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SHORT RESEARCH REPORT

The acceptability of a direct oral anticoagulant monitoring regimen among patients with atrial fibrillation: a pilot study

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Abstract

Background The direct oral anticoagulants (DOACs) offer several advantages over warfarin in the management atrial fibrillation, including the provision of fixed dosing without a requirement for regular monitoring. Recently however the subject of DOAC monitoring has been probed after several post-hoc analyses demonstrated an association between plasma levels and efficacy and safety events. *Objective* The aim of this pilot study was to explore the acceptability of DOAC plasma monitoring amongst patients with atrial fibrillation and the factors that may influence these attitudes. *Method* A simple DOAC monitoring schedule based on the dabigatran pharmacokinetic profile was developed. A cross-sectional survey was distributed to patients with atrial fibrillation asking them to indicate their likelihood of taking a particular DOAC subjected to plasma monitoring. *Results* Thirty patients participated in the study. Most patients (63.3%) favoured taking a DOAC subjected to monitoring under the proposed schedule, citing increased efficacy and reduced toxicity as the reasons for their response. *Conclusion* There is some suggestion that atrial fibrillation patients may in fact favour taking a DOAC subjected to infrequent monitoring if this enhanced safety and efficacy.

Keywords Anticoagulants · Atrial fibrillation · Attitude to health · Australia · Dabigatran · Drug monitoring

Impacts on practice

- A simple DOAC monitoring regimen may not deter patients from taking these medications
- There is a need for larger studies to continue to explore the anticoagulant preferences of patients in a general atrial fibrillation population. This would provide grounds for further research assessing the real-world benefit of plasma-level directed dosing of DOACs.

Introduction

For several decades, warfarin remained as the primary oral anticoagulant used in the management of atrial fibrillation (AF) [1]. The introduction of direct oral anticoagulants (DOACs) has broadened the scope of treatments available. Their favourability lies largely in the fact that they do not require the rigorous dose titration and monitoring that is required for warfarin [2].

Recent analyses, however, have brought to question the utility of monitoring with these agents. An analysis of plasma samples from over 9000 patients from the RE-LY trial demonstrated a 5.5-fold variability in patient dabigatran plasma concentrations [3]. Moreover, the efficacy and safety of the drug correlated with these concentrations. This association may also hold true for several other DOACs. Selected case reports for example highlight the risks with rivaroxaban and apixaban where supratherapeutic concentrations are implicated [4, 5]. In a large post hoc analysis of the ENGAGE AF-TIMI 48 trial, plasma concentrations of the factor Xa inhibitor edoxaban varied by up to threefold, again correlating with the risk of stroke and major bleeds [6]. It remains plausible that directed plasma monitoring could

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enhance the efficacy and safety of these agents, a hypothesis that requires validation through quality randomised-controlled trials.

Before pursuing these trials, an important clinical question is whether patients would be willing to adhere to a monitoring regimen with these hypothesised benefits. DOACs are at least as safe and effective as warfarin even in the absence of laboratory controls [2]. Thus, any real-world benefit of DOAC monitoring would only be realised if accompanied by widespread acceptance amongst patients. To our knowledge, no study has assessed the acceptability of monitoring as it pertains specifically to DOACs.

Aim of the study

In this pilot study, we aimed to develop and distribute a survey that examined the potential effect of DOAC monitoring on anticoagulant preferences of patients with AF, along with the patient factors that may influence these preferences.

Ethics approval

The study was approved by the Concord Repatriation General Hospital Human Research Ethics Committee under the expedited Low and Negligible Risk process (LNR/15/CRGH/193).

Method

Development of a DOAC monitoring schedule

Within our study survey, we proposed a simple schedule to realistically depict what DOAC monitoring would encompass. Using dabigatran as a model, we derived a schedule which involves blood samples taken at (1) 1 week after commencing therapy, (2) 6 months after commencing therapy and (3) additional times as clinically indicated. Assuming the five half-lives convention, 1 week would allow sufficient time for the drug to reach steady state concentrations across all renal functions [7], and a second reading at 6 months would confirm the drug remains within the desired therapeutic range.

