Recent Advances in Clinical Application of Direct Oral Anticoagulants in Special Populations with Venous Thromboembolism (Postprint)

Authors: Xiao Yao, ten thousand jun, 万钧 (wàn jūn): a term denoting immense weight or overwhelming force, literally "ten thousand *jun*" (钧, an ancient unit of weight equivalent to 30 catties); often used metaphorically to describe something of extraordinary power or momentous impact, as in the idiom *léitíng wànjūn* (雷霆万钧, "thunderous might").

Date: 2025-02-24T00:00:00+00:00

Abstract

Direct oral anticoagulants (DOACs) have been approved for the treatment and primary and secondary prevention of venous thromboembolism (VTE). In recent years, they have been steadily adopted in clinical practice and their indications have gradually expanded. Although standard-dose DOACs do not require routine monitoring, they introduce therapeutic uncertainty in special patient populations with extreme body weight, impaired hepatic or renal function, advanced age, pregnancy and lactation, and multiple comorbidities, potentially requiring dose adjustment or rendering them unsafe for use, thus necessitating administration of traditional anticoagulants such as heparin or vitamin K antagonists (VKA). Currently, an increasing number of scholars have conducted research on these special VTE patient populations to evaluate the safety and efficacy of DOACs in clinical practice. This review compiles and analyzes the latest research progress on DOACs in special patient populations, providing evidence and insights for more rational clinical application of DOACs and optimization of anticoagulation strategies.

Full Text

Treatment of Venous Thromboembolism in Special Populations with Direct Oral Anticoagulants

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Abstract

Direct oral anticoagulants (DOACs) have been approved for the treatment and secondary prevention of venous thromboembolism (VTE), achieving stable application among clinicians in recent years with an expanding scope of use. Although routine monitoring is not required for fixed-dose DOACs, therapeutic uncertainties arise when managing special patient populations presenting with factors such as extreme body weight, impaired hepatic or renal function, advanced age, pregnancy and lactation, and multiple comorbidities. These scenarios may necessitate dose adjustment or preclude DOACs use altogether, requiring consideration of traditional anticoagulants such as heparin or vitamin K antagonist (VKA). Increasing numbers of studies have been conducted to assess the safety and effectiveness of DOACs in these special VTE patient populations across diverse clinical settings. This review consolidates and analyzes the latest research progress on DOACs in these special patient populations, providing evidence and insights for more rational use of DOACs in clinical practice and optimizing anticoagulation strategies.

Keywords: Anticoagulants; Venous thromboembolism; Direct oral anticoagulants; Special population; Treatment; Review

Introduction

Traditional anticoagulants such as vitamin K antagonists (VKA) and low molecular weight heparin (LMWH) have several limitations, including inconvenient administration, narrow therapeutic windows, frequent drug-food interactions, and relatively high bleeding risk. To overcome these deficiencies, direct oral anticoagulants (DOACs) were developed and introduced into clinical practice. Non-inferiority studies of DOACs for VTE treatment have demonstrated that their anticoagulant efficacy is not inferior to conventional LMWH/VKA sequential therapy (e.g., warfarin) while reducing bleeding risk. Additionally, DOACs offer advantages including short half-life, convenient use, favorable pharmacokinetics at fixed doses, fewer drug interactions, and no requirement for routine monitoring. Based on accumulating evidence, current guidelines continue to update and expand the clinical indications for DOACs.

Unlike VKA, which can be monitored via international normalized ratio, or LMWH, which can be dose-titrated based on anti-Xa factor activity or body weight, fixed-dose DOACs do not require routine clinical monitoring. However, in special VTE patient populations with extreme body weight, impaired hepatic or renal function, advanced age, or multiple comorbidities, DOACs may present therapeutic uncertainties. An increasing number of studies have investigated the safety and efficacy of DOACs in these special populations. This review

synthesizes the latest research progress on DOACs in special patient populations to provide evidence and insights for optimizing anticoagulation strategies in clinical practice.

Literature search strategy: Computerized searches of CNKI and PubMed databases were conducted from January 2014 to November 2024. Chinese search terms included "venous thromboembolism,""direct oral anticoagulants,""extreme body mass," "hepatic impairment," "renal function," "advanced age," "pregnancy and lactation," "malignant tumor," "antiphospholipid syndrome," and "chronic thromboembolic pulmonary hypertension." English search terms included "venous thromboembolism,""Direct oral anticoagulants,""Extreme body mass,""impaired hepatic,""renal function,""advanced age,""pregnancy,"and "hypertension." Inclusion criteria comprised literature on the clinical application of DOACs in special VTE populations; exclusion criteria included studies with poor credibility or irrelevant to the topic. A total of 39 articles were included.

