Practical use of Direct Oral Anti Coagulants (DOACs) in the older persons with atrial fibrillation.

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ABSTRACT

Direct Oral Anticoagulants (DOACs) consistently demonstrated a greater net clinical benefit compared to Vitamin K Antagonists (VKAs) also in persons aged 75 years and over, who account for the largest proportion of AF patients; however, major uncertainties in DOACs prescription have to do with this age group. In this review, persistent uncertainties and implications of frailty and geriatric syndromes on DOACs prescription, and practical use of DOACs in real-world older persons, and will be discussed.

Keywords

aged, atrial fibrillation, direct oral anticoagulants, frail elderly

Introduction

Current European guidelines recommend oral anticoagulant therapy (OAT) with direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) irrespective of age for patients with atrial fibrillation (AF) and a CHA_2DS_2-VASc score ≥ 2 in men and ≥3 in women, and without contraindications to DOACs (mechanical prosthetic valves or moderate-to -severe mitral valve stenosis) [1, 2]. Phase III DOAC randomized clinical trials (RCTs) enrolled a significant proportion of elderly subjects, and consistently demonstrated a greater net clinical benefit compared to VKAs also in persons aged 75 years and over, who account for the largest proportion of AF patients. Barco et al reported a significant reduction in stroke and thromboembolic events and in intracranial hemorrhages, compared to warfarin, in patients receiving full-dose dabigatran and apixaban, this latter being also associated with a reduced incidence of major bleedings [3]. In a review of DOACs phase III trials, including also the data from the ENGAGE AF TIMI 48 study, in patients aged ≥ 75 years [4], apixaban and higher-dose dabigatran were associated with a significant reduction of stroke/systemic embolism, whereas major bleeding were significantly reduced in patients receiving apixaban and edoxaban compared with warfarin; all DOACs, with the exception of rivaroxaban, were associated with a significant reduction of intracranial bleedings [4]. A very recent meta-analysis including 28135 AF elderly patients (≥ 75 years) demonstrated that DOACs were associated with a significant reduction in stroke/systemic embolism and, with the exception of rivaroxaban, with a significant reduction of intracranial bleeding events, with apixaban showing the best combination of efficacy and safety in these older patients [5].

However, despite consistent evidence of clinical benefit and increasing prescription of these drugs [6], they are yet widely underused, particularly in the oldest patients [7-14]. In this review, implications of frailty and geriatric syndromes and persistent uncertainties on DOACs use in real-world older persons will be discussed, and an approach for practical use of DOACs in older patients will be proposed.

Material and methods

Several studies and meta-analysis based on results of DOAC phase III RCTs have provided extensive information about efficacy, safety and clinical benefit of DOACs compared with warfarin in elderly persons [3-5], and recent European recommendations dealt with some wedge issues concerning use of DOACs in older persons [2]. For a more in depth evaluation of persistent uncertainties about DOACs practical use in real world elderly people, scientific literature focused on use of DOACs in older persons published in the last 8 years was retrieved by the authors (MB, NM) from the MEDLINE database using the terms “atrial fibrillation” AND “antithrombotic

therapy", OR "new oral anticoagulants" OR "direct oral anticoagulants", OR "aged" OR "elderly" OR "older" as keywords. Reviews, recommendations and expert opinions, as well as clinical trials and large observational studies in English published until March 2019 were systematically analyzed and included according to their relevance to the objective. Additional references were obtained from the reference list of the selected full-text manuscripts.

Real world patients, frailty and geriatric syndromes

Some uncertainties in DOACs use in older patients might arise from the concern that the significant proportion of older persons enrolled in DOACs RCTs might not be not fully representative of real world (RW) patients. Indeed, only 40-60% of RW AF patients enrolled in the Michigan Anticoagulation Quality Improvement Initiative (MAQI2) registry taking warfarin would have met the selection criteria adopted for phase III DOACs trials [15]. Whereas patients with severe comorbidities, reduced life expectancy, potentially interacting drugs, and mild-to-moderate blood work abnormalities were systematically excluded from phase III DOACs trials [4], RW AF patients are older, more frequently of female gender, with high prevalence of comorbidities and of functional and/or cognitive impairment [9,12,13,16,17].

