Original article

Anticoagulation Therapy in Patients With Heart Failure Due to Systolic Dysfunction and Sinus Rhythm: Analysis of REDINSCOR Registry

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A B S T R A C T

Introduction and objectives: In patients with heart failure, left ventricular ejection fraction \( \leq 35\% \) and sinus rhythm without conditions such as atrial fibrillation, thrombus or history of thromboembolic events, the use of anticoagulation is controversial. Our objective was to evaluate the anticoagulation strategy in these patients, variables associated with its use, and its effects on various cardiovascular events.

Methods: Of the patients included in the REDINSCOR registry with left ventricular ejection fraction \( < 35\% \) and sinus rhythm without other anticoagulation indications (including patients with heart failure from 19 Spanish centres), we compared those who received this treatment with the remaining patients.

Results: Between 2007 and 2010, 2263 patients were included, of whom 902 had left ventricular ejection fraction \( < 35\% \) and sinus rhythm. Of these, 237 (26\%) were receiving anticoagulation therapy. Variables associated with this treatment were a lower left ventricular ejection fraction, ischemic etiology, advanced functional class, wider QRS, larger left atrial diameter, and hospitalization. After 21 (11-32) months of median follow-up, there were no significant differences in total mortality (14\% versus 12.5\%) or stroke (0.8\% versus 0.9\%). A propensity score adjusted multivariate analysis showed a reduced in a combined end-point including cardiac death, heart transplantation, coronary revascularization, and cardiovascular hospitalization (hazard ratio=0.74; 95\% confidence interval, 0.56-0.97; P=0.03) in patients receiving anticoagulation therapy. No information regarding bleeding was collected in the follow-up.

Conclusions: In a large and contemporary series of patients with heart failure, left ventricular ejection fraction \( < 35\% \) and sinus rhythm, 26\% received anticoagulation therapy. This was not associated with lower mortality or stroke incidence, although there was a reduction in major cardiac events.

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Tratamiento anticoagulante en pacientes con insuficiencia cardíaca por disfunción sistólica y ritmo sinusal: análisis del registro REDINSCOR

R E S U M E N

Introducción y objetivos: En pacientes con insuficiencia cardíaca, fracción de eyeción del ventrículo izquierdo \( \leq 35\% \) y ritmo sinusal, en ausencia de fibrilación auricular, trombos intracavitarios o tromboembolia previa, la indicación de anticoagulación es controvertida. Nuestro objetivo fue evaluar la actitud actual respecto de la anticoagulación en estos pacientes, variables asociadas a su utilización y su efecto sobre diversos eventos cardiovasculares.

Métodos: De los pacientes con fracción de eyeción del ventrículo izquierdo \( \leq 35\% \) y ritmo sinusal sin otra indicación de anticoagulación incluidos en el registro REDINSCOR (pertenecientes a 18 centros españoles), se compararon los que recibían este tratamiento frente al resto.

Resultados: Entre 2007 y 2010 se incluyeron 2.263 pacientes; 902 tenían fracción de eyeción del ventrículo izquierdo \( \leq 35\% \) y ritmo sinusal. De ellos, 237 (26\%) recibían anticoagulación. Las variables asociadas a su utilización fueron menor fracción de eyeción del ventrículo izquierdo, etiología no isquémica, clase funcional avanzada, mayor anchura del QRS, mayor diámetro auricular izquierdo y hospital prescriptor del tratamiento anticoagulante. Tras una mediana de seguimiento de 21 (11-32) meses no se observaron diferencias significativas en mortalidad (14 frente a 12.5\%) ni ictus (0.8 frente 0.9\%). El análisis multivariado ajustado por propensity score mostró una reducción en la combinación de mortalidad cardíaca, trasplante cardíaco, revascularización coronaria e ingresos cardiovasculares.

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INTRODUCTION

Heart failure (HF) with systolic dysfunction of the left ventricle poses an increased risk of thromboembolic events (TE), with an annual incidence of 1%-4%, which contributes to a high number of hospital admissions as well as high morbidity and mortality in these patients. Some authors have suggested the presence of hypercoagulability, mediated by increased platelet activation and coagulation markers such as D-dimer, beta thromboglobulin, and thrombin-antithrombin III complexes. To all this, stasis due to the reduction in intraventricular blood flow experienced by these patients is added.

