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REVIEW

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An update on applications and limitations of direct oral anticoagulants

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Abstract

A major advancement in the field of medicine has been the introduction and usage of direct oral anticoagulants (DOACs) such as dabigatran (Pradaxa), apixaban (Eliquis), and rivaroxaban (Xarelto). DOACs have been increasing in popularity for mainstay anticoagulation pharmacotherapy and are being preferred by physicians over warfarin due to their rapid onset, fewer drug and food interactions, and lack of frequent blood monitoring. DOACs have been indicated in the management of thromboembolic conditions and have been extensively researched in various medical trials and studies before the approval of dabigatran (Pradaxa) in 2010 by the FDA. DOACs, like warfarin, are associated with a risk of bleeding, requiring clearance of the drug from the bloodstream or administration of reversal agents. It is important for physicians to familiarize themselves with the various types of DOACs and their dosages, along with their advantages and disadvantages in comparison to other non-DAOC classes of medications before incorporating them into their patient management plans.

Keywords DOACs, Apixaban, Nonvalvular atrial fibrillation, Rivaroxaban, Factor Xa, Warfarin

Introduction

History of the evolution of oral anticoagulants over decades included the discovery of warfarin in the 1940s, dabigatran in 2010, rivaroxaban in 2011, and apixaban in 2012 followed by edoxaban in 2014 [1]. Dabigatran was the first US FDA-approved oral anticoagulant for nonvalvular atrial fibrillation and was subsequently studied for other indications [2]. Vitamin K antagonists such as coumadin were the only known oral anticoagulant for decades until the recent introduction of DOACs which target the specific steps of the coagulation cascade, are efficacious, and can be used without regular monitoring [3], but it has been found that DOACs have some interaction with food particles like St. John Worts and dietary fiber [4]. The widely used oral anticoagulants include warfarin, phenprocoumon, acenocoumarol which acts as a vitamin K antagonist, dabigatran, a thrombin inhibitor, and factor Xa inhibitor including apixaban, edoxaban, and rivaroxaban and commonly used parenteral anticoagulants include heparin, thrombin inhibitors (bivalirudin, argatroban) and fondaparinux [5]. DOACs like dabigatran, apixaban, edoxaban, and rivaroxaban are used for the prevention and treatment of arterial and venous thromboembolic diseases, prevention of stroke and systemic embolism in non-valvular atrial fibrillation (NVAF), prevention of recurrent VTE, thromboprophylaxis in major orthopedic surgeries including knee and hip arthroplasty, and treatment of left ventricular (LV) thrombus [6, 7]. A meta-analysis of 14 studies and 2498 patients found the use of DOACs as non-inferior to vitamin K inhibitors with a better safety profile and patient quality of life [8]. The indication associated dosage of DOACs is tabularized in (Table 1) [9]. A newly studied indication for use of DOACs is the role of low-dose

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Table 1 Indications and the dose regimen for usage of DOACs

DOAC	VTE treatment and prophylaxis	Non-valvular atrial fibrillation	Prophylaxis of VTE post hip surgeries	Renal dosing in ESRD
Apixaban (Eliquis)	10 mg twice daily for 1 week, then 5 mg twice daily	5 mg twice daily	2.5 mg twice daily	5 mg twice daily CrCl > 50 mL/min; or 2.5 mg twice daily for those with any two of the following: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL. Dose adjustment is required in patients with CrCl < 15 ml/min
Rivaroxaban (Xarelto)	15 mg twice daily with food for 3 weeks; then 20 mg once daily with food	20 mg once daily with food	10 mg once daily, with or without food	For AF, 20 mg once daily for CrCl > 50 mL/min and 15 mg once daily for CrCl ≤ 50 mL/min. Contraindicated in patients with CrCl < 15 ml/min
Edoxaban (Lixiana)	Parenteral anticoagulation for 5 to 10 days; then edoxaban 60 mg once daily	60 mg once daily		Contraindicated in patients with CrCl > 95 and < 15 mL/min; for CrCl 15–50 mL/min dose reduction to 30 mg once daily
Dabigatran (Pradaxa)	Parenteral anticoagulation for 5 to 10 days; then dabigatran 150 mg twice daily	150 mg twice daily	110 mg for the first day, then 220 mg once daily	Dose reduction to 75 mg twice daily in CrCl 15–30 mL/min, contraindicated in CrCl < 15 mL/min

