Early Experience of New Oral Anticoagulants for Stroke Prevention in Octogenarian Patients with Atrial Fibrillation

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ABSTRACT

Background and Objectives: The safety of new oral anticoagulants (NOACs) depends largely on renal function. As renal function deteriorates with aging, the safety of NOACs is clinically important for very old cardiac patients. This study analyzed the efficacy and safety of NOACs prescribed to an octogenarian population in a university hospital.

Subject and Methods: A total of 158 consecutive patients aged ≥ 80 years and who had been prescribed NOACs for non-valvular atrial fibrillation (54 patients on dabigatran, 104 patients on rivaroxaban) were included. Demographic features, laboratory findings, and clinical follow-up results were retrospectively reviewed.

Results: Reduced doses were prescribed in 105 (66.2%) patients. The estimated GFR curve in octogenarian patients shifted left compared to that of patients aged < 80 years. There were two strokes or systemic embolic events during the follow-up period of 276 days. Major bleeding occurred in 13 patients, where gastrointestinal bleeding and anemia of unknown origin were the major causes.

Conclusion: NOACs seem to be highly effective for the prevention of stroke or systemic embolism in octogenarian populations. Bleeding events occurred in a considerable number of the study patients. Further studies on optimum dose ranges are required for very old subjects.

Key Words: ■ Atrial Fibrillation ■ Stroke ■ Embolism ■ Bleeding ■ Anticoagulants

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Introduction

The prevalence of atrial fibrillation (AF) and AF-related stroke events have been shown to increase with age.¹⁻⁶ Anticoagulation

using warfarin is effective for the prevention of stroke or systemic embolic events. However, warfarin requires periodic blood monitoring and interacts with numerous drugs and food; thus, it is underutilized in elderly patients for fear of a higher risk of

bleeding and poor tolerability.⁷ Unlike warfarin, new oral anticoagulants (NOACs) do not require regular blood monitoring. They have more predictable pharmacokinetics and pharmacodynamics and less drug and food interactions when compared with warfarin. In recent, randomized clinical trials; NOACs have been shown to be non-inferior to warfarin for the prevention of long-term stroke in patients with non-valvular AF.^{8,9} Moreover, they are associated with a significantly lower rate of intracranial hemorrhagic events and favorable survival benefits.¹⁰ However, use of NOACs is dictated by the patient's renal function because a significant proportion of these drugs are excreted via the renal route. As renal function in elderly patients decreases, prescription of NOACs in the elderly, especially octogenarians, requires caution.¹¹ The present study aimed to analyze the efficacy (prevention of stroke or systemic embolism) and safety (risk of bleeding) of NOACs prescribed in a Korean octogenarian population.

Methods

Study Design and Subjects

The medical records of 158 patients aged ≥ 80 years and with non-valvular AF who started NOAC treatment for primary or secondary prevention of ischemic stroke or systemic embolism at the Asan Medical Center, Korea; between January, 2011 and September, 2014; were retrospectively reviewed. Non-valvular AF was defined as AF occurring in the absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair.¹¹ The baseline characteristics of the enrolled study patients are presented in Table 1. The mean follow-up duration was 276 ± 202 days. The mean CHA₂DS₂-VASc score, a cumulative score of congestive heart failure, hypertension, age (≥ 75 years or ≥ 65 years), diabetes, stroke, vascular disease, and sex (female); was 4.7. Of the 158 patients who received NOACs, 54 (34.2%) had received dabigatran (50 on a low dosage of 110 mg, twice daily; 4 on a normal dosage of 150 mg twice daily) and 104 (65.2%) received rivaroxaban (54 on a low dosage of 10-15 mg daily; 50 on a normal dosage of 20 mg daily). In order to evaluate renal function, estimated glomerular filtration rate (eGFR) obtained in the octogenarian population was compared with that obtained from a

younger age group of subjects ($n=496$) selected from the NOAC patient pool at the Asan Medical Center. This study was approved by the institutional review board of the Asan Medical Center.

Outcome Assessments

The efficacy outcome was the composite of ischemic stroke or systemic embolism. Stroke was defined as sudden onset of a focal neurological deficit lasting at least 24 hours. Systemic embolism was defined as acute vascular occlusion of an extremity or major organ as documented either at the time of autopsy or with angiography or vascular imaging.

The safety outcome was major bleeding. Major bleeding was defined as a decrease in hemoglobin levels ≥ 2 g/dL, transfusion of ≥ 2 units of packed red blood cells, symptomatic intracranial hemorrhage, and death from bleeding.

Two investigators reviewed the patients' medical records during the follow-up period and adjudicated all stroke, systemic embolism, and bleeding events that contributed to these pre-specified outcomes. Event rates were presented as the number of events per 100 patient-years of follow-up.

Statistical Analysis

Statistical analysis was performed using the SPSS software package (Version 21, SPSS Inc., Chicago, IL), and data were expressed as the mean $\pm$ SD (continuous variables) or as frequency (categorical variables).

