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Inappropriate dosing of direct oral anticoagulants: findings from a clinical vignette study and physician survey

Ahmet Fuat[a], Emmanuel Ako[b], David Hargroves[c], Douglas Holden[d], Amrit Caleyachetty[d], Matthew Carter[d], James Harris[d], Carol Roberts[e], Nnanyelu Nzeakor[e], Burcu Vardar[f] and Helen Williams[g]

[a]Carmel Medical Practice, Nunnery Lane, Darlington, UK; [b]Cardiology, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK; [c]Stroke Medicine, East Kent Hospitals University NHS Foundation Trust, Canterbury, UK; [d]Wickenstones Ltd, Carlow, Ireland; [e]Bayer PLC, Reading, UK; [f]Bayer AG, Berlin, Germany; [g]Department of Medicines Optimisation, South East London Integrated Care System, and UCL Partners, London, UK

ABSTRACT

Objective: Direct oral anticoagulants (DOACs) are first-line therapy for stroke prevention for 1.4 million atrial fibrillation (AF) patients in the UK. However, the rates of DOAC dosing below evidence-based recommendations are estimated between 9% and 22%. This study explores specific patient and physician factors associated with prescribing inappropriate DOAC underdoses.

Methods: DOAC-prescribing physicians within the UK completed both a clinical vignette survey, which contained 12 hypothetical patient profiles designed to replicate DOAC prescribing scenarios, and a physician survey to capture sociodemographic, clinical experience, and prescriber-related beliefs and motivations related to DOAC prescribing. Eight patient factors based on a literature search and an expert consultation process were varied within the vignettes. Associations between the prescribers' dosing choices and patient factors were explored via multilevel logistic regression. The analysis is focused on the most frequently selected DOACs, apixaban and rivaroxaban, both of which have different dosing guidelines.

Results: In all, 336 prescribers (69% male; 233/336) completed the survey, mostly general physicians (GPs) (45%) or cardiology specialists (36%) with a mean of 17.9 years' experience. Most prescribers (73%; 244/336) inappropriately underdosed at least once; rates between GPs and specialists were nearly identical. Patient factors most strongly associated with apixaban inappropriate underdosing included a history of major bleeding and falls. For rivaroxaban, these were major bleeding and severe frailty. Only 32% (106/335) of prescribers reported DOAC dosing guidelines as the sole influence on their prescribing behaviour. Among prescribers who did not inappropriately underdose, greater prescribing confidence was aligned to increased perception of inappropriate underdose risk.

Conclusions: Overall, patient factors such as major bleeding and severe frailty were found to be associated with inappropriate underdosing of apixaban and rivaroxaban. Furthermore, prescribers who were more confident in DOAC prescribing, and were more worried about the risk of stroke, were significantly less likely to inappropriately underdose. These findings suggest that all prescribers, regardless of speciality, may benefit from education and training to raise awareness of the risks associated with inappropriate DOAC underdosing.

KEY QUESTIONS

What is already known about this subject?

DOAC dosing below evidence-based recommendation is a common occurrence in patients with AF that has been associated with adverse outcomes. Until now the factors associated with inappropriate underdosing have not been explored.

What does this study add?

This study provides insight into both physician and patient factors that are associated with inappropriate DOAC underdosing and is the first study to use a clinical vignette survey approach for this topic. DOAC dosing guidelines were the sole influence on prescribing behaviour for only a third of prescribers, and two-thirds inappropriately underdosed at least once. History of major bleeding, falls, and frailty are patient factors associated with inappropriate underdosing.

How might this impact clinical practice?

Raised awareness on potential drivers of inappropriate dosing and an emphasis that all prescribers may benefit from information and training may improve outcomes for patients who are prescribed DOACs.

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CONTACT Helen Williams Helen.Williams@selondonics.nhs.uk Department of Medicines Optimisation, NHS South East London CCG, 160 Tooley Street, London SE1 2TZ, UK

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Introduction

In the UK, atrial fibrillation (AF) affects 1.4 million people, whose stroke risk is five-fold compared to those unaffected. Furthermore, AF-related strokes are associated with greater morbidity and mortality than non-AF-related strokes [1]. Patients with AF often have a comorbidity that requires management alongside AF, including ischemic heart disease, diabetes, and frailty (of which falling may be a feature) [2–4].

Direct oral anticoagulants (DOACs) are recommended globally as first-line therapy to minimise stroke risk in patients with non-valvular AF at high risk of stroke [5–9]. A body of evidence supports dose adjustments for patients with specific comorbidities (i.e., chronic kidney disease and low body weight [<60 kg]) and specific characteristics (i.e., age and renal clearance) [10,11]. Evidence-based dosing recommendations are disseminated in national and international guidelines, such as those published by the European Society of Cardiology as well as the product information sheet of each DOAC. Studies have shown, however, that DOAC dosing outside of evidence-based recommendations occurs commonly [12]. Depending on the DOAC, dosing below evidence-based recommendations occurs at a rate between 9% and 22% in the UK [10].

A recent systematic review demonstrated that dosing below evidence-based recommendations (referred to as 'inappropriate underdosing' hereafter) is not associated with reduced bleeding risk but does increase the risk of all-cause mortality for AF patients [13]. As such, the evidence suggests there is a strong clinical rationale for adhering to dosing guideline recommendations. The NHS Long-Term Plan has made improved treatment of cardiovascular disease a priority and, more specifically, the improved management of AF is included within the Academic Health Science Network (AHSN) initiative as part of the '*Detect, Protect, Perfect*' agenda. This aims for optimised anticoagulation in line with NICE AF treatment guidance [14].

