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Correspondence

Association between direct-acting oral anticoagulants vs. warfarin with the risk of osteoporosis in patients with non-valvular atrial fibrillation

Non-valvular atrial fibrillation (NVAF) is the most common arrhythmia causing significant morbidity and mortality secondary to cardioembolic complications, mainly stroke. Direct-Acting Oral Anticoagulants (DOACs) are the newer class of anticoagulants for the prevention of cardioembolic complications in NVAF patients and currently approved DOACs for stroke prophylaxis include dabigatran, rivaroxaban, apixaban, and edoxaban. DOACs were introduced to circumvent the limitations associated with warfarin, including the need for international normalized ratio (INR) monitoring, overlapping with the therapeutic heparin dosing until the achievement of target INR, significant food and drug interaction, and an unpredictable anticoagulant effect. Osteoporosis, a disease characterized by reduced bone mineral density leading to an increased propensity for fractures, is being increasingly recognized as significant comorbidity in NVAF patients given the common association with old age. Moreover, the presence of osteoporosis leading to fragility and increased susceptibility to falls and fractures has theoretically been proposed to predispose to anticoagulant induced bleeding complications in elderly patients with NVAF. It may also lead to underutilization of the anticoagulation with an increased risk of strokes in such patients. Several studies have highlighted the role of prolonged warfarin therapy in predisposition to osteoporosis [1–4]. Multiple mechanisms have been proposed to explain the association of warfarin use with osteoporosis. Warfarin is an endogenous vitamin K antagonist and acts by inhibiting the γ-carboxylation of vitamin K dependent proteins, including coagulation factors (II, VII, IX, and X), Osteocalcin (OC), matrix G1a protein (MGP) and growth arrest-specific 6 (GAS6). OC plays an important role in bone matrix formation, and inactivation of OC interrupts ossification. The fraction of imperfect γ-carboxylated OC is referred to as undercarboxylated OC (ucOC), which serves as a marker of vitamin K deficient state and a cut-off value of serum ucOC of 4.5 ng/ml has been proposed by a study to determine vitamin K insufficiency or deficiency for osteoporotic fractures [5]. Moreover, the dietary restriction of vitamin K can also lead to dietary deficiency of folic acid and predispose to hyperhomocysteinemia, which promotes bone resorption through enhanced activity of osteoclasts in addition to inhibiting the osteoblast cells. Hyperhomocysteinemia can also promote the activity of matrix metalloproteinase leading to increased degradation of the extracellular bone matrix [1,4]. DOACs, given their vitamin K independent mechanisms of action, appears to be promising as a safer alternative to warfarin in reducing the risk of osteoporosis among NVAF patients. In an animal study, rats receiving warfarin for six weeks showed a greater degree of trabecular separation and reduced bone volume as compared to dabigatran and placebo based on histomorphic analysis of femur and vertebrae. Erosion depth was also significantly higher in warfarin-treated rats suggesting an increased osteoclastic activity [6]. Namba et al. demonstrated that replacing warfarin by rivaroxaban after one year of therapy in patients with NVAF resulted in significant improvement in the profile of bone markers from baseline, including the increase in bone alkaline phosphatase (BAP) and decrease in ucOC suggesting enhanced osteoblastic activity [4]. Lau et al., in their retrospective population cohort study demonstrated that long term dabigatran use (>1 year) was associated with a significantly lower risk of osteoporotic fractures as compared to warfarin among patients with NVAF. On subgroup analysis, they also reported that this statistically significant difference in terms of lower fracture risk with dabigatran also persisted with short term use (<1 year) [3]. In a recently published retrospective cohort study, Bindings et al. demonstrated that in patients with NVAF, the use of DOAC (dabigatran, rivaroxaban, apixaban, and edoxaban) for at least six months was associated with a significantly lower relative risk of any fracture, major osteoporotic fractures and initiating osteoporotic medications as compared to VKA over a follow-up period of 2 years. The analysis of the combined endpoint revealed that patients treated with DOAC had a significantly lower relative risk of experiencing any fracture or initiating osteoporosis medication as compared to VKA [1]. Similarly, Lutsey et al., in their retrospective study showed that DOACs, particularly apixaban was associated with a lower risk of fractures as compared to warfarin in patients with NVAF and this association was strongest in patients with baseline osteoporosis [7]. Gu et al., in their meta-analysis of 12 randomized controlled trials (RCTs) involving patients treated with DOAC and warfarin for NVAF and venous thromboembolism (VTE) showed that the long term use of DOAC (>1 year) was associated with a significantly lower risk of fractures as compared to warfarin in patient cohort of NVAF only, and this difference was not evident in short term use (<1 year).

While there is well-established literature suggesting the increased risk of osteoporosis with long term VKA therapy in patients with NVAF, there are also studies reporting no such association [8,9]. Misra et al., in their retrospective, propensity matched study, concluded that long term warfarin use (>1 year and >3 years) was not significantly associated with any fractures in NVAF patients as compared to non- warfarin users [9]. Similarly, a meta-analysis by Fiordellisi et al., including 22 observational studies and 1 RCT showed that VKA therapy for a period of >1 year was not associated with increased odds of fracture as compared to DOAC; however, they reported a small statistically significant odds of increased fractures associated with VKA use in females and elderly patients aged >65 years as compared to the controls. It is noteworthy that their study population was not restricted to NVAF [10].

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In conclusion, osteoporosis is a significant problem in patients with NVAF and may have important therapeutic implications in terms of selection of anticoagulation strategy. The association of VKA use with osteoporosis remains controversial despite the biological plausibility, and also, the duration of use to cause such an effect remains unclear. Recent observational studies have demonstrated the beneficial effect of DOAC on bone metabolism with reduced fractures as compared to VKA in patient cohorts with NVAF. Randomized controlled trials are needed to provide further evidence that will help to form a strategy for anticoagulation use based on baseline osteoporosis risk in this patient cohort.

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Tauseef Akhtar
Adrija Hajra
Poonam Bhyan
Raktim K. Ghosh
Dhrubajyoti Bandyopadhyay *
Wilbert S. Aronow
John's Hopkins University School of Medicine, Baltimore, USA
Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA
Cape Fear Valley Hospital, Fayetteville, NC, USA
Medstar Union Memorial Hospital, Baltimore, USA
Icahn School of Medicine at Mount Sinai/Mount Sinai St Luke's Roosevelt Hospital, Manhattan, NY, USA
Westchester Medical Center/NYMC, Westchester, NY, USA
* Corresponding author at: Icahn School of Medicine at Mount Sinai/Mount Sinai St Luke's Roosevelt Hospital, Manhattan, NY, USA.
E-mail address: dhrubajyoti.bandyopadhyay@mountsinai.org (D. Bandyopadhyay).
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