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Oral Anticoagulants - Utilisation and Expenditure under the Community Drugs Schemes

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Abstract

Aims
This study determined the impact of the direct oral anticoagulants (DOACs) on the utilisation and expenditure on oral anticoagulants (OACs) in the Irish Community healthcare setting. We also investigated aspects of DOAC prescribing.

Methods
Using anonymised prescription data from the HSE pharmacy claims database we investigated anticoagulant prescribing over the study period (1/1/2014 – 31/12/2018).

Results
Some 74,748 patients were being treated with OACs by the year end 2018 an increase of 30,319 over 5 years. Warfarin prescribing fell from 32,751 patients in 2014 to 16,166 by the year end 2018. Apixaban is the most frequently prescribed OAC and annual expenditure on DOACs now exceeds € 51 million. Patients treated with DOACs are older than participants in the pivotal clinical trials and are frequently co-administered interacting drugs.

Conclusion
The introduction of DOACs has resulted in an overall increase in anticoagulant prescribing, a significant reduction in warfarin usage and a large increase in expenditure.

Introduction

For years warfarin has featured in the top 20 most frequently prescribed medicines under the General Medical Services (GMS) and Drugs Payment (DP) scheme [1]. However, its limitations are well documented including slow onset and offset of action, drug-drug interactions and the requirement for monitoring the international normalised ratio (INR) to enhance efficacy and reduce toxicity[2]. The last 10 years has seen the introduction of the direct acting oral anticoagulants (DOACs) as an alternative to warfarin therapy. Dabigatran, a direct thrombin inhibitor and rivaroxaban, a factor Xa inhibitor, were first to enter the market, followed by two other factor Xa inhibitors; apixaban in 2012 and edoxaban in 2015. These agents have a number of advantages including swift onset and offset of action, less clinically significant drug - drug interactions and no requirement for monitoring[3]. However, the DOACs are much more expensive than warfarin therapy even when INR monitoring is considered. Here we consider the utilisation and expenditure on OACs under the Community drugs schemes in addition to aspects of DOAC prescribing.

Methods

This study was carried out using anonymised individual-level prescription data from the HSE – PCRS pharmacy claims database over the study period (01/01/2014 – 31/12/2018). Drugs were coded according to WHO-ATC classification and anticoagulant drugs were identified using the relevant ATC codes i.e. warfarin (B01AA03), dabigatran (B01AE07), rivaroxaban (B01AF01, B01AX06), apixaban (B01AF02) and edoxaban (B01AFO3) and extracted from the database. Further subcategorization according to dosage was carried out. Patients were categorised into the following age groups: 0-44, 45-64, 65-79 and 80 years or over to determine utilisation in the different age cohorts. Drugs that are contraindicated or cautioned in combination with DOACs were also identified including: non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, amiodarone, verapamil, systemic anti-mycotics and antidepressants. It is important to note that this is a non-exhaustive list, and other drugs to be used with caution can be found in the individual anticoagulant Summary of Product Characteristics, or in the Medicines Management Programme's 'Anticoagulation Prescribing Tips' [4]. It should be noted that indication for treatment is not recorded in this database, and we cannot determine the clinical demographics of the patients.

Results

The number of patients dispensed an OAC from January 2014 to December 2018 is shown in Figure 1. In January 2014 warfarin was dispensed to 32,751 patients accounting for 74% of all anticoagulant use. Rivaroxaban was the most frequently prescribed DOAC (6,286 patients) at that time followed by dabigatran (4,972 patients) and apixaban (420 patients). Over the next 5 years the total number of patients anticoagulated increased by 30,319 giving a total of 74,748. The prescribing of warfarin fell to 16,166 patients by December 2018, representing just 21.6% of OAC use. Apixaban is now the most frequently prescribed OAC with 27,316 patients being treated (36.5% of all OAC use), followed by rivaroxaban (22,352 patients; 30% of all OAC use). The number of patients being treated with dabigatran increased to 5,286 and edoxaban was prescribed for just 3,628 patients.

