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ORIGINAL ARTICLE

# Is the prescription right? A review of non-vitamin K antagonist anticoagulant (NOAC) prescriptions in patients with non-valvular atrial fibrillation. Safe prescribing in atrial fibrillation and evaluation of non-vitamin K oral anticoagulants in stroke prevention (SAFE-NOACS) group

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## Abstract

**Background** Non-vitamin K antagonist oral anticoagulants (NOACs) are a major advance for stroke prevention in atrial fibrillation (AF). Use of the vitamin K antagonist (VKA), warfarin, has dropped 40% since 2010 in our institution. There is limited Irish hospital data on NOAC prescribing for stroke prevention.

**Method** Single centre, retrospective observational cohort study of consecutive AF patients at increased risk of stroke and/or awaiting electrical cardioversion. Data on prescribed NOACs from February 2010 till July 2015 was collected from the electronic inpatient record. Appropriateness of prescriptions was based on CHA2DS2–VASC score and accuracy on individual NOAC SPCs. Potential drug interactions and bleeding risk were also quantified.

**Results** A total of 348 patients AF and increased risk of stroke (CHA2DS2–VASC score > 1 for men and > 2 for women) were studied. Forty-eight percent were female with a mean age 71 ± 18.6 years, 52% of whom were > 75. Mean CHA2DS2-Vasc and HAS-BLED scores were 4.1 ± 1.8 and 1.4 ± 0.8, respectively. Rivaroxaban, dabigatran and apixaban were prescribed to 154 (54.2%), 106 (34.3%) and 41 (13.2%) patients, respectively. 20.4% had inaccurate prescriptions; 92.9% ($n = 65$) underdosed and 7.1% ($n = 5$) on inappropriately higher doses. Neither choice of NOAC, age, history of anaemia, previous bleeding or co-prescribed antiplatelets influenced the accuracy of prescription ($p$ = NS), but decreased renal function appeared to do so ($p = 0.05$).

**Conclusion** Our study highlights significant inaccuracies in NOAC prescribing. Patients commenced on NOACs should be assessed and followed up in a multidisciplinary AF clinic to ensure safe and effective prescribing and stroke prevention.

**Keywords** Anticoagulation · Atrial fibrillation · NOAC · Non-vitamin K oral anticoagulants · Prescription errors

## Introduction

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and affects at least 1–2% of world population [1], and 5.5 to 7 million of Europeans [2]. By the year 2050, an ageing population with an increasing prevalence of risk factors will increase the prevalence of AF by an estimated 2.5-fold [3]. AF is associated with up to five times increased risk of stroke, poor quality of life, heart failure, increased risk of death rate and dementia [4–9] and greatly increased healthcare costs [5, 6].

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A million strokes occur in Europe annually [10], of which 25% at least are AF-related [11]. Oral anticoagulants (OAC) decrease risk of AF-related stroke by two thirds though they have been used in only 60–70% of at-risk patients historically [3]. Vitamin K antagonists (VKA) have been the only available class of OAC for many years for prevention of stroke and systemic embolism in patients with non-valvular AF (NVAF) though their narrow therapeutic index, potential for drug interactions and need for frequent monitoring have limited their use and applicability as a population-wide strategy for stroke prevention in AF [12]. These limiting factors of VKAs and robust non-inferiority randomised trial evidence for stroke prevention in non-valvular AF with non-vitamin K antagonists, oral anticoagulants (NOACS), namely the direct thrombin inhibitor (dabigatran) and three factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), have led to their widespread use and adoption in guidelines as the preferred class of OAC recent years [[13–17] .

Though NOACs have comparable efficacy and enhanced safety compared to VKAs, appropriateness and accuracy of prescribing is important particularly without the laboratory guidance of INRs to prevent stroke or risk of bleeding [18, 19]. Clinicians should assess both risks in all cases with recommended scores (currently $CHA_2DS_2$–Vasc and HAS-BLED) prior to prescription of anticoagulation and discuss this with their AF patients [2, 20].

### Aim

To study the appropriateness and accuracy of NOAC prescribing in the period 2010–2015 in AF patients in a large teaching hospital prior to a specialised AF pathway of care.

