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CLINICAL RESEARCH

Clinical events preceding switching and discontinuation of oral anticoagulant treatment in patients with atrial fibrillation

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Aims Switching between oral anticoagulants and treatment discontinuation are common events related to therapy with non-vitamin K antagonist oral anticoagulants (NOACs). However, knowledge on the reasons leading to these treatment changes is scarce. The aim of this study was to identify clinical events preceding anticoagulant switching and NOAC discontinuation during oral anticoagulant therapy in patients with atrial fibrillation.

Methods and results We performed a nationwide register-based study including Danish atrial fibrillation patients initiating a NOAC between August 2011 and February 2016 ($n = 50\,623$). We explored potential reasons leading to changes in anticoagulant treatment by identifying clinical events preceding switches from vitamin K antagonists (VKA) to NOAC, switches from NOAC to VKA, and discontinuations of NOACs. Among 23 531 anticoagulant users changing treatment, we identified 13 295 switches from VKA to NOAC, 5206 switches from NOAC to VKA, and 8995 discontinuations of NOACs. Approximately half of all treatment changes were preceded by a hospitalization. A relevant specific clinical event or procedure was identified prior to 18.3% of switches from VKA to NOAC, prior to 23.0% of switches from NOAC to VKA, and prior to 26.6% of discontinuations. Switches from VKA to NOAC were most often preceded by thromboembolic events (7.0%), whereas cardioversion was the most common specific event prior to a switch from NOAC to VKA (11.4%). Discontinuations were most often preceded by bleeding events (7.6%).

Conclusion For about one in five patients, treatment changes during anticoagulant therapy were preceded by a major clinical event. However, the majority of patients changed treatment for reasons not recorded in health registries.

Keywords Anticoagulants • Atrial fibrillation • Bleeding • Drug substitution • Thromboembolism

Introduction

Oral anticoagulants effectively prevent ischaemic stroke in patients with atrial fibrillation (AF) but confer a risk of serious bleedings. In recent years, a new generation of oral anticoagulants has been introduced: the non-vitamin K antagonist oral anticoagulants (NOACs). Treatment with NOACs in AF is recommended by international guidelines and is well-established in clinical practice.[1] Accordingly, a large proportion of newly diagnosed AF patients initiate treatment with a NOAC.[2,3] However, important clinical aspects of NOAC treatment remain unclarified, thus potentially preventing the optimal use of NOACs.

Drug utilization studies addressing 'real-world' NOAC use have revealed that at least one in three new users of NOACs is switching from vitamin K antagonists (VKA)[3–5] and that one in five patients discontinues NOAC treatment within the first year.[3,4,6] Switching from NOAC to VKA is also observed, although the reported frequency varies considerably.[3,5,7,8] While switching or discontinuation

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What's new?

- One in five treatment changes involving non-vitamin K antagonist oral anticoagulant (NOAC) therapy among patients with atrial fibrillation was preceded by a major clinical event.
- The most common major clinical event occurring in the period leading up to a switch from vitamin K antagonist (VKA) to NOAC was thromboembolism (7.0% of patients).
- The most common major clinical event occurring in the period leading up to a switch from NOAC to VKA was cardioversion (11.4% of patients). Among these, 48.9% had an atrial fibrillation ablation performed subsequently.
- Bleeding was the most common preceding major clinical event among patients discontinuing NOAC therapy (7.6% of patients).
- Detailed knowledge on reasons for changes during oral anticoagulant therapy requires data collected directly from the patient or physician.

may be based on a rational decision, knowledge about reasons for these treatment changes during NOAC therapy is essential to evaluate if the observed utilization patterns should cause concern.

The aim of the present study was to investigate clinical events preceding switches to and from NOAC as well as discontinuation of NOAC among patients with AF.

Methods

In this nationwide register-based study, we collected health registry data on all patients with AF who either switched between VKA and NOAC or discontinued NOAC therapy between August 2011 and February 2016. Using data on hospital contacts, we analysed clinical events preceding these treatment changes.

