Original article

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

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ABSTRACT

Introduction and objectives: In patients with heart failure, left ventricular ejection fraction ≤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 reduction 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

RESUMEN

Introducción y objetivos: En pacientes con insuficiencia cardíaca, fracción de eyeción del ventrículo izquierdo ≤ 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 ≤ 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 ≤ 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%). El análisis multivariado ajustado por propensión score mostró una reducción en la combinación de mortalidad cardíaca, trasplante cardíaco, revascularización coronaria e ingresos cardiovasculares.

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INTRODUCCIÓN

El fracaso cardíaco (HF) con disfunción sistólica del ventrículo izquierdo (VI) constituye un riesgo aumentado de eventos tromboembólicos (TE), con una incidencia anual de 1%-4%, lo que contribuye a una alta proporción de hospitalizaciones así como a una alta morbilidad y mortalidad en estos pacientes. Algunos autores han sugerido la presencia de hipercoagulabilidad, mediada por aumento de la activación de plaquetas y marcadores como D-dimer, beta tromboglobulina, y trombina-antitrombina III complejos. Este fenómeno, atribuible a la reducción en la circulación intraventricular, ha sido observado en estos pacientes.

En el contexto clínico, la anticoagulación oral (OAC) es indicada en pacientes con HF que presentan fibrilación auricular, tromboembolismo intracavitario, o un historial de tromboembolismo.

El beneficio de la OAC observado en estos pacientes puede extenderse a otros subgrupos, ya sean pacientes con HF y fracción de eyección ventricular (FVE) del VI (SR) inferior a 35%. La mayoría de las publicaciones que describen este subgrupo de pacientes son basadas en ensayos clínicos que analizan pacientes con HF y FR, los que concluyen que la FR es un factor de riesgo independiente para el evento. En algunos casos, la suspensión de la OAC fue necesario en casos de hipotensión arterial.

A pesar de los eventos tromboembólicos, no se ha establecido un beneficio clínico para la OAC en los pacientes con HF y FR. En estudios recientes, la FR ha sido considerada como un factor de riesgo independiente para eventos tromboembólicos, y la OAC ha sido recomendada para estos pacientes.

Algunos estudios posteriores han mostrado que la OAC puede mejorar la supervivencia en pacientes con HF y FR. Sin embargo, hay poca evidencia sobre la utilidad de la OAC en estos pacientes, ya que los ensayos clínicos han tenido resultados inconsistentes.

En la actualidad, se requiere un mayor estudio para establecer la eficacia de la OAC en pacientes con HF y FR. Por lo tanto, es importante realizar más estudios con mayor número de pacientes para determinar la eficacia de la OAC en estos pacientes.

En resumen, la OAC es un tratamiento efectivo para la prevención de eventos tromboembólicos en pacientes con HF y FR. Sin embargo, se requiere de más estudios para establecer su beneficio clínico en estos pacientes. También es importante tener en cuenta los efectos secundarios y la seguridad de la OAC en estos pacientes.

**Statistical Analysis**

Los datos cuantitativos con distribución normal fueron expresados como media ± desviación estándar y los datos no normalizados, como mediana (rango intercuartil). Las comparaciones entre grupos se realizaron mediante análisis de varianza de dos vías, seguido por test post hoc de Bonferroni, en caso de ser necesario. La asociación entre variables categóricas se determinó mediante pruebas de chi-cuadrado y análisis de regresión logística. Los resultados fueron considerados significativos cuando el valor de p fue menor a 0,05.

**Conclusions**

Nuestros hallazgos sugieren que la OAC puede ser un tratamiento efectivo para la prevención de eventos tromboembólicos en pacientes con HF y FR. Sin embargo, se requiere de más estudios para establecer su beneficio clínico en estos pacientes. También es importante tener en cuenta los efectos secundarios y la seguridad de la OAC en estos pacientes.

**Abbreviations**

- HF: Heart failure
- HT: Heart transplantation
- FVE: Fraction of ejection ventricular
- OAC: Oral anticoagulation therapy
- SR: Sinus rhythm
- TE: Thromboembolic events

**Methods**

**Population**

Este es análisis del REDINSCOR (Red de Investigación en Insuficiencia Cardiaca), un registro Objetivo de la HF, que incluye 19 centros correspondientes a 7 regiones y registra varios hospitales, electrocardiográficos, ecocardiográficos, y otras variables obtenidas en el periodo de tiempo basal y durante el seguimiento. Este es un estudio de cohorte prospectivo que incluye a pacientes con more años de edad con síntomas de HF (clase funcional FC II-IV de la New York Heart Association [NYHA]) que fueron hospitalizados en 24 h en los 12 meses previos a la inclusión, y que se presentaron de los siguientes síntomas cardíacos: HF, LVEF ≤40%, diámetro télediastolico >60 mm, presencia de la lesión del septum, y/o posterior post-14 mm y ventriculares relajadas abnormales. El registro está disponible en el Internet (www.redinscor.org), y tiene un módulo de administración con bases de datos y un generador de informes. Su estructura organizacional incluye una unidad de información (consistiendo en un epidemióloga y un estadístico que diseñan y mantienen el registro, controlan la calidad de los datos, los outliers, las inconsistencias internas, y la precisión de la información), una comisión para la mortalidad y el cierre de los eventos (analizan los casos de muerte, la clasificación de los eventos y el análisis de la mortalidad y la mortalidad causada por eventos relacionados con la muerte, y la mortalidad causada por eventos relacionados con la muerte), y la comisión científica.15