## Methods

This is a single centre retrospective review of consecutive AF patients who had received at least one dose of any of the NOACs from 12 Feb 2010 to 06 July 2015 for primary stroke prevention with or without planned electrical cardioversion. Primary outcome measures were appropriateness and accuracy of prescription. Appropriateness of NOAC prescription was defined as administration where $CHA_2DS_2$–Vasc score $\geq 1$ for men and $\geq 2$ for women. Accuracy of prescription was assessed on drug dose and frequency as recommended by individual NOAC SPCs as per patient eGFR calculated by the Cockcroft-Gault equation [21–24]. Secondary measures analysed were risk of bleeding by HAS-BLED score and the potential for drug-drug interactions on review of co-prescriptions.

Ethics approval was obtained from the Joint Research and Ethics Committee. Patient data was collected from 'TEAMS' (an online electronic patient discharge summary) and clinical notes. Relevant clinical information collected included age, gender, background history and indications for anticoagulant therapy. $CHA_2DS_2$–Vasc and HAS-BLED scores were calculated on all patients contemporaneous to the time of prescription. Past and present medications were recorded to search for relevant drug interactions with prescribed NOACs.

### Exclusion criteria

Any patients on VKA or taking NOACs prophylactically or therapeutically for venous thromboembolic disease including pulmonary embolism were excluded.

### Renal profile and NOACs dosing

Individual NOACS are excreted by the kidney to different extents. The presence of chronic kidney disease CKD) was defined as eGFR less than 60 ml/min per 1.73 $m^2$ [25]. Assessment of renal function and dose adjustment forms an important part of pharmacovigilance in NOAC prescribing and is determined by individual SPCs (see Table 1) [22–24]**.** All NOACs should be avoided when eGFR is less 15 ml/min/1.73 $m^2$ currently. Dabigatran is licenced in AF stroke prevention at doses of 110 and 150 mg twice daily in the Republic of Ireland. Doses of 75 mg once or twice daily and 110 mg once daily were considered underdosing and 110 mg BD in a patient who is $\leq 75$ years of age with eGFR $\geq 60$ ml/min/1.73 $m^2$ as potentially underdosing in this study.

### Drug-drug interaction effects on NOACs

Interaction mechanisms for all NOACs after absorption in the gut include significant re-secretion over a p-glycoprotein (p-gp) transporter and CYP3A4-type cytochrome P450-dependent elimination. Concomitant drugs that inhibit or induce either pathway have the potential to interfere with NOAC plasma levels. For this study, interactions were considered if a co-prescribed drug is known to decrease or increase the plasma levels of NOACs and individual NOAC SPC advises avoidance of co-administration or dose reduction [22–24].

### Statistical analysis

IBM SPSS 20.0 was used for statistical analysis. Continuous variables were reported as mean ± SD and/or median. Among group comparisons of means was by ANOVA test and variables were compared by chi-square or Fisher's exact test if any expected cell count is $< 5$. A two-sided $p$ value of $\leq 0.05$ was considered statistically significant.

**Table 1** Dose adjustment of NOACs in relation to renal impairment

| eGFR (ml/min/1.73 $m^2$) | Dabigatran | Rivaroxaban | Apixaban* |
|---|---|---|---|
| > 50 | 150 mg or 110 mg BD | No dose adjustment<br>20 mg OD | No dose adjustment<br>5 mg BD |
| 30–49 | No dose adjustment but better avoided | Dose decrease to<br>15 mg OD | No dose adjustment<br>5 mg BD |
| < 30 | Contraindicated | Contraindicated | Dose decrease to 2.5 mg BD |
| < 25 | Contraindicated | Contraindicated | Contraindicated |
| DOAC renal clearance | 80% | 35% | 25% |

*2.5 mg of apixaban BD if creatinine ≥ 133 micmol plus age ≥ 80 or weight ≤ 60 kg

## Results

### Patient's characteristics

A total of 348 patients with atrial fibrillation who had been consecutively prescribed NOACs from Feb 2012 to July 2015 for primary prevention of stroke with or without planned cardioversion. The mean age was 71.8 ± 18.6 years and 53.6% ($n = 179$) were males. Baseline characteristics of patients are summarised in Table 2(a) and (b). 52.2% of study patients were ≥ 75 years of age. Dabigatran was prescribed to 34.2% ($n = 106$), rivaroxaban to 54.2% ($n = 163$) and apixaban to 13.2% ($n = 41$) over this period. Hypertension was the most common co-morbidity in 69.8% of patients and 67.9% had evidence of chronic kidney disease (CKD).

