Postprint: Evaluation of Potentially Inappropriate Medication Use of Direct Oral Anticoagulants in Hospitalized Elderly Patients with Non-valvular Atrial Fibrillation Based on the Beers Criteria

Authors: Liu Puqing, Chen Jingwen, Zhang Shouxuan, Shou Zhangxuan

Date: 2023-07-18T00:00:00+00:00

Abstract

Background Direct oral anticoagulants (DOACs) have gradually replaced vitamin K antagonist warfarin as the preferred medication for anticoagulation therapy in non-valvular atrial fibrillation, yet the safety and effectiveness of their clinical use require continuous attention.

Objective Through investigation and analysis of potentially inappropriate medication (PIM) of DOACs in elderly hospitalized patients with atrial fibrillation in the cardiology department, to promote the rational clinical use of DOACs.

Methods By integrating the Beers Criteria, DOACs drug labeling, and guidelines related to anticoagulation therapy for atrial fibrillation patients, we developed PIM evaluation criteria for DOACs, including criteria for indications of DOACs for atrial fibrillation, PIM evaluation criteria for matching DOACs dosage with renal function levels, criteria for DOACs use in patients with different hepatic function levels, PIM evaluation criteria for DOACs drug-drug interactions, references for age-related DOACs dosage PIM evaluation, references for body weight-related DOACs dosage PIM evaluation, and references for bleeding risk-related DOACs dosage PIM evaluation. We retrospectively collected data on atrial fibrillation patients hospitalized in the cardiology department of The Second Affiliated Hospital of Zhejiang Chinese Medical University in 2022 who received anticoagulation therapy with DOACs (including rivaroxaban tablets, edoxaban tablets, and dabigatran etexilate capsules) from the Hospital Information System (HIS). The target population was screened according to inclusion and exclusion criteria, and each case was evaluated based on the PIM evaluation criteria.

Results A total of 89 elderly patients with atrial fibrillation were included, with a mean age of (77.9$±$8.1) years, and the PIM incidence rate was 56.18% (50/89). Among the three DOACs groups, a total of 58 PIM instances occurred, including 47 instances (81.03%) in rivaroxaban-treated patients, 6 instances (10.35%) in edoxaban-treated patients, and 5 instances (8.62%) in dabigatran etexilate-treated patients. The distribution of PIM types was as follows: renal function-related PIM in 44 instances (75.86%), drug-drug interaction-related PIM in 9 instances (15.52%), hepatic function-related PIM in 4 instances (6.89%), and body weight-related PIM in 1 instance (1.72%).

Conclusion There exists non-negligible PIM in DOACs anticoagulation therapy for elderly patients with non-valvular atrial fibrillation: rivaroxaban-treated patients had the highest PIM incidence rate, followed by edoxaban-treated patients, mainly manifested as renal function-related PIM, drug-drug interaction-related PIM, and hepatic function-related PIM. Therefore, anticoagulation therapy for elderly patients with non-valvular atrial fibrillation requires comprehensive consideration of individual patient conditions to develop personalized anticoagulation regimens, thereby reducing PIM in the clinical use of DOACs.

Full Text

Evaluation of Potentially Inappropriate Medication of Direct Oral Anticoagulants in Hospitalized Elderly Patients with Non-valvular Atrial Fibrillation Based on Beers Criteria

LIU Puqing[1], CHEN Jingwen[2], SHOU Zhangxuan[1]*

[1]Department of Pharmacy, the Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, China [2]Department of Cardiology, the Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310005, China

*Corresponding author: SHOU Zhangxuan, Chief pharmacist; E-mail: 20214021@zcmu.edu.cn

---

Abstract

Background: Direct oral anticoagulants (DOACs) have gradually replaced the vitamin K antagonist warfarin and become the first-line drugs for anticoagulant therapy in patients with non-valvular atrial fibrillation (NVAF). However, the safety and efficacy of DOACs in clinical use require sustained attention.

Objective: To promote rational use of DOACs by investigating and analyzing the potentially inappropriate medication (PIM) of DOACs in elderly patients with atrial fibrillation hospitalized in the Cardiology Department.

