Prescribing direct-acting oral anticoagulants - mind the evidence gap

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Prescribing direct-acting oral anticoagulants – mind the evidence gap

ABSTRACT

Direct-acting oral anticoagulants (DOACs) are licensed for the prevention of thromboembolism in non-valvular atrial fibrillation amongst other indications. Prescribers use information derived from the summary of product characteristics which is based on the key trials supporting the DOAC's market authorisation. However, prescribers may be aware of the limitations of these trials regarding underrepresentation of patient populations commonly encountered in clinical practice and how this may adversely impact them. This review highlights the gaps in the licensing evidence using 3 clinical vignettes that explore prescribing challenges in the elderly, obese and female patients.

INTRODUCTION

Direct-acting oral anticoagulants (DOACs) are used to prevent and treat thrombo-embolism. Dabigatran was first introduced in the UK in 2008, followed by rivaroxaban, apixaban and edoxaban.[1–4] Each has been shown to be non-inferior to the vitamin K antagonist (VKA) warfarin for the prevention of cardioembolic stroke in non-valvular atrial fibrillation (NVAF) in large randomized clinical trials (RCTs).[5–9] In comparison with VKAs, DOACs require less monitoring, have fewer interactions with other drugs and food, and have a more rapid onset and offset of action.[10]

DOACs, like all new medicinal products, may only be marketed after regulatory agencies such as the Medicines and Healthcare Products Regulatory Agency (MHRA) and European Medicines Agency (EMA), who assess the efficacy and safety in the proposed indications, recommend authorisation (licensing). The Marketing Authorisation Applicant, typically a pharmaceutical company, drafts a Summary of Product Characteristics (SPC or SmPC) to guide clinical use of the medicine. The regulatory agency must approve the SPC, which forms the basis for nationally approved prescribing guides such as the British National Formulary (BNF).

A new medicinal product is typically licensed on evidence from controlled clinical trials. However, the elderly, women (including those who are pregnant or breastfeeding), obese patients, non-Europid patients, and those with multimorbidity are often under-represented in the trial populations. Yet these are the very patients commonly met in clinical practice. As a result, there can be gaps in the evidence a prescriber needs to treat real patients.

Here we explore the use of DOACs for NVAF in three patient groups where licensing information, and often post-licensing evidence, are lacking. We review the SPC guidance for prescribing of DOACs in three groups: the elderly, women including pregnant women, and obese patients, using vignettes of patients commonly encountered in practice.

136 Table 1: Therapeutic indications of DOACs and warfarin (adapted from the SPCs)

Anticoagulant drug	Therapeutic indications
Apixaban[3]	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II). Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.
Dabigatran[1]	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension. Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
Edoxaban[4]	Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA. Treatment of DVT and PE, and for the prevention of recurrent DVT and PE in adults
Rivaroxaban[2]	Prevention of stroke and systemic embolism in adults with NVAF, with one or more of the following risk factors: previous stroke or TIA, age 75 years or more, hypertension, diabetes mellitus, symptomatic heart failure (NYHA Class 2 or higher). Prevention of VTE in adults undergoing elective hip or knee replacement surgery. Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults. Prevention of atherothrombotic events after ACS in people with elevated cardiac biomarkers.
Warfarin[11]	Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation. Prophylaxis after insertion of prosthetic heart valves. Prophylaxis and treatment of venous thrombosis and PE. Transient attacks of cerebral ischaemia.

137

138 Abbreviations: ACS, acute coronary syndrome; DVT, deep vein thrombosis; NVAF, non-valvular atrial fibrillation; NYHA,

139 New York Heart Association; PE, pulmonary embolism; TIA, transient ischaemic attack; VTE, venous thromboembolic

140 events

Table 2: Numbers of participants, age and proportions of female, non-Europid, obese and multimorbid (as inferred from a CHA_2DS_2-VASc score ≥3) patients included in the clinical trials supporting EMA authorisation for the NVAF indication of the four commonly utilised DOACs

