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# Breaking bad: Higher risk of osteoporosis with vitamin K antagonists compared to direct oral anticoagulants in patients with atrial fibrillation

Atrial fibrillation (AF) is the predominant form of heart rhythm disorder and a leading cause of stroke. Therapy with antiarrhythmic drugs is still suboptimal and is associated with substantial toxicity [1]. During AF, atria may not empty completely into the ventricle, leading to blood stasis and atrial thrombus formation. If clot fragments detach and lodge in the arteries to the brain, ischemic stroke results. Anticoagulation (OAC) for stroke prevention is, although complex in the individual patient population, therefore a mainstay of AF clinical management. The direct oral anticoagulants (DOAC) are progressively replacing the classical vitamin K antagonist (VKA) warfarin, but whole-scale adoption in real-world practice remains slow. This can be attributed in part to regional differences in availability and cost reimbursement. Cost-effectiveness of DOAC compared to warfarin is tightly linked with time in therapeutic range (TTR) [2]; this factor may have delayed subsidization of DOAC-based treatments in regions where patients on warfarin are generally well-managed. There is also a wide-spread skepticism regarding the varied bleeding risk amongst the DOAC [3], and practitioner unfamiliarity with DOAC pharmacology. A comprehensive review of DOAC pharmacokinetics and how this aspect must be considered in clinical use was recently published [4]. While the new agents certainly show less propensity for *food*-drug interactions, *drug*-drug interactions are a major problem, as with traditional VKA. Moreover, individual DOAC vary greatly in terms of hepatic metabolism and renal excretion rates, making them unsuitable for certain co-morbidities [5]. While high plasma protein binding (up to 97%) is considered a critical cause of warfarin drug-drug or disease interactions [6], it must be noted that this pharmacokinetic downside applies also to rivaroxaban and apixaban, with up to 95% and 87% protein binding respectively. Given the extensive polypharmacotherapy of patients taking DOAC, protein binding should not be neglected when considering potential shifts in the pharmacokinetics of these agents.

A significant consideration for the conservative choice to remain with warfarin is that data on comparative risk-benefit profiles in specific patient populations are still limited [5]. Patients with concomitant AF and acute coronary syndromes, cancer or on dialysis for example represent difficult scenarios for anticoagulant treatment [7–10]. Particularly in Asian patient populations, older patients or those with higher $CHA_2DS_2$-VASc scores, who might actually benefit most from a DOAC-based treatment, the prescription patterns in favor of DOAC over warfarin are evolving only slowly [11]. Even in European countries like Germany, use of the VKA phenprocoumone remains high, particularly for the management of patients with AF and cancer [8]. This is despite the accumulating evidence supporting superiority of DOAC in patient subpopulations, such as those with very low body weight or history of intracranial bleeding [12,13], or in women who generally present with a higher risk of stroke than male patients with AF [14].

Putting their anticoagulant actions aside, the DOAC may also present advantages over warfarin in terms of pleitropic actions including potential antiarrhythmic effects [15]. VKA barely penetrate tissues, but the tissue distribution of DOAC, and hence access to cellular sites of action of thrombin and activated factor X, is by comparison quite considerable [4]. Various DOAC therefore exert coagulation-independent effects by preventing coagulation factor-stimulated signaling of protease-activated receptors in different organs including the heart [15]. In this issue of the *International Journal of Cardiology Heart & Vasculature*, Akhtar and colleagues highlight a further advantage of DOAC that has until recently been largely overlooked in its potential importance [16]. In a brief but comprehensive overview of the available literature, the authors identify a lower risk of osteoporosis in patients receiving DOAC compared to warfarin. VKA, by inhibiting vitamin K-dependent carboxylation of osteocalcin, can promote bone remodeling and fragility [17], although definitive data on bone tissue modification by VKA remains lacking [18,19]. More clear and convincing by contrast is the evidence for a lower risk of osteoporosis with DOAC versus warfarin as reviewed by Akhtar et al. [16]. During the writing of this editorial, another retrospective cohort study was published [20] that confirms the significantly reduced osteoporosis risk in patients with AF treated with rivaroxaban or apixaban, compared to warfarin – or dabigatran for that matter. This may be highly relevant for the treatment of frail and elderly patients, who are prone to falls, and whose propensity for both bone fractures and bleeding are much higher than in other patient groups. Studies like this by Akhtar et al. [16] clearly highlight the importance of considering the expanded personal risk profile, including osteoporosis of each patient when choosing the best suitable anticoagulant.

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