Gaps in translation from trials to practice: Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in atrial fibrillation

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Summary
Worldwide there is a tremendous need for affordable anticoagulants that do not require monitoring. The advent of the non-warfarin oral anticoagulant drugs represents a major advance for stroke prevention in atrial fibrillation (AF). The objectives of this review are to 1) identify gaps in our current knowledge regarding use of these single target anticoagulant drugs; 2) outline the potential implications of these gaps for clinical practice, and thereby, 3) highlight areas of research to further optimise their use for stroke prevention in AF.

Introduction
Worldwide there is a tremendous need for affordable anticoagulants that do not require monitoring (1, 2). The advent of the non-vitamin K antagonist oral anticoagulants (NOACs) represents a major advance for stroke prevention in atrial fibrillation (AF) (3-6). All of these agents dramatically reduced the risk of intracranial haemorrhage (ICH) compared to warfarin. Because trial populations are often younger, less ill, and more adherent to medications, the results of randomised trials may not always translate into clinical practice. The structured follow up of trial participants is also likely to ensure better control of other key stroke risk factors, most notably hypertension and diabetes mellitus. In addition to differences in patient characteristics, specialised clinical situations and complicated episodes of care may not be well represented among the selected participants in a randomised trial. The objectives of this review are to 1) identify gaps in our current knowledge regarding use of these single target anticoagulant drugs; 2) outline the potential implications of these gaps for clinical practice, and thereby, 3) highlight areas of research to further optimise their use for stroke prevention in AF.

Intracranial haemorrhage (ICH)
Will the NOACs achieve the same reduction in ICH as they did in the randomised trials?
Reproducing the trial rates of ICH in clinical practice will be contingent on several factors: the burden of degenerative cerebral microangiopathies (small vessel cerebral diseases) and cerebral microbleeds in the targeted patient population, blood pressure control, concomitant antiplatelet use, and trauma. These factors are all potent independent risk factors for ICH. Amyloid angiopathy, leukoaraiosis, and cerebral microbleeds are all age-related vasculopathies (7–9). The presence of cerebral microbleeds among individuals age 80 and older is estimated to be 35.7% (10). The approximate mean age of trial participants was 71 years. For this reason, the effectiveness of these agents in the oldest age groups with the highest prevalence of these cerebral microangiopathies is uncertain. Because these vascular changes are associated with cognitive impairment, it is unlikely that this subgroup of patients was well-represented in the randomised trials.

Given these microangiopathies, control of the modifiable ICH risk factors will be critically important in the older age groups. Hypertension is a potent risk factor for both ischaemic and haemorrhagic stroke (11). Hypertension was well controlled in the clinical trials as shown by the median systolic and diastolic blood pressures in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY), Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention
of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, respectively: 131/77, 130/80, 130/82 (3–5). Recent data from Denmark demonstrates this degree of blood pressure control is difficult to attain in practice. Among 37,651 hypertensive individuals, 33.2% achieved blood pressure levels ≤140/90 (12). A lower proportion of effectively treated patients was reported from the Copenhagen City Heart Study, 26% (13). Uncontrolled hypertension is a contraindication to anticoagulant therapy given the heightened risk for intracerebral haemorrhage.

Aspirin was recently confirmed in the RE-LY trial to be an independent risk factor for ICH, nearly doubling the risk for warfarin-associated spontaneous intracerebral haemorrhage (14). These findings are similar to those reported from a meta-analysis of six randomised trials; the combination of aspirin and oral anticoagulants more than doubled the risk of ICH (relative risk [RR] = 2.4, 95% confidence interval [CI] = 1.2–4.8, p = 0.02) (15). Baseline aspirin use among trial participants ranged from 40% in RE-LY to 29% in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). The baseline prevalence of prior myocardial infarction was 17% and 12%, respectively, raising questions regarding the indication for aspirin among these patients. The role of aspirin in primary prevention and among individuals with stable coronary artery disease, i.e. excluding acute coronary syndrome (ACS) and percutaneous coronary intervention, has been seriously questioned in recent years, particularly among individuals with AF older than age 75 years (16, 17). Reducing the risk of ICH and gastrointestinal (GI) haemorrhage (see below) will be contingent upon increased scrutiny of the risk versus benefit of dual and triple therapy among high risk patient subgroups (18–20).

Gastrointestinal (GI) haemorrhage

Will the NOACs result in more GI bleeds in practice than in the trials? Are there interventions to mitigate this risk?