Most of the RW studies on DOAC use are registry-based and retrospective, mainly include community-dwelling older persons, use 65 years as the cut-off for defining older patients, and may be flawed by undocumented selection bias, although they used statistical tools such as the propensity score to correct selection bias within heterogeneous groups of RW patients. Despite these inherent limitations, these studies confirm a greater net clinical benefit of DOACs compared with VKAs also in older patients, with an apparent better safety profile for apixaban and low dose dabigatran [18 - 22]. Few studies focused on the oldest AF patients. A propensity-matched analysis of patients ≥ 90 years of age from the National Health Insurance Research Database in Taiwan showed similar efficacy and reduced incidence of intracranial hemorrhage with DOACs over warfarin [23]. In 3285 elderly patients from the PREFER in AF registries, the primary net composite end-point (ischemic cardiovascular events and major bleeding) was lower with DOACs than with VKAs (6.6% vs 9.1%, respectively, OR 0.71, 95% CI 0.51-0.99), with a net clinical benefit of DOACs primarily due to lower rates of major bleedings [24]. In a propensity score adjusted analysis of a retrospective US Medicare cohort of new-user AF patients who initiated warfarin or full doses of dabigatran, rivaroxaban and apixaban, compared to warfarin each DOAC was associated with reduced risks of thromboembolic stroke (20-29%), intracranial hemorrhage (35-62%) and mortality (19-34%) [25].

However, geriatric syndromes such as frailty, cognitive impairment and functional dependence, which have been demonstrated to influence physicians' decision about DOACs use in older persons [9 - 11, 13, 26, 27], were not considered in RW studies as well as in DOACs trials. Although cardiologists usually recognize frailty based on the presence of a mix of problems of motility, cognition, nutrition and inappropriate loss of body weight and muscle mass [28], there are two basic conceptualizations of frailty (Table 1). The frailty "phenotype" is based on the presence of at least three of five criteria – slow gait speed, low physical activity, unintentional weight loss, self-reported exhaustion, and muscle weakness –, and is associated with worsening mobility and disability, hospitalizations, and mortality over 7 years in community-dwelling older persons [29]. This "frailty phenotype", which should not be confused with disability or comorbidity, may also be identified using other tools, such as the Simplified Fried test, the Short Physical Performance Battery (SPPB) [30], the 5 meter gait speed [31], the Study of Osteoporotic Fractures (SOF) index [32, 33] and the simple Frail Scale [34]. On the other side, the Frailty Index [35] is a 70-item form based on the accumulation of deficits (including functional limitations and disabilities, cognitive and sensory impairment, psycho-social variables and number of diseases), whose score is associated with increased short term risk of institutionalization, mortality and hospitalization. The 7-point Clinical Frailty Scale (a semi-quantitative eye-ball global judgment of frailty or vulnerability) was shown to be highly correlated with the Frailty Index and significantly associated with increased risk of death and entry into an institution [36]. The Multidimensional Prognostic Index (MPI) [37] (including information on functional basic and instrumental activities of daily living, cognitive and nutritional status, comorbidities, medications, and social support network) has also been demonstrated to be predictive of mortality and adverse clinical outcomes [38]. In summary, the "frailty phenotype" based tools identify patients at risk of disability, but not of short term mortality, whereas high scores in the Frailty Index, Clinical Frailty Scale and MPI identify patients with poor health status and increased risk of mortality. Despite inherent limitations according to different frailty tools adopted, frail older patients with AF are less likely to receive an appropriate anticoagulant prescription and, at the same time, are at greater risk of embolic stroke and death [10, 13, 14, 17, 28, 39,40]. The lack of evidence to guide optimal care for patients with AF and frailty might in part explain the gap between current guidelines and clinical practice in management of these patients [40]. On the basis of current evidence there is general agreement that the "frailty phenotype" should not be an exclusion criterion to anticoagulate, since these patients are at an increased risk of stroke and have been shown to benefit from OAC [2]. The benefit of NOACs over VKA has best been demonstrated for edoxaban and apixaban in this patient population [2].

Predisposition to falls is common in frail patients, and is often perceived as an important issue in starting DOACs [41, 42]. Patients on OAT at high risk of falls did not consistently have a significantly increased risk of major bleedings [43 - 45]. Current guidelines do not require fall risk estimation in candidates to OAT, and the risk of fall per se should not be considered a contraindication to the use of DOAC [1, 2]. However, use of simple falls risk tools has been recommended (Table 2) [46, 47]. and patients at high risk for fall on OAC should be referred to a falls service for multi-disciplinary assessment and to address remediable pathology, correct polypharmacy and inappropriate prescriptions and/or prescribe interventions (e.g. exercise programs; home environmental assessment etc.) that reduce risk of further falls [2]. There is evidence that these patients may derive greater benefit from apixaban and edoxaban compared to warfarin [46, 48].

