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## Original Research

# Prescribers' perceptions of benefits and limitations of direct acting oral anticoagulants in non-valvular atrial fibrillation

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### Abstract

**Background:** There is an acknowledged lack of robust and rigorous research focusing on the perspectives of those prescribing direct acting oral anticoagulants (DOACs) for non-valvular atrial fibrillation (AF).

**Objective:** The objective was to describe prescribers' experiences of using DOACs in the management of non-valvular AF, including perceptions of benefits and limitations.

**Methods:** A cross-sectional survey of prescribers in a remote and rural area of Scotland. Among other items, the questionnaire invited free-text description of positive and negative experiences of DOACs, and benefits and limitations. Responses were independently analysed by two researchers using a summative content analysis approach. This involved counting and comparison, via keywords and content, followed by interpretation and coding of the underlying context into themes.

**Results:** One hundred and fifty-four responses were received, 120 (77.9%) from physicians, 18 (11.7%) from nurse prescribers and 10 (6.4%) from pharmacist prescribers (6 unidentified professions). Not having to monitor INR was the most cited benefit, particularly for prescribers and patients in remote and rural settings, followed by potentially improved patient adherence. These benefits were reflected in respondents' descriptions of positive experiences and patient feedback. The main limitations were the lack of reversal agents, cost and inability to monitor anticoagulation status. Many described their experiences of adverse effects of DOACs including fatal and non-fatal bleeding, and upper gastrointestinal disturbances.

**Conclusions:** While prescribers have positive experiences and perceive benefits of DOACs, issues such as adverse effects and inability to monitor anticoagulation status merit further monitoring and investigation. These issues are particularly relevant given the trajectory of increased prescribing of DOACs.

### Keywords

Attitude of Health Personnel; Atrial Fibrillation; Factor Xa Inhibitors; Drug Prescriptions; Health Knowledge, Attitudes, Practice; Cross-Sectional Studies; Scotland

## INTRODUCTION

Direct acting oral anticoagulants (DOACs) have superseded warfarin as the treatment of choice for stroke reduction in non-valvular atrial fibrillation (AF).<sup>1-4</sup> Guideline recommendations have translated to practice, with UK primary care prescribing data showing a 17-fold increase in new DOAC users from 2012 to 2015.<sup>5</sup> There is, however, a gap in the literature concerning the experiences of those prescribing DOACs. The one systematic review, published in 2018, identified only ten studies, nine surveys and one qualitative study.<sup>6</sup> Survey participant numbers ranged from 38 to 450 (total of 1,246) with response rates of 9.0-35.9%, with outcome measures of oral anticoagulant of choice, factors influencing prescribing, and experiences.<sup>7-13</sup> While the one qualitative study provided rich data of physicians'

decision-making processes regarding DOACs, the sample size of seven limits the likely transferability of findings.<sup>14</sup> One further key limitation of these studies was the omission of theory (e.g. cognitive, behavioural, organisational) in questionnaire development. There is acknowledgement that considering the theoretical basis is likely to yield a data collection tool with comprehensive coverage of all key factors.<sup>15,16</sup>

Quantitative data of a recent cross-sectional survey of medical and non-medical prescribers (nurse and pharmacist independent prescribers) in a remote and rural area of Scotland were recently reported.<sup>17</sup> The study was a cross-sectional survey of medical and non-medical prescribers in all settings of NHS Highland, an area of low population density with 40% of residents living in 'remote rural' locations (defined as settlements <3000 people with a drive time of >30 minutes to a settlement of ≥10,000).<sup>18</sup> Survey outcome measures were: prescribing of DOACs (as a pharmacological group); views of potential influences on DOAC prescribing; knowledge of prescribing guidelines; and experiences. Items on potential influences were based on the Theoretical Domains Framework (TDF, which is derived from 33 theories of behaviour change).<sup>19</sup> Principal component analysis identified four components of potential influences on DOAC prescribing. Component scores for (a) role of professionals, their knowledge and skills and (b) influences on prescribing were somewhat

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positive. Those for (c) consequences of prescribing and (d) monitoring for safety and effectiveness were more neutral. There were generally low levels of respondent agreement for statements about DOACs being more effective, safer and cost-effective than warfarin.

Open response options were included in the questionnaire to provide the respondents with opportunities to describe in their own words their perceptions of the benefits and limitations of prescribing DOACs. The aim of this paper is to describe these perceptions of benefits and limitations of using DOACs in the management of non-valvular AF.

