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Safety of digoxin in nonagenarian patients with atrial fibrillation: lessons from the Spanish Multicenter Registry

Pablo Domínguez-Erquicia[1], Sergio Raposeiras-Roubín[1,2,✉], Emad Abu-Assi[1,2], María Cespón-Fernández[1], David Alonso-Rodríguez[3], Santiago Jesús Camacho-Freire[4], Naiara Cubelos-Fernández[3], Álvaro López-Masjuán Ríos[4], María Melendo-Viu[1], Andrés Íñiguez-Romo[1,2]

1. Department of Cardiology, University Hospital Álvaro Cunqueiro, Vigo, Spain; 2. Health Research Institute Galicia Sur, Vigo, Spain; 3. Department of Cardiology, University Hospital of León, León, Spain; 4. Department of Cardiology, University Hospital Juan Ramón Jiménez, Huelva, Spain

✉ Correspondence to: raposeiras26@hotmail.com

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ABSTRACT

BACKGROUND The association between digoxin and mortality is an unclear issue. In older patients with atrial fibrillation (AF), where use of digoxin is frequent, the evidence of its safety is scarce. Our aim is to assess the safety of digoxin in nonagenarian patients with AF.

METHODS We evaluated data from 795 nonagenarian patients with non-valvular AF from the Spanish Multicenter Registry. We analyzed the relationship between digoxin and all-cause mortality with the Cox proportional-hazards model.

RESULTS Follow-up was 27.7 ± 18.3 months. Mean age was 92.5 ± 3.8 years, and 71% of nonagenarian patients were female. Digoxin was not associated with increased risk of mortality [adjusted hazard ratio (aHR) = 1.16, 95% CI: 0.96–1.41, P = 0.130]. However, we found a significant increase in mortality in the subgroup with estimated glomerular filtration rate (eGFR) < 30 mL/min per 1.73 m^2 (aHR = 2.01, 95% CI: 1.13–3.57, P = 0.018), but not in the other subgroups of eGFR (30–59 mL/min per 1.73 m^2 and ≥ 60 mL/min per 1.73 m^2). When exploring the risk of mortality according to sex, male subgroup was associated with an increase in mortality (aHR = 1.48, 95% CI: 1.02–2.14, P = 0.041). This was not observed in females subgroup (aHR = 1.03, 95% CI: 0.81–1.29, P = 0.829). Based on the presence or absence of heart failure, we did not find significant differences (aHR = 1.20, 95% CI: 0.87–1.65, P = 0.268 *vs.* aHR = 1.15, 95% CI: 0.90–1.47, P = 0.273, respectively).

CONCLUSIONS In our large registry of nonagenarian patients with AF, we did not find an association between digoxin and mortality in the total sample. However, in the subgroup analyses, we found an increase in mortality with the use of digoxin in men and in patients with an eGFR < 30 mL/min per 1.73 m^2.

After the diagnosis of atrial fibrillation (AF), the new European guidelines propose the approach of three key points, also called the Atrial Fibrillation Better Care (ABC).[1] In the first place, to consider the need for oral anticoagulant therapy; secondly, to control symptoms and, finally, to address the main comorbidities that predispose and perpetuate AF. Focusing on the second point, there are classically two possible strategies, the rate control and the rhythm control. It was a substudy of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) that showed that in patients ≥ 65 years of age, the rate control strategy conferred a better prognosis than the rhythm control strategy.[2] More recent studies have addressed the issue of symptoms control, like the Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA trial)[3] or the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4)[4], with different conclusions. These studies included therapies like catheter ablation for rhythm control. But procedures like this, are not usually performed in older patients due to the benefit-risk balance. Thus, for older patients, the most widely used strategy today is rate control.

The most used drugs for rate control in AF are beta-blockers (BB), non-dihydropyridine calcium channel blockers (NDCCB), and digoxin. European guidelines propose BB and NDCCB as first line and digoxin as second line.[1] An American study analyzed the trends in the prescription of digoxin in their country from 2007 to 2014.[5] They reported a nearly 50% decrease in digoxin prescriptions dispensed among adults ≥ 65 years. Across age strata, the number of prescriptions decreased from 2.2 million to 1.2 million for patients aged ≥ 85 years over the study period.