rivaroxaban in the prophylaxis of LV thrombus post-PCI in anterior wall myocardial infarction [10]. Absolute contraindications to the use of DOACs include atrial fibrillation in mechanical valves as studied in the RE-ALIGN trial [11]. DOACS have been studied in inherited thrombophilia and are proven to be non-inferior to vitamin K antagonists but due to limited supporting data, the guidelines still do not recommend DOACs as the drug of choice for inherited thrombophilia, especially antiphospholipid syndrome [12]. Use of DOACs has been associated with a lower risk of major bleed or a clinically relevant non-major bleed in patients with chronic kidney disease or end stage renal disease (on dialysis) as compared to warfarin [13]. Dose adjustment is warranted for apixaban in patients with Creatinine clearance (CrCl) < 30 ml/min but dabigatran is avoided in patients with CrCl < 30 ml/min and drugs like betrixaban, edoxaban, and rivaroxaban are avoided in CrCl < 15 ml/min. Although previously DOACS were not used in patients post bioprosthetic valves implantation and repair, ENVALE study prove that DOACs were non-inferior to warfarin and DOACs were also previously not indicated in cancer-associated VTE, but its use was proven to be non-inferior to low molecular weight heparin (LMWH) in ADAM VTE trial [14–16]. The ARISTOPHANES study showed that apixaban, rivaroxaban, and dibigatran were superior to vitamin K inhibitors and increased event free time after 12 months of initiation [17].

There are limited studies on the effect of obesity on the pharmacokinetics and dynamics of DOACs; however, available evidence suggests the standard dose use of certain DOACs such as apixaban and rivaroxaban for VTE and AF in patients with BMI > 40 kg/m^2 and weight > 120 kg [15, 18, 19]. Apixaban and Endoxaban may be used in elderly patients (age > 75) for the treatment of NVAF [20]. Due to limited studies, the role of apixaban as an anticoagulant in pediatric patients, patients with cancer, low or high body BMI, identified thrombophilia, heparin-induced thrombocytopenia (HIT), and poor renal function is questionable [21]. A recent open-label, non-inferiority trial by Agnelli et al. concluded that apixaban was non-inferior to subcutaneous dalteparin for the treatment of cancer-associated venous thromboembolism without an increased risk of major bleeding. DOACs are relatively contra-indicated in patients with cancer due to increased risk of bleeding, but this trial showed comparable rates of bleeding including major gastrointestinal bleeding in both the patient arms. Patients with high thromboembolic risk like lung and colorectal cancer were well represented in this study and no anticancer therapy was excluded, which lead to the inclusion of patients receiving various cytotoxic and biologic therapies. Patients with a diagnosis of brain cancer with metastasis and acute leukemia were excluded from this study due to increased risk of bleeding and hence the results are not generalizable to this group [22].

The guidelines prohibit the use of DOACs in post-bariatric patients due to concerns regarding absorption. However, there are limited studies to validate this concern and a recent institutional retrospective review showed no recurrent VTE after apixaban use and only 1 case with rivaroxaban [23]. Another cohort of 110 patients showed safety in the use of rivaroxaban as a prophylactic agent in patients undergoing bariatric surgery at a 6 months follow-up [13].

The use of DOACs is associated with major side effects like fatal bleeding (0.06 to 0.30%) spontaneous hemorrhage including gastrointestinal bleeding (0.35 to 2.09%), intracranial hemorrhage (0.09 to 0.51%), and renal disease progression [6, 24].

The presence of gastrointestinal bleeding (GIB) does not preclude high-risk patients from receiving DOACs, but recognition of risk of GIB in order to take preventive measures or close monitoring and finally a benefit versus risk ratio discussion is of utmost importance [25]. The use of concomitant medications which increase the risk of bleeding in patients on DOACs and should be reviewed include NSAIDs, SSRIs or SNRIs, and norepinephrine. Studies regarding the reinstitution of DOACs in patients with ICH recommend holding anticoagulation for at least 4 weeks [26]. This article aims not only to highlight the various types of DOACs, their mechanisms of action, their indications, and advantages but also sheds light on the risks and disadvantages associated with them relative to other anticoagulant medications.