Table 3(a) and (b) summarises risk of stroke and bleeding. The mean $CHA_2DS_2$–Vasc and HAS-BLED scores were 4.1 ± 1.8 and 1.4 ± 0.8, respectively. Patients with lower $CHA_2DS_2$-Vasc scores (i.e. of < 2) and on NOACs were

**Table 2** (a) and (b): Summary of baseline characteristics of the patients enrolled

| | |
|---|---|
| (a): Patients demographics | |
| Number of patients $N = 348$ | |
| Gender | *n* (%) |
| Male | 181 (52.0) |
| Female | 167 (48.0) |
| Age (year ± SD) | 71.8 ± 18.6 years |
| < 65 | 66/341 (19.4) |
| 65–74.9 | 97/341 (28.4) |
| ≥ 75 | 178/341 (52.2) |
| NOACs prescription | |
| Dabigatran | 106 (34.3%) |
| Rivaroxaban | 154 (54.2%) |
| Apixaban | 41 (13.2%) |
| (b) Patients' comorbidities | |
| | *n*/*N* (%) |
| Hypertension | 222/324 (69.8) |
| Diabetes | 102/322 (31.7) |
| Heart failure | 83/321 (25.9) |
| Ischaemic heart disease | 122/325 (37.3) |
| Peripheral vascular disease | 68/297 (22.7) |
| Stroke | 120/324 (37.0) |
| Dual prescription of DOAC and antiplatelet | 91/313 (29.1) |
| Renal disease | 218/321 (67.9) |
| Previous cancer | 30/300 (10.0) |

*NOACs* direct oral anticoagulants, *SD* standard deviation

**Table 3** (a) and (b): Summary of patients' stroke and bleeding risk assessments as quantified by the ESC guidelines

| | |
|---|---|
| (a) Stroke risk assessment | |
| CHADS2Vasc score | |
| 0 | 3 (0.8%) |
| 1 | 14 (4.0%) |
| 2 | 56 (16.1%) |
| 3 | 71 (20.4%) |
| 4 | 75 (21.6%) |
| 5 | 55 (15.8%) |
| 6 | 31 (8.9%) |
| 7 | 33 (9.5%) |
| 8 | 8 (2.3%) |
| 9 | 2 (0.5%) |
| Mean CHA2DS2Vasc ± SD | 4.1 ± 1.8 |
| CHADS2Vasc < 2 | |
| 0 | 3/341 (0.8%) |
| 1 | 13/341 (3.8%) |
| (b) Stratified by bleeding risk | |
| HASBLED score | *n* |
| 0 | 34 (10.0%) |
| 1 | 185 (54.3%) |
| 2 | 90 (6.5%) |
| 3 | 22 (6.4%) |
| 4 | 9 (2.6%) |
| 5 | 1 (0.2%) |
| Mean HASBLED ± SD | 1.4 ± 0.8 |
| HASBLED groups | |
| Low-moderate risk (< 3) | 310/341 (90.9%) |
| High risk (> 3) | 31/341 (9.1%) |

generally either awaiting or already had electrical cardioversion for AF. 9.1% ($n = 31$) of patients on NOACS were potentially at high risk of bleeding (HAS-BLED score ≥ 3).

## Outcome measures

There were no inappropriate prescriptions regarding the indications for stroke prevention as recommended by the European Society of Cardiology. All patients had a $CHA_2DS_2$–Vasc sore ≥ 2 for women or ≥ 1 for men (moderate to high risk of stroke).

