Editorial

Tecarfarin: A Novel Vitamin K Antagonist

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Vitamin K antagonists are used for the prevention of arterial and venous thrombosis since more than 60 years and were the most widely prescribed anticoagulants in the world.[1] Despite their unexcelled efficacy, the narrow therapeutic window is associated with many challenges in clinical practice.

Warfarin, a racemic mixture of (R)- and (S)-enantiomers, is metabolized by seven different isoenzymes of the cytochrome P450 system, making it prone to many food and drug interactions. Furthermore, other factors such as genetic polymorphisms (specifically CYP2C9 variants), age, concomitant diseases and renal function may reduce drug efficacy and increase the possibility of over- and under-dosing, associated with an enhanced risk of bleeding or thrombotic complications predominantly in the early phase of warfarin therapy.[2] Not least the inconvenient need for a dense monitoring of the international normalized ratio (INR) has spurred the development of newer anticoagulant agents.[3]

Unlike vitamin K antagonists, the direct oral anticoagulants target one specific factor, currently either factor IIa or factor Xa, and are more convenient to administer due to a fixed dose without routine monitoring.[4] Nonetheless, in some critical circumstances, for example, in emergency surgery or acute renal failure, the measurement of drug levels and the anticoagulant effect may become necessary.[5]

While non-vitamin K antagonist oral anticoagulants are as effective as warfarin to prevent stroke in non-valvular atrial fibrillation patients,[6] apixaban and dabigatran initiation was associated with significantly less major bleeding complications than warfarin in the early phase. In contrast to apixaban, initial rivaroxaban intake resulted in a higher bleeding risk.[7] Notably, some of the newer agents are associated with a higher incidence of gastrointestinal bleeding, which however can often be controlled by temporarily withholding treatment due to their relatively short half-lives. Dabigatran was less effective than warfarin in patients with mechanical heart valves[8] and also associated with an increased rate of bleeding events.[9]

In general, minimizing the bleeding risk includes precautions such as dose reduction in higher-risk populations (e.g., renal impairment) and to avoid non-vitamin K antagonist oral anticoagulants in patients with contraindications such as severe chronic kidney disease (creatinine clearance rate [CrCl] < 15 mL/min, for dabigatran < 30 mL/min).[5]

Chronic kidney disease is a circumstance that per se complicates anticoagulation. On the one hand, it occurs more frequently in patients with venous thromboembolism and arterial fibrillation. On the other hand, a low glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 vice versa increases the risk of stroke and venous thromboembolism. Oral anticoagulants are known to be beneficial in patients with chronic kidney disease, but despite the recommendation to use vitamin K antagonists in severe CKD there are several concerns regarding their safety in this patient population. Among others, comorbidities may increase the risk for thrombotic and bleeding complications, and concomitant drugs and uremic toxins are likely to interfere with the metabolism of (S)- and (R,S)-warfarin mediated by the CYP450 system, requiring dose adaptions according to GFR-dependent algorithms. Regarding all these drawbacks, there is a strong need for an alternative to warfarin in this clinical setting.[10]

One possible alternative is presented in this issue of *Thrombosis and Haemostasis*: Albrecht and colleagues describe the pharmacokinetics of tecarfarin—a novel vitamin K antagonist under development—in patients with severe chronic kidney disease.[10]

Tecarfarin (ATI-5923) is a structural analogue of warfarin with the same mechanism and duration of action. As a non-competitive vitamin K epoxide reductase (VKOR) antagonist, tecarfarin impairs the activation of the vitamin K–dependent clotting factors II, VII, IX and X. Like for warfarin, anticoagulant efficacy is monitored using the INR. Unlike warfarin, which is metabolized by the CYP450 pathway, tecarfarin undergoes hydrolysis mediated by human carboxylesterase 2 (hCE-2), yielding a single inactive carboxylic acid metabolite (ATI-5900),[3,11] which is excreted by the kidney. Since hCE-2 is unlikely inhibited by renal