Development of the patient survey

The survey itself consisted of 23 items encompassed within four domains (supplementary material). In the first domain, we asked patients to rank the properties of anticoagulants they consider most desirable. We then presented an information box simplifying the findings of recent analyses [3] and asked patients to indicate the likelihood of taking a hypothetical DOAC with the proposed monitoring schedule. The second domain of our survey examined participants' demographics. The third gauged their experiences surrounding their primary care physician as a surrogate for the level of inconvenience caused by monitoring. Finally, we asked patients about their experiences with anticoagulant treatment, including previous antithrombotic therapy and incidences of adverse events.

Participants and recruitment

Patients were recruited through convenience sampling from inpatient departments at a tertiary referral teaching hospital between September 2015 and May 2016. Eligible participants had a current diagnosis of AF, had capacity to consent and were deemed clinically well enough by attending staff to complete a questionnaire. These patients were identified through written records, nursing handover sheets, electronic records, nurses and/or clinicians on duty.

Results

Patient attitudes towards DOACs

Thirty patients participated in the study. A summary of their baseline characteristics is detailed in Table 1. The total pool of patients ranked doctor's belief in the medication (83%), effectiveness of drug (77%) and minimal side-effects (70%) as the three most desirable properties of anticoagulants. Nineteen patients (63.3%) indicated they would be more likely to take a DOAC subjected to drug monitoring. The potential increase in efficacy (68%) and reduced toxicity (63%) were the most common reasons for embracing a monitoring regimen. Conversely, patients that were less likely to accept our regimen cited inconvenience (18%) and disbelief that it will make a difference in outcomes (27%).

Effect of participants' characteristics and experiences on acceptability of DOAC with monitoring

Experiences surrounding primary care physicians (PCPs) were generally positive, with 90% of patients rating their PCP 4 or 5 on a 5-point satisfaction scale (mean: 4.4 ± 1.07). Satisfaction with travelling arrangements was similarly positive (mean: 4.4 ± 0.99). Private car was the most frequent mode of transportation (70%) and 61% of patients did not require a companion when travelling. A third (33%) of patients had average waiting times of greater than 30 min despite 87% travelling to their PCP in under 30 min.

Table 1 Baseline characteristics of the 30 patients that completed and returned the questionnaire

Baseline characteristics	No. (%)
Age	
51–60	1 (3)
61–75	14 (47)
> 75	15 (50)
Gender	
Male	16 (53)
Female	14 (47)
Primary language	
English	29 (97)
Other	1 (3)
Place of residence	
Private home	28 (93)
Aged-care facility (e.g. nursing home)	2 (6)
Education	
Higher degree (Ph.D./masters)	1 (3)
Bachelor's degree/diploma	8 (27)
Year 12 or equivalent	3 (10)
Did not complete year 12	18 (60)
Living arrangements	
Living with a companion	22 (73)
Living alone	8 (27)
Employment status	
Full time/part time work	0 (0)
Volunteer work	2 (6)
Unemployed or retired	28 (93)
Current Antithrombotic	
Warfarin	11 (37)
DOAC	11 (37)
Aspirin	4 (13)
Clopidogrel	1 (3)
Unknown/not answered	3 (10)

Regarding experiences with therapy, 37% of those favouring DOAC monitoring had previously used warfarin, compared with 36% of those that did not favour monitoring. Table 2 summarises the characteristics and experiences of patients favouring vs those not favouring monitoring. There were no statistically significant associations between patients' characteristics or experiences and the likelihood of embracing a monitoring regimen.

Discussion

We describe a suitable method for understanding the anticoagulant preferences of patients in light of emerging data on the concentration variability of DOACs. Our data suggests that patients prioritise safety, efficacy and the assurance of their clinician over the absence of monitoring when selecting therapy. There was a trend favouring preference for these agents if monitoring enhanced the safety and efficacy profile. This trend if substantiated could provide grounds for further research that aims to optimise the use of these medications through plasma-level directed dosing. Thus, there is clinical utility in further affirming these findings in a larger population, such as through a cardiology clinic or outpatient community pharmacy.

