Oral anticoagulation in octogenarians with atrial fibrillation

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Abstract

Background. Vitamin K antagonists (VKAs) are still largely employed, even in nonvalvular atrial fibrillation (AF). Our aim was to study the clinical profile of octogenarians treated with oral anticoagulation and to study the effect of age on the quality of VKAs anticoagulation.

Methods. Data are from a prospective national registry in an adult Spanish population of nonvalvular AF. We included 1637 patients who had been receiving VKAs for at least 6 months before enrolment.

Results. Mean age was 73.8 ± 9.4 years. Patients aged > 80 years (N = 429) had a high risk profile with higher risk of stroke and bleeding than younger patients; CHA_2DS_2-VASc (Cardiac failure, Hypertension, Age > 74, Diabetes, Stroke, Vascular disease, Age 65–74 years, and Sex category) 4.5 ± 1.3 vs. 3.5 ± 1.6, $p < 0.001$, HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 64 years), Drugs/alcohol concomitantly) 2.4 ± 0.9 vs. 1.9 ± 1.1, $p < 0.001$. Creatinine clearance was lower in octogenarians than in younger patients (54.3 ± 16.1 ml/min vs. 69.5 ± 23.7 ml/min, $p < 0.001$) and severe renal disease with creatinine clearance < 30 ml/min was more frequent in octogenarians (5.2% vs. 2.2%, $p < 0.001$). In patients treated with VKAs (N = 1637), the international normalized ratio values of the 6 months previous to enrollment were similar in all age quartiles, as was the time in the therapeutic range.

Conclusion. In this large registry octogenarians with nonvalvular AF had high risk of stroke and bleeding and frequent renal disease. VKAs anticoagulation quality was similar in octogenarians and in younger patients.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia occurring in 1−2% of the general population and is associated with substantial mortality and morbidity, including stroke and other embolic events [1]. In octogenarians, AF is particularly frequent and is responsible of a quarter of cerebrovascular accidents [2]. In patients with non-valvular AF, Direct Oral Anticoagulants (DOACs) have been proven to be more effective and safer than vitamin K antagonists (VKAs) [3] but VKAs are still largely employed, mainly due to their low price and the recommendation not to use DOACs in patients, mostly elderly, with severe renal disease [4]. The coagulation status with VKAs needs to be monitored carefully with the international normalized ratio (INR), and the time in the therapeutic range (TTR) calculated by the Rosendaal method [5] is the most widely used formula to assess the quality of anticoagulation, using a linear interpolation to assign an INR value to each day between successive observed INRvalues [6]. Poor anticoagulation control is defined as an estimated < 65% TTR [7].

Although AF prevalence increases with age [1] previous data show a high rate of inappropriate anticoagulation among octogenarians with AF [8] and [9], however the data reported in the last five years suggest that this might be changing [10] and [11].Our aim was to study the clinical profile of octogenarians who receive oral anticoagulation due to nonvalvular AF and to study the effect of age on the quality of VKAs anticoagulation assessed by TTR.

2. Methods

We used data from FANTASIIA (Spanish acronym for Atrial fibrillation: Influence of anticoagulation level and type on stroke and bleeding event incidence) [12], a prospective national registry in an adult population of Spanish patients with nonvalvular AF who had been receiving oral anticoagulant therapy (by design 80% VKA and 20% DOACs) for at least 6 months before enrolment. We analyzed a cross-sectional baseline data set from the FANTASIIA enrolment visit to study the association of different risk variables and indexes with age and, specifically to compare INR values of the 6 months previous to the study entry and TTR of octogenarians with younger age groups.

Chronic kidney disease was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2. The glomerular filtration rate was estimated using the Cockcroft-Gault, Modification of Diet in Renal Disease or Chronic Kidney Disease Epidemiology Collaboration equations.

The FANTASIIA Registry complies with all the principles of the Declaration of Helsinki and the study protocol was approved by the Clinical Research Ethics Committee at Hospital Universitario de Alicante and by all the local ethics committees. All study participants signed the informed consent.

2.1. Statistical analysis

Quantitative variables were described using the mean ± standard deviation. For between-group comparisons, we used the Student t test or ANalysis Of Variance (ANOVA) for continuous variables and the chi-square test for qualitative variables. Statistical analysis was performed with the SPSS 20.0 statistical package (IBM Corp., Armonk, NY, USA).