Despite the decrease in its prescription, digoxin continues to be a common drug in clinical practice. Well, although it is less effective than BB or NDCCB, it is a reasonable option for older patients with little physical activity, in whom other treatments are ineffective or contraindicated, or as an additional drug to optimize rate control.

Although there are several studies and meta-analysis that analyzed the relationship between digoxin and mortality in AF with contradictory results,[6] the evidence for the use of digoxin in older or very older patients is scarce, despite being a group in which it is used frequently. Motivated by this gap in the evidence, the aim of our study is to determine the safety of digoxin in nonagenarian patients with AF and a rate control strategy by evaluating the mortality related to this drug.

METHODS

Study Design and Population

This study was based on data from the "NONagenarians with Atrial Fibrillation" (NON-AF NONVALV) project, which provided a multicenter registry of patients aged ≥ 90 years with a confirmed diagnosis of non-valvular AF from three health areas in Spain (Vigo, Leon, and Huelva). More information about this registry can be consulted in prior publications.[7,8] As summary, we identified patients with an inpatient or outpatient diagnosis of AF (International Classification of Diseases, Ninth Revision code 427.31; International Classification of Diseases, Tenth Revision codes I48.0, I48.1, and I48.2) between January 2013 and December 2017. The clinical history of all patients with AF identified was retrospectively reviewed by cardiologists to confirm the diagnosis of non-valvular AF and collect data on baseline variables, treatment, and follow-up. Non-valvular AF was defined as AF without moderate-severe mitral stenosis and without mechanical prosthetic valve replacement.[9]

Of all the patients with AF aged ≥ 90 years, we identified the 795 nonagenarian patients who were under treatment with heart rate control drugs. We divided the patients in two groups based on whether they were taking digoxin (380 nonagenarian patients) or not taking digoxin (415 nonagenarian patients). In the second group, patients with BB and NDCCB were included. In the case of a combination of drugs, those taking digoxin were included in the digoxin group. To assess treatment patterns, all outpatient prescriptions dispensed during follow-up were identified. Observation ended in the case of death.

Follow-up and baseline variables had < 2% missing data (n < 35). No method was used to impute missing values or adjust the model for the presence of missing data. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local Ethics Committee (Autonomic Committee of Research Ethics from Galicia, code HAC-ACO-2018-01, registry 2018/258).

Statistical Analysis and Outcomes

Quantitative variables are expressed as mean ± SD, and they were compared using the Student's t-test. The qualitative variables are shown in number of observations and percentage in relation to the total and they were compared with the Pearson's chi-squared test.

The endpoint analyzed was all-cause mortality, and it was assessed using the Cox proportional-hazards model. Hazard ratios (HRs) with their 95% confidence intervals (CIs) were obtained, as well as a Kaplan-Meier survival probability curves. Multivariable model was adjusted for those variables with clinical significance (biological plausibility) or with statistical significance (P < 0.05 in the univariable analysis): age, sex, previous history of heart failure (HF) (HF was defined as congestive HF or known left ventricular ejection fraction < 40%), chronic obstructive

pulmonary disease, anticoagulation therapy (yes or not) and direct oral anticoagulant (yes or not).

We performed analyses by subgroups of patients: (1) according to estimated glomerular filtration rate (eGFR) [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] categorized as < 30 mL/min per 1.73 m^2, 30–59 mL/min per 1.73 m^2 or ≥ 60 mL/min per 1.73 m^2; (2) depending on whether or not they had a previous history of HF; and (3) basing on sex.

Values were considered statistically significant when the two-sided *P*-value < 0.05. All the analyses and figures were made with STATA Intercooled software, version 15.0 (Stata Corp, College Station, Texas, USA) and SPSS for Windows, version 25.0 (SPSS Inc., IBM, Armonk, New York, USA).