Setting and data sources

Virtually all healthcare services in Denmark are furnished by the national health authorities, thus enabling true population-based studies including all Danish citizens (5.7 million individuals).[9] Data from different Danish healthcare registries can be linked using the unique personal identification number ('CPR number') assigned to all citizens.[9] In this study, we obtained data from three nationwide registers. From the Danish National Prescription Registry,[10] we collected information on filled prescriptions. Patients' admission history were retrieved from the Danish National Registry of Patients.[11] Finally, we used the Civil Registration System[9] to keep track of study individuals with respect to deaths and migrations. Definitions of drugs, diseases, and procedures used in this study are detailed in Supplementary material online, *Appendix S1*.

Study population

The study population consisted of Danish patients initiating a NOAC (dabigatran etexilate, rivaroxaban, or apixaban) for AF for the first time in the period of August 2011 to February 2016. To ensure the validity of the AF diagnosis, we required that patients were registered with a diagnosis of AF in the Patient Registry and were not registered with a diagnosis of other indications for NOAC (i.e. any history of venous thromboembolic disease as well as recent hip or knee replacement procedures). Lastly, to be included, each patient had to have been residing in Denmark for a minimum of 5 years and had to be ≥18 years old at the time of filling the first NOAC prescription. A flow chart of the selection process is provided in Supplementary material online, *Figure S1*.

Treatment changes

Within the study population, we identified subjects with at least one treatment change, defined as (i) a switch from VKA to NOAC (defined as at least one VKA prescription filled within 180 days prior to NOAC initiation), (ii) a switch from NOAC to VKA (defined as a filled prescription for VKA during NOAC treatment, as sustained concomitant treatment with VKA and NOAC is strictly contraindicated[12]), or (iii) a discontinuation of NOAC treatment (defined as not filling a prescription for any oral anticoagulant in the number of days supplied by the last NOAC prescription plus 90 days).

Clinical events preceding a treatment change

As potential reasons for treatment changes, we included hospital diagnoses compatible with (i) serious clinical events where physicians might reconsider the indication for anticoagulant treatment (e.g. thromboembolic or bleeding complications), (ii) the emergence of a contraindication for the given treatment (e.g. mechanical heart valve replacement during NOAC treatment),[12] and finally (iii) indicators of stable sinus rhythm. Specific events were (i) any hospitalization and hospitalizations with AF; (ii) a new diagnosis of a thromboembolic event (arterial embolism, venous thromboembolism, ischaemic stroke/transient ischaemic attack, and myocardial infarction); (iii) a new diagnosis of anaemia or bleeding categorized into (a) any, (b) gastrointestinal, (c) intracranial, and (d) other bleedings; (iv) a new diagnosis of a contraindication for VKA and/or NOAC other than bleeding (acute and chronic renal failure, cancer, and artificial heart valve replacement); and (v) cardioversions and catheter ablations as indicators of stable sinus rhythm. A diagnosis was considered 'new' when it occurred for the first time within a time frame of 6 months for acute conditions (thromboembolic complications, bleeding, and acute renal failure) and 5 years for chronic conditions (cancer, chronic renal failure, and heart valve replacement). Each individual could contribute with multiple diagnoses.

Finally, to explore if patients had been hospitalized for conditions other than the ones specified above, we identified the five most frequent unique discharge diagnoses (excluding AF) for hospitalizations preceding a treatment change.

Analysis

We determined the proportion of patients experiencing hospitalization as well as each of the pre-specified clinical events prior to the treatment change. For patients switching from VKA to NOAC or from NOAC to VKA, we included hospitalizations and events occurring within 60 days prior to the date of the switch, defined as the date where the prescription for the 'new' treatment was filled. For patients discontinuing NOAC treatment, hospitalizations and events were included if they occurred within 180 days prior to the date of discontinuation, defined as the date following the number of days supplied by the last NOAC prescription plus an additional 90 days.

Analyses were performed using STATA Release 14.1 (StataCorp, College Station, TX, USA).

Ethics

The study was approved by the Danish Health Data Authority. According to Danish law, no ethical approval was necessary for this study.

Results

Among 50 623 NOAC users with AF, 23 531 (46.5%) experienced one or more treatment changes during the study period: 13 295 individuals switched from VKA to NOAC, 5206 switched from NOAC to VKA, and 8995 discontinued NOAC therapy (Supplementary material online, *Table S1*). In the latter two groups, 1894 (36.4%) and 2071 (23.0%) had used VKA prior to NOAC initiation, i.e. had previously switched from VKA to NOAC.