The reasons for underdosing are presently unclear but may be driven by intentional (e.g., deliberate prescription of reduced dose based on clinical experience) or unintentional (e.g., certain patient characteristics that influence physicians unknowingly) factors. Both patient and prescriber characteristics may influence DOAC dosing decisions, and these are difficult to evaluate by analysing routinely collected electronic health records or randomised clinical trials [13].

The aim of this study was to use a clinical vignette survey and physician survey to identify specific patient and physician factors associated with prescribing an inappropriate underdose.

Methods

Study design and setting

A cross-sectional study with a fractional factorial experimental design was conducted with UK general practitioners (GPs), secondary care specialists, and clinical pharmacists. The study consisted of clinical vignettes[1] based on patient factors, and a physician survey. During protocol development, it was confirmed that this research did not require approval by either the UK National Health Service (NHS) Research Ethics Committee (REC) or the UK Health Research Authority (HRA). Participant consent for aggregated use of survey responses in publications was collected through the survey platform.

Recruitment and sample size

Recruitment of GPs, secondary care specialists, and clinical pharmacists in either primary or secondary care in the UK was conducted independently by SurveyEngine, using pre-defined screening criteria for each of the expert groups. Participants were excluded if they did not have DOAC prescribing responsibilities.

The target sample size was 300 prescribers (150 primary care and 150 secondary care prescribers). This calculation was developed by an independent external statistician who considered the percentage of initial inappropriate dosing from historical UK data [10] (see Supplementary materials Section 1.4).

An initial 43 physicians responded to all 12 vignettes in the first round of survey rollout. Due to recruitment challenges during the COVID-19 pandemic, a second round was required with an added financial incentive (€70 for GPs and €96 for secondary care specialists). A further 293 physicians subsequently responded to the second round, for a total of 336 survey participants. Aside from the added financial incentive, both rounds were conducted identically. For all participants, the survey was conducted anonymously via SurveyEngine (https://surveyengine.com).

Survey development and content

A multidisciplinary group of healthcare professionals (one cardiologist, two clinical pharmacists, one general practitioner, and one stroke physician) participated in a stepwise

[1]A clinical vignette is a brief, written case history (patient profile) of a fictitious patient that is based on a realistic clinical situation 15

process to develop the study protocol. The eight patient factors and their levels evaluated within the vignettes were selected based on a literature search and expert consultation process (see Supplementary materials).

In the vignette part of the survey, respondents were asked to evaluate 12 clinical vignettes[1] which simulated a DOAC prescribing situation and required a binary response (prescribe a lower DOAC dose or not). Most vignettes presented were those where the patient should receive a standard dose, according to guideline recommendations. Respondents were able to choose the DOAC and dose they wanted to prescribe as well as provide comments on their DOAC prescribing decision (additional experimental design information can be found in Supplementary materials).

Following the completion of the vignettes, participants also completed a physician survey on sociodemographic characteristics, clinical experience, and prescriber-related beliefs and motivation for DOAC prescribing (see Supplementary materials).

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design.

Statistical analysis

Data was analysed in STATASE 17 for Windows [16]. Descriptive statistics were used to describe prescriber characteristics. Qualitative explanations for inappropriate underdosing decisions provided by free-text entry are summarised in Supplementary materials. The associations between the prescribers' dosing choices and patient factors were explored by means of multilevel logistic regression. A cut-off of $P < 0.05$ was used for statistical significance, and odds ratios (OR) and their associated 95% confidence intervals (CI) were calculated to show the magnitude and precision of effects in the regression models. A t-test was used to compare statistical differences between group means in the physician survey.

All patient factors that varied within the vignettes were included within regression models for statistical analysis. Exceptions to this were creatinine clearance, which could not be investigated for rivaroxaban dosing choices, as the levels of this variable were perfectly correlated with the outcome of interest, and body weight for apixaban doses, as all standard dose vignettes had body weight ≥60 kg. Due to the differences in dosing guidelines, separate regressions were performed for each DOAC. Only responses related to standard, not reduced dose vignettes were included for logistic regression analysis.

Regression analysis for dabigatran was considered infeasible and not performed due to the statistical methodology, which was developed to capture drivers of the most commonly prescribed DOACs, apixaban, and rivaroxaban, not being well suited for dabigatran dosing guidelines.

Results

Description of sample

Overall, 336 prescribers completed the physician survey, of whom 69% (233/336) were male, with 17.9 mean years of clinical experience mostly as GPs (150/336; 45%) or cardiology (122/336; 36%) specialists distributed evenly throughout NHS England. One respondent did not complete the physician survey but did respond to all 12 vignettes and therefore was included in the latter, but not former datasets.

DOAC selection

Only vignettes for which apixaban and rivaroxaban were selected were included for multiple regression analysis (see Methods and Supplementary materials for further discussion). The most common prescribing choices in the clinical vignette survey were apixaban (56.7%; 2288/4032) and rivaroxaban (19.1%; 772/4032), with 88.7% (298/336) of respondents prescribing apixaban at least once, and 48.5% (163/336) prescribing rivaroxaban at least once. Edoxaban was also not included, due to an inadequate spread of patient factors within the sample of responses where edoxaban had been selected.