RESULTS

Basal Characteristics

A total of 795 nonagenarian patients aged ≥ 90 years were evaluated. Mean age was 92.5 ± 3.8 years, and 71% of patients (*n* = 565) were female. The main baseline characteristics are reported in Table 1.

Among the most prevalent comorbidities, arterial hypertension stands out, present in 70% of patients, a history of HF in approximately 40% of patients, and anemia in 30% of patients. If we compare digoxin group with non-digoxin group, we find significant differences in the eGFR. The patients taking digoxin had a mean eGFR of 53 ± 17 mL/min per 1.73 m^2 and those who did not take digoxin had a mean eGFR of 47 ± 17 mL/min per 1.73 m^2. Other variables with differences between groups were sex, with a higher proportion of women in the digoxin group (75.3% *vs.* 67.2%) and coronary artery disease most prevalent in the non-digoxin group (12.6% *vs.* 20%).

Digoxin, BB and NDCCB

In the group of patients who did not take digoxin, BB were the most used drugs (381 nonagenarian patients, 48%). NDCCB were the least used drugs. On

Table 1 Baseline characteristics in total population and by groups (digoxin *vs.* not digoxin).

Variables	Total population (*n* = 795)	Digoxin (*n* = 380)	Not digoxin (*n* = 415)	*P*-value
Age, yrs	92.5 ± 3.8	92.7 ± 3.8	92.4 ± 3.8	0.241
Female	565 (71%)	286 (75.3%)	279 (67.2%)	0.013
Hypertension	579 (72.8%)	276 (72.6%)	303 (73%)	0.904
Diabetes mellitus	143 (18%)	63 (16.6%)	80 (19.2%)	0.322
Coronary artery disease	131 (16.5%)	48 (12.6%)	83 (20%)	0.005
Prior stroke	139 (17.5%)	70 (18.4%)	69 (16.6%)	0.506
Peripheral artery disease	33 (4.1%)	15 (3.9%)	18 (4.3%)	0.783
Prior heart failure	306 (38.5%)	151 (39.7%)	155 (37.4%)	0.409
Chronic obstructive pulmonary disease	67 (8.4%)	33 (8.7%)	34 (8.2%)	0.803
Prior cancer	103 (13%)	48 (12.6%)	55 (13.3%)	0.794
CHA_2DS_2-VASC	4.6 ± 1.3	4.6 ± 1.4	4.6 ± 1.3	0.730
HAS-BLED	2.8 ± 1.0	2.8 ± 1.0	2.8 ± 1.0	0.765
Anemia*	235 (29.6%)	111 (29.2%)	124 (29.9%)	0.836
eGFR&, mL/min per 1.73 m^2	50 ± 17	53 ± 17	47 ± 17	< 0.001
< 30	95 (12%)	33 (8.7%)	62 (14.9%)	
30–59	472 (59.4%)	204 (53.7%)	268 (64.6%)	< 0.001
> 60	228 (28.7%)	143 (37.6%)	85 (20.5%)	
Oral anticoagulation therapy	620 (78%)	289 (76%)	331 (79.8%)	0.208
Direct oral anticoagulants	370 (46.4%)	178 (46.8%)	191 (46%)	0.817

Data are presented as means ± SD or *n* (%). *Presented as anemia is defined as hemoglobin levels < 12.0 g/dL in women and < 13.0 g/dL in men. &Presented as eGFR was calculated according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). eGFR: estimated glomerular filtration rate.

the total of the sample, alone or in combination, only 44 nonagenarian patients (5.5%) were taking NDCCB. Figure 1 (Venn Diagram) shows the proportion of patients with each drug, as well as the number of patients taking some combination of them. The most widely used combination was BB with digoxin, up to 10% of all patients.

