Analysis of Octogenarian Stroke Patients under Anticoagulation Therapy with Direct Oral Anticoagulant

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Abstract

Purpose: Stroke severity has been reported to be milder in patients taking direct oral anticoagulant (DOAC), compared with those taking warfarin. However, since elderly patients tend to have multiple complications, it is under debate whether such preferable effect of DOAC can be expected even in elderly patients. Therefore, we aimed to reveal if there is any difference of clinical manifestation between elderly and younger stroke patients who had been treated with DOAC.

Methods: From the consecutive acute ischemic stroke patients between April 2015 and March 2019, embolic stroke patients with anticoagulant medication by DOAC prior to the index stroke were selected in this study (n=55). The elderly was defined as aged over 80 years-old. Appropriate dosing of DOAC was determined by drug information documents. Clinical characteristics, neurologic severity, ischemic lesion size and outcome were accessed between patients over 80 years-old (≥80) (n=24) and less than 80 years-old (<80) (n=31).

Results: Appropriate dosing rate was significantly higher in the ≥ 80 compared with the <80 groups (87.5% and 61.3%, respectively: p=0.037). Neurologic severity on admission and the outcome at discharge were not significantly different between two groups. The distribution of lesion size was not different between the ≥ 80 and the <80 groups within patients taking appropriate dosing of DOAC.

Conclusion: It can be said the preferable effects of DOAC might be expected even in elderly patients as long as appropriate dose is prescribed.

INTRODUCTION

Cardioembolic stroke (CE), is the most prevalent stroke subtype among elderly people [1], because the morbidity of atrial fibrillation which can be a strong risk factor of CE is increasing in that generation [2]. Since CE tends to show severe neurologic deficits, importance of primary prevention will increase. Moreover, CE has a higher recurrence rate compared with other stroke subtypes [3], so it is also important to strictly continue secondary prevention using anticoagulation medication. Recently, because of their efficacy and safety [4-7], direct oral anticoagulants (DOAC) are preferably prescribed as an anticoagulation agent instead of warfarin [8]. As another feature of DOAC, it does not need dose adjustment unlike warfarin; however, a stable anticoagulation effect of DOAC can be obtained as long as the prescribed dose is followed by standard regimen [4-7]. Meanwhile, among elderly patients, not only the morbidity of atrial fibrillation is increasing, but also the frequencies of various kinds of complication, such as chronic heart failure, chronic kidney disease and orthopedic diseases, are increasing. As the results, many elderly patients tend to take multiple drugs [9,10]. In this regard, attempting to reduce the risk of hemorrhagic complication, some physicians may prescribe inappropriate dose of DOAC to elderly patients without following the standard regimen.

On the other hand, there are not a few patients who suffer from stroke despite taking DOAC [11]. These patients, however, have been reported to show smaller lesion size and better outcomes compared with those taking warfarin [12, 13]. Of course, for obtaining these preferable effects of DOAC, the appropriate dose of DOAC has to be prescribed. Therefore, it may contribute to encourage the appropriate prescription of DOAC for elderly patients to explore whether or not elderly patients can take benefits of DOAC unless they are treated with recommended dose in the standard regimen. In this study, we observed CE cases who had been taking DOAC, and investigated if there is any clinical difference between elderly and younger CE patients.
PATIENTS AND METHODS

All procedures of this study were approved by the ethical committee of Akita Cerebrospinal and Cardiovascular Center and the Certified Clinical Research Review Board, Akita University. The institutional review board waived the need for patient consent, as this is a retrospective study and all data were deidentified.

Acute ischemic stroke patients who were admitted within 24 hours following onset to our hospitals (Akita Cerebrospinal and Cardiovascular Center Hospital and Akita University Hospital) were consecutively screened between April 2015 and March 2019 (n=1099). Stroke subtype was confirmed by the medical record and classified into CE, large artery atherosclerosis (LAA), small-vessel disease (SVD), and others following a classification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) [14]. Then, patients of CE with anticoagulation therapy using DOAC prior to the index stroke were selected in this study (n=55).