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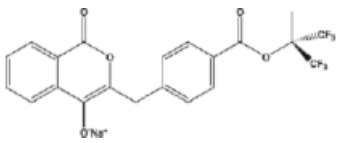
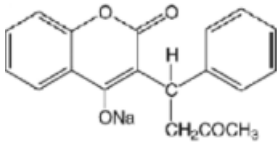
Table 1 Major differences between the oral anticoagulants tecarfarin and warfarin

	Tecarfarin	Warfarin
Structural formula		
Monitoring	International normalized ratio (INR)	INR
Metabolism	Hydrolysis mediated by hCE-2	CYP450 pathway (seven different enzymes)
Genetic variations	No relevant variations known	CYP2C9
Food and drug interactions	Unlikely	Prone to many interactions

Abbreviations: CYP450, cytochrome P450; CYP2C9, cytochrome P450 2C9; hCE-2, human carboxylesterase 2.

failure and chronic kidney failure is not expected to affect tecarfarin clearance, probably a more stable anticoagulation could be achieved in this specific patient population,[10] while drug interactions mediated by the CYP450 system may be eliminated.[11]

Furthermore, anticoagulant activity of tecarfarin is unaffected by genetic variations in CYP2C9. Reducing the early dosing inter-subject variability in plasma levels and in therapeutic response, tecarfarin may decrease the risk of bleeding and minimize adverse effects due to over- and under-dosing. Although there was no significant difference in maintenance doses between CYP2C9 genotypes, doses varied between VKORC1 genotypes. Plasma concentrations of tecarfarin correlated with VKORC1 genotype, with the GG genotype having twofold higher plasma concentrations than the AA genotype, resulting in twofold difference in maintenance dose. Importantly, there was no relationship between plasma concentrations of tecarfarin and INR. Therefore, tecarfarin does not appear to have any special advantages over warfarin in subjects with VKORC1 polymorphisms and a genotype-guided initial dosing may be useful in this subset of patients.[12]

Beyond the reduced probability for CYP450-mediated drug interactions and the promising results in chronic kidney disease, it remains questionable if tecarfarin exhibits any further advantages over warfarin (►**Table 1**). In the EmbraceAC trial, tecarfarin did not meet the primary endpoint so that superiority of tecarfarin over warfarin for time in therapeutic range (TTR) was not demonstrated in patients who require chronic oral anticoagulation. Treatment emergent adverse events were reported for 88% of patients on warfarin and 90% on tecarfarin. Both drugs exhibited comparable TTR, which correlates with clinical outcome, and no difference in the frequency of clinical events, concluding that only patients with CYP2C9-variant alleles or taking CYP2C9-interacting drugs may benefit from tecarfarin.[13]

A second study performed by Albrecht and colleagues published in *Thrombosis and Haemostasis* describes the pharmacokinetics and pharmacodynamics of tecarfarin after single and multiple dosing in healthy volunteers. Single doses of tecarfarin up to 40 mg are associated with a dose proportionality in drug concentrations and half-life. The maintenance dose required to keep the target INR range of 1.7 to 2 varies between 10 and 20 mg, and the INR declines within 1 to 3 days after cessation of tecarfarin.[14] However, further studies are required to investigate the effects of tecarfarin after multiple dosing in chronic kidney disease and patients with mechanical heart valves. The inactive metabolite (ATI-5900), which is excreted by the kidney, was present at concentrations approximately 10% of the parent drug in healthy volunteers[14] and at twofold higher concentrations in chronic kidney disease as compared with healthy volunteers.[10] Hence, there is a need to characterize its detailed profile and to exclude any toxic effect of the metabolite, particularly after multiple dosing in high-risk populations such as chronic kidney patients.

Furthermore, tecarfarin is known to inhibit CYP2C9-mediated metabolism, at least in transfected cells,[12] and it remains to be answered if the metabolite also has an inhibitory effect on CYP450 enzymes. Therefore, it should not be forgotten that a potential to cause drug–drug interactions in any manner can definitively not be excluded for tecarfarin.

Once all of these issues have been addressed in subsequent trials, tecarfarin may become an interesting alternative to achieve a stable anticoagulation in patient populations, which cannot be satisfactorily treated with good old warfarin.

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