DOAC	Year of authorisation	Supporting clinical study	*n*[b]	Median age in years (IQR)	Female (%)	Non-Europid (%)	Definition of obesity	Obese (%)	CHA_2DS_2-VASc score ≥ 3 (%)[c]	Post -authorisation study requested
Apixaban[d] [9,12,13]	2012	ARISTOTLE	21,105	70 (63-76)	35.5	37.3	Weight > 120 kg	5.4	30	No
Apixaban[d] [7,12]	2012	AVERROES	5,599	70 (61-79)	41	-	-	-	28	No
Dabigatran [13–15]	2011	RE-LY	18,113	71.5 (62.7-80.3)	36.4	30	BMI >36 kg/m^2	10	32.5	Yes[e] [16]
Edoxaban [13,17–19]	2015	ENGAGE AF–TIMI 48	21,105	72 (64-78)	38	17	BMI >40 kg/m^2	5.5	22.6 (>4)	No
Rivaroxaban[d] 6,13,20	2011	ROCKET-AF	14,264	73 (65-78)	39.7	17.4	BMI >35 kg/m^2	15.5	87	No
Rivaroxaban[d] 13,20,21	2011	J-ROCKET-AF	1,280	71.1 (34–90)	19.4	100	-	-	83.4	No

Abbreviations: BMI, body mass index; IQR, inter-quartile range
[a] Post-authorisation study requested by EMA
[b] *n* = Number of participants
[c] CHA_2DS_2-VASc score ≥ 3 indicates high cardiovascular comorbidity and increased annual risk of stroke
[d] Both apixaban and rivaroxaban had two main trials that supported market authorisation whereas dabigatran and edoxaban where authorised based on evidence from single clinical trials.
[e] Due to significant increase in incidence of bleeding events identified from post-marking pharmacovigilance, the EMA requested that the market authorisation holder undertake detailed analysis of these events in 2012. Following this, the EMA concluded that there was still a positive risk benefit with dabigatran but the SPC was modified to minimise bleeding risks. There have been safety further assessments and the SPC has been updated to reflect this.

CASE VIGNETTES

The elderly patient

Consider the following patient encountered on an acute medical ward round:

> A 90-year-old man is admitted with pneumonia and is found to have new-onset NVAF. He has a past medical history of poorly controlled hypertension and early dementia. He mobilises with a walking stick and hasn't had any recent falls. Serum creatinine concentration 110 micromoles/L, haemoglobin 110 g/L. His weight is 75 kg.

His CHA_2DS_2-VASc score is 4 (two points for age over 75 years, one for hypertension, one for diabetes), indicating an annual stroke risk of 5–7%.[22] The most recent NICE guidance for AF[23] advises using the ORBIT score to assess bleeding risk. His ORBIT score is 3 (one point for age > 74 years, two points for haemoglobin <13 g/dL), indicating a medium bleeding risk (4.7 bleeds per 100-patient years). Should he be offered a DOAC, and if so which one and at what dose?

Table 3: Special populations data for the elderly, adapted from the summary of product characteristics (European Medicines Agency)

DOAC	**Prescribing in the elderly**
Apixaban	Dose reductions in patients who have at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 micromole/L).
Dabigatran	Dose reduction recommended in patients aged ≥80 years Consider dose reduction in patients between 75-80 years In patients over 75 renal function should be monitored annually as well as prior to treatment initiation.
Edoxaban	No dose reduction is required.
Rivaroxaban	No dose adjustment is required.

Elderly patients are under-represented in the trial-based dosing evidence, as illustrated in Table 2. For example, the median age of participants in the ARISTOTLE trial, providing the evidence base for apixaban licensure in NVAF, was 70 years with interquartile ranges of 63–76 years.[9] Only 13% of participants were 80 years old or older. The prevalence of AF increases with age[24] and the elderly are more likely to experience significant adverse effects from medications than younger patients.[25]

All four DOACS are licensed for use in the elderly (Table 3). The individual SPCs do not guide as to the preferred option in elderly patients. There are no head-to-head trials of the four commonly used DOACs. There is some weak indirect evidence from network meta-analysis suggesting that apixaban

may be associated with less gastrointestinal bleeding.[26,27] If initiating apixaban for the patient in our vignette, he should have a full dose of apixaban (5 mg twice daily) based on the licensing criteria (table 3) as he does not meet criteria for dose reduction.[3]

The female patient

Consider the patient below, encountered on acute medical take:

> A 37-year-old woman is admitted with pyelonephritis. She has a past medical history of hypertension and recently diagnosed NVAF. Her average home blood pressures over the past few months has been 165/95 mmHg.