Methods: Beers criteria, DOACs drug inserts, and anticoagulant treatment guidelines were integrated to develop PIM evaluation criteria for DOACs therapy, including criteria for the indication of DOACs for atrial fibrillation, PIM evaluation of DOACs dose matched to renal function, DOACs application in patients with different liver function and PIM evaluation of DOACs drug interaction, evaluation references for age-related PIM, body weight-related PIM, and bleeding risk-related PIM. A retrospective analysis was performed to collect NVAF patients from the Hospital Information System (HIS) who were admitted to the Department of Cardiology and received DOACs (rivaroxaban tablets, edoxaban tablets, and dabigatran etexilate capsules) therapy from January 2022 to December 2022 at the Second Affiliated Hospital of Zhejiang Chinese Medical University. The target population was screened according to inclusion and exclusion criteria and evaluated individually according to the PIM evaluation criteria.

Results: A total of 89 elderly NVAF patients were enrolled with an average age of (77.94$±$8.06) years, and the incidence of PIM was 56.18% (50/89). There were 58 cases of PIM across the three DOACs groups, including 47 cases (81.03%) in the rivaroxaban group, 6 cases (10.35%) in the edoxaban group, and 5 cases (8.62%) in the dabigatran etexilate group. Sorted by PIM categories, the incidence of renal function-related PIM was 75.86% (44 cases), drug interaction-related PIM was 15.52% (9 cases), liver function-related PIM was 6.89% (4 cases), and weight-related PIM was 1.72% (1 case).

Conclusion: Anticoagulation treatment with DOACs in elderly patients with NVAF is associated with non-negligible PIM. Rivaroxaban-treated patients had the highest incidence of PIM, followed by edoxaban-treated patients, which mainly manifested as renal function-related PIM, drug interaction-related PIM, and liver function-related PIM. Therefore, clinicians need to develop individualized anticoagulation regimens integrating patient-specific conditions for elderly patients with NVAF, thereby reducing the PIM of DOACs therapy.

Keywords: Non-valvular atrial fibrillation; Anticoagulant therapy; Direct oral anticoagulants; Beers criteria; Potentially inappropriate medication

Introduction

The stroke risk in patients with atrial fibrillation is five times higher than in those without atrial fibrillation, and this risk increases with age, making standardized anticoagulation therapy particularly important for stroke prevention in elderly atrial fibrillation patients [1]. With the continuous launch of direct oral anticoagulants (DOACs) and updates to domestic and international anticoagulation guidelines, DOACs have gradually replaced vitamin K antagonists—warfarin—to become the preferred drugs for anticoagulation therapy in patients with non-valvular atrial fibrillation (NVAF) [2]. Although DOACs offer definite clinical efficacy and do not require routine coagulation function monitoring,

they exhibit large individual differences in plasma concentration [3], and their metabolism in vivo is affected by liver and kidney function as well as drug interactions [4]. Consequently, numerous potential safety concerns remain in clinical use. Elderly patients often have extensive disease spectra, multiple comorbidities, poorer liver and kidney function, and serious polypharmacy, making anticoagulation therapy safety issues—namely potentially inappropriate medication (PIM)—a focus of attention for both clinicians and pharmacists. The Beers criteria represent the earliest developed and most widely applied clinical PIM evaluation tool, designed to reduce adverse drug events [6]. The 2019 version of the Beers criteria includes corresponding updates regarding PIM issues for direct oral anticoagulants in elderly patients and hospitalized elderly patients. However, the Beers criteria section on DOACs requires supplementation with anticoagulation treatment guidelines and DOACs drug inserts in clinical practice. While various countries have DOACs usage guidelines or manuals, no unified standard has been formed, and guidelines suggest that medical institutions can develop their own anticoagulation treatment manuals and rational medication evaluation principles [7-13]. Therefore, this study integrated the Beers criteria with domestic and international DOACs drug inserts and atrial fibrillation anticoagulation treatment guidelines [1-2, 10-13] to develop PIM evaluation criteria for three direct oral anticoagulants (rivaroxaban tablets, edoxaban tablets, and dabigatran etexilate capsules) at our hospital. As the Cardiology Department is the primary unit admitting atrial fibrillation patients, we conducted this retrospective investigation and analysis to identify PIM issues in anticoagulation therapy for elderly atrial fibrillation patients in our Cardiology Department, providing a reference for guiding rational DOACs use in clinical practice.

