The association between increasing oral anticoagulant prescribing and atrial fibrillation related stroke in Ireland

Cormac Kennedy1,2 | Ahmed Gabr1 | Joan McCormack3 | Rónán Collins4 | Michael Barry1,2 | Joe Harbison5,6

1Department of Pharmacology and Therapeutics, Health Sciences Centre, Trinity College Dublin, Dublin 8, Ireland
2Department of Pharmacology, St James Hospital, Dublin 8, Ireland
3National Office of Clinical Audit, St Stephens Green, Dublin, Ireland
4Department Geriatrics and Stroke Medicine, Tallaght University Hospital, Dublin, Ireland
5Mercer’s Institute for Successful Ageing, St James Hospital, Dublin, Ireland
6Discipline of Medical Gerontology, School of Medicine, Trinity College Dublin, Ireland

Aims: Recent increases in the number of patients with atrial fibrillation (AF) prescribed oral anticoagulants (OAC) are evident in Ireland and internationally, largely due to the availability of direct oral anticoagulants (DOACs). This study aimed to determine the rate of stroke in the context of increasing anticoagulation utilisation, with a focus on AF-related ischaemic stroke (IS).

Methods: Dispensing data for OACs were identified for the period 2010–2018 as well as hospital discharges for IS (2005–2018). Irish National Stroke Register data were used to elucidate the characteristics of patients with acute ischaemic stroke.

Results: The number of patients prescribed OACs increased by 94% from 2010–2018 with a significant change from 2013 (β = 2.57, P = .038), associated with a large increase in the number of patients on DOACs. There was a 3.3-fold increase in expenditure on OACs nationally from 2013 to 2018, of which 94% was DOAC related. Using the 2013 timepoint, ischaemic stroke rates until 2018 did not show a significant deviation from the previous trend (β = 0.00, P = .898). The percentage of AF-related ischaemic stroke was stable from 2013 to 2017 with a 4.5% decrease in 2018. The percentage of ischaemic stroke patients with previously diagnosed AF decreased from 2013 to 2018; however, there was an increase in the percentage of ischaemic strokes while on OAC in this cohort.

Conclusion: Large increases in OAC utilisation have not resulted in changes in ischaemic stroke rates at a national level. The percentage of ischaemic strokes with a previous diagnosis of AF has decreased indicating a possible benefit from greater OAC utilisation. However, the percentage presenting with an ischaemic stroke while on OAC treatment is increasing. The increase in patients presenting with stroke while treated with OAC may largely reflect the national increase in patients prescribed DOACs but the findings raise concerns about treatment failures. The real-world effectiveness of DOACs requires further examination.

KEYWORDS
anticoagulation, atrial fibrillation, direct oral anticoagulant, ischaemic stroke, novel oral anticoagulant, warfarin
1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and an ischaemic stroke is a devastating sequela of the condition.\(^1^2\) Prevention of these events with warfarin in high-risk patients with atrial fibrillation has been extensively studied, providing unequivocal evidence of benefit. However, two UK primary care-based studies estimated that 34% and 49% of patients with AF were not prescribed oral anti-coagulants (OACs), with similar findings in an Irish study.\(^3^5\) These findings of underutilisation also extended to secondary stroke prevention in those with AF, particularly the elderly and higher risk patients.\(^6\)

Direct oral anticoagulants (DOACs) are recent additions to the treatment options for AF-related stroke following clinical trials demonstrating a non-inferiority to warfarin in many scenarios. DOACs received authorisation for stroke prevention in AF from the European Commission from 2011 onwards. Their rapid adoption has been evident in multiple jurisdictions, possibly due to the convenience they offer to patients and prescribers as well as their endorsement by various clinical guidelines.\(^7^10\) In an Irish context, studies have attempted to assess the patterns of DOAC uptake but its diffuse nature did not indicate that specific underserved populations benefitted from the new therapeutic option.\(^11\) It is intuitive that a substantial increase in utilisation of OAC, as a result of DOAC availability, should improve outcomes for patients with AF at a population level. Such improvements in population health would justify increases in expenditure.

