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*Letter to the Editor* · **Open Access** ·

# Anticoagulation in frail older people

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Frailty is a multidimensional dynamic condition characterized by decreased physiological reserves.

Therefore, frail people are more vulnerable to stressors. Indeed, minor stimuli, like a new drug prescription, can alter their homeostatic equilibrium determining adverse clinical outcomes (*i.e.*, falls, institutionalization, disability, and death).[1,2] Since the risk of atrial fibrillation[3] and venous thromboembolism[4] increase with ageing, frail people might require long term anticoagulation. On the other side, anticoagulated patients have also an increased bleeding risk and such complication is more frequent in the elderly. For these reasons, prescribing anticoagulant treatment in frail people is challenging and many patients remain untreated despite the clinical indication. Comorbidities, in particular renal and liver insufficiency, polypharmacy, reduced compliance to medications, anticoagulant dose adjustment errors, falls and a greater susceptibility to gastrointestinal haemorrhages further complicate their management.[5] Hence, a correct balance of the risks should be performed. *Ad hoc* scores have been elaborated (i.e., $CHA_2DS_2$-VASc score[6] for the thrombotic risk and HAS-BLED score[7] for the haemorrhagic risk) and are routinely used in clinical practice. Unfortunately, both scores share many criteria (age, hypertension, and previous stroke) making treatment decision more difficult.

Despite the evidence of anticoagulation benefits,[8,9] many physicians fear haemorrhagic complications and therefore don't treat older people. Real world data show that less than half of older patients requiring anticoagulant therapy are treated.[10-12] Moreover, doctors frequently have concerns about the inability of older people to cope with warfarin monitoring. Direct oral anticoagulants (DOACs) have been proposed also to overcome this problem. In clinical trials DOACs had a favourable risk-benefit profile showing a significant reduction in stroke, intracranial haemorrhage, and mortality. DOACs displayed also a similar major bleeding risk as for warfarin.[13]

DOACs do not need require routine laboratory monitoring. However, their anticoagulant effect correlates to their plasmatic concentration,[14–16] therefore bleeding risk is higher in patient with elevated drug levels.[17] Indeed, a recent study[18] casted doubt on the safety of apixaban in older people: apixaban concentrations during routine clinical practice where found to be higher than it would be expected from the results of clinical trials. Older people inappropriately receiving reduced dosages of apixaban (i.e., without meeting the criteria for dosage reduction) displayed instead apixaban concentrations in the range indicated for people assuming the recommended doses of the drug. Moreover, some patients receiving a correct dose of apixaban according to prescription criteria had greater plasmatic concentrations than it was observed in clinical trials. Such findings could raise concerns when prescribing DOACs in patients with labile renal liver function.

Actually, oldest olds were underrepresented in the pivotal phase of DOACs randomized clinical trials. Subsequent subgroup analyses revealed that DOACs could have a different effectiveness and safety profile in older patients.[19–22] A 2019 systematic review and meta-analysis of observational studies[23] in people aged 75 years or older showed that there were no significant differences in effectiveness outcomes between DOACs and vitamin K antagonists (VKAs).

Moreover, in observational studies,[23] the risk of major bleeding was comparable between DOACs and VKAs even if there were some differences in hemorrhages sites. DOACs decreased the risk of intracranial hemorrhage compared to VKAs at the cost of an increased risk of gastroin-

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testinal bleeding. In particular, rivaroxaban performed less favourably than other DOACs in all safety outcomes. A recent New Zeland observational study underlined the difficulty in extrapolating trial data into clinical practice and emphasized the need for post-marketing surveillance by reporting increased bleeding events in frail older patients assuming dabigatran.[24]

Therefore, in the 2019 update of the Beers Criteria,[25] rivaroxaban and dabigatran were included among the list of potentially inappropriate medications that should be used with caution in older adults.

All DOACs, and in particular dabigatran, require renal dose adjustment. Reduction of the renal clearance slows drug elimination increasing the bleeding risk.[26] Older patients are at a higher risk for acute renal failure because of dehydration, comorbid conditions and medications use. What is more, body weight changes, which are not unusual in older people, can influence DOACs pharmacokinetics.

Finally, similarly to vitamin K antagonists, DOACs are also involved in unpredictable and potentially fatal drug-drug and herb-drug interactions.[27,28] For example, some types of cinnamon can be a source of coumarin[29] with and addictive anticoagulant effect. Ginger can interfere with P-glycoprotein dabigatran clearance[30] in addition to inhibiting platelet aggregation.[31] The risk of potentially severe herb-drug interactions is augmented by the fact that both patients and physicians usually underestimate and under-report the use of herbal products or over-the-counter drugs. Under this perspective, DOACs seem not to represent a safer alternative to vitamin K antagonists.

Considering the difficulties in managing anticoagulants in frail older people, it is not surprising that anticoagulants are among the most frequent cause of adverse drug reactions (ADRs). These ADRs frequently require emergency department (ED) visits and hospitalization.

In a 2013–2014 survey of ED visits for ADR among older adults, the rate of hospitalization for warfarin (55%) and DOAC (49.8%) ADRs was similar in spite of a less widespread use of DOAC in that period.[32] Rivaroxaban is now the fifth and dabigatran the tenth most commonly implicated drug in ED visits for ADRs among older adults.

Since DOACs are not routinely dosed, the increased risk of bleeding cannot be detected until the bleeding event occurs. Until now, the lack of effective reversal agents (except for dabigatran) determined pronged bleeding with deleterious consequences in term of morbidity and mortality. On the contrary with VKAs, we can discover people at increased risk of bleeding by monitoring periodically INR and we can reduce that risk by adjusting the dose of the drug and eventually administering vitamin K.

The use of DOACs appears to be still difficult in geriatric clinical practice. Post marketing surveillance let emerge important adverse events related to the use of these drugs in frail older people.

The number of comorbidities, the high polypharmacy and the rapidity with which the homeostatic equilibrium can be broken in frail people challenge the use of DOACs. What is more, in a World which is rapidly ageing, drug costs should also be taken into account. Lack of evidence of clinical superiority of DOACS versus the VKAS in the oldest old let us consider that the cheapest option could be the best choice also from a health policy point of view.[33]

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