Review

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The problem of underdosing with direct-acting oral anticoagulants in elderly patients with nonvalvular atrial fibrillation

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Unless contraindicated, anticoagulant therapy should be prescribed to elderly patients with atrial fibrillation. Direct-acting oral anticoagulants (DOACs) are superior to vitamin K antagonists for preventing stroke. This, together with their higher net clinical benefit, makes DOACs the treatment of choice in this population. However, due to the concerns about bleeding and the need for dose adjustment based on clinical variables, underdosing of DOACs is common and the risk of stroke high. Drugs with more easily adjusted doses are likely associated with a lower risk of dosing errors and, therefore, a greater protective effect. Correct dosing can ensure a maximal net benefit of DOACs in elderly patients with atrial fibrillation.

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Relevance of atrial fibrillation in the elderly patient

Atrial fibrillation (AF) is the most common type of arrhythmia in clinical practice. Its prevalence increases exponentially with age, and it is now epidemic in elderly persons [1]. It is estimated that the prevalence of AF will increase 2.5-fold in the next 50 years, mainly as a consequence of aging of the population [1]. However, despite the high prevalence of AF in elderly persons, the condition is frequently underdiagnosed. In addition, patients do not receive appropriate therapy, thus increasing the risk of thromboembolic complications [2]. In fact, results from a recent study have shown that more than a third of elderly patients did not know that they had AF [3].

Elderly patients with AF have a considerable number of co-morbid conditions. This notably complicates management not only owing to the high prevalence of risk factors and associated cardiovascular disease but also owing to the greater risk of frailty, cognitive impairment, dependence and risk of falls [4–6]. In the NONAVASC registry, which included more than 800 persons with nonvalvular AF aged more than 75 years hospitalized in internal medicine departments in Spain (mean age: 85 years), 50% had sarcopenia, 51% frailty and 42% moderate–severe cognitive impairment. Mortality reached 38% at 1 year of follow-up and was more frequent in patients with any of these conditions [7].

Kidney failure is common in elderly patients with AF and increases the risk of stroke and bleeding. This is particularly relevant when trying to establish optimal antithrombotic treatment [8,9]. Consequently, both age and the high number of co-morbidities in elderly patients with AF account for the high number of admissions and readmissions in this population, as does the higher frequency of mortality than reported in elderly persons without AF [10,11].

Also noteworthy in the elderly population, and of relevance when deciding on optimal anticoagulant treatment, is the presence of polymedication. Associated interactions and the pharmacokinetic and pharmacodynamic changes that occur with age and must be taken into account if we are to reduce the risk of adverse effects and drug-induced toxicity [12–14]. In this context, a more suitable approach would involve drugs that do not require adjustment for age-associated changes [15,16]. Therefore, choosing optimal antithrombotic treatment is essential not only for purposes of prognosis but also to ensure suitable quality of life and prevent future complications [15,16].

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Assessment of the risk of stroke & bleeding in the elderly patient

Undoubtedly, increased risk of stroke is the complication of AF that gives greatest cause for concern. AF-associated stroke has a high mortality rate, which can reach 50% at 1 year of follow-up in some series [17]; in survivors, the frequency of disability is high, as is the risk of recurrence. These figures are worse in the elderly [2,18,19], thus making appropriate prevention of thromboembolic complications essential in this population [20]. Therefore, the risk of stroke and bleeding must be assessed on an individual basis [21]. The two factors that most increase the risk of stroke are age and a history of cerebrovascular disease. In fact, depending on the study, age increases this risk between two- and threefold, and this risk may become greater as patients get older [22].

The risk of bleeding also increases with age [23–27]. Guidelines clearly highlight that while it is important to identify those factors that increase the risk of bleeding in order to take specific measures to reduce the risk, anticoagulation should not be contraindicated [20]. Even though the risk of major bleeding increases with age, the risk of intracranial hemorrhage and fatal hemorrhage as a consequence of anticoagulant treatment remains low in the elderly population [23–25]. For example, a study performed in extreme elderly Japanese patients with AF showed a higher incidence of stroke but not of major bleeding compared with the younger AF population [28]. Therefore, when evaluating the risk–benefit ratio of anticoagulant treatment, it is important to take into account the risk of thromboembolic complications (which are associated with high morbidity and mortality) and that of major bleeding (which is fatal in a small percentage patients), as well as the risk of intracranial/fatal bleeding. Furthermore, the increased risk of bleeding depends more on the patient's age and individual characteristics than the fact that he/she has received anticoagulant therapy [29]. In this sense, other studies carried out in hospitalized frail patients aged more than 75 years and nonagenarians found that anticoagulation was associated with low rates of stroke and bleeding, with a net benefit that was clearly superior to not being anticoagulated [30,31]. Moreover, anticoagulation has been associated with reduced cognitive impairment in patients with AF [32].

In summary, elderly patients with AF have a higher risk of stroke and bleeding, but the benefits of anticoagulation for thromboembolic complications or mortality remain regardless of increasing age [33]. Consequently, anticoagulation is clearly beneficial in elderly patients with AF. However, the current situation continues to give cause for concern. In fact, elderly AF patients are less anticoagulated despite their less favorable risk profile, including a higher CHA_2DS_2-VASc score [34,35]. While studies differ with respect to the figures they report, overall, anticoagulation rates in elderly patients with AF vary from only 25 to 75%. In clinical practice, it has been shown that anticoagulation does not depend so much on thromboembolic risk or bleeding as on other factors [36–39]. In fact, several studies have analyzed the main independent factors that favor not anticoagulating the elderly patient, namely, advanced age (anticoagulation therapy is prescribed less frequently with age), the degree of dependence, cognitive impairment, frailty and the risk of falls [40,41]. However, none of these factors alone should contraindicate anticoagulation [42].