## METHODS

Study methods have been previously described, and are briefly outlined for completeness.<sup>17</sup> The study was conducted within NHS Highland in Scotland, an area of low population density covering approximately 40% of the land mass of Scotland yet representing only 6% of the Scottish population.

An online questionnaire was developed, pretested and piloted prior to use. Questionnaire items were in sections of: demographics; DOAC prescribing; potential influences on DOAC prescribing; knowledge of local prescribing guidelines; and experiences. While most question types were closed, 5-point Likert scales, respondents were invited to describe: (i) their perceptions of benefits and limitations of prescribing DOACs; (ii) positive patient experiences; and (iii) negative patient experiences, whilst respecting anonymity. The questionnaire was formatted in Snap 10 Professional® (software for web and email questionnaire design, publication, data entry and analysis) and tested for compatibility with platforms (e.g., laptop, tablet and smartphone), browsers, and NHS email and internet filters. Data collection took place from April to July 2017. An email from a senior member of the research team based within NHS Highland was sent all prescribers (medical and non-medical), with a link to the participant information leaflet and the questionnaire. The questionnaire was to be completed only by those prescribing oral anticoagulants at the time of the study or likely to do so in the near future. Two email reminders were sent to all prescribers at 4-weekly intervals. Free text comments relating to benefits, limitation and experiences were analysed using a summative content analysis approach.<sup>20</sup> This involved counting and comparison, via keywords and content, followed by interpretation and coding of the underlying context into themes. Analysis was undertaken independently by two researchers (DG, DS) and a third (SC) consulted when non-consensus arose.

This study was approved by the Ethics Committee of the School of Pharmacy and Life Sciences at Robert Gordon University, UK; the study was deemed exempt from NHS ethical review by the North of Scotland Research Ethics Committee. Management approval was obtained from NHS Highland Research and Development Committee (ID1158).

## RESULTS

One hundred and fifty-four responses were received, 120 (77.9%) from physicians (76 general practitioners), 18 (11.7%) from nurse prescribers and 10 (6.4%) from

pharmacist prescribers (6 unidentified professions). As the questionnaire was to be completed by those for whom DOAC prescribing was relevant to their practice, a response rate could not be calculated. Respondent mean age was 43.3 years (standard deviation 11.9 years); just over half (n=84, 54.5%) had >20 years' experience as health professionals and slightly less (n=61, 39.6%) as prescribers; two thirds (n=100, 64.9%) were based in primary care. Counts of the number of respondents and illustrative quotes are given for the major themes identified in the summative content analysis.

Ninety-nine respondents (71.7%) provided responses around perceived benefits and limitations.

### Perceived benefits

The overwhelming benefit, cited by 47 respondents, was the absence of need for INR monitoring,

"We have been overwhelmed with the need to do regular blood monitoring of patients in recent years...No additional resources have been made available in spite of a 300% increase in blood tests...anything which reduces this, such as the use of DOACs instead of warfarin, helps us to survive."

The absence of need for monitoring was often mentioned in the context of other benefits such as particular patient groups,

"No need for monitoring, especially practical in elderly/housebound."

This was also relevant to those in remote settings,

"It is much easier for patients who live in rural areas to be prescribed a DOAC especially in the winter where it is difficult to travel to have INR checked."

Cost was also a consideration,

"No need to monitor therefore cost-effective"

Thirteen respondents commented on the likelihood of better adherence,

"Patients understand why they take these drugs and often state how it is much easier to take than warfarin especially with the interactions of diet."

Eleven noted benefits in terms of the evidence base,

"Overall the evidence is that DOACs are at least as good as warfarin for preventing stroke and have a lower incidence of fatal bleeding".

Ten commented on the more favourable dosing regimens compared to warfarin,

"...and a single daily dose, not changing like warfarin."

Ten respondents remarked on the benefits in those with labile INRs,

"less likely to get out of therapeutic range...suitable for patients with fluctuating INR."

Less commonly cited benefits were better use of general practitioner (GP) time, especially in remote areas, reduced

frequency of adverse drug reactions (ADRs), and easier patient management.

#### Perceived limitations

The key limitation, cited by 31 respondents, was the lack of a suitable reversal agent,

"Significant concerns regarding how to reverse anticoagulation in patients who then sustain injury/head trauma."

"No antidote yet for rivaroxaban or apixaban."

The high acquisition costs of DOACs compared to warfarin was considered a limitation by 17 respondents,

"I'd prescribe it more for patients with AF if health board not breathing down my neck about cost."