Oral anticoagulation therapy (OAC) is only indicated in current clinical practice guidelines in patients with systolic HF who also present atrial fibrillation, intracavitary thrombi, or a recent history of thromboembolism. The benefit of OAC observed in these patients might be extended to other subgroups, such as patients with HF and low left ventricular ejection fraction (LVEF) in sinus rhythm (SR). Most publications on this strategy describe “post-hoc” substudies from clinical trials that analyzed patients with systolic HF, including subgroups with increased thromboembolic risk, such as atrial fibrillation and prosthetic valves, which makes it difficult to draw conclusions about the possible benefit of OAC in patients with HF in SR. The few available randomized clinical trials suffer from insufficient sample sizes, and in some cases have been halted early. It is not known whether the variables associated with the incidence of TE in patients with atrial fibrillation (summarized by the acronym CHA2DS2-VASC) also induce these events in patients with HF in SR, although it seems that these same variables may be associated with the incidence of stroke even in patients without atrial fibrillation.

Among the drawbacks that have limited the use of traditional anticoagulation with coumadin agents are hemorrhagic risk, drug interactions, and the need for close monitoring of the international normalized ratio (INR), issues that may be overcome in the near future by next generation anticoagulants.

For these reasons, the routine indication for OAC in all patients with left ventricular dysfunction in SR is controversial, but there are currently no clear directives. This indication is not mentioned in current clinical practice guidelines.

Our objective was to assess the approach to OAC in a large contemporary cohort of patients with HF, LVEF<35%, and SR, to determine the variables associated with its indication, and to assess its effect on mortality and other cardiovascular events.

METHODS

Population

This is an analysis of the REDINSCOR (Red de Investigación en Insuficiencia Cardiaca), a research network registry of HF, which includes 19 centers belonging to 7 Spanish regions and registers numerous laboratory, electrocardiographic, echocardiographic, and therapeutic variables obtained at baseline and during follow-up. This is a prospective cohort study that includes patients over 18 years of age with symptomatic HF (functional class [FC] II-IV of the New York Heart Association [NYHA]) who were hospitalized for 24 h in the 12 months before their inclusion, and who present some of the following echocardiographic disorders: LVEF<40%, telediastolic diameter>60 mm, thickness of the septum, and/or posterior wall>14 mm and ventricular relaxation abnormalities. The database is available on the Internet (www.redisncor.org), and has a management module with online statistics and a report generator. Its organizational structure includes an information unit (consisting of an epidemiologist and a statistician who designs and maintains the database, controls the quality of data, outliers, internal inconsistencies, and the accuracy of the information), a committee for mortality and case closure (analyzes cases of death, cataloging types of death and conflicts regarding the closure of cases and loss of follow-up), and a science committee. Patient follow-up is performed in the cardiology department of participating hospitals.

For this study, patients were selected with LVEF<35% and SR, with no other indications for OAC, such as history of pulmonary thromboembolism, prosthetic valves, intracavitary thrombi, or other thromboembolic phenomena. Within this group, patients who were administered OAC (group I) were compared to those who did not take OAC (group II).

Events Considered

The following outcome variables were established:

- Overall mortality.
- Combined event of cardiac death and heart transplantation (HT).
- Admissions for HF.
- Coronary revascularization.
- Stroke.
- Combined event of cardiac death, HT, coronary revascularization, and cardiovascular admissions.
- Sudden death and stroke.

Although the combined outcome variables were not included in the REDINSCOR registry at the time of data collection, they were predefined for our study.

Statistical Analysis

Continuous variables with normal distribution were reported as mean and standard deviation. Those without normal distribution...
were reported as median and range. Dichotomous variables were expressed as percentages. The characteristics of both groups were compared using the Student t-test for continuous variables and chi-squared for categorical variables. Continuous variables that did not have normal distribution were compared using the Mann-Whitney U test.

In accordance with indications for OAC in atrial fibrillation in established guidelines, the CHA2DS2-VASc score was calculated for each group according to each patient’s baseline characteristics.16

Given the nonrandomized nature of the study and the numerous factors that may have influenced the type of treatment each patient received, a propensity score17 analysis was performed using logistic regression for the use of OAC. This analysis was based on 33 variables with the objective of eliminating differences in baseline patient characteristics that may affect events comparison. For the creation of the propensity score, we used variables that had less than 10% missing values in the database, and therefore N-terminal fragment of brain natriuretic peptide (NT-proBNP) and left atrial diameter could not be used. The area under the curve was 0.75 (0.71-0.78); P<.0001. Variables included in the propensity score were ischemic etiology, diabetes mellitus, hypertension, previous myocardial infarction, revascularization, NYHA FC, duration of the QRS, LVEF, sex, smoking, dyslipidemia, hemoglobin, glomerular filtration rate, age, systolic blood pressure, diastolic blood pressure, decompensated HF, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, calcium antagonists, statins, anti diabetic agents, loop diuretics, thiazide diuretics, aldosterone antagonists, oral inotropic agents, intravenous inotropic agents, antiarrhythmic agents, nitrates, hyalurazine, iron, and hospital-prescribed OAC.