Methods

1.1 Development of PIM Evaluation Criteria The PIM evaluation criteria for DOACs were developed based on the Beers criteria [9], primarily according to drug inserts approved by the China Food and Drug Administration (CFDA) for rivaroxaban tablets, edoxaban tablets, and dabigatran etexilate capsules, with reference to drug inserts approved by the U.S. Food and Drug Administration (FDA) and the UK's Medicines and Healthcare products Regulatory Agency (MHRA), and in combination with domestic and international atrial fibrillation anticoagulation treatment guidelines and DOACs clinical use and pharmacotherapy management guidelines, including "Atrial Fibrillation: Current Understanding and Treatment Recommendations (2021)" [2], "2022 Scientific Statement: Stroke Prevention in Atrial Fibrillation (Part 2)" [10], "2021 APSC Consensus Recommendations: Direct Oral Anticoagulants in Asian Atrial Fibrillation Patients" [11], "2020 CCS/CHRS Comprehensive Guidelines: Management of Atrial Fibrillation" [12], and "2021 EHRA Practice Guidelines: Use of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation Patients" [13]. The expert panel for developing the DOACs PIM evaluation

criteria consisted of five members, including the director of the Pharmacy Department, the director of the Cardiology Department, the deputy director of the Medical Affairs Department, a cardiologist, and a cardiovascular clinical pharmacist. After two rounds of roundtable discussions, the PIM evaluation criteria for three DOACs in atrial fibrillation patients were finalized, comprising seven components: (1) Indication criteria for DOACs in atrial fibrillation (Table 1); (2) PIM evaluation criteria for matching DOACs dose to renal function level (Table 2); (3) Criteria for DOACs use in patients with different liver function levels (Table 3); (4) PIM evaluation criteria for DOACs drug interactions (Table 4); (5) Age-related DOACs dose PIM evaluation reference: generally, for elderly atrial fibrillation patients aged >80 years, the recommended dose of dabigatran etexilate capsules is 110 mg per dose, twice daily; (6) Body weight-related DOACs dose PIM evaluation reference: generally, for elderly atrial fibrillation patients with body weight $ $60 kg, the recommended dose of edoxaban tablets is 30 mg per dose, once daily; (7) Bleeding risk-related DOACs dose PIM evaluation reference: generally, when Has-Bled score $ $3, low-dose DOACs are recommended.

1.2 Inclusion and Exclusion Criteria We retrospectively collected atrial fibrillation patients from the HIS system of the Second Affiliated Hospital of Zhejiang Chinese Medical University who were hospitalized in the Cardiology Department and received DOACs (including rivaroxaban tablets, edoxaban tablets, and dabigatran etexilate capsules) anticoagulation therapy in 2022. Inclusion criteria were: (1) diagnosed with atrial fibrillation; (2) age $ $65 years; (3) hospitalization duration of 3-30 days; (4) receiving anticoagulation therapy with rivaroxaban tablets, edoxaban tablets, or dabigatran etexilate capsules. Exclusion criteria were: (1) diagnosis without atrial fibrillation; (2) hospitalization duration $ $2 days; (3) hospitalization duration >30 days; (4) death during hospitalization. By reviewing electronic medical records, we extracted patients' basic information including hospital number, name, gender, age, diagnosis (disease name and number), renal function, liver function, anticoagulant drugs (type, dose, frequency), number of drug types, length of hospital stay, major bleeding events during hospitalization, thrombotic events during hospitalization, and anticoagulation-related death during hospitalization (thrombosis or bleeding). Renal function level was calculated using the creatinine clearance formula: CrCl (mL/min) = [(140 - age) × body weight] / [72 × serum creatinine (mg/dL)] × (0.85 for female) [14]. Liver function level was assessed using the Child-Pugh evaluation scale [15].

1.3 PIM Evaluation Standards One cardiovascular clinical pharmacist reviewed all involved medical records according to the developed PIM evaluation criteria for direct oral anticoagulants (DOACs). The review results were verified by one cardiovascular clinician. If disagreements arose, the case was referred to the Medical Affairs Department for final determination.

1.4 Statistical Methods Original data were collected using Excel software, and statistical analysis was performed on patients' basic information and evaluation results. Measurement data were expressed as ($\bar{x}\pm s$), and count data were expressed as relative numbers.

