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Authors	Murphy, Aileen;Kirby, Ann;Bradley, Colin
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Article Title:

Monitoring of Atrial Fibrillation in Primary Care Patients prescribed Direct Oral Anticoagulants for Stroke Prevention

Authors:

Murphy, A., Kirby, A., Bradley, C.

Dr Aileen Murphy,
Department of Economics,
Cork University Business School,
Aras na Laoi, Western Rd.
University College Cork,
Cork,
Ireland.
Aileen.murphy@ucc.ie

Dr Ann Kirby,
Department of Economics,
Cork University Business School,
Aras na Laoi, Western Rd.
University College Cork,
Cork,
Ireland.
a.kirby@ucc.ie

Prof Colin Bradley,
Department of General Practice,
School of Medicine,
Brookfield Health Science Complex,
University College Cork,
Cork,
Ireland.
c.bradley@ucc.ie

Corresponding Author: Dr Aileen Murphy
Department of Economics,
Cork University Business School,
University College Cork,
Cork,
Ireland.
aileen.murphy@ucc.ie
021 4903489

Abstract

Background: Direct Oral Anticoagulants (DOACs) are widely marketed as medicines that don't require routine laboratory monitoring. However, they do have complex pharmacological properties and side effects hence prescribing and monitoring guidelines, such as the European Heart Rhythm Association (EHRA) guidelines, have emerged. These advocate monitoring for renal and hepatic impairment; bleeding episodes; liver function; co-medication; circulation and occurrence of side effects. Though three to six month follow up is advocated, this is currently not routine and its implementation creates a potential obligation for general practitioners (GP)s managing Atrial Fibrillation (AF) patients in the community.

Aims: This study investigates the frequency, the type of follow-up, and the factors that influenced follow-up amongst Irish GPs, who prescribed DOACs to patients with AF, to prevent strokes in 2015.

Methods: The frequency and type of follow-up care is estimated and a count model regression analysis is applied to determine the GP and practice characteristics that are associated with the implementation of follow-up.

Results: The EHRA guidelines most frequently followed were those pertaining to renal function (82%), bleeding episodes (71%), liver function (69%), circulation (54%) and side-effects (55%). The regression analysis revealed that female GPs (P=0.05) and GPs who follow all seven guidelines (P=0.06), practice more frequent follow-up while those in training practices (P=0.09) provide less frequent follow-up.

Conclusions: Results show that there was incomplete adherence to the 2013 EHRA prescribing guidelines with only 24% adhering to all seven guidelines and patient follow-up was less frequent than has been suggested.

Key words: Anticoagulation, GP prescribing, Follow-up care, Adherence

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- Ethics approval and consent to participate

Ethical approval was acquired from University's Social Research Ethics Committee.
Informed consent was obtained from all individual participants included in the study.

- Consent to publish

Not applicable.

- Availability of data and materials

The raw data supporting this study are publicly available.

- Competing interests

The authors declare that they have no competing interests.

- Funding

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- Authors' Contributions

AM and AK had primary responsibility for analysis and interpretation of the data. All authors contributed to the conception and planning of the work and drafting the manuscript.

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INTRODUCTION

The adoption and diffusion of the new anticoagulants (based on pharmacological mechanisms other than vitamin K antagonism) into routine care for patients with Atrial Fibrillation (AF) to prevent strokes is clearly gathering pace [1]. Hence, they are no longer referred to as Novel Oral Anticoagulants (NOACs) but have been relabeled Direct Oral Anticoagulants (DOACs). Their relatively high price tag (compared to vitamin K antagonists) is perhaps not surprising as this is the case for most newly patented medicines replacing older therapies. However, there are additional requirements and costs of follow-up and maintenance required for AF patients prescribed DOACs that are sometimes overlooked. Without adequate monitoring, there is a risk that DOACs will fail to achieve therapeutic goals or cause avoidable harms in AF patients. Furthermore, costs of this monitoring may not be taken into consideration or is being underestimated when introducing these drugs. This study focuses on medicines management; managing the patients use of medicine or medicines through review and follow-up of aspects of their condition relevant to the medicine.

Lack of regular follow-up could result in sub-optimal adherence in the long-term, thereby increasing stroke risk [2, 8]. Already, across Europe, research suggests adherence to DOAC product information is sub-optimal [9] as real world patients differ to those recruited for clinical trials and more monitoring is required in these patients compared to those studied in trials. Despite this, no clear consensus has yet been reached on how, when and what laboratory measurements of anticoagulation levels are required or how to properly manage complications [10]. Cuker et al [11] reported that, to establish consensus on monitoring, more information on the relationship been drug levels and clinical outcomes is needed.