Over 7000 patients are hospitalised following a stroke annually in Ireland.\(^12\) In 2010, a national stroke programme was initiated in the Irish health service to align resources with care for stroke patients.\(^13\) The programme aimed to ensure high-quality care provision and improve patient outcomes using an integrated care model. As part of this programme, measurement of stroke interventions and outcomes was required to guide national recommendations, allocate funding and determine the success of new interventions such as stroke units. A National Stroke Register was therefore established by the National Clinical Programme for Stroke.

On preliminary assessment of National Stroke Registry data, it was notable that the proportion of AF ischaemic strokes with AF as the aetiology was unchanged, despite more patients presenting on OAC. Following this observation, an examination of OAC prescribing patterns and stroke rates in Ireland was planned. At present, healthcare data in Ireland is disjointed, sitting in numerous databases without a functional national identifier. Also, data for conditions which would most reliably be informed by primary care data, such as AF, are not centralised. Within these constraints, the aims of the study were as follows:

1. Describe the increase in OAC utilisation and expenditure due to the utilisation of DOACs in Ireland.
2. Report the rate of ischaemic and haemorrhagic stroke in Ireland.
3. Determine the rate of AF-related stroke as a proportion of ischaemic stroke presentations.
4. Determine antithrombotic treatment in patients presenting with ischaemic stroke.

What is already known about this subject

- Oral anticoagulation (OAC) is underutilised in patients for stroke prevention.
- Direct oral anticoagulants overcome some issues inherent in the use of warfarin therapy, leading to an increase in the use of OAC.
- It might be expected that the rate of stroke related to atrial fibrillation has reduced.

What this study adds

- There has been a substantial increase in patients on OAC while the overall ischaemic stroke (IS) and atrial fibrillation (AF) related IS rates have remained stable.
- The percentage of IS patients with previously diagnosed AF is decreasing; however, the percentage of these patients on OAC prior to admission with an ischaemic stroke is increasing.
- This may reflect the increasing numbers of patients prescribed OAC but it may also indicate increasing treatment failures on OAC. This possibility requires further study and changes to care provision for AF patients.

2 | METHODS

2.1 | Oral anticoagulant prescribing in Ireland

The Health Services Executive (HSE—the national health service provider) General Medical Services (GMS) scheme is a means-tested system in Ireland providing prescribed medicines for a small co-payment per item.\(^14\) The scheme covers approximately one third of the population, but represents three-quarters of prescribing by volume, and over-represents females and the elderly.\(^14\) The HSE-Primary Care Reimbursement Service (PCRS) pharmacy claims database used for this study contains reimbursement records of medicines dispensed by pharmacies to patients in primary care. This database was used to report OAC prescribing trends and the associated cumulative expenditure. Medicines were identified by their WHO Anatomical Therapeutic Chemical (ATC) classification code. The number of patients with an OAC prescription each month under the GMS scheme were extracted from the HSE-PCRS database and combined to give a monthly average for each year from 2010 to 2018 inclusive. The dispensing figures are considered a surrogate for patients prescribed OAC. The number of patients eligible under the GMS scheme (all ages, 65–74 years, 75 years and older) in each calendar year was identified from the HSE-PCRS annual reports. The monthly figures were adjusted for the number of GMS eligible...
patients prior to analyses. Expenditure figures were also attained in a similar manner and the monthly figures were added to give total annual expenditure.

2.2 Stroke event rates in Ireland

The Hospital In-Patient Enquiry (HIPE) is a health information dataset which collects data on discharges from acute hospitals in Ireland funded by the HSE.\textsuperscript{15} This database was used to report the number of patients discharged with a primary diagnosis of an acute stroke (ischaemic and haemorrhagic) as a rate adjusted for the national population. The data pertains to admitted patients only. Diagnoses are coded using the International Classification of Disease 10 Australian Modification system. A move to Australian Refined Diagnosis Related Groups and the Australian Classification of Health Interventions occurred in 2005, changing the data collected. HIPE data coverage is reported to be 99.74% of hospital discharges.\textsuperscript{15} Patients coded with a primary diagnosis of stroke (ICD codes I61, I63, I64 including subcategories) are included in this study for the period 2005–2018.

