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Chapter

Use of Non-Vitamin K-Dependent Oral Anticoagulants in Elderly and Fragile Patients with Atrial Fibrillation

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Abstract

Atrial fibrillation is a frequently observed entity in medical practice, with cases on the rise if we focus on age groups of frail elderly patients. It is important to identify them since advanced age and comorbidities suppose greater numbers of cases of thromboembolic diseases and strokes, entities that can be prevented with the non-vitamin K antagonist oral anticoagulants (NOACs), managing a balance between prevention and safety and thus avoiding complications, for this, a correct search and screening must be made to reach the largest number of patients who could benefit from this therapy. Old age is not a synonym of frailty, so, we must be cautious with the loss of autonomy of our patients and we must have a multidisciplinary approach to accompany this increasingly frequent and extended period, being very alert to drug interactions and decreased daily life skills.

Keywords: elderly, direct oral anticoagulants, fragility, nonagenarian, non-vitamin K antagonist oral anticoagulants, atrial fibrillation, anticoagulation

1. Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia in the elderly in daily medical practice, with a correlation of decade-by-decade growth in the world population, being the onset and may also be part of various concomitant diseases that worsen the health of the population.

In the elderly patient, AF anticoagulation is used to prevent systemic embolic events (SEE) and stroke phenomena and their consequences; vascular dementia; worsening of heart failure (HF) and kidney function, among other pathologies.

In the indication of anticoagulation, the use of direct oral anticoagulants (DOACs) is gaining ground over treatment with vitamin K antagonist (VKA), this is due to their easy use of the indicated medication, their wide therapeutic window, the few adverse effects, and extensive support of scientific information that supports them.

The four large randomized pivotal works in Non-Valvular Atrial Fibrillation (NVAF) on anticoagulation [1–4] have included approximately 27,000 patients,
mostly under 75 years of age, so later works were generated with observational evidence from the database in different countries on patients over 75 years of age, octogenarians and, a little less, in nonagenarians and patients over 90 years old.

Frailty has taken on a notorious relevance in recent decades due to the increase in life expectancy, thanks to improvements in the care of elderly patients, better medical treatments, and early diagnoses of comorbidities.

The age segment of nonagenarians has constant growth worldwide, and in addition, this group of patients, who suffer greater comorbidities and increase in embolic episodes, which can be prevented, gives rise to a dilemma that we hope to clarify, the fears of anticoagulation and the benefits of using DOACs.

2. An elderly patient with AF

2.1 Epidemiology

The elderly world population >65 years old in 2004 was 461 million, and it is estimated that it will grow 4.3 times by 2050 [5].

The challenge proposed by diagnosing a supraventricular arrhythmia, as frequent as atrial fibrillation (AF), is important to avoid future complications, such as systemic embolism (SEE) diseases, stroke, heart failure, tachycardiomyopathies, worsening cognitive disorders and dementia, increased fragility syndrome, and polypharmacy.

AF screening in the elderly population is of paramount importance. It is at 4.6% which positions it in a perfect cost-benefit balance (it takes only 70 elderly individuals to find a patient with AF) [6].

2.2 Diagnosis of AF in the elderly

AF can be detected in the patient in different medical areas, such as in an emergency service, in clinical consultation, in a pre-competitive check-up for sports, and in an immediate postoperative period.

Semiology should be used with the simple manual pulse socket or with different devices; electrical tensiometers, smartwatches, and in those who have some type of external monitoring the multi parameters, Holter, etc., or some instrument for internal monitoring are the loop recover, pacemakers, defibrillators, etc. In this way, it is about looking for, when interrogating these devices, the atrial high-frequency episodes (AHFE) characteristic of AF, which will then be corroborated with 12-lead electrocardiogram “Gold Standard” to be able to make the diagnosis of clinical AF and if it cannot be compared with ECG, it will be a subclinical AF.

