

## Is the use of warfarin becoming obsolete?

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**ARTICLE HISTORY** Received 9 January 2021; Accepted 14 April 2021

**KEYWORDS** VTE; thromboembolism; NOAC; DOAC

To the Editor,

Warfarin is a well-known vitamin K antagonist (VKA) established for decades for a variety of clinical indications, including venous thromboembolism (VTE), prevention of cardioembolic phenomena in the setting of atrial fibrillation (a-fib), and thromboprophylaxis in post-operative settings and chronic illnesses [1]. Warfarin is typically dosed once daily based on a targeted laboratory test known as prothrombin time (PT) and international normalized ratio (INR) [1]. Depending on the clinical indication, warfarin dosing is adjusted to target a specific INR range value, necessitating frequent INR value checks, requiring interpretation and medical decision-making to adjust the warfarin dosing to target the desired INR level [1]. Although newer monitoring strategies may improve the safety of warfarin, including home INR testing, increased duration between INR testing in stable patients, and introduction of novel surveillance methods not impacted by factor VIIa, unpredictable INR variation and its broad interaction patterns still make warfarin usage unpredictable [2–4]. Possibly dangerous and challenging, it poses a see-saw risk of thrombosis or bleeding based on INR levels [1].

In the early 2010s, the discovery of new anticoagulants has revolutionized our approach and prescribing patterns. Direct oral anticoagulants (DOACs) started with dabigatran, a direct thrombin inhibitor; with time, the class was broadened to include rivaroxaban and apixaban, factor-Xa inhibitors, and later betrixaban and edoxaban [5].

DOAC use is increasing every year in the USA (US), and close to 6 million US adults are on DOACs therapy [3]. In a recent analysis of first-time anticoagulant users amongst 137 203 VTE patients, in early 2012, 98.7% were prescribed warfarin, which dropped to 17.5% in late 2017; over the same period, DOACs prescriptions increased rapidly, with rivaroxaban and apixaban accounting for over 80% of first-time oral anticoagulant prescriptions in

late 2017 [6]. Compared to warfarin, DOACs are recommended over VKAs for stroke prevention in patients with non-valvular a-fib [7] and treatment of venous thromboembolism [8] since they are associated with half the risk of intracranial hemorrhage, which carries a high risk of mortality or subsequent disability and they do not require any monitoring [1]. Simultaneously, DOAC superiority over warfarin has not been demonstrated in clinical trials preventing thrombotic events, and the inherent risk of bleeding is not unknown [1,2]. An additional impairment in widespread adoption is high costs and insurance coverage compared to warfarin for many patients in the US and across the world (Table 1).

While VKA had established antidotes (vitamin k, fresh frozen plasma, or prothrombin complex concentrate) with additional favorable profiles such as lower cost and safety profile, DOACs lacked this benefit for years. While many have used 4-factor cryoprecipitates and fresh frozen plasma to reverse severe bleeding from DOACs, the rise of idarucizumab and andexanet-alfa as bonafide reversal agents for dabigatran and factor-Xa inhibitors due to cost reduction and widespread availability have diminished this concern [9]. Additionally, warfarin is a contraindication for fibrinolytic use in patients with ischemic strokes, only if INR >1.7, while current use of direct thrombin inhibitors or direct factor Xa inhibitors is an absolute contraindication [10].

The majority of guidelines, including the American Society of Hematology (ASH), continue to include warfarin for anticoagulation or thromboprophylaxis; however, DOACs are preferred [8]. In their last report, the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society reiterated warfarin as a viable anticoagulant for a-fib treatment with a preference to DOACs except in moderate to severe mitral stenosis or mechanical heart valve [7]. Warfarin continues to be used in a handful of specific patient populations, including

**Table 1.** The market price for the different DOACs, Warfarin and PT/INT testing in the US.

|   | Rixaroxaban | Apixaban | Dabigatran | Betrixaban | Edoxaban | Warfarin | PT/INR laboratory test |
|---|-------------|----------|------------|------------|----------|----------|------------------------|
| Market Price in US dollar for month supply of standard dosing | 564.57\$    | 564.52\$ | 551.99\$   | 600\$      | 471.52\$ | 12.53\$  | 4 to 31\$              |

triple-positive antiphospholipid syndrome, valvular a-fib, and patients with prosthetic cardiac valves due to the paucity of DOAC safety data [7,11]. Despite existing guidelines still recommending warfarin as an anticoagulant option for VTE treatment with and without cancer, cardioembolic illnesses in the setting of a-fib or thromboprophylaxis, a design trend amongst newer clinical trials are the use of LMWH instead of warfarin in the comparative arm [12,13]. This rapid shift limits our ability to develop improved methods of using warfarin in the DOAC era.

In conclusion, warfarin has been one of the earliest and heavily used anticoagulants for many clinical indications in the setting of anticoagulation and thromboprophylaxis for many decades. Over the past decade, DOACs have paved the way as the mainstay anticoagulant for numerous conditions, overcoming some of the limitations of warfarin with a net improvement in patient quality of life. Practice patterns, insurance reimbursements, and society guidelines are slowly reflecting these changes.

### Disclosure statement

No potential conflict of interest was reported by the author(s).

### Funding

No financial disclosure to declare.

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