This patient's CHA_2DS_2-VASc score is 2 (scoring for female sex and poorly controlled hypertension). Her annual risk of stroke is 2.2% per year.[22] Her ORBIT bleeding risk score is 0, suggesting a low bleeding risk (2.4 bleeds per 100 patient-years).[23] What other factors should be taken into consideration if offering a DOAC to this patient?

Table 4: Special populations data for gender and pregnancy patients, adapted from the summary of product characteristics (European Medicines Agency)[1–4]

DOAC	Prescribing in women	Prescribing in Pregnancy
Apixaban	No dose adjustment required	Avoid use during pregnancy. No data from use in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Dabigatran	No dose adjustment is necessary	Should not be used during pregnancy unless clearly necessary. There is limited amount of data in pregnant women. The potential risk for humans is unknown. Studies in animals have shown reproductive toxicity.
Edoxaban	No dose reduction is required	Contraindicated during pregnancy. Safety and efficacy of edoxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity.

Rivaroxaban	No dose adjustment required	Contraindicated during pregnancy. Safety and efficacy have not been established in pregnant women. Studies in animals have shown reproductive toxicity.

The impact of sex differences in cardiovascular disease and treatment outcomes has received growing interest. Women tend to be older than men when the diagnosis of AF is made and have a higher prevalence of hypertension and valvular heart disease.[28] They are also less likely to be referred to an electrophysiologist.[28,29] Women comprise roughly half of the adult population world-wide and cardiovascular disease accounts for 55% of deaths in females in Europe but this burden is not reflected in cardiovascular clinical trial populations.[30] Whilst the SPCs do not advise any adjustment for sex, the evidence for this is based on trials in which only 35.5-39.7% of participants were female, as shown in table 2.[30]

The SPCs state that DOACs should be avoided in pregnancy (Table 4).[1–4] The evidence base for DOAC safety and efficacy in pregnancy is limited to retrospective pharmacovigilance reporting and published literature, as pregnant patients were excluded from clinical trials. Breastfeeding and fertility evidence is limited to pre-clinical animal studies.[2–4] As with any medication prescribed to women of childbearing age, counselling on pregnancy and contraception is advisable when initiating DOAC therapy.[1–4]

The obese patient

Obesity presents another complex prescribing challenge. Consider this case:

> A 69-year-old woman presents to the emergency department with palpitations. She has past medical history of hypertension and diabetes. She is diagnosed with NVAF. A recent echocardiogram shows no valvular disease. She weighs 130 kg and her body mass index (BMI) is 42 kg/m^2.

Her CHA_2DS_2-VASc is 4 (scoring for age, female sex, hypertension, and diabetes) thus supporting anticoagulation.[22]

Table 5: Special populations data for obese patients, adapted from the summary of product characteristics (European Medicines Agency)[1–4]

DOAC	**Prescribing in obese patients**
Apixaban	No dose adjustment required. Apixaban exposure was approximately 30% lower in subjects with body weight > 120 kg than in those with body weight 65–85 kg.
Dabigatran	No dose adjustment is necessary. The dabigatran trough concentrations were about 20% lower in patients with a body weight > 100 kg compared with 50–100 kg.
Edoxaban	No guidance given for use in increased body weight.
Rivaroxaban	No dose adjustment required. Extremes in body weight (< 50 kg or > 120 kg) had only a small influence (less than 25%)on rivaroxaban plasma concentrations.

The SPCs for all four DOACs support their use in obese patients. Body weight was not among the exclusion criteria in any of the main RCTs from which the SPC information was derived yet obese populations were relatively under-represented (see Table 2). Meta- and sub-group analyses of these RCTs showed no significant differences in terms of safety and efficacy between patients with normal versus high BMI.[31,32] However, these studies were underpowered to find differences in outcomes between these groups. Furthermore, binary outcomes may not adequately characterize risk over the full range of body weight and BMI.

Due to concerns about the evidence in this population, in 2016 the International Society of Thrombosis and Haemostasis recommended VKA therapy instead of DOACs for oral anticoagulation in patients with a BMI >40 kg/m^2 or weight > 120 kg.[33] If DOAC is the only option available, then the advice is to

prescribe a fixed dose and regularly monitor drug concentrations. However, in clinical practice DOAC drug levels are not routinely available, difficult to interpret, and the correlation between clotting parameters and clinical outcomes is unknown.