To establish the association between the OAC use and events, a multivariate analysis was performed with Cox proportional-hazards regression. All models were adjusted for the propensity score covariate except for stroke, due to the low number of events.

Survival curves were analyzed and represented using Cox proportional-hazards regression adjusted for the propensity score, and compared with the hazard ratio (HR) (95% confidence interval [95% CI], P value). We also evaluated the proportionality assumption of the Cox models.

Lastly, we performed Cox proportional-hazards models adjusted for the propensity score covariate with interactions of variables that characterized subgroups to determine if these variables were factors modifying the association between OAC use and the different events. To do this, we assessed the interaction of treatment with LVEF as the continuous variable and the following subgroups:

- LVEF≥20% vs LVEF<20%.
- NYHA FC III vs FC III-IV.
- Ischemic vs non ischemic etiology.

This analysis was repeated for each event studied, except for “coronary revascularization procedures” and “stroke events”, for which interactions were not assessed due to the low number of events.

Significance was established at P<.05. Statistical analysis was performed with SPSS version 17.

RESULTS

Between 2007 and 2010, 2263 patients were included in the REDINSCOR registry, of which 902 had LVEF<35% and were in SR. Of these, 237 patients (26%) received OAC (group I): 153 received only OAC and 84 received OAC plus antiplatelet therapy. Table 1 shows the percentage of OAC prescribed in each hospital. Overall characteristics and comparisons between both groups can be seen in Table 2. Prior to the propensity score adjustment, patients who received OAC had lower LVEF, lower frequency of ischemic etiology, more advanced FC, greater QRS width, and greater left atrial diameter. The prevalence of hypertension and diabetes and the CHA2DS2-VASc score were lower for group I. The percentage of OAC differed between the various hospitals participating in the registry (P<.001). There were no significant differences between the two groups in the standard treatment of HF or in NT-proBNP levels.

After adjustment, the baseline characteristics of both groups were balanced, except for the left atrial diameter and the NT-proBNP level, which were not included in the propensity score.

The median follow-up was 21.1 (11.4-32.2) months. Table 3 shows the results. There were 116 (12.8%) total deaths, 120 (13.3%) events of the “cardiac death and HF” combination, 167 (18.5%) admissions for HF, 27 (3%) coronary revascularization procedures, 8 (0.9%) strokes, 337 events (37.4%) of the “cardiac death, HT, coronary revascularization, and cardiovascular admissions” combination, and 32 (3.5%) cases of “sudden death and stroke.” There were no significant differences between the two groups in the univariate analysis. The multivariate logistic regression analysis adjusted for propensity score showed a reduction in the combined event “cardiac death, HT, coronary revascularization, and cardiovascular admissions” (hazard ratio [HR]=0.74; 95%CI, 0.56-0.97; P=0.03). There was no association between the OAC variable and the other analyzed events.

Figure 1 shows the curve for survival free of the combination event “cardiac death, HT, coronary revascularization, and cardiovascular admissions.”

As for the prespecified analysis of subgroups, also adjusted for propensity score (Table 4), we observed that anticoagulation was associated with a reduction in “cardiac death and HT” in patients with ischemic etiology (HR=0.47; 95%CI, 0.25-0.90; P=0.02). For the other potential modifying factors analyzed, the association between OAC use and the various events studied was homogenous. There were also no statistically significant interactions when LVEF was analyzed as a continuous variable. We did not perform an analysis of modifying factors for coronary revascularization or stroke due to the low number of events.

