efficacy. In addition, low-dose regimen demonstrated to significantly reduce the risk of hemorrhagic stroke, all-cause mortality, and intracranial hemorrhage".

Similarly, authors of a Cochrane review[vii] concluded that direct thrombin inhibitors (e.g. dabigatran) was comparable to vitamin K antagonists in terms of all-cause mortality and the composite outcome of vascular death and ischaemic events (with the higher dose of dabigatran 150 mg twice daily only being superior to warfarin).

Likewise, authors of a Cochrane review[viii] of factor Xa inhibitors (e.g. rivaroxaban) compared to vitamin K antagonists for the prevention of cerebral or systemic embolic events in people with

atrial fibrillation, concluded that these agents "significantly reduced the number of strokes and systemic embolic events compared with warfarin in patients with atrial fibrillation".

B: ROCKET-AF[ix]

Double blind, double-dummy, multi-centred, non-inferiority RCT of 14264 patients with non-valvular atrial fibrillation (of moderate to high risk) comparing fixed dose rivaroxaban to dose-adjusted warfarin (INR 2-3) to reduce the risk for ischaemic stroke and systemic embolism. The study was funded by pharmaceutical industry.

The study analysed 3 population data sets [per protocol, safety-on-treatment and intention to treat (ITT)]. However, only the ITT analysis, followed to the end of the study period (median follow up of 1.94 years), will be reviewed.

Efficacy:

The ITT population confirmed noninferiority (HR 0.88, 95% CI 0.744 to 1.03; $p < 0.001$) of rivaroxaban compared to warfarin in preventing stroke and systemic embolism, at the pre-specified non-inferiority margin of 1.46; however, superiority of rivaroxaban compared to warfarin was not shown (p=0.12).

Rivoroxaban did not reach superiority over warfarin for the secondary outcome of all-cause mortality (HR 0.85, 95% CI 0.70 to 1.02, p=0.073).

Safety:

Overall adverse event rate of rivaroxaban and warfarin were comparable, 20.7% vs 20.3%, respectively. However, rates of intracranial haemmorhage was significantly lower in the rivaroxaban group (0.77% vs 1.18%; $p < 0.05$); although rivaroxaban was associated with significantly more major gastrointestinal bleeds (3.15% vs 2.16%; $p < 0.001$) and bleeding events requiring transfusion (1.6% vs 1.3%; p =0.04).

Quality [vii, x, xi]:

Double blind, double-dummy RCT, with prespecified outcomes. Study being of good quality in terms of sample size, randomisation, allocation concealment, blinding, data assessment (ITT analysis) and other potential bias.

The study population consisted of mostly high risk patients (87% had a $CHADS_2 \geq 3$) and comparison of baseline patient demographics was generally balanced between the two study cohorts; however, more patients in the warfarin group had a history of myocardial infarction (18% vs 16.6 %; $p < 0.05$), suggesting that the warfarin group were at a greater risk of ischaemic events.

Furthermore, the complex double blind, double-dummy methodology may introduce selection bias, based on investigator's subjective evaluation of whether a patient is eligible for consideration to participate in the study; and subject retention bias, with an increased pill burden in a double-dummy design and logistic challenges regarding the frequent study visits.

Attrition bias resulted in the ITT analysis confirming noninferiority, rather than superiority of rivaroxaban compared to warfarin as more patients in the rivaroxaban group who prematurely

discontinued anticoagulants permanently and transitioned to open label warfarin therapy developed a primary event (81 vs 66 primary events, respectively).

Systemic embolism was diagnosed radiologically, which may be clinically silent in clinical practice, possibly resulting in over reporting of this primary event.

The median time in therapeutic range (TTR) of 58% (95% CI 43 to 71%) amongst the warfarin study cohort, suggests that the frequent INR monitoring did not result in improved INR control. However, the low TTR reported may bias the results, overinflating the efficacy of rivaroxaban. TTRs differed across study sites.

C: RE-LY[xii]

A non-inferiority RCT (n=18113), in which two blinded doses of dabigatran (110 mg and 150 mg twice daily) were compared with open-label dose-adjusted warfarin (INR 2.0- 3.0) in non-valvular atrial fibrillation with at least one risk factor for stroke, to prevent ischaemic stroke or systemic embolism. Median follow up period was 2 years. This study design accommodated the need for regular INR tests for patients receiving warfarin. Although sham INR testing is possible, it was considered to be complex and time consuming and thus, the open-label design for the warfarin arm. Study was sponsored by pharmaceutical industry.

Efficacy:

Dabigatran 110 mg and 150 mg twice daily doses were shown to be non-inferior to warfarin to prevent the primary event (ischaemic stroke or systemic embolism): The relative risk for dabigatran 110 mg vs warfarin was 10 % (182/6015 vs 199/6022 events; RR 0.91, 95% CI 0.74 to 1.11, p<0.001) and for dabigatran vs warfarin was 35% (134/6076 vs 199/6022 events; RR 0.66, 95% CI 0.53 to 0.82, p<0.001). Dabigatran 150 mg was thus, also shown to be superior to warfarin. To prevent one primary event, the number of patients who would need to be treated with dabigatran at a dose of 150 mg twice daily, rather than warfarin, is approximately 173.

