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REFERENCES

1. Götberg M, Cook CM, Sen S, et al. The evolving future of instantaneous wave-free ratio and fractional flow reserve. *J Am Coll Cardiol.* 2017;70:1379–1402.
2. Tebaldi M, Biscaglia S, Fineschi M, et al. Evolving routine standards in invasive hemodynamic assessment of coronary stenosis. *JACC Cardiovasc Interv.* 2018;11:1482–1491.
3. Pijls NH, De Bruyne B, Peels K, et al. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med.* 1996;334:1703–1708.
4. Sen S, Escaned J, Malik IS, et al. Development and validation of a new adenosine-independent index of stenosis severity from coronary wave-intensity analysis. *J Am Coll Cardiol.* 2012;59:1392–1402.
5. Svanerud J, Ahn J-M, Jeremias A, et al. Validation of a novel non-hyperaemic index of coronary artery stenosis severity: the Resting Full-cycle Ratio (VALIDATE RFR) study. *EuroIntervention.* 2018;14:806–814.
6. Cortés C, Carrasco-Moraleja M, Aparisi A, et al. Quantitative flow ratio — meta-analysis and systematic review. *Catheter Cardiovasc Interv.* 2020. http://dx.doi.org/10.1002/ccd.28857.

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High use of direct oral anticoagulants in elderly patients with atrial fibrillation: data from the REFLEJA registry

Uso amplio de anticoagulantes de acción directa en pacientes ancianos con fibrilación auricular: datos del registro REFLEJA

To the Editor,

The prevalence of atrial fibrillation (AF) increases with age and peaks at the age of ≥ 80 years (17.7%).[1] Decisions on oral anticoagulation (OAC) therapy are challenging in patients of this age due to a higher stroke and bleeding risk. Although direct oral anticoagulants (DOACs) have been shown to be an attractive option for elderly patients—they are at least as effective as vitamin K antagonists and substantially reduce intracranial hemorrhage—they are clearly underused.[2]

The aim of this study was to assess the use of DOACs in a contemporary clinical series of patients aged ≥ 80 years and to analyze predictors of DOAC use and the influence of age on choice of doses.

The REFLEJA AF study is a prospective registry of 1039 consecutive outpatients with nonvalvular AF (NVAF) evaluated between October 2017 and June 2018 at a single hospital in Jaen, Spain. The registry includes all patients aged ≥ 18 years with NVAF evaluated by the cardiology unit. We compared the baseline characteristics of patients aged < 80 years and ≥ 80 years by bivariate analysis, using the chi-square test for qualitative variables and the *t* test for quantitative variables. We then performed binary logistic regression to identify independent predictors of DOAC use in these populations and calculated their respective odds ratios (ORs).

The characteristics of the population are summarized in table 1. Compared with younger patients, the group of patients aged ≥ 80 years (n = 376) comprised significantly more women (57.7% vs 41.5%, $P < .001$) and patients with heart failure (29.8% vs 20.2%, $P < .001$) or vascular disease (19.7 vs 12.8%, $P = .003$). Although the differences were not significant, older patients were also more likely to have a history of bleeding (5.9% vs 3.8%, $P = .12$) or stroke (9.3% vs 7.1%, $P = .20$).

Despite their less favorable profile, patients aged ≥ 80 years were more likely to be on AOCs (94.9% vs. 90% for those aged < 80 years, $P = .005$). The difference for the prescription of DOACs, however, was not significant (64.1% v. 69.3%; $P = .08$), although a higher proportion of older patients were on low doses (29.9% vs 7.6%, $P < .001$). The only significant difference observed in terms of the use of specific DOACs was for dabigatran, which was prescribed less often to patients aged ≥ 80 years (figure 1).

On multivariate analysis, an age ≥ 80 years was not associated with a lower use of DOACs (OR = 1.16; 95% confidence interval [95%CI], 0.58-2.31; $P < 0.67$). By contrast, both heart failure (OR = 0.60; 95%CI, 0.40-0.90; $P = .013$) and chronic kidney failure (CKF) (OR = 0.55; 95%CI, 0.41-0.76; $P < .001$) were independent predictors of lower DOAC use.

Generally speaking, there is sufficient evidence to recommend AOC therapy to elderly patients as it produces a net benefit in terms of a reduced risk of death, ischemic stroke, and intracranial hemorrhage (in this last case even in patients with a HAS-BLED score ≥ 3).[3] There is also evidence that AOCs result in an absolute reduction of stroke risk in elderly patients and that the reduction in this population is even higher than in younger patients.[4]

One notable finding of our study was that over 90% of patients with NVAF were on AOC therapy, and there were no differences between patients aged < 80 years and ≥ 80 years. This rate is even higher than that reported in a quality US clinical practice registry, where less than 80% of patients with NFAF were on AOCs and use was higher in younger patients.[5]