Table 1

<table>
<thead>
<tr>
<th>Anticoagulant Therapy by Hospital</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital Universitario Puerta de Hierro</strong></td>
<td>41 (52)</td>
</tr>
<tr>
<td><strong>Hospital Universitari Joan XXIII</strong></td>
<td>9 (18)</td>
</tr>
<tr>
<td><strong>Hospital Clinic de Barcelona</strong></td>
<td>29 (32)</td>
</tr>
<tr>
<td><strong>Hospital de la Santa Creu i Sant Pau</strong></td>
<td>23 (36)</td>
</tr>
<tr>
<td><strong>Hospital Clínico Universitario de Santiago</strong></td>
<td>7 (15)</td>
</tr>
<tr>
<td><strong>Hospital Clínico San Carlos</strong></td>
<td>13 (30)</td>
</tr>
<tr>
<td><strong>Hospital 12 de Octubre</strong></td>
<td>21 (39)</td>
</tr>
<tr>
<td><strong>Hospital Universitario Virgen de la Arrixaca</strong></td>
<td>6 (12)</td>
</tr>
<tr>
<td><strong>Hospital Universitario Nuestra Señora de Valme</strong></td>
<td>18 (17)</td>
</tr>
<tr>
<td><strong>Hospital Universitari Arnau de Vilanova</strong></td>
<td>7 (23)</td>
</tr>
<tr>
<td><strong>Hospital Universitario La Fe</strong></td>
<td>14 (33)</td>
</tr>
<tr>
<td><strong>Hospital Universitario Virgen Macarena</strong></td>
<td>3 (30)</td>
</tr>
<tr>
<td><strong>Hospital de Guadarrama</strong></td>
<td>1 (50)</td>
</tr>
<tr>
<td><strong>Hospital Universitario Son Dureta</strong></td>
<td>20 (26)</td>
</tr>
<tr>
<td><strong>Hospital Francesc de Borja</strong></td>
<td>3 (19)</td>
</tr>
<tr>
<td><strong>Hospital Municipal de Badalona</strong></td>
<td>3 (43)</td>
</tr>
<tr>
<td><strong>Hospital General Universitario Morales Meseguer</strong></td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Hospital Universitario Puerta del Mar</strong></td>
<td>19 (16)</td>
</tr>
</tbody>
</table>

P<.001. P after adjusting for propensity score: 1.
Table 2
Baseline and Differential Characteristics Between Both Groups

<table>
<thead>
<tr>
<th></th>
<th>Total (n=902)</th>
<th>Group I (OAC: n=237)</th>
<th>Group II (n=665)</th>
<th>P</th>
<th>P after adjusting for propensity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>689 (76.3%)</td>
<td>178 (75%)</td>
<td>511 (77%)</td>
<td>.500</td>
<td>.999</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.5±12.2</td>
<td>61.7±13</td>
<td>65±12.5</td>
<td>.174</td>
<td>.998</td>
</tr>
<tr>
<td>Hypertension</td>
<td>559 (61.9%)</td>
<td>134 (57%)</td>
<td>425 (64.4%)</td>
<td>.050</td>
<td>.995</td>
</tr>
<tr>
<td>Diabetes</td>
<td>364 (40.3%)</td>
<td>78 (33%)</td>
<td>286 (43%)</td>
<td>.007</td>
<td>.994</td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>483 (53.5%)</td>
<td>109 (46%)</td>
<td>374 (56%)</td>
<td>.007</td>
<td>.991</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>328 (36.3%)</td>
<td>72 (30.5%)</td>
<td>256 (38.6%)</td>
<td>.026</td>
<td>.996</td>
</tr>
<tr>
<td>Previous infarction</td>
<td>473 (52.4%)</td>
<td>91 (39%)</td>
<td>382 (42.9%)</td>
<td>.140</td>
<td>.997</td>
</tr>
<tr>
<td>NYHA FC III-IV</td>
<td>505 (55.9%)</td>
<td>147 (62%)</td>
<td>358 (53.6%)</td>
<td>.025</td>
<td>.994</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26.3±6</td>
<td>25.6±6.4</td>
<td>26.6±6</td>
<td>.020</td>
<td>.995</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>46±7</td>
<td>47.3±7</td>
<td>45.3±7</td>
<td>.001</td>
<td>-</td>
</tr>
<tr>
<td>NT-proBNP, pmol/L</td>
<td>197 (79-485)</td>
<td>199 (77-529)</td>
<td>195 (80-463)</td>
<td>.900</td>
<td>-</td>
</tr>
<tr>
<td>Duration of QRS, ms</td>
<td>125±33</td>
<td>129.6±32</td>
<td>124±33.4</td>
<td>.020</td>
<td>.994</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min/1.73 m²</td>
<td>60.7±22.5</td>
<td>69.4±24.3</td>
<td>72±26.4</td>
<td>.200</td>
<td>.996</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>781 (86.5)</td>
<td>206 (86.9)</td>
<td>575 (86.7)</td>
<td>.940</td>
<td>1</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>631 (69.9)/157(17.4)</td>
<td>172 (73)/33 (14)</td>
<td>459 (69)/124 (19)</td>
<td>.330</td>
<td>.998/.999</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>574 (63.6)</td>
<td>161 (67.9)</td>
<td>413 (62.2)</td>
<td>.115</td>
<td>.996</td>
</tr>
<tr>
<td>CHAD2DS2-VASc</td>
<td>3.5±1.5</td>
<td>3.3±1.6</td>
<td>3.6±1.4</td>
<td>.020</td>
<td>-</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; FC, functional class; LA, left atrium; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal fragment of brain natriuretic peptide; NYHA, New York Heart Association; OAC, oral anticoagulation therapy.

Data are expressed as no. (%) or mean±standard deviation (percentiles 25-75).