An additional problem to not receiving anticoagulation therapy in elderly patients is that the antithrombotic strategies used are unsuitable. Unfortunately, owing to the risk of bleeding, it is not uncommon for these patients to be prescribed antithrombotic strategies that are clearly not efficacious. For example, a significant percentage of patients are still receiving antiplatelet therapy [43]. However, several trials have clearly shown that antiplatelet therapy is poorly efficacious for preventing stroke in these patients and does not reduce the risk of bleeding compared with warfarin [44,45]. A recent meta-analysis have shown in older patients with AF that warfarin is superior to aspirin and no antithrombotic therapy in reducing the risk of thromboembolic complications, but with a possible increase in major bleeding, in contrast to DOACs that are superior to warfarin for thromboembolic and bleeding complications [46].

Another example can be found in the maintenance of an international normalized ratio in subtherapeutic ranges (1.5–1.9) in patients treated with vitamin K antagonists (VKAs). This approach is applied to prevent bleeding, despite its lower efficacy for reducing the risk of stroke. These erroneous strategies have been compounded in recent years by inappropriate underdosing of direct-acting oral anticoagulants (DOACs) [47].

DOACs in the elderly patient with AF

For decades, VKAs were considered the standard oral anticoagulant therapy in patients with AF, even in the elderly population [44,45,48]. However, VKAs have a number of disadvantages (e.g., variable response, need for periodic control of anticoagulation and multiple interactions), which, together with concern over bleeding and difficult management, have limited their use in daily clinical practice [2,48].

Table 1. Baseline characteristics of the pivotal clinical trials comparing direct-acting oral anticoagulants with warfarin in the overall population and in patients aged ≥75 years including net clinical benefit.

Characteristics	RE-LY (Dabigatran)		ROCKET-AF (Rivaroxaban)		ARISTOTLE (Apixaban)		ENGAGE AF (Edoxaban)	
	Overall	≥75 years	Overall	≥75 years	Overall	≥75 years	Overall	≥75 years
Age ≥75 years (%)	40	100	44	100	31	100	40	100
Heart failure (%)	32	25	63	66	35	24	57	45
Arterial hypertension (%)	79	75	90	89	87	83	94	93
Diabetes (%)	23	20	40	45	25	21	36	28
Previous stroke/TIA (%)	20	19	55	42	19	22	28	25
$CHADS_2$	2.1	2.6	3,5	3.7	2.1	2.7	2.8	3.2
– 0–1 (%)	32	32	0	0	34	10	0	0
– 2 (%)	35	35	13	9	36	41	47	68
– 3–6 (%)	33	36	87	91	30	49	53	32
HAS-BLED ≥3 (%)	10.4	–	62.5	–	22.9	–	46.4	–
Net clinical benefit (DOAC vs warfarin)†	Favors dabigatran		Favors rivaroxaban		Favors apixaban		Favors edoxaban	

†Ischemic cerebrovascular accident + systemic embolism + myocardial infarction + hemorrhagic cerebrovascular accident + adjusted major bleeding (major bleeding minus hemorrhagic stroke).
AF: Atrial fibrillation; DOAC: Direct-acting oral anticoagulant; TIA: Transient ischemic attack.
Data taken from [27,49–57].

DOACs overcome most of the limitations of VKAs by ensuring linear and predictable anticoagulation (no need for monitoring of anticoagulant activity and doses that can be tailored to the individual patient). Furthermore, their improved safety and efficacy profile has been demonstrated in clinical trials [27,49–51]. The elderly population has been analyzed in the main clinical trials. Data from RE-LY showed that, while the results on risk of stroke with dabigatran compared with warfarin were independent of patient age, there were differences with respect to extracranial bleeding, since patients aged ≤80 years had a similar risk with a dose of 110 mg, but a greater risk with that of 150 mg compared with warfarin [52]. In ROCKET-AF, elderly patients presented greater rates of stroke and major bleeding; however, compared with warfarin, the relative safety and efficacy of rivaroxaban were consistent, irrespective of age [53]. In the ARISTOTLE study, the benefits of apixaban compared with warfarin were not associated with age, although in absolute terms, the benefit was greater, as the population had a greater risk of complications [54]. In ENGAGE AF-TIMI 48, the risk of bleeding increased with age; consequently, the benefit in absolute terms for the safety of edoxaban compared with warfarin was greater in the elderly population than in younger subjects [55].

While several attempts have been made to compare DOACs based on the results of clinical trials, baseline patient characteristics differ widely according to the study, both overall and in the elderly population. The greatest risk was that recorded in patients included in the ROCKET-AF trial (Table 1) [27,49–57]. Consequently, the results of clinical trials cannot be compared directly, thus necessitating real-world studies. What they do show, however, is that net clinical benefit, a composite variable comprising thromboembolic and bleeding events, clearly favors DOACs over VKAs, both in the overall population and in elderly patients [56–58]. This also occurs in nonagenarians, as it has been reported that whereas warfarin is associated with a lower risk of ischemic stroke and positive net clinical benefit, compared with warfarin, DOACs have a lower risk of intracranial hemorrhage [59]. Furthermore, we observed that this benefit also extended to the elderly population at greatest risk, such as that with the highest degree of frailty or risk of falls [60]. One important aspect is the demonstration of a lower incidence of dementia and progression of dementia in elderly patients treated with DOACs than in those treated with VKAs [61].

Therefore, their net clinical benefit (which increases with the degree of risk), their ease of administration, low risk of interaction, low risk of intracranial hemorrhage, reduced progression of kidney disease and favorable effect on cognitive impairment make DOACs the drugs of choice in a population that is at very high risk owing to multiple diseases, co-morbidities and polymedication. However, in order to obtain suitable results, it is necessary to prescribe these agents at the correct dose based on data from clinical trials. Thus, when using low doses of DOACs in elderly AF patients, the favorable overall benefit–risk profile compared with VKA may differ [62].