One respondent commented that whilst the drug costs were higher, there were savings when considering other associated costs,

"Costly but saves on nurse/lab/doctor time to dose warfarin."

Ten respondents were concerned by the lack of ability to monitor anticoagulation status,

"the main negative is the lack of longer term follow up to ensure patients CONTINUE to take the drug as prescribed regularly and on time."

This was a particular concern in specialist areas of practice,

"When injecting a joint I prefer to know a patient is on warfarin as I can just check their INR. If they are on DOAC, they have to stop their medication the previous day, I then have to book them in early in the morning and then they take their next dose mid-day."

Eight noted concerns over the lack of long-term evidence of benefit,

"Concerned that long term benefits may not be as great as expected, i.e. problems of this group of drugs will show after they have been used for more years"

Less commonly cited limitations were around increased prevalence of adverse effects and dose adjustment in renal impairment.

#### Positive patient experiences

Seventy-two respondents (52.2%) described positive experiences of DOACs. As with benefits, the main positive experiences surrounded the absence of need to monitor INR, cited by 38 respondents,

"90 year old on warfarin for AF for 20 years. Became unable to drive and a lot of strain on family for weekly INR with no capacity in single handed GP to visit frequently."

Several described similar experiences, which were considered particularly relevant to those living in remote areas,

"Initiating anticoagulation in patient who lives miles away, avoiding blood tests, living over 30 miles from GP surgery".

Nineteen respondents described positive feedback from patients,

"Feedback from patients has been positive - they no longer have to frequently attend the surgery, they can go on holiday more easily, they can be more relaxed with the choice of diet."

In some situations, patients had declined warfarin but were willing to commence DOACs,

"Another patient would not accept warfarin but did DOAC".

Seven respondents commented on enhanced management of those with previously labile INRs,

"A patient whose INR was impossible to keep in therapeutic range was able to get proper treatment".

Less commonly cited experiences were around better patient management and more rapid, effective anticoagulation.

#### Negative patient experiences

Descriptions of negative patient experiences were provided by 64 respondents (46.4%), with an additional 19 (13.8%) stating that they had no negative experiences to report.

The key negative experience was around adverse events of bleeding, described by 24 respondents,

"Patient admitted with severe upper GI bleed while on prophylactic dose after hip replacement",

Two respondents reported that bleeding had led to patient death. One noted particular concerns for those in more remote areas,

"In the first month of prescribing DOACs we had 2 major bleeds. Likely coincidence but shook everyone's confidence a bit, especially in a rural setting."

An additional five respondents commented on issues related to bleeds,

"Emergency admission for surgery - prolonged operation due to increased bleeding".

Thirteen commented on their experiences of non-bleeding adverse events of varying severity and with diverse consequences,

"Patient developed side effect from DOACs (severe nausea) and returned to warfarin",

"Terrible oesophagitis with dabigatran".

Three described issues relating to the consequences of rapid anticoagulation reversal on discontinuing DOACs,

"We have had 3 patients who have had strokes shortly after discontinuing DOACs".

Table 1. Summary of key themes identified			
Perceived benefits	Perceived limitations	Positive patient experiences	Negative patient experiences
Absence of the need for INR monitoring (n=47)	Lack of suitable reversal agents (n=31)	Absence of the need for INR monitoring (n=38)	ADRs, bleeding (n=24)
Better patient adherence (n=13)	High acquisition costs (n=17)	Positive patient feedback (n=19)	ADRs, non-bleeding (n=13)
Positive evidence base (n=11)	Lack of ability to monitor anticoagulation status (n=10)	Enhanced management in those with labile INRs (n=7)	Rapid anticoagulation reversal on discontinuation of DOACs (n=3)
More favourable dosing regimen compared to warfarin (n=10)	Lack of long-term evidence (n=8)	Less commonly cited – better patient management, more rapid and effective anticoagulation	Less commonly cited – inadequate monitoring prior to commencing DOACs, poor clinician recognition of DOAC names as anticoagulants, patient anxiety
Useful in those with labile INRs (n=10)	Less commonly cited – increased prevalence of ADRs, dose adjustment in renal impairment		
Less commonly cited – better use of GP time, reduced frequency of ADRs, easier patient management			

Less commonly cited negative experiences included issues relating to inadequate monitoring of patients prior to commencing DOACs,

“Colleagues not monitoring renal function and LFTs so overdosed DOAC and patient admitted.”

There were also issues related to clinician lack of recognition of the names of DOACs as anticoagulants,

“DOAC not stopped despite bleeding as not noted as a blood thinner in same way as warfarin.”

