Anticoagulation in Atrial Fibrillation: *The Role of the Pharmacist*

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Introduction

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia affecting at least 3% of the Irish population currently. AF is an age-related condition with worldwide prevalence predicted to more than double in the coming decades. This presents a significant health burden as almost one in every three strokes are associated with AF and AF-related strokes tend to be more severe, posing the greatest risk for neurological disability.

Management of AF generally includes the implementation of either a rate or rhythm control strategy and for most patients, initiation of oral anticoagulation (OAC) to prevent stroke.

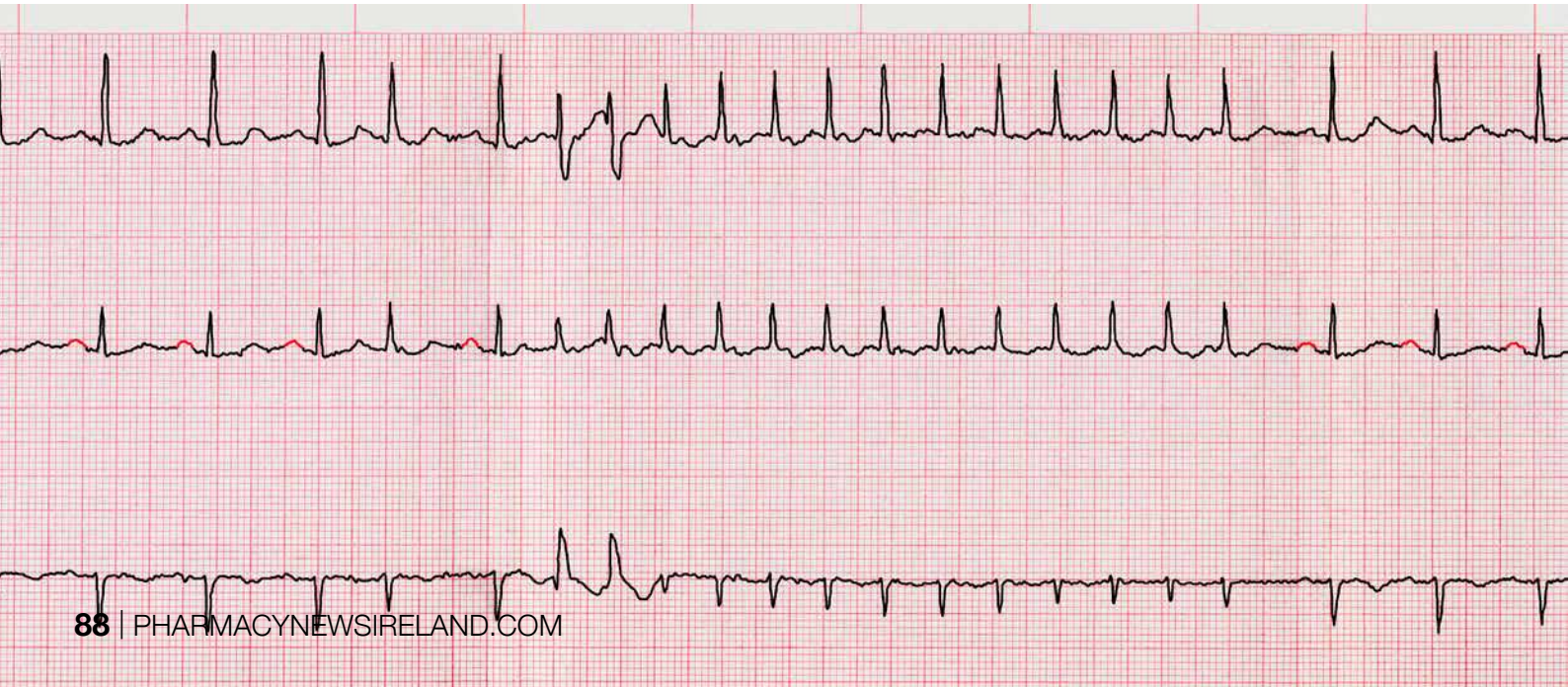
The risk of stroke is calculated using the CHA2DS2-VASc Score as outlined in Table 1. For most patients with AF we err on the side of anticoagulation. The European Society of Cardiology (ESC) recommends that all patients scoring 1 or greater should be considered for OAC (except females scoring only 1 on the basis of gender alone who are considered low risk).

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age > 75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease*	1
Age 65–74	1
Sex category (ie, female sex)	1
Maximum score	9

Note: *Prior myocardial infarction; peripheral artery disease; aortic plaque.
Abbreviations: LV, left ventricular; TIA, transient ischemic attack.

Table 1

Direct Oral Anticoagulants (DOACs) have widely replaced warfarin as the agents of choice due to their efficacy, convenience and reduced, but by no means eliminated, potential for interactions. As increasing age is a prominent AF risk factor, all patients with AF will eventually qualify for lifelong anticoagulation therapy and so it is really important for pharmacists to have an in-depth understanding of these medications.



DOAC Dosing and Method of Administration

There are four DOACs currently available – dabigatran, apixaban, rivaroxaban and edoxaban. All are licensed for a number of different indications and have different dose reduction criteria. The HSE medicines management programme have produced a succinct table[1] which amalgamates the information from the four individual summary of product characteristics (SPCs) and is very useful as a quick reference guide.

All four DOACs are renally cleared to some degree. Therefore creatinine clearance must be calculated using the Cockroft and Gault equation at initiation of therapy and recalculated periodically to ensure accurate dose selection. In hospital, with access to laboratory results, one of the primary roles of the pharmacist in relation to anticoagulant therapy is confirmation that the patient is prescribed the appropriate dose for their renal function. Both over- and under- dosing in the area of anticoagulation puts the patient at risk of the severe consequences of either a serious bleeding event or stroke.

There are however a number of checks that can be performed in the community pharmacy setting to ensure safe DOAC prescribing and dispensing without the need to access laboratory results.

Pharmacists and their teams should ensure an appropriate dosing schedule has been prescribed for the specific indication. Apixaban and dabigatran should always be prescribed twice daily in the setting of AF and any alternative dosing schedule should be queried.

Where patients have their medications blister packed in a Monitored Dosage System (MDS) by the pharmacy team it is important to ensure the DOAC times of administration are spaced appropriately. In the case of twice daily DOACs the administration times should ideally be at 12 hourly intervals.

Dabigatran is not suitable for MDS dispensing and should always be supplied to the patient in its original packaging. Where patient adherence would be compromised by supplying dabigatran separately this should be discussed with the prescriber. There is likely an alternative DOAC the patient could be switched to which is suitable for MDS dispensing, thereby increasing adherence and safety.

It is possible to confirm that an appropriate dose of DOAC has been prescribed in some situations. For example a reduced dose of dabigatran is recommend for all patients 80 years and over and the presence of certain P-glycoprotein (P-gp) inhibitors necessitates a licensed dose reduction for both edoxaban and dabigatran. Where such cases are encountered in the pharmacy it should be flagged to the prescriber and a dose reduction recommended.

There are other prescribing decisions which are less clear-cut e.g. where patients prescribed dabigatran are between 75 and 80 years old or have gastritis. In these cases prescribers are advised to *consider* a dose reduction. These decisions are made on a risk-benefit basis and it can be difficult for pharmacists to make meaningful clinical interventions around dosing for these patients in the absence of a full clinical history.

Patient Education and Adherence

Patient and carer education is one of the most important interventions by healthcare professionals (HCPs) for patients on DOACs. In-depth education should be provided at initiation of DOAC therapy and reinforced periodically thereafter. Patients should be counselled on the following points - indication for DOAC therapy, importance of strict adherence (no DOAC = no protection from stroke), modality of intake (once or twice daily, intake with food for rivaroxaban etc.), management of missed doses, increased risk of bleeding, over the counter medications to avoid and advice given to inform HCPs of DOAC therapy in advance planned procedures (dentist etc.).

Written information should be provided. An alert card is included in the packaging of each of the four DOACs and patients should be advised to carry this on their person at all times. The Irish Medication Safety Network (IMSN) have produced a patient information booklet on anticoagulation in AF. It contains information on the condition of AF and includes general and specific information on all four DOACs. It can be accessed, along with the link to a patient safety video, on the IMSN website (https://imsn.ie/direct-oral-anticoagulants-doacs/) or hard copies can be ordered from Bayer. (dominic.redmond@bayer.com).

Adherence should be assessed on an ongoing basis. Asking patients in a non-judgemental way whether they have missed any doses of medication recently can open this conversation. Twice daily dosing regimens have been associated with reduced adherence. Patients who report missing doses of a twice daily DOAC despite adequate education should be advised that there are once daily DOAC options available and should be referred to the prescriber for consideration of a switch in therapy.

Interactions

Interactions affecting DOACs can be pharmacokinetic or pharmacodynamic in nature. For the most part information on important interactions can be found in the SPC and/or the BNF - reference sources familiar to all pharmacists. The European Heart Rhythm Association (EHRA) have produced a Practical Guide[2] on many different aspects of DOAC therapy in AF. The guide was first produced in 2013 and is currently in its third iteration. It contains a wealth of information in relation to DOAC prescribing and ongoing monitoring and is one of the key references I consult regularly. The EHRA guide includes an extensive section on DOAC interactions which is a really useful resource for pharmacists in practice.

DOAC pharmacokinetics are affected by concomitant administration of medications which either inhibit or induce the P-gp transporter and/or CYP3A4 isoenzyme. Some combinations such as dabigatran and the P-gp inhibitor dronedarone are contraindicated by the manufacturer due to an unacceptable increase in plasma concentrations of DOAC. The EHRA guide contains information on additional potential interactions not included in the SPCs and also provides some guidance around instances where a patient may have more than one risk factor affecting DOAC plasma levels present.

Clinically relevant pharmacodynamic drug-drug interactions generally involve the co-prescription of medications which increase the risk of bleeding. Patients taking DOACs should be advised to avoid the use of non-steroidal anti-inflammatory drugs. The concomitant administration of a low dose antiplatelet such as aspirin or clopidogrel with a DOAC is indicated in some instances. However, pharmacists should query the ongoing need for antiplatelet therapy in patients who are newly prescribed a DOAC. Where the indication for the antiplatelet was primary prevention it should be discontinued to minimise the bleeding risk.

A complex scenario arises when AF patients undergo coronary stenting. Such patients will require a period of treatment with "triple therapy" following their stenting procedure i.e. dual antiplatelet therapy (with clopidogrel and aspirin) and a DOAC. Where such a situation arises clear instruction from the cardiology team in secondary care should be communicated to the patient, the GP and the pharmacist outlining the short, intermediate and long-term plan for antiplatelet and DOAC therapy.

In most instances DOACs should not be prescribed alongside other anticoagulants and any such prescription should be clarified with the prescriber. An exception however is the scenario where a patient is switching from DOAC to warfarin therapy where continuation of DOAC may be required for a number of days due to the slow onset of action of warfarin. Full details on switching between anticoagulants is discussed in detail in the EHRA guide.

Selective serotonin reuptake inhibitors (SSRIs), and other antidepressants with affinity for serotonin receptors, are associated with an increased risk of bleeding. This risk increases further in the presence of DOACs. Where a combination of medications which increase a patients bleeding risk are co-prescribed, it's worth highlighting that gastroprotection with a proton pump inhibitor or H2-receptor antagonists should be considered.

Conclusion

DOACs are an essential treatment for the prevention of stroke in patients with AF. They are also high-risk medications. Pharmacists and their teams in community are central to ensuring the safe and effective use of DOACs through patient education, adherence checks and regular medication review.

References

1. Medicines Management Programme HSE: Anticoagulation Prescribing Tips. https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/oral-anticoagulants/ (2020). Accessed 27/02/2022.

2. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. EP Europace. 2021;23(10):1612-76. doi: 10.1093/europace/euab065.