2.3 Atrial fibrillation-related ischaemic stroke rates: National Stroke Register data

The Irish National Clinical Programme for Stroke was established in 2010 following an audit of stroke care in 2008.\textsuperscript{12} The programme had a number of workstreams, one of which was the establishment of the National Stroke Register. The register was used to report the percentage of ischaemic stroke patients with a diagnosis of AF and to determine the anti-thrombotic treatment of patients with ischaemic stroke. The register was developed in partnership with the Health, Research and Information Division at the Economic and Social Research Institute (ESRI) and its function is overseen by a Steering Group. The register is embedded within the HIPE data collecting system. The register is completed by most but not all hospitals with acute stroke services—18 of 24 hospitals had >80% stroke patient coverage in 2018. Data validity is checked against the HIPE dataset. Data collected by the register relevant to this study include hospital admissions due to stroke, the category of stroke (ICD codes I61, I63, I64 including subcategories), a diagnosis of AF prior to admission (documented by the admitting doctor), a diagnosis of AF at any timepoint during the inpatient episode and the medications on admission. Medication-related data have been collected since 2013. The data were therefore limited to the 2013–2018 timeframe during which time the hospital coverage was constant.

2.4 Data and statistical analysis

All data had been de-identified prior to its provision for analysis. Following a review of the data trends for OAC prescriptions, a transition point was chosen at the beginning of 2013 (Figure 1), in line with the method put forward by Wagner et al. for segmented regression analyses.\textsuperscript{16} This divided the study period into two segments; 2010–2012 and 2013–2018. This segmentation was consistent with the approved reimbursement of DOACs for prevention of stroke in non-valvular AF in late 2012. Segmented regression analyses were used to analyse the PCRS data over the study period using the chosen cut-off.\textsuperscript{16} The effect of DOAC prescribing was quantified in terms of the slope change ($\beta$ coefficient) for the periods above. As patients may repeat prescriptions monthly, the Durbin-Watson (DW) statistic was applied to test for first-order autocorrelation in the residuals from the statistical regression analysis of this dataset. Data trends for stroke discharges (HIPE data) were analysed by linear regression. As a secondary method, change point analysis was performed to identify a joinpoint (point at which a significant change in slope is evident) which best fits the data while reporting annual percent change (APC) for each segment.\textsuperscript{17}

Linear regression was used to analyse trends for AF-related ischaemic strokes using the National Stroke Register data. Differences in slopes of two variables were analysed using the t-test assuming equal variance as appropriate.\textsuperscript{18} Using this method, it was determined

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1}
\caption{Anticoagulant prescribing trends (utilisation and expenditure) for General Medical Scheme eligible patients} \end{figure}
if the numbers of patients were consistently higher for one group of interest compared to another over the period of interest (e.g., OAC patients under 75 compared to OAC patients 75 and older). As standard, the minimum level of statistical significance was 5% ($P < .05$). Analysis was performed using Microsoft Excel (Microsoft Corporation, Seattle, WA, USA), SPSS software version 24 (IBM Corp, Armonk, NY, USA) and Joinpoint Regression Program version 4.8.0.1 (https://surveillance.cancer.gov/joinpoint/).

3 | RESULTS

A large increase in expenditure on OAC was evident, from €5.3 million in 2010 to €40.3 million in 2018 (Figure 1). During the same period, DOAC expenditure increased by a factor of 53, albeit from a low baseline of €0.7 million, to be the main component of OAC expenditure in 2018 at €38.1 million. Expenditure on warfarin halved (51% decrease) over the entire period. As a percentage of the total expenditure on OAC, warfarin’s share decreased from 86.7% to 5.7%.

GMS patients on OAC almost doubled from a monthly average of 17.9 patients per 1000 eligible patients in 2010 to 34.7 per 1000 in 2018 (Figure 1). As can be seen in Figure 1, a significant change in slope was evident at the 2013 cut-off ($\beta = 2.57$, 95% confidence interval [CI] 0.20–4.95, $P = .038$). This increase was related to an increase in the patients prescribed DOACs from 0.2 patients per 1000 in 2010 to 25.6 per 1000 in 2018. A significant change in the rate of DOAC prescribing in 2013 was noted ($\beta = 3.91$, 95% CI 1.07–6.75, $P = .017$). For the same period, the patients on warfarin almost halved, having decreased by only 2% from 2010 to 2012. On secondary analysis, a joinpoint was identified at 2012 with an APC of 0.94 for 2010–2012 and 10.69 for 2012–2018, indicating a significant change in trend at this point ($P = .022$).