Although the risk of ICH was reduced by the NOACs, the rate of GI haemorrhage was increased compared to warfarin with the higher dose of dabigatran, 150 mg twice daily, (RR 1.50; 95% CI: 1.10–1.89), rivaroxaban (3.15% vs 2.16%, p<0.001), and edoxaban (RR 1.23; 95% CI: 1.02–1.50). Rates of GI haemorrhage were similar to warfarin with apixaban (RR 0.89; 95% CI: 0.70–1.15). Although the 30-day mortality of extracranial haemorrhage is far less than that of ICH, 5.1% vs 48.6% (21), GI haemorrhage is associated with significant cost and morbidity. Approximately 85% of individuals with warfarin-related GI haemorrhage are admitted to the hospital (22). Most importantly, GI haemorrhage often leads to termination of anticoagulant therapy which is associated with increased mortality (23).

Age-related changes in GI physiology render the aging gut more vulnerable to injury. Increased gastric atrophy coupled with decreased mucosal protection and reparative capacity contributes to the deleterious effects of aspirin and non-steroidal anti-inflammatory drugs (24). Without a compelling reason supported by evidence, concomitant use of these agents with an anticoagulant should be avoided, particularly in the older adult. The role of proton pump inhibitors (PPI) as prophylaxis in the absence of symptoms is unproven. Because peptic ulcer disease is the leading cause of upper GI tract haemorrhage, individuals with peptic ulcer disease should be tested for *Helicobacter pylori*. The prevalence of *H. pylori* infection has been reported to be as high as 80% among individuals age 80 years and older (25). The cost effectiveness of testing in the absence of symptoms is unknown.

A major limiting factor to the development of targeted strategies to mitigate the risk of incident and recurrent GI haemorrhage is the failure to identify the culprit anatomic lesion in many cases despite comprehensive investigation. Because the risk of recurrent haemorrhage varies according to the underlying mechanism, the optimal interval to withhold anticoagulant therapy is unknown and has never been formally tested. In addition, because we lack data on any differential anatomic site-specific risk by drug, it is doubtful that drug selection based on aggregate GI haemorrhage rates from the trials will significantly influence the risk of recurrent GI haemorrhage in clinical practice. Consistent with the current standard of care, patients identified with iron deficiency anaemia warrant a thorough investigation of the upper and lower GI tracts to identify the source and any remediable lesion (26).

Renal function

*Is there adequate guidance on optimal drug management in the setting of fluctuating renal function?*

Trial evidence supports use of these agents among individuals with mild to moderate renal impairment as determined by the Cockcroft-Gault calculation (27–29). However, the proportion of individuals enrolled in the trials with moderate renal impairment, creatinine clearance of 30–50 ml/minute (min), ranged from 15% for apixaban to 21% for rivaroxaban. Individuals with severe renal impairment, creatinine clearance <30 ml/min (<25 ml/min for apixaban), were excluded from the trials and thus, trial results cannot be extrapolated to this group of patients. The NOACs are not recommended for individuals with end-stage renal disease or who are dialysis-dependent.

Another area of uncertainty is the management of patients with acute kidney injury with and without bleeding and outcomes related to fluctuations in renal function over time (30). Certain patient groups may be particularly susceptible to significant fluctuations in renal function, e.g. advanced heart failure, erratic fluid intake. Because wide variability in renal function may be a marker of poorer health status, these patients may not have been well represented in the clinical trials. Guo et al. have shown that an absolute reduction in estimated glomerular filtration rate (eGFR) ≥25 ml/min or a relative reduction of eGFR ≥25% more than doubles the risk of ischemic stroke compared to individuals with stable
renal function (31). Given the reduced dependence on renal pathways for elimination, the factor Xa inhibitors may be preferred for individuals with highly variable renal function.

Although a rational suggestion, the overall cost effectiveness of periodic screening of renal function is uncertain (14). Acute deterioration in renal function would most frequently occur outside these pre-specified monitoring windows and therefore, scheduled measurement of renal function would likely do little to mitigate bleeding complications related to acute kidney injury. A more gradual decline in renal function that would trigger a dose change for dabigatran (<30 ml/min), rivaroxaban (<50 ml/min), or apixaban (creatinine >1.5 mg/dl in addition to age 80 years and older or weight < 60 kg) would most likely be detected by scheduled interval assessment of renal function. Identification of patient subgroups that would most benefit from a regular monitoring strategy is needed. Additional longitudinal data on the safety and efficacy of NOACs among individuals with moderate or widely fluctuating renal impairment would inform the optimal management of these patients.