This study's findings contrast to those of a Dutch study which determined that the absence of laboratory controls provided the greatest incentive to switch to DOACs [8]. Their questionnaire employed the treatment trade-off technique and involved presenting a series of scenarios where desirable anticoagulant properties are successively added. Participants would then indicate the first scenario which they would be willing to trial a DOAC. The limitation of this method is that it can be difficult to quantify the relative contribution of each anticoagulant property within a scenario. In contrast, two other recent discrete-option surveys affirm that safety, efficacy and other convenience factors are preferred over the absence of laboratory monitoring [9, 10]. These latter studies suggest that the lack of statistical significance in our findings may be attributable to our small sample size.

Several components of our study design distinguish it from those cited above. Firstly, beyond analysing the ideal properties of anticoagulants, we directly asked participants the likelihood of embracing therapy under a specific set of circumstances. Secondly, our surveys gauged the anticoagulant preferences of participants in the context of monitoring specifically as it pertains to DOACs. Patients in the aforementioned studies are likely to have perceived monitoring as it relates to warfarin, which is a more onerous regimen than that proposed for DOACs. Finally, we included a clinically relevant patient population with a current diagnosis of AF. Previous studies opted to survey the general public [10] or a subset of AF patients on a particular therapy [9].

We explored a number of demographic and experiential factors which may influence attitudes to anticoagulants. The degree of inconvenience caused by monitoring may be influenced by doctor waiting times and the circumstances surrounding travel. Past experiences of patients with anticoagulants and their associated adverse events may also play a role in shaping opinions towards therapy. Although we did not expect to detect any differences given our limited sample size, larger studies should continue to explore these variables.

Additional limitations of our study include the fact that the patient population sample lacked heterogeneity in some regards (primary language, living arrangements and employment status), which may in part be explained by recruitment from a single institution. Moreover, there may be an element of selection bias as our study was restricted to hospitalised

Table 2 Effect of participants' characteristics and experiences on acceptability of DOAC with monitoring

	Favouring DOACs with monitoring (n = 19)	Not favouring DOACs with monitoring (n = 11)	P- value[a]
Mode of transport to PCP[b]			
Car	13 (68)	8 (73)	> 0.99
Taxi	3 (16)	0 (0)	0.28
Bus	4 (21)	0 (0)	0.27
Walking	1 (5)	2 (18)	0.54
Unanswered	1 (5)	1 (9)	> 0.99
PCP travel time			
< 5 min	4 (21)	0 (0)	0.41
5–15 min	5 (26)	8 (73)	
15–30 min	7 (37)	2 (18)	
> 30 min	3 (16)	0 (0)	
Unanswered	0 (0)	1 (9)	
PCP wait time			
< 5 min	2 (11)	2 (18)	0.46
5–15 min	6 (32)	3 (27)	
15–30 min	4 (21)	0 (0)	
> 30 min	7 (37)	3 (27)	
Unanswered	0 (0)	3 (27)	
Companion required for PCP travel			
Yes	8 (42)	3 (27)	> 0.99
No	11 (58)	8 (73)	
Satisfaction with travel arrangements[c]			
MEAN ± SD	4.32 ± 1.06	4.45 ± 0.93	0.72
Overall satisfaction with PCP[c]			
MEAN ± SD	4.53 ± 0.96	4.27 ± 1.27	0.54
Current antithrombotic			
Warfarin	7 (37)	4 (36)	> 0.99
DOAC	7 (37)	4 (36)	
Antiplatelet	3 (16)	2 (18)	
Don't know/unanswered	2 (10)	1 (9)	
Length of time taking current antithrombotic			
< 6 m	3 (16)	0 (0)	0.15
6mo – 1y	3 (16)	1 (9)	
1–2y	6 (32)	3 (27)	
> 2y	5 (26)	4 (36)	
Don't know/unanswered	2 (10)	3 (27)	
ADRs with previous antithrombotics[b]			
External bleeding	7 (37)	6 (55)	0.45
Internal bleeding	3 (16)	2 (18)	> 0.99
Bruising	11 (58)	6 (55)	> 0.99
Previously used alternative agent			
Yes	10 (53)	5 (45)	0.61
No	7 (37)	6 (55)	
Unanswered	2 (11)	0 (0)	
Reason/s for cessation of previous agent[b]			
Adverse reaction	3 (30)	1 (20)	> 0.99
Requirement for blood tests	2 (20)	0 (0)	0.52
Doctor's discretion	8 (80)	5 (100)	0.52