Pharmacokinetics and pharmacodynamics of DOACs

The common pathway of the coagulation cascade starts with factor Xa. Factor Xa is trypsin like serine protease, and is essential for conversion of prothrombin to thrombin, which in turn is needed for clot formation. Thrombin is an enzyme which activates platelets and catalyzes the conversion of fibrinogen to fibrin (Fig. 1). Antithrombin III is a serine protease inhibitor and functions as a natural anticoagulant, mainly inhibiting activity of factor Xa and II [27]. In an attempt to overcome the nuances associated with warfarin use, DOACs like apixaban, rivaroxaban, edoxaban, and dabigatran were developed, and it was hypothesized that inhibition of factor Xa or thrombin directly can prevent clot formation as shown in Fig. 1 below [28].

Apixaban is a neutral bicyclic pyrazole with a molecular weight of 459.5 g/mol. It inhibits platelet activation and clot formation via direct, selective, and reversible inhibition of free as well as clot-bound factor Xa [29]. Additionally, antithrombin III is not needed for its

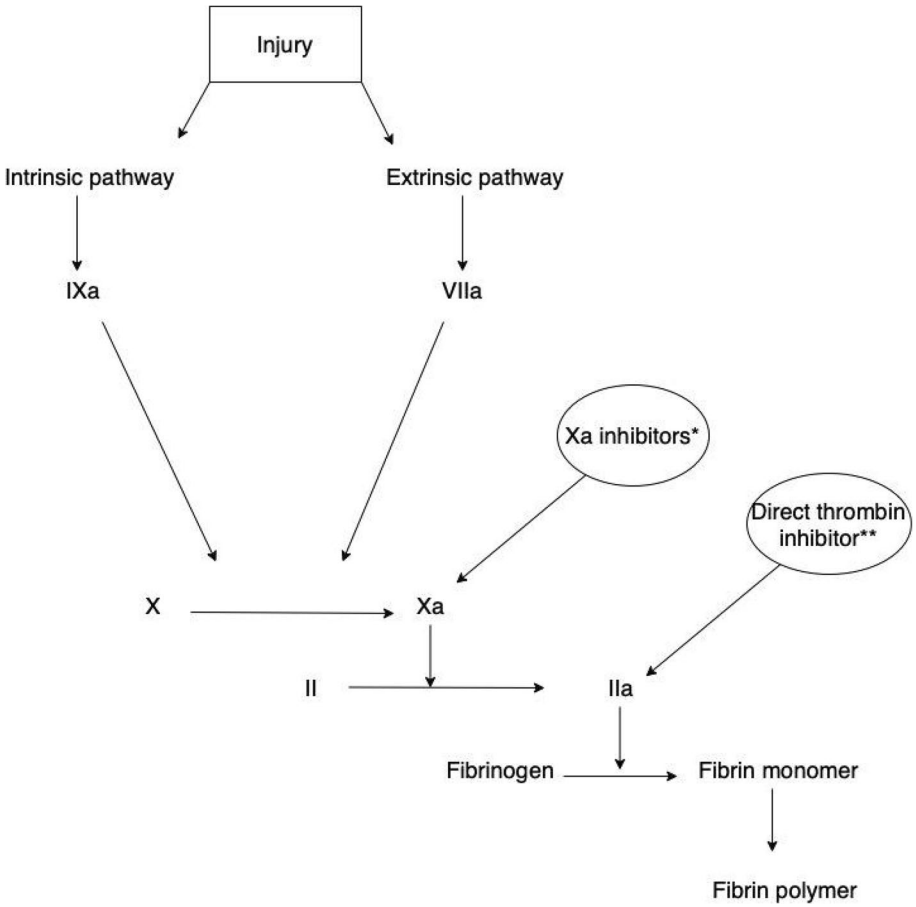

Fig. 1 Simplified coagulation cascade. *Apixaban, Rivaroxaban, Edoxaban. **Dabigatran

antithrombotic activity [30]. Apixaban has no direct effect on platelet aggregation but by inhibiting thrombin activity, it indirectly inhibits thrombin-induced platelet aggregation [31]. Given that it has a half-life of approximately 8–15 h, and it takes 5 half-lives for anticoagulation to resolve, the timing of last dose can be used as a rough estimate to gauge the anticoagulation effect.