Table 3
Overall Events and Events by Group: Results of the Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>Total (n=902)</th>
<th>Group I (OAC: n=237)</th>
<th>Group II (n=665)</th>
<th>P</th>
<th>Multivariate analysis adjusted for the propensity score covariate HR (95%CI); P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>116 (12.8%)</td>
<td>33 (14%)</td>
<td>83 (12.5%)</td>
<td>.56</td>
<td>0.91 (0.59-1.42); .69</td>
</tr>
<tr>
<td>Cardiac death and HT</td>
<td>120 (13.3%)</td>
<td>33 (13.9%)</td>
<td>87 (13.1%)</td>
<td>.74</td>
<td>0.76 (0.49-1.18); .21</td>
</tr>
<tr>
<td>Admissions for HF</td>
<td>167 (18.5%)</td>
<td>44 (18.6%)</td>
<td>123 (18.5%)</td>
<td>.98</td>
<td>0.98 (0.67-1.44); .93</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>27 (3%)</td>
<td>3 (1.3%)</td>
<td>24 (3.6%)</td>
<td>.07</td>
<td>0.43 (0.12-1.52); .19</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (0.9%)</td>
<td>2 (0.8%)</td>
<td>6 (0.9%)</td>
<td>1</td>
<td>0.90 (0.18-4.45); .90</td>
</tr>
<tr>
<td>Cardiac death, HT, coronary revascularization, and cardiovascular admissions</td>
<td>337 (37.4%)</td>
<td>87 (36.7%)</td>
<td>250 (37.8%)</td>
<td>.81</td>
<td>0.74 (0.56-0.97); .03</td>
</tr>
<tr>
<td>Sudden death and stroke</td>
<td>32 (3.5%)</td>
<td>6 (2.5%)</td>
<td>26 (3.9%)</td>
<td>.32</td>
<td>0.60 (0.23-1.53); .28</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; HF, heart failure; HT, heart transplantation; OAC, oral anticoagulation therapy.

* Not adjusted for the propensity score variable due to the low number of events.

DISCUSSION

Our study includes a large and current cohort of patients with HF participating in an HF research network and properly treated according to clinical practice guidelines.2 Patients were included between 2007 and 2010 from 19 cardiology departments at secondary and tertiary level centers in 7 regions of Spain. We therefore believe that it reasonably shows the current clinical practice of cardiologists in our environment. With a median follow-up of 21 months, the overall mortality of 12.8% may seem relatively low, taking into account the characteristics of this population, with mean LVEF of 26%, 54% with ischemic etiology and 56% with NYHA FC III-IV. Due to the high quality of the data (with >95% of clinical and follow-up variables completed) and the performance of at least one follow-up every 6 months, it is unlikely that significant events have not been recorded. A possible explanation for this low incidence in mortality may be the mean age of 64.5 years (ie, this was a young population) and the high proportion of patients who received treatment according to current evidence (Table 1).

We have confirmed in our series that 26% of patients with HF and LVEF≤35% in SR, with no other embolic risk factors, were prescribed anticoagulants by their cardiologists. This anticoagulation rate is similar to the 28% reported in both the SAVE (Survival and Ventricular Enlargement) vs study6 and (Survival and Ventricular Enlargement) the SCD-HeFT (Sudden Cardiac Death-Heart Failure Trial) analysis,18 and to the 29% in the BEST (Beta Blocker Evaluation of Survival Trial) substudy,19 and exceeds those of the SOLVD (Studies of Left Ventricular Dysfunction)9 (9%), V-HeFT 1 (19%) and V-HeFT 2 (21%) trials.5 However, the percentage of OAC differed between hospitals participating in the registry, with a range of 12% to 52%. Although we do not know the reasons, this is evidence of different criteria for anticoagulation of patients. Among the factors associated with OAC use in our study are a more advanced FC, greater QRS width, and greater left atrial dilation, which reflect a more advanced stage
The disease, greater dilatation of cavities, and greater blood stasis. In our cohort, patients who received OAC had a lower frequency of ischemic etiology, prior revascularizations and acute myocardial infarction, perhaps due to the systematic use of antiplatelet therapy with acetylsalicylic acid-clopidogrel for one year after the event. Moreover, among the characteristics associated with the use of OAC in our series are lower LVEF and a lower percentage of diabetes and hypertension, findings similar to those of the aforementioned BEST substudy.\(^{19}\)

It is noteworthy that when reviewing the CHA\(_2\)DS\(_2\)-VASc score, the anticoagulated patients had lower scores, contrary to expectations. This is worrying since the components of this scale seem to increase the risk of stroke mediated by atrial fibrillation and other factors present in the general population.\(^{10}\) This would advise for OAC. The question may only be clarified with data from large series of patients with systolic HF in SR and long follow-up periods. If these factors were to be confirmed as predictors of TE in populations without atrial fibrillation, a radical change would be necessary in current cardiology practice.