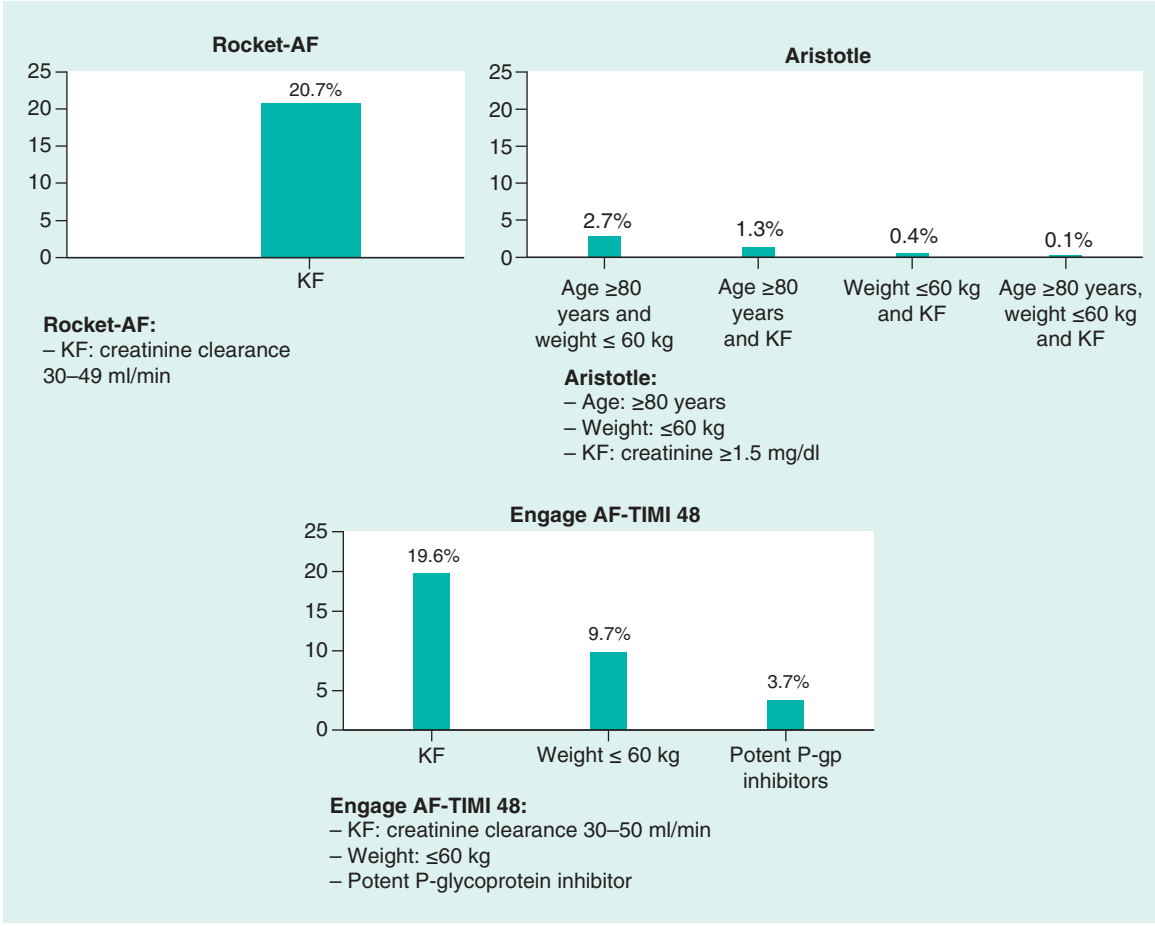

Figure 1. Percentage of patients included in the clinical trials ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 with appropriate criteria for dose reduction.
Data taken from [27,50,51,63].
AF: Atrial fibrillation; KF: Kidney failure.

Importance of appropriate dosing of DOACs in elderly patients

The efficacy and safety of low doses were tested in a specific patient subpopulation in the four pivotal trials. The assessment was based on various pharmacodynamic and pharmacokinetic criteria. The four main determinants for dose reduction were age, kidney function, weight and interactions.

The percentage of patients who received appropriate low doses differs widely between the four trials. For example, around 21% of patients were taking a reduced dose in ROCKET-AF, although this percentage was much lower in ARISTOTLE (4.7%). Therefore, data on the efficacy and safety of the reduced dose of apixaban are much scarcer than for rivaroxaban (Figure 1) [27,50,63]. However, the four trials show that the efficacy and safety profile is similar to that of the standard dose.

Real-world studies, whose findings are consistent with those of the pivotal trials, show that DOACs are effective and safe when used at appropriate doses [64–66].

Although both clinical trials and real-world studies have shown that DOACs have a better safety and efficacy profile than VKAs, a major problem observed in clinical practice is that of incorrect prescription that is prescribing a dose that is not consistent with the summary of product characteristics. Various studies performed in different clinical contexts have shown that inappropriate prescription of DOACs is not uncommon, especially underdosing [5,67,68]. Thus, the results of real-world studies have shown that inappropriate dosing of these drugs is common. This problem may be due to inappropriate prescription by the physician or poor adherence on the part of the patient. Prescription of reduced doses that are not consistent with the summary of product characteristics is observed mainly in elderly patients, either because of poor knowledge of the summary of product characteristics or as the result

Table 2. Use of direct-acting oral anticoagulants in real-world studies.