Outcomes

A total of 415 nonagenarian patients (52.2%) died during a mean follow-up of 27.7 ± 18.3 months (median: 24 months). Crude mortality rates were similar in those taking digoxin [24.4 (95% CI: 21.3–27.9) per 100 patient-years] and those not taking digoxin [21.1 (95% CI: 18.4–24.2) per 100 patient-years].

The use of digoxin was not associated with increased risk of mortality in both univariable model (crude HR = 1.16, 95% CI: 0.96–1.40, P = 0.130) and multivariable model [adjusted HR (aHR) = 1.16, 95% CI: 0.96–1.41, P = 0.128] (Figure 2).

However, when analyzing mortality based on categorized glomerular filtration rate (< 30 mL/min per 1.73 m^2, 30–59 mL/min per 1.73 m^2 and ≥ 60 mL/min per 1.73 m^2), we found a significant increase in mortality in the group with eGFR < 30 mL/min per 1.73 m^2 (aHR = 2.01, 95% CI: 1.13–3.57, P = 0.018). The use of digoxin in patients with eGFR of 30–59 mL/min per 1.73 m^2 (aHR = 1.11, 95% CI: 0.85–1.43, P = 0.443) or with eGFR ≥ 60 mL/min per 1.73 m^2 was not associated with increased risk of death in the multivariable model (aHR = 1.12, 95% CI: 0.77–1.63, P = 0.557) (Figure 3).

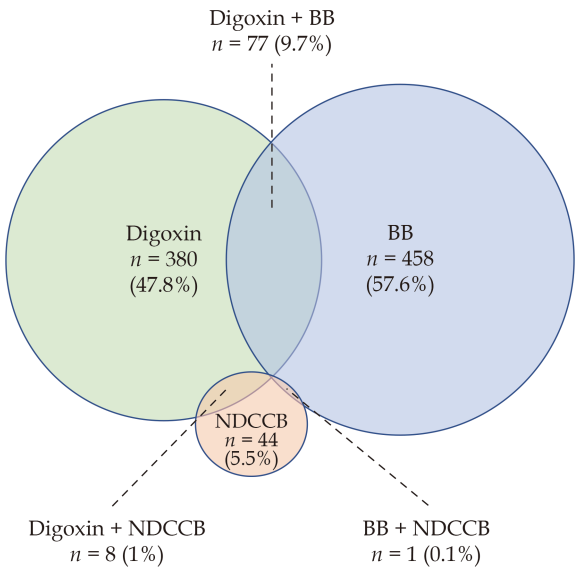

Figure 1 Venn diagram. Number and proportion of patients with digoxin, BB, NDCCB and combinations. BB: beta-blockers; NDCCB: non-dihydropyridine calcium channel blockers.

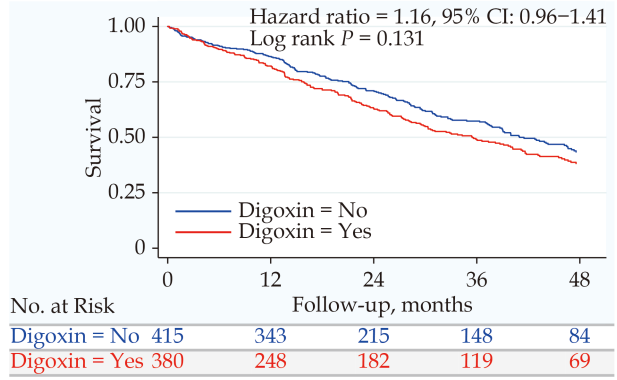

Figure 2 Kaplan-Meier estimates survival function (all-cause death).

Following the same analysis, but this time based on the presence or absence of a history of HF, we did not find significant differences in the association between digoxin and all-cause mortality (aHR = 1.20, 95% CI: 0.87–1.65, P = 0.268 *vs.* aHR = 1.15, 95% CI: 0.90–1.47, P = 0.273, respectively) (Figure 3).

When exploring the risk of mortality according to sex in the multivariable model, we found a significant increase in the subgroup of male (aHR = 1.48, 95% CI: 1.02–2.14, P = 0.041). The subgroup of female was not associated with an increase in mortality in the adjusted model (aHR = 1.03, 95% CI: 0.81–1.29, P = 0.829) (Figure 3).

