Reduced Doses of Direct Oral Anticoagulants in Ischemic Stroke Patients with Nonvalvular Atrial Fibrillation

Ichiro Deguchi, MD, PhD, and Masaki Takao, MD, PhD

Background: The choice of standard or reduced doses of direct oral anticoagulants (DOACs) depends on patients' age, body weight, and renal function based on package instructions. Our aim was to conduct a simulation of DOAC dose using patients' data obtained on admission. Methods: This retrospective study included 314 ischemic stroke patients with nonvalvular atrial fibrillation admitted to our hospital between September 2014 and February 2018. Data on age, body weight, creatinine, and creatinine clearance were collected for each subject, and simulation was conducted for the dose of each DOAC. Results: The mean age of 314 subjects was 77.2 years; those aged 75 years or older accounted for 61.5% (193 patients). It was suggested that a standard dose of rivaroxaban could be used in 67.5% of patients and that of apixaban in 65.9%. By contrast, a standard dose of dabigatran could be used in only 16.9% of patients and that of edoxaban in only 32.5%. The simulation analysis for patients aged 75 years or older showed that a standard dose of rivaroxaban could be used in 54.9% of patients and that of apixaban in 44.6%, while that of edoxaban could be used in only 19.7% of patients. Conclusions: When DOACs are prescribed for secondary prevention of cerebral infarction in patients with nonvalvular atrial fibrillation, the rate of standard or reduced dose varies depending on the kind of DOAC. Further analysis is required to clarify whether a standard dose of one DOAC or reduced dose of another DOAC yields the best result for each patient.
Keywords: Acute ischemic stroke—direct oral anticoagulants—dosage—nonvalvular atrial fibrillation—secondary prevention

Introduction

Four types of approved direct oral anticoagulants (DOACs) are available in Japan for prevention of ischemic stroke in patients with nonvalvular atrial fibrillation (NVAF). The efficacy and safety of DOACs have been proved to be superior to those of warfarin in a meta-analysis of randomized controlled trials (RCTs) in patients with atrial fibrillation.[1] Compared with warfarin, DOACs have a rapid onset of effect and do not require measurement of the prothrombin time/international normalized ratio.[2] As a result, the use of DOACs has been increasing.[3] However, when DOACs are administered, their doses vary depending on patient's renal function, body weight (BW), and age. This is associated with the problem of off-label dosing in clinical practice.[3,4] Reports on off-label dosing of DOACs have indicated that overdosing is significantly associated with increased all-cause mortality as compared with the recommended doses, while underdosing is significantly linked to increased cardiovascular hospitalization.[4] Accordingly, when DOACs are prescribed, it is important to adhere to the doses described in the package insert. At present, we are able to choose four types of DOACs for NVAF patients. DOAC selection depends on the patient's age, BW, and renal function.

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Table 1. *Approved Japan labeling for dose reduction of direct oral anticoagulants (DOACs)*

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosage reduction criteria*	Age ≥70 y or CrCl 30-50 mL/min	CrCl 15-49 mL/min	Two of the following criteria: Age ≥80 y Weight ≤60 kg Serum Cr ≥1.5 mg/dL	Weight ≤60 kg or CrCl 30-50 mL/min
Dosing DOACs standard/reduced	150 mg/110 mg twice daily	15 mg/10 mg once daily	5 mg/2.5 mg twice daily	60 mg/30 mg once daily
Not recommended	CrCl <30 mL/min	CrCl <15 mL/min	CrCl <15 mL/min	CrCl <15 mL/min

Abbreviations: Cr, creatinine; CrCl, creatinine clearance; DOACs, direct oral anticoagulants.
*Consideration for dabigatran alone.

Since there are no strict rules for DOAC selection, the rate of regular dose may be different among DOAC types. The purpose of this study is to conduct a simulation of DOAC dose using patients' data obtained on admission.