3. Results

We enrolled 2178 patients. For the present analysis we selected 1637 patients (75.2%) treated with VKAs. Mean age was 73.8 ± 9.4 years, 56.2% were men. The comparison of baseline characteristics of the last age quartile (> 80 years) with the first three quartiles is shown in Table 1. Octogenarians had a high risk profile with higher risk of stroke (CHADS2 [Congestive heart failure, Hypertension, Age, Diabetes, Stroke/Transient Ischemic Attack] and CHA$_2$DS$_2$-VASc [Cardiac failure, Hypertension, Age > 74, Diabetes, Stroke, Vascular disease, Age 65–74 years, and Sex category]) and bleeding (HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 64 years) Drugs/alcohol concomitantly]). Moreover renal disease was more frequent and more severe in octogenarians than in younger patients (Fig. 1). In fact, severe renal disease with creatinine clearance < 30 ml/min affected only 1.5% of the patients in the first quartile (37–67 years) but was found in 5.2% of the patients in the last quartile. The main treatment strategy in octogenarians was rate control, while rhythm control was more frequent in the first three age

quartiles. Finally, patients aged > 80 year also had paroxysmal atrial fibrillation less frequently. In spite of this different profile, in patients treated with VKAs (N = 1637), the INR values of the 6 months previous to enrolment were similar in all age quartiles, as was the TTR (Table 2).

Table 1. Comparison of baseline characteristics between the first three quartiles and the last age quartile (> 80 years).

	All N = 1637	Q1–Q3 (37–80 years) N = 1208	Q4 (> 80 years) N = 429	p
Women (%)	717 (43.8)	473 (39.2)	244 (56.9)	<0.001
Hypertension (%)	1322 (80.8)	966 (80.0)	356 (83.0)	0.18
Hyperlipidemia (%)	868 (53.0)	661 (54.7)	207 (48.3)	0.02
Diabetes (%)	499 (30.5)	384 (31.8)	115 (26.8)	0.04
Tobacco consumption (%)	84 (5.1)	80 (6.6)	4 (1.0)	<0.001
COPD (%)	290 (17.7)	216 (17.9)	74 (17.3)	0.78
Previous bleeding (%)	51 (3.1)	34 (2.8)	17 (3.9)	0.34
Heart failure (%)	503 (30.7)	358 (29.6)	145 (33.8)	0.10
Coronary heart disease (%)	314 (19.2)	227 (18.8)	87 (20.3)	0.42
Diuretics (%)	971 (59.3)	690 (57.1)	281 (65.5)	0.002
ACE inhibitors (%)	540 (33.0)	401 (33.2)	139 (32.4)	0.76
ARBs (%)	640 (39.1)	480 (39.7)	160 (37.3)	0.49
Statins (%)	895 (54.7)	683 (56.5)	212 (49.4)	0.01
Antiplatelet drugs (%)	172 (10.5)	133 (11.0)	39 (9.1)	0.27
CHADS2	2.2±1.2	2.1±1.2	2.7±1.1	<0.001
CHA2DSVasc2	3.7±1.6	3.5±1.6	4.5±1.3	<0.001
HASBLED	2.0±1.0	1.9±1.7	2.4±0.9	<0.001
Previous stroke (%)	264 (16.1)	197 (16.3)	67 (15.6)	0.97
Creatinine	1.1±0.6	1.0±0.5	1.2±0.7	<0.001
GFR	65.5±22.9	69.5±23.7	54.3±16.1	<0.001
Electrical cardioversion (%)	282 (17.2)	256 (21.2)	26 (6.1)	<0.001
Pharmacological cardioversion (%)	370 (22.6)	316 (26.2)	54 (12.6)	<0.001
Pulmonary vein ablation (%)	64 (3.9)	60 (5.0)	4 (0.9)	<0.001
Rhythm control (%)	621 (37.9)	515 (42.6)	106 (24.7)	<0.001
Paroxysmal atrial fibrillation (%)	460 (28.1)	358 (29.6)	102 (23.8)	<0.001

COPD: chronic obstructive pulmonary disease. ACE: angiotensin converting enzyme. ARB: angiotensin receptor blocker. CHADS2: Congestive heart failure, Hypertension, Age > 74, Diabetes, Stroke/Transient Ischemic Attack. CHA$_2$DS$_2$-VASc: Cardiac failure, Hypertension, Age > 74, Diabetes, Stroke, Vascular disease, Age 65–74 years, and Sex category. HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (> 64 years) Drugs/alcohol concomitantly. GFR: Glomerular filtration rate. Q: Quartile.
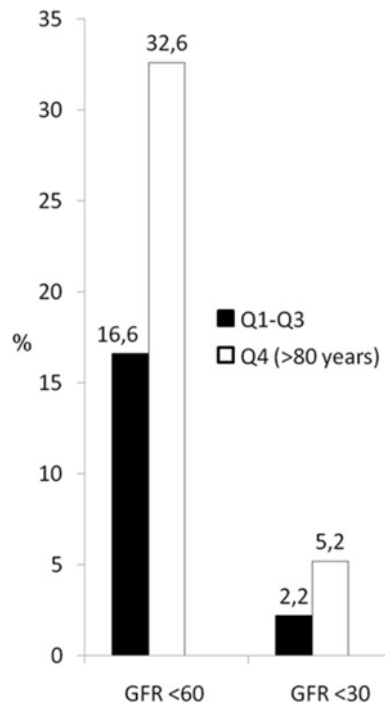
Fig. 1. Glomerular filtration rate (GFR) in ml/min according with age quartile (Q).