Patient factors associated with selecting inappropriate underdoses

Apixaban analysis

Patient factors most strongly associated with apixaban inappropriate underdosing included history of major bleeding and falls. Major bleed history was associated with increased odds of an inappropriate underdose (OR 4.25, 95% CI [2.23, 8.13]) and so was one fall in the previous year (OR 1.73, 95% CI [1.04, 2.88]). Severe frailty also had some association with inappropriate underdosing; however, this was not statistically significant (Figure 1a). Details of prescribers' qualitative explanations are provided Supplementary materials.

Patient factors associated with inappropriate underdosing by GP and specialist subgroups. Stratified regression was performed for DOAC dosing choices made by GPs (119 selected apixaban for at least one vignette) compared to those made by specialists (166 selected apixaban for at least one vignette). The patient factor most strongly associated with a GP's

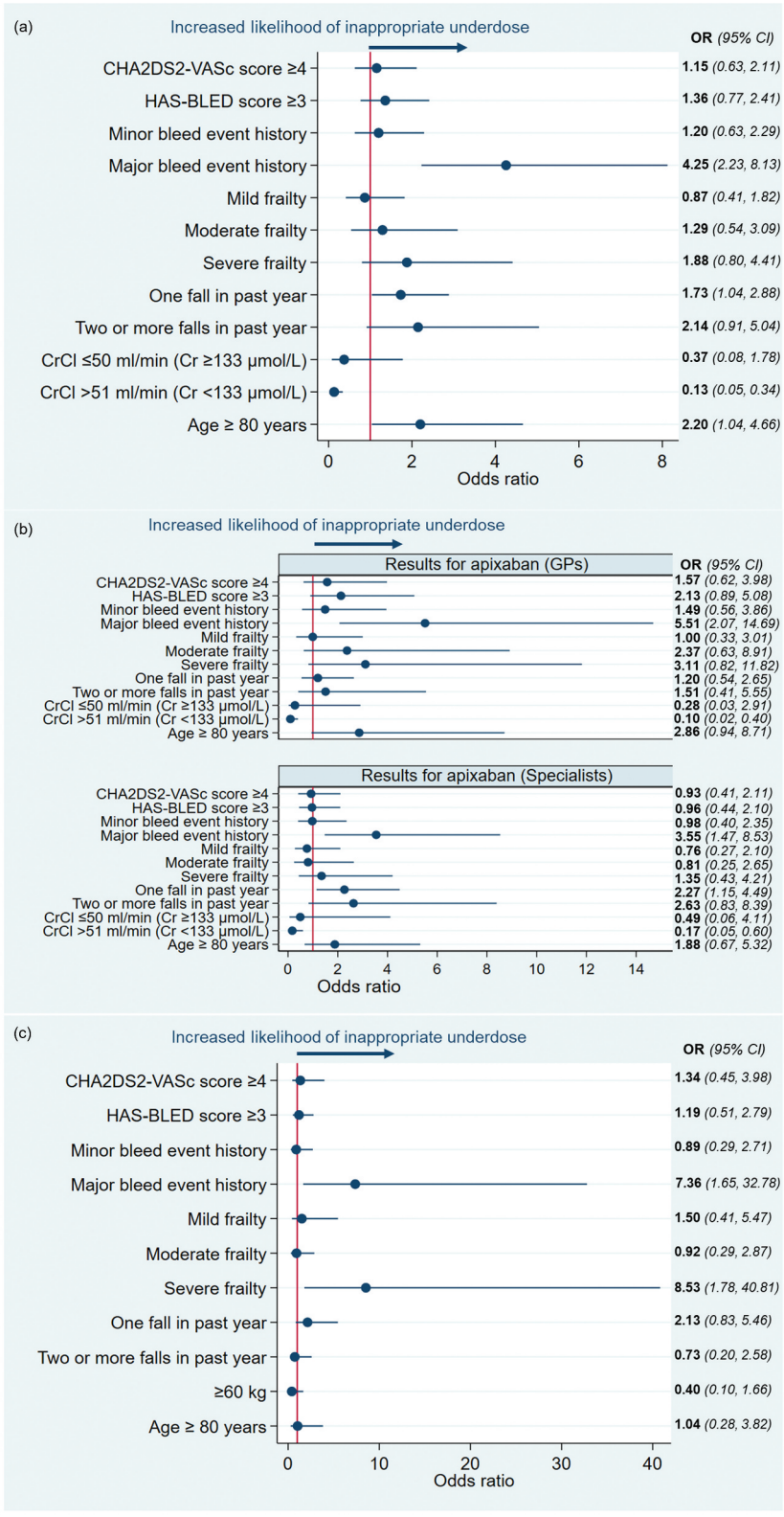

Figure 1. Patient factors for (a) apixaban (all prescribers), (b) apixaban (GP/specialist subgroups), and (c) rivaroxaban (all prescribers), inappropriate underdoses from the clinical vignette survey.

inappropriate apixaban underdose was a major bleeding event history (OR 5.51, 95% CI [2.07, 14.7]). Moderate and severe frailties, as well as fall history, were also correlated with greater odds of inappropriate apixaban underdosing by GPs; however, these were not found to be statistically significant. Among specialists, the patient factors most strongly associated with an inappropriate apixaban underdose were one fall in the past year (OR 2.27, 95% CI [1.15, 4.49]), as well as major bleed event history (OR 3.55, 95% CI [1.47, 8.53]) (Figure 1b).