Patients and Methods

This retrospective study included 314 ischemic stroke patients with NVAF who were admitted to our hospital between September 2014 and February 2018. Echocardiography was performed in all patients to evaluate the presence of valvular disease. NVAF was defined as the presence of AF without rheumatic mitral valve disease (mitral valve stenosis) or artificial valve replacement.[5] AF was confirmed based on medical records such as ECGs, bedside ECG monitoring, and 24-hour Holter monitoring. Data on age, BW, and renal function (creatinine [Cr] and creatinine clearance [CrCl; Cockcroft-Gault equation]) were obtained.[6] Using the obtained data and regulation of DOAC administration (Table 1), we simulated prescription of DOACs for these patients. The 3 populations in the simulation comprised all patients, those aged 75 years or older, and those aged 85 years or older.

Patients who were included in this study had stroke with obvious NVAF only. Therefore, embolic patients with stroke of undetermined source[7] were not included in this study. Moreover, this study excluded patients with a CrCl of less than 15 mL/min in whom DOACs were contraindicated. The institutional review board of Saitama Medical University International Medical Center approved the study protocol (No.18-034).

Results

The clinical characteristics of the study patients are shown in Table 2. The mean (standard deviation) age of the patients was 77.2 (8.5) years. Patients aged 75 years or older accounted for 61.5% (193 patients) of the total patients. Patients aged 85 years or older accounted for 21.7% (68 patients) of all patients. The median $CHADS_2$ score before stroke onset (interquartile range [IQR]) was 2 (1-3). Patients who were taking oral anticoagulants on admission accounted for 29.3% (92 patients). Figure 1 shows the values of CrCl by age. The median CrCl (IQR) for all subjects was 58.9 (45.2-75.7) mL/min. CrCl decreased as age increased. Cr values by age are shown in Figure 2. The median Cr (IQR) for all subjects was .77 (.63-.93) mg/dL. There were minimal differences in the Cr value among age groups. Figure 3 shows BW by age. The median weight (IQR) for all subjects was 55 (48-65) kg. BW decreased as age increased. The number of patients weighing more than 60 kg accounted for 36.6% (115 patients) and those weighing 60 kg or less accounted for 63.4% (199 patients). Figure 4 shows the results of the simulation of DOAC dosing in patients. The standard DOAC dose would frequently be used for rivaroxaban and apixaban, accounting for 67.5% and 65.9%, respectively. Conversely, reduced doses were common, accounting for 67.5% for edoxaban and 80.2% for dabigatran (Fig 4A). In the simulation of DOAC dosing in patients aged 75 years

Table 2. *Clinical characteristics of the study patients*

	Total n = 314
Age, years	77.2 ± 8.5
Age ≥75 y	193 (61.5)
Age ≥85 y	68 (21.7)
Female sex	124 (39.5)
Hypertension	192 (61.1)
Diabetes mellitus	58 (18.5)
Heart failure	51 (16.2)
Coronary artery disease	30 (9.6)
Prior ischemic stroke/TIA	53 (16.9)
$CHADS_2$ score before stroke onset	2 (1-3)
NIHSS score on admission	7 (3-14)
Treatment with oral anticoagulants on admission	
Warfarin	36 (11.5)
DOACs	56 (17.8)

Abbreviations: DOACs, direct oral anticoagulants; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Data are presented as mean ± standard deviation, median (interquartile range), or number (%). $CHADS_2$, congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, and stroke/transient ischemic attack.