Nevertheless, these agents are being used routinely and given the patient cohorts in which it is being used; the elderly, patients with extremes of body weight, patients with multiple co-morbidities and polypharmacy; a greater degree of monitoring and follow-up is required [2, 12]. Additionally, Palareti and Poli [10] highlight the importance of involving family doctors in such follow-up, with support from expert centres. This is in line with global advances towards integrated care and the European Society of Cardiology's promotion of a structured, integrated approach to managing AF that is patient-centered and deploys multidisciplinary teams [13]. Thus education for clinicians on managing DOACs in real life is necessary [14]. Despite the emergence and widespread adoption of DOACs, use of oral anticoagulants in patients with AF and compliance with guidelines by physicians remains suboptimal [15].

This study examines General Practitioners (GPs) experience and practice of follow-up for managing AF patients prescribed DOACs using primary data collected from a survey of GPs in 2015, for stroke prevention. In particular, we investigate the type and frequency of follow-up employed by a sample of Irish GPs when managing AF patients prescribed DOACs in the community. In addition, GP and practice characteristics that are associated with implementation of follow-up recommendations are determined.

Ireland provides an interesting case study to examine medicines management of AF patients prescribed DOACs, as the State's Medicines Management Programme has advised on a preferred drug for this indication [16]. Despite their advocating warfarin as the anticoagulant of choice, DOACs are being prescribed in increasing volumes in Ireland [1]. Furthermore, through various drug cost reimbursement schemes, the State is paying for DOACs for most patients receiving them [17] (Given Ireland's unique categorisation system for health care entitlements [17] this is unusual). However, costs of monitoring are not accounted for through these schemes, as they are for some other medicines, such as methadone and warfarin. Thus, the cost of follow-up when managing AF patients prescribed DOACs is falling to GPs or is being borne by patients through out-of-pocket payments. Follow-up costs arising from the diffusion of DOACs can therefore be considered an externality. It fulfills the definition of an externality in economic terms in that the cost affects the GP, a party who did not choose to incur that cost, nor are they compensated for it [18]. This presents a potentially dangerous situation in which, through trying to avoid these costs, therapeutic anticoagulation goals may not be being met; side effects may develop; and the risk of stroke increases.

METHODS

In November 2015 a dedicated postal survey for Irish GPs was designed and disseminated to GPs to collect cross sectional data. No patients were involved in the study. Prior to dissemination, ethical approval was granted (University's Social Research Ethics Committee) and the survey was piloted. Estimates of the number of practicing GPs in Ireland ranges between 2,500 and 2,841 [19, 20]. There is no comprehensive list of GPs available as a sampling frame. Consequently, the telephone directory was used to compile a listing of over 1,422 GPs, accounting for multiple practices, retired and deceased GPs as per Bourke and Bradley [21]. The postal survey yielded a sample size of 307 (22%) respondents with a total of 299 (97%) GPs having some experience prescribing and maintaining patients on anticoagulants.

Data on GP characteristics, frequency and type of follow-up for managing AF patients prescribed DOACs were collected (Table 1). For the purposes of the study, follow-up for managing AF patients prescribed DOACs as per EHRA (European Heart Rhythm Association) 2013 guidelines should be completed either monthly or every 3 to 6 months and includes examination of the following: systemic and pulmonary circulation; frequency and type of nuisance bleeding; side effects; co-medications; blood sampling for hemoglobin, renal and kidney functions [4, 22]. We acknowledge that, subsequent to the survey being conducted, the EHRA 2018 guidelines have been published but the 2013 guidelines were in place when the survey was conducted (See tables 1 & 2). A continuous variable is used to measure annual frequency of follow-up. While binary variables are used to represent the observance of each of the diagnostics listed above as well as GP and practice characteristics.

Methodology

To examine the factors associated with the frequency of follow-up for AF patients prescribed DOACs amongst GPs in 2015 a count model is employed. A count model is a type of regression analysis that accounts for count outcome variables such as the number of follow-up visits for AF patients. Additional factors considered in the model were, GP characteristics, practice characteristics and adherence to 2013 EHRA guidelines.