Patient anxiety was noted as a concern,

“patients are often wary to start treatment with a DOAC as they are aware of the lack of antidote.”

Table 1 provides a summary of the key themes identified.

## DISCUSSION

Content analysis of the textual comments captured in this survey complement the quantitative data recently published.<sup>17</sup> Not having to monitor INR was the most cited benefit, particularly for prescribers and patients in remote and rural settings, followed by potentially improved patient adherence. These benefits were reflected in descriptions of positive experiences and patient feedback. The main limitations were the lack of reversal agents, cost and inability to monitor anticoagulation status. Many described experiences of adverse effects including fatal and non-fatal bleeding, and upper GI disturbances.

This study adds to the limited evidence base of prescribers' experiences of DOACs, and is timely given that DOACs are now recommended first line for those with non-valvular AF.<sup>1-6</sup> However, given that data were collected in one remote and rural area of Scotland, the results may lack generalisability and transferability to other settings. Furthermore, the data were collected using a cross-sectional survey methodology rather than through a qualitative approach (e.g. interviews and focus groups) which limited the depth of enquiry. As the findings represent perceptions of benefits and limitations, the analysis was not informed by any theoretical framework.

Studies of healthcare provision in remote and rural areas have identified access as an issue, particularly in older populations and those with higher healthcare utility.<sup>21-26</sup>

While many positive perceptions of DOACs identified in this study may be generic to all settings, these are particularly relevant in such areas. The specific site of action of DOACs on the coagulation cascade, predictable pharmacokinetic and pharmacodynamic properties and fixed dosages eliminate the need and usefulness of INR monitoring.<sup>27</sup> Not having to monitor was perceived as a major benefit, and was highlighted in descriptions of patient positive experiences. However, lack of monitoring was also perceived a limitation, specifically the lack of ability to closely monitor coagulation status. These are original findings, not having been reported in the systematic review of clinicians' experiences, nor any systematic reviews of patients' experiences.<sup>6,28,29</sup>

Adverse reactions, most notably bleeding related, were described by many respondents. It is, however, worth noting that evidence so far indicates that DOACs are associated with clinically important reductions in the frequency of major bleeding, including life-threatening bleeding events and, especially, intracranial bleeding, when compared with patients receiving warfarin.<sup>2-4</sup> In the UK, DOACs are labelled 'black triangle drugs' meriting reporting of all adverse reactions (irrespective of severity) to the Medicines and Healthcare products Regulatory Agency.<sup>30</sup> Given that under-reporting is a major limitation of pharmacovigilance processes, further research on DOAC reporting is warranted. There were also descriptions of adverse events attributed to rapid reversal of anticoagulation following DOAC discontinuation prior to surgical intervention, as noted by others.<sup>31,32</sup> Guidelines on the management of patients prescribed DOACs requiring elective and emergency procedures are emerging.<sup>27</sup> Concerns of managing DOAC related bleeding may also diminish with the licensing of idarucizumab to reverse dabigatran in patients with life threatening haemorrhage or need for urgent surgery.<sup>33</sup> Andexanet alfa, a class-specific antidote for the factor Xa inhibitors, is now available and other DOAC reversal agents are in development.<sup>34</sup>

Different views were given in relation to DOAC cost, with some describing cost as a limitation while others believed

costs reduced given the additional resources incurred in warfarin monitoring. Systematic reviews and meta-analyses of the cost-effectiveness of DOACs versus warfarin have recommended that, while further real world data are required, DOACs are more cost-effective despite higher prescribing costs.<sup>35,36</sup>

There was a range of views around the widespread adoption of DOACs with some supporting the evidence base of effectiveness, cost-effectiveness and safety while others were more cautious due to the lack of real-life, long-term evidence. This finding has been identified for many newly launched agents; in a recent study of the adoption of cardiovascular drugs in the United States, physicians were found to be generally conservative, with a minority adopting dabigatran, aliskiren or pitavastatin in the first 15 months of market launch market.<sup>37</sup>

Given the findings of this study and the change in Scottish national recommendations, there is a need for quantitative and qualitative data on views and experiences of prescribers and patients. Focus should be placed on identifying, characterising and reporting adverse drug reactions.

## CONCLUSIONS

Prescribers in the Scottish Highlands highlighted positive and negative perceptions of DOACs in the management of non-valvular AF. While absence of INR monitoring was considered a key benefit, there were concerns around adverse effects, most notably bleeding. These issues merit further monitoring and investigation, particularly relevant given the trajectory of increased prescribing of DOACs.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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