DISCUSSION

Using a large multicenter cohort of nonagenarian patients with AF and a rate control strategy, the main findings are: (1) digoxin was not associated with an increased risk of mortality in the total population; (2) analyzing according to glomerular filtration, patients taking digoxin with eGFR < 30 mL/min per 1.73 m^2 showed a risk of mortality twice as high as patients not taking digoxin; (3) analyzing by sex, in the subgroup of men, digoxin was associated with an increased risk of mortality; and (4) analyzing according to the presence or absence of HF, digoxin was not associated with increased mortality in either of the two groups. As far as we know, this is the largest observational study assessing the association between digoxin and mortality in patients aged ≥ 90 years with AF.

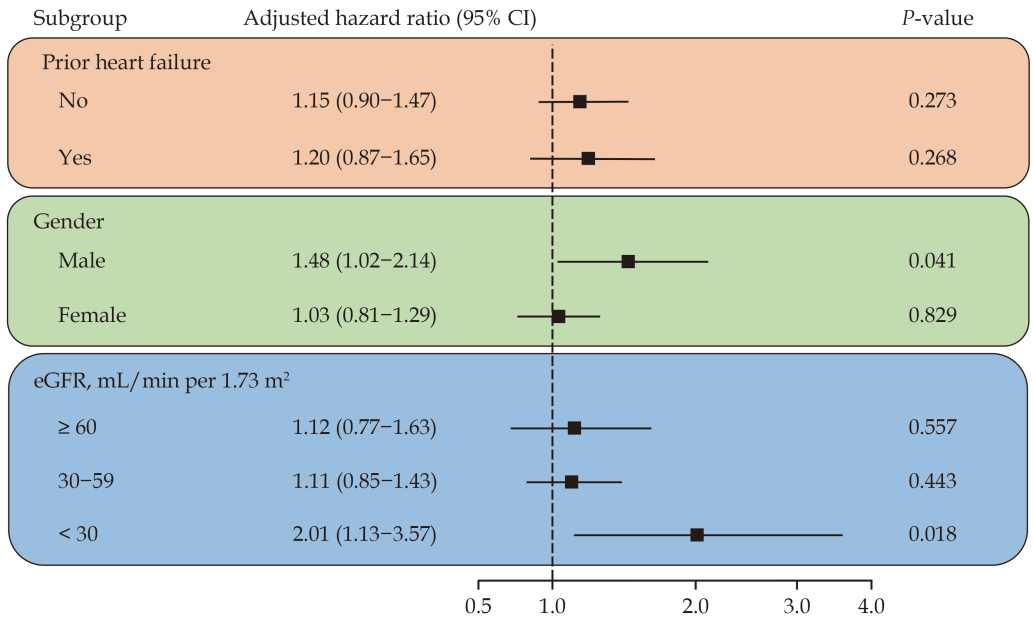

Figure 3 Forest plot. Stratifies analyses of multivariable model for digoxin associated risk of mortality by subgroups of eGFR, sex, and heart failure. eGFR: estimated glomerular filtration rate [according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)].

We have found a neutral effect of the use of digoxin on mortality in the total sample analyzed in both univariable and multivariable analyses. The relationship between the use of digoxin and increased mortality is an unclear issue. The evidence is conflicting. One of the first studies that showed an increased risk of mortality in AF patients taking digoxin was a subanalysis of the AFFIRM trial.[10] Two more recent AFFIRM sub-analyzes presented disagreeing results.[11,12] Gheorghiade, *et al.*[12] point out that the association found between digoxin and mortality could be derived from the time-dependent analysis used in previous studies.[10,11] The key is that this model assumes that changes in treatment during follow-up occur randomly and not due to clinical changes in the patients. This point is important since digoxin is commonly used in patients with poor clinical conditions. Therefore, using the same data from the AFFIRM study, different results have been obtained depending on the statistical modeling used. So, we must keep in mind that the adjustment of observational data does not remove all confounding, and even techniques such as propensity score matching cannot replace randomized allocation.

