European Journal of Internal Medicine 62 (2019) e11–e12

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Horizontal vs. vertical dose reduction of direct oral anticoagulants in patients with non-valvular atrial fibrillation: definition and implications for practice

ARTICLE INFO

Keywords:
Atrial fibrillation
Direct oral anticoagulants
Dabigatran
Rivaroxaban
Apixaban
Edoxaban

To the Editor-in-Chief,

Post-marketing surveillance is being showing a widespread use of the lower doses of direct oral anticoagulants (DOACs), namely dabigatran 110 mg, rivaroxaban 15 mg, apixaban 2.5 mg, and edoxaban 30 mg, for the prevention of stroke/systemic embolism in patients with non-valvular atrial fibrillation (NVAF) [1]. Use of the lower doses has been reported inappropriate, that is, inconsistent with drug labeling, in as many as 57% of cases [1]. Inappropriate dosing, and especially underdosing, has been associated in turn, with unfavourable outcomes [1]. When interpreting the above findings, considerations on both pharmacology of DOACs, and design of phase III trials of DOACs against warfarin in NVAF [2–5] should be made.

As regards pharmacology, all four DOACs show a first-order kinetic, which means that the correlation between dose, plasma concentration, and anticoagulant effect is linear. Indeed, an inverse, and respectively direct, relationship between drug plasma concentration and probability of stroke/systemic embolism and major bleeding has been shown for both dabigatran and edoxaban [6,7]. The dabigatran dose of 150 mg, which is 36% higher than 110 mg dose, is associated to a proportional (approximately 40%) increase of drug mean plasma concentration [6]. Halving the dose of apixaban from 5 to 2.5 mg, is associated to an approximate 50% proportional reduction of maximum drug plasma concentration [8]. Similarly, halving both the high and low dose of edoxaban from 60 to 30 mg, and 30 to 15 mg respectively, is associated to an approximate halving of drug mean plasma concentration and anti-factor Xa activity [7] (Fig. 1). Of note, such halving of edoxaban dose when ≥1 of creatinine clearance (CrCl) 30–50 ml/min, body weight ≤ 60 kg, and concomitant treatment with potent glycoprotein-P inhibitors (such as, verapamil), all of which ultimately lead to an increase in drug plasma concentration, are present, is associated to only an approximate 25% reduction of drug mean plasma concentration and anti-factor Xa activity [7] (Fig. 1). Rivaroxaban plasma concentration is proportional to renal function over values of CrCl between < 30 and ≥ 80 ml/min [9]. Maximum plasma concentration of rivaroxaban is increased by an approximate 20% in the presence of CrCl 30–49 ml/min, which is the criterion mandating a (comparable) 25% dose reduction (from 20 to 15 mg), in ROCKET AF trial [3]. Indeed, rivaroxaban plasma concentrations are comparable when the doses of 20, and respectively 15 mg, are given when CrCl is > 50 and 30–50 ml/min [9].

As regards the design of phase III trials of DOACs against warfarin in NVAF [2–5], one same population of patients was randomized in RE-LY trial [2] to a higher and lower dose of dabigatran, namely 150 and 110 mg, with no further adjustment based on any patient characteristics (Fig. 2). The aim of such “horizontal” dose reduction was to decrease the intensity of oral anticoagulation. In accordance, efficacy and safety of dabigatran 110 mg was lower, and respectively, higher than dabigatran 150 mg [2]. In comparison to warfarin, dabigatran 150 mg was more effective and comparably safe, whereas dabigatran 110 mg BID was comparably effective but safer [2]. In ROCKET AF [3], ARISTOTLE [4], and ENGAGE AF-TIMI 48 [5] trials, two different patient populations were assigned to either a full or reduced dose of the factor Xa-inhibitors rivaroxaban apixaban, and edoxaban respectively, based on the absence, and respectively presence, of factors known to increase drug plasma concentration, including CrCl 30–49 ml/min in ROCKET AF [3], ≥2 of age ≥ 80 years, serum creatinine ≥1.5 ml/min, and body weight ≤ 60 kg in ARISTOTLE [4], and ≥ 1 of CrCl 30–50 ml/min, body weight ≤ 60 kg, and concomitant use of potent glycoprotein-P inhibitors in ENGAGE AF-TIMI 48 [5] (Fig. 2). The aim of such “vertical” dose reduction was to not increase, rather than decrease, the intensity of oral anticoagulation. In accordance, no significant interaction was observed as regards both efficacy and safety between full and reduced dose of factor Xa-inhibitors (with the exception of edoxaban which at reduced dose was further safer compared to warfarin) [5].