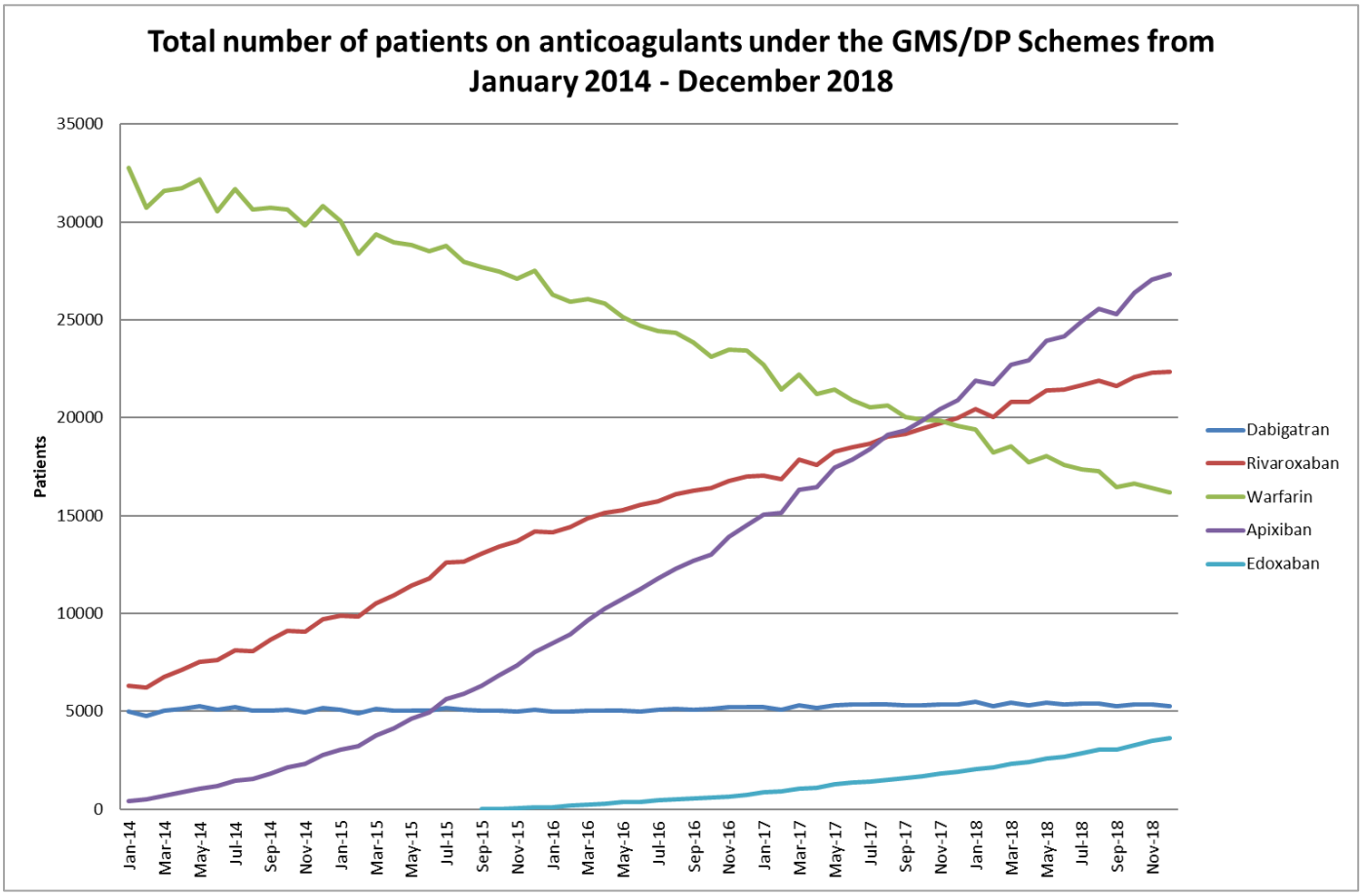

Figure 1. Number of patients receiving an oral anticoagulant under the GMS and DP community drugs schemes from January 2014 to December 2018

