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Direct Oral Anticoagulant Use and the Incidence of Bleeding in the Very Elderly With Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is a major risk factor for stroke in the elderly population. The use of anticoagulation in patients with AF greatly reduces the risk for stroke, but results in an increased risk of bleeding. Over the past several years, direct oral anticoagulants (DOACs, dabigatran, rivaroxaban, and apixaban) have been used in place of warfarin for stroke prevention in AF. We conducted a retrospective cohort study to assess the safety of DOACs in very elderly patients (75+) managed in a health care system encompassing both community and academic settings. We found that 36% of patients had moderate to severe renal failure (estimated glomerular filtration rate <59 ml/min/1.73m²) at the time of DOAC initiation. 142 patients were followed for a mean of 2.56 years, and five experienced a major bleeding episode while on anticoagulation, for a rate of 1.37 per 100 person years. All major bleeding episodes were associated with a decline in GFR compared to baseline. There were 12 non-major bleeding episodes reported. HAS-BLED scores were similar for those patients who experienced bleeding complications compared to those who did not. 21% of patients were prescribed an inappropriately low dose of DOAC based on approved recommendations. DOACs appear to be a safe form of anticoagulation in very elderly patients with AF. However, the decline in GFR among patients with major bleeding highlights the importance of routine renal function monitoring.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. The prevalence of AF increases with advanced age and is almost 9% in patients aged 80 years and older [1]. From a public health perspective, perhaps the most burdensome aspect of AF is its role as a major risk factor for systemic embolism and stroke. The risk of stroke increases by 5-fold in patients with AF. In individuals aged >80 , AF accounts for 36% of strokes[2]. The use of anticoagulation to reduce this risk, therefore, requires strong consideration in all eligible individuals. Unfortunately, increased age is not only a risk factor for AF and stroke, but also poses a higher bleeding risk with anticoagulation[3].

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For over five decades, vitamin K antagonists (VKA) were the mainstay for anticoagulation in AF. More recently, the approval of the direct anticoagulants (DOACs) for this indication has increased therapeutic options for anticoagulation in this sub-group of patients. There are now four DOACs, dabigatran, rivaroxaban, apixaban and edoxaban that are licensed in the United States for use in AF [4-7]. The DOACs have been widely adopted in clinical practice due to their practical advantages. Their predictable pharmacokinetic profiles eliminate the need for routine monitoring. Also unlike the VKAs, there are fewer drug-drug and drug-food interactions. This is an especially attractive and advantageous feature in an elderly population with multiple co-morbidities and concurrent medications.

Whereas pivotal phase III trials included all age groups, several sub-analyses of patients aged 75 years and older have confirmed that DOACs retain their safety and efficacy in the elderly population[8-10]. The purpose of our study was to evaluate the risk of bleeding complications in the very elderly prescribed long-term anticoagulation therapy with DOACs in the community setting.

METHODS

Fairview Health Services is a community based health care system with cardiology services provided through multiple clinics. This includes both community-based clinics as well as an academic clinic at the University of Minnesota. A cohort of all AF patients initiated on dabigatran, rivaroxaban, or apixaban from January 2011 to December 2013 was identified. Edoxaban use had not been adopted in our health care system at that time. Only patients who were 75+ years at the time of the encounter and initiated on DOACs with the intent of long-term anticoagulation were included. Patients who were anticoagulated for less than three months were excluded. Records were reviewed to confirm the diagnosis of atrial fibrillation, use of DOACs, concomitant antiplatelet therapy use and laboratory results. Information was collected on the following co-morbidities: hypertension (defined as uncontrolled blood pressure or systolic blood pressure > 160 mmHg), chronic kidney disease (dialysis-dependent, post-renal transplant or creatinine > 2.6), liver disease (cirrhosis, liver enzymes 2x upper limit of normal or albumin <3.6), history of prior imaging-proven ischemic or embolic cerebrovascular accident, history of major bleeding or predisposition to bleeding (life-threatening bleeding or > 2g drop in hemoglobin), alcohol use (> 8 drinks/week), active malignancy, diabetes, anemia, congestive heart failure, smoking status, and frequent falls. HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history of predisposition, labile international normalized ratio (INR), age ≥ 65 years, drugs/alcohol concomitantly) [11] scores were calculated for the study cohort. All patients were assigned a score of 0 for labile INR as this information was not available in most cases. Individual charts were also reviewed to document the occurrence of new cerebrovascular events (transient ischemic attacks or imaging-proven cerebrovascular accidents) during the course of follow-up. Drug-exposure period was calculated by determining the duration between the date of DOAC initiation and discontinuation or most recent patient encounter. Estimated glomerular filtration rate (GFR) was extracted directly from the laboratory reports from the electronic medical records. The estimated GFRs from the Fairview System laboratories are based on the formula developed from the Modification of Diet in Renal Disease (MDRD) Study. We did not calculate estimated creatinine clearances using the Cockcroft-Gault

formula, since this was a retrospective study and we did not have weights on all patients. All GFRs were presumed non-African American, since we did not have data on race.