1. Extreme Body Weight

Obesity is an independent risk factor for VTE. A key clinical concern is whether standard-dose DOACs can prevent thrombus recurrence in overweight VTE patients. Studies have shown no significant difference in DOACs exposure between obese and normal-weight matched controls, and plasma anti-Xa factor activity demonstrates a direct linear relationship with DOACs plasma concentration independent of body weight. The efficacy and safety of DOACs in obese patients appear comparable to those in the general population. However, data on pharmacokinetics, pharmacodynamics, efficacy, and safety in morbidly obese patients (BMI $>$ 40 kg/m^2 or body weight $>$ 120 kg) remain relatively limited.

Real-world studies on VTE treatment in morbidly obese patients have found that, compared with warfarin, apixaban and rivaroxaban both reduce VTE recurrence without increasing major bleeding risk, though evidence for dabigatran and edoxaban is lacking. Some experts recommend that if patient weight exceeds 150 kg, initial VTE anticoagulation should employ conventional LMWH/VKA sequential therapy to reduce thrombosis recurrence risk.

Whether standard-dose DOACs increase bleeding risk in underweight VTE patients also warrants attention, but large-scale phase III RCTs in low-body-weight patients are lacking, and no consensus or guidelines exist for DOACs use in this population. Low-body-weight patients often have comorbidities (e.g., advanced age, frailty, cancer cachexia, renal insufficiency), making drug accumulation-related bleeding a primary clinical concern requiring close monitoring. Since low-body-weight patients typically have lower muscle mass, renal function is often overestimated; therefore, DOACs use in this population should be assessed in conjunction with creatinine clearance (CrCl). Low body weight ($\leq$ 60 kg) is associated with increased systemic DOACs exposure. Studies have found that dose reduction using apixaban (5 mg twice daily) or edoxaban (30 mg once daily) yields non-inferior clinical efficacy compared with conventional anticoagulation

while reducing bleeding risk.

In summary, DOACs are safe and effective for most extreme-body-weight VTE patients. Morbidly obese patients (BMI $>$ 40 kg/m^2 or weight $>$ 120 kg) may preferentially receive standard-dose rivaroxaban or apixaban; those weighing $>$ 150 kg may consider initial conventional therapy; while low-body-weight patients should have renal function monitored using CrCl, with dose reduction considered for those weighing $\leq$ 60 kg to improve safety.

2. Hepatic Impairment

All DOACs undergo partial hepatic metabolism. Apixaban relies most heavily on hepatic metabolic clearance (75% of its elimination pathway), followed by rivaroxaban (65%), edoxaban (50%), and dabigatran (20%). Apixaban and rivaroxaban metabolism is primarily affected by cytochrome P450. Compared with traditional anticoagulation strategies, DOACs demonstrate better safety and efficacy in patients with hepatic impairment. A retrospective real-world cohort study of chronic liver disease patients with acute VTE found that DOACs reduced the composite risk of recurrent VTE hospitalization and major bleeding hospitalization compared with warfarin, with apixaban providing greater clinical benefit than rivaroxaban. Another meta-analysis of DOACs for VTE treatment in advanced liver disease or cirrhosis patients found that DOACs reduced major bleeding by 61%, intracranial hemorrhage by 52%, and thrombus recurrence progression risk by 82% compared with conventional anticoagulants. However, other studies suggest that spontaneous bleeding from DOACs use correlates significantly with liver disease severity, warranting caution in advanced liver disease patients.

Current guidelines recommend that for mild hepatic impairment (Child-Pugh class A), no DOACs dose adjustment is needed; for moderate impairment (Child-Pugh class B), dabigatran, apixaban, and edoxaban may be cautiously selected; for severe impairment (Child-Pugh class C), only warfarin is recommended. In VTE treatment for patients with hepatic impairment, baseline and periodic blood tests to assess liver function and coagulation parameters should be performed throughout DOACs therapy.

3. Renal Impairment

Different DOACs exhibit varying degrees of renal clearance, which determines anticoagulation strategies in patients with renal insufficiency. Dabigatran has the highest renal clearance as an active metabolite (up to 80%), while apixaban has the lowest. Evidence suggests that DOACs anticoagulation offers better safety and efficacy than VKA in patients with renal disease. A meta-analysis of DOACs for VTE that included six phase III RCTs with over 7,000 patients with renal impairment found that standard-dose DOACs were effective for VTE treatment in mild-to-moderate renal insufficiency, with safety non-inferior to LMWH/VKA conventional regimens. Another observational cohort study of

VTE patients with CrCl < 30 mL/min found no statistical difference in thrombosis recurrence or bleeding outcomes between DOACs and VKA groups. Additionally, a retrospective study of end-stage renal disease VTE patients on long-term hemodialysis found that apixaban reduced recurrent VTE and major bleeding events compared with warfarin, with similar mortality rates.