Rivaroxaban competitively inhibits free factor Xa, factor Xa bound to prothrombinase as well as factor Xa bound to clot [32], thus inhibiting thrombin and clot formation. Similar to apixaban, it has no direct effect on platelet aggregation and antithrombin III is not required to exert antithrombotic effects [33]. It has a half-life of 5–9 h and anticoagulation usually resolves 1–2 days after the last dose.

Edoxaban is a selective, competitive, dose-dependent, and direct inhibitor of free as well as prothrombinase complex bound factor Xa with a rapid onset of action around 1.5 h [34]. Similar to apixaban and rivaroxaban, it also inhibits thrombin-induced platelet aggregation.

Dabigatran is a direct and reversible thrombin inhibitor. It competitively and selectively binds to the active site of free, clot bound as well as fibrin-bound thrombin, thus inhibiting the conversion of soluble fibrinogen to insoluble fibrin [35]. Additionally, by binding to thrombin, dabigatran inhibits thrombin-induced platelet aggregation [36]. Dabigatran etexilate is a prodrug and is metabolized into the active compound dabigatran by enzymes in the plasma and liver [37]. It is a fast-acting drug with peak plasma concentration achieved in 1–2 h with a half-life of 12–17 h in comparison to the half-life of the other DOACs as mentioned in Table 2. Timing of the last dose aids to gauge the effect of anticoagulation as it is usually resolved after

Table 2 Pharmacokinetics of DOACs

Drug	Half life	Time to elapse 5 half lives
Apixaban	8–15 h	1.5–3 days after last dose
Rivaroxaban	5–9 h	1–2 days after last dose
Edoxaban	6–11 h	1.3–2 days after last dose
Dabigatran	12–17 h	2.5–3.5 days after last dose

5 half-lives. In patients with normal renal function, the following considerations apply [38].

For apixaban, rivaroxaban, and edoxaban, anti-factor Xa levels, though not commonly available, can be used to assess anticoagulation effects [39]. As the usage of DOACs is increasing, so are the life-threatening bleeds associated with them, it is imperative to be familiar with the current guidelines for the reversal of DOACs to prevent any major bleeds.

Treatment and role of DOAC

DOACs like dabigatran, rivaroxaban, apixaban, and edoxaban are used to lower stroke and embolism risk in NVAF, DVT, and PE treatments. Betrixaban is used for VTE prophylaxis in adults hospitalized for acute illnesses [15, 40]. Some limitations of DOAC include higher cost, shorter half-life, and limited specific reversal agents and monitoring tests**.** The cost of DOACs has increased from 200 to 400 USD from 2011 to 2020 [41]. DOAC reversal is indicated in life-threatening bleeds, trauma, emergency surgeries, or invasive procedures. Reversal can be accomplished by drug removal, non-specific reversal agents, and specific reversal agents. Currently, Idarucizumab and Andexanet are the only FDA approved specific reversal agents for DOACs. Other off-label management options include clotting factors such as prothrombin complex concentrate (PCC), activated platelet complex concentrate (aPCC), and recombinant factor VIIa [40]. Four factors' PCC, also known as Kcentra, contains inactive forms of 4 coagulation factors II, VII, IX and X along with protein C and S, and has been studied extensively in vivo in humans. Randomized controlled trials have shown that a maximum dose of 50 U/kg can be used for emergency reversal of anticoagulation with factor Xa inhibitors [42, 43].

Idarucizumab

Idarucizumab is a humanized monoclonal antigen fragment, first approved in 2015, and is the only reversal agent that binds with direct thrombin inhibitor dabigatran to inhibit its effect [44]. The recommended dose of Idarucizumab is 5 g [45] and the cost for two 2.5 g/50 mL vials is approximately $3662 [46].