Table 1 Events potentially contributing to switching anticoagulant treatment in atrial fibrillation patients in the period of August 2011 to February 2016

Event	VKA to NOAC[a] (n = 13 295)	NOAC to VKA[b] (n = 5206)
Hospitalization		
Any hospitalization	40.6% (n = 5402)	45.1% (n = 2348)
Hospitalization with atrial fibrillation	11.7% (n = 1552)	25.9% (n = 1348)
Hospitalization with a pre-specified event or procedure	18.3% (n = 2431)	23.0% (n = 1197)
Hospitalization, other[c]	16.3% (n = 2164)	10.4% (n = 544)
Thromboembolic complications		
Arterial embolism	0.2% (n = 23)	0.1% (n = 6)
Venous thromboembolism	0.8% (n = 100)	1.2% (n = 61)
Ischaemic stroke/TIA	5.0% (n = 666)	2.7% (n = 142)
Myocardial infarction	1.0% (n = 133)	1.7% (n = 86)
Bleeding complications		
Anaemia	2.2% (n = 287)	1.9% (n = 101)
Bleeding, any	4.3% (n = 576)	2.8% (n = 145)
Bleeding, gastrointestinal	1.7% (n = 228)	1.4% (n = 72)
Bleeding, intracranial	0.7% (n = 93)	$n < 5$[d]
Bleeding, other	2.3% (n = 303)	1.5% (n = 80)
Absolute or relative contraindications[d]		
Acute renal failure	n/a[e]	0.5% (n = 26)
Chronic renal failure	n/a[e]	1.2% (n = 61)
Cancer	0.8% (n = 110)	0.6% (n = 31)
Mechanic heart valve replacement	n/a[e]	0.2% (n = 12)
Procedures		
Direct-current cardioversion	3.1% (n = 417)	11.4% (n = 595)
Radiofrequency ablation	0.2% (n = 28)	0.3% (n = 16)

Assessed 60 days prior to a switch. Percentage of all patients switching treatment.
VKA, vitamin K antagonist; NOAC, non-vitamin K oral anticoagulant; TIA, transient ischaemic attack.
[a]Defined as the first filling of a NOAC prescription among subjects with previous VKA use.
[b]Defined as filling a VKA prescription during NOAC therapy.
[c]Defined as hospitalization with other conditions than atrial fibrillation and pre-specified events/procedures.
[d]To ensure anonymization, cells with numbers lower than five are not reported.
[e]n/a: not a contraindication to the initial drug.

Approximately half of subjects in all three groups were hospitalized prior to a treatment change (*Tables 1* and *2*). Two-thirds of hospitalizations were coded with a discharge diagnosis compatible with 'atrial fibrillation' and/or one of the predefined clinical events or procedures. Overall, a predefined clinical event or procedure was identified prior to 18.3% of switches from VKA to NOAC, prior to 23.0% of switches from NOAC to VKA, and prior to 26.6% of NOAC discontinuations.

The frequency of thromboembolic complications was similar in the three groups (5.6–7.0%). Ischaemic stroke/transient ischaemic attacks were the dominating events in all three groups and constituted 64.8% of all thromboembolic events. The emergence of a new contraindication was most frequent prior to NOAC discontinuation (4.4%), most often cancer (2.8%) and chronic renal failure (1.0%). Among switchers, bleedings (2.8–4.3%) were less common

Table 2 Events potentially contributing to discontinuation of NOAC treatment in atrial fibrillation patients in the period of August 2011 to February 2016

Event	Discontinuations[a] (n = 8995)
Hospitalization	
Any hospitalization	47.4% (n = 4262)
Hospitalization with atrial fibrillation	18.2% (n = 1634)
Hospitalization with a pre-specified event or procedure	26.6% (n = 2392)
Hospitalization, other[b]	14.1% (n = 1264)
Thromboembolic complications	
Arterial embolism	0.2% (n = 14)
Venous thromboembolism	0.8% (n = 76)
Ischaemic stroke/TIA	3.4% (n = 306)
Myocardial infarction	1.2% (n = 107)
Bleeding complications	
Anaemia	5.6% (n = 500)
Bleeding, any	7.6% (n = 685)
Bleeding, gastrointestinal	3.4% (n = 305)
Bleeding, intracranial	0.9% (n = 80)
Bleeding, other	4.0% (n = 357)
Absolute or relative contraindications	
Acute renal failure	0.6% (n = 50)
Chronic renal failure	1.0% (n = 94)
Cancer	2.8% (n = 253)
Mechanic heart valve replacement	$n < 5$[c]
Procedures	
Direct-current cardioversion	6.0% (n = 542)
Radiofrequency ablation	0.3% (n = 25)