Characteristics	Vall d'Hebron study (Barcelona)	ESPARTA study	ORBIT AF II Registry	FANTASIIA	Sato
Study population (n)	1443	244	7925	530	2272
Age (years)	77.2	82.6	71.0	73	72
CHA_2DS_2-VASc	4.1	4.9	≥2: 87.2%	3.6	$CHADS_2$ 1.96
Creatinine clearance (ml/min)	59.0	53.3	81.7	69.3	61.6
Dabigatran: – 150/110 mg – Inappropriate dose	 17.9/82.1% 150 mg: 6.3% 110 mg: 48.1%	 18.8/81.2% Overall: 27%	 91.3/8.7% 150 mg: 0.4% 110 mg†: 84%	 43/57% 20%	 150 mg: 1.2% 110 mg: 20.7%
Rivaroxaban: – 20/15 mg‡ – Inappropriate dose	 75.1/24.9% 20 mg: 16.8% 15 mg: 12.1%	 60/40% Overall: 21%	 84.5/15.5% 20 mg: 5% 15 mg: 48%	 66/34% 15%	 20 mg‡: 3.1% 15 mg‡: 23.9%
Apixaban: – 5/2.5 mg – Inappropriate dose	 49.2/50.8% 5 mg: 15.0% 2.5 mg: 28.5%	 20.9/79.1% Overall: 49%	 81.9/18.1% 5 mg: 2% 2.5 mg: 63%	 77/23% 14%	 5 mg: 0.4% 2.5 mg: 22.5%
Edoxaban – 60/30 mg – Inappropriate dose	 80.6/19.4% 60 mg: 6.0% 30 mg: 0%	 Not reported	 82.9/17.1% 60 mg: 45% 30 mg: 75%	 Not reported	 60 mg: 1.5% 30 mg: 12.4%

†Includes patients treated with 75 mg.
‡Rivaroxaban approved doses in Japan are 15/10 mg.
Data taken from [4,67–70].AF: Atrial fibrillation.

of an attempt to reduce the risk of bleeding. Dosing of rivaroxaban, which is adjusted only according to kidney function, seems to be simpler than that of other DOACs, which is more limited by various factors (creatinine, weight, age, treatment with P-glycoprotein inhibitors). Consequently, prescribing this agent would reduce the risk of errors (Table 2) [5,67–70], although dosing errors arising from the single criterion of kidney function have also been reported [71]. This is in line with different studies performed in real-life patients that have shown that despite rivaroxaban is underdosed in a significant proportion of patients, rates of thromboembolic and bleeding complications are low [72,73].

Halving the dose (1 single daily dose) has been reported in those DOACs whose dosing requires administration every 12 h. This situation occurs in up to 30% of patients [74]. Consequently, dosing should be simplified and single doses administered in order to improve treatment, especially in patients with good adherence. Figure 2 shows the criteria recommended for selecting the dose of the four DOACs [20,75].

In recent years, several published studies have analyzed the factors associated with underdosing. The main factors are advanced age, kidney failure, co-morbidities and having a high risk of bleeding and thromboembolic events (Table 3) [76–80].

It is very worrying that the factors associated with a greater risk of stroke also lead to frequent incorrect use of reduced doses of DOACs, thus indicating that doses are not adjusted in line with the summary of product characteristics, but according to other – probably subjective – variables, which distort the perception of the risk of bleeding.

Inappropriate dosing can lead to results that are more unfavorable than those obtained in clinical trials. In fact, in general terms, it seems that the risk of stroke is much lower with rivaroxaban than with VKAs in real-world patients, in contrast with other DOACs (Table 3) [81–83]. In addition, the use of inappropriate doses of DOACs is associated with a greater risk of stroke and of bleeding (Table 3) [80,84,85]. In a recent subanalysis of the FANTASIIA study, the risk of stroke (HR: 16.7; 95% CI: 1.7–164.4; p = 0.016) and of all embolic events (HR: 7.3; 95% CI: 1.2–44.5; p = 0.03) was greater in patients who received inappropriately low doses of DOACs than in those who received appropriate doses, with no differences recorded in the risk of severe bleeding [86].

In elderly patients, the greatest net clinical benefit with DOACs is obtained in those who receive the standard dose of DOACs and not in those treated with low doses, thus indicating that habitual reduced dosing of DOACs in the elderly patient, simply because of age or frailty, is an error that carries a greater risk of thromboembolic and bleeding complications [87].

Table 3. Factors predicting unsuitable dosing of direct oral anticoagulants in real-life patients with atrial fibrillation and impact on events (overall and in case of unsuitable dosing).