For the study of events arising in follow-up, given the nonrandomized character of the study and in order to make the two groups comparable, a multivariate logistic regression analysis was performed, using the propensity score as the adjustment covariate.\(^{17}\) This has allowed the baseline characteristics to be statistically "balanced", reducing the influence of variables other than the OAC itself. The percentage of OAC prescriptions in each center was one of the variables that most improved the adjustment capacity of the propensity score, as evidenced by an increase in the area under the curve when inserting this variable, which in some cases showed a capacity for discrimination superior to that of certain clinical variables.

After this analysis, anticoagulation was not associated with lower mortality or stroke, although there was a reduction in the combination event of “cardiac death, HT, coronary revascularization, and cardiovascular admissions.” There were no differences in the other events analyzed either.

In the prespecified analysis of subgroups, we observed that OAC was associated with a reduction in “cardiac death and HT”
### Table 5
Summary of Available Evidence on Anticoagulant Therapy in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>No.</th>
<th>Population</th>
<th>Ischemic etiology</th>
<th>Follow-up</th>
<th>Treatment</th>
<th>Final points</th>
<th>Results</th>
<th>Bleeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOLVD subtudy</td>
<td>1998</td>
<td>Observational</td>
<td>6378</td>
<td>HF with AF (24%), stroke (19%), VT (2.1%)</td>
<td>Death</td>
<td>70%</td>
<td>Warfarin (9%), ASA</td>
<td>Death or admissions for HF Cardiovascular death</td>
<td>HR = 0.76; 95% CI, 0.65-0.89</td>
<td>Not reported</td>
<td>More patients of the warfarin group had AF (19.3%) vs 4.5% and cerebrovascular disease (13.8%) vs 5.5%</td>
</tr>
<tr>
<td>V HEFT 1</td>
<td>1993</td>
<td>Observational</td>
<td>642</td>
<td>HF with AF (16%), prosthetic valves</td>
<td>TE</td>
<td>44.2%</td>
<td>Warfarin (19%), ASA</td>
<td>Neutral: (2.9/100 patients/year vs 2.7/100 patients/year; P=NS)</td>
<td>HR = 0.82; 95% CI, 0.72–0.93</td>
<td>Not reported</td>
<td>More TE in patients with AF and prosthetic valves</td>
</tr>
<tr>
<td>V HEFT 2</td>
<td>1993</td>
<td>Observational</td>
<td>804</td>
<td>HF with AF (15%), prosthetic valves</td>
<td>TE</td>
<td>53%</td>
<td>Warfarin (21%), ASA</td>
<td>Reduction of TE with warfarin (4.9/100 patients/year vs 2.1/100 patients/year); P&lt;0.01</td>
<td>HR = 0.72; 95% CI, 0.61-0.86</td>
<td>Not reported</td>
<td>More TE in patients with AF and prosthetic valves</td>
</tr>
<tr>
<td>SAVE</td>
<td>1997</td>
<td>Observational</td>
<td>2231</td>
<td>HF with AF (10%), prosthetic valves</td>
<td>Stroke</td>
<td>Not</td>
<td>Warfarin (28%)</td>
<td>LVEF 28%; RR 0.17; P&lt;0.001 LVEF 29%-35%; RR, 0.14; P&lt;0.001 LVEF&gt;35%; RR, 0.23; P&lt;0.001</td>
<td>Not reported</td>
<td>More patients in patients with AF and prosthetic valves</td>
<td></td>
</tr>
<tr>
<td>BEST</td>
<td>2011</td>
<td>Observational</td>
<td>2708</td>
<td>HF in SR with no indication for OAC</td>
<td>Overall mortality Cardiovascular death</td>
<td>56.5%</td>
<td>Warfarin (29%)</td>
<td>HR = 0.86; 95% CI, 0.62-1.19 HR = 0.97; 95% CI, 0.68-1.38 HR = 1.09; 95% CI, 0.82-1.44</td>
<td>Not reported</td>
<td>Halted early due to low recruitment</td>
<td></td>
</tr>
<tr>
<td>WASH</td>
<td>2004</td>
<td>Randomized, open</td>
<td>279</td>