In 2018 the mean age of patients receiving DOACs was 77 years and a large proportion were 80 years or over varying from 40% of patients treated with rivaroxaban up to 50% of those treated with apixaban. Under half of all patients were female ranging from 42% treated with dabigatran to 49% of patients on apixaban. In relation to dosing only 41.2% of prescriptions for dabigatran were for the 150mg twice daily dose. For rivaroxaban over 70% of prescriptions were for the 20mg once daily dose whilst 60% of apixaban prescriptions were for the higher 5mg twice daily dose. Over half of all edoxaban prescriptions (57%) were for the higher 60mg daily dose. For patients 80 years and over treated with dabigatran 14% of prescriptions were for the higher 150 mg twice daily dose while 39% of apixaban prescriptions in this age group were for the higher 5mg twice daily dose as compared with rivaroxaban where 53% of prescriptions were for the higher 20mg once daily dose and 36% of patients treated with edoxaban were on 60mg once daily.

Co-prescribing of cautioned or contraindicated drugs is shown in Table 1 and includes medications that affect haemostasis such as; nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin and antidepressants (SSRIs and SNRIs) and drugs that inhibit cytochrome P4503A4 (CYP3A4) and P-glycoprotein (P-gp) such as azole antifungals, verapamil, amiodarone and dronedarone.

Table 1. Frequency of OAC claims in 2018 with co-prescribing of contraindicated or cautioned drugs

OAC:		**Dabigatran**		**Rivaroxaban**		**Apixaban**		**Edoxaban**		**Warfarin**	
	Total claims:	51,554		207,350		255,306		26,787		200,273	
	Co-prescribed with:	n	%	n	%	n	%	N	%	N	%
	NSAID	775	1.50	3,819	1.84	2,789	1.09	367	1.37	1,315	0.66
	Aspirin	4,940	9.58	18,425	8.89	24,625	9.65	3,003	11.21	18,907	9.44
	Amiodarone	1,540	2.99	7,255	3.50	10,262	4.02	1,317	4.92	5,238	2.62
	Verapamil	876	1.70	2,255	1.09	2,637	1.03	357	1.33	2,711	1.35
	Antidepressants	5,768	11.19	23,815	11.49	29,696	11.63	2,681	10.01	18,258	9.12
	Dronedarone	79	0.15	929	0.45	2,569	1.01	378	1.41	1,112	0.56
	Azole antimycotic	16	0.03	142	0.07	185	0.07	27	0.10	56	0.03
		13,994	27.14	56,640	27.32	72,763	28.50	8,130	30.35	47,597	23.77

***n**: number of prescription claims within that OAC, **%**: percentage of claims within that OAC.*

Total expenditure on OACs from January 2014 to December 2018, under the GMS and DP Community Drugs Scheme is shown in Figure 2. Monthly expenditure increased over three fold from €1,474,797 in January 2014 to €4,797,871 in December 2018. Apixaban is the number one selling DOAC at over € 2.1 million per month followed by rivaroxaban at € 1.8 million monthly. Total expenditure on DOACs in 2018 was €51,337,571 accounting for over 95% of all expenditure on OACs.