Appropriate choice of anticoagulant dose is necessary to ensure effective protection against stroke and to prevent an increased risk of bleeding. Subjective judgements based on age could erroneously lead to the prescription of low DOAC doses in elderly patients if other factors such as low body weight (<60 kg) or CKF are not taken into account. It is noteworthy that underdosing (18.5%) and overdosing (38%) were common in our series, even though almost 35% of patients had a glomerular filtration rate < 50 mL/min, which is a criterion for using lower doses for certain DOACs. After adjusting for sex, bleeding risk, CKF,

Table 1
Clinical and epidemiological characteristics of the study population by age

	Total (n = 1039)	< 80 y (n = 663)	≥ 80 y (n = 376)	*P*
Hypertension	81.5	77.9	88	< .001
Type 2 diabetes mellitus	26.3	25.7	26.7	.71
History of cancer	6.6	6.5	6.9	.78
Coronary artery disease	12.1	10.8	14.4	.08
Anemia	16.3	12.5	23.2	< .001
Permanent AF	50.5	42	66.5	< .001
Prior AF	79.8	77.2	84.3	.006
Sinus rhythm (consultation)	35	42.5	21.9	< .001
CHA_2DS_2-VASc score	3.4 ± 1.6	2.9 ± 1.6	4.4 ± 1.1	< .001
HAS-BLED score (without labile INR)	1.2 ± 0.8	1.1 ± 0.8	1.4 ± 0.7	< .001
GFR, mL/min/1.73 m^2	70.9 ± 24.9	76.2 ± 23.1	61.5 ± 25	< .001
Antiarrhythmic treatment	7.3	9.6	3.1	.005
Beta-blockers	71.6	75.7	64.4	< .001
Digoxin	18.8	15.1	25.3	< .001
Aspirin (prior use)	10.2	10.4	9.8	.77
P2Y12 receptor blockers (prior use)	2.3	2	2.9	.32
Low-molecular-weight heparin (prior use)	3.4	3.3	3.5	.90
DOACs	67.6	69.3	64.1	.08
Low-dose DOACs	15.3	7.6	29.9	< .001
DOAC underdosing[a]	10.5	6.4	18.5	< .001
DOAC overdosing[b]	18.8	8.8	38	< .001

AF, atrial fibrillation; DOACs, direct oral anticoagulants; GFR, glomerular filtration rate; INR, international normalized ratio.
[a] Use of a lower than indicated dose according to summary of product characteristics.
[b] Use of a normal dose in a patient with a n indication for low-dose DOAC therapy according to the summary of product characteristics.

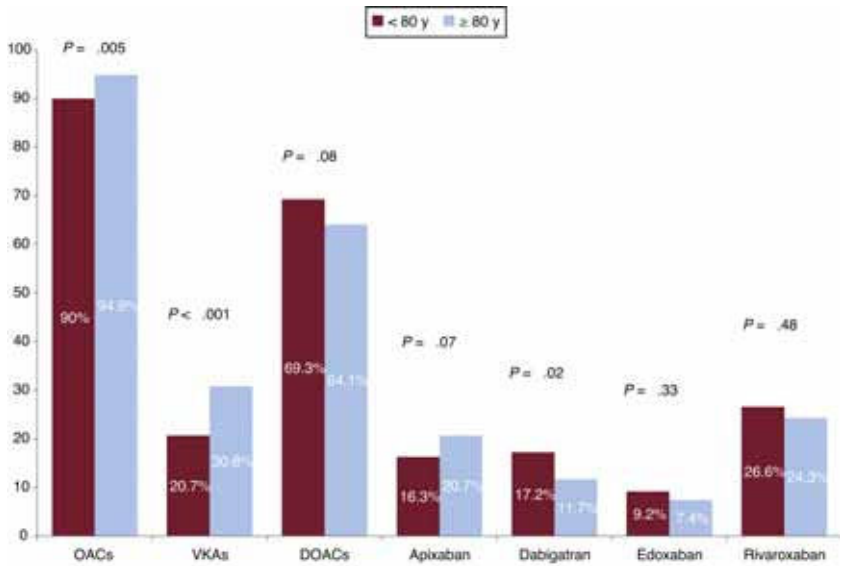

Figure 1. Differences in anticoagulant use according to age. DOACs, direct anticoagulants; OACs, oral anticoagulants; VKAs, vitamin K antagonists.

and prior bleeding, an age of ≥ 80 years was independently associated with a 3-fold increased odds of underdosing (OR = 3.01; 95%CI, 1.83-4.92; $P < .001$). It was also associated with an increased odds of overdosing (OR = 3.11, 95%CI, 1.66-5.84, $P < .001$), although the strongest independent predictor of overdosing, irrespective of age, was CKF, as 99% of these patients had a glomerular filtration rate < 60 mL/min.

In conclusion, our findings from a clinical AF registry indicate that DOAC use among elderly patients may be common, although the prognostic benefits of this treatment might be lower than expected, as we found that age ≥ 80 years was associated with both an inappropriate use of low doses and an excessive use of higher-than-indicated doses (primarily in patients with CKF).