Individual charts were reviewed to capture the details of all bleeding encounters. Major bleeding episodes were defined per the International Society on Thrombosis and Hemostasis criteria as one of the following events:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
3. Clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dl or transfusion of at least 2 units of packed red cells [12].

The incidence rate of major bleeding was calculated using a person-time approach. In patients experiencing multiple bleeding episodes, only the first event was used to calculate incidence rate. Any reported bleeding episode that did not meet the criteria for major bleeding was defined as a minor or non-major bleed.

RESULTS

We identified 142 patients who were 75 years or older at the time of initiation of DOAC and were initiated on the medication with the intent of long-term anticoagulation. Of these, 76 received rivaroxaban, 52 received dabigatran and 14 were on apixaban. The mean age was 81.21 ($\pm$ 4.73) and 74/142(52.1%) patients were female. The mean duration of anticoagulation was 2.56 ($\pm$ 1.2) years. The majority (122/142) of patients were maintained on anticoagulation for > 1 year. GFR at the time of initiation of DOAC therapy was not available for 4 patients. Among the remaining 138 patients, 36% had moderate-severe renal insufficiency at the time of DOAC initiation with GFR <59 ml/min/1.73m². The baseline demographics and clinical characteristics of patients are summarized in Table 1.

There were 5 episodes of major bleeding at a rate of 1.37 per 100 person-years. In patients that suffered major bleeding episodes, there were 3 episodes of gastrointestinal bleeding (2 on rivaroxaban and 1 on dabigatran), 1 hip hematoma (on rivaroxaban) and 1 intracranial bleed (on rivaroxaban) (Table2) . Two of the patients were on concomitant anti-platelet therapy (aspirin 81mg in each case). All patients had normal platelet counts at the time of bleeding. The mean GFR for major bleeders at initiation was 73.4 ml/min/1.73m², however, in all 5 patients there was an overall decrease in GFR at the time of bleeding (mean decrease of 24% compared to time of initiation) with average GFR of 49.2 ml/min/1.73m² at the time of bleed. The average duration of anticoagulation for patients with major bleeding episodes was 1.99 years. Two of the five major bleeding episodes occurred within the first year of anticoagulation.

There were 12 non-major bleeding episodes in our cohort (7 on rivaroxaban, 4 on dabigatran and 1 on apixaban). Table 3 summarizes the details of non-major bleeding episodes.

Recurrent epistaxis was the most commonly reported minor bleeding event (N=4), followed by hematuria (N=3), vaginal bleeding (N=2), subconjunctival hemorrhage (N=1), hematochezia (N=1), easy bruising (N=1). None of the minor bleeding events were associated with significant fluctuations in GFR at the time of bleeding compared to baseline. In 2/3 cases of hematuria, the DOAC had to be discontinued due to ongoing bleeding. One of the patients was found to have a bladder tumor on further work-up. The patient was re-started on DOAC therapy after resection of the bladder lesion. The other patient was suspected of having an underlying bleeding diathesis as he continued to have recurrent minor bleeding episodes even after discontinuation of DOAC therapy. In all other minor bleeding cases, the patients remained on the prescribed DOAC. The HAS-BLED scores were similar for patients who experienced either minor or major bleeding compared to those who did not have any bleeding complication. There were no documented treatment failures (transient ischemic attack or cerebrovascular accident) in the study cohort. DOAC dosing information could accurately be ascertained for 140 patients. Among these, 21 patients (15%) were on an inappropriately low dose of the prescribed medication. Each of the 21 patients were prescribed an inappropriate dose of Rivaroxaban (in 7 patients, the dose was reduced to 10 mg, 14/21 patients were prescribed 15 mg).