Many older adults have both cognitive impairment or overt dementia and AF. Moreover AF is a recognized risk factor for later occurrence of cognitive impairment and dementia [49], and there is suggestive evidence that OAT might have the potential for reducing this risk [50, 51]. Dementia is a well-recognized risk factor for under-use of OAT [7, 8, 10]. A retrospective cohort study of 2572 older patients with AF (73% aged ≥ 75 years) showed that after diagnosis of dementia, those who persisted on OAT had lower rates of stroke and all-cause mortality, with no significant differences in risk of major bleedings [52]. Although cognitive impairment and frailty were associated with increased risk of death and reduced probability of receiving OAT among older AF patients enrolled in the ORBIT-AF registry [53], there was no interaction between OAT use and cognitive impairment or frailty in their association with mortality, major bleeding and a composite end-point of stroke, systemic thromboembolism, myocardial infarction and cardiovascular death [53]. Although cognitive impairment at mild-to moderate stage should not be viewed as a general contraindication to DOAC therapy, especially if well-managed from a logistically point of view, in states of poor physical functioning, limited life-expectancy and high risk for competing causes of death there may be limited benefit from OAT [2].

Prescription, follow-up and surveillance

In our view, in older patients candidate to OAT, at least a short Comprehensive Geriatric Assessment (CGA) should be routinely included as a part of the initial clinical evaluation, aimed to assess cognitive status, functional limitations, comorbidities, estimated residual life-expectancy and daily medications burden. In patients with cognitive impairment, a proxy or a caregiver should be identified as the person responsible for a correct assumption of therapy and as the referent for

clinical surveillance. A formally designated coordinator should be responsible for therapy and follow-up planning [2, 54]. A leaflet anticoagulation card containing education and practical information about the medication, its potential side effects, relevant drug interactions and contraindications, "what to do when" and a phone number or an e-mail to seek advice for emergencies might be very appreciated, and motivate patients to drug adherence [54]. Modifiable bleeding risk factors should be corrected, and baseline blood works (including hemoglobin, liver and renal function and full coagulation panel) routinely performed. Measures of creatinine levels and the estimated glomerular filtration (using the Cockroft-Gault equation) rate are recommended every 3, 6 or 12 months, with increasing frequency along with decreasing renal function or with dehydrating illness [55]. At every follow-up contact or visit, the checklist should address thromboembolic and bleeding events, adherence, side-effects, careful review of co-medications, reassessment of correct dosing and blood sampling (mainly hemoglobin and renal function) [45, 54].

Selection and dosing of DOAC

Medical history and comorbidities may drive the choice of a particular DOAC. Patients with AF and hepatic insufficiency Child-Pugh category A may receive full dose DOAC; dabigatran, apixaban and edoxaban may be used with caution in patients with hepatic insufficiency Child-Pugh category B, whereas all DOACs are contraindicated in category C [2]. It has been reported that patients with chronic liver disease treated with DOACs have a lower incidence of major bleeding compared with VKAs [56, 57]. Several DOACs rankings [58-60] and expert opinions have been published to assist physicians to fit the best DOAC according to individual patient's characteristics [61-64]. Apixaban has been suggested as a reasonable first choice either in older patients and in subjects with chronic renal failure [63]. The recently updated 2019 American Geriatrics Society Beers criteria recommend a cautious use of dabigatran and rivaroxaban in AF patients aged ≥ 75 years because of greater risk of gastrointestinal bleeding [65]. In a recent report from the Fit-fOR-The-Aged (FORTA) classification (evaluating benefit, risk and appropriateness of drugs for older patients in everyday clinical settings) [66, 67], apixaban was labelled A among OATs, meaning it was seen as the drug with the most favorable risk/benefit ratio in older patients [68].

AF patients who are going to receive a DOAC prescription should be assessed for DOAC specific dose-reduction criteria and for other factors with potential effect on DOACs plasma level [2], such as age > 80 years, low body weight (< 60 kg), reduced renal function, concomitant use of non-steroidal anti-inflammatory drugs (to be avoided), previous bleeding, frailty and fall risk [2]. Table 3 reports approved doses for DOAC use in clinical practice, and dose reduction of all DOACs is