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REFERENCES

1. Gómez-Doblas JJ, Muñiz J, Alonso Martin JJ, et al. en representación de los colaboradores del estudio OFRECE. Prevalencia de fibrilación auricular en España. Resultados del estudio OFRECE. *Rev Esp Cardiol.* 2014;67:259–269.
2. Ruff CT, Giugliano RP, Braunwald E. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with auricular fibrillation: A meta-analysis of randomised trials. *Lancet.* 2014;383:955–962.
3. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation.* 2012;125:2298–2307.
4. Andreotti F, Rocca B, Husted S, et al.Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J.* 2015;36:3238–3249.
5. Piccini JP, Xu H, Cox M. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable — first results from Get With The Guidelines–Atrial Fibrillation (GWTG-AFIB). *Circulation.* 2019;139:1497–1506.

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Cardiac phenotype in glycogen storage disease type XV: a rare cardiomyopathy to bear in mind

Fenotipo cardiológico de la glucogenosis tipo XV: una miocardiopatía muy infrecuente a tener en cuenta

To the Editor,

Glycogen storage diseases (GSD) may mimic hypertrophic cardiomyopathy (HCM).[1] Some more recently identified GSD, also with heart involvement, are barely known and thus difficult to suspect (table 1). Herein we highlight that GSD type XV (OMIM #613507) can also present as myocarditis or even evoke a left ventricular (LV) arrhythmogenic cardiomyopathy.

A young proband reported limiting chest pain, vague presyncopal spells, and progressive weakness. A mild increase in blood troponin T and urine protein levels were detected with normal creatinine phosphokinase. His electrocardiogram demonstrated sinus rhythm, atypical complete right bundle branch block, and left posterior hemiblock (figure 1A); isolated infrequent supraventricular and ventricular premature beats were noted by Holter and implanted loop recorder. Coronary stenosis was ruled out by coronary computed tomography angiography. Cardiac imaging by echocardiography and cardiac magnetic resonance imaging identified structural abnormalities limited to the left ventricle. Abnormal features included LV mild-to-moderate hypertrophy only at the basal septal segment, lower limit LV ejection fraction (LVEF), a slightly decreased global longitudinal strain, slightly increased volumes, thinned and hypokinetic apical and lateral walls with a laminar thrombus, severe epi/intramyocardial edema and scarring (figure 1B-F). Myocarditis was diagnosed and the patient was put on colchicine, bisoprolol, and oral anticoagulants. The patient soon had a cerebellar stroke with an *ad integrum* recovery but otherwise symptoms and tests have remained unchanged during the 24-month follow-up. Persisting chest pain prompted an endomyocardial biopsy, which showed no disarray or abnormal fibrosis and revealed a severe myocardial vacuolization peripherally displacing the nuclei. The marked periodic acid-Schiff (PAS) positivity at the vacuoles gave the diagnosis of GSD and its partial attenuation if pretreatment with diastase was included in the staining protocol and was consistent with polyglucosan deposits (figure 1G-H). Ultrastructural images also fitted with the diagnosis (figure 1I). Next generation sequencing (NextSeq 500, Illumina Technologies) was used to assess for GSD, HCM, and arrhythmogenic cardiomyopathy genes. The proband carried 2 already published pathogenic variants in the *GYG-1* gene, namely the p.Asp102His and the p.Gly135Arg.*2* Skeletal muscular involvement was further ruled out with a thorough clinical examination by an expert neurologist, a whole-body computed tomography, standard respiratory function tests, and an exercise test. The need for anticoagulation prevented us from performing a muscle biopsy. Regarding treatment, colchicine and beta-blockers were withdrawn and anticoagulation intensified. The 6 relatives of the 3-generation family study were phenotype negative and heterozygous for only 1 of the mutations.

The term GSD type XV is preferred for the cardiomyopathic phenotype while polyglucosan body myopathy type 2 (PGBM2, OMIM #616199) applies for an allellic disease characterized by late onset and slowly progressive myopathy without cardiac involvement.[2–5] Thirty-eight patients with PGBM2 have been described so far and ours is the fifth case of GSD type XV.[2–4] All these patients harbor 2 *GYG-1* mutations and polyglucosan accumulation is identified either in cardiomyocytes or the skeletal muscle. Of note, nonsense mutations are more common among myopathic patients than in cardiomyopathic patients.[3,5]

Having reviewed the available evidence[3,4] and our proband, we stress that GSD type XV represents a cardiological diagnosis, with microscopic biventricular involvement, although cardiac imaging only detects an isolated LV disease. Of note, this disease may not necessarily exhibit massive LV hypertrophy (14-23 mm in the 5 patients so far identified) and has never been associated with cognitive impairment, atrioventricular block or pre-excitation, as have other well-known GSD, such as PRKAG2, Danon and Pompe diseases.[1] Instead, long-lasting chest pain (80%), LV regional abnormalities (60% thinning, 40% hypo/akinesis), LV tissue characterization alterations (100% scarring, 20% edema), and systemic embolic events (40% stroke, 20% LV thrombus) are the