Results

2.1 Patient Baseline Characteristics A total of 89 elderly atrial fibrillation patients were ultimately enrolled in this study (Figure 1 [Figure 1: see original paper]), including 45 males (50.56%) and 44 females (49.44%); age ranged from 65 to 92 years, with an average age of $(77.9\$\pm 8.1) years; body weight ranged from 39.5 to 88.5 kg, with an average body weight of (62.6\pm 11.4) kg; renal func$ $Bled score ranged from 0 to 3 points, with an average of (1.42\pm 0.64) points; number of medication types ranged fron$ days. Among all enrolled elderly atrial fibrillation patients, 63 cases (70.79%) received rivaroxaban tablets anticoagulation therapy; 18 cases (20.22%) received edoxaban tablets; and 8 cases (8.99%) received dabigatran etexilate capsules. Patient baseline characteristics are shown in Table 5 .

2.2 PIM Evaluation Results The evaluation results showed that among 89 hospitalized elderly atrial fibrillation patients, 50 patients had DOACs-related PIM, with a total incidence rate of 56.18%. Among them, 41 patients (82.00%) had PIM with rivaroxaban; 5 patients (10.00%) had PIM with edoxaban; and 4 patients (8.00%) had PIM with dabigatran etexilate (Table 6). Calculated by occurrence frequency, there were 58 cases of PIM related to the three DOACs anticoagulation therapies, including 47 cases (81.03%) with rivaroxaban, 6 cases (10.35%) with edoxaban, and 5 cases (8.62%) with dabigatran etexilate.

Renal function level mismatch with DOACs dose caused 44 cases of PIM, ranking first among all PIM categories and accounting for 75.86%: 37 cases (82.22%) with rivaroxaban PIM, including 35 cases of underdosing and 2 cases of overdosing; 3 cases (8.89%) with edoxaban PIM, including 1 case of underdosing and 2 cases of contraindicated use in CKD stage 5; and 4 cases (8.89%) with dabigatran etexilate PIM, including 2 cases of underdosing and 2 cases of contraindicated use in CKD stage 4.

Drug interaction-related PIM with DOACs dosing totaled 9 cases, ranking second among all PIM categories and accounting for 15.52%: 6 cases with rivaroxaban PIM, including 2 cases combined with dronedarone and 4 cases combined with Chinese herbal medicine forsythia; 2 cases with edoxaban, including 1 case combined with clarithromycin tablets and 1 case combined with dronedarone; and 1 case with dabigatran etexilate, where the patient was combined with dronedarone. No indication-related PIM was found.

Liver function level mismatch with DOACs dose caused 4 cases of PIM, ranking third and accounting for 6.89%, all from rivaroxaban: 4 atrial fibrillation

patients with Child-Pugh grade B liver function (Table 5) received rivaroxaban tablets 10 mg per dose, once daily anticoagulation therapy.

Body weight mismatch with dose caused 1 case of DOACs PIM, ranking last and accounting for 1.72%: the patient was treated with edoxaban, with body weight <60 kg, receiving edoxaban tablets 60 mg per dose, once daily.

2.3 DOACs-Related Adverse Events A total of 4 cases of DOACs anticoagulation therapy-related adverse events were recorded during hospitalization, with an adverse event rate of 4.5%: 2 rivaroxaban tablet patients had hemoglobin decrease >30 g/L, 1 patient had cerebral infarction; 1 edoxaban tablet patient had cerebral infarction; and no adverse events occurred with dabigatran etexilate capsules (Table 7).

Discussion

The elderly are generally defined as $ 65 $ $ years $ $ old, $ $ with the World Health Organization further subdividing the mi $ $ old (65-74 years), old-old (75-84 years), and oldest-old (85 years) [16]. Elderly atrial fibrillation patients (65 ye $ point for males, $ $2 points for females) [17]. Cardiologists were relatively active in initiating anticoagulation therapy for atrial fibrillation with good indication control, and no indication-related PIM was found, but there were many PIM issues in DOACs dose selection.

Renal function level has very significant safety relevance to DOACs anticoagulation therapy dosing. On one hand, the kidney is the main excretory organ for DOACs, and decreased renal function can lead to drug accumulation and greatly increase bleeding risk [18]; on the other hand, impaired renal function reduces hematopoietic function, easily causing anemia and decreased coagulation function [19]. This study showed that the renal function levels of enrolled patients were: rivaroxaban > dabigatran etexilate > edoxaban, and the incidence of PIM due to mismatch between renal function level and DOACs dose was: rivaroxaban tablets > dabigatran etexilate capsules > edoxaban tablets. We found that rivaroxaban-treated patients with the best renal function had the highest incidence of dose-renal function mismatch PIM, while edoxaban-treated patients with the poorest renal function had the lowest PIM incidence. Edoxaban-treated patients had lower renal function levels than patients on the other two DOACs, possibly because clinicians were particularly cautious when facing patients with moderate renal insufficiency, believing that the edoxaban 30 mg per dose, once daily anticoagulation regimen had lower bleeding risk than rivaroxaban 15 mg per dose, once daily and dabigatran etexilate capsules 110 mg per dose, twice daily. Reviewing the DOACs evaluation table, among 37 rivaroxaban-treated patients with renal function-dose mismatch PIM, 35 cases were unreasonable use of low-dose rivaroxaban, including 16 patients who used low-dose rivaroxaban 15 mg per dose, once daily when renal function permitted, and another 19 patients who used low-dose rivaroxaban 10 mg per dose, once