Rivaroxaban analysis

Patient factors most strongly associated with rivaroxaban inappropriate underdosing again included history of major bleeding but additionally included frailty. Increased odds of an inappropriate underdose were found for patients with major bleed event history (OR 7.36, 95% CI [1.65, 32.8]), or with severe frailty (OR 8.53, 95% CI [1.78, 40.8]) (Figure 1c). Details of prescribers' qualitative explanations are provided in the Supplementary materials. Stratified regression by prescriber speciality was not performed for rivaroxaban due to small sample sizes (N GPs = 65, N specialists = 66) and imbalanced selection which confounded results when separated by the subgroups.

Prescriber characteristics associated with inappropriate underdosing decisions

Prescriber understanding of DOAC guidelines, confidence, and perception of underdose risk

Most prescribers (211/335; 63%) reported having a good understanding of DOAC dosing guidelines but allowed their clinical judgement to influence their prescribing behaviour (97/150; 65% of GPs and 114/185; 62% of specialists, respectively); 106/335 (32%) of all prescribers reported a good understanding of DOAC dosing guidelines which solely influenced their prescribing behaviour (41/150; 27% and 65/185; 35% of GPs and specialists, respectively) (Figure 2a).

Overall prescribers reported confidence in their DOAC dose decision-making, with over half (184/335; 55%) being 'very sure' (150/335; 45%) or 'extremely sure' (34/335; 10%) of selecting DOACs doses appropriately (Figure 2b).

In total, 309/335 (92%) of all prescribers reported a degree of worry that DOAC inappropriate underdosing would not optimally reduce stroke risk; 186/335 (56%) were either 'moderately' or 'very worried' and 123/335 (37%) were 'a little worried' (Figure 2c).

Prescriber profiles associated with DOAC inappropriate underdosing

Overall, across all DOACS, most prescribers (244/336; 73%) inappropriately underdosed at least once (Table 1), with near identical rates between GPs and specialists (108/150; 72% and 136/186; 73%, respectively). In the group that did not inappropriately underdose (92/336; 27%), the rates between GPs and specialists were also similar (Table 1). The mean years of practice since qualification (17.7) among prescribers who made at least one inappropriate underdose was similar to that of prescribers who did not (18.2) (Table 1).

The perception of underdose risk was different between prescribers who chose an inappropriate underdose and those who did not. A greater proportion (44/91; 48%) of the prescribers who did not select inappropriate underdoses responded being 'very worried' that a reduced DOAC dose would not optimally reduce stroke risk versus the prescribers who selected an inappropriate underdose at least once (45/244; 18%) ($P < 0.001$) (Table 1).

There was an increased tendency for prescribers who selected an inappropriate underdose at least once to report that their 'clinical judgement also affects their prescribing behaviour' compared with prescribers who did not select an inappropriate underdose (163/244; 67% vs 48/91; 53%, respectively) (Table 1). There was also a stronger tendency for prescribers who did not inappropriately underdose to only follow DOAC guidelines when prescribing and be either 'very' or 'extremely' sure of their prescribing decision-making confidence compared with the prescribers who selected an inappropriate underdose at least once (38/91; 42% vs 68/244; 28%, and 62/91; 68% vs 122/244 50%, respectively) (Table 1).

Relationship between perception of underdose risk and prescribing confidence. Since prescribers who did not inappropriately underdose tended to have a high perception of DOAC underdose risk, and more often tended to demonstrate a high prescribing confidence (Table 2) than those who selected at least one inappropriate underdose, the relationship between perception of DOAC underdose risk and prescriber confidence was explored more closely. Heatmaps of responses to the physician survey questions 'How worried would you be, if at all, that prescribing a reduced dose of DOAC for an AF patent, would not optimally reduce stroke risk?' and 'If you were to prescribe a DOAC for stroke prevention in an AF patient, how sure are you that you would dose appropriately?' revealed differences between prescribers who did not select inappropriate underdoses and those who did (Supplementary Figure S1a and S1b).