Elderly is defined as aged over 80 years-old. Neurologic severity on admission was assessed by National Institute of Health stroke scale (NIHSS). Premorbid degree of independence and functional outcome at discharge were assessed by modified Rankin Scale (mRS). All ischemic lesions were confirmed by brain magnetic resonance imaging (MRI) or computer assisted tomography (CT), on admission. Ischemic lesion size was classified into four categories: “large” was defined as the lesion size larger than one third of total middle cerebral artery or anterior cerebral artery or posterior cerebral artery perfusion areas or the lesion including cerebellar hemisphere, “small” was defined as the lesion size less than 2cm in maximum diameter, “medium” was defined as the lesion size between large and small, “multiple small” was defined as the small lesions are observed in multiple. If lesion distribution does not match above mentioned criteria, one largest lesion in a patient is applied to the classification; for example, a patient had one large and one small lesions, this patient was classified into the large. The hemorrhagic transformation of the ischemic lesion was identified by CT images at 1 week following onset. Hemorrhagic transformation was diagnosed according to the European Cooperative Acute Stroke Study classification [15]. In this study, parenchymal hemorrhage (PH-1: heterogeneous hematoma in <30% of the infarcted area with some mass effect and PH-2: homogeneous hematoma ≥ 30% of the infarcted area with significant mass effect or any hemorrhagic lesion outside the infarcted area) was included as a complication. Stroke risk factors were defined as follows: hypertension (>140 mmHg systolic or >90 mmHg diastolic, or currently prescribed anti-hypertensive medication), diabetes mellitus (spontaneous blood sugar level >200 mg/dL, or currently prescribed anti diabetic medication), dyslipidemia (>140 mg/dL serum low-density lipoprotein or >150 mg/dL triglyceride, or currently prescribed anti hyperlipidemia medication), smoking, atrial fibrillation (observed by electric cardiogram on admission) and chronic heart failure (previously diagnosed, or confirmed by echo cardiograph). Past medical history and above mentioned risk factors were obtained from a patient’s clinical record. The laboratory data was obtained from blood sampling on admission. Renal function was assessed by calculating creatinine clearance. Medications including antithrombotic agents were checked in a patient’s medical record and complemented by an interview with the patient or a member of their family. The drug information document was used to determine whether the prescription dose of DOAC was following the standard regimen which took for “appropriate” or not which took for “inappropriate”. All patients were treated in the stroke care unit during the acute phase. Stroke treatment was following the guidelines [16].

Statistical analysis

Data are presented as average ± standard deviation (SD) or as a number and percentage. The clinical characteristics were compared by Pearson’s t-test for continuous variables and by χ² test for percentage variables. The distributional differences of neurologic severity and ischemic lesion size between the groups were compared by Mann-Whitney U test. All statistical analysis was performed by JMP9 software (SAS Institute Inc, Cary, NC). Values of p<0.05 were considered significant.

RESULTS

The distribution of age was shown in Figure 1. The mode was observed in late seventies and late eighties. The number of patients aged over 80 years-old was 24 (43.6%) (Table 1). The frequency of female was significantly higher in the over 80 years-old (≥80) group compared with the less than 80 years-old (<80) group (58.3% and 22.6%, respectively: p=0.0113). The percentage of smoking was significantly lower in the ≥80 compared with the <80 groups (20.8% and 48.4%, respectively: p=0.0491). The frequency of appropriate dosing of DOAC was significantly higher in the ≥80 compared with the <80 groups