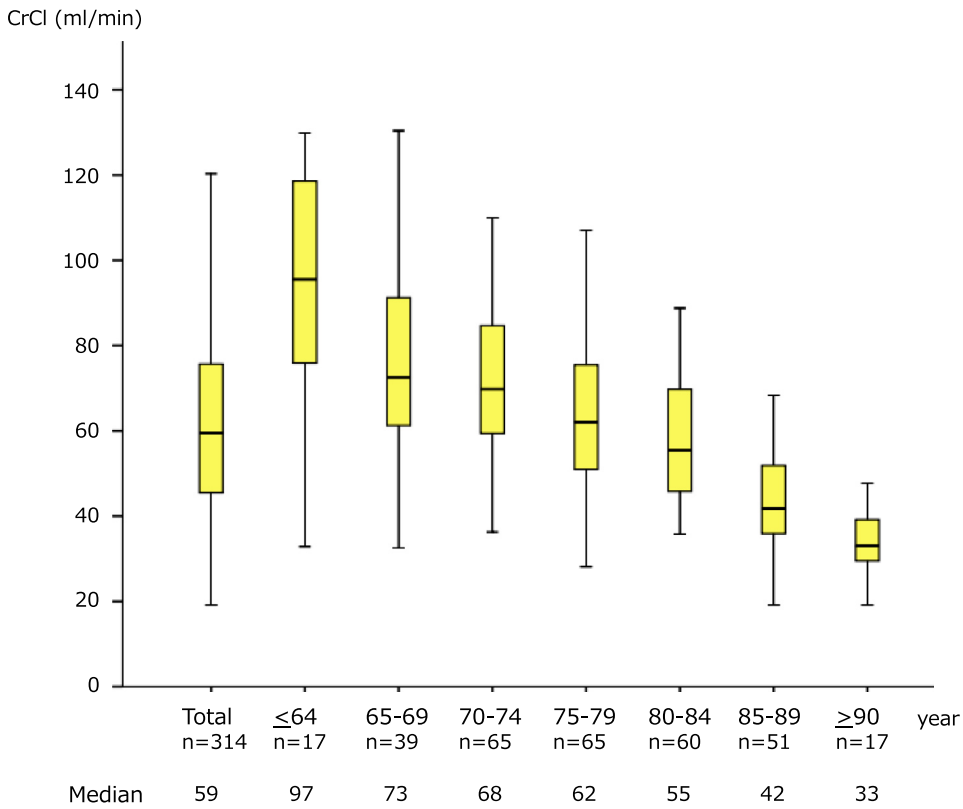

Figure 1. *Creatinine clearance (CrCl) values by age. The median CrCl value IQR in all patients was 58.9 (45.2-75.7) mL/min. CrCl decreased as age increased.*

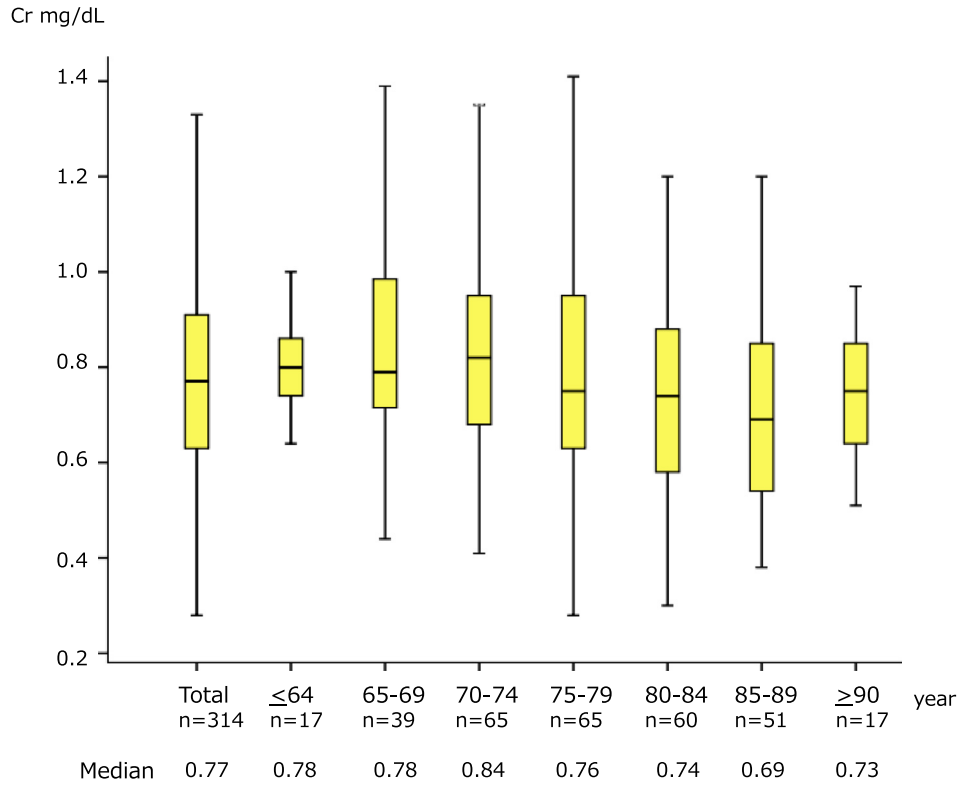

Figure 2. *Creatinine (Cr) values by age. The median Cr value (IQR) in all patients was .77 (.63-.93) mg/dL. No difference was noted in Cr values among age groups. CrCl values decreased with age.*