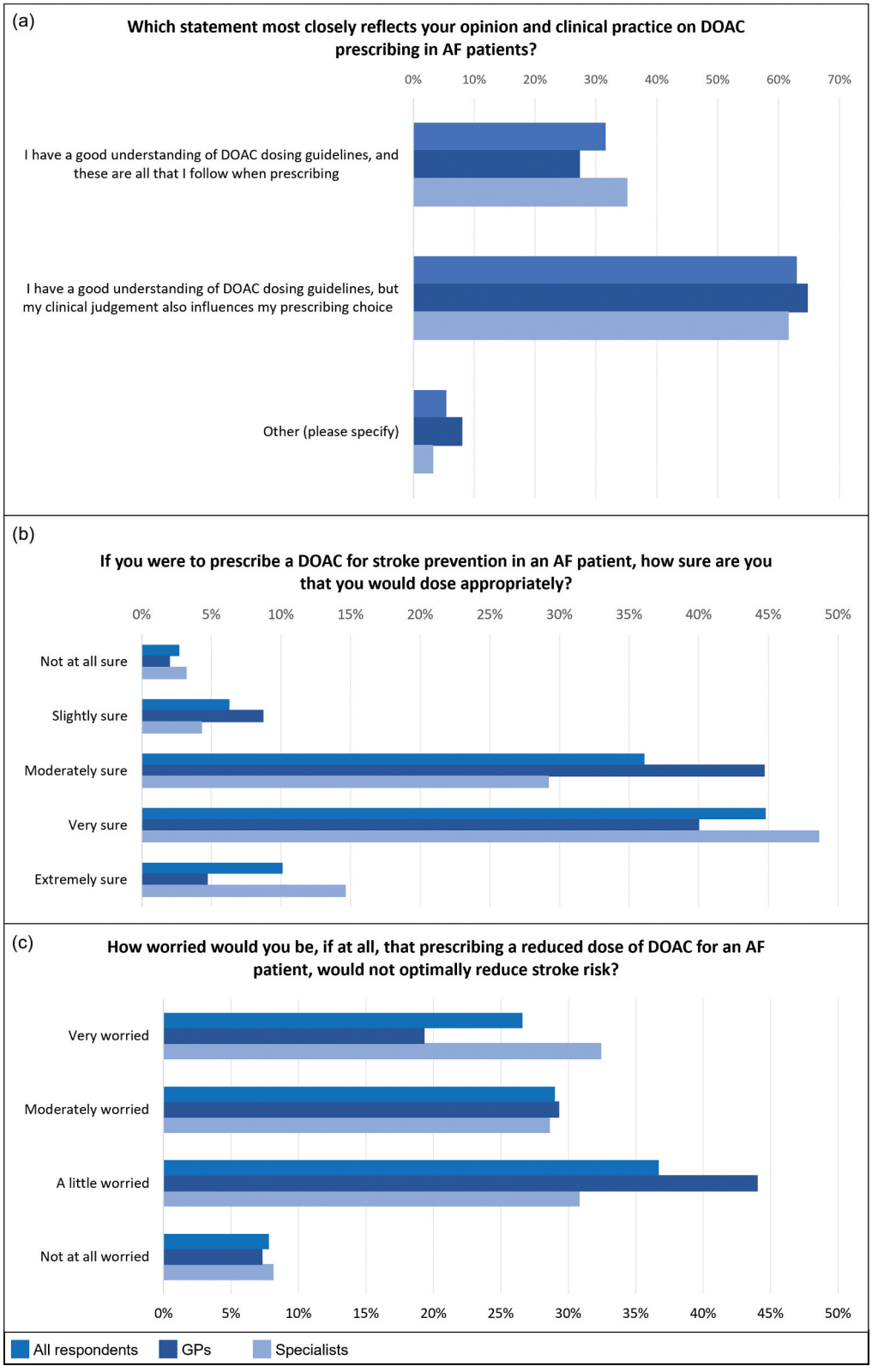

Figure 2. Self-reported (a) Understanding of DOAC guidelines and approach, (b) Perception of DOAC dosing confidence, and (c) Perception of DOAC underdose risk, all respondents (N=335; 150 GPs, 185 specialists), derived from the physician survey.

Table 1. Demographics, characteristics, and comparison of prescribers who selected no and ≥1 inappropriate underdose(s)* (N = 336; 150 GPs, 186 specialists).

Demographics	No inappropriate underdose(s)*			≥1 inappropriate underdose (s)*		
Total	GPs	Specialists	All	GPs	Specialists	All
Speciality, N (%)	42/150 (28)	50/186 (27)	92/336 (27)	108 (72)	136 (73)	244 (73)
Gender, N (%)						
Female	17/42 (40)	11/50 (22)	28/92 (30)	42/108 (39)	27/136 (20)	69/244 (28)
Not specified	0/42(0)	2/50 (4)	2/92 (2)		4/136 (3)	4/244 (2)
Age (years), N (%)						
25–29	1/42 (2)	0/50 (0)	1/92 (1)	1/108 (1)	3/136 (2)	4/244 (2)
30–39	13/42 (31)	14/50 (28)	27/92 (29)	35/108 (32)	30/136 (22)	65/244 (27)
40–49	15/42 (36)	18/50 (36)	33/92 (36)	39/108 (36)	54/136 (40)	93/244 (38)
50–59	11/42 (26)	16/50 (32)	27/92 29)	21/108 (19)	36/136 (26)	57/244 (23)
60–69	2/42 (5)	2/50 (4)	4/92 (4)	11/108 (10)	11/136 (8)	22/244 (9)
70+	0/42 (0)	0/50 (0)	0/92 (0)	1/108 (1)	2/136 (1)	3/244 (1)
Medical speciality, N (%)						
Cardiology	N/A	33/50 (66)	33/92 (36)	N/A	89/136 (65)	89/244 (36)
Clinical pharmacy	N/A	6/50 (12)	6/92 (7)	N/A	9/136 (7)	9/244 (4)
Elderly care	N/A	8/50 (16)	8/92 (9)	N/A	21/136 (15)	21/244 (9)
GP	42/42 (100)	N/A	42/92 (46)	108/108 (100)	N/A	108/244 (44)
Stroke medicine	N/A	2/50 (4)	2/92 (2)	N/A	10/136 (7)	10/244 (4)
Other	N/A	1/50 (2)	1/92 (1)	N/A	7/136 (5)	7/244 (3)
Years practising since qualifying, (mean ± SD)	17.1 ± 9.1	19.2 ± 8.6	18.2 ± 8.9	17.2 ± 9.7	18.2 ± 8.8	17.7 ± 9.2
NHS England region, N (%)						
North East and Yorkshire	4/42 (10)	6/50 (12)	10/92 (11)	17/108 (16)	13/136 (10)	30/244 (12)
North West	3/42 (7)	10/50 (20)	13/92 (14)	11/108 (10)	27/136 (20)	38/244 (16)
East of England	5/42 (12)	3/50 (6)	8/92 (9)	11/108 (10)	9/136 (7)	20/244 (8)
Midlands	12/42 (29)	5/50 (10)	17/92 (18)	18/108 (17)	18/136 (13)	36/244 (15)
London	4/42 (10)	7/50 (14)	11/92 (12)	14/108 (13)	29/136 (21)	43/244 (18)
South East	4/42 (10)	7/50 (14)	11/92 (12)	13/108 (12)	15/136 (11)	28/244 (11)
South West	3/42 (7)	4/50 (8)	7/92 (8)	11/108 (10)	14/136 (10)	25/244 (10)
Not specified	7/42 (17)	8/50 (16)	15/92 (16)	13/108 (12)	11/136 (8)	24/244 (10)