daily when renal function permitted. Some real-world studies from Asia ACC guidelines, Japan, and China Taiwan have found that rivaroxaban 10 mg per dose, once daily may have equivalent clinical effects in Asian populations to 15 mg used in European and American Caucasian populations [20-21]. However, this anticoagulation dosing regimen is not included in the Chinese rivaroxaban drug insert or atrial fibrillation guidelines.

Drug interactions related to DOACs dosing are caused by changes in DOACs plasma concentration [22]. Among the 89 enrolled elderly atrial fibrillation patients, 9 cases (8.99%) had drug interaction-related PIM, with an overall incidence that is not high but warrants vigilance. The most common drug interactions causing PIM were dronedarone (4 cases) and Chinese herbal medicine forsythia (4 cases). Dronedarone has an antiarrhythmic mechanism similar to amiodarone but with significantly reduced adverse reactions. Dronedarone can increase NOACs plasma concentration by inhibiting P-glycoprotein and reducing NOACs efflux, thereby increasing bleeding risk. Rivaroxaban and dabigatran etexilate should avoid combined use with dronedarone, while edoxaban combined with dronedarone should use low dose [23]. Forsythia, also known as St. John's wort, can simultaneously induce P-glycoprotein and CYP3A4, promoting DOACs efflux and metabolism, causing plasma concentration to significantly decrease and leading to insufficient anticoagulation. The plasma concentration decrease is most significant when rivaroxaban and dabigatran etexilate are combined with forsythia, which should be avoided, while edoxaban plasma concentration decrease is relatively smaller and should be used with caution [24-25].

Liver function level is related to DOACs metabolism and intrinsic coagulation function. Pharmacokinetic studies show that in Child-Pugh grade B, the area under the curve (AUC) of rivaroxaban tablets can increase by 125%, with elevated plasma concentration increasing bleeding risk, and its use should be avoided; edoxaban exhibits similar pharmacokinetic and pharmacodynamic characteristics in grade B patients as in grade A, and is not recommended but can be used cautiously; dabigatran etexilate capsules show large individual differences in pharmacokinetic characteristics and plasma concentration in grade B patients, and are not recommended but can be used cautiously; all DOACs should be avoided in grade C patients [26].

Regarding the relationship between body weight and DOACs dose, only edoxaban randomized controlled trial (RCT) subgroup analysis indicated that patients with body weight $ $60 kg using the low-dose 30 mg per dose, once daily anticoagulation regimen is safer and more effective [27]. For elderly atrial fibrillation patients, studies have shown that using DOACs anticoagulation therapy carries significantly higher major bleeding risk, especially gastrointestinal bleeding risk, compared to warfarin [28]. Dabigatran etexilate capsules explicitly recommend low-dose 110 mg per dose, twice daily for patients over 80 years old; edoxaban recommends that for patients over 80 years old who cannot tolerate 30 mg per dose, once daily, 15 mg per dose, once daily may be considered [29];

however, for rivaroxaban tablets, there are no explicit regulations in current guidelines or drug inserts on whether low dose can be selected when advanced age is the only risk factor. Bleeding risk is an important factor that must be considered in clinical use of DOACs. A Has-Bled score $ $3 indicates high bleeding risk but is not a contraindication for anticoagulation therapy. When bleeding risk factors are irreversible, low-dose DOACs should be selected.