Table 2. International normalized ratio (INR). Values in the 6 months prior to enrollment.

	Q1: 37–67 years N = 390	Q2: 68–74 years N = 371	Q3: 75–80 years N = 447	Q4: 81–99 years N = 429	p
Month 1	2.5±0.6	2.5±0.6	2.5±0.7	2.5±0.7	0.477
Month 2	2.5±0.8	2.5±0.6	2.4±0.7	2.5±0.8	0.684
Month 3	2.5±0.82	2.5±0.7	2.5±0.7	2.4±0.7	0.42
Month 4	2.5±0.8	2.5±0.7	2.5±0.7	2.5±0.7	0.729
Month 5	2.5±0.8	2.4±0.6	2.5±0.8	2.5±0.8	0.872
Month 6	2.5±0.7	2.5±0.7	2.5±0.8	2.5±0.7	0.75
TTR	61.9±24.6	60.5±24.6	62.6±24.5	59.9±26.1	0.511

Q: quartile. TTR: time in the therapeutic range, calculated by the Rosendaal method.

4. Discussion

Octogenarians with nonvalvular AF have high risk of stroke (mean $CHA_2DSVasc_2$ 4.5) and bleeding (mean HASBLEED 2.4) and frequent renal disease. In our registry VKAs anticoagulation quality was not associated with age. This is relevant as over 5% of octogenarians have severe renal disease where DOACs are not recommended [13]. Our results confirm that the use of VKAs in octogenarians is feasible in routine clinical practice. This is an important finding as the prevalence of AF increases with age [1] and [14]. Costa et al. [10] also found that elderly patients achieved a good quality of VKAs anticoagulation despite having a higher levels of comorbidities and polypharmacy. In the Swedish national quality registry for atrial fibrillation and anticoagulation (AuricuLA) [11] a correlation between age and major bleeding was found, but no correlation was seen between age and thrombo-embolic events. In this registry, age was associated with the need of a lower warfarin dose but elderly patients manage their warfarin therapy as well or even better than younger patients. On the other hand, Okumura et al.

found the opposite [8], with a poorer TTR in the elderly, presumably related to physicians anxiety of major bleeding. A French national cross-sectional study [9] performed in octogenarians found that low-quality control of INR was mainly associated with comorbidities and the Veterans AffaiRs Study to Improve Anticoagulation (VARIA) [15] found an association in elderly patients between the number of concomitant medications and low-quality control of INR. Finally, Lefebvre et al. [16] have recently reported that the number of octogenarians with AF that receive anticoagulation is increasing and that 70% of them already anticoagulation therapy, with rates of anticoagulation clearly diminished among patients who are severely frail with advanced disability. Taken together these data suggest that more than age itself the presence of numerous comorbid conditions and polypharmacy may be the key issues and probably require greater attention by clinicians.

For more than 60 years, VKAs have been the only available oral anticoagulants for the prevention of stroke and systemic embolism in AF. Several new molecules, with a favorable pharmacokinetic profile and avoiding routine monitoring, have been recently developed, opening a new era in anticoagulation. However, DOACs are contraindicated in patients with severe renal disease [13], raise cost-effectiveness issues, and are not approved in patients with valvular AF [4] and [13]. Due to these reasons, VKAs are still largely used worldwide [11] and [17] and this will probably be true for the near future.

Our results are representative of Spain, but previous reports have shown that in Spain INR control is equal or superior to that in other Western countries such as Italy, France, the United States, or Canada [18] and [19]. Another peculiarity of our study is that in Spain the predominant VKA is acenocoumarol, as opposed to most Western countries, where warfarin is mainly used. Finally, by design, this study analyses drug treatment at the time of the enrollment visit, and does not include drug history or changes. On the other hand the FANTASIIA registry provides data of a large real-life population treated with VKAs with over a quarter > 80 years.

5. Conclusion

In this large, nationwide survey, octogenarians with nonvalvular AF had high risk of stroke and bleeding and frequent renal disease. VKAs anticoagulation quality was similar in octogenarians and in younger patients.

Appendix A.
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