Characteristics of prescribers who selected no and ≥1 inappropriate underdose	No inappropriate underdose (N=91**)	≥1 inappropriate underdose (N=244)
Understanding of guidelines and approach, N (%)		
DOAC dosing guidelines are all that I follow when prescribing	38 (42)	68 (28)
Clinical judgement also influences my prescribing choice	48 (53)	163 (67)
Other	5 (5)	13 (5)
Decision making confidence, N (%)		
Not at all sure	2 (2)	7 (3)
Slightly sure	4 (4)	17 (7)
Moderately sure	23 (25)	98 (40)
Very sure	44 (48)	106 (43)
Extremely sure	18 (20)	16 (7)
Perception of DOAC underdose risk, N (%)		
Not at all worried	5 (5)	21 (9)
A little worried	17 (19)	106 (43)
Moderately worried	25 (27)	72 (30)
Very worried	44 (48)	45 (18)

*As according to guideline recommendations during the clinical vignette exercise; **One respondent did not complete the physician survey; N/A, Not applicable.

Table 2. Comparison of key prescriber demographics or characteristics by no or ≥1 inappropriate underdose decisions (t-test).

	No inappropriate underdose (*N*=91*)	≥ 1 inappropriate underdose (*N*=244)	P-value
Mean number of years of practice since qualification	18.2	17.7	0.670
DOAC dosing guidelines are all that I follow when prescribing (%)	42	28	0.0181
Clinical judgement also influences my prescribing choice (%)	53	67	0.0134
DOAC prescribing confidence ('very' or 'extremely sure' of their prescribing) (%)	68	50	0.0024
Perception of DOAC underdose risk ('very worried' reduced dose would not optimally reduce stroke prevention) (%)	48	18	<.001

*One respondent did not complete the physician survey.

Among prescribers who selected no inappropriate underdoses ($N = 91$), prescribing confidence was associated with high concern of DOAC underdose risk, the most common combination (22% of responses; 20/91) of responses among this group was 'very worried' (that a DOAC reduced dose may not optimally

Table 3. Key characteristics of survey participants by specialty×.

	GP (*N*=150)	Cardiologists (*N*=122)	Elderly care (*N*=29)	Stroke medicine (*N*=12)	Clinical pharmacy (*N*=15)
No. of inappropriate underdoses selected, (%)**					
0	28	27	28	17	40
≥1	72	73	72	83	60
≥3	37	41	28	33	20
≥5	13	17	4	8	7
Understanding of guidelines and approach, (%)					
DOAC dosing guidelines are all that I follow when prescribing	27	41	21	0	53
Clinical judgement also influences my prescribing choice	65	57	72	100	33
Decision making confidence, (%)					
'Very' or 'extremely' sure	45	67	59	67	47
Perception of DOAC underdose risk, (%)					
'Very' worried	19	32	14	58	60

*Based on groups with a minimum *N* ≥10.
**As according to guideline recommendations during the clinical vignette exercise.

reduce stroke risk) and 'very sure' (that their decision was correct) (Supplementary Figure S1a). For prescribers who selected five or more inappropriate underdoses (*N* = 47), the most common combination of responses (30% of responses; 14/47) was 'a little worried' (that a DOAC reduced dose may not optimally reduce stroke risk) and 'moderately sure' (that their decision was correct) (Supplementary Figure S1b).

Overall, prescribers with high perception of risk and high prescribing confidence exhibited different prescribing behaviour compared with those with a lower perception of risk and lower prescribing confidence. The majority (14/22; 64%) of participants describing themselves as both 'very worried' and 'extremely sure' did not inappropriately underdose. The vast majority (53/58; 91%) of participants describing themselves as both 'a little worried' and 'moderately sure' selected ≥1 inappropriate underdose. The majority (2/3; 67%) of participants describing themselves as both 'not at all worried' and 'not at all sure' selected ≥5 inappropriate underdoses. These data are reported in text only.

Key characteristics by prescriber medical speciality..