NOACS were inaccurately prescribed however in 20.4% ($n = 70$) of patients. Underdosing was the commonest error in 92.9% ($n = 65$) of inaccurate prescriptions while 7.1% ($n = 5$) were for an inappropriate high dose. When compared, no statistical difference ($p = 0.31$) was observed in the inaccurate prescribing of any one NOAC. 16.0% ($n = 24$) patients on rivaroxaban, 22.6% ($n = 24$) on dabigatran and 22.0% ($n = 9$) on apixaban were underdosed or potentially undertreated (see Table 4).

We also assessed if other factors influenced inaccurate prescription. The presence of significant CKD seemed to be associated with inaccurate prescribing of NOACs ($p = 0.05$) but neither being anaemic ($p = 0.61$), older than 75 years ($p = 0.25$), history of anaemia or bleeding ($p = 0.09$) and co-prescription of antiplatelets ($p = 0.59$) were associated with inaccurate prescribing (see Table 5). There was a non-significant trend of greater incidents of underdosing incidents in 'twice daily' prescribed NOACs (22.6% in dabigatran and 22.0% in apixaban) compared to once daily prescribed NOAC (16% for rivaroxaban); $p = 0.31$. Inaccuracies were noted in both initial prescription dosages and where drug doses had to be adjusted to suit the patient's estimated glomerular filtration rate.

Inaccurate overdosing of NOACs was rare and found in < 1.0% ($n = 1$) of dabigatran and in 3.8% ($n = 4$) of rivaroxaban prescriptions. Overdosing was due to poor assessment of worsening renal impairment. Though numbers were small, being older did not seem to influence incidence of overdosing prescription error.

Regarding drug-to-drug interactions with NOACs, 6.6% ($n = 7$) patients in the dabigatran group, 13.6% ($n = 21$) patients in the rivaroxaban group and 7.3% ($n = 3$) patients in the apixaban group were on drugs that had potential to interaction with individual NOACs. Drugs that had low potential for interaction with NOACs by P-glycoprotein/ABCB1 inhibition were mostly prescribed, 5.5% ($n = 19$), followed by agents with antiplatelet properties, 2.0% ($n = 7$). There was also a 0.8% ($n = 3$) incidence of strong CYP3A4 inducers and 0.2% ($n = 1$) of P-glycoprotein/ABCB1 inducer concomitantly prescribed. One patient was on dronedarone which is a moderate CYP3A4 and P-glycoprotein/ABCB1 inhibitor. Table 6 summarises these findings and highlights the practical recommendations to maximise patient safety.

## Discussion

This is a retrospective single-centre study assessing the appropriateness and accuracy of NOAC prescribing in an Irish teaching hospital. The main finding of this study is that at least 1 in 5 patients with AF who were started on NOACs for primary stroke prevention between 2010 and 2015 had inaccurate prescriptions. This is lower than other international studies where prescription errors were as high as 26% for wrong dosage and 28% for inappropriate drug choice [26, 27]. This study adds to the literature in support of good governance and regular monitoring of prescribed NOACs involving a specialist multidisciplinary AF clinic as recommended by the latest European Heart Rhythm Association practical guide on NOAC use [20].

**Table 4** Overall assessment of initial NOAC prescription appropriateness

| Am | Dabigatran errors | | Rivaroxaban errors | | Apixaban errors | |
|---|---|---|---|---|---|---|
| | *n* | (%) | *n* | (%) | *n* | (%) |
| Inappropriate by CHA2DS2Vasc score | 0 (0) | | 0 | | 0 | |
| Inappropriate by HASBLED score | 0 (0) | | 0 | | 0 | |
| Contraindicated due to renal profile | 20/106 | (18.9) | 16/154 | (10.4) | 0 | |
| Inappropriate by frequency | 8/106 | (7.5) | 2/154 | (1.2) | 0 | |
| Inappropriate by drug dose | | | | | | |
| (a) Underdosing | 24/106 | (22.6) | 25/156 | (16.0) | 9/41 | (22.0) |
| (b) Overdosing | 1/106 | (1.0) | 4/106 | (3.8) | 0/40 | (0) |
| Possible Interactions with NOACs | 8/106 | (7.5) | 21/154 | (13.6) | 2/41 | (4.8) |