DISCUSSION

The prevalence of atrial fibrillation increases with age as does the associated risk of embolic stroke[1]. Vitamin K antagonists have long been the only option for oral anticoagulation. In spite of ample evidence that Vitamin K antagonists reduce the risk of stroke and disability [13], anticoagulation has historically been underutilized in the very elderly population[14]. An increased risk of bleeding in this patient sub-group as well as frequent falls have been commonly cited reasons for avoiding anticoagulation [15].

In more recent years, the DOACs have been shown to be non-inferior to VKA in the prevention of stroke and embolism in patients with AF [4-7]. The safety and efficacy data of DOACs in the very elderly comes from over 30,000 patients aged > 75 that were included in the pivotal trials that led to the approval of these medications. However, interpretation of subgroup data from clinical trials requires caution as these studies were not designed and powered to detect differences between various age groups. Further, the presence of multiple co-morbidities, poly-pharmacy, frailty and high prevalence of renal dysfunction makes the extrapolation of data from the general population to the very elderly all the more challenging. A meta-analysis of randomized trials of DOACs for bleeding outcomes in the very elderly compared to VKAs found that dabigatran was associated with a higher risk of gastrointestinal bleeding compared to VKA, but could not clarify the bleeding risk for other DOACs due to insufficient data[16]. A subgroup analysis of the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial demonstrated that very elderly patients continue to derive benefit from apixaban and increased age does not increase the risk of bleeding compared to aspirin[17].

The purpose of our observational study was to report bleeding outcomes in the very elderly prescribed long-term anticoagulation with DOACs. The emergence of real-time data from

large observational cohorts has confirmed the safety and efficacy of DOACs demonstrated in clinical trials. However, there is scant information on the very elderly. Further, most studies have a limited follow-up duration. We found, that in our population of very elderly, who were anticoagulated for more than three months, the incidence rate of major bleeding with DOAC therapy was 1.37 per 100 person-years. This is lower than what has previously been reported from other 'real-world' studies of DOACs in AF.

The Xantus study, which assessed the safety and efficacy of rivaroxaban in clinical practice, followed patients for up to 1 year and found a major bleeding rate of 2.1 events per 100 patient-years[18]. Another large study of electronic medical records using Department of Defense database found a rate of 2.9 events per 100 patient-years [19]. Each of these studies included patients of all ages, and both men and women. In a study investigating the real world risk of gastrointestinal bleeding associated with dabigatran and rivaroxaban compared with warfarin, the incidence of gastrointestinal bleeding associated with dabigatran was 2.29 per 100 patient years and 2.84 per 100 patient years with Rivaroxaban. The authors also found that the risk of gastrointestinal bleeding increased after age 65, and by age 76 the risk exceeded that with warfarin among patients taking dabigatran [20]. One possible explanation for why the rate of major bleeding was lower in our study compared to others is that we excluded patients who stopped anticoagulation for any reason before three months. It is possible, that as seen in anticoagulation with VKA, the initial three months of treatment with DOACs may be associated with a higher risk of bleeding and bleeding risk plateaus thereafter. In our study, the mean follow-up period was longer than what has previously been reported (2.56 years) and 80% of patients had been maintained on DOAC therapy for greater than a year.

Our study is limited by its retrospective nature and small sample size. However, there is minimal data in the medical literature with long-term follow-up (>12 months). The only other real-life study that specifically evaluated bleeding outcomes in the very elderly followed patients for up to one year [21]. In contrast, the majority of patients in our cohort were followed for > 1 year. Mild renal insufficiency was commonly seen in very elderly patients with AF, with most patients having GFR between 60-89 ml/min/1.73m². In all cases of major hemorrhage, there was a decline in the GFR compared to the time of DOAC initiation. The clinical trials that led to approval of the DOACs excluded patients with low GFR. However, decreased dosing of dabigatran, rivaroxaban, and apixaban in patients with low GFR has been included in the FDA approval of these drugs, based on pharmacokinetic data. It remains to be seen whether such use is safe and effective in the clinical setting. Elderly patients being initiated on DOAC therapy should undergo routine monitoring of GFR (every six to twelve months) as has been advocated by a number of Canadian medical organizations [22]. In conclusion, the use of DOACs is likely to increase several-fold in the coming years. In our study, DOACs proved to be a reasonably safe option for anticoagulation in the very elderly population with a major bleeding rate of 1.37 per 100 person-years.