Rates of myocardial infarction were lower with warfarin compared to both doses of dabigatran 110 mg (0.72%) and 150 mg (0.74%) compared to warfarin (0.53%), with a NNT of 500.

In terms of all cause mortality, dabigatran showed non-inferiority for both doses: dabigatran 110 mg vs warfarin (446/6015 vs 487/6022 deaths; RR 0.90, 95% CI 0.77 to 1.06, p=0.04) and dabigatran 150 mg vs warfarin (438/6076 vs 487/6022 deaths; RR 0.88; 95% CI 0.77 to 1.00, p=0.051). Although, a reduction in all-cause mortality was seen, this did not reach statistical significance.

Safety:

Both doses of dabigatran were associated with a lower rate of major bleeding, life-threatening bleeding and intracranial bleeding compared to warfarin.

	Warfarin vs dabigatran 110 mg twice daily	**Warfarin vs dabigatran 150 mg twice daily**
Major bleeding	RR 0.80, 95% CI 0.69 to 0.93; p=0.003	RR 0.93, 95% CI 0.81 to 1.07; p=0.031
Life-threatening bleeding	RR 0.68, 95% CI 0.55 to 0.83, p<0.001	RR 0.81, 95% CI 0.66 to 0.99; p=0.04
Intracranial bleeding	RR 0.31, 95% CI 0.20 to 0.47; p<0.001	RR 0.40, 95% CI 0.27 to 0.60; p<0.001

However, warfarin had a lower rate of gastrointestinal bleeds compared to both doses of dabigatran; but the risk difference compared to the 150 mg dose regimen was statistically significantly.

	Warfarin vs dabigatran 110 mg twice daily	Warfarin vs dabigatran 150 mg twice daily
Gastrointestinal bleeding	RR 1.10, 95% CI 0.86 to 1.41; p=0.43	RR 1.50, 95% CI1.19 to 1.89; p<0.001

Comparison of dabigatran doses:
Dabigatran 150 mg dose had a greater reduction in preventing ischaemic stroke and systemic embolism compared to the 110 mg dose (RR 0.73, 95% CI 0.58 to 0.91; p=0.005).

In terms of adverse bleeding events, a significant reduction of major bleeding was only seen with the 110 mg dose; whilst the 150 mg dose was associated with a higher rate of gastrointestinal bleeding.

Quality [xi xiii ix xiv] *:*
Open-label, randomised, multi-centred, controlled trial.

Although the warfarin arm of the study was open-label, with a possibility of bias being introduced; outcome assessors (two independent investigators) were blinded reducing the risk of detection bias. Furthermore, measurement of clinical outcomes was more objective.

A protocol amendment during subject enrollement was done to further minimise selection bias, to ensure balanced enrollment between vitamin K antanosist- experienced and vitamin K antagonist- naïve patients in the respective study arms.

Attrition bias was low with 20 patients lost to follow up and the rates of discontinuation of 110 mg dabigatran, 150 mg dabigatran and warfarin at 2 years being 20.7%, 21.2% and 16.6% respectively. The higher rate of gastrointestinal adverse effects with dabigatran (11.8% in the dabigatran 110 mg group vs 11.3% in the dabigatran group vs 5.8% in the warfarin group) may probably have contributed to the higher discontinuation rate of dabigatran.

The percentage of time within the therapeutic range in the warfarin group was 64%, higher than the TTR of 58% reported in the ROCKET-AF trial. However, TTR of 64% has been reported to be comparable to other trials: 64% in ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) W[xv xvi] and 66% to 68% in the SPORTIF (Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation) trials[xvii xviii]. RE-LY being an open-label RCT, encouraged easier management of bridging therapy, and this is reflected in there not being increased stroke rates when patients transitioned from dabigatran to warfarin; whilst in the ROCKET-AF trial an excess of stroke occurred when patients transitioned from blinded rivaroxaban to warfarin.

Summary:
Available evidence suggests that NOACs is an alternate option to warfarin in non-valvular atrial fibrillation (moderate to high risk) to prevent ischaemic stroke and systemic embolism.

There appears to be a trend towards less major bleeding and a significant reduction of intracranial hemorrhage with NOACs compared to warfarin. However, less gastrointestinal bleeding was observed with warfarin compared to NOACs.

The cost of NOACs need to be analysed and TTR, INR monitoring and monitoring costs are additional factors that need consideration, in order to inform a decision of including NOACs to the secondary level Essential Medicines List for adults.

Additional concerns that have been raised is the availability of antidotes if bleeding occurs with dabigatran and rivaroxaban. There are no agents currently registered with the Medicine Control Council in South Africa. However, in 2015 a dabigatran-specific reversal agent, idarucizumab[xix], has been approved by the United States Health Regulatory Authority[xx].

Of note is that NOACs have not been tested in a numerous patient populations including pregnancy, adolescents, HIV-infected patients on HAART and those on TB therapy. In the South African setting, these patient groups constitute a significant proportion of patients who would require anticoagulation and any decision should be informed by consideration of their needs.

Lastly, there is lack of comparative RCTs directly comparing the various NOACs, and worth mentioning is that the study population varies between the RE-LY and ROCKET-AF RCTs, with the RE-LY study population having a mean $CHADS_2$ of 2.1, whilst the ROCKET-AF study population were mostly high risk (mean $CHADS_2$ of 3.5).

Level of Evidence: I Meta-analyses, RCTs

References

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