Fixed-dose and therapeutic window

**Will individualised dose adjustment lead to greater efficacy and safety?**

The NOACs are thought to have a wide therapeutic window that obviates the need for monitoring. In stark contrast to the nine available doses for warfarin, a fixed dose is used for the newer agents with a reduced dose indicated for renal impairment. Recent data from the RE-LY trial demonstrates that dabigatran concentration is dependent on several factors including renal function, age, weight, and female sex (32). Dabigatran trough levels were associated with ischemic stroke and dabigatran plasma levels with major hemorrhage among RE-LY participants. The clinical implications of this study are unclear and guidance on how to translate these findings into individualised dose selection is currently lacking.

In a genetic association study based on 2,944 participants from the RE-LY trial, a mutation in the enzyme responsible for the bio-transformation of dabigatran was identified in 32.8%. These individuals carried the CES1 rs2244613 minor allele that resulted in lower drug concentrations and reduced risk of haemorrhage (33). Its effect on thrombotic events is unclear. The role of genetic testing and the selected patient characteristics previously mentioned to guide dabigatran dose is currently unknown. Given the recent failure of dabigatran in the setting of mechanical prosthetic heart valves, it is reasonable to surmise that this genetic mutation may also have contributed to the lower than projected drug concentrations and the subsequent increase in stroke and valve thrombosis (34, 35). We await similar pharmacokinetic, pharmacodynamic, and genetic association studies for the factor Xa inhibitors.

**Stable time in the therapeutic range (TTR)**

**Should patients with stable TTR be switched to a NOAC?**

The debate whether or not to switch stable warfarin patients to a novel unmonitored anticoagulant will continue as this question cannot be answered by any of the randomised AF trials. One would need to randomise patients within pre-trial TTR quartile to provide insights into these different patient groups. The question becomes more complex with the added confounding factors induced by practice variation among the international centers represented. TTR is contingent upon many factors including testing frequency, drug adherence, warfarin dosing algorithms, dietary vitamin K, interfering medications, and patient characteristics, e.g. active malignancy, decompensated heart failure (36). There is an abundance of evidence that supports the association between individual patient TTR and outcomes on warfarin therapy (37–39). In the RE-LY trial, a 10% increase in center algorithm-consistent warfarin dosing predicted a 6% increase in TTR and an 8% decrease in rate of the composite clinical outcome (41).

Warfarin will remain the preferred anticoagulant for patients who are unwilling to switch to a newer agent, have severe renal dysfunction, have a mechanical heart valve, or for whom the transition is cost prohibitive. Although the rationale to switch patients with suboptimal control on warfarin to a NOAC seems intuitive, the precipitants of poor INR control are not well understood. To the degree that international normalised ratio (INR) variability reflects fluctuations in CYP enzyme activity, drug adherence, or in vivo thrombin generation, the effect of switching to agents with considerably shorter half-lives and/or dependence on hepatic metabolism is unclear.

**Adherence**

**Will poor adherence have a greater negative impact with the NOACs than with vitamin K antagonists?**

From a pharmacokinetic standpoint, it is logical to assume that non-adherence will be less well tolerated with the newer unmonitored drugs than with warfarin. The 40-hour (h) average half-life of warfarin ensures some residual anticoagulant effect up to 72 h following the last dose. This is in contrast to the approximate 10-h half-life of the NOACs (42). The extended half-life of warfarin may underlie, at least in part, its efficacy in prevention of ischaemic stroke. In a well-designed, albeit small study of 136 patients enrolled from three anticoagulation clinics, 36% of patients missed 1-2 doses of warfarin per week (43, 44). Adherence outside of a structured setting is likely to be worse. Reinforced teaching of patients and families regarding the heightened risk of stroke with AF and the greatly reduced risk of this debilitating complication by taking medications as prescribed will help to ensure translation of trial results to clinical practice.
Race
Given the reported differences in risk factor burden and polymorphisms in the CYP enzymes, can we extrapolate the trial results to all racial groups?

The lack of racial diversity among trial participants should raise some question about the translation of trial results to different racial groups. Prevalence of key covariates may differ across these groups which may lead to treatment heterogeneity (45–47). The J-ROCKET AF trial randomised 1,280 Japanese patients to either the lower dose of rivaroxaban, 15 mg per day, or warfarin adjusted to the lower target range consistent with Japanese clinical practice (48). The rate of GI haemorrhage tended to be lower in the rivaroxaban group compared with those randomised to warfarin, which differed from the global ROCKET AF trial.