Assessed 180 days prior to a discontinuation. Percentage of all patients discontinuing NOAC treatment.
VKA, vitamin K antagonist; NOAC, non-vitamin K antagonist oral anticoagulant; TIA, transient ischaemic attack.
[a]Defined as no filled prescription of any oral anticoagulant in the number of days supplied by the last NOAC prescription plus 90 days.
[b]Defined as hospitalization with other conditions than atrial fibrillation and pre-specified events/procedures.
[c]To ensure anonymization, cells with numbers lower than five are not reported.

than thromboembolic complications (5.7–7.0%). Conversely, bleedings were more frequent events (7.6%) compared with thromboembolic events (5.6%) in subjects who discontinued NOAC treatment. Gastrointestinal bleeding was a more common type of bleeding among patients using NOACs prior to a switch or discontinuation than among patients using VKA (45.4 vs. 39.6% of all bleedings). Intracranial bleedings constituted 16.1 and 11.7% of bleedings prior to a switch from VKA to NOAC and discontinuation, respectively, and were rare prior to a switch from NOAC to VKA (<5% of bleeding episodes). Cardioversion had been performed most frequently prior to a switch from NOAC to VKA (11.4%). The corresponding number was 3.1 and 6.0% for switchers from VKA to NOAC and patients discontinuing NOAC therapy, respectively. The explorative analysis identifying causes of hospitalization outside the pre-specified diagnoses did not contribute with any new diagnoses (data not shown).

To further explore the mechanisms underlying the observed treatment changes in relation to cardioversion, we performed two *post hoc* analyses. First, receiving numerous cardioversions may lead to referral for catheter ablation, which in some patients will involve a switch of anticoagulant treatment (only VKA are currently recommended for this indication[1]). We explored this by determining the proportion of patients with a cardioversion prior to a treatment change that also received catheter ablation within 180 days after the change. This proportion was markedly higher among patients who had switched from NOAC to VKA upon cardioversion (48.9%) than among patients who had switched from VKA to NOAC (4.3%) or discontinued NOAC therapy (1.9%). Second, in AF patients with a low stroke risk (CHA_2DS_2-VASc score = 0), stroke prophylactic treatment with oral anticoagulants is indicated only in relation to high-risk procedures such as cardioversion.[1,12] To explore to which extent temporary NOAC use among low-risk AF patients could explain the observed discontinuations following cardioversion, we tabulated CHA_2DS_2-VASc scores of the 542 patients discontinuing NOAC therapy after cardioversion. The calculation of the CHA_2DS_2-VASc scores is described in Supplementary material online, *Appendix S2*. In this specific group, 46% had a CHA_2DS_2-VASc score of 0, 20% had a CHA_2DS_2-VASc score of 1, and 34% had a CHA_2DS_2-VASc score of ≥2.

Discussion

In this large nationwide study, including the largest sample to date of AF patients experiencing treatment changes before and during NOAC therapy, we found that treatment changes during oral anticoagulant therapy in AF is common, with a major clinical event identified for about one in five patients changing treatment, most often thromboembolism, bleeding, or cardioversion.

Compared with the present study, prior studies[5,13–17] have generally identified reasons for treatment changes in a larger proportion of the patients experiencing a change in anticoagulant treatment. However, these studies are based on data collected directly from the patient, physician, or the patient files. Thereby, in addition to major events included in the present study, they include minor events handled outside the hospital setting. In these studies, the majority of treatment changes are prompted by minor events that will rarely lead to hospitalization, e.g. dyspepsia,[5,13–16] minor bleedings,[5,13–17] and change/instability in laboratory values [e.g. international normalized ratio (INR) and creatinine clearance],[5,14–17] or due to physicians' or patients' preference towards a specific treatment regime.[5,14,16] In the Dresden NOAC Registry,[5] only 4.5% of 223 treatment changes observed during rivaroxaban therapy were caused by a thromboembolic event (stroke, transient ischaemic attack, or acute coronary syndrome). We therefore find that our study is in line with the previous studies in that only around one in five treatment changes is preceded by a major clinical event requiring hospitalization. This is further supported by a previous Danish study reporting that two-thirds of switches to and from NOAC were carried out by general practitioners.[8]