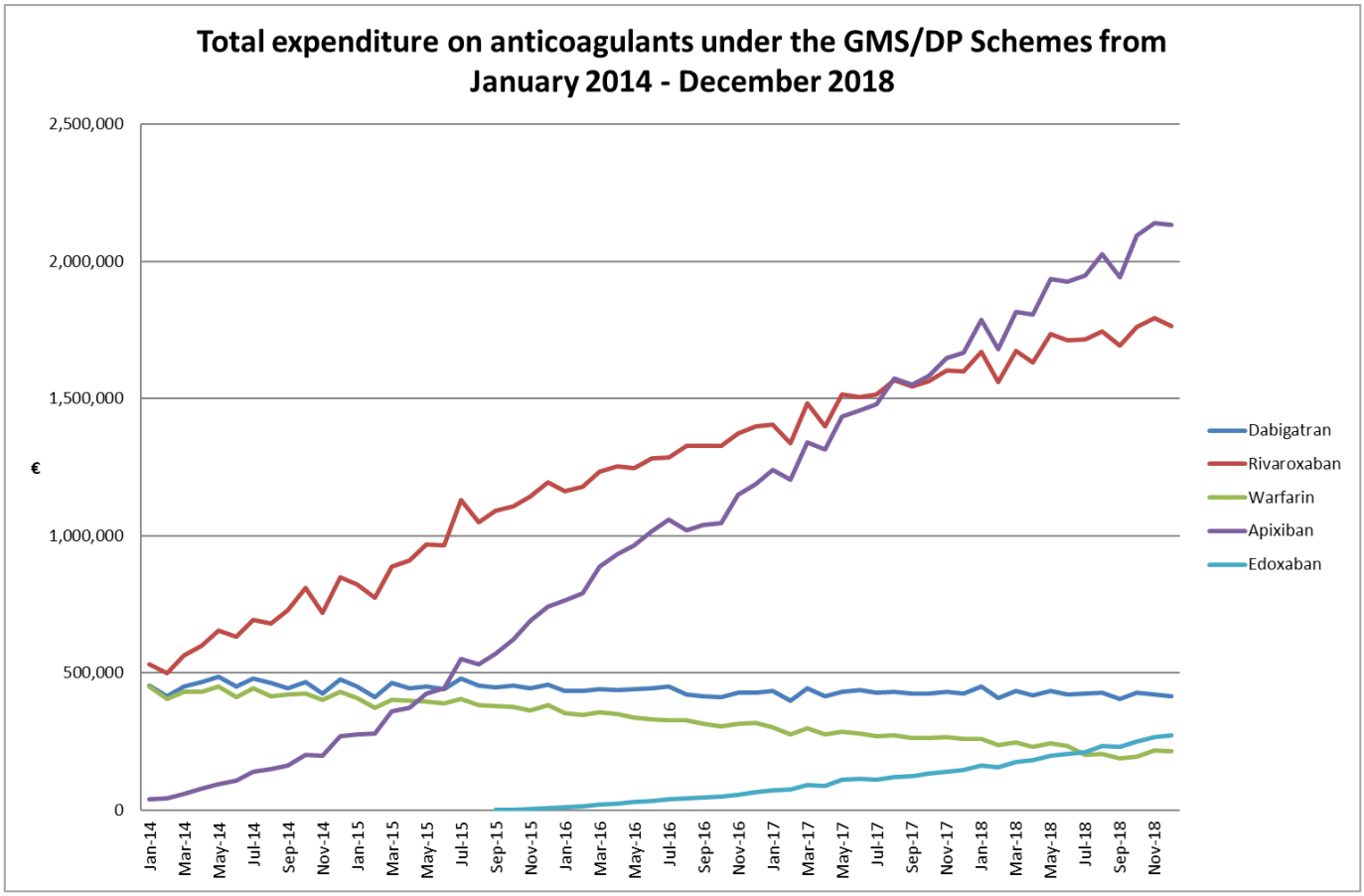

Figure 2. Total expenditure on oral anticoagulants under the GMS and DP schemes from January 2014 to December 2018

Discussion

It is seen that prescribing trends in the OAC class has changed dramatically over the past 5 years where an additional 30,319 patients have been anticoagulated and the number of patients on warfarin has fallen from 32,751 to just 16,166. Since late 2017, apixaban, the HSE-Medicines Management Programme preferred DOAC, has been the most frequently prescribed OAC accounting for 27,316 patients the end of 2018 (36.5% of all OACs). Following a review published in March 2019, apixaban is considered the DOAC of choice by the Medicines Management Programme. Following on from this, as of 1st September 2019, there is no longer a requirement to make an online application for reimbursement of apixaban. Current evidence suggests apixaban has an advantage in terms of safety and reduced bleeding, compared to warfarin and other DOACs [5].

