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Oral anticoagulants and outcomes in adults ≥80 years with atrial fibrillation: a global federated health network analysis

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Running title: Use of oral anticoagulants in people aged ≥80

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Key Points

- Clinical studies have shown non-inferiority or superiority of non-vitamin-K antagonist oral anticoagulants (NOACs) to warfarin for people with atrial fibrillation in preventing stroke and systemic embolism, with lower rates of major bleeding and lower mortality, but there is a paucity of data for older people aged ≥80 years

- In this study of >700,000 people aged ≥80 years with atrial fibrillation, compared to no oral anticoagulation (OAC) or warfarin, participants receiving a NOAC had better outcomes including incident stroke, mortality and dementia, with the exception of a small but statistically significant higher risk of major bleeding compared to no OAC.

- Within this cohort, the proportion of people aged ≥80 years receiving any OAC increased over time, but remained low (from 32.4% (n=27,647) in 2011 to 43.6% (n=110,412) in 2019).

Why does this matter?

Clinical decision making regarding the use of oral anticoagulants for older people is complex due to concerns of bleeding and polypharmacy. The results of the current study add to the body of evidence to suggest that the use of a NOAC for people aged ≥80 years with atrial fibrillation improves outcomes including reducing risk of stroke, all-cause mortality and dementia.

Abstract

Background The objective of this study was to determine associations between use of oral anticoagulation (OAC) and stroke and bleeding-related outcomes for older people ≥80 years with atrial fibrillation (AF), and determine trends over time in prescribing of OAC for this population.

Methods A retrospective cohort study was conducted. People aged ≥80 years with AF receiving 1) no OAC; 2) warfarin; or 3) a non-vitamin-K antagonist oral anticoagulant (NOAC) between 2011 and 2019 were included. Propensity score matching was used to balance cohorts (no OAC, warfarin or a NOAC) on characteristics including age, sex, ethnicity and co-morbidities. Cox proportional hazard models were used to derive hazard ratios (HRs) and 95% confidence intervals (CIs).

Results The proportion of people aged ≥80 years receiving any OAC increased from 32.4% (n=27,647) in 2011 to 43.6% (n=110,412) in 2019. After propensity score matching, n=169,067 individuals were included in the cohorts receiving no OAC or a NOAC. Compared to no OAC, participants receiving a NOAC had a lower risk of incident dementia (HR 0.68, 95% CI 0.65-0.71), all-cause mortality (HR 0.49, 95% CI 0.48-0.50), first-time ischaemic stroke (HR 0.87, 95% CI 0.83-0.91), and a higher risk of major bleeding (HR 1.08, 95% CI 1.05-1.11). Compared to participants receiving warfarin, participants receiving a NOAC had a lower risk of dementia (HR 0.90, 95% CI: 0.86-0.93), all-cause mortality (HR 0.74, 95% CI: 0.72-0.76), ischaemic stroke (HR 0.86, 95% CI: 0.82-0.90) and major bleeding (HR 0.88, 95% CI: 0.85-0.90). Similar results were observed when only including people with additional bleeding risk factors.

Conclusions The proportion of people aged ≥80 years receiving OAC has increased since the introduction of NOACs, but remains low. Use of a NOAC was associated with improved

3

outcomes compared to warfarin, and compared to no OAC, with the exception of a small but statistically significant higher risk of major bleeding.

Key words: atrial fibrillation, oral anticoagulants, older adults

Introduction

Oral anticoagulation (OAC) should be prescribed to the majority of older patients with atrial fibrillation (AF) to reduce the risk of stroke, in line with appropriate treatment pathways.[1, 2] However, concerns regarding bleeding risk for older individuals with AF may lead to under-prescription of OAC in this population.