To determine the appropriate count model both the Poisson and negative binomial models were estimated and compared, using Stata Version 14 [23]. Upon examining goodness of fit (chi-squared test) of the models, as well as the Hosmer-Lemeshow test on the Poisson model

and the dispersion parameter, α, on the negative binomial model, the Poisson model was rejected. The associated chi-squared value (α = 216.9) on the negative binomial model strongly suggested that α (parameter that measures over-dispersion) is non-zero and significant and was therefore more appropriate than the Poisson model. Also, there was over-dispersion in the data and the equi-dispersion did not hold (i.e. the conditional variance is not equal to the conditional mean). The negative binomial model can accommodate this additional unobservable heterogeneity which can cause the distribution to spread out towards the tails of the distribution.

The model specified is as follows:

$$P(Y = y_j|\mathrm{u}) = \frac{e^{-\lambda je(uj)}\lambda j^{uj}}{y_j!} \quad (\textit{Equation 1})$$

Where *y* is the probability of treatments for patients and *j* are patients prescribed DOACs. The e^{uj} has a gamma distribution with a mean and variance equal respectively to 1 and α. Therefore while keeping the unconditional mean the same and increasing the conditional variance the negative binomial overcomes the Poisson's over dispersion issue [24]. The model assumes that the individual error terms comes from a gamma probability distribution [25].

RESULTS

The survey had 309 responses, of which 97% of GPs had some experience prescribing and managing patients on anticoagulants (Table 3). Amongst those (n=299), the average age of GPs in the sample was 54 years and 67% were male. 60% of responding GPs indicated they had initiated prescribing of a DOAC to at least one patient. Most GPs were in practices in urban areas (81%); 34% reported having an anticoagulation clinic on site and 32% of GPs practice in dedicated GP training practices.

<<<<<Table 3>>>>>>>>

With regards to the following the EHRA 2013 guidelines, 24% of GPs reported following all seven recommended guidelines when managing AF patients prescribed DOACs. The frequency of follow-up varied from monthly (9%), to every three months (56%), to every six months (29%), to annually (2%). Remaining GPs indicated follow-up was based on patient

request (2%) or did not report frequency (2%) (These were excluded from the count model). The seven EHRA guidelines (systemic and pulmonary circulation; frequency and type of nuisance bleeding; side effects; co-medications; blood sampling for haemoglobin, renal and kidney functions) were followed by 24% of GPs. The most frequently followed are checking for renal function (82%), bleeding episodes (71%) and liver function (69%). Checking for side effects (55%) and checking circulation (54%) are the least frequently followed (Figures 1 and 2).

>>>> Figures 1 & 2 >>>>>

The negative binomial results (Table 4, n=287) reveal follow-up frequency of AF patients prescribed DOACs is less amongst female GPs, compared to males (P=0.05). While follow-up frequency for patients prescribed DOACs is higher amongst GPs who follow all seven EHRA guidelines compared to those that don't follow all seven (P=0.06). Of the three practice characteristics included in the model (location, anticoagulation clinic and training practice) only training practice status is found to be statistically significant. GPs located in a dedicated training practice have lower follow-up for AF patients prescribed DOACs than those not in dedicated training practices (p=0.09).

<<<<<<<table 4>>>>>>>

DISCUSSION

Globally health systems are moving towards an integrated approach to delivering health care. In particular, the European Society of Cardiology advocate a structured, integrated approach to managing AF that is patient-centered with multidisciplinary teams [13]. Consequently GPs need to be involved in this integrative approach when managing AF patients in communities [10] and, therefore, require appropriate education to do so in practice [14].

The benefits of DOACs have been widely reported and they are being marketed internationally as not requiring routine laboratory monitoring [2]. The latter claim, though, is based on one Phase III clinical trial [3]. However, the reporting of side effects, along with the emergence of EHRA and other guidelines advocating follow-up and maintenance, as well as real world experience, suggest some more comprehensive form of management, which

includes regular review and follow-up, is required. While DOACs have been marketed internationally as not requiring routine laboratory monitoring [2], side effects of DOACs are widely reported [3] and guidelines advocating follow-up and maintenance in specific areas have been published [4]. The latter include recommendations to monitor renal and liver function, check for unexpected bleeding or thrombosis, ascertain compliance to therapy, as well as avoiding combining DOAC administration with certain drugs such as some antibiotics ([5, 6] in [7]).

As well as avoiding adverse events, this sort of medicines management can improve patient adherence [2, 8]; suggesting a potential moral hazard issue. Stroke prevention is a key objective when anticoagulating AF patients. Given the major debilitating nature of stroke, getting anticoagulation right is vital. However, despite advancements offered by DOACs, as well as published guidelines, oral anticoagulation amongst AF patients is suboptimal in Ireland [15].