<td>HF in SR with no indication for OAC</td>
<td>Combination of death, infarction and stroke</td>
<td>60%</td>
<td>Warfarin, ASA or control</td>
<td>26% in warfarin and in control; P=NS</td>
<td>HR = 0.84; 95% CI, 0.5-1.3; P&lt;0.45 HR = 0.71; 95% CI, 0.46-1.1; P=0.14 HR = 0.89; 95% CI, 0.61-1.29; P&lt;0.56 HR = 0.33; 95% CI, 0.10-1.10; P=0.07 HR = 0.89; 95% CI, 0.18-4.40; P&lt;0.89 HR = 0.74; 95% CI, 0.55-0.99; P&lt;0.04 HR = 0.52; 95% CI, 0.21-1.32; P&lt;0.17</td>
<td>7 h events, greater with warfarin. 17% vs 5% minor H; P&lt;0.03</td>
<td>Planned to include 3000 patients</td>
</tr>
<tr>
<td>WATCH</td>
<td>2009</td>
<td>Randomized</td>
<td>1587</td>
<td>HF in SR with no indication for OAC</td>
<td>Combination of death, infarction and stroke</td>
<td>70%</td>
<td>Warfarin, ASA or clopidogrel</td>
<td>19.6% in warfarin; 20.7% in ASA; 21.6% in clopidogrel; P=NS Reduction of non-fatal stroke with warfarin</td>
<td>HR = 0.84; 95% CI, 0.5-1.3; P=0.45 HR = 0.71; 95% CI, 0.46-1.1; P=0.14 HR = 0.89; 95% CI, 0.61-1.29; P&lt;0.56 HR = 0.33; 95% CI, 0.10-1.10; P=0.07 HR = 0.89; 95% CI, 0.18-4.40; P&lt;0.89 HR = 0.74; 95% CI, 0.55-0.99; P&lt;0.04 HR = 0.52; 95% CI, 0.21-1.32; P&lt;0.17</td>
<td>Not available</td>
<td>Separated analysis ischemic etiology-idiopathic patients, under recruitment</td>
</tr>
<tr>
<td>HELAS</td>
<td>2006</td>
<td>Randomized</td>
<td>197</td>
<td>HF in SR with no indication for OAC</td>
<td>Combination of death, stroke, embolism, infarction, rehospitalization, and HF</td>
<td>58%</td>
<td>Warfarin-ASA warfarin-placebo</td>
<td>Ischemic etiology: 8.9% with warfarin vs 14.9% with ASA; P=NS Idiopathic: 8.9% with warfarin vs 14.8% with placebo; P not reported</td>
<td>HR = 0.84; 95% CI, 0.5-1.3; P=0.45 HR = 0.71; 95% CI, 0.46-1.1; P=0.14 HR = 0.89; 95% CI, 0.61-1.29; P&lt;0.56 HR = 0.33; 95% CI, 0.10-1.10; P=0.07 HR = 0.89; 95% CI, 0.18-4.40; P&lt;0.89 HR = 0.74; 95% CI, 0.55-0.99; P&lt;0.04 HR = 0.52; 95% CI, 0.21-1.32; P&lt;0.17</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>REDINSCOR</td>
<td>2011</td>
<td>Observational</td>
<td>2234</td>
<td>HF in SR with no indication for OAC</td>
<td>Overall mortality Cardiovascular death and HT Admissions for HF Coronary revascularization Stroke</td>
<td>53.5%</td>
<td>Acenocoumarol (26%)</td>
<td>Sudden death and stroke</td>
<td>HR = 0.84; 95% CI, 0.5-1.3; P=0.45 HR = 0.71; 95% CI, 0.46-1.1; P=0.14 HR = 0.89; 95% CI, 0.61-1.29; P&lt;0.56 HR = 0.33; 95% CI, 0.10-1.10; P=0.07 HR = 0.89; 95% CI, 0.18-4.40; P&lt;0.89 HR = 0.74; 95% CI, 0.55-0.99; P&lt;0.04 HR = 0.52; 95% CI, 0.21-1.32; P&lt;0.17</td>
<td>Not available</td>
<td></td>
</tr>
</tbody>
</table>

ASA, acetylsalicylic acid; 95%CI, 95% confidence interval; AF, atrial fibrillation; H, hemorrhage; HF, heart failure; HR, hazard ratio; HT, heart transplantation; LVEF, left ventricular ejection fraction; NS, not significant; OAC, oral anticoagulation therapy; RR, relative risk; SR, sinus rhythm; TE, thromboembolic events; VTE, venous thromboembolism.
in patients with ischemic heart disease. If this is confirmed in randomized studies with long follow-ups, it may be useful in practical decision-making for individual patients.

In our cohort, we did not find any LVEF influence in the possible beneficial effect of OAC. By contrast, the SAVE study observed that the risk of stroke increased as LVEF decreased (4.1% with LVEF>35%; 7.8% with LVEF between 29% and 35%, and 8.9% with LVEF<28%) and that the benefit of OAC increased as LVEF decreased.