Given the racial differences reported among the CYP enzymes responsible for the metabolism of warfarin, it is reasonable to expect that racial differences may exist for the NOACs (49, 50). The major enzyme involved in the oxidative metabolism of the factor Xa inhibitors, rivaroxaban, apixaban and edoxaban (least dependent <4%) is CYP3A4. To date, approximately 78 genetic variants of CYP3A4 have been identified. As an example, a specific CYP3A4 polymorphism responsible for the oxidative deactivation of testosterone has been reported in blacks and hypothesised to underlie their heightened risk of prostate cancer (51). Blacks comprised 5% of the ROCKET AF trial population, and 1% or less of participants enrolled in RE-LY, ARISTOTLE, and the Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial (52).

Translation across different indications for anticoagulant therapy
Will the differences in dose and dose frequency across the spectrum of arterial and venous thromboembolic disease lead to unintended errors?
The European Medicines Agency recently approved the lower dose of rivaroxaban (2.5 mg twice daily) for secondary prevention among individuals with ACS in combination with standard antiplatelet therapy. Data driven guidance on the optimal management of patients with AF who experience an ACS is lacking but trials are either underway or are being planned. Treatment of acute venous thrombosis requires rivaroxaban 15 mg twice daily for the first three weeks followed by 20 mg per day (the AF dose) (53, 54). Apixaban was tested using a 10 mg twice daily dose for the first week followed by 5 mg twice daily (the AF dose) (55). Physicians need to be cognisant of these differences in dose, dose frequency, and treatment interval to ensure appropriately timed dose transition. Discharge orders will need to include these changes and plans for how they will be implemented in the ambulatory setting.

Management of life-threatening haemorrhage and drug reversibility
What do we know about warfarin reversal and how different are the NOACs?
Fatal bleeding and critical organ bleeding were reduced by the NOACs compared to warfarin in the randomised trials. Antidotes for dabigatran and the factor Xa inhibitors are currently under development. Administration of fresh frozen plasma or vitamin K would not be expected to have an effect on NOAC-related haemorrhage and are not recommended. In the setting of dabigatran-related life-threatening haemorrhage, dabigatran can be dialysed with the removal of about 60% of drug over 4 h (56). Although prothrombin complex concentrates (PCCs) are recommended for urgent reversal in the setting of life-threatening haemorrhage, to date there are no convincing data that PCCs affect haemostatic endpoints (14). A small study of healthy volunteers suggested a greater effect of PCCs on rivaroxaban versus dabigatran, but this exercise included six people in each treatment arm, and efficacy was based on the magnitude of change in the prothrombin time and partial thromboplastin time, respectively (57). Neither of these tests accurately reflects the anticoagulation status, and results should be interpreted with caution. Clinicians are encouraged to consult the specific package inserts for more detailed guidance on the monitoring and reversal of these agents. Currently, there are no studies to inform use of recombinant factor VIIa in the setting of severe haemorrhage. Of note, the lack of data on reversal of the NOACs is balanced by a lack of data supporting warfarin reversal and meaningful haemostatic endpoints (58). In the setting of warfarin-related major haemorrhage, infusion of a non-activated four-factor PCC rapidly corrected the INR, but there was no difference in haemostatic efficacy assessed over a 24-h period (59).

Clinical implications and future research
The non-vitamin K antagonist oral anticoagulants represent a major breakthrough for the prevention and treatment of thromboembolic disease. Their limited interactions with drugs and diet and wide therapeutic window obviate routine monitoring which has been a significant barrier for many patients who require anticoagulant therapy. The reductions in fatal and ICH were unexpected and constitute compelling reasons for their use. To optimise the effectiveness of NOACs in routine practice across a wide spectrum of patients, further data are needed to inform the clinical questions as presented in this overview. Despite warfarin’s first approval for therapeutic use in 1954, pivotal issues, including reversal, are still being investigated. Continued rigorous research will improve the efficacy and safety of the NOACs as well, and assuage any residual physician or patient concerns regarding their use.

Conflicts of interest
EMH has served on advisory boards for Boehringer-Ingelheim, BMS, Daiichi Sankyo, Janssen, Pfizer and Roche. None of the other authors declares any conflicts of interest.
References


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