Results

Renal Function in Octogenarians

The renal function as measured by eGFR showed a left-shift in the octogenarian population when compared with that measured of the younger population (Figure 1). In the younger population, serum creatinine levels of 0.5-1.0 mg/dL indicated eGFR > 50 mL/min; while in octogenarians, serum creatinine levels of 0.5-1.0 mg/dL indicated moderately depressed (50 mL/min or below) eGFR in 51% of patients. Serum creatinine levels were influenced by medical illness or administered medications. Factors

Table 1. Clinical characteristics of study patients

Demographics	
Age (years)	84.2±3.5 y, men 63 (37.5%)
Body weight (kg)/SBP (mmHg)	58.5±11.3/131.7±22.7
Paroxysmal AF	62 (36.9%)
Creatinine (mg/dL)	1.0±0.3
eGFR (mL/min/1.73 m ²)	48.0±14.0
CV risk factor	
Prior stroke/TIA or systemic embolism	84 (50.0%)
Previous PCI/Previous MI	37 (22.0%)/8 (4.8%)
CHF/HT/DM	30 (17.9%)/118 (70.2%)/42 (25.0%)
Treatment	
Duration of NOACs use (days)	275.8±201.8
Dose reduction	105 (66.2%)
Prior ASA use/Current ASA use	79 (47.0%)/17 (10.8%)
Prior warfarin use	110 (65.5%)
CHA ₂ DS ₂ -VASc	4.8±1.4
HAS-BLED	2.0±0.9

Values are expressed as the mean±SD, median (interquartile range) or number (percentage).

Dose reduction refers to dabigatran 110 mg bid, dabigatran 10 or 15 mg qd.

AF, atrial fibrillation; ASA, acetylsalicylic acid; CHF, congestive heart failure; CV, cardiovascular; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HT, hypertension; MI, myocardial infarction; NOACs, new oral anticoagulants; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic stroke.

CHA₂DS₂-VASc is the cumulative score of congestive heart failure, hypertension, age (≥75 years or ≥65 years), diabetes, stroke, vascular disease, and sex (female).

HAS-BLED is the cumulative score of hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly (age >65 years), and drugs or alcohol.

aggravating renal functions included trauma, hospitalization, dehydration, poor oral intake, administration of antibiotics, medical imaging, and more. An example of fluctuating renal function is illustrated in Figure 2.

Efficacy of NOACs in the Octogenarian Population

No systemic embolic events were observed during the follow-up period. Stroke occurred in 2 patients (1.16 events/100 patient-years). The clinical profiles of patients with ischemic stroke or

bleeding are presented in Figure 3. One patient experienced ischemic stroke and showed a border zone infarction at the parieto-occipital region with simultaneous and significant narrowing of the carotid artery. Therefore, a clear cause of infarction was not clear when considering both cardioembolic and large artery disease. A patient with intracranial bleeding (subarachnoid hemorrhage) showed electrocardiographic features of tachycardia-bradycardia syndrome. The cause of the subarachnoid hemorrhage was not clear and may have been caused by either dabigatran or by trauma from a fall.

Figure 1. Plot of serum creatinine (Cr) vs. estimated glomerular filtration rate (eGFR).

The association of eGFR and creatinine levels from patients who were prescribed new oral anticoagulant is shown. Panel A depicts patients younger than 80 years, and B depicts those 80 years or older. The curves are shifted to the left in the older patients group. eGFRs were higher than 50 mL/min when serum creatinine levels were between 0.5 and 1.0 mg/dL in patients younger than 80 years, while eGFRs were below 50 mL/min in approximately half (51%) of octogenarian patients.

Figure 2. Temporal changes of serum creatinine levels in two octogenarian patients. Serum creatinine levels were highly vulnerable and influenced by patients' medical conditions or other external factors. The two graphs show transient elevation of serum creatinine levels after infection, exposure to contrast dyes, or changes in other medical conditions in octogenarian patients.

Safety of NOACs in the Octogenarian Population

Clinically significant bleeding occurred in 13 patients (8.9% per 100 patient-years). Gastrointestinal bleeding including anemia of unknown origin was the most common cause of major bleeding ($n=7$). Hematuria, intramuscular and intracranial bleeding occurred in 4, 2, and 1 patient, respectively. NOAC use was discontinued in 30 (18.9%) patients, largely due to bleeding complications. Other side effects that required discontinuation of NOACs were dyspepsia, chest pain, fatigue, and increased creatinine (Figure 4).

Discussion

The major findings of the present study are as follows: (1) NOACs were effective for the prevention of stroke or systemic embolism in octogenarian patients; (2) NOACs were discontinued in 18.9% of patients and the major cause of discontinuation was bleeding complications; and (3) considering

the high risk of bleeding while maintaining its efficacy, a systematic study aimed at determining the optimum dosage in an aged patient population is required.