This change in anti-coagulation is in a backdrop of an aging population in Ireland and an increased awareness of screening for atrial fibrillation [6,7]. In 2010, the HSE introduced a range of clinical programmes, one of these being The National Stroke Programme. An Atrial Fibrillation/Stroke Prevention Working Group was formed and the group carried out a review of warfarin services in the acute hospitals, developed an atrial fibrillation care pathway and recommended that a study on the feasibility of atrial fibrillation screening in General Practice be undertaken [7].

The demise of warfarin therapy is likely related to the recognised limitations as outlined above, particularly the requirement for frequent INR monitoring which is time consuming and incurs a cost. The failure of the HSE to invest in INR monitoring in the general practice setting likely hastened the observed switch to DOACs as there remains little incentive for prescribers to commence or maintain patients on warfarin therapy. The trend towards increased DOAC prescribing has been observed in the UK and other European countries [8–11].

The use of DOACs for stroke prevention in non-valvular atrial fibrillation is the most frequent clinical indication (over 85% of indications, based on an internal audit of a subset of DOAC applications from the PCRS) and there are important differences between patient populations in the pivotal trials and those in the Irish clinical setting. It is important to note that without information on co-morbidities and clinical parameters (such as creatinine clearance and weight), it is difficult to assess the appropriateness of the DOAC prescribing patterns seen in this study. However, there are some interesting observations when comparing this study population to that of the pivotal clinical trials. In the RE-LY study

dabigatran 150mg twice daily was associated with lower rates of stroke and systemic embolism and similar rates of major haemorrhage as compared to warfarin [12]. Dabigatran 110mg twice daily was associated with similar rates of stroke and systemic embolism but lower rates of major haemorrhage. However, the majority of prescriptions (57%) for dabigatran in the Irish healthcare setting are for the 110mg twice daily dose. The ARISTOTLE trial demonstrated that apixaban 5mg twice daily was superior to warfarin in preventing stroke or systemic embolism and caused less bleeding, however 39.5% of all prescriptions for apixaban in clinical practice are for the lower 2.5 mg twice daily dose [13]. Similarly for rivaroxaban and edoxaban; 25.7% and 41.8% of prescriptions were for the lower 15mg and 30 mg once daily doses, respectively. Whether the greater use of low dose DOACs in the 'real world' setting will impact on health outcomes remains to be seen.

As the majority of patients treated with DOACs for atrial fibrillation will be elderly where renal elimination of drugs is reduced, age is an important factor. Furthermore, age related dose adjustments are recommended for some DOAC therapies such as dabigatran and apixaban. In the pivotal DOAC atrial fibrillation trials, the percentage of patients over 80 years of age ranged between 13.5% in the RE-LY trial (dabigatran) to 18.3% in the ROCKET AF trial (rivaroxaban) [12,14]. We found that Irish patients being treated with DOACs are older with 40% to 50% of prescriptions issued for patients aged 80 years or over, such patients are more likely to experience haemorrhagic complications.

For dabigatran, a dose reduction to 110mg twice daily is recommended for patients 80 years of age or older, however our study shows that 3,350 patients (14%) of this age group were dispensed the higher dose of 150mg twice daily in 2018. Low dose apixaban at 2.5 mg twice daily is recommended for stroke prevention in atrial fibrillation if patients have at least two of the following characteristics: age ≥ 80 years, body weight ≤ 60kg or serum creatinine ≥ 133µmol/l. It is noted that 38.5% of this age group were dispensed the higher 5mg twice daily dose in 2018. Caution is advised when DOACs are co-prescribed with medications that may adversely affect haemostasis such as NSAIDs, aspirin and SSRIs/SNRIs. Co-prescribing rates for DOACs with aspirin and SSRIs/SNRIs was approximately 10% but much lower for NSAIDs at under 2% suggesting that prescribers may be more aware of interactions with NSAIDs.