Idarucizumab has a high affinity for dabigatran, which is 350 times greater than thrombin. It does not bind thrombin substrates and thus does not enhance thrombin-mediated feedback of coagulation [47]. The initial half-life is 45 min and depending on the dose some amounts can be detected in the blood after 24 h [48]. Idarucizumab reversed the effects of dabigatran in the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study [49]. This study looked at the effects of 5 g of IV Idarucizumab in patients that required dabigatran reversal. Idarucizumab's effect lasted for 24 h in most patients. Group A ($n=301$) consisted of individuals who had uncontrolled bleeding (45.5% GI bleed and 32.6% intracranial hemorrhage). Group B ($n=202$) consisted of individuals that required urgent surgery or an invasive procedure that could not be delayed by more than 8 h. dTT or ECT tests were used, and they showed a 100% median maximum reversal of dabigatran within 4 h after the idarucizumab use. Individuals assessed in group A took 2.5 h (median time) to stop their respective bleedings. In group B, the individuals had their procedures 1.6 h (median time) after the first infusion of idarucizumab. Additionally, the study showed that reversal was quick and occurred independently of age, sex, renal function, and dabigatran concentration at baseline. There were some side effects of the drug. At 90 days thrombotic events occurred in 6.8% of patients. The mortality rate was similar in both groups, 18.8% in group A and 18.9% in group B [49].

Andexanet

Andexanet is a modified recombinant inactive form of factor Xa protein. It binds specifically to and sequesters factor Xa inhibitors (rivaroxaban, apixaban, and betrixaban) to rapidly reverse their effect in a dose-dependent manner. It has a half-life of 1 h [50]. It was approved in 2018 for the reversal of apixaban and rivaroxaban in patients with uncontrolled or life-threatening bleeding or in the event of emergent surgeries [51].

Andexanet showed a reversal of apixaban and rivaroxaban in healthy individuals (mean age 57.9 years old) in the ANNEXA-A and ANNEXA-R trials. The participants in the ANNEXA-A trial received 5 mg of apixaban twice a day ($n=48$) and the participants in the ANNEXA-R trial received 20 mg of rivaroxaban once a day ($n=53$). This was a randomized, double-blind, placebo-controlled trial. All the patients were divided into groups that received either Andexanet or a placebo. Both trials showed that a bolus of Andexanet, with or without the addition of a 2-h infusion, reduced anti–factor Xa activity more than the placebo. Andexanet's effect lasted for 2 h with the bolus and continued for a longer period of time with the addition of the 2-h infusion. Additionally, Andexanet also restored thrombin generation within 2–5 min of treatment [52].

ANNEXA-4 looked at the effects of Andexanet bolus followed by 2-h infusion on patients ($n=352$, mean age of 77 years old) who had major bleeding events within 18 h after taking apixaban, rivaroxaban, edoxaban, or enoxaparin. Most patients in this trial had cardiovascular disease and the bleeding was mostly intracranial ($n=227$) or gastrointestinal ($n=90$). In patients who had received apixaban and rivaroxaban, the median

anti–factor Xa activity decreased 92% after the Andexanet bolus. In the 249 patients evaluated for hemostasis status, 82% ($n=204$) had excellent or good hemostasis after 12 h of administration. At 30 days, 10% ($n=34$) had a thrombotic event and 14% (=49) died. This study did not show any relationship between reduction in anti-factor Xa activity and hemostatic efficacy overall [53]. The dose studied for off-label use in patients to reverse the effect of edoxaban or betrixaban is 800 mg IV bolus administered at a rate of 30 mg/min, followed by an IV infusion of 8 mg/min for up to 120 min. For patients who received apixaban or rivaroxaban, the dose for reversal of the anticoagulant effects may require either a low dose which is 400 mg IV bolus at a rate of 30 mg/min followed by 4 mg/min, or a high dose which is 800 mg IV bolus followed by an IV infusion of 8 mg/min. If the drug administration was more than 8 h or ≤ 5 mg for apixaban and ≤ 10 mg for rivaroxaban within an 8-h window, a low dose of andexanet is indicated. Administration of >5 mg of apixaban or >10 mg of rivaroxaban within the 8-h period is an indication for reversal with a high dose of andexanet [54].