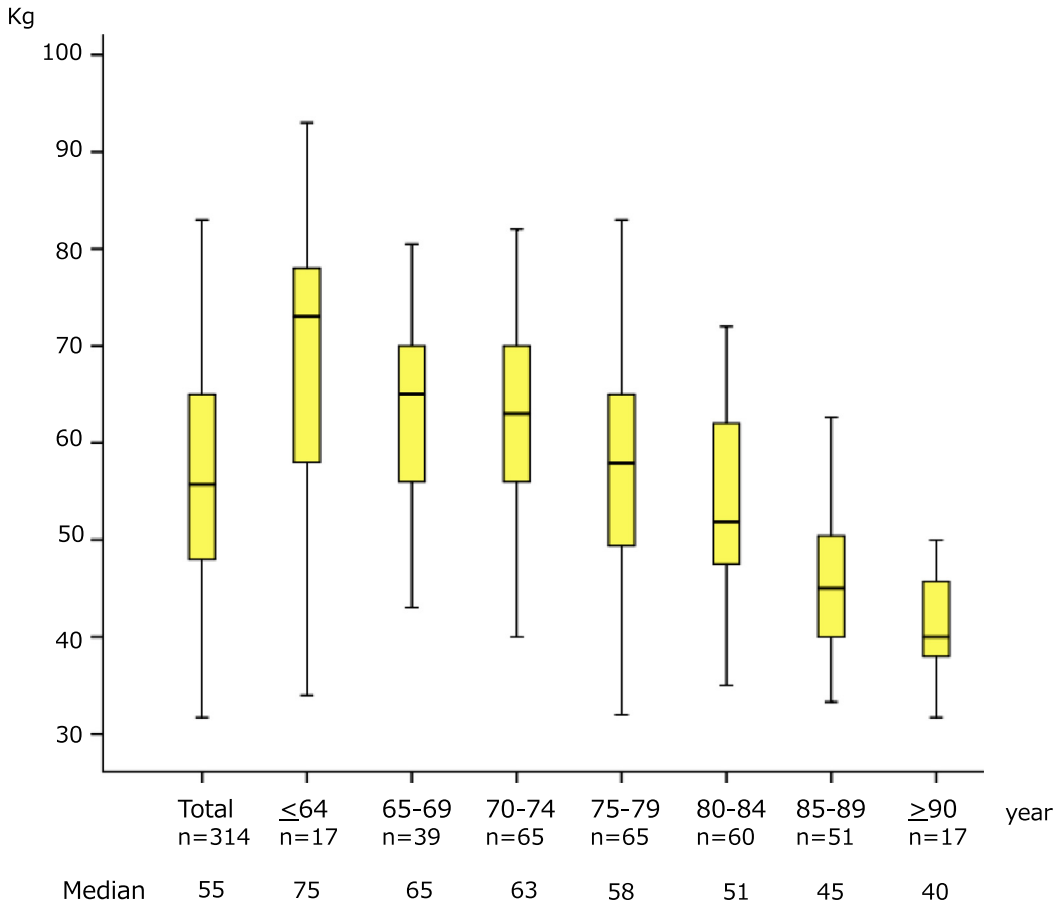

Figure 3. *Body weight by age. The median weight (IQR) in all patients was 55 (48-65) kg. Body weight decreased as age increased.*

or older, the frequency of the standard dose was the highest (54.9%) for rivaroxaban, followed by 44.6% for apixaban. Conversely, the frequency of reduced doses was 80.3% for edoxaban (Fig 4B). Simulation of DOAC dosing in patients aged 85 years or older revealed that the frequency of reduced doses was 95% for apixaban and edoxaban, whereas the standard dose of rivaroxaban would be used in 23.5% of patients (Fig 4C).