More patients in the 65–74 years group and those 75 years and older were prescribed OAC compared to those younger than 65 years throughout the 2010–2018 period (Figure 2, both $P < .001$). For those 65 years and over, OAC patients increased by 50% from 2010 to 2018, while patients prescribed DOACs increased 113-fold. These increases were more pronounced for those 75 years and older, 109% for OAC and a 145-fold increase for DOACs. There was a 47% decrease in patients 75 years and over prescribed warfarin, while 25.1% of these patients on OAC were prescribed warfarin in 2018 having been 98.9% and 77.3% in 2010 and 2013 respectively.

As seen in Figure 3, the ischaemic stroke rate in Ireland was 1.10 per 1000 in 2005 and it remained at 1.10 in 2018 ($\beta = 0.00$, 95% CI –0.00–0.00, $P = .949$). There was no significant change in the trend when the period 2005–2012 is compared to 2013–2018 ($\beta = 0.00$, 95% CI –0.01–0.01, $P = .898$). Also, change point analysis did not identify a significant joinpoint ($P = .640$). The haemorrhagic stroke rate was 0.332 in 2005 and 0.287 in 2018. There was a significant change in slope comparing the small downward trend in haemorrhagic strokes from 2005 to 2012 to the upward trend for the 2013–2018 period ($\beta = 0.01$, 95% CI 0.00–0.02, $P = .045$). This finding is likely influenced by the highest haemorrhagic stroke rate at the start of the first period in 2005 (0.33/1000), while the lowest stroke rate was at the start of the second period in 2013 (0.258/1000). When the entire period from 2005 to 2018 is analysed, there is no evident change in slope ($\beta = -0.00$, 95% CI –0.00–0.00, $P = .097$). The stroke mortality rate fell 40%, from 0.25 per 1000 in 2005 to 0.15 in 2018, with a 51% reduction in ischaemic stroke mortality and a 18% reduction in haemorrhagic stroke mortality.

The National Stroke Register data in Figure 4 shows the percentage of AF-related ischaemic strokes was consistent from 2013 (30.5%) to 2017 (29.8%), with a 4.2% reduction in 2018 ($\beta = -0.76$,
The percentage of ischaemic strokes related to AF was notably higher for those 75 years and older when compared to those in younger age groups. For the 2013–2018 cohort (n = 10,194), almost half (49.7%) of ischaemic stroke patients were 75 and older. More than two-thirds (68.7%) of AF-related ischaemic stroke patients were of this age group. It is apparent from Figure 4 that the trend for ischaemic stroke cases in those with previously diagnosed AF is reducing steadily from 2013 (19.2%) to 2018 (15.3%), except for 2017 (β = −0.55, 95% CI −1.09–0.01, P = .047). Those with ischaemic stroke and AF diagnosed after admission remained consistent around an average of 11.4 per 1000 (range 9.9–12.3) from 2013 to 2018.

On analyses of medication on admission, 68.8% of ischaemic stroke patients with previously diagnosed AF were on an anti- thrombotic in 2013 and this increased to 79.3% in 2018 (β = −1.72, 95% CI −3.56 – 1.09, P = .061; Figure 5). The equivalent percentage of these patients on OAC increased from 36.6% to 62.2% (β = 4.84, 95% CI 3.74–5.93, P < .001), and from 6.7% to 45.1% for DOACs (β = 7.68, 95% CI 6.71–8.65, P < .001). However, the percentage on an antiplatelet fell from 32.2% in 2013 to 17.1% in 2018 (β = −3.12, 95% CI −5.04–−12.0, P = .011). It is apparent from Figure 6 that those 65–74 and those over 75 years with previously diagnosed AF are admitted more often with ischaemic stroke while on OAC compared to those under 65.
This study found an increasing trend in the use of OAC in Ireland. This increase was driven by patients prescribed DOACs, particularly from 2013 onwards. The rapid adoption of this new anticoagulant class resulted in a large increase in expenditure on OAC but without an evident reduction in ischaemic stroke rates at a national level. There was an apparent increase in the trend of haemorrhagic strokes from 2013 but this should be interpreted with caution as event rates at the start of the comparison periods (2005 and 2013) deviated from those for other years. The stroke register data indicated that the percentage of patients presenting with ischaemic stroke and AF was steady apart from a decline in 2018. As a percentage of all ischaemic strokes, a decline was noted for patients presenting with previously diagnosed AF. However, the percentage of ischaemic stroke patients with previously diagnosed AF on OAC treatment at presentation increased consistently from 2013 to 2018.