Among groups with a minimum sample size of *N* = 10, cardiologists represented the specialist group with the highest proportions of prescribers who selected ≥3 and ≥5 inappropriate underdoses (50/122; 41% and 21/122; 17%, respectively) (Table 3). Cardiologists also had the equal highest proportion being either 'very' or 'extremely' sure of their DOAC dose decision-making (82/122; 67%) (Table 3).

Clinical pharmacy specialists had the highest proportion who selected no inappropriate underdoses (6/15; 40%), as well as the lowest proportion who selected ≥1 and ≥3 inappropriate underdoses (9/15; 60% and 3/15; 20%, respectively) (Table 3). This group also had the highest proportion who responded that they only followed DOAC dosing guidelines when prescribing (8/15; 53%) and were 'very worried' about risks of DOAC underdose (9/15; 60%) (Table 3).

Summary of key results

The main characteristics associated with either an increase or decrease in inappropriate underdosing are summarised in Figure 3. Overall, prescriber characteristics associated with less frequent inappropriate underdosing included reported adherence to guidelines, confidence in prescribing, and worry about the risks of inappropriate underdosing. Patient factors associated with increased risk underdosing included previous major bleeding event history, frailty, and history of falls.

Discussion

To our knowledge, this is the first study to explore in a clinical vignette the relative importance of specific patient factors influencing the decision to prescribe an inappropriate underdose of DOAC to AF patients. This study also examined the association between prescriber-related factors and inappropriate underdosing decisions.

The vignette analysis identified major bleeding, as well as frailty and history of falls, as key patient characteristics associated with inappropriate underdosing of apixaban and rivaroxaban. Prescribers who reported being more confident in DOAC prescribing and worried about the risk of stroke were significantly less likely to inappropriately underdose, compared to prescribers lacking prescribing confidence or being less worried

Having had a previous major bleeding event was the patient characteristic most strongly associated with

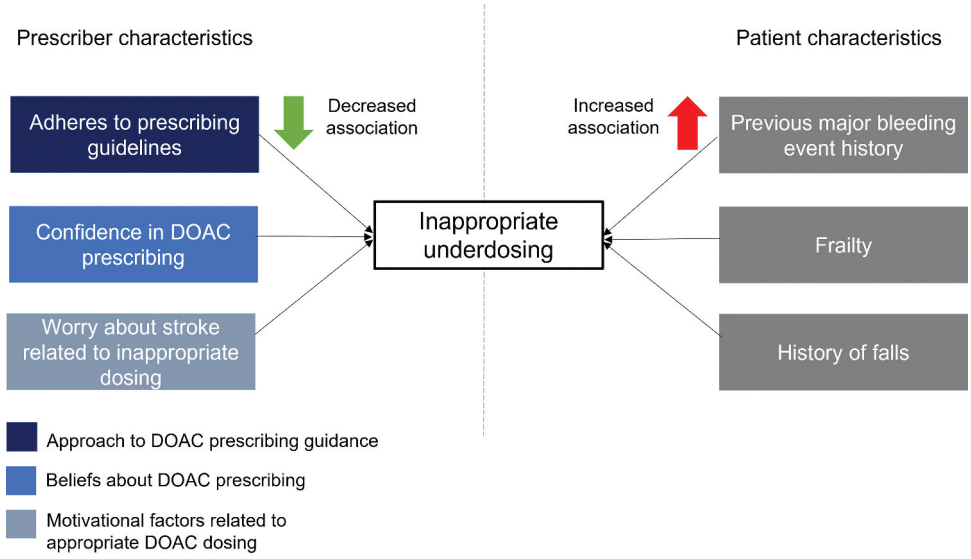

Figure 3. Schematic of main characteristics* associated with inappropriate underdosing of DOACs.

* Patient characteristics based on clinical vignette analysis of most common prescribing choices (apixaban and rivaroxaban); prescriber characteristics based on survey analysis.

selecting an inappropriate underdose. This could reflect a greater weight placed by physicians on bleeding-related harms versus protection against thromboembolic complications of AF, which include not only stroke but also cognitive impairment [17]. Previous research has shown that bleeding-related harms are the most frequent concern of physicians prescribing DOACs for AF patients [18]. Indeed, guidelines state that current or recent major bleeding events are contraindications to DOACs. However, following sufficient recovery time from a bleeding event, guidelines recommend prescribing DOACs, but at the evidence-based dose (and not below) [11].

The prevalence of frailty among AF patients is considered to be substantial with estimates as high as 56% [19]. Frailty in AF patients is associated with an increased risk of stroke, mortality, and longer hospitalisations, with mixed evidence on the risk of bleeding [20,21], compared with AF patients with no frailty. Based on our findings, severely frail patients face a double risk because they are also at an increased risk of inappropriate underdosing. This finding is in line with a recent review which showed an association between frailty and inappropriate anticoagulation prescription [20]. Given the absence of specific clinical practice guidelines on the management of frail adults with AF [19], we hypothesise that physicians may intentionally or unintentionally perceive frail patients as being less able to tolerate full DOAC doses and, consequently, select an inappropriate underdose.

Physician beliefs, experience, and motivational factors related to DOAC prescribing are likely to play a key role in inappropriate DOAC underdosing. Prescriber awareness of the risks of stroke with DOAC underdoses appeared to be associated with prescribing according to guidelines. It is plausible that increased worry about stroke risk may motivate physicians to give greater consideration to DOAC dosing guidelines.