Bleeding risk is increased when DOACs are prescribed in combination with strong inhibitors of CYP3A4 and P-gp such as the azole anti-fungals (ketoconazole, itraconazole) as bioavailability of DOACs will be increased. Although apixaban, dabigatran and rivaroxaban are not recommended in combination with azole anti-fungals there were 343 instances of co-prescribing in 2018. The lower 30mg once daily dose of edoxaban is recommended in the presence of strong inhibitors. Anti-arrhythmic drugs and verapamil are likely to be co-prescribed in atrial fibrillation but they are not contraindicated, except for dronedarone with rivaroxaban, and a dose reduction for dabigatran is required when prescribed with verapamil.

The average annual cost per patient being treated with DOACs is in the region of €900 as compared with €160 for warfarin (not including monitoring costs). It is seen that total expenditure increased approximately 4.5 fold from €1,023,067 per month at the start of 2014 to €4,582,874 by the year end 2018. At current growth rates the DOACs are set to become one of the most expensive therapies reimbursed under the community drugs schemes. Whether this increased expenditure is reflected in much improved health outcomes remains to be seen.

Declaration of Conflict of Interest:
There are no conflicts of interest to disclose.

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References:

1. PCRS. PCRS - Statistical Reporting. https://www.sspcrs.ie/portal/annual-reporting/report/annual. Accessed April 17, 2020.

2. Pirmohamed M. Warfarin: almost 60 years old and still causing problems. Br J Clin Pharmacol. 2006;62(5):509-511. doi:10.1111/j.1365-2125.2006.02806.x
3. Vinogradova Y, Coupland C, Hill T, Hippisley-Cox J. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362:k2505. doi:10.1136/bmj.k2505
4. Prescribing Tips for NOACs. https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/noac-prescribing-tips-for-noacs.pdf. Accessed April 17, 2020.
5. Medicines Management Programme. Oral Anticoagulants For Stroke Prevention In Non-valvular Atrial fibrillation. https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/preferred-drugs/oral-anticoagulants-for-stroke-prevention-in-non-valvular-atrial-fibrillation.pdf. Accessed April 17, 2020.
6. Census of Population 2016 - Profile 3 An Age Profile of Ireland - CSO - Central Statistics Office. https://www.cso.ie/en/releasesandpublications/ep/p-cp3oy/cp3/. Accessed April 17, 2020.
7. Health Services Executive. Atrial Fibrillation Screening in General Practice. https://www.hse.ie/eng/services/publications/clinical-strategy-and-programmes/atrial-fibrillation-screening-in-general-practice.pdf. Accessed April 17, 2020.
8. Loo SY, Dell'Aniello S, Huiart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. Br J Clin Pharmacol. 2017;83(9):2096-2106. doi:10.1111/bcp.13299
9. de Jong LA, Koops M, Gout-Zwart JJ, et al. Trends in direct oral anticoagulant (DOAC) use: health benefits and patient preference. Neth J Med. 2018;76(10):426-430.
10. Protty MB, Hayes J. Dawn of the direct-acting oral anticoagulants: trends in oral anticoagulant prescribing in Wales 2009-2015. J Clin Pharm Ther. 2017;42(2):132-134. doi:10.1111/jcpt.12481
11. Kjerpeseth LJ, Ellekjær H, Selmer R, Ariansen I, Furu K, Skovlund E. Trends in use of warfarin and direct oral anticoagulants in atrial fibrillation in Norway, 2010 to 2015. Eur J Clin Pharmacol. 2017;73(11):1417-1425. doi:10.1007/s00228-017-2296-1
12. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561
13. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039
14. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638