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Table 1**Baseline Demographics and Clinical Characteristics of Patients**

Age (years), mean+/- SD	81.21 +/- 4.73
Age >75-80, n (%)	70 (49.3)
Age >80-85, n (%)	41 (28.9)
Age >85-90, n (%)	24 (16.9)
Age >90, n (%)	7 (4.9)
Gender (female), n(%)	74 (52.1)
Glomerular Filtration Rate (ml/min), n(%)	
15-29 (severe decrease in GFR)	3 (2.1)
30-59 (mild decrease in GFR)	48 (34.8)
80-89 (moderate decrease in GFR)	66 (47.8)
>90 (normal or increased GFR)	21 (15.2)
Duration of anticoagulation (years), n(%)	
<1	20 (14)
1 to <2	26 (18.3)
2 to <3	40 (28.2)
3 to <4	40 (28.2)
>4	16 (11.3)
Existing co-morbidities, n(%)	
Uncontrolled HTN (SBP > 160 mm Hg)	3 (2.1)
Liver disease (cirrhosis, LFT 2X ULN or albumin <3.6)	1 (0.7)
CKD (dialysis-dependent, s/p renal transplant or Cr > 2.6)	1 (0.7)
Malignancy (actively being treated)	22 (15.5)
Diabetes mellitus	29 (20.4)
Congestive heart failure	42 (29.6)
Prior CVA (imaging-proven)	33 (23.2)
Frequent falls	23 (16.2)
Alcohol use (>8 drinks/week)	7 (5)
Bleeding diathesis or history of life-threatening bleed	11 (7.7)
Anemia	26 (18.3)
Concomitant anti-platelet therapy	34 (24)

Table 2

Details of Major Bleeding Episodes

Patient	Age	Sex	Medication Dose Appropriate (Y/N)	Site of Bleeding	Platelet count at the time of bleeding	Concomitant anti-platelet therapy	GFR at initiation of DOAC	GFR at the time of bleed	Anticoagulation (Continued / Discontinued)
1	84	M	Rivaroxaban 20 mg daily (Y)	Thalamus	200	N	90	84	Discontinued
2	90	M	Rivaroxaban 10 mg daily (N)	GIB	218	N	72	33	Switched to Coumadin
3	83	F	Rivaroxaban 20 mg daily (Y)	GIB	168	Y	87	71	Discontinued
4	77	F	Dabigatran 75 mg bid (Y)	GIB	283	Y	57	31	Switched to rivaroxaban
5	77	F	Rivaroxaban 15mg daily (Y)	Fall and hip hematoma	264	N	61	27	Discontinued

GIB- gastrointestinal bleeding

Table 3

Details of Non-major Bleeding Episodes

Patient	Age	Sex	Medication Dose Appropriate (Y/N)	Site of Bleeding	Platelet Count at the time of bleeding	Concomitant anti-platelet therapy	GFR at initiation of DOAC	GFR at the time of bleed	Anticoagulation (Continued/ Discontinued)
1	82	M	Dabigatran 150 mg bid (Y)	Hematuria	230	N	76	71	Discontinued transiently, currently on rivaroxaban
2	75	F	Dabigatran 150 mg bid (Y)	Hematuria	221	N	78	72	Discontinued
3	91	F	Rivaroxaban 15 mg daily (Y)	Epistaxis	175	N	47	33	Discontinued
4	89	M	Rivaroxaban 15 mg daily (N)	Recurrent epistaxis	Not checked	N	>90	Not checked	Continued
5	91	M	Dabigatran 150 mg bid (N)	Hematochezia	161	N	55	47	Continued
6	86	F	Dabigatran 75 mg bid (Y)	Vaginal bleeding	147	N	46	47	Switched to coumadin
7	89	F	Apixaban 2.5 mg bid (Y)	Intermittent hematuria	Not checked	N	79	Not checked	Continued
8	79	M	Rivaroxaban 20 mg daily (Y)	Epistaxis	174	N	77	86	Continued
9	75	F	Rivaroxaban 20 mg daily (Y)	Easy bruising	Not checked	N	70	55	Switched to coumadin
10	81	F	Rivaroxaban 20 mg daily (Y)	Vaginal bleeding	195	N	>90	>90	Switched to apixaban
11	76	M	Rivaroxaban 15 mg daily (N)	Subconjunctival hemorrhage	163	Y	63	68	Continued
12	84	F	Rivaroxaban 20 mg daily (Y)	Recurrent Epistaxis	Not checked	N	42	Not checked	Continued