Recent studies have investigated the effects of NOACs and consequently established their role in the field of stroke prevention in AF. In addition, sub-group analysis on the Asian population has reported even more improved results with the use of NOACs. The reported events rate of stroke or systemic embolism ranges between 1.26-2.6%/year in patients on NOACs, and 2.61-3.4%/year in patients on warfarin.¹²⁻¹⁴ Our study showed a similar efficacy profile of NOACs in the octogenarian population, confirming that NOACs may be non-inferior or more effective than warfarin for the prevention of embolic events in much older (≥ 80 years) AF patients. Risk of major bleeding was reported to be 4.43-5.10/100 patient-years for NOACs and 4.37-4.40/100 patient-years for warfarin in patients aged ≥ 75 years.^{15,16} Although there have as yet been no reports on the risk of bleeding from NOACs in this extreme age group, the risk of major

Figure 3. Magnetic resonance (MR) imaging of patients with ischemic stroke and intracranial hemorrhage.

A) An 84 year-old female patient visited the emergency room for left side weakness and gait disturbance. She had been diagnosed with hypertension and atrial fibrillation and had been prescribed rivaroxaban 10 mg qd. Cerebral infarction involving a border zone of the right parieto-occipital junction was noted by MR imaging (large arrow, left panel). MR angiography showed a complete occlusion of the left internal carotid artery and severe concentric stenosis at the bulb portion of the right internal carotid artery (small arrows, right panel).

B) An 80 year-old female patient with hypertension and paroxysmal atrial fibrillation (AF) visited the emergency room for evaluation of syncope. She had been taking dabigatran 110 mg bid. MR imaging showed curvilinear high signal intensity along the sulci in the left central sulci suggestive of minor subarachnoid hemorrhage (arrow, left panel). No significant steno-occlusive lesions in the intracranial or proximal neck vessels were found (right panel). The cause of syncope was sinus pause following termination of AF. A DDDR type permanent pacemaker was implanted.

bleeding (8.9/100 patient-years in our study) does not appear to be significantly different from that observed with the use of warfarin therapy (13.1/100 patient-years) and reported in previous studies of octogenarian patients.⁷ In addition, a recent prospective observational Italian study reported that the rate of major bleeding was low (1.87/100 patient-years) in octogenarians

on warfarin.¹⁷ Thus, considering the reduced renal excretion capacity in an aged patient population and our own results regarding the risk of major bleedings in octogenarian patients, the currently recommended NOAC dosage may be higher than ideal. Future prospective randomized clinical trials in a larger number of patients are required to investigate optimum NOAC dosage this

Figure 4. Causes for discontinuation of new oral anticoagulants.

extreme age group of patients. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, risks of stroke or systemic embolism were not found to be statistically different across doses of dabigatran (110 mg and 150 mg) in elderly patients aged ≥ 75 years.¹⁵ In a Japanese trial using low dosage rivaroxaban (15 mg once daily; mean age of study population, 71 years), a strong trend towards a decreased rate of stroke or systemic embolism with low dose rivaroxaban vs. warfarin was observed (HR=0.49; $p=0.050$).¹² Therefore, low dose NOAC administration may be non-inferior over normal doses for the prevention of stroke or systemic embolism in East Asian octogenarians. Moreover, low dose NOAC was significantly associated with a decreased risk of total or major bleeding when compared with normal dose NOAC. Based on these results, NOAC therapy, especially low dose use, may be non-inferior or superior to warfarin for preventing total and major

bleeding in frail patients such as octogenarians.

This study had several limitations. First, this was a retrospective analysis and the number of patients was relatively low. Second, different types and doses of NOACs were prescribed in our analysis. Thus, the efficacy and safety of different NOACs could not be compared. Despite these limitations, the present study shows that NOACs are highly effective for prevention of stroke or systemic embolism in the octogenarian population.

Conclusions

NOACs are highly effective for the prevention of stroke or systemic embolism in Korean octogenarian patients with non-valvular AF. Risk of major bleeding with NOACs use was not uncommon.

Table 2. Causes of bleeding

Age (year)	Sex	Bleeding site	NOAC dose	HAS-BLED	Anti-platelet use	eGFR (mL/min/1.73 m ²)
84	M	hematemesis	Xrt 10	1	clopidogrel	48
83	M	melena	Prd 220	2	-	58
88	F	melena	Xrt 10	1	-	50
84	M	Hg 12 to 10	Xrt 10	1	-	38
82	M	Hg 10 to 7.4	Xrt 10	1	-	106
82	F	Hg 11 to 5.0	Xrt 20	2	aspirin	30
80	F	ICH	Prd 220	3	aspirin	36
82	M	thigh hematoma/hemoptysis /hematuria/melena	Xrt 10	1	-	82
85	M	thigh hematoma	Prd 220		-	
89	F	hematuria	Xrt 10	1	-	67
83	M	hematuria	Prd 220	1	-	61
91	M	hematuria	Xrt 15	4	aspirin, clopidogrel	27
90	M	hematuria	Xrt 15	3	-	51

eGFR, estimated glomerular filtration rate; F, female; Hg, hemoglobin (g/dL); ICH, intracranial hemorrhage; M, male; NOACs, new oral anticoagulants; Prd 220, dabigatran 110 mg bid; Xrt 10, rivaroxaban 10 mg qd; Xrt 15, rivaroxaban 15 mg qd; Xrt 20, rivaroxaban 20 mg qd.

HAS-BLED is the cumulative score of hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly (e.g., age >65 years), and drugs or alcohol.

Disclosures

The authors have no conflicts of interest to disclose.

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