The large increase in OAC utilisation in Ireland has been reported previously and is accompanied by a large increase in expenditure due to the cost of reimbursing DOAC prescriptions. Warfarin has been the gold standard for prevention of stroke in high-risk patients with AF, but it has numerous disadvantages leading to considerable

**FIGURE 5** Ischaemic stroke patients with previously diagnosed atrial fibrillation and their antithrombotic treatment at the time of admission in the National Stroke Register dataset

**FIGURE 6** Ischaemic stroke patients with previously diagnosed atrial fibrillation prescribed an oral anticoagulant prior to admission in the National Stroke Register dataset

4 | DISCUSSION
underutilisation. Its narrow therapeutic window along with its numerous drug and food interactions make it less appealing and problematic to manage. The inability to monitor a patient on warfarin and the risk of bleeding are significant concerns for patients and prescribers, particularly OAC use in frail patients. DOACs are a more convenient alternative due to reduced patient monitoring burden and less drug interactions. The increase in OAC prescribing is likely multifactorial with the availability of DOACs being a key component.

A large increase in OAC expenditure was evident from our analysis, with an associated increase in DOAC prescriptions. In general, DOACs have been determined to be cost-effective in European and US settings. These estimates are sensitive to time-in-therapeutic range for warfarin, drug costs and the cost of anti-coagulation support services. Apixaban was determined to be the most cost-effective DOAC in both US analyses as well as in European studies. Despite the favourable cost-effectiveness analyses, the use of DOACs for a prevalence condition such as AF presented a substantial affordability issue for many healthcare systems. In Ireland, a reimbursement application system was implemented to ensure the safe, effective, cost-effective and affordable use of DOACs in the Irish healthcare setting.

Our study did not find a meaningful decrease in ischaemic stroke rates in Ireland from 2005 to 2018 (Figure 3), using either segmented regression or change point analysis. A change in ischaemic stroke rates might have been expected given the increase in OAC prescribing since 2013; however, such a change may be difficult to detect at a population level. Firstly, there are numerous risk factors and aetiologies of ischaemic stroke of which only some are mitigated by OAC. Secondly, the increase in OAC prescribing may be concentrated on low-risk subpopulations so that the benefit is not as large as expected. Lastly, the increase in OAC prescribing may, in part, be due to greater use of DOACs in secondary stroke prevention. While ischaemic stroke rates have not decreased, this was against a backdrop of an ageing population, an increased focus on stroke reporting and changes in the case definition of stroke (e.g., infarction on magnetic resonance imaging). At the same time, the reductions in stroke mortality were notable.

An effect of increased OAC prescribing may be more apparent when focused on AF-related ischaemic strokes. An English study for the 2006–2016 period suggested that the declining AF-related stroke rate was significantly associated with increased OAC use from 2011. The authors note that guideline changes, quality improvement initiatives and DOAC availability all may have contributed to this finding. However, in this study, apart from a reduction in 2018, the percentage of patients with AF-related ischaemic stroke as a percentage of all ischaemic strokes was unchanged (Figure 4). The reduction in patients with previously diagnosed AF as a percentage of those presenting with ischaemic stroke is positive and may indicate some beneficial effect of greater OAC prescribing. The steady percentage of those with AF diagnosed after admission suggests that detection of AF is an ongoing issue.