Showing assessment of the appropriateness of NOAC prescription on the following areas: whether the use of $CHA_2DS_2$Vasc score for the stroke risk assessment, drug dose and frequency were as recommended by the guidelines or as in the pivotal NOAC trials

**Table 5** Possible determinants of inappropriate prescription

| | Appropriate prescription | Inappropriate prescription | *p* value |
|---|---|---|---|
| Anaemia | 49/249 (19.7%) | 10/40 (25%) | 0.61 |
| Presence of antiplatelet | 32/232 (13.8%) | 11/91 (12.1%) | 0.59 |
| Renal disease | 94/276 | 9/45 | 0.05 |
| Previous bleed | 60/294 | 4/47 | 0.09 |

Summarises the overall assessment of initial NOAC prescription appropriateness. That is whether NOACs' inappropriate prescription was influence by patients being anaemic, elderly, having previous bleed or renal disease or co-prescription with antiplatelets. The presence of renal disease seemed to have influence inappropriate prescription of NOACs

The potential for drug-drug interactions was observed in 8.9% ($n = 31$) of prescriptions that had potential to cause harm. For example, one patient was on dabigatran and phenytoin, a P-glycoprotein/ABCB1 inducer with potential to reduce the anticoagulant effect and efficacy [28]. Three were co-prescriptions for rivaroxaban with strong CYP3A4 agents like the barbiturate, primidone, again with potential to reduce the OAC effect [29]. These examples emphasise the need for increased pharmacovigilance of co-prescriptions with NOACs so that potential for interactions can be monitored if not corrected. Our study also showed that 92% of inaccurate prescriptions involving almost 20% of patients had lower than recommended doses of NOACs. This is a concerning large percentage of patients who may be unprotected from risk of stroke. We feel that these errors may well have been avoided or at least identified early if there had been a clear platform or pathway to review patients within short intervals after initiation of treatment.

The annual estimated stroke risk in our study population was between 8.5 and 12.5%, with mean $CHA_2DS_2$-Vasc score of $4.1 \pm 1.8$. This is higher than the populations included in the all randomised control trials for NOACs [14–16]. The study had also shown that clinicians were appropriate and accurate in the assessment for risk of stroke and risk of bleeding prior to prescription of NOACs in accordance and recommendation by the ESC guidelines [17].

Though there were no obvious major complications related to inaccurate prescription of the NOACs in the observed period, this study highlights the need for pharmacovigilance and monitoring of patients on NOACs. This is perhaps best achieved through patient pathways for AF with structured clinical follow-up as is normally the case with the more frequent VKA clinics. The lack of dedicated NOAC clinics or lack of appropriate follow-up for patients on NOACs raises some concerns with an ageing population more likely to have bleeds and shifts in renal function over time, and multidisciplinary clinics that may include physicians experienced in management of AF and stroke prevention, pharmacists and nursing are now recommended in updated European Heart Rhythm Association [20] and the European Society of Cardiology AF guidelines for the management of AF [17]. These guidelines also recommend these multidisciplinary teams (MDTs) be responsible for assessing drug-drug interactions and pharmacokinetics, monitoring of patients especially with chronic kidney disease through regular calculation of creatinine clearance, and to address dosing errors within prespecified time intervals [20]. MDT AF clinics also have an important role in patient education and compliance, facilitating switches from one OAC to another where necessary and