In our study, the rate of stroke was low (0.9%), with no significant differences between groups. Thus, if the only reason for using OAC were to reduce stroke, it would seem extremely difficult to further reduce such a low incidence. In fact, the first trials performed in the 1950s that assessed this issue and showed benefits studied specific populations of patients with HF, generally those with atrial fibrillation and rheumatic heart disease, for whom the incidence of TE events is greater.

The most recent evidence is controversial and is based on post hoc subanalyses of 4 randomized trials and on 3 small randomized trials, as can be seen in Table 5.

The first were post hoc subanalyses of the randomized trials SOLVD, V-HeFT I and 2 and SAVE, where the use of OAC was at the discretion of the researcher. Although all agree on the indication for OAC in patients with atrial fibrillation and prosthetic valves, there is not much evidence on the usefulness of OAC in patients in SR, and therefore its findings cannot be extrapolated to patients with no indications for OAC, according to clinical practice guidelines.

The latest published substudy of this type was an analysis of the best study, which included a population similar to ours, although with a more advanced symptomatic degree of HF (93% of patients in NYHA FC III). Its results are consistent with ours, since OAC was not associated with a reduction in overall mortality (HR=0.86; 95%CI, 0.62-1.19), cardiovascular mortality (HR=0.97; 95%CI, 0.68-1.38), or hospitalizations for HF (HR=1.09; 95%CI, 0.82-1.44).

The three randomized clinical trials specifically aimed at assessing the effect of OAC on patients with HF in SR are the WASH (Warfarin/Aspirin Study in Heart Failure), WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure), and HELAS (Heart failure Long-term Antithrombotic Study). None of these 3 trials found significant differences in the events analyzed. However, the number of patients included in the trials was small and in some cases the follow-up was halted early, which limits the trials' ability to generate evidence. A meta-analysis performed on the data from the WATCH and WASH trials also had neutral results for mortality (HR=0.90; 95%CI, 0.67-1.22). However, these results are derived primarily from the WATCH study due to its greater sample size (1587 vs 279 patients).

Due to its limitations, WATCH results should be considered preliminary until the WARCEF trial (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) is published, which is prospective, double blind, and randomizes patients with LVEF>35 in SR to receive warfarin or placebo. Its main objective is to determine differences in the combined incidence of death and stroke.

Complications during OAC may be significant and pose important risks, which must be weighed before making the decision to recommend OAC to an individual patient. The main complication is bleeding, with a variable incidence estimated at between 10 and 17 events per 100 patient-years in the case of overall bleeding, and between 2 and 5 events per 100 patient-years for major bleeding. It should be noted that none of the post hoc analyses reported bleeding rates. In the randomized trials, between 1% and 7% of patients treated with OAC had hemorrhaging defined as a major episode, figures that were always higher than those of the groups without OAC.

It should be taken into account that this patient population was generally elderly and had various comorbidities, possible hepatic dysfunction secondary to congestion, and susceptibility to drug interactions, which may complicate the narrow therapeutic range within which OAC must be managed. Other considerations include the patient's willingness to undergo close monitoring of INR, the risk of falls, and the need for changes in the diet. Some of these disadvantages will not be a problem with the introduction to the market of alternative oral anticoagulant drugs currently in the development phase, although their role in this population will be defined in future studies.

**Limitations**

The limitations of our study are mainly linked to its observational design and lack of statistical strength in some of the results. Although the use of the propensity score as a tool for analysis has allowed us to reduce treatment-effect biases, this does not rule out the possibility that the adjustment capacity was insufficient. Moreover, the physicians' reasons for prescribing OAC are unknown, which may have influenced the results. We also note the limitation that the INR values and the rates of bleeding were not recorded during follow-up.

**CONCLUSIONS**

In this cohort of patients with HF, severe left ventricular dysfunction, and SR, and with no other indications for OAC, the prevalence of anticoagulant therapy was 26%. These patients had lower LVEF, more advanced FC, greater QRs width and left atrial dilation, and lower prevalence of diabetes and hypertension, compared to those who were not anticoagulated. The presence of factors within the CHA2DS2-VASc system did not influence the decision to anticoagulate these patients, a decision that varied significantly between the various centers participating in the registry.

Although in our series anticoagulation was associated with a reduction of the combined variable “cardiac death, HT, coronary revascularization, and cardiovascular admissions”, it did not reduce the incidence of mortality or stroke.

Our results, along with the currently available evidence, do not support the need for routine anticoagulation in patients with severe ventricular dysfunction in SR with no other indications. Among the subgroups that may benefit from this treatment are patients with ischemic heart disease.

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**CONFLICTS OF INTEREST**

None declared.

**REFERENCES**