In summary, this retrospective investigation and analysis study demonstrates that numerous PIM issues exist in clinical use of DOACs in elderly atrial fibrillation patients, particularly the inappropriate use of low-dose rivaroxaban, followed by drug interactions with concomitant medications (dronedarone, forsythia), and anticoagulation therapy with rivaroxaban in patients with moderate liver function impairment. These PIM issues in clinical use of DOACs can lead to major bleeding or thrombotic adverse events. Although this study is retrospective, it reflects real-world PIM issues of DOACs in elderly atrial fibrillation patients and provides direction and reference for clinical pharmacists to conduct rational drug use work in the future. Atrial fibrillation anticoagulation therapy is a very complex pharmacotherapy process that requires consideration of various factors including age, body weight, disease status, liver and kidney function, thrombotic and bleeding risks, and drug interactions, weighing the pros and cons to develop individualized anticoagulation regimens for patients. Clinical pharmacists will use these PIM evaluation criteria to conduct in-hospital education and intervention on PIM-related prescriptions to promote rational clinical use of DOACs.

Author Contributions

LIU Puqing and CHEN Jingwen were responsible for literature review and drafting the DOACs electronic medical record data. LIU Puqing and CHEN Jingwen conducted prescription review, data collation and analysis, and wrote the initial manuscript. SHOU Zhangxuan provided guidance, supervision, and responsibility for the overall research design and clinical issues.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Correction to: 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society[J]. Circulation, 2019, 140(6): e285. DOI: 10.1161/CIR.0000000000000719.

[2] Chinese Society of Pacing and Electrophysiology, Chinese Association of Arrhythmia of Chinese Medical Doctor Association, Atrial Fibrillation Center Alliance of China Atrial Fibrillation Prevention and Treatment Expert Working Committee, et al. Atrial fibrillation: current understanding and treatment recommendations (2021)[J]. Chinese Journal of Cardiac Arrhythmias, 2022, 26(1): 15-88.

[3] VAN DER LINDEN L, HIAS J, VANASSCHE T. The value and limitations of new oral anticoagulant plasma level assessments[J]. Eur Heart J Suppl, 2022, 24(Suppl A): A32-41. DOI: 10.1093/eurheartj/suab153.

[4] GELOSA P, CASTIGLIONI L, TENCONI M, et al. Pharmacokinetic drug interactions of the non-vitamin K antagonist oral anticoagulants (NOACs)[J]. Pharmacol Res, 2018, 135: 60-79. DOI: 10.1016/j.phrs.2018.07.016.

[5] DOVJAK P. Polypharmacy in elderly people[J]. Wien Med Wochenschr, 2022, 172(5/6): 109-113. DOI: 10.1007/s10354-021-00903-0.

[6] American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults[J]. J Am Geriatr Soc, 2012, 60(4): 616-631. DOI: 10.1111/j.1532-5415.2012.03923.x.

[7] By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American geriatrics society 2019 updated AGS beers criteria® for potentially inappropriate medication use in older adults[J]. J Am Geriatr Soc, 2019, 67(4): 674-694. DOI: 10.1111/jgs.15767.

[8] GORZONI M L, ROSA R F. Beers AGS 2019 criteria in very old hospitalized patients[J]. Rev Assoc Med Bras, 2020, 66(7): 918-923. DOI: 10.1590/1806-9282.66.7.918.

[9] By the 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults[J]. J Am Geriatr Soc, 2023. DOI: 10.1111/jgs.18372.

[10] CHIANG C E, CHAO T F, CHOI E K, et al. Stroke prevention in atrial fibrillation: a scientific statement of JACC: asia (part 2)[J]. JACC Asia, 2022, 2(5): 519-537. DOI: 10.1016/j.jacasi.2022.06.004.

[11] CHONG D T, ANDREOTTI F, VERHAMME P, et al. Direct oral anticoagulants in Asian patients with atrial fibrillation: consensus recommendations by the Asian Pacific society of cardiology on strategies for thrombotic and bleeding risk management[J]. Eur Cardiol, 2021, 16: e23. DOI: 10.15420/ecr.2020.43.

[12] ANDRADE J G, AGUILAR M, ATZEMA C, et al. The 2020 Canadian cardiovascular society/canadian heart rhythm society comprehensive guidelines for the management of atrial fibrillation[J]. Can J Cardiol, 2020, 36(12): 1847-1948. DOI: 10.1016/j.cjca.2020.09.001.

[13] STEFFEL J, COLLINS R, ANTZ M, et al. 2021 European heart rhythm association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation[J]. Europace, 2021, 23(10): 1612-1676. DOI: 10.1093/europace/euab065.