Other characteristics – such as prescribers reporting that they only followed prescribing guidelines and having confidence in their DOAC prescribing – were more often demonstrated by prescribers who did not inappropriately underdose. Incorporating clinical judgement into the DOAC dosing decision could, therefore, lower guideline adherence. Notably, cardiologists often prescribed inappropriate underdoses despite self-reporting high DOAC prescribing confidence. This may be because their confidence is grounded in years of specialist clinical experience that allows nuanced refinements to DOAC doses beyond what may be feasible for those with more generalist experience. Interestingly, 100% of stroke medicine specialists reported incorporating clinical judgement into their DOAC prescribing, yet also self-reported high levels of worry about risks of underdosing and were the specialist group who most often inappropriately underdosed at least once. This suggests that these specialists are aware of the risk of inappropriate underdosing but also believe that dosing outside of guidelines is occasionally necessary based on their clinical judgement.

While a key strength of this study was its ability to identify the relative importance of patient factors such as frailty, a limitation of the clinical vignette approach is that these factors were explicit. In clinical practice, however, the perception of frailty is dependent on medical speciality. Furthermore, inappropriate dosing was considered as a binary outcome, and whilst previous studies have demonstrated the consequences of

inappropriate dosing, our analysis did not differentiate by severity of outcomes. Second, information provided by participants on the relative importance of patient factors and their interactions was limited; as, while the survey provided an opportunity for experts to provide open-text rationales for their feedback, responses were not data rich. Third, the eight patient factors included in the vignettes were selected via an expert panel process, and the number of factors was determined according to sampling feasibility considerations, which meant that other potentially important factors (such as cognitive impairment and multi-morbidity) were not included. Fourth, logistic regression analysis of patient factors was restricted to apixaban and rivaroxaban. This was due to limitations of the study design which meant ensuring a sufficient spread of patient factors for all DOAC choices whilst leaving the choice of DOAC (particularly those selected less frequently) open for each vignette was challenging. However, apixaban and rivaroxaban were the most commonly selected DOACs in the survey, which is reflective of UK clinical practice at the time of the survey. Finally, initial recruitment challenges led to the introduction of financial incentivization for participation in the study. This may have introduced a degree of bias due to unidentified confounding differences between respondents; however, both sets of respondents undertook identical surveys. Moreover, analysis prior to combining datasets demonstrated similar findings and overall conclusions. Whilst this analysis is focused on the UK only, it may be interesting to contrast these findings in further geographies, as similarities may be present. Finally, this analysis was designed to take a perspective on the drivers of inappropriate underdosing that was primarily focused on patient characteristics; further work investigating prescriber subgroups, and heterogeneity across clinician subtypes, would be beneficial. Further research utilising a causal inference framework would be beneficial to supplement the findings of this analysis.

These findings indicate that a multi-faceted intervention through effective prescriber education, training, and communication is necessary. Strategies should be tailored to specific medical specialities since there appear to be differences in beliefs and motivations for DOAC prescribing. The target population of such an intervention should be well understood to enable the most effective selection of approach(es). For primary care physicians (typically GPs), framing messages to emphasise the negative consequences of inappropriate DOAC underdosing to enable best-practice prescribing behaviour could be considered [22]. Additionally, for this group of physicians, the provision of access to specialist healthcare professionals for DOAC prescribing guidance may improve their prescribing decision-making. Further, this study suggests that clinical pharmacists could be delivery agents for prescribing guidance, since they were less likely to inappropriately underdose and were more likely to adhere to DOAC dosing guidelines, compared to other specialist groups. However, evidence from a systematic review on interventions for improving the appropriate prescription of oral anticoagulants (OACs) for stroke in AF showed that pharmacist-led prescribing reviews are less likely to be effective than those conducted by peer clinicians [23]. An exploratory analysis (Figure 1b) suggested that key patient factors influencing underdosing are similar between prescriber medical specialities, and that future educational strategies can not only underline the importance of adhering to guideline recommendations but also incorporate a new emphasis on frailty and the potential risks of inappropriately underdosing unintentionally.

Conclusion

This research suggests that UK prescribers, regardless of speciality, may benefit from education, training, and communication regarding appropriate DOAC dosing. Encouraging wider awareness of frailty as a potential influencer of DOAC decision-making, as well as greater clarity on the management of AF patients with frailty, should also be considered.

Disclosures and competing interests

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Contributions

Ahmet Fuat, Emmanuel Ako, David Hargroves, Helen Williams, Carol Roberts, Nnanyelu Nzeakor, and Burcu Vardar contributed towards study conception, design, and analysis and interpretation of results. Douglas Holden and Amrit Caleyachetty contributed to data collection, analysis, and interpretation, as well as draft manuscript preparation. Matthew Carter contributed to data analysis and drafting, James Harris contributed to

interpretation and draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript. Support for recruitment of participants and conduct of the survey was provided by SurveyEngine GmbH, Germany.

Disclosure statement

Carol Roberts, Nnanyelu Nzeakor and Burcu Vardar are employees of Bayer. Ahmet Fuat, Emmanuel Ako, David Hargroves and Helen Williams report fees and other non-financial support received from Bayer AG during the conduct of the study. Matthew Carter and James Harris are employees of Wickenstones Ltd which received consultancy fees from Bayer AG. Douglas Holden and Amrit Caleyachetty are former employees of Wickenstones Ltd.

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