While prescribing and educational tools are emerging, consensus on which to use is yet to be reached. The EHRA 2013 guidelines were inclusive of several risk factors and domains and were chosen here as a benchmark to assess experience and practice for managing AF patients prescribed DOACs amongst Irish GPs. EHRA guidelines were chosen given their association with the European Society of Cardiology whose guidelines on other aspects of cardiology care are widely endorsed by Irish GPs.

The dedicated GP survey utilized in this study, revealed 24% of respondents followed all seven guidelines and 15% followed all seven guidelines on a quarterly basis. The most frequently followed guidelines are those pertaining to renal function (82%), bleeding episodes (71%) and liver function (69%). Recommendations regarding checking circulation (54%) and for side-effects (55%) are least frequently followed. The regression analysis revealed that female GPs and GPs who follow all seven EHRA guidelines, practiced greater follow-up frequency and GPs in training practices provide less frequent follow-up.

The suboptimal routine monitoring of renal and hepatic impairment is concerning as these impairments are common in the typically older patient who has AF. Likewise, monitoring of haemoglobin can detect otherwise unsuspected bleeding. Regular follow-up also affords doctors an opportunity to check patients are taking their medicines as prescribed. This result

reveals the importance of adequate and accessible education and decision support tools for GPs when managing AF patients prescribed DOACs.

We acknowledge in the practice type and frequency of follow-up variables they can often be influenced by patient profile. Unfortunately, it was not feasible to collect patient characteristics here. So this could not be controlled for in the model on a per patient basis, rather the average is employed. GP follow-up was also self-reported and may be vulnerable to reporting bias. Furthermore, we acknowledge the small but respectable sample size that could be subject to response bias. Nonetheless, the sample characteristics are similar to other published GP surveys [21, 26, 27] thereby providing a reasonable cross-section of data for analysis.

Furthermore, we acknowledge that cost may influence GP behavior although this was not captured in the survey. While the side effects of DOACs are well reported and EHRA and other guidelines advocate follow-up and maintenance, the cost of this is not accounted for in the market price. Furthermore, responsibility for follow-up and maintenance is falling on clinicians not the supplier (the pharmaceutical company). This phenomenon is not novel, and was a key feature of DOAC's predecessor, warfarin (Vitamin K antagonist). Although warfarin is an inexpensive drug (3% of average DOAC prices [28]) the need for associated international normalized ratio (INR) monitoring (INR is a measure of blood coagulation) with warfarin is well established and the cost was, historically, borne by the secondary system in Ireland where it was factored into hospital budgets. Recently owing to overcapacity and patient convenience some GP practices are offering INR monitoring services paid for through out-of-pocket payments of private patients and, in some instances, state funding for public patients.

A unique selling point of DOACs was the elimination of the need for INR monitoring. The associated cost of follow-up and maintenance for AF patients prescribed DOACs is an externality. We acknowledge one needs to be cautious when applying economic theory to health care owing to its unique features [29]. Nevertheless, as primary care centers, GPs and hospitals continue to operate in an environment with scarce resources and increasing demands on those resources, economic principles and tools are increasingly used to inform decision-making influence behavior and guide policy. To overcome the externality associated with DOAC prescribing, some Irish general practices are charging patients for follow-up and

maintenance. For example, local anecdotal evidence suggests a €10 charge per patient amounting to €40 per annum (if, for example, they complete quarterly reviews). However, this is not standardized and is problematic when the majority of patients are receiving DOACs either entirely provided by or heavily subsidized by the State. Given the adherence issues with DOACs [2, 8], caution needs to be exercised. We need to avoid creating further adherence barriers amongst patients whilst simultaneously ensuring GPs provide routine structured follow-up.

CONCLUSION

Maintaining therapeutic anticoagulation levels amongst AF patients and avoiding adverse effects is imperative to reduce stroke risk and avoid the accompanying disability and costs while avoiding the risk of bleeding. Appropriate regular follow-up by GPs on managing AF patients prescribed DOACs could reduce such risks but a mechanism for covering the cost of this is required in order to ensure optimal monitoring of these patients. The results of this study indicate that GPs did not appear to be fully adhering to the 2013 EHRA and maintenance guidelines. While education and decision support tools for GPs are available they require more active dissemination and additional resources for practices are needed to enable their implementation. Further research is warranted to investigate if the situation has changed now that more recent guidelines are available and DOACs are diffused further into routine practice.

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