[14] SHAHBAZ H, GUPTA M. Creatinine clearance[M]. Treasure Island (FL): StatPearls Publishing, 2022.

[15] TSORIS A, MARLAR C A. Use of the Child Pugh Score in liver disease[M]. Treasure Island (FL): StatPearls Publishing, 2022.

[16] BEARD J R, OFFICER A, DE CARVALHO I A, et al. The World report on ageing and health: a policy framework for healthy ageing[J]. Lancet, 2016, 387(10033): 2145-2154. DOI: 10.1016/S0140-6736(15)00516-4.

[17] DIENER H C, AISENBERG J, ANSELL J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2[J]. Eur Heart J, 2017, 38(12): 860-868. DOI: 10.1093/eurheartj/ehw069.

[18] DEREBAIL V K, RHEAULT M N, KERLIN B A. Role of direct oral anticoagulants in patients with kidney disease[J]. Kidney Int, 2020, 97(4): 664-675. DOI: 10.1016/j.kint.2019.11.027.

[19] MANNUCCI P M, TRIPODI A. Hemostatic defects in liver and renal dysfunction[J]. Hematology Am Soc Hematol Educ Program, 2012, 2012: 168-173. DOI: 10.1182/asheducation-2012.1.168.

[20] HORI M, MATSUMOTO M, TANAHASHI N, et al. Safety and efficacy of adjusted dose of rivaroxaban in Japanese patients with non-valvular atrial fibrillation: subanalysis of J-ROCKET AF for patients with moderate renal impairment[J]. Circ J, 2013, 77(3): 632-638. DOI: 10.1253/circj.cj-12-0899.

[21] BANDO S, NISHIKADO A, HIURA N, et al. Efficacy and safety of rivaroxaban in extreme elderly patients with atrial fibrillation: analysis of the Shikoku Rivaroxaban Registry Trial (SRRT)[J]. J Cardiol, 2018, 71(2): 197-201. DOI: 10.1016/j.jjcc.2017.08.005.

[22] SANDHU R K, ISLAM S, DOVER D C, et al. Concurrent use of P-glycoprotein or Cytochrome 3A4 drugs and non-vitamin K antagonist oral anticoagulants in non-valvular atrial fibrillation[J]. Eur Heart J Qual Care Clin Outcomes, 2022, 8(2): 195-201. DOI: 10.1093/ehjqcco/qcab002.

[23] SUN Y H, MA C S, WU S L. Chinese expert consensus on clinical application of dronedarone[J]. Chinese Journal of Internal Medicine, 2021, 60(12): 1139-1147. DOI: 10.3760/cma.j.cn112138-20210505-00326.

[24] SCHOLZ I, LIAKONI E, HAMMANN F, et al. Effects of Hypericum perforatum (St John's wort) on the pharmacokinetics and pharmacodynamics of rivaroxaban in humans[J]. Br J Clin Pharmacol, 2021, 87(3): 1466-1474. DOI: 10.1111/bcp.14553.

[25] GRZEŚK G, ROGOWICZ D, WOŁOWIEC Ł, et al. The clinical significance of drug-food interactions of direct oral anticoagulants[J]. Int J Mol Sci, 2021, 22(16): 8531. DOI: 10.3390/ijms22168531.

[26] QAMAR A, VADUGANATHAN M, GREENBERGER N J, et al. Oral anticoagulation in patients with liver disease[J]. J Am Coll Cardiol, 2018, 71(19): 2162-2175. DOI: 10.1016/j.jacc.2018.03.023.

[27] BORIANI G, RUFF C T, KUDER J F, et al. Edoxaban versus warfarin in patients with atrial fibrillation at the extremes of body weight: an analysis from the ENGAGE AF-TIMI 48 trial[J]. Thromb Haemost, 2021, 121(2): 140-149. DOI: 10.1055/s-0040-1716540.

[28] VERSO M, GIUSTOZZI M, VINCI A, et al. Risk factors and one-year mortality in patients with direct oral anticoagulant-associated gastrointestinal bleeding[J]. Thromb Res, 2021, 208: 138-144. DOI: 10.1016/j.thromres.2021.10.022.

[29] OKUMURA K, AKAO M, YOSHIDA T, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation[J]. N Engl J Med, 2020, 383(18): 1735-1745. DOI: 10.1056/NEJMoa2012883.

(Received date: 2023-04-03; Revised date: 2023-07-08)

Note: Figure translations are in progress. See original paper for figures.