primarily recommended along the published dose reduction criteria [2].. However, there is some rationale for reducing the dose of NOACs in patients with a high bleeding risk and/or when a higher plasma level of the drug can be anticipated based on a combination of factors, including potential drug-drug interactions, especially when combined with other clinical factors affecting DOACs plasma levels, such as advanced age, low body mass and reduced renal function [2]. DOACs have less food and drug-drug interactions than warfarin. Main drug-drug interactions of DOACs involve P-glycoprotein (P-gp) and CYP3A4 CYP2Y2 competition and inhibition. Major contraindications for increased anticoagulant effect include concomitant use of anti-fungal drugs (Itraconazole, Ketoconazole, Voriconazole, Posaconazole) and quinidine virtually for all DOACs. Clarythromicin and Erythromicin increase the anticoagulant effect in DOAC-treated patients, as well as Amiodarone and Dronedarone do in patients receiving dabigatran, rivaroxaban and edoxaban: dose-adjustment or use of a different DOAC should be considered in these circumstances. Verapamil increases the anticoagulant effect in patients treated with dabigatran and edoxaban. There is evidence that concurrent use of amiodarone, rifampin, fluconazole and phenytoin in patients taking DOACs is associated with increased risk of major bleeding compared with use of DOACs alone [69]. Either St John wort or rifampicin (P-gp inducers) reduce the anticoagulant effect of DOACs and are therefore contraindicated. There is increasing evidence of several other drug interactions with potential clinical significance, including antineoplastic and antiepileptic drugs, of common use in older patients [2]. Therefore, use of DOACs in older patients mandate a careful evaluation of co-medications in order to select the most appropriate drug and dose. Although antiplatelet drugs in combination with DOAC therapy increase the risk of bleeding, there is some evidence that use of apixaban and low-dose edoxaban with concomitant aspirin therapy was associated with better safety profile compared with VKAs and aspirin [70, 71]. The EHRA algorithm shown in Figure 1 may assist physicians in a rational selection of a specific DOAC according to drug–drug interactions and other clinical risk factors [2].

In RW clinical practice reduced-dose DOACs, particularly of apixaban, are largely used, mainly in the oldest patients and with poor health status [72-75]. Inappropriate DOAC under-dosing is associated with increased risk of stroke/thromboembolism and hospitalization [73, 75, 76]. Indeed, inappropriate low dose regimen is associated with lower DOAC levels [77] and with increased thromboembolic risk [78]. AF patients eligible for DOAC reduced-doses represent a common and troublesome scenario in clinical practice, as it has been recently demonstrated that these patients are at increased risk both of thromboembolic and hemorrhagic complications [72, 79, 80]. However, in phase III DOAC trials patients who were appropriately dose-adjusted, had a better benefit/harm ratio compared to warfarin [79]. A post-hoc analysis of the ARISTOTLE trial demonstrated that

patients fulfilling just one of the pre-specified criteria for apixaban dose-reduction, and appropriately treated with the standard dose, had similar rates of major bleedings compared to those receiving full-dose apixaban in the absence of any dose-reduction criteria [81]. Therefore, adherence to DOAC approved dose should be recommended also in older patients, along with the EHRA recommendations for a rational selection of DOAC (Figure 1).

Clinical uncertainties and open questions

Despite recent studies reinforced the evidence of net clinical benefit of OAT, including DOACs, in extremely elderly community-dwelling persons (aged >=85 years) [82], prescription of OAT to older AF patients is often a troublesome decision, involving a global evaluation of health, residual life-expectancy, functional and cognitive status, rather than a simple addition of variables within cardio-embolic and bleeding risk scales [4]. It is likely that sometimes physicians perceive OAT as "futile" or potentially harmful in patients with multi-morbidity and short life-expectancy, and, moreover, cost-effectiveness considerations might affect decision about DOACs prescription in these patients. Indeed, when considering OAT with DOACs in older persons, the high risk of competing cardiovascular and non-cardiovascular causes of death in this population should be considered. In fact, while the adjusted overall mortality in landmark phase III DOAC trials was 4.72%/year, with cardiac death contributing for 46% of deaths [83], all-cause mortality in real-world older patients are definitely higher, with difference in cause-specific mortality. In the ORBIT-AF registry, patients not on OAT (mean age 73 years) experienced higher mortality rates (7.42 vs 5.78%, p=0.006) over a 2.5 years follow-up without significant differences in thromboembolic event rates, compared with patients receiving OAT [84]. In a prospective study in nonagenarians with AF receiving OAT, the rate of ischemic stroke/TIA/systemic embolism was low (2.4%) with a not negligible rate of major bleeding (5.5%), within the context of high one-year all-cause mortality rate (17.2%) [85]. Data from the Galician Healthcare Service showed that among patients aged 80 years and older (45.6% of those with AF) two-year all-cause mortality was higher than in younger counterparts (27.8% vs 8.05%, p<0.001), as well as thromboembolic and hemorrhagic events (2.03% vs 0.9%, p<0.01 and 2.5% vs 1.7%, p=0.01, respectively) [86]. In two studies including hospital discharged older AF patients (mean age over 80 years) we documented high mortality rates, mainly for non-cardiovascular causes, which were about two-fold higher in untreated patients, reflecting the higher proportion of poor health status in these latter patients [16, 87]. Indeed, it has been demonstrated that the large reduction in thromboembolism with OAT use (HR=0.57, 95% CI=0.50-0.65) may be substantially attenuated after accounting for competing death events (HR=0.87, 95% CI=0.77-0.99) [88]. Furthermore, mortality in individuals not prescribed OAT is

markedly higher than in those receiving OAT, and not accounted for by an excess of thromboembolic fatal events, but rather reflecting the higher proportion of oldest old with complex comorbidities and poor health status in untreated population [88]. Data from the Swedish National Patient Registry [89] demonstrated that, although AF is an independent risk factor for all-cause mortality, the long-term relative all-cause mortality risk in the age-categories ≤ 65, 65-74 and 75-85 years, adjusted for concomitant diseases was 2.15, 1.72 and 1.44 ($p<0.001$) for women and 1.76, 1.36 and 1.24 ($p<0.001$) for men, respectively [89]; neoplasms, chronic renal failure, and chronic obstructive pulmonary disease contributed most to the increased all-cause mortality in older patients [89]. A recent systematic review and meta-regression analysis demonstrated that in older AF patients DOACs are superior to warfarin for stroke/thromboembolism prevention, with reduced risk of major bleeding, thereby reinforcing the evidence that DOACs should be preferred for stroke prevention in older AF patients [90]. However, some older AF patients are at risk of increased short-term all-cause mortality, thereby diluting the undisputable benefit of DOACs. Unfortunately, by now there are not validated methods to identify those few older patients who, because of their poor general health and/or functional status, are expected not to have a net clinical benefit from anticoagulation.

Conclusions

The availability of DOACs has dramatically increased the proportion of older AF patients receiving appropriate OAT. Because of their potential for clinical benefit, DOACs should be recommended for “fit and robust” older subjects, as well as for persons with the frailty phenotype, irrespective of age; risk of falls, cognitive impairment without functional limitations, and mild disability should not be regarded as contraindications to DOAC use in these patients. However, as for many other preventive therapies, actually there is no evidence of net clinical benefit from OAT in older patients with advanced dementia, and/or with loss of functional independence, and/or short life expectancy [37]. Hopefully, further studies will provide information in this setting of patients. Individual selection of DOAC and use of recommended appropriate dose, careful clinical surveillance, periodic review of co-medications, and minimization of bleeding risk are mandatory in these patients.

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Table 1: Main frailty tools for practical use

CHS Frailty Scale – Frailty phenotype SOF Frailty Scale SPPB & Gait speed Green score	«physical» frailty tools, not including disability and disease burden
Frail Scale Vulnerable Elders Survey-13 Groningen Frailty Indicator (GFI)	«hybrid» frailty tools, including measures of disease burden
Clinical Frailty Scale Frailty Index	«Deficit accumulation» tools, identifying frail and vulnerable patients, including measures of disabilities, disease burden, sensorial deficits and psycho-social variables

Abbreviations: CHS: Cardiovascular Health Study; SOF: Study of Osteoporotic Fractures; SPPB: Short Physical Performance Battery

Table 2: Fall risk tools

High risk of fall with presence of one or more of:
Prior history of falls
Lower extremity weakness
Poor balance
Cognitive impairment
Orthostatic hypotension
Use of psychotropic drugs
Severe arthritis
Dizziness

from ENGAGE-AF TIMI 48[47]

Probability falls assessment [47] **1 point for each**
Previous falls
Medications>4
Psychotropics
Low visual acuity
Diminished sensation
Near tandem stand 10 s
Alternate step test 10 s
Sit to stand 12 s

Score	Probability of fall per year
0-1	7%
2-3	13%
4-5	27%
6+	49%

Table 3: DOACs and approved doses [2]

	STANDARD DOSE	COMMENTS/DOSE REDUCTION
APIXABAN	2 x 5 mg	2 x 2.5 mg if two out of three: weight <=60, kg >=80 years, serum creatinine>= 1.5 mg/dl (or Creatinine Clearance 15-29 ml/min)
DABIGATRAN	2 x 150 mg/ 2 x 110 mg	No pre-defined dose- reduction criteria
EDOXABAN	1 x 60 mg	1 x 30 mg if weight <=60 kg, Creatinine Clearance <=50 ml/min, concomitant therapy with strong P-Gp inhibitor
RIVAROXABAN	1 x 20 mg	1 x 15 mg if Creatinine Clearance <=50 ml/min

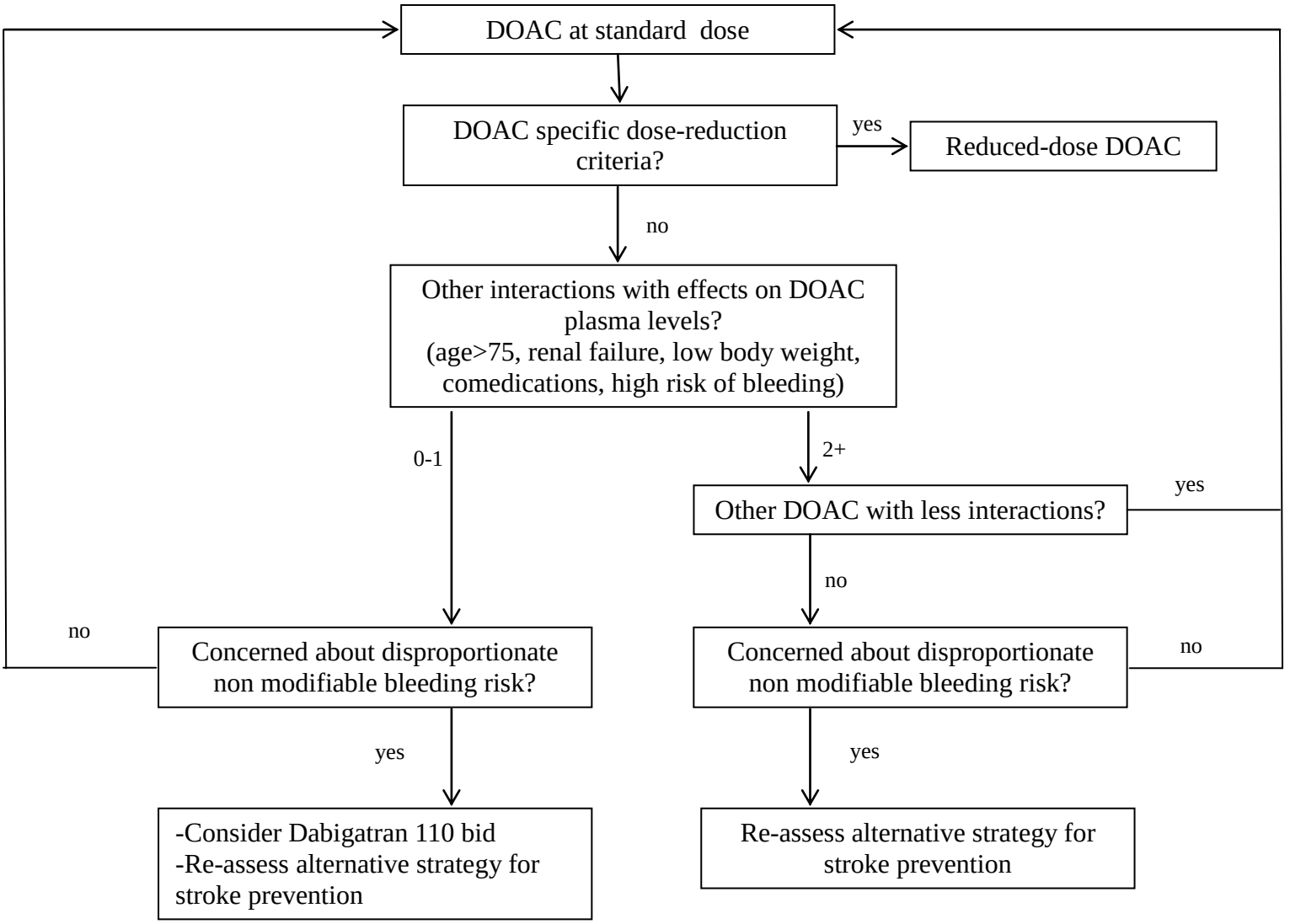

Figure 1: DOAC selection based on drug-drug interactions and/or risk of bleeding.
Modified, from Eur Heart J 2018; 39: 1330-1393