![Figure 1: Distribution of age. The X axis expresses age groups separated by every 5 years. The Y axis stands for the number of patients.](image)

| Table 1: Clinical characteristics of all patients. |
|--------------------------------|-----------------|-----------------|-----------------|-----------------|
| n                             | Total           | <80             | ≥80             | p               |
| Male / Female                  | 34/21           | 24/7            | 14-Oct          | 0.0113          |
| Age (averages±SD)              | 78.3±7.4        | 72.7±4.6        | 85.4±2.7        | <0.0001         |
| Hypertension (%)               | 87.3            | 83.9            | 91.7            | 0.4508          |
| Hyperlipidemia (%)             | 45.5            | 35.5            | 58.3            | 0.109           |
| Diabetes mellitus (%)          | 30.9            | 25.8            | 37.5            | 0.3908          |
| Smoking(%)                     | 36.4            | 48.4            | 20.8            | 0.0491          |
| Atrial fibrillation (%)        | 90.9            | 87.1            | 95.8            | 0.3728          |
| Appropriate dosing (%)         | 72.7            | 61.3            | 87.5            | 0.0371          |
(87.5% and 61.3%, respectively: p=0.0371). Then, for further analysis, patients were classified into the appropriate and the inappropriate dosing groups in both the ≥ 80 and the <80 groups.

There was no significant differences of age, sex distribution, frequency of hypertension and existing of past stroke history between the appropriate and the inappropriate dosing groups in both the ≥ 80 and the <80 groups (Table 2). Percentage of diabetes mellitus was higher in the inappropriate dosing group compared with the appropriate dosing group among the ≥ 80 group, although it was not significant (66.7% and 33.3%, respectively: p=0.2646). Patients who were taking antiplatelet medicine along with DOAC were not observed in the inappropriate dosing group of both the ≥80 and the <80 groups. Number of patients with pacemaker was significantly higher in the ≥ 80 group compared with the <80 group (25.0% and 3.2%, respectively: p=0.0352). Renal function, assessed by creatinine clearance, was significantly lower in the ≥ 80 group compared with the <80 group (49.2 ± 13.4ml/min and 73.2 ± 23.3ml/min, respectively: p=0.0015). However, there was no significant difference of creatinine clearance between the appropriate and the inappropriate dosing groups of both the ≥ 80 and the <80 groups, respectively.

The average score of NIHSS was lower in the appropriate compared with the inappropriate dosing groups of the ≥80 group (6.5 ± 5.4 and 14.3 ± 11.6: p=0.0550), while the difference of NIHSS between the appropriate and the inappropriate dosing groups of the <80 group was very small (7.2 ± 8.7 and 8.7 ± 7.7: p=0.6383) (Table 3). The average score of NIHSS was also not significantly different between patients of the appropriate dosing groups in the ≥80 and the <80 groups (p=0.7630). There was no difference in the premorbid mRS score between the ≥80 and the <80 groups (0.9 ± 1.1 and 1.1 ± 1.3, respectively: p=0.4010), and the outcome at discharge was also not different between the ≥ 80 and the <80 groups (2.4 ± 1.5 and 2.5 ± 1.6, respectively: p=0.6748) (Table 3). When neurologic severity, assessed by NIHSS on admission, was classified into five categories, i.e. 0~4, 5~9, 10~14, 15~19 and 20~ (Figure 2A), the distribution was significantly different between the appropriate and the inappropriate dosing groups of the ≥ 80 group (p=0.0130). That is, patients with appropriate dosing of DOAC tended to show milder neurologic deficits. Among the <80 group, distribution of neurologic severity was also shifted to milder in the appropriate dosing group compared with the inappropriate dosing group, although it was not significant (p=0.0931).

There was no statistical difference of the distribution of ischemic lesion sizes between patients of the ≥80 and the <80 groups (Figure 2B). Particularly in the ≥ 80 group, although the large lesion size was observed in 33% in the appropriate dosing group, all patients in the inappropriate dosing group showed the large lesion size (not significantly different: p=0.5483). The rate of hemorrhagic transformation within one week following onset was not significantly different between the appropriate dosing patients of the ≥80 and the <80 groups (26.3% and 9.5%, respectively: p=0.2258) (Table 3).