Study	Design/population	Results	Ref.
Factors predicting unsuitable dosing of DOACs			
Sato *et al.* (2018)	Retrospective analysis in Japan of 2272 patients with NVAF who received DOACs for 2 years	Independent factors for inappropriate dosing: – Apixaban: HAS-BLED score – Edoxaban: age – Dabigatran: age – Rivaroxaban: age, creatinine clearance, HAS-BLED and $CHADS_2$ scores, antiplatelet treatment	[76]
Jacobs *et al.* (2019)	3231 patients with AF who were prescribed DOACs in 2012 and 2016 in Holland. An inappropriate dose was prescribed in 10.7%, and in 14.1% it was not possible to determine whether the dose was suitable, mainly because there were no data on kidney function	– Receiving a reduced dose of DOACs was an independent predictor of inappropriate prescription (OR: 2.70; 95% CI: 2.13–3.41). – Age ≥80 years was a predictor of inappropriate prescription of apixaban – Altered kidney function and use of verapamil were predictors of incorrect prescription of dabigatran	[77]
Xing *et al.* (2019)	Danish registry of patients with NVAF who started treatment with the standard dose of DOACs between 2011 and 2017. Of the 24,489 patients included, 12.2% were switched to the reduced dose	– Greater risk of dose reduction: treatment with dabigatran, advanced age, high score on the CHA_2DS_2-VASc and HAS-BLED scales – Independent predictors of dose reduction (present at initiation of the study): ischemic heart disease, heart failure, cancer, chronic kidney disease, COPD and hypertension	[78]
Lee *et al.* (2019)	3080 patients with AF in Korea who were prescribed DOACs (dabigatran 27.2%; rivaroxaban 23.9%; apixaban 36.9% and edoxaban 12.0%) between 2016 and 2017	– Reduced doses not adjusted to the summary of product characteristics were prescribed to 36.4% of patients – Inappropriate reduced doses were more common in elderly patients (≥75 years), women, underweight patients (≤60 kg), patients with kidney failure (creatinine clearance ≤50 ml/min), previous stroke, previous bleeding, hypertension, concomitant use of dronedarone and antiplatelet agents	[79]
Steinberg *et al.* (2016)	5738 patients treated with DOACs from the ORBIT-AF II registry (9.4% were underdosed, 3.4% were overdosed and 87.2% were taking the correct dose)	– Patients who received inappropriate doses were older, more frequently women, less frequently treated by an electrophysiologist, and had a higher risk of thromboembolic events and bleeding	[80]
Impact on events in clinical practice of DOACs compared with warfarin			
Escobar *et al.* (2019)	Meta-analysis of 27 studies from 30 publications. Patients with NVAF treated with dabigatran, rivaroxaban and apixaban compared with warfarin	Risk of ischemic stroke • Dabigatran: – Overall: HR: 0.95; 95% CI: 0.80–1.13 – Standard dose: HR: 0.97; 95% CI: 0.68–1.38 – Reduced dose: HR: 0.94; 95% CI: 0.66–1.36 • Rivaroxaban – Overall: HR: 0.83; 95% CI: 0.73–0.94 – Standard dose: HR: 0.86; 95% CI: 0.72–1.03 – Reduced dose: HR: 0.93; 95% CI: 0.71–1.22 • Apixaban – Overall: HR: 0.93; 95% CI: 0.71–1.20 – Standard dose: HR: 1.11; 95% CI: 0.94–1.31 – Reduced dose: HR: 1.19; 95% CI: 0.95–1.49	[83]
Impact of inappropriate doses of DOACs on events in clinical practice			
Arbel *et al.* (2019)	8425 patients with newly diagnosed NVAF (5140 [61%] treated with suitable doses according to the summary of product characteristics and 3285 [39%] with inappropriately reduced doses) between 2011 and 2017 in Israel	Inappropriate reduced doses (vs appropriate doses) were associated with the following: – Effectiveness (death, stroke or myocardial infarction): HR: 1.57; 95% CI: 1.34–1.83; $p < 0.001$ – Safety (bleeding requiring hospitalization): HR: 1.63; 95% CI: 1.14–2.34; $p = 0.008$	[84]
Yao *et al.* (2017)	14,865 patients with AF treated with dabigatran, rivaroxaban or apixaban between 2010 and 2015. Patients were from a US database. Of the 1473 patients with an indication for a dose reduction, 43% were overdosed. Of the 13,392 patients with no renal indications for reducing the dose, 13.3% were underdosed	Events associated with overdosing: • Risk of stroke or systemic embolism: – Overall: HR: 1.66; 95% CI: 0.40–6.88; p = 0.48 • Major bleeding: – Overall: HR: 2.19; 95% CI: 1.07–4.46; p = 0.03 Events associated with underdosing: • Risk of stroke or systemic embolism: – Apixaban: HR: 4.87; 95% CI: 1.30–18.26; p = 0.02 – Dabigatran: HR: 0.92; 95% CI: 0.30–2.87; p = 0.89 – Rivaroxaban: HR: 0.71; 95% CI: 0.24–2.09; p = 0.54 • Major bleeding: – Apixaban: HR: 1.29; 95% CI: 0.48–3.42; p = 0.61 – Dabigatran: HR: 0.91; 95% CI: 0.45–1.85; p = 0.80 – Rivaroxaban: HR: 1.09; 95% CI: 0.63–1.87; p = 0.76	[85]
Steinberg *et al.* (2016)	5738 patients treated with DOACs from the ORBIT-AF II registry (9.4% were underdosed, 3.4% were overdosed and 87.2% were taking the appropriate dose)	– Overdosing was associated with increased mortality (adjusted HR: 1.91; 95% CI: 1.02–3.60; p = 0.04) – Underdosing with increased hospitalization for cardiovascular disorders (adjusted HR: 1.26; 95% CI: 1.07–1.50; p = 0.007)	[80]

AF: Atrial fibrillation; COPD: Chronic obstructive pulmonary disease; DOAC: Direct-acting oral anticoagulant; HR: Hazard ratio.
Data taken from [76–80,83–85].