Retrospective studies such a post-hoc analysis of Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), found an increase in mortality associated with the use of digoxin.[13] Similarly, in a meta-analysis by Vamos, *et al.*,[14] an increased risk of mortality associated with digoxin was observed, especially in patients without proper serum level control. On the contrary, another meta-analysis of randomized trials and observational studies with 600,000 patients found a neutral effect on mortality and a reduction in hospital admissions.[15] This work shows how the studies with the highest risk of bias found a greater association between digoxin and risk of mortality. Therefore, we must bear in mind that even the most sophisticated methods of statistical adjustment are not 100% effective, and the conclusions must be based more on randomized studies than on post-hoc analysis and observational studies.

In summary, the evidence is conflicting, and our results are in consonance with some prior studies. Moreover, it is worth mentioning that patients included in this registry are very elderly, with the inherent increased risk of mortality. This aspect may play a role in the observed results.

An adjustment of the maintenance dose of digoxin is recommended in patients with renal failure since its excretion is decreased and its plasma levels may increase.[16] So, the monitoring of plasma levels is warranted in renal dysfunction patients with chronic

digoxin treatment. A post-hoc digoxin subgroup analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial[17] showed that patients with a serum digoxin concentration ≥ 1.2 ng/mL had an increased hazard of mortality compared with those not on digoxin. This same relationship was studied and described in a post-hoc analysis of the Digitalis Investigation Group (DIG) trial in patients with HF.[18] Therefore, given the relationship between renal function and plasma digoxin levels, the findings of our study are plausible. Similar results were shown in a retrospective observational study where chronic kidney disease stage III-V was significantly associated with increased cardiac and cerebrovascular mortality in AF patients with chronic digoxin use.[19]

Even though the results of our study are based on subgroup analyses, in addition to the limitations inherent in its design, the objective of these data is to make the clinician think about the patient's renal function before prescribing digoxin. It must be considered that in patients aged ≥ 90 years like those represented here, a normal plasma creatinine level is not enough to rule out kidney disease. We should calculate the eGFR and consider that the greater the deterioration of renal function, the greater the probability of adverse effects.

We did not find prognostic differences based on the presence or absence of a history of HF. The evidence in this context is also contradictory. A meta-analysis showed increased mortality in patients with AF without HF but did not in patients with AF and HF.[20] An aforementioned AFFIRM substudy found a consistent increased risk of mortality in both subgroups of patients, with and without HF.[10] Probably the group of patients with AF without HF is underrepresented in most randomized studies, so the conclusions in this regard are limited.

In our results, we found an increase in mortality associated with the use of digoxin only in the men subgroup. One of the first studies that evaluated this aspect was a subanalysis of the DIG trial in which a harmful effect of digoxin was evidenced in certain subgroups of patients with HF, such as women.[21] It was unclear whether this increase was due to higher serum drug concentrations or an unidentified sex-specific toxicity. In contrast, there are studies that have described an increase in mortality in the group of men[13] and others that have not found differences between sex groups.[10,22] In our sample, the mean eGFR for men was lower than for women (42.4 *vs.* 53.2 mL/min per 1.73 m^2, $P < 0.001$). This aspect could explain the differences observed.

LIMITATIONS

Our study has several limitations. First and foremost, this work is based on a retrospective registry with unselected real-life patients, with the limitations related to the design. Therefore, the possible presence of biases and many confounding factors must be considered. Also, authors did not have information about plasma digoxin levels or other important biochemical conditions as plasma potassium concentration that could interact with digoxin. We present a cohort of very older patients where survivorship bias can play an important role in the results. For this reason, the conclusions of this study must be understood taking into account possible biases. So, these data need confirmations by a randomized, prospective, clinical studies.