**Table 6** Mode of drug-to-drug interaction and prescribed drugs with potential interactions with NOACs

| Mode of drug-to-drug interaction | Drugs interacting with dabigatran | Drugs interacting with rivaroxaban | Drugs interacting with apixaban | Number of prescriptions per mode of interaction |
|---|---|---|---|---|
| P-glycoprotein/ABCB1 inhibitors | Ranolazine ($n = 1$) (D)<br>Amiodarone ($n = 1$) (D)<br>Azithromycin ($n = 1$) (D)<br>Quinine ($n = 1$) (D) | Amiodarone ($n = 9$) (B)<br>Ranolazine($n = 4$) (B) | Ranolazine ($n = 2$) © | 19 |
| Both CYP3A4 (moderate) and P-glycoprotein/ABCB1 inhibitors | | Dronedarone ($n = 1$) (D) | | 1 |
| Agents with antiplatelet properties | Escitalopram ($n = 1$) ©<br>Sertraline ($n = 1$) © | Venlafaxine ($n = 2$) ©<br>Paroxetine ($n = 2$) © | Escitalopram ($n = 1$) © | 7 |
| P-glycoprotein/ABCB1 Inducers | Phenytoin ($n = 1$) (x) | | | 1 |
| CYP3A4 inducers (strong) | | Primidone ($n = 3$) (x) | | 3 |
| Total | | | | 31/348 |

give advice in patient management pre-procedure and in event of major bleeding complications.

A randomised controlled trial has shown that this integrated AF management can reduce cardiovascular hospitalisation and cardiovascular death by approximately one third over a mean follow-up of 22 months [30]. The same group has also found using the specialised atrial fibrillation clinics to be cost effective when compared with the standard care for ambulatory AF patients [31] and involvement of clinical pharmacists has been shown to lead to major reductions in morbidity and healthcare costs and improve prescribing safety particularly in older patient cohorts [32–34]. Such models of care could well integrate and complement the existing anticoagulation and pharmacovigilance expertise in VKA ('warfarin') clinics rather than be seen as completely new and separate clinical entities, an important resource consideration as more clinicians and patients prefer and migrate to NOAC use. The Irish Health Services Executive (HSE), like most European countries, has a network of VKA clinics around the country that are well equipped to manage patients on VKAs. These clinics could potentially incorporate NOACs patients at a higher risk of bleeding into their monitoring systems especially as software used for VKA monitoring has been widely adapted for NOAC use.

Surprisingly, in our study, the prescribing errors were not influenced by the patient's history or presence of anaemia, age, presence of impaired renal function, co-prescription with antiplatelet drugs or whether the patient had previous bleeds.

## Strength and limitations

To our knowledge, this is one of the first studies of NOACs prescribing in a large cohort of AF patients at high risk of stroke in an Irish teaching hospital. This is a retrospective study of a specific group of patients and may not be reflective of the prescribing of NOACs in general in our institution. There was insufficient data available regarding follow-up of patients' clinical status to comment or quantify potential complications of NOAC prescribing errors. This highlights the need for systematic pathways of care. While randomised trials have shown a good safety profile for NOACs and real-world clinical data is further encouraging, nevertheless this is usually in the setting of more controlled registries. The study period did not encompass a significant period post-licencing of the factor Xa inhibitor, edoxaban, and hence, limited data was available on the use and accuracy of prescribing with this drug in our institution. Other potential areas of prescribing concern with NOACs such as in patients with high body mass index were not analysed in this study. While not in individual NOAC SPCs, the International Society on Thrombosis and Haemostasis (ISTH) 2016 guidelines have not recommended the use NOACs in patients with a BMI > 40 kg/m$^2$ or weight > 120 kg due the lack of clinical data in this population [35].

## Conclusion and recommendations

We found on review of large cohort of patients with AF at high risk of stroke with or without planned cardioversion that NOACs were appropriately but inaccurately prescribed in up to 20% of patients. The study highlights the importance of dedicated oral anticoagulation surveillance clinics involving multidisciplinary teams consisting of clinicians (cardiologist, neurologist, stroke physicians and haematologists) nurses and pharmacists as recommended ESC guidelines and should be the model of choice where resources are available [36]. These clinics may ultimately provide a platform for rapid access assessment of an ever-growing population of patients with AF who require anticoagulation for stroke prevention and rhythm control.

## Compliance with ethical standards

**Conflict of interest** Dr. Ronan Collins has spoken at educational meetings sponsored by Bayer, Boehringer Ingelheim, Daichii-Sankyo and Pfizer, the manufacturers of non-vitamin k oral anticoagulants,

**Ethical approval** Collection of data was approved by the chairman of the SJH/AMNCH Joint Research and Ethics Committee on behalf of the regional Research and Ethics Committee.

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