Para este estudio, los pacientes se seleccionaron con LVEF ≤35% y HF, con otros indicadores de OAC, de la misma forma que para la HF, pero con otros síntomas de PCR tromboembólicos, prostéticos, intracavitarios, o otros fenómenos tromboembólicos. En este grupo, los pacientes que fueron administrados OAC (grupo I) fueron comparados con los que no tomaron OAC (grupo II).

**Events Considered**

Los eventos considerados fueron:

- Mortalidad total.
- Combinado de evento cardíaco y trasplante de corazón (HT).
- Admisiones de HF.
- Revascularización coronaria.
- Síndrome.
- Combinado de evento cardíaco, HT, revascularización coronaria, y admisiones cardiovascular.
- Muerte súbita y muerte.

A pesar de los eventos considerados, el REDINSCOR no incluyó eventos en el registro de los datos de la recopilación, fueron definidos para este estudio.

**Statistical Analysis**

Los datos cuantitativos con distribución normal fueron expresados como media ± desviación estándar y los datos no normalizados, como mediana (rango intercuartil). Las comparaciones entre grupos se realizaron mediante análisis de varianza de dos vías, seguido por test post hoc de Bonferroni, en caso de ser necesario. La asociación entre variables categóricas se determinó mediante pruebas de chi-cuadrado y análisis de regresión logística. Los resultados fueron considerados significativos cuando el valor de p fue menor a 0,05.

**Conclusions**

Nuestros hallazgos sugieren que la OAC puede ser un tratamiento efectivo para la prevención de eventos tromboembólicos en pacientes con HF y FR. Sin embargo, se requiere de más estudios para establecer su beneficio clínico en estos pacientes. También es importante tener en cuenta los efectos secundarios y la seguridad de la OAC en estos pacientes.
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 CHA\textsubscript{2}DS\textsubscript{2}-VASc score was calculated for each group according to each patient's baseline characteristics.\textsuperscript{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 score\textsuperscript{17} 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, antidiabetic agents, loop diuretics, thiazide diuretics, aldosterone antagonists, oral inotropic agents, intravenous inotropic agents, antiarrhythmic agents, nitrates, hydralazine, 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 nonischemic 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 CHA\textsubscript{2}DS\textsubscript{2}-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 time 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 HT” 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=.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; %CI, 0.25-0.90; P=.02). For the other potential modifying factors analyzed, the association between OAC use and the various events studied was homogeneous. 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.

\begin{table}[h]
\centering
\caption{Anticoagulant Therapy by Hospital}
\begin{tabular}{|c|c|}
\hline
Hospital & No. (%) \\
\hline
Hospital Universitario Puerta de Hierro & 41 (52) \\
Hospital Universitari Joan XXIII & 9 (18) \\
Hospital Clinic de Barcelona & 29 (32) \\
Hospital de la Santa Creu i Sant Pau & 23 (36) \\
Hospital Clínico Universitario de Santiago & 7 (15) \\
Hospital Clínico San Carlos & 13 (30) \\
Hospital 12 de Octubre & 21 (39) \\
Hospital Universitario Virgen de la Arrixaca & 6 (12) \\
Hospital Universitario Nuestra Señora de Valme & 18 (17) \\
Hospital Universitari Arnau de Vilanova & 7 (23) \\
Hospital Universitario La Fe & 14 (33) \\
Hospital Universitario Virgen Macarena & 3 (30) \\
Hospital de Guadarrama & 1 (50) \\
Hospital Universitario Son Dureta & 20 (26) \\
Hospital Francesc de Borja & 3 (19) \\
Hospital Municipal de Badalona & 3 (43) \\
Hospital General Universitario Morales Meseguer & 0 (0) \\
Hospital Universitario Puerta del Mar & 19 (16) \\
\hline
\end{tabular}
\label{tab:table1}
P<.001. P after adjusting for propensity score: 1.
\end{table}
Table 2
Baseline and Differential Characteristics Between Both Groups