Guidelines recommend standard DOACs doses when CrCl > 30 mL/min; dabigatran is not recommended when CrCl < 30 mL/min; when CrCl is 15–30 mL/min, reduced DOACs doses should be used (rivaroxaban 15 mg once daily, edoxaban 30 mg once daily, or apixaban 2.5 mg twice daily); patients with CrCl < 15 mL/min or receiving renal replacement therapy should avoid DOACs. Since drug exposure increases as renal function declines, especially in elderly patients and those taking multiple medications, regular renal function assessment and dose adjustment are necessary.

4. Elderly Patients

Elderly patients have higher VTE risk but also increased anticoagulation-related bleeding risk. Underdosing DOACs in elderly VTE patients is common due to bleeding concerns and other clinical variables; however, dose reduction may not provide benefits in safety or efficacy. A prospective cohort study of VTE patients aged ≥ 85 years receiving VKA or DOACs found that approximately 45% of cases received low-dose DOACs regimens, yet bleeding risk remained high in this elderly group receiving reduced-dose DOACs, with thrombotic event rates similar to the VKA group but significantly lower mortality.

Compared with VKA, DOACs may offer better safety and efficacy in elderly patients. Polypharmacy is common in this population, and concurrent use of cardiovascular drugs, anti-infectives, and neurological medications may affect anticoagulation efficacy or increase bleeding risk. A study comparing edoxaban versus warfarin in elderly VTE patients found that VTE recurrence in the warfarin group increased with age, comorbidities, and concomitant medications, but this was not observed in the edoxaban group. Edoxaban showed similar bleeding risk to well-managed warfarin but was more effective than warfarin in patients ≥ 75 years old and those with multiple comorbidities.

With extensive research, elderly patients generally do not require routine age-based DOACs dose adjustment. Studies support safe and effective anticoagulation with edoxaban in elderly populations. For older adults, strict indication criteria should be applied, with individualized adjustments based on bleeding risk, renal function, concomitant medications, and overall health status, with close monitoring of coagulation parameters.

5. Pregnancy and Lactation

Pregnant or breastfeeding patients were excluded from DOACs clinical trials. Animal studies have demonstrated reproductive toxicity and fetal developmental effects for dabigatran, edoxaban, and rivaroxaban, while no direct or indirect

harmful effects on fetal development have been confirmed for apixaban. Limited data suggest that rivaroxaban and dabigatran have acceptable milk excretion thresholds, whereas apixaban excretion in breast milk exceeds the maximum allowable range.

LMWH does not cross the placenta and remains the preferred anticoagulant for pregnant women. During breastfeeding, guidelines still do not recommend any DOACs, instead recommending LMWH, warfarin, acenocoumarol, fondaparinux, unfractionated heparin, or danaparoid.

6. Malignancy

Cancer and its treatment are associated with hypercoagulable states and represent risk factors for VTE. VTE in cancer patients is termed cancer-associated thrombosis (CAT). LMWH has traditionally been the preferred anticoagulation therapy for cancer patients, but subcutaneous injection imposes economic burden and physical discomfort, reducing compliance.

Increasing evidence supports DOACs use for CAT treatment. The Hokusai-VTE Cancer and SELECT-D studies confirmed the efficacy and safety of DOACs for CAT, with subsequent evidence leading multiple international clinical practice guidelines to endorse DOACs as an alternative to LMWH monotherapy, and some even recommend DOACs over LMWH for initial CAT anticoagulation. A meta-analysis comparing DOACs and LMWH for CAT treatment included six RCTs and found that DOACs significantly reduced VTE recurrence risk without significant difference in major bleeding risk compared with LMWH, though clinically relevant non-major bleeding was higher (absolute risk increase 3.8%). All-cause mortality did not differ between groups. DOACs-treated patients had lower treatment discontinuation rates, suggesting better compliance. Among gastrointestinal malignancy patients, bleeding was more common with edoxaban or rivaroxaban, while no increased bleeding risk was observed with apixaban.

Another real-world study comparing observational data from two VTE registries across the warfarin and DOACs eras evaluated changes in clinical characteristics, management strategies, and long-term outcomes in CAT patients. Compared with the warfarin era, treatment strategies in the DOACs era changed significantly, with reduced risks of recurrent VTE and major bleeding, though DOACs-related gastrointestinal bleeding remains a clinically important issue.

In summary, growing evidence supports DOACs as an effective and safe treatment option for cancer patients with VTE. However, LMWH remains the preferred anticoagulant for high bleeding-risk cancer VTE patients, such as those with gastrointestinal cancers, chemotherapy-induced thrombocytopenia requiring frequent dose adjustment, patients receiving anticancer therapy with potential drug interactions, and those with brain metastases.

7. Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an acquired autoimmune disease characterized by thrombosis (in arterial, venous, or microvascular circulation) and obstetric events with persistent antiphospholipid antibody positivity. Warfarin is the standard anticoagulation therapy. Increasing research has introduced DOACs for APS anticoagulation, but DOACs efficacy may differ for arterial versus venous thrombosis. Potential reasons why DOACs may inadequately suppress thrombosis in APS include: (1) VKA inhibits multiple coagulation factors while DOACs inhibit only one; (2) DOACs have relatively short half-lives with lower trough concentrations, whereas VKA has prolonged action providing more stable anticoagulation; (3) Hyperfiltration in younger patients leads to suboptimal DOACs concentrations.

A real-world prospective cohort study evaluated apixaban versus warfarin in APS patients and found similar thromboembolic and bleeding risks between groups. The apixaban group had 4 thrombotic events (6.1%): 3 VTE and 1 ischemic stroke, while the warfarin group had 12 events (14%): 9 VTE, 2 ischemic strokes, and 1 myocardial infarction. Major bleeding risk was similar. Thromboembolic events were more common in "triple-positive" APS patients (positive for antiphospholipid antibodies, lupus anticoagulant, and $ $2-glycoprotein antibodies). In the apixaban group, patients with higher baseline D-dimer levels experienced more thromboembolic events. A series of RCTs evaluating DOACs for secondary thrombosis prevention in APS found significantly increased subsequent arterial thrombosis risk with DOACs treatment. Related systematic reviews and meta-analyses indicated increased arterial thrombosis risk with DOACs but no difference in VTE or major bleeding risk compared with VKA.

Currently, VKA remains the recommended first-line anticoagulant for APS patients, particularly for "high-risk" APS patients (triple-positive, arterial thrombosis, small-vessel thrombosis or organ involvement, and antiphospholipid antibody-related cardiac valvular disease). Whether DOACs can replace VKA, or whether DOACs may be selected for APS patients with VTE phenotype, requires more evidence.

8. Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but serious complication of pulmonary embolism requiring lifelong anticoagulation. The 2019 European guidelines for acute pulmonary embolism still recommended VKA for CTEPH patients due to lack of large-scale safety and efficacy data for both VKA and DOACs. As DOACs have proven effective in preventing VTE recurrence after acute pulmonary embolism, increasing numbers of CTEPH patients are receiving DOACs. One study found that the proportion of CTEPH patients taking DOACs increased from <1% to 55% over 10 years.

Recent research on DOACs in CTEPH patients has increased, but safety and efficacy data remain inconsistent. Researchers from the University of California

San Diego performed retrospective histopathological analysis of pulmonary endarterectomy (PEA) specimens from 40 CTEPH patients. Acute or subacute thrombus evidence was observed in 6.7% of the VKA group versus 13.3% in the DOACs group. After adjusting for age, race, sex, and APS presence, the risk of recent thrombus was potentially 2-fold higher in the DOACs group, suggesting insufficient DOACs efficacy in CTEPH treatment. However, this was a retrospective study with relatively few patients and potential selection bias. A meta-analysis showed no significant difference in all-cause mortality, VTE recurrence, or major bleeding between VKA and DOACs groups. Another study comparing VKA and DOACs after PEA found comparable hemodynamic and functional improvement, similar survival, and equivalent major bleeding events, but higher VTE recurrence with DOACs than VKA.

Consequently, the Chinese Guidelines for Diagnosis and Treatment of Chronic Thromboembolic Pulmonary Hypertension (2024 Edition) recommend cautious DOACs application in specific populations, such as APS patients and post-PEA patients, with warfarin preferred.

Conclusion

DOACs have ushered in a new era of anticoagulation therapy. Their significant advantages have rapidly established them as first-line treatment options. However, in certain special populations, DOACs application requires more evidence, and traditional anticoagulation regimens still play an indispensable role. Anticoagulation strategies must integrate individual patient factors with real-time assessment of the benefit-risk ratio between anticoagulation and bleeding, with close monitoring and continuous adjustment to maximize clinical benefit. Well-designed, larger-scale RCTs and real-world studies are needed to provide robust evidence for individualized treatment and long-term management strategies in special populations.

Author Contributions: XIAO Yao was responsible for conceptualization, literature collection, and manuscript drafting. WAN Jun was responsible for manuscript revision, quality control, overall article supervision, and project administration.

Conflict of Interest: None declared.

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(Received: November 19, 2024; Revised: January 26, 2025) (Editor: KANG Yanhui)

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