In elderly patients, it is recommended to use the nominal classification of AF; previously undiagnosed AF, paroxysmal AF, persistent AF, long-term persistent AF, and permanent AF. All AF modalities must be anticoagulated or look for all the tools to be able to do so, except those that are contraindicated [6].

One term that falls into disuse is Non-Valvular Atrial Fibrillation (NVAF) [6, 7] which encompasses all AF except those for which anticoagulation with DOACs does not represent a benefit; moderate or severe mitral stenosis and those concomitant with mechanical heart valves.

In an elderly patient with NVAF, the thromboembolic probability he/she suffers must be weighted, by using the CHA2DS2VASc scale [8] where it is established that the elderly patient who is ≥75 years old, provides information to establish a crucial score
of 2, with an embolic probability of 4% per year, and if the patient is also female, 1 point with this sum of data, anticoagulation is a priority (Class I A) [9].

When the stroke prevention score is established, the probability of bleeding should be assessed with the HAS-BLED scale, which is a daily example of a 65-year-old patient with knee osteoarthritis, added to this a history of the previous stroke, who drinks wine daily and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), gives a count of four with a probability of bleeding of 4.9–1.9% annually. But it is advisable to suppress alcohol consumption and change the type of painkillers to non-NSAIDs, the eventuality of future bleeding is reduced to 1.88–3.2% per year [10].

Glomerular Filtration Rate (GFR) is another important factor to be able to assess renal function with a calculation formula, “Crockoft Goul formula” (CG) estimated by the patient's serum creatinine, age, weight, and a constant numeric denominator. The result of this equation is corrected in the case of female patients [9, 11].

When studying healthy elderly people aged 70–101 years, a significant correlation between age and GFR measured with CG was observed, where it was concluded that GFR figures decrease by 1.01 ml/min per year [12].

An anticoagulation card was designed to be taken to each medical consultation and which includes useful tools to help decide on anticoagulation and to make dose corrections at each medical visit if the patient required it (Figure 1).

Once it is decided to treat with anticoagulant an elderly patient, the challenge is to choose the right anticoagulant for each patient. DOACs or Warfarin? If you choose the first one, the options are—dabigatran, rivaroxaban, apixaban, or edoxaban. An attempt will be made to bring the right option closer during this chapter.

### 2.3 Elderly anticoagulated patient

In the pivotal trials on anticoagulation in patients with NV AF, individuals with an average age of 70 years, small ethnic groups, with a lower percentage of women, and none with renal failure on dialysis enrolled.

The four large studies, such as ARISTOTLE included 3658 patients >75 (31%); in RE-LAY, n = 7258 (40%); in a subgroup of ROCKET–AF, N = 6259 (44%) and in the ENGAGE AF–TIMI 48 trial, n = 8474, (40.05%).

All this forceful but scarce information in relation to the elderly led to multiple analyses of real-life data.

In 2017, a group of patients (n = 110) who were between 66 and 100 years old (average age of 80.4 years) was studied, of which 45% were women. The use of apixaban at maximum doses of 5 mg every 12 hours or doses lower than 2.5 every 12 hours was observed when they met 2 of 3 criteria stipulated in the ARISTOTLE study (>80 years, weight < 60 kg, and plasma creatinine >1.5 mg/dl).

Patients who received the maximum recommended doses, approximately 10% had drug concentrations above the expected range, as did 2/3 of the patients who used apixaban 2.5 mg every 12 hours.

Differences in the proportion of apixaban concentrations within or outside the expected ranges were not significantly different. However, four patients had apixaban dosage above the expected range.

This increase in drug concentrations found in this small group of elderly people could allow the possibility of a blood dosage of the anticoagulant drug, to minimize inconveniences, since these patients, old as such, have not been taken into account in large randomized studies [13].
In a Canadian meta-analysis of three cohorts (n = 227,579) in which different DOACs were compared (rivaroxaban vs. dabigatran, apixaban vs. dabigatran, and apixaban vs. rivaroxaban). It served to assess each other’s effectiveness and safety.