Older people are often excluded from randomised controlled trials (RCTs), and there is an underrepresentation of older people with cognitive impairment and frailty in RCTs.[3] RCTs for non-vitamin-K antagonist oral anticoagulants (NOACs, also referred to as direct oral anticoagulants, DOACs) have shown non-inferiority or superiority to warfarin for people with AF in preventing stroke and systemic embolism, with lower rates of major bleeding and lower mortality.[4] However, the RCTs had an average age of 70-73 years and exclusion criteria such as 'serious concomitant illness associated with a life expectancy of less than two years', which may limit the generalisability of findings to older individuals, including those approaching end-of-life. More recently, low-dose edoxaban was shown to be superior to placebo in preventing stroke or systemic embolism in individuals aged ≥80 years, and did not result in a significantly higher incidence of major bleeding or intracranial haemorrhage.[5]

Overall, a paucity of data on the use of OAC for older individuals with AF, particularly those with additional bleeding risk factors may result in complex decision making for clinicians.

Therefore, the aim of this study was to use a global federated health research network to examine a cohort of older people ≥80 years with AF to: 1) determine the association between use of OAC and outcomes including ischaemic stroke, major bleeding, dementia and all-cause mortality, including in individuals with additional bleeding risk factors; and 2) determine trends over time in the prescribing of OAC in this population.

Methods

A cohort study was conducted using TriNetX, a global federated health research network. As a federated research network, studies using the TriNetX health research network do not require ethical approval as no patient identifiable identification is received. Further information about TriNetX is available in the supplementary material. Available data within the health research network include demographics, diagnoses using International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-10-CM) codes and medications.

The TriNetX online research platform was searched on 30th November 2021 for individuals aged ≥80 years with AF (ICD-10-CM code I48) recorded in their electronic medical records between 01/01/2011 and 12/31/2019. The start date was chosen because NOACs were introduced and became available for stroke prevention for AF from 2010, and the end date was chosen to allow for at least one-year potential follow-up for all participants. The baseline date is the date the ICD-10-CM code I48 was first recorded in the participant's electronic medical records. Any diagnoses recorded before or on this date were deemed to be the participant's baseline characteristics. Participants were censored when they experienced an outcome or when they died.

The cohort was divided into three groups using electronic health records to determine if an individual had a record of receiving an oral anticoagulant during the study period: 1) individuals with AF and at least one NOAC (dabigatran, rivaroxaban, edoxaban, apixaban) received in the study time period with no record of warfarin; 2) individuals with AF and warfarin received in the study time period with no record of any NOAC; and 3) individuals with AF and no record of any OAC received in the study time period. Individuals who had a record of receiving both warfarin and a NOAC in the study time period were excluded.

Statistical analysis

Statistical analyses were completed on the TriNetX online research platform. 1:1 propensity score matching was used to create well balanced cohorts. Standardised mean differences (SMDs) <0.1 were considered well balanced and propensity score density graphs were examined. The following variables were included in propensity score matching: age, sex, ethnicity, and co-morbidities. Further details are provided in the supplementary material. Following propensity score matching, Cox proportional hazard models were used to examine the associations between OAC use and the outcomes of interest: all-cause mortality, ischaemic stroke (ICD-10-CM code 163), dementia (ICD-10-CM codes: G30, F01, F02 or F03), and major bleeding (ICD-10-CM codes listed in Supplementary Table 1). The TriNetX platform calculates hazard ratios (HRs) and 95% confidence intervals (CIs) using R's survival package v3.2-3.

Sensitivity analyses

In sensitivity analyses, the cohort was reduced to only include individuals with bleeding risk factors in addition to age >65 years, as stated in the HAS-BLED bleeding risk score. As these individuals had at least one additional bleeding risk factor, in addition to aged >65 years, all participants in this sensitivity analysis had a HAS-BLED score of ≥2.

Results

Participant characteristics

In the TriNetX health research network, between 2011 and 2019, 763,627 people aged ≥80 years with AF were identified. Of these, 21.7% (n=165,580) received warfarin, 22.2% (n=169,594) received a NOAC and 49.9% (n=381,393) had no record of receiving OAC. A further 6.2% (n=47,060) had records of receiving both warfarin and a NOAC and were subsequently excluded from analyses, resulting in a total cohort of n=716,567 individuals.