The inverse trends of OAC and antiplatelet treatment in those presenting with ischaemic stroke are worth further consideration (Figure 5). Despite the evident benefit of OAC for stroke prevention in frail elderly patients with AF, the use of antiplatelets instead has been reported. DOACs offered another option with convenient initiation and monitoring, thus reducing the burden on prescribers and patients. Clinical guidelines became more definite on the use of OAC in lower risk patients with AF, removing antiplatelets from the recommendations. Also, guidelines clarified subpopulations in which multiple anti-thrombotic treatment is beneficial, reducing the prescribing of multiple agents in AF patients.

Of those presenting with ischaemic stroke and previously diagnosed AF, 36% were on OAC in 2013, consistent with UK figures (Figure 6). From our data, it is evident that the percentage of those presenting with AF-related ischaemic stroke on OAC is increasing. This suggests an improved prescribing rate of OAC in those with AF and may reflect the increase in OAC prescribing at a population level. However, it is also a cause for concern as the OAC should significantly attenuate the risk of stroke in these patients. Does this finding suggest potential treatment failures as a contributory factor and why might failures occur?

Firstly, poor adherence to OAC treatment is associated with an increased risk of stroke, particularly in higher risk patients. In this study the percentage of ischaemic stroke patients with previously diagnosed AF increased from 36% to 62% with three-quarters of these on DOACs by 2018. It is unclear whether adherence to OAC may be improved by use of DOACs due to conflicting evidence. Even if OAC adherence is improved on DOACs, it is not certain that this results in less ischaemic stroke events. Drug forgiveness is a feature of warfarin, given its half-life of 40 hours, and non-adherence to DOACs may have more significant consequences due to their shorter half-lives.

Secondly, underdosing of DOACs is a possible contributory factor. A previous Irish hospital-based study noted that 20.4% of patients had inadequate DOAC prescriptions, most being underdosed. In a UK study which enrolled hospitalised patients with AF, only 32.6% had adequate OAC treatment on admission, with DOAC underdosage as the most common error. Thirdly, less interaction with the healthcare system and less monitoring should be considered as factors. It has been shown that a warfarin clinic is associated with improved OAC adherence compared with community-based care. Nurse and pharmacist input, which may be provided in a clinic setting, has been shown to improve outcomes for warfarin-treated patients. Regular measurement of renal function is recommended for patients on DOACs, particularly those 75 and over, the frail and those with renal disease. This monitoring is very likely a quality of care issue as it will rarely occur in hospital outpatient clinics without dedicated resources, and it therefore places a large burden on primary care.

The suboptimal use of DOACs is also worth considering as a factor in the underwhelming change in AF-related ischaemic stroke seen in this study. How might this be addressed? Patients have a preference for treatment in a specialist anti-coagulation clinic. The authors of an Irish study of DOAC prescribing recommended a dedicated AF clinic. This approach may be expanded to develop an integrated care pathway for AF with potential reductions in cardiovascular hospitalisations and all-cause mortality. Some warfarin
clinics have redefined their role to incorporate the management of DOACs. However such a service is defined, it should involve a multi-disciplinary approach. Of course, the development of these services increases the health expenditure required for DOAC use and raises further questions regarding their cost-effectiveness.

4.1  |  Strengths and limitations

Strengths of the study include the large dataset of reliable administrative dispensing data. The figures for those with AF-related stroke are as a proportion of those with all ischaemic stroke types, thus removing factors which may affect the rate of all ischaemic stroke as well as AF-related strokes.

In terms of limitations, firstly, the prescribing data does not include an indication for OAC use. A proportion of patients included in the prescription dataset were treated for venous thromboembolism, though it is expected that most OAC is prescribed for stroke prevention in the setting of atrial fibrillation due to its higher prevalence and continuous use. Secondly, the HIPE data was not adjusted for age. However, a significant deviation from the prevailing trend in ischaemic stroke would remain evident without this adjustment given the consistent background increase in the population 65 and over (3% annually). Thirdly, the period for which National Stroke Registry data is available does not allow a comparison of stroke trends from this dataset for the years preceding the rapid adoption of OAC. Fourthly, while the registry data is validated against available hospital data, the registry coverage is incomplete as not all hospitals submit data. Also, given the possibility of treatment failures, the adherence to treatment is unknown.

5  |  CONCLUSION

Large increases in the utilisation and expenditure of OAC have not resulted in changes in ischaemic stroke rates on a national level, nor have they resulted in significant reductions in AF-related ischaemic stroke presentations. While the percentage of ischaemic stroke patients with previously diagnosed AF is decreasing, the percentage of these patients presenting with ischaemic stroke while on OAC treatment is increasing. The reasons for these findings are likely multifactorial and require further examination.

ACKNOWLEDGEMENTS

The role of Ms Niamh Geragthy in extracting the prescribing data is gratefully acknowledged. No funding was associated with this research.

Open access funding provided by IReL.

COMPETING INTERESTS

Professor Ronan Collins has spoken at educational meetings sponsored by Bayer, Boehringer Ingelheim, Daichii-Sankyo and Pfizer, the manufacturers of direct oral anticoagulants. None of the other authors has any potential conflicts of interest to declare.

CONTRIBUTORS

C.K., M.B. and J.H. were responsible for the concept and study design. C.K., J.M. and J.H. analysed the data. C.K. and A.G. prepared the manuscript. All authors reviewed and revised the manuscript.

DATA AVAILABILITY STATEMENT

The datasets analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Coramac Kennedy https://orcid.org/0000-0002-2577-0242

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001;285(18):2370-2375.
2. Zoni-Berisso M, Lercari F, Carazza T, Dominiciucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213-220.
3. Holt TA, Hunter TD, Gunnarsson C, Khan N, Cloud P, Lip GY. Risk of stroke and oral anticoagulant use in atrial fibrillation: a cross-sectional survey. Br J Gen Pract. 2012;62(603):710-717.
4. Kassianos G, Arden C, Hogan S, Dew R, Fuat A. Current management of atrial fibrillation: an observational study in NHS primary care. BMJ Open. 2013;3(11):e003004.
5. Mahmud A, Bennett K, Okechukwu I, Feely J. National underuse of anti-thrombotic therapy in chronic atrial fibrillation identified from digoxin prescribing. Br J Clin Pharmacol. 2007;64(5):706-709.
6. Abdul-Rahim AH, Wong J, McAlpine C, Young C, Quinn TJ. Associations with anticoagulation: a cross-sectional registry-based analysis of stroke survivors with atrial fibrillation. Heart. 2014;100(7):557-562.
7. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-2962.
8. National Institute for Health and Care Excellence. Atrial fibrillation: the management of atrial fibrillation 2014. Available from: http://guidance.nice.org.uk/CG180. Accessed December 31, 2018.
9. Apenteng PN, Gao H, Hobs FR, Fitzmaurice DA. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ Open. 2018;8(1):e018905.
10. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. EP Europace. 2018;20(8):1231-1242.
11. Kennedy C, Ni Choitir C, Clarke S, Bennett K, Barry M. Direct oral anticoagulants uptake and an oral anticoagulation paradox. Br J Clin Pharmacol. 2019;88(2):392-397.
12. McElwaine P, McCormack J, Harblion J. National Stroke Audit 2015. Dublin: Irish Heart Foundation (IHF) & Health Service Executive; 2016.
13. Department of Health. Changing Cardiovascular Health: National Cardiovascular Health Policy 2010–2019. Dublin: Government Publications; 2010.
14. Sinnott S-J, Bennett K, Cahir C. Pharmacoepidemiology resources in Ireland—an introduction to pharmacy claims data. Eur J Clin Pharmacol. 2017;73(11):1449-1455.
15. Healthcare Pricing Office. *Activity in Acute Public Hospitals in Ireland Annual Report 2017*. Dublin: Health Service Executive; 2018.

16. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther*. 2002;27(4):299-309.

17. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for point regression with applications to cancer rates. *Stat Med*. 2000;19(3):335-351.

18. Andrade JM, Estévez-Pérez MG. Statistical comparison of the slopes of two regression lines: a tutorial. *Anal Chim Acta*. 2014;838:1-12.

19. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GYH. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638-645.e4.

20. Sen S, Dahlberg KW. Physician’s fear of anticoagulant therapy in non-valvular atrial fibrillation. *Am J Med Sci*. 2014;348(6):513-521.

21. Verhoef Ti, Redekop WK, Hasrat F, de Boer A, Maitland-van der Zee AH. Cost effectiveness of new oral anticoagulants for stroke prevention in patients with atrial fibrillation in two different European healthcare settings. *Am J Cardiovasc Drugs*. 2014;14(6):451-462.

22. Shah A, Shewale A, Hayes CJ, Martin BC. Cost-effectiveness of oral anticoagulants for ischemic stroke prophylaxis among nonvalvular atrial fibrillation patients. *Stroke*. 2016;47(6):1555-1561.

23. Janzic A, Kos M. Cost effectiveness of novel oral anticoagulants for stroke prevention in atrial fibrillation depending on the quality of warfarin anticoagulation control. *Pharmacoeconomics*. 2015;33(4):395-408.

24. You JHS. Novel oral anticoagulants versus warfarin therapy at various levels of anticoagulation control in atrial fibrillation—a cost-effectiveness analysis. *J Gen Intern Med*. 2014;29(3):438-446.

25. Loo SY, Dell’Aniello S, Hulart L, Renoux C. Trends in the prescription of novel oral anticoagulants in UK primary care. *Br J Clin Pharmacol*. 2017;83(9):2096-2106.

26. Cowan JC, Wu J, Hall M, Orłowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. *Eur Heart J*. 2018;39(32):2975-2983.

27. Mant J, Hobbs FDR, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007;370(9586):493-503.

28. Clinical audit first pilot public report. Sentinel Stroke National Audit Programme (SSNAP). London: Clinical Effectiveness and Evaluation Unit, Royal College of Physicians; 2013.

29. Yao X, Abraham NS, Alexander GC, et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc*. 2016;5(2):e003074.

30. Burn J, Pirrhmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old? *Open Heart*. 2018;5(1):e000712.

31. Alamnkh EA, Chalmers L, Bereznicki LR. Suboptimal use of oral anticoagulants in atrial fibrillation: has the introduction of direct oral anticoagulants improved prescribing practices? *Am J Cardiovasc Drugs*. 2016;16(3):183-200.

32. Hughes DA. Medication adherence—key considerations for clinical pharmacologists. *Br J Clin Pharmacol*. 2020;86(4):628-629.

33. Phanithi RB, Ranganathan D, O’Brien J, et al. Is the prescription right? A review of non-vitamin K antagonist anticoagulant (NOAC) prescriptions in patients with non-valvular atrial fibrillation. Safe prescribing in atrial fibrillation and evaluation of non-vitamin K oral anticoagulants in stroke prevention (SAFE-NOACS) group. *Ir J Med Sci*. 2018;188(1):101-108.

34. Angel Y, Zeitser D, Berliner S, et al. Hospitalization as an opportunity to correct errors in anticoagulant treatment in patients with atrial fibrillation. *Br J Clin Pharmacol*. 2019;85(12):2838-2847.

35. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm*. 2009;15(3):244-252.

36. Gallagher J, Mc Carthy S, Woods N, Ryan F, O’Shea S, Byrne S. Economic evaluation of a randomized controlled trial of pharmacist-supervised patient self-testing of warfarin therapy. *J Clin Pharm Ther*. 2015;40(1):14-19.

37. Garton L, Crosby JF. A retrospective assessment comparing pharmacist-managed anticoagulation clinic with physician management using international normalized ratio stability. *J Thromb Thrombolysis*. 2011;32(4):426-430.

38. Bartoli-Abdou JK, Patel JP, Crawshaw J, et al. Exploration of adherence and patient experiences with DOACs one year after switching from vitamin-K antagonists—insights from the switching study. *Thomb Res*. 2018;162:62-68.

39. Gallagher C, Elliott AD, Wong CX, et al. Integrated care in atrial fibrillation: a systematic review and meta-analysis. *Heart*. 2017;103(24):1947-1953.

40. Annual Population Ireland [Internet]. Central Statistics Office. 2005–18. Available from: https://statbank.cso.ie/. Accessed December 30, 2019.