Table 2 (continued)

	Favouring DOACs with monitoring (n = 19)	Not favouring DOACs with monitoring (n = 11)	P- value[a]
Survey Completion method			
Self-directed	14 (74)	7 (64)	0.83
Assistance of companion	2 (11)	1 (9)	
Investigator facilitated	3 (16)	3 (27)	

Data in the format of No. (%)

[a]*P*-values calculated using Fisher's exact test for nominals, Cochran-Armitage trend test for ordinals, and an unpaired *t* test for comparison of means. "Don't know" and unanswered responses were excluded from the Cochran–Armitage trend test

[b]Patients could select more than one response. Accordingly, individual *P*-values were calculated for each response

[c]Satisfaction on a 5-point scale

ADR Adverse drug reaction, *PCP* primary care physician, *mo* month, *No.* number, *SD* standard deviation, *y* years

inpatients who may place greater emphasis on efficacy and safety than their healthier counterparts. Finally, our results may have been influenced by the response-order effect which is a generic limitation of written questionnaires.

Conclusions

Our study provides a method for approximating adherence to a realistic DOAC monitoring schedule. Our results suggest that a DOAC monitoring regimen would not necessarily deter their uptake. Rather, the potential implications for efficacy and safety may incentivise patients to take these medications. Larger studies may assist in confirming the findings of this pilot study. With affirmation of these results, studies that evaluate the effect of plasma level supported dose adjustment on the safety and efficacy outcomes of DOACs should be prioritised.

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Conflicts of interest Authors Ali Mourad and Mario D'Souza declare that they have no conflict of interest. Parisa Aslani serves on the editorial board for the International Journal of Clinical Pharmacy. David Brieger has served on advisory boards for Boehringer Ingelheim, BMS/Pfizer, and Bayer.

References

1. Pirmohamed M. Warfarin: almost 60 years old and still causing problems. Br J Clin Pharmacol. 2006;62(5):509–11.
2. Joppa SA, Salciccioli J, Adamski J, Patel S, Wysokinski W, McBane R, et al. A practical review of the emerging direct anticoagulants, laboratory monitoring, and reversal agents. J Clin Med. 2018;7(2):29.
3. Reilly PA, Lehr T, Haertter S, Connolly SJ, Yusuf S, Eikelboom JW, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY trial (Randomized evaluation of long-term anticoagulation therapy). J Am Coll Cardiol. 2014;63(4):321–8.
4. Yamaguchi Y, Koga M, Matsuki T, Hino T, Yokota C, Toyoda K. Intracranial subdural hematomas with elevated rivaroxaban concentration and subsequently detected spinal subdural hematoma: a case report. Thromb Res. 2016;143:127–9.
5. Denetclaw TH, Tam J, Arias V, Kim R, Martin C. Case report: Apixaban-associated gluteal artery extravasation reversed with PCC3 without FFP. J Pharm Pract. 2016;29(4):427–30.
6. Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF, et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. The Lancet. 2015;385(9984):2288–95.
7. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49(4):259–68.
8. Boom MS, Berghuis EM, Nieuwkerk PT, Pinedo S, Buller HR. When do patients prefer a direct oral anticoagulant over a vitamin K antagonist? Neth J Med. 2015;73(8):368–72.
9. Bottger B, Thate-Waschke IM, Bauersachs R, Kohlmann T, Wilke T. Preferences for anticoagulation therapy in atrial fibrillation: the patients' view. J Thromb Thrombolysis. 2015;40(4):406–15.
10. Ghijben P, Lancsar E, Zavarsek S. Preferences for oral anticoagulants in atrial fibrillation: a best–best discrete choice experiment. Pharmacoeconomics. 2014;32(11):1115–27.