Discussion

This study showed that about 60% of patients with acute cerebral infarction and NVAF were aged 75 years or older. In Japan, the number of patients with cerebral infarction accompanied by AF is increasing in line with aging. Analysis of data from the Japan Standard Stroke Registry Study showed that the frequency of accompanying AF was higher in the older age groups, and the frequency of cardioembolic stroke was also higher.[8] Most patients with cerebral infarction accompanied by NVAF were those with cardioembolic stroke, reflecting the age distribution of patients in this study. Dose simulation for each DOAC showed that use of the standard dose was common for rivaroxaban and apixaban, whereas reduced doses were common for dabigatran and edoxaban. Simulation in patients aged 75 years or older showed that the standard dose could be used in more than 50% of patients on rivaroxaban. Simulation in patients aged 85 years or older showed that the standard dose could also be used in about one fourth of patients on rivaroxaban, whereas reduced doses had to be used in 95% of patients on apixaban and edoxaban. For edoxaban, in particular, 80% of patients aged 75 years or older also required reduced doses. The criteria for dose reduction for each DOAC might have affected these results. Dose reduction of rivaroxaban depends only on the CrCl value. By contrast, dose reduction of apixaban is not based on the CrCl value but instead on age, BW, and Cr value, while dose reduction of edoxaban is based on the CrCl value and BW. Although the CrCl value decreased with age, the median CrCl remained higher than 50 mL/min until age 84 years. In addition, there were minimal changes in the Cr value in relation to the age of patients.

By contrast, 76.7% of patients aged 75 years or older weighed 60 kg or less. Therefore, most patients aged 75 years or older require reduced doses of apixaban and edoxaban because dose reduction criteria for these drugs include BW (60 kg or less), and the dose of edoxaban in