The follow-up period was approximately 5 years, with an average participation age close to 75 years, with a low percentage of women, CHA2DS2VASC = 2.5. These patients were treated with high doses and reduced doses of non-vitamin K antagonist oral anticoagulants (NOACs).

The meta-analysis concludes that apixaban in these elderly patients was associated with fewer ischemic stroke events and systemic embolic (ES). When compared to rivaroxaban, a 15% decrease was found, and with respect to major bleeding (MB) the data obtained in favor of apixaban was 39% [14].

Regarding dabigatran in the RE-LAY study compared to warfarin when segmented by age in over 75 years of age (n = 7258), it significantly reduced stroke and intracerebral hemorrhage (ICH) and was also shown that at a dose of 110 mg every 12 hours it is a safe option for patients >80 years old when it comes to reducing the slight increase in extracranial bleeding [15].

Based on the ROCKET-AF study, where 44% of patients were >75 years old, rivaroxaban prevented stroke and reduced bleeding in life-threatening critical anatomical areas and bleeding from all causes. The reduction of the hemorrhagic stroke was 41%, with a p < 0.02. This group of patients was more polymorphic and they benefit from the use of rivaroxaban if they had the previous stroke as history, both young and elderly patients [16].

In 2015, 30,655 patients >75 years old were recruited in eight studies published as a meta-analysis. The different DOACs vs. warfarin (two studies for apixaban, n = 2850; one study for dabigatran, n = 2466; two studies for edoxaban, n = 2838; three studies for rivaroxaban, n = 3082) were compared with a follow-up of 3 months to 2.8 years.

This meta-analysis evaluated the efficacy of each drug in elderly people with stroke events and systemic embolisms (ES), also MB and clinically nonrelevant mayor bleeding (CNRMB).
All DOACs compared to warfarin were significantly better, by an average of 29%. Regarding safety, edoxaban and apixaban turned out to be more beneficial in this group of elderly. Dabigatran in doses of 150 mg and 110 mg, both in two daily doses, had a higher number of gastrointestinal (GI) bleeding, along with rivaroxaban, which also had a lower safety profile (Figures 2 and 3) [17].

Based on data collected in the Norwegian patient registry and the database of the same country, from 2012 to 2017, where the use of NOACs (standard dose and reduced doses) vs. warfarin is compared, it was observed.

The total population studied was 31,041 of >75 years (average 82 years), 52% women with an average of CHA$_2$DS$_2$VASC = 4.5.

The use of DOACs in standard and reduced doses decreased stroke and systemic embolism like warfarin, but the administration of low doses of DOACs is either similar or reduces bleeding complications. A door could be opened for future randomized subdose studies [18].

Three prespecified groups of edoxaban vs. warfarin were studied, with a follow-up of approximately 2.8 years, in patients with NVAF. The third group, >75 years old, had 52% permanent AF. The direct oral factor Xa inhibitor was used in the standard and reduced doses, the latter by 41%.

About 2.3% stroke and SEE were observed, 4.8% of MB with significant data. Embolisms were reduced by 17% and the same percentage of reduction was achieved in bleeding, so a safety tool is provided in the elderly when compared to younger patient groups [19].

START T Register 2, studied in people over 85 years of age, showed that using DOACs there was low mortality, similar bleeding when compared to warfarin treatment. In addition, a small increase was observed in very elderly patients with embolic events with the use of direct oral anticoagulants [20].

The use of warfarin has its disadvantages in long-lived patients; such as the need for frequent measurements of the International Normalized Ratio (INR), which is not always in a standardized window, and therefore has the difficulty in entering the Time in Therapeutic Range (TTR).

![Figure 2](image.png)

*Stroke and systemic embolism in subjects older than 75 years with DOACs.*
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Warfarin interrupts the necessary recycling of vitamin K, which is an essential cofactor for the carboxylation of glutamic residues responsible for producing proteins indispensable for clotting. An example of this is the decrease in protein C levels, which can favor calcium deposits in the skin and other organs; as well as, this vitamin is required in the primary phases of bone matrix formation, effects of paramount importance in this advanced age group [21, 22].