Our study expands current knowledge due to its size and, contrary to the majority of prior studies, has differentiated between the types of treatment changes (i.e. switching from VKA to NOAC, switching from NOAC to VKA, or complete discontinuation). As an example, reasons for switching from NOAC to VKA specifically have, to the best of our knowledge, been reported only for 14 AF patients switching from dabigatran to VKA in a study by Beyer-Westendorf *et al.*[16]

Similar to other studies,[5,13–17] bleedings were among the most common clinical events preceding a treatment change in the present study. Bleeding was, however, a less common event prior to a switch from NOAC to VKA than prior to a switch from VKA to NOAC and discontinuation. This is in accordance with results from the Dresden NOAC Registry[5,16,17]: none of the 14 registered switches from dabigatran to VKA were caused by bleeding,[16] as opposed to 18% of 568 switches from VKA to NOAC[17] and 22% of 32 dabigatran discontinuations without subsequent anticoagulant treatment.[16] There is currently no firm evidence addressing whether an AF patient experiencing bleeding during oral anticoagulant therapy (VKA or NOAC) should continue the treatment, switch to another oral anticoagulant, or discontinue oral anticoagulant treatment permanently. However, a subgroup analysis of the AVERROES trial demonstrated that AF patients who had previously failed VKA therapy, e.g. due to bleeding events, profited more from treatment with apixaban than aspirin in terms of thromboembolic risk and had similar risk of new bleeding events.[18] Furthermore, two recent Danish cohort studies have explored the risks conferred by re-initiation of anticoagulant therapy in AF patients experiencing an intracranial[19] or gastrointestinal bleeding[20] during oral anticoagulant therapy. Compared with no anticoagulant treatment, both studies found re-initiation to be associated with lower rates of all-cause mortality and thromboembolic complications while not causing a significantly higher risk of recurrent bleedings.[19,20]

In the present study, hospitalizations with AF were more common prior to switches from NOAC to VKA than prior to the other types of treatment changes. We believe this to be a reflection of the high number of cardioversions in this group as an admission with cardioversion will often be registered with a discharge diagnosis of AF. Our finding of a high proportion of cardioversions prior to a switch from NOAC to VKA followed by an AF ablation in almost half of the patients most likely reflects two distinct clinical issues. First, as 3–4 weeks of effective and stable anticoagulant treatment is required prior to cardioversion,[1] NOAC may often be preferred as pre-treatment over VKA in anticoagulant-naive patients. Patients, who prefer long-term treatment with VKA, may then be switched

from NOAC to VKA after cardioversion. Second, there is limited data on the use of NOAC in the context of AF ablation, and, therefore, NOAC users should be switched to VKA prior to ablation.[1] Our observation that 6% of discontinuations were preceded by a cardioversion is in accordance with a study by Suzuki *et al.*[15] that identified a cardioversion prior to 7.6% of 170 discontinuations of dabigatran. However, in that study, all discontinuations following cardioversion were scheduled prior to the cardioversion. Thus, all the involved patients likely had a low stroke risk (i.e. CHA_2DS_2-VASc score = 0), and as such anticoagulant therapy was therefore indicated only due to the high-risk procedure of cardioversion. In our study, temporary NOAC use among low-risk AF patients in relation to cardioversions could explain only around half of the discontinuations that followed a cardioversion.

The principal strength of our study was the nationwide analyses, including complete follow-up of all Danish citizens registered with AF and initiating NOAC treatment since the first NOAC was marketed for AF in 2011. Another important strength is the completeness of the registries employed[9–11] and the high validity of the AF diagnosis.[11] There are limitations as well. Although the majority of diagnoses used to identify clinical events in the study have been validated with acceptable results,[11] the validity of some diagnoses remains unknown. Furthermore, our data sources did not enable the identification of patients with poor INR control during VKA therapy, which was the most common reason for switching from VKA to NOAC in the Dresden NOAC Registry.[17]

Conclusion

In conclusion, treatment changes before and during treatment with NOACs in AF patients are common and about one in five is preceded by a relevant major clinical event. More research exploring reasons for specific types of treatment changes related to NOAC therapy is needed and should preferably be based on data collected directly from the patient or physician.

Supplementary material

Supplementary material is available at *Europace* online.

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