New reversal agent in development

Ciraparantag (PER977) is a small, synthetic, water-soluble molecule that can reverse the anticoagulant effects of low-molecular-weight heparin, unfractionated heparin, and DOACs. It acts by inactivating heparin and DOAC through noncovalent hydrogen binding and charge interaction. This promising reversal agent has undergone phase 1 and 2 trials which have shown reversals of DOACs in healthy individuals. Additionally, Ciraparantag (100–300) mg IV injectable dosage appears safe and well tolerated [55]. In the ongoing trials, the only drug-related adverse effects reported are periorbital and facial flushing which occurred in 74% of the patients who were administered Ciraparantag, and no serious thrombotic episodes or death have been reported [56].

However, more prospective studies need to be conducted to test the use of these drugs in patients with acute indications like major bleeds or emergency surgeries [56].

Post reversal complications

Some complications that may present after reversal include thrombotic events and death. These complications were seen in a small percentage of individuals in the ANNEXA-4 and REVERSE AD trials. There is also the risk of incomplete reversal. Overall, Andexanet and Idarucizumab have been shown to be mostly well-tolerated [49, 53]. They are generally safe to use and their ability to rapidly reverse the effects of DOAC allows for better management of major bleeding episodes.

Conclusion

The introduction of DOACs into clinical medicine and subsequent approval by the FDA in 2010 has proven to be greatly beneficial to the progression of anticoagulation medication. They are preferable over other anticoagulant medications as they present a lower risk of bleeding, ability to act rapidly from the time of initiation, lack of frequent monitoring, and have predictive pharmacokinetic properties. They can be used for both prophylactic and therapeutic treatment of thromboembolic events. DOACs are not exempt from their share of limitations with the most striking concern with these drugs being the potential risk of causing life-threatening bleeding conditions such as ICH and GIB. This results in the need for immediate removal of the drug through hemodialysis or administration of reversal agents. Idarucizumab and andexanet are specific reversal agents that bind to dabigatran and factor Xa to cause inhibitory effects, respectively. The shorter half-life and higher cost of DOACs relative to warfarin also prove disadvantageous. Overall, the use of DOACs has significantly contributed to the advancement of anticoagulation therapy and eventual patient well-being, having an ultimately net positive effect despite their limitations.

Abbreviations

AF	Atrial fibrillation
ANNEXA-4	A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors
ANNEXA-A	A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors-Apixaban
ANNEXA-R	A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors—Rivaroxaban
aPCC	Activated platelet complex concentrate
CrCl	Creatinine clearance
DOAC	Direct oral anticoagulant
dTT	Diluted thrombin time
DVT	Deep venous thrombosis
ECT	Ecarin clotting time
ENAVLE	Explore the Efficacy and Safety of Edoxaban in Patients After Heart Valve Repair or Bioprosthetic Valve Replacement
FDA	Food and Drug Administration
GI	Gastrointestinal
GIB	Gastrointestinal bleeding
HIT	Heparin induced thrombocytopenia
ICH	Intracranial hemorrhage
LMWH	Low molecular weight heparin
LV	Left ventricular
NSAID	Non-steroidal anti-inflammatory drug
NVAF	Non-valvular atrial fibrillation
PER977	Ciraparantag
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PE	Pulmonary embolism
rFVIIa	Recombinant factor VIIa
RE-ALIGN	A Randomised, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients After Heart Valve Replacement
RE-VERSE AD	Reversal Effects of Idarucizumab on Active Dabigatran
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
USD	United States dollar
VTE	Venous thromboembolism

Authors' contributions
The information on DOAC reversibility has been contributed by Sharon Wei, the introduction part has been written by Aanchal Sawhney, the pharmacokinetics has been written by Harshwardhan Khandait, the abstract and conclusion have been contributed by Amit Medha, figures and tables have been conceptualized by Vasu Gupta, and conceptualization of the idea and formatting has been done by Dr. Rohit Jain. The author(s) read and approved the final manuscript.

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