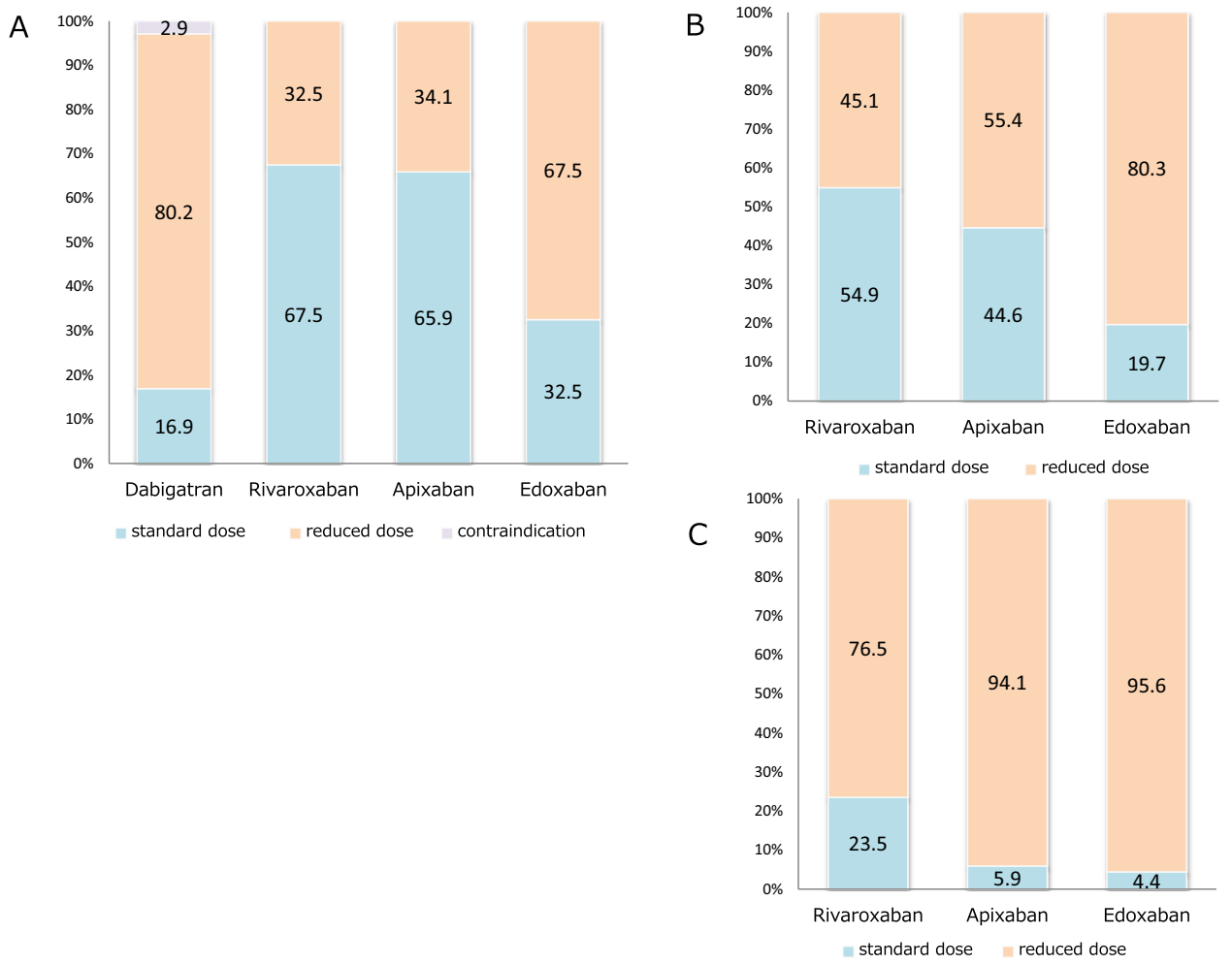

Figure 4. *Simulation of dosing for each DOAC. (A) Overall. High percentages of patients on rivaroxaban (67.5%) and apixaban (65.9%) received standard doses, whereas high percentages of patients on dabigatran (80.2%) and edoxaban (67.5%) received reduced doses. (B) Patients aged 75 years or older. The percentage of patients who received standard doses was the highest for rivaroxaban (54.9%), followed by apixaban (44.6%) and edoxaban (19.7%). (C) Patients aged 85 years or older. Reduced doses were used in 95% of patients on apixaban and those on edoxaban, while standard doses were used in 23.5% of patients on rivaroxaban.*

particular is reduced based on BW alone. On the contrary, the standard dose of rivaroxaban is more usable in older patients. Therefore, it is expected that underdosing may likely occur if a reduced dose is applied in clinical practice based only on patients' characteristics such as age, renal impairment, and lower BW when the CrCl value is well maintained. Postmarketing surveillance of rivaroxaban in Japan showed that the CrCl level in 50.8% of patients who received reduced doses was 50 mL/min or higher.[9] A report on cerebral infarction during DOAC therapy in our hospital showed that the rate of underdosing was 22.7% for dabigatran, 27.8% for rivaroxaban, and 27.3% for apixaban, whereas there was no underdosing of edoxaban.[10]

There is no marked difference in the efficacy or safety among different DOACs. However, dose compliance is important in any therapy. The efficacy demonstrated in randomized controlled trials will only be observed in practice when the dose regimen specified in the package insert is followed. Currently, there is no evidence that supports other usage. The results of this study showed that the frequencies of standard and reduced doses vary widely among different DOACs, even in the same patient population. Furthermore, we were able to identify which DOACs are most likely to be administered at standard or reduced doses in each age group. To prevent off-label dosing of DOACs, which is currently a clinical problem, clinicians should memorize the exact dose reduction criteria for each DOAC to determine which DOAC can be administered at standard or reduced doses. Clinicians should also use different DOACs according to the needs of individual patients. However, the present study also revealed an issue that should be addressed in the future. Even in the same patients, some DOACs need to be administered at standard doses, while others require reduced doses. In such cases, the effects exerted by DOACs administered at standard doses and reduced doses on secondary

prevention of cerebral infarction caused by NVAF, as well as these effects of DOACs vary among doses, remain unclear.

The simulation in this study was conducted based on dose reduction criteria only (age, BW, and renal function) and did not take into consideration other characteristics of patients. However, in the clinical setting (especially in older patients), DOAC prescriptions and dosing are also influenced by factors other than dose reduction criteria, such as underlying diseases and social background. Further accumulation of cases is required to examine differences in DOAC prescriptions between simulation results and the actual clinical setting, the type of patients who are prescribed each DOAC agent, and differences in effectiveness among different DOAC doses.

Conclusion

When DOACs are prescribed for secondary prevention of cerebral infarction in patients with NVAF, the rate of standard or reduced dose varies depending on the kind of DOAC. Further analysis is required to clarify whether a standard dose of one DOAC or a reduced dose of another DOAC yields the best result for each patient.

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