**DISCUSSION**

Our results clearly indicated that stroke severity and outcome were not different between the over and the less than 80 years-old CE patients who were under anticoagulation therapy with DOAC.

Neurologic deficits caused by cardioembolic stroke were reported to be milder in patients taking DOAC compared with those taking warfarin [12]. Preferable stroke outcome during anticoagulation could be expected in patients taking warfarin of therapeutic intensity or standard dose DOAC [17,18]. Since the sufficient anticoagulation effect can be expected by prescribing appropriate dose, guidelines recommend the appropriate dosing of DOAC prescription. On the other hand, elderly patients tend to have various kinds of complication, such as chronic heart failure, chronic kidney disease and orthopedic diseases, resulting in high frequency of taking multiple drugs [9,10]. When prescribing antithrombotic agents in this situation, physicians may sometimes concern about bleeding risk, leading to the inappropriate dosing of DOAC prescription. Actually, it has been reported that older age, lower body weight and lower kidney function associate to the inappropriate dosing of DOAC prescription. As the result, it has been recommended to prescribe appropriate dose of DOAC especially for elderly patients. According to the clinical trials of DOAC, safety and noninferiority of DOAC against warfarin were reported. However,

![Figure 2](https://example.com/image.png)
these studies did not include enough data of elderly patients (Percentage of patients aged 80 or older was 13-17%) [6,7,22,23]. Many prospective studies have also reported the efficacy and safety of DOAC in the real world [24-26]; however, there are few studies which focused on clinical features in elderly patients. In this context, it is desired to reveal whether the effectiveness and safety of DOAC can be also expected in elderly patients or not. It can be said that our results in which elderly patients presented no significant difference of neurologic manifestation compared with younger counterparts might support the effectiveness of DOAC in elderly patients.

Hemorrhagic transformation is sometimes observed in an ischemic lesion and relates to the worsening of outcome [27, 28]. Its frequency increases particularly after a thrombolytic therapy and in cardioembolic stroke. It was reported that factors associated to hemorrhagic transformation were aging, atrial fibrillation, renal impairment and antithrombotic medicine use [29]. Therefore, elderly patients with antithrombotic agent might be at high risk of hemorrhagic transformation. Actually, according to our results, patients in the ≥ 80 group showed higher frequencies of clinical factors which relate to CHADS2-VASc and HAS-BLED scores [30,31], suggesting that these patients were at high risk of embolism and bleeding complications. However, in this study, the ratio of hemorrhagic transformation was not different between the ≥ 80 and the <80 groups. Therefore, it can be said that appropriate dosing of DOAC might not increase the hemorrhagic risk following CE even in elderly patients.

There are several limitations in this study. First, number of subjects was small. There might be a risk of type II error, so careful interpretation is needed. Second, all data were from two stroke centers in a central city area, leaving a possibility of biased patients’ distribution. Third, this study was retrospective and all cases were only new admission patients who were diagnosed CE. This bias might be one of the reason why we could not find any specific factors which relate to the inappropriate dosing of DOAC prescription. And also, it was not able to analyze the relationship between the onset of CE and the inappropriate dosing of DOAC. In the future, it needs to conduct a prospective larger multicenter study to confirm the current results.

CONCLUSION

Prescribing the appropriate dosing of DOAC would provide milder neurologic deficit at stroke onset and preferable outcomes regardless of patient’s age. Even elderly patients might be able to receive a benefit from DOAC, as long as the prescription is appropriately followed by the guidelines.
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Ethical approval

This study was approved by the ethical committee of the Akita Cerebrospinal and Cardiovascular Center and the Certified Clinical Research Review Board, Akita University.

Availability of data

All relevant data are available within the paper.

Authors' contribution

TN conducted the study, analyzed the data and wrote the manuscript. YT supported the statistical analysis. AH and JM screened the data. TI designed and advised the analysis. HS advised and supported this study. All authors reviewed the manuscript.

REFERENCES