CONCLUSIONS

In our large cohort of nonagenarian patients with AF, we did not find an association between digoxin use and mortality. However, in the subgroup analyses, we found an increase in mortality with the use of digoxin in men and in patients with an eGFR < 30 mL/min per 1.73 m^2. These results suggest that digoxin seems to be safe in patients aged ≥ 90 years, although aspects such as kidney function must be considered when prescribing it. Due to the limitations of the study, these conclusions are only valid to generate hypotheses that should be confirmed in randomized clinical trials in this older population.

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REFERENCES

[1] Hindricks G, Potpara T, Dagres N, *et al*. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibril-

lation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373–498.
[2] Curtis AB, Gersh BJ, Corley SD, *et al*. Clinical factors that influence response to treatment strategies in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Am Heart J* 2005; 149: 645–649.
[3] Packer DL, Mark DB, Robb RA, *et al*. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019; 321: 1261–1274.
[4] Kirchhof P, Camm AJ, Goette A, *et al*. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020; 383: 1305–1316.
[5] Angraal S, Nuti SV, Masoudi FA, *et al*. Digoxin use and associated adverse events among older adults. *Am J Med* 2019; 132: 1191–1198.
[6] Van Gelder IC, Rienstra M, Crijns HJ, *et al*. Rate control in atrial fibrillation. *Lancet* 2016; 388: 818–828.
[7] Raposeiras-Roubín S, Alonso Rodríguez D, Camacho Freire SJ, *et al*. Vitamin K antagonists and direct oral anticoagulants in nonagenarian patients with atrial fibrillation. *J Am Med Dir Assoc* 2020; 21: 367–373.e1.
[8] Domínguez-Erquicia P, Raposeiras-Roubín S, Abbu-Assi E, *et al*. Incidence, predictors of bleeding and prognosis of bleeding in anticoagulated nonagenarian patients with atrial fibrillation. *Int J Cardiol* 2021; 327: 217–222.
[9] Lip GYH, Collet JP, Caterina R, *et al*. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace* 2017; 19: 1757–1758.
[10] Corley SD, Epstein AE, DiMarco JP, *et al*. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* 2004; 109: 1509–1513.
[11] Whitbeck MG, Charnigo RJ, Khairy P, *et al*. Increased mortality among patients taking digoxin-analysis from the AFFIRM study. *Eur Heart J* 2013; 34: 1481–1488.
[12] Gheorghiade M, Fonarow GC, van Veldhuisen DJ, *et al*. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post-hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013; 34: 1489–1497.
[13] Washam JB, Stevens SR, Lokhnygina Y, *et al*. Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Lancet* 2015; 385: 2363–2370.
[14] Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015; 36: 1831–1838.
[15] Ziff OJ, Lane DA, Samra M, *et al*. Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data. *BMJ* 2015; 351: h4451.
[16] Jelliffe RW. An improved method of digoxin therapy. *Ann Intern Med* 1968; 69: 703–717.
[17] Lopes RD, Rordorf R, De Ferrari GM, *et al*. Digoxin and mortality in patients with atrial fibrillation. *J Am Coll Cardiol* 2018; 71: 1063–1074.
[18] Rathore SS, Curtis JP, Wang Y, *et al*. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003; 289: 871–878.
[19] Shin JH, Kang KW, Kim JG, *et al*. Concurrent renal dysfunction with ischemic heart disease is an important determinant for cardiac and cerebrovascular mortality in patients on chronic digoxin therapy for atrial fibrillation. *Kidney Res Clin Pract* 2018; 37: 130–137.
[20] Chamaria S, Desai AM, Reddy PC, *et al*. Digoxin use to control ventricular rate in patients with atrial fibrillation and heart failure is not associated with increased mortality. *Cardiol Res Pract* 2015; 2015: 314041.
[21] Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. *N Engl J Med* 2002; 347: 1403–1411.
[22] Domanski M, Fleg J, Bristow M, *et al*. The effect of gender on outcome in digitalis-treated heart failure patients. *J Card Fail* 2005; 11: 83–86.

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