Curiously, obese patients have more favourable thromboembolic outcomes than non-obese patients. This observation, the so-called 'obesity paradox', has been reported in patients with AF, congestive heart failure, coronary heart disease and end-stage kidney disease.[31–35]A post-hoc analysis of the ARISTOTLE trial demonstrated a significant risk reduction in all-cause mortality and the composite endpoint of stroke and systemic embolism, myocardial infarction and death in obese compared with non-obese patients.[35] It may be that patients with higher body weight are more frequently given optimal doses of cardiovascular medications, resulting in a lower risk of thromboembolic and cardiovascular outcomes.[35,36]

DISCUSSION

The three cases highlight evidence gaps in DOAC licensing evidence and the SPCs used to guide prescribing.

The elderly were under-represented in the pivotal trials that provided the evidence on which the SPCs are based. This makes it uncertain whether the SPC information can be generalized to this ever-growing cohort of patients whose management is complicated by frailty, multimorbidity and problematic polypharmacy . In AF, the competing risks of thromboembolism and haemorrhage are perhaps the hardest to balance, highlighting the need for robust evidence to assist in guiding DOAC use. The elderly are more likely to receive a non-licensed dose of DOAC, which is associated with increased morbidity and mortality.[24]

Women are less likely to be prescribed the SPC recommended dose of DOACs. Additionally, there has been little progress in obtaining further evidence in pregnancy and breastfeeding since authorisation and the SPCs' recommendations have been unchanged. In this population, where there is a dearth of robust clinical prescribing information, professional bodies such as the Royal College of Obstetricians and Gynaecologists, produce useful guidance to assist in making safer prescribing choices.[37] Ongoing universal pharmacovigilance reporting for DOAC exposure in women and in pregnancy could help to provide important safety information, especially on maternal safety and foetal outcomes.[38]

Currently, in the management of obese patients, the DOACs' SPCs recommendations are at odds with guidance from the International Society of Thrombosis and Haemostasis due to the lack of evidence present in the original licensing trials. There have been studies post-authorisation that have attempted to demonstrate safety and efficacy in this population.[39,40]They may inform future prescribing guidance.

Real-world evidence suggests that around a quarter of patients are prescribed non-licensed doses of DOACs.[24] The observational Global Anticoagulant Registry in the Field-Atrial Fibrillation study (GARFIELD-AF) suggested that patients prescribed a dose lower than recommended in the SPC had higher all-cause mortality than correctly dosed patients (HR 1.25 (95% CI 1.04-1.50)).[24] The increase in deaths was due to cardiovascular complications such as myocardial infarction and heart failure rather than embolic disease. Although the study reported that there was no difference in major bleeding between those prescribed a dose higher than recommended and those having a recommended dose (HR 1.29, 95% CI 0.59-2.78), the confidence intervals were too large to exclude a clinically relevant risk.[24] Patients receiving non-recommended low doses did not experience a higher rate of stroke or systemic embolism compared with those receiving the correct doses (HR 0.92 (95% CI 0.62–1.37)). Clinicians may be more likely to prescribe inappropriately low doses of DOACs due to perceptions about risk and responsibility for resultant complications versus longer term intended

benefits.[41] Importantly, they may be unaware of the limitations of the SPC information when prescribing for certain populations, which could lead to harm.

Regulation has a key role in ensuring patients receive effective, safe medicines in a timely fashion. These intentions may conflict, especially when there is a desire for rapid access to new therapies. Nevertheless, pre-licensing, market authorisation applicants and medicines regulators could ensure that relevant populations, especially those commonly encountered in practice, some highlighted here in the case of DOACs, are adequately represented in pivotal trials supporting licensing. If this proves impossible, then regulators could require focused post-authorisation studies, permitting later evidence-based SPC and labelling revisions to guide optimal prescribing in patient groups under-represented or not represented in the pivotal trials.

CONCLUSION

Commonly encountered gaps in prescribing information for DOACs include prescribing for patients with obesity, the elderly, and pregnant women. Medicines regulators can require that such gaps are filled, ultimately improving DOAC prescribing and, consequently, the associated health outcomes for patients.

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