<table>
<thead>
<tr>
<th>Characteristic</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±12.5</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>123.6±32</td>
<td>124±33.4</td>
<td>.028</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>.330/0.96</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>CHAD2-Ds2-PISC</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>Event</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 (37.6%)</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 covariate 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. 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 study (2010) and (Survival and Ventricular Enlargement) the SCD-HeFT (Sudden Cardiac Death-Heart Failure Trial) analysis, and to the 29% in the BEST (Beta Blocker Evaluation of Survival Trial) subsudy, and exceeds those of the SOLVD (Studies of Left Ventricular Dysfunction) (9%), V-HeFT 1 (19%) and V-HeFT 2 (21%) trials. 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.
of the disease, greater dilation 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 antplatelet 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 CHA₂DS₂-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”
\begin{table}
\centering
\caption{Summary of Available Evidence on Anticoagulant Therapy in Heart Failure}
\begin{tabular}{|l|c|c|c|c|c|c|c|}
\hline
Study & Year & Design & No. & Population & Ischemic etiology & Follow-up & Treatment & Final points & Results & Bleeding & Comments \\
\hline
SOLVD substudy\(^a\) & 1998 & Observational retrospective & 6378 & HF with AF (24%), stroke (19%), VTE (2.1%) & 70% & 39 months & Warfarin (9%), ASA & Death & HR = 0.76; 95%CI, 0.65-0.89 & Not reported & More patients of the warfarin group had AF (19.3% vs 4.5%) and cerebrovascular disease (13.8% vs 5.5%) \\
\hline
Substudy V HEFT 1\(^b\) & 1993 & Observational retrospective & 642 & HF with AF (16%), prosthetic valves & 44.2% & 27 months & Warfarin (19%), ASA & TE & Neutral: (2.9/100 patients/year vs 2.7/100 patients/year; \(P=NS\)) & Not reported & More TE in patients with AF and prosthetic valves \\
\hline
Substudy V HEFT 2\(^c\) & 1993 & Observational retrospective & 804 & HF with AF (15%), prosthetic valves & 53% & 30 months & Warfarin (21%), ASA & TE & Reduction of TE with warfarin (4.9/100 patients/year vs 2.1/100 patients/year); \(P=0.01\) & Not reported & More TE in patients with AF and prosthetic valves \\
\hline
Substudy SAVE\(^d\) & 1997 & Observational retrospective & 2231 & HF with AF (10%), prosthetic valves & & Not reported & Warfarin (28%) & Stroke & LVEF 28%; RR 0.17; \(P=0.001\) LVEF 29%-35%; RR, 0.14; \(P=0.001\) LVEF>35%; RR, 0.23; \(P=0.001\) & Not reported & More patients in patients with AF and prosthetic valves \\
\hline
Substudy BEST\(^e\) & 2011 & Observational & 2708 & HF in SR with no indication for OAC & 56.5% & 25 months & Warfarin (29%) & Overall mortality Cardiovascular death & 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 & Not reported & \\
\hline
WASH\(^f\) & 2004 & Randomized, open & 279 & HF in SR with no indication for OAC & 60% & 27 months & Warfarin, ASA or control & Combination of death, infarction and stroke & 26% in warfarin and in control; \(P=NS\) & 5 h events, greater with warfarin. 17% vs 5% minor H; \(P<0.03\) & Halted early due to low recruitment \\
\hline
WATCH\(^g\) & 2009 & Randomized & 1587 & HF in SR with no indication for OAC & 70% & 23 months & Warfarin, ASA or clopidogrel & Combination of death, infarction and stroke & 19.6% in warfarin; 20.7% in ASA; 21.6% in clopidogrel; \(P=NS\) Reduction of non-fatal stroke with warfarin & 7 h events, greater with warfarin & Planned to include 3000 patients \\
\hline
HELAS\(^h\) & 2006 & Randomized & 197 & HF in SR with no indication for OAC & 58% & 24 months & Warfarin-ASA warfarin-placebo & Combination of death, stroke, embolism, infarction, rehospitalization, and HF & Ischemic etiology: 8.9% with warfarin vs 14.9% with ASA; \(P=NS\) Reduction of fatal stroke with warfarin & 7 h events, greater with warfarin & Separated analysis ischemic etiology-idiopathic patients, under recruitment \\
\hline
REDINSCOR & 2011 & Observational & 2234 & HF in SR with no indication for OAC & 53.5% & 21 months & Atenocoumarol (26%) & Overall mortality Cardiac death and HT Admissions for HF Coronary revascularization Stroke Cardiac death, HT, coronary revascularization, and cardiovascular admissions Sudden death and stroke & 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; \(P=0.56\) HR = 0.83; 95%CI, 0.10-1.10; \(P=0.07\) HR = 0.89; 95%CI, 0.18-4.40; \(P=0.89\) HR = 0.74; 95%CI, 0.55-0.99; \(P=0.04\) HR = 0.52; 95%CI, 0.21-1.32; \(P=0.17\) & Not available & \\
\hline
\end{tabular}
\end{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-20,21 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,4 V-HeFT 1 and 2 and SAVE,6 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,19 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 HELAS9 (Heart failure Long-term Antithrombotic Study). studies. 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-analysis22 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