In conclusion, “horizontal” dose reduction can, and should, only be performed with dabigatran. Being independent of any patient characteristics, selection of the 110 mg lower dabigatran dose is entirely at the physician's discretion, and should never be regarded as inappropriate. Conversely, “vertical” dose reduction can, and actually must, only be performed with factor Xa-inhibitors. Being mandated by specific patient characteristics, selection of the reduced dose is independent of the physician's preference. “Horizontal” dose reduction of factor Xa-inhibitors in the absence of the specific criteria is associated to increased safety but uncertain, and likely insufficient, efficacy on (ischemic) stroke

https://doi.org/10.1016/j.ejim.2019.01.005
Received 10 December 2018; Received in revised form 13 January 2019; Accepted 14 January 2019
Available online 20 January 2019
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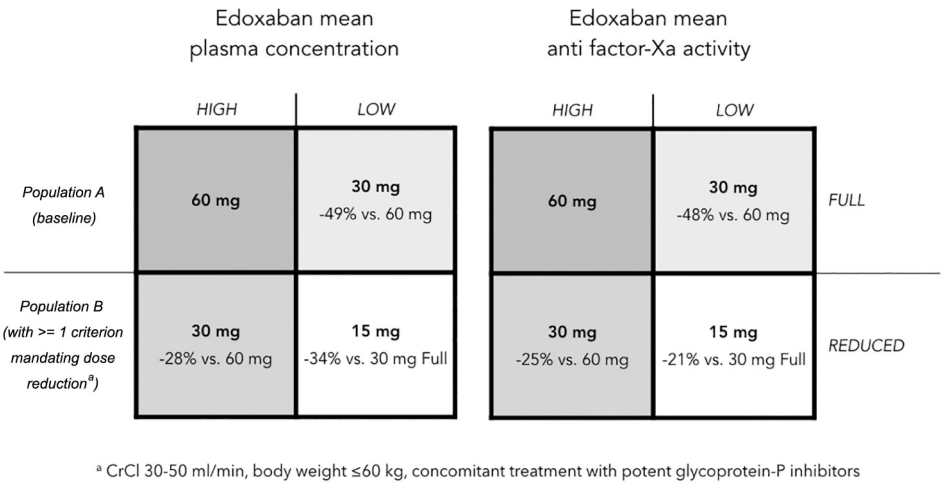

Fig. 1. Relationship between edoxaban dose and mean plasma concentration and anti factor-Xa activity in the two populations included in the ENGAGE AF-TIMI 48 trial [5]. CrCl: creatinine clearance.

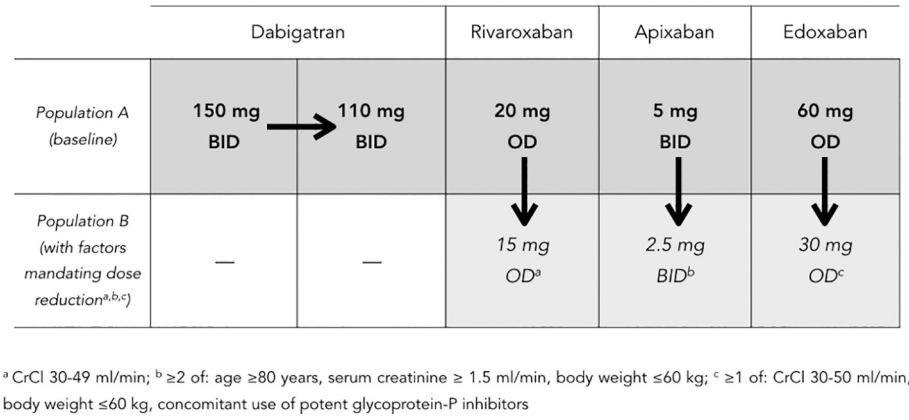

Fig. 2. Design of phase III trials comparing DOACs to warfarin for the prevention of stroke/systemic embolism in NVAF. DOAC: direct oral anticoagulant; NVAF: non-valvular atrial fibrillation; BID: twice daily; CrCl: creatinine clearance; OD: once daily.

prevention, and should therefore be regarded as inappropriate.

A few exceptions to the above rule need to be kept in mind. Based on pharmacological modeling and/or interpretation of the RE-LY results [2], "vertical" reduction of dabigatran dose from 150 mg to 75 mg (in North America only), and 110 mg (in Europe only) must be performed in the presence of CrCl < 30 ml/min, and age ≥ 80 years and/or concomitant use of verapamil, respectively. Based on the results of the PIONEER AF-PCI trial [10], "horizontal" dose reduction of rivaroxaban from 20 to 15 mg should be performed in the absence of CrCl 30–49 ml/min when combined to clopidogrel in NVAF patients undergoing percutaneous coronary intervention with stent.

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