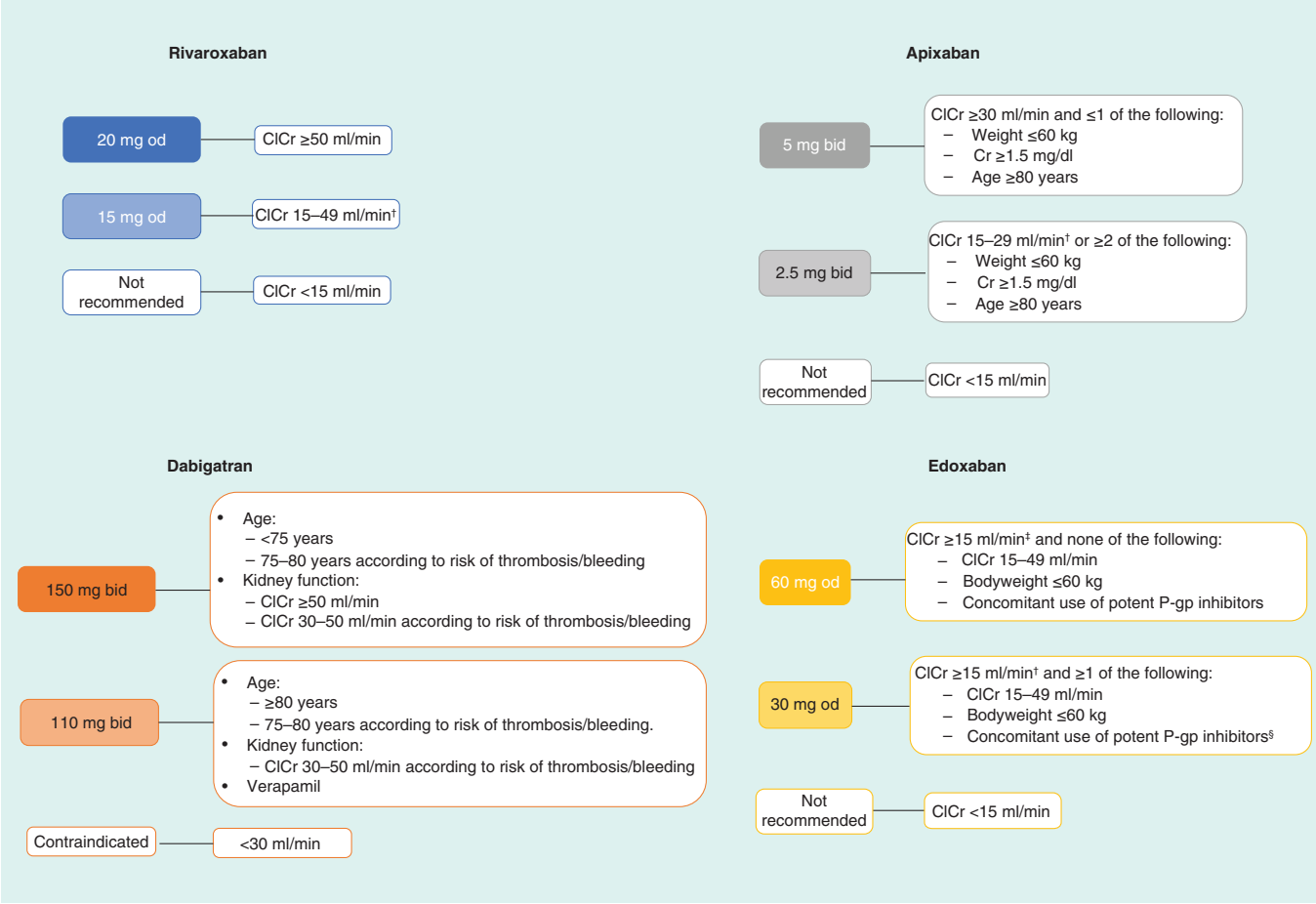

Figure 2. Dose adjustments for direct-acting oral anticoagulants according to the summary of product characteristics.
†Rivaroxaban, Apixaban, Edoxaban should be used with caution in patients with CrCl 15–29 ml/min.
‡Edoxaban should be prescribed with caution in patients with CrCl >95ml/min.
§Concomitant use of the following P-gp inhibitors: cyclosporine, dronedarone, erythromycin, and ketoconazole.
Data taken from [20,75,88,89].
bid: Twice daily; Cr: Creatinine; ClCr: Creatinine clearance; od: Once daily; P-gp, P-glycoprotein.

Overdosing – the opposite of underdosing – clearly carries a greater risk of bleeding. This is particularly important in the elderly patient, whose increased risk of baseline bleeding is often compounded with impaired kidney function and multifactorial fluctuation of the glomerular filtration rate, which requires periodic monitoring. This should be more frequent as the severity of kidney failure increases and in patients with borderline values for impairment of kidney function (glomerular filtration or creatinine) that make it advisable to modify the dose [75].

In this context, current European guidelines for the use of DOACs in patients with AF clearly recommend the need to prescribe appropriate doses of DOACs according to the summary of product characteristics in order to ensure the maximum benefit with these drugs and to prevent unnecessary complications [75].

Discussion

While AF can occur at any time during a person's life, its prevalence is the highest in elderly persons [1]. In fact, all elderly persons should be assessed for AF, especially in cases where the patient has specific co-morbidities (e.g., hypertension, diabetes, ischemic heart disease, heart failure), since the disease is often asymptomatic. Stroke can be the first manifestation, with dramatic consequences [20].

Stroke is the most common and feared complication in elderly patients with AF who have not received anticoagulant therapy. It should therefore no longer be a priority but mandatory to administer the best antithrombotic treatment possible, which in this population is anticoagulant therapy and not antiplatelet therapy [20,88,89]. While the risk of bleeding is increased in elderly patients, this does not seem to depend so much on whether the patient

is anticoagulated or not, but on his/her individual characteristics [29]. Therefore, the risk of bleeding does not mean that anticoagulation should be contraindicated or that the patient should be undercoagulated, but rather that the risk of bleeding should be minimized. In fact, there are very few reasons for contraindicating anticoagulation therapy in a population such as the elderly, who are at a high risk of thromboembolic complications [42].

DOACs, which are free of many of the limitations of VKAs and have a better safety and efficacy profile, have facilitated prescription of anticoagulation therapy [2]. Although empirical data on dose adjustment have many weaknesses, and a causal inference between underdosing and stroke or bleeding risk from real-life studies cannot directly been established, the majority of studies suggest that prescription of DOACs is currently hampered by underdosing, which entails a greater risk of stroke [4,67–70,76–85]. One of the reasons for underdosing is that physicians attribute greater importance to the risk of bleeding (which is rarely fatal) than to the risk of stroke (which is fatal in almost half of patients at 1 year of follow-up). This is clearly an erroneous approach with potentially catastrophic consequences for the patient. In addition, the fact that there are differences in the criteria for dose adjustment between DOACs means that physicians are sometimes not sure how to adjust the dose for a specific drug [2,4,67–70]. In addition, while prescription of VKAs is hampered by poor anticoagulation resulting from our inability to achieve a suitable time within the therapeutic range in around half of patients [90,91], with DOACs, we are placing patients at a reducible risk of stroke, with the only supporting argument being that an inadequate dose is indicated [83].

Poor dosing could eliminate the beneficial effects of DOACs in terms of stroke prevention. For example, while apixaban was more efficacious for the prevention of stroke and systemic embolism in the ARISTOTLE trial [54], some studies have pointed to a lesser benefit when reduced doses are used inappropriately in clinical practice [66,82]. In this context, adjusting a drug such as rivaroxaban based only on creatinine clearance could enable correct prescription in a greater proportion of patients with AF. Furthermore, in clinical practice, this agent could be associated with a lower risk of stroke than VKAs [4,67,68,76–85].

In addition to the problem of prescribing an inappropriate dose (mainly underdosing, although overdosing also occurs), we must not forget the importance of adherence, which depends on factors such as daily pill burden. The data presented above highlight the importance of simplifying dosing and the usefulness of a single dose to favor appropriate dosing and adherence, both of which are essential for ensuring that patients benefit as much as possible from their treatment [92].

A number of guidelines provide similar recommendations with respect to elderly patients with AF. These can be summarized as follows. First, all patients with AF should receive anticoagulation therapy, unless this is contraindicated. Second, anticoagulation therapy is underused in this population. Third, DOACs are preferable to VKAs for anticoagulation therapy. Fourth, the dose of DOACs should be adjusted according to the clinical characteristics of the patient, as set out in the summary of product characteristics (Table 4 & Figure 2) [20,75,88,89,93–97]. Therefore, adjusting the dose of DOACs according mainly to the physician's perception of the risk of bleeding or frailty is erroneous and can lead to underdosing and, therefore, an unnecessarily high risk of stroke [47,98]. Appropriate prescription is essential if we are to ensure the efficacy and safety of DOACs. The optimal dose should be administered according to the summary of product characteristics and should be as simple as possible. Simpler dose adjustments minimize the risk of errors. Despite that, in frail patients, subjects with cognitive impairment or older individuals and a high bleeding score, and although net clinical benefit is in favor of anticoagulation in all these cases, a thoughtful discussion should be promptly performed between physician and patient/family, in order to also consider patient's preferences [94].

In summary, attention should be drawn to the need for appropriate dosing, and we must remember that elderly patients with AF require more meticulous care that is not based on prescribing lower doses (underdosing) out of a fear of bleeding (thus ignoring the risk of stroke). They also require closer follow-up, earlier detection and correction of modifiable risk factors for bleeding, and regular monitoring of kidney function.

Conclusion

Elderly patients frequently have AF, and their risk of thromboembolic complications is very high. In fact, except for contraindications, elderly patients with AF should receive long-term therapy with oral anticoagulants. While VKAs were the first oral anticoagulant agents, their numerous disadvantages and the difficulty in controlling the international normalized ratio in this population mean that many patients do not receive appropriate anticoagulant treatment. DOACs have been proven to have a better safety and efficacy profile, even in elderly patients. However, underdosing is a common problem in clinical practice, especially in elderly patients, that reduces protection against thromboembolic complications. Therefore, DOACs should not be adjusted based on the physician's perception of

Table 4. Recommendations by clinical practice guidelines on atrial fibrillation with respect to anticoagulation.

Guideline	Recommendations	Ref.
European guidelines on AF 2016	– Age is one of the most potent predictors/risk factors for ischemic stroke in patients with AF – Older patients with AF are at greater risk of stroke and are more likely to benefit from oral anticoagulants than younger patients – The risk of stroke without oral anticoagulation is normally greater than the risk of bleeding (even at more advanced ages), dementia, frequent falls and frailty – DOACs are preferred over VKAs – Anticoagulation is underused in elderly patients – Anticoagulation should only be avoided in patients who experience uncontrolled severe falls (e.g., epileptic patients, patients with advanced multisystemic atrophy and backward falls) and in selected patients with dementia whose caregivers cannot ensure adherence to treatment	[20]
American guidelines on AF 2014 and 2019	– The risk of stroke increases with age. The CHA_2DS_2-VASc scale identifies age 65–74 years as a minor risk factor and age $\geq$75 years as a major risk factor for stroke – Anticoagulation therapy is recommended in all male patients with a CHA_2DS_2-VASc score $\geq$2 and in women with a score $\geq$3 – DOACs are preferred over VKAs	[88,89]
European Heart Rhythm Association guidelines on the management of DOACs 2018	– Prevention of stroke in elderly patients is important, since the risk increases with age – Anticoagulation is recommended in elderly patients (absolute reduction of major risk in young patients). However, anticoagulation is underused in elderly patients – DOACs are preferred over VKAs – Elderly patients have more co-morbidities, including kidney failure. This is important when adjusting the dose of the DOAC – Frailty, dementia and the risk of falls alone do not contraindicate anticoagulation	[75]
ACCP 2018	• For patients with AF without valvular heart disease, including those with paroxysmal AF: – CHA_2DS_2-VASc 0 in males or 1 in females: no antithrombotic therapy – CHA_2DS_2-VASc 1 in males or 2 in females: oral anticoagulation rather than no therapy, aspirin or combination therapy with aspirin and clopidogrel – CHA_2DS_2-VASc >1 in males or 2 in females: oral anticoagulation rather than no therapy, aspirin or combination therapy with aspirin and clopidogrel – DOACs are suggested over VKA. – Attention to modifiable bleeding risk factors should be made at each patient contact – AF and AF-stroke related is associated with age – Aspirin has no benefit in the elderly	[93]
Australian clinical guidelines 2018	– Thromboembolic risk of stroke in AF increases strongly with increasing age – Oral anticoagulation therapy is recommended in patients with nonvalvular AF whose CHA_2DS_2-VA score – the sexless CHA_2DS_2-VASc score – is $\geq$2, and should be considered in case of CHA2DS2-VA score is 1 – DOACs are recommended in preference to warfarin – Antiplatelet therapy is not recommended, regardless of stroke risk – In frail people and older people, a high bleeding score should be promptly discussed between physician and patient. But the net clinical benefit is in favor of treating older people – Patients with a high risk of falling benefit from anticoagulant therapy due to the high risk of stroke over intracranial hemorrhage risk	[94]
Canadian guidelines 2018	– For patients with AF aged >65 years or with a $CHADS_2$ score $\geq$1 and coronary or arterial vascular disease (peripheral vascular disease or aortic plaque), long-term oral anticoagulation alone is recommended – When an oral anticoagulant is indicated in the presence of coronary or arterial vascular disease, a DOAC over warfarin is suggested	[95]
Korean guidelines 2018	– For patients with AF without valvular heart disease, including those with paroxysmal AF: ○ CHA_2DS_2-VASc score of 0 in males or 1 in females: no antithrombotic therapy ○ CHA_2DS_2-VASc score of 1 in males or 2 in females: oral anticoagulation rather than no therapy, aspirin or combination therapy with aspirin and clopidogrel ○ CHA_2DS_2-VASc score $\geq$2 in males or $\geq$3 in females: oral anticoagulation rather than no therapy, aspirin or combination therapy with aspirin and clopidogrel – Elderly increases the risk of stroke and bleeding – Oral anticoagulation has a positive net clinical benefit in elderly patients – DOACs are preferred over VKA – Falls risk and cognitive impairment: the benefits of ischemic stroke reduction generally outweigh the risk of harm from serious bleeding with anticoagulation – The Korean AF guideline recommends low-dose rivaroxaban (15 mg q.d.) in patients aged $\geq$80 years	[96]
Asia Pacific Heart Rhythm Society 2017	– CHA_2DS_2-VASc score 0 for males or 1 for females: no antithrombotic therapy is recommended – CHA_2DS_2-VASc score $\geq$1 for males or $\geq$2 for females: oral anticoagulation should be considered, and DOACs are recommended over VKA – Aspirin is not recommended solely for stroke prevention in AF	[97]

Dose adjustment consistent with the summary of product characteristics.
AF: Atrial fibrillation; DOAC: Direct-acting oral anticoagulant; VKA: Vitamin K antagonist.
Data taken from [20,75,88,89,93–97].

the risk of bleeding, but on the indications of the summary of product characteristics of the individual DOAC. Simpler dose adjustment could reduce the risk of dosing errors and improve patient protection. In addition, a single daily dose favors adherence. Attention should be drawn to dose adjustment in order to ensure appropriate use of DOACs and to improve protection against stroke in patients with AF.

Future perspective

Strategies for dosing of DOACs should be periodically reviewed to ensure that appropriate doses are being administered and patients receive optimal anticoagulation therapy. Differences in the criteria for doses adjustment between DOACs and reassessment of the perception of bleeding can help physicians to adopt the best approach for an individual patient and thus prevent stroke. Efforts should be made to simplify dosing in order to improve adherence.

Executive summary

Relevance of atrial fibrillation in the elderly patient
- Atrial fibrillation (AF) is highly prevalent in the elderly, and prevalence is expected to rise in the coming years.
- AF is underdiagnosed.
- Co-morbid conditions and polymedication can hamper management.
- Kidney failure increases the risk of stroke and bleeding in patients with AF.

Assessment of the risk of stroke & bleeding in the elderly patient
- The risk of stroke and bleeding must be assessed on an individual basis.
- The risk of stroke increases with age.
- While several independent factors favor not anticoagulating elderly patients (e.g., advanced age, dependence, cognitive impairment, frailty and risk of falling), none of these alone should contraindicate anticoagulation.
- Antiplatelet therapy and vitamin K antagonists (VKAs) are less efficacious than direct-acting oral anticoagulants (DOACs) for preventing stroke in elderly patients with AF.

DOACs in the elderly patient with AF
- DOACs overcome most of the limitations of VKAs and have a proven safety and efficacy profile.
- DOACs have become the drug of choice because of their net clinical benefit, ease of administration, low probability of interactions, low risk of intracranial hemorrhage, reduced progression of kidney disease and favorable effect on cognitive impairment.
- While differences in patient characteristics make it difficult to compare results, there seems to be general agreement that DOACs are preferable to VKAs in elderly patients.

Importance of appropriate dosing of DOACs in elderly patients
- DOACs are effective and safe when used at appropriate doses.
- DOACs are often administered without taking into account the recommendations of the summary of product characteristics.
- Underdosing is associated with advanced age, kidney failure, co-morbidities and a high risk of bleeding and thromboembolic events.

Discussion
- All elderly patients should be assessed for AF, since the disease is often symptomatic.
- The risk of bleeding does not mean that anticoagulation should be contraindicated.
- Adherence can be improved by simplifying dosing.

Conclusion
- Elderly patients with AF should receive long-term therapy with anticoagulants.
- Underdosing is a common problem in clinical practice that reduces protection against thromboembolic complications.

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