In a database, a retrospective cohort of the city of Taiwan was observed (n = 17,008), an average of 28% reduction in osteoporosis was observed when comparing DOACs vs. warfarin.

DOACs, especially the use of apixaban, minimize osteoporosis by 62% and rivaroxaban also does so by 32%, a decrease that is not statistically significant in those compared to dabigatran [23].

DOACs do not deteriorate the γ-carboxylation of osteoclastine and do not disfavor the formation of the bone matrix, a very interesting topic for good “bone health.”

3. Frail patient with AF

3.1 Epidemiology

The collection of information and quantification on fragility syndrome leads to analyzing a wide range of data dispersion, from different ethnic groups, various forms of measurements, in addition to the disparate life expectancy in different countries.

Fragility in the US has a higher incidence in white ethnicity [24], in Latin America and the Caribbean, there is data of great percentage disintegration, from 7.7 to 42%, with an average of 19.6% (data surpassed in North America, Europe, and Oceania) [25].

Atrial fibrillation (AF) is the unprevalent supraventricular arrhythmia in the young population, 2–3 cases per 1000 inhabitants, but the number of cases grows
considerably to 50–90 per 1000 people ranging from 62 to 92 years [26, 27], and its number will multiply by 2.5 times by 2050 [9, 28], the product of its greater emphasis on the detection of arrhythmia.

The finding can range from the simple taking of the pulse looking for its classic irregularity to the need to search for information through the use of implanted devices (pacemaker, cardio-defibrillators, loop recorder) or diagnostic methods, such as 24-hour Holter, smartwatches, pulse meters.

In fragile patients, AF is more frequent, although the data can widely vary from 4.4–75% by different measurement modalities [29].

In a systematic review that included 21 studies, from 1998 to 2010 on four continents, with a total of 61,500 participants over 65 years of age, a variable range of data ranging from 4.0% to 59.1% was found with a fragility prevalence of 10.7% (95% CI = 10.5–10.9). As is already known, this percentage increases with age and female sex with significant statistical data of p < 0.001; and when talking about pre-fragility, the percentage found is close to 42% [30].

The Framingham Heart Study shows us that age as a solitary variable is sufficient predictive value in elderly people aged 80–90 years to increase the probability of suffering a stroke or transient ischemic attack (stroke/TIA) by 23.5%. In this population follow-up, one in three people of European descent will suffer from AF throughout their lives [31, 32].

In the totality of patients over 85 years of age, between a quarter and half of the patients are fragile, so it could be considered, who expect that two-thirds of the long-lived population could be prevented or detected to avoid disabilities.

### 3.2 Definition

Fragility as a syndrome is more frequent in patients in the last decades of their lives. It is characterized by a state of greater vulnerability, where different stressors contribute to the loss of physiological reserves, with the subsequent rupture of the homeostatic balance.

The most frequent stressors that trigger this physiological harmony can be of different characteristics; from chronic conditions, such as diabetes mellitus, chronic obstructive disease, skin infections, such as erysipelas, respiratory sequelae left by COVID-19, heart failure, atrial fibrillation, hip fracture, and long periods of bed rest, stroke, loss of loved ones, widowhood, loneliness, and low economic level.

Fried et al. in 2004 [33] establishes a clinical syndrome, describing the presence of three or more criteria that are summarized in Figure 4.

When the loss of physiological reserves is affected by two noxas, it is called pre-fragility, which when new noxas are added to them, becomes fragility syndrome. Subsequently, if more decompensating factors are added, a dreaded disability could arise (Figure 5) [34].

### 3.3 Fragile patient assessment tools

To recognize fragility early, a comprehensive assessment is needed, using clinical, functional, behavioral and biological markers [35, 36] that can help measure or quantify through the weighting Activity of Daily Living (ADLs), using the Katz index (eating, clothing, personal hygiene, bathroom use, continence management, and mobility). At earlier stages, you can use the assessment of the Instrumental Activity
of Daily Living (IADLs), measured by the LOWTON index (use of the phone, shopping, preparing meals, take care of your home, laundry, use of transport, the correct taking of your own medication, the management of the home economy) [37] and the Charlson comorbidity index [38, 39].