Table 1 shows the characteristics of the study participants according to OAC status. In all analyses, the propensity score matched cohorts were well balanced on all included characteristics [all SMDs <0.1 (Supplementary Tables 2-4), and propensity score density graphs also indicated that the covariates were well balanced after matching (Supplementary Figures 1-3)].

Warfarin compared to no OAC

After propensity score matching, 159,774 individuals were included in each cohort. Compared to participants receiving no OAC, participants receiving warfarin had a lower risk of incident dementia (HR 0.76, 95% CI 0.73-0.79) and all-cause mortality (HR 0.67, 95% CI 0.66-0.68). Warfarin was associated with a higher risk of major bleeding compared to no

OAC (HR 1.05, 95% CI 1.03-1.07), and there was no statistically significant difference observed in risk of ischaemic stroke between the groups (HR 0.99, 95% CI 0.95-1.04) (Figure 1).

NOAC compared to no OAC

After propensity score matching, 169,067 individuals were included in each cohort. Compared to receiving no OAC, receiving a NOAC was associated with a lower risk of dementia (HR 0.68, 95% CI 0.65-0.71), all-cause mortality (HR 0.49, 95% CI 0.48-0.50), ischaemic stroke (HR 0.87, 95% CI 0.83-0.91) and a higher risk of major bleeding (HR 1.08, 95% CI 1.05-1.11).

NOAC compared to warfarin

After propensity score matching, 150,850 individuals were included in each cohort. Compared to participants receiving warfarin, participants receiving a NOAC had a lower risk of dementia (HR 0.90, 95% CI: 0.86-0.93), all-cause mortality (HR 0.74, 95% CI: 0.72-0.76), ischaemic stroke (HR 0.86, 95% CI: 0.82-0.90) and major bleeding (HR 0.88, 95% CI: 0.85-0.90).

Sensitivity analyses

Of the included individuals, in addition to age >65 years, 90.0% (n=644,727) were identified as having further bleeding risk factor(s) from the HAS-BLED score. When only including individuals with additional bleeding risk factors in analyses, there were no significant changes in any of the reported results, with the exception of major bleeding when comparing warfarin to no OAC. When only individuals with additional bleeding risk factors

were included, the hazard ratio for the association between warfarin and risk of major bleeding was 1.21 (95% CI: 1.18-1.21), compared to 1.05 (95% CI: 1.03-1.07) when including all participants (Supplementary Figure 4).

Trends over time in use of OAC

In 2011, within the TriNetX research network, 3.0% (n=2,523) of people aged ≥80 years with AF were receiving a NOAC, 29.5% (n=25,124) were receiving warfarin and 67.5% (n=57,425) were receiving no OAC. The proportion of people receiving a NOAC increased over time to 30.0% (n=75,885) in 2019, and the proportions of people receiving warfarin or no OAC decreased to 13.6% (n=34,527) and 56.4% (n=142,884), respectively. Overall, the proportion of people aged ≥80 years receiving OAC increased over time from 32.4% (n=27,647) in 2011 to 43.6% (n=110,412) in 2019 (Figure 2).

Discussion

In this large retrospective study of older people aged ≥80 years with AF, receiving a NOAC compared to no OAC was associated with lower risk of dementia, ischaemic stroke and all-cause mortality, but a higher risk of major bleeding. Second, receiving warfarin compared to no OAC was also associated with lower risk of dementia and all-cause mortality and a higher risk of major bleeding, but there were no statistically significant differences observed in risk of ischaemic stroke. Compared to warfarin, receiving a NOAC was associated with a lower risk of all outcomes examined.

Between 2011 and 2019, there was a significant increase in the use of a NOAC and a reduction in the use of warfarin. Overall, there was significant increase in the proportion of

people aged ≥80 years with AF receiving OAC, but more than half of the study population were still not receiving OAC in 2019.

There has been an underrepresentation of people aged ≥80 years in clinical trials of OAC for the prevention of stroke in patients with AF. Only one RCT has been specifically designed to focus on the use of a NOAC compared to placebo in individuals aged ≥80 years.[5] In this RCT, only participants deemed to be inappropriate candidates for OAC at the recommended therapeutic strength were included. The results of this RCT showed that the use of once daily edoxaban 15mg improved prevention of stroke or systemic embolism and the rates of major bleeding were not significantly different to the rates observed with a placebo.[5] However, within this RCT, 31% of participants discontinued the trial mainly due to adverse events unrelated to bleeding or because they were no longer capable of participation. This highlights the difficulties in completing RCTs in older populations with AF and co-morbidities, and therefore observational evidence is needed to understand how these individuals are currently being managed in clinical practice and which approaches are associated with improved outcomes.

The results of the current study concur with the results of previous observational studies that have suggested the use of a NOAC in people with AF at advancing age may have many benefits including reduced risk of stroke and all-cause mortality, compared to warfarin or no OAC.[6-9] The results for trends over time in the use of OAC for older people with AF suggest that although there has been an increase in the use of OAC for people aged ≥80 years, hesitancy still remains in their use in this population. This is despite current clinical guidance supporting the use of a NOAC in patients with AF, irrespective of their age.[1, 2, 10] Clinicians

may often be hesitant to prescribe OAC to older people with AF due to a higher bleeding risk determined with an established bleeding risk score, or due to the presence of other factors which may impact bleeding or falls risk such as dementia and history of falls and fractures.[11]

In the current study, in addition to lower risk of all-cause mortality and ischaemic stroke, the use of a NOAC was also associated with a reduced risk of incident dementia compared to warfarin or no OAC. Previous registry-based studies have suggested an association between use of a NOAC and reduced risk of dementia compared to warfarin, but only for individuals aged 65-74 years.[6, 12] The current study was able to examine the association in a large contemporary population of people aged ≥80 years and suggested the significant reduced risk of incident dementia observed with the use of a NOAC, may be apparent even in older age groups.

Limitations

Several limitations should be considered when interpreting the results of the current study. The participant information is based on electronic medical records, and from this, dose or duration of OAC prescription could not be ascertained and participants could not be censored when anticoagulation exposure was no longer certain. Individuals may switch or discontinue OAC treatment, and although individuals with a record of receiving both warfarin and a NOAC were excluded in the current analyses, it is possible that some changes to prescriptions may have been made outside of healthcare organisations captured within the TriNetX health research network. Therefore, these changes to prescriptions would not have been known to the study investigators. In the analyses completed, many co-morbidities were included in the propensity score matching to account for differences in the

health status of the participants. However, within the TriNetX research platform, certain analyses cannot currently be performed such as inverse probability of treatment weighting which may be used to assess for confounding by indication. Furthermore, if a participant experienced an outcome but it was not recorded in a healthcare organisation which contributes data to the TriNetX research network, then this may have not been captured.

The level of data that each participant has available within the TriNeX network varies depending on how frequently they visited a healthcare organisation within the TriNetX network. Of the participants who had AF recorded between 2011 and 2019, 90.9% had at least one previous recorded visit to a healthcare organisation within TriNetX. The healthcare organisations also vary in the earliest date which data were made available to the TriNetX platform. Within the TriNetX platform, it was not possible to adjust any results for the date a participant entered the cohort. Further residual confounding may be present as some variables of interest were not available within the TriNetX health research network, such as function or cognitive function measures, and some health conditions may be underreported in electronic medical records. The use of ICD codes to identify people living with dementia within the TriNetX research network has not been previously validated. A systematic review has previously determined that routinely collected health data using ICD codes to identify dementia can achieve a high positive predictive value and reasonable sensitivity in certain settings, but there was heterogeneity in estimates.[13]

Conclusions

Clinical decision making regarding the prescription of oral anticoagulants for older people is complex because of concerns of bleeding. The results of the current study add to the body

of evidence to suggest that the use of a NOAC for people aged ≥80 years with AF improves

outcomes including reducing risk of stroke, all-cause mortality and dementia.

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Legends

Figure 1. Risk of dementia, all-cause mortality, ischaemic stroke and major bleeding in people with atrial fibrillation ≥80 years, by anticoagulation status, after propensity score matching. HR: hazard ratio; NOAC: non-vitamin-K antagonist oral anticoagulant; OAC: oral anticoagulation.

Figure 2. Changes in the proportion of people aged ≥80 years with atrial fibrillation receiving oral anticoagulation in the TriNetX research network 2011-2019. AF: atrial fibrillation; OAC: oral anticoagulation; NOAC: non-vitamin K antagonist oral anticoagulant.

Supplementary Table 1. List of ICD-10-CM codes used to define major bleeding in this study.

Supplementary Table 2. Characteristics of participants aged ≥80 years with atrial fibrillation prescribed warfarin or no oral anticoagulation, before and after propensity score matching.

Supplementary Table 3. Characteristics of participants aged ≥80 years with atrial fibrillation prescribed a non-vitamin-K antagonist oral anticoagulant or no oral anticoagulation before and after propensity score matching.

Supplementary Table 4. Characteristics of participants aged ≥80 years with atrial fibrillation prescribed warfarin or a non-vitamin K antagonist oral anticoagulant, before and after propensity score matching.

Supplementary Figure 1. Propensity score density graphs for the warfarin and no OAC groups before and after propensity score matching.

Supplementary Figure 2. Propensity score density graphs for the NOAC and no OAC groups before and after propensity score matching.

Supplementary Figure 3. Propensity score density graphs for the warfarin and NOAC groups before and after propensity score matching.

Supplementary Figure 4. Risk of dementia, all-cause mortality, ischaemic stroke and major bleeding in people with atrial fibrillation and with additional bleeding risk factors, aged ≥80 years by anticoagulation status, after propensity score matching. HR: hazard ratio; NOAC: non-vitamin-K antagonist oral anticoagulant; OAC: oral anticoagulation.

Table 1. Baseline characteristics of participants aged ≥80 years with atrial fibrillation prescribed warfarin, non-vitamin K antagonist oral anticoagulants or no oral anticoagulants.

Characteristic	Warfarin (n=165,580)	NOAC (n=169,594)	No OAC (n=381,393)
Age (years), mean (SD)	81.3 (5.3)	82.0 (4.8)	82.3 (5.4)
Female	47.6 (78,807)	52.3 (88,773)	52.3 (199,407)
Ethnicity			
White	84.3 (139,593)	83.4 (141,441)	81.2 (309,614)
Black or African American	5.9 (9,731)	5.2 (8,891)	6.1 (23,293)
Asian	0.7 (1,221)	1.4 (2,401)	1.2 (4,534)
Native Hawaiian or other Pacific Islander	0.1 (82)	0.1 (96)	0.1 (246)
American Indian or Alaska Native	0.1 (199)	0.1 (202)	0.1 (536)
Unknown	8.9 (14,754)	9.8 (16,563)	11.3 (43,170)
Hypertensive Diseases	57.2 (94,781)	59.2 (100,384)	36.5 (139,174)
Ischaemic Heart Disease	34.8 (57,649)	32.6 (55,247)	20.0 (76,117)
Heart failure	28.7 (47,460)	23.0 (38,950)	12.3 (46,990)
Diabetes mellitus	22.9 (37,877)	20.3 (34,417)	13.9 (52,991)
Chronic kidney disease	22.9 (37,897)	19.5 (33,031)	12.6 (48,148)
Cerebral infarction	8.7 (14,417)	8.6 (14,660)	3.7 (14,116)
Peripheral vascular disease	8.1 (13,447)	7.4 (12,518)	4.9 (18,832)
Liver disease	3.7 (6,200)	3.6 (6,068)	1.9 (7,181)
Aortic plaque	3.2 (5,324)	3.5 (5,986)	2.4 (9,149)

Values are % (n), unless otherwise stated. SD: standard deviation; NOAC: non-vitamin-K antagonist oral anticoagulant; OAC: oral anticoagulation.