If the evolution of the clinical phenotype of fragility is followed at 3 years, F patients with lower economic resources suffer greater comorbidities, such as frequent falls, stroke, thus worsening mobility and ADLs [40].
3.4 Fragility and anticoagulation

The interest in information on anticoagulation and fragility is growing, thanks to more available information and a better understanding on the subject that being elderly is not the same as having fragility syndrome. Although many elderly individuals suffer from three frequent criteria, such as physical fatigue, weight loss, and slowness when traveling, these items can be reversed if patients are educated in better nutrition, regulated weekly physical activity, if possible with the supervision of trained staff (aquagym, hiking, Tai Chi, etc.) and in turn prevent sarcopenia with improvements in postural balancing and in this way, falls would be avoided [41]. Age ≥ 75 years provides the crucial points to prevent the probabilities of thromboembolism (TE) and stroke with anticoagulants (OACs), according to the CHA2DS2-VASC score in patients with NVAF.

This data is relevant, since, for example, it was observed in 2018, in Argentina, it had registered 31,700 visits per year to a Hospital Emergency Service with a large dispersion in the age range, the average age of 75 years was recorded [42].

Fumagalli et al. studied frail elderly patients older than 70 years with AF (10%) in 14 European countries; they were divided into three age groups. It was observed that 37% of patients, medicated with DOAC (37%) and 5.7% of individuals who cannot be given anticoagulants, were treated with left atrial appendage closure (LAAC).

Less than 11% of the treating physicians considered age as an individual factor for not medicating with anticoagulants, a fact not sufficiently explained by the authors [43].

In a survey conducted in 41 European centers, patients considered fragile and their influence on the management of arrhythmia was studied. AF was found in 72% of patients.

About 57% were diagnosed as fragile patients; 29% were pre-fragile; and 8% of the studied population was >85 years old, which had a higher number of comorbidities and higher rate of drug use, data that reached statistical significance [44].

In relation to falls and the use of DOACs, two studies were carried out; the first was a retrospective subanalysis of ARISTOTLE. It included 753 patients aged 65–74 years, who suffered falls and had a greater number of comorbidities. An 80% benefit was observed in terms of the reduction of intracerebral hemorrhage (ICH) when compared to this group of patients, the use of apixaban vs. that of warfarin [45].

In the second prospective study, a subanalysis of ENGANGE AF, TIMI 48 where patients were treated with edoxaban or warfarin, patients who had falls and those who did not have it were analyzed.

This observed population group (n = 900), older (average 77 years), with more comorbidities (Charlson Comorbidities Index > 5, CHA2DS2-VASC > 5, HAS-BLED > 3, 50% permanent AF), had a reduction in mortality and significant severe bleeding, with a considerable decrease in the dreaded intracerebral hemorrhage (ICH) [46].

In the analysis of a subgroup of ARISTOPHANES, considered the largest retrospective observational study using a US database, from 2013 to 2015, they were a population group of fragile elderly people with NVAF with an average age of 83–84 years. Comparing cohorts of patients medicated with DOACS (apixaban, dabigatran, and rivaroxaban) or warfarin, significant weights were established referring to stroke/ES and MB risks [47].

All patients with AF were 150,487, 34% of these were fragile, 90% had a CHA2DS2-VASC score ≥ 4, taken as a high risk of stroke, and in more than 80% a HAS-BLED ≥ 3, was considered a threat to bleeding.
Better response with respect to SEE and stroke risk was found with patients who received apixaban (49%) and rivaroxaban (21%), compared to those treated with warfarin.

In relation to MB, apixaban (38%) and dabigatran (21%) had less bleeding and with regard to rivaroxaban vs. warfarin, in the former, there was a small increase in bleeding.

In the SAFIR Cohort study, 995 fragile elderly people were admitted to 33 centers and then followed for a year, it was sought to compare the use of rivaroxaban vs. warfarin.

This group of elderly people with many comorbidities was made up of 23% of nonagenarian people, almost half suffered from a decrease in kidney function, 77% high blood pressure, 50% malnourished, 41% anemia, 39% dementia, and 27% falls (an average of the different scores: $\text{CHA}_2\text{DS}_2\text{VAsc} = 4.8$, HAS-BLED = 2.3, mini-mental test = 21.5, activities of daily life 4.4, CCI = 6.7).

When comparing the two Cohorts (rivaroxaban vs. warfarin), adjusted to comorbidities, age, and previous treatment, fragile elderly patients who used rivaroxaban had a significant reduction in MB of 33%, a lower percentage of ICH of 48%, with no differences in mortality decrease and stroke [48].

So, the use of DOACs in fragile patients is a good therapeutic alternative, due to the wide use in the treatment of these patients, wide therapeutic range, predictable pharmacokinetics, easy administration, and little drug interaction; without the need for frequent monitoring and dose adjustment, what is very important in this age group.

The fragile patient is significantly vulnerable due to the polypharmacy by which the use of DOACs in AF dispenses with therapeutic bridge with low molecular weight heparin and helps expand the range of a better diet, being able to incorporate leafy vegetables, contained with the use of vitamin K antagonist [49].

4. Nonagenarian patient with AF

4.1 Epidemiology

Improvements in health systems and education in human care progressively lead to an increase in life expectancy, especially in developed countries.

The population census of Spain 2021 had a total of 47,394,223 inhabitants, with a record of 491,369 (1.03%) individuals $\geq$ 90 years old [50]. In Argentina, 45,808,747 people were projected for 2021, of whom 242,409 (0.53%) would be ultra-elderly people [51].

In Germany, according to population growth projection data in 2021, the total population of 83,450,000 and is expected by 2030 to be 82,857,000, with a slight population decrease of 593,000 people (0.71%). Paradoxically, the numerical count of residents will increase in the age group $\geq$ 90 years, from 878,000 to 1,403,000 (1.69%); and in this way, it is speculated that the number of very long-lived individuals will grow by 59.79% [52].

In the prospective longitudinal study in Gothenburg, Sweden, which initiated the enrolment of patients at 70 years and was then followed for 30 years; an AF prevalence of 16.8% at 90 years was recorded, with an incidence of approximately 47/1000/year in both sexes; and in the 95–99-year group ($n = 189$) it had an almost double incidence of 93/1000/year; with an increase in men [53].
4.2 Anticoagulated nonagenarian patient

In the subanalysis of very elderly patients with NVAF, J-RHYTHM registry, 7406 consecutive individuals were enrolled who were divided into three age groups (<70 years; 70–84 years, and >85 years).

This elderly population of the third age group with the highest preponderance to polypathologies (n = 330) had an average age of 87.4 ± 2.8 (4.4%), with 58.8% permanent AF. The combination of thrombus embolism and major bleeding was lower in those who used warfarin at an International Normalized Ratio (INR) between 1.6 and 2.59 with a p < 0.001.

The registry compared the ultra-elders the use of warfarin with a TTR of 67.1 vs. the other group, those who did not use warfarin. It was postulated that it could be used in very long-lived, with a lower INR range than that used in large anticoagulation works [54].

Based on the National Registry of Taiwan 2012, T.-F. Chao et al. [55] investigated patients >90 years with NVAF in a total of n = 16,798 with an average age of 92.5 years.

N = 7362 were observed with different pre-existing diseases, such as chronic kidney disease, n = 3151 (CKD); intracerebral bleeding, n = 950 (ICH); and gastrointestinal bleeding, n = 5370 (GI).

About 67.3% of the patients studied, n = 4955, were not treated with anticoagu-
lants (N-OACs), and 32.7%, n = 2407 were anticoagulated (OACs).

Of the OAC, DOACs was used in 23.6%; apixaban (n = 190), 2.6%; rivaroxaban (n = 927), 12.6%; dabigatran (n = 620), 8.4%; as a vitamin K antagonist, warfarin (n = 670), 9.1%.

Rivaroxaban was the most used DOACs in doses of 10 mg, 15 mg, and 20 mg once a day, with a preference of treating physicians with doses of rivaroxaban 15 mg/day at 41%. Regarding apixaban, the doses of 2.5 mg every 12 hours and dabigatran 110 mg twice a day were the most frequently chosen drug presentations (Figure 6) [55].

A total of 1750 patients with AF >90 years of age were identified from three regions of Spain, these enrolled individuals were divided into three groups; the nonanticoagulated n = 534; those anticoagulated with vitamin K antagonist (VKA), n = 500 with INR = 2–3. Those who were treated with DOACs, n = 716. Patients had a creatinine clearance close to 50 ml/min [56].

In a subanalysis of the FREFER-AF study, 6412 adult patients with AF were enrolled and followed for 12 months. In this European registry, they were divided into three age groups (<85 years old; >85 years old; and >90 years old), 84 of them were extremely elderly.

This segment of ultra-elderly people suffered a net clinical benefit when they were anticoagulated with DOACs, a balance given by a reduction in thromboembolic events of 43%, which is evident when treating 50 individuals to avoid an event.

A significant difference was established in favor of anticoagulantes of 4.6%; p < 0.48, with an increase in major bleeding similar to patients >75 years (younger), the comparison was made by age groups who took only anticoagulants, only anti-platelets, or the sum of the two, p < 0.025.

Regarding MB, it had only a 10% increase compared to the extremely elderly (>90) who were not anticoagulated.

The net clinical benefit is observed in the three groups, with greater intensity in those over 90 years of age, being 8.02% with a p < 0.0036 (Figure 7) [57].
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It was found among the best net benefit of reducing embolic phenomena and bleeding to anticoagulated patients >90 years old (6.1% use of DOACs).

Nonagenarian patients aged 90–100.1 years (n = 300) with an age average of 91 years who suffered from AF and were medicated with OACs were studied.

Extremely elderly individuals were divided into three groups; those who took DOACs (n = 93), those who took warfarin (n = 147), and a third group (N-OACs) n = 80 who were not medicated with anticoagulants.

Regarding the stroke/TIA/SEE the DOACs were statistically significant reduction (Figure 8) and it was observed on the bleeding events the DOACs had twice the percentage of bleeding—5%/year vs. 2.5% from warfarin use (p < 0.048) (Figure 9) [58].

As already observed, in the subanalysis of the START-T Register, done in Italy, patients enrolled from 2012 to 2013, elderly people with NVAF, who were mostly treated with warfarin as an anticoagulant since the spread of the use of DOACs was beginning in this country. Two-thirds of the elderly were observed to have moderate or severe kidney disease [20].

In the START-T Registry 2 subanalysis, elderly people enrolled with VNAF, with average age 88.4 ± 2.8, compared DOACs (41.3%) vs. warfarin in the range 2–3 (58.7%).

The study was divided into two groups, <85 years and >85 years (n = 3209), in the second group, >90 years out of age 55 patients (1.7%).

In very elderly patients it was obtained; a mortality rate and a lower risk of sacred with a small thromboembolic increase [59].

In the Swedish design of 30 years of follow-up of patients with and without AF, separated by sex, it was observed that among survivors, the cumulative incidence of AF was more than 50%. Patients with AF had twice the chance of death [60].

In a geriatric institute, 77 geriatric patients with an average age of 80 ± 7 years, anticoagulated with warfarin and DOACs, were retrospectively enrolled after a
fall from their own height or less. After admission to the hospital, he/she had a brain CT scan where the tomography image was accepted as positive if an ICH was observed.

The first brain CT had 20.8% positivity, then in an average control of 8 hours, in those patients with images that were negative, 9.8% HIC was found not detected previously.

Figure 7.
Net clinical benefit adjusted for the mortality risk, of OAC vs. no OAC (adapted).

Figure 8.
Annual STROKE and TIA events.
In the group of patients who took warfarin, there was 30% HIC vs. 14% of those who took DOACs. Patients who used DOACs had a higher rate of use of aspirin and clopidogrel [61].

In the Japanese study on anticoagulated elderly people, SAKURA-AF Registry, three groups of elderly people were enrolled, the third group, of very elderly with an average age of 87.3 years ± 2.5 (>85 years of age and under <97 years of age) where the use of DOACs and warfarin were compared.

About 45.8% DOACs were used and of these, 79% were in low doses. The study described those embolic events increase, in proportion, more than hemorrhagic events, and suggested the effective use of DOACs in very old people [62].

In a larger prevalence study of nonagenarian patients with anticoagulated AF made in the city of Madrid, published 2019, 10,077 nonagenarians (17%) had a high prevalence of comorbidities, 67.2% were anticoagulated; they used 11.6% DOACs [63].

The Berlin Registry ≥89 years studied by Wutzler et al., with an average age of 92-year-old patients who received anticoagulants by 26.5%; they used 21.1% vitamin K antagonist, and 5.4% used DOACs [64].

Regarding the falls, very frequently in nonagenarian, with the classic analysis of the Markov model, it was shown that to suffer from a dreaded subdural hematoma in anticoagulated patients with warfarin over 1 year, a hypothetical number of 295 falls is needed, to overcome the benefit of said anticoagulation [65].

When studied in patients aged 90 years old vs. <60 years old, fall mortality increases considerably (5.5% vs. 0.9%).

In a 10-year retrospective cohort study, which included 5088 traumatized patients, young and nonagenarian patients were compared.

It was observed that the <60 years had an early home discharge of 73.7% vs. 18.2% (p < 0.001). Patients who used aspirin had greater intracerebral bleeding (p = 0.001).
As for mortality caused by all injuries caused by trauma, added to death from cerebral hemorrhage, aspirin (p = 0.046) and warfarin (p = <0.001) show worse rates [66].

In the population analyzed in Spain in patients over 90 years of age in acute renal failure, the functional decline was the most frequent cause, presenting with 71% of hypertensive patients, 43% chronic kidney disease, 26% with AF among others [67].

A Korean database under review (n = 20,575) was used, where the use of DOACs and warfarin in elderly people with AF was compared.

In the total group of patients over 80 years of age, a positive benefit was observed on the outcomes of the clinical combination (ischemia, stroke and major bleeding), but there were no significant differences in people over 90 years of age; however, the largest East Asian study showed that extremely elderly patients (≥ 90 years (n=2142)), who were anticoagulated with NOACs, had benefits over the use of Warfarin.

Treatment with NOACs was preferred (83.3%), and warfarin was also used (almost 16%); of the total number of patients taking NOACs, 80% used low doses of anticoagulants [68].

GFR is extremely important in nonagenarians and we must keep in mind the Crockroft-Gaul formula for anticoagulation, it is of the simple and practical equation that contemplates a wide age range (25–100 years) [11].

Taking into account that renal function declines in elderly people, especially GFR and effective glomerular flow, with a 10% drop in the latter per milliliter/minute/body surface [69].

5. Conclusions

Over the years, patients with AF, the elderly, the very elderly, and the fragile increase the likelihood of thromboembolic diseases, as well as having bleeding with gastrointestinal predominance, after a stroke or after falls.

Since the appearance of DOACs, an optimal, versatile, and easy-to-use treatment has been found to maintain the thin balance between patients who most need to be prevented from SE and Stroke, and bleeding.

A reduction given by the drug group was obtained, an average of about 50% of HICs with a decrease in major bleeding, including GI.

The decision of the type of DOACs must be made to the measure of each patient and taking into account the precautions of a prior comprehensive assessment of the long-lived person.

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Conflict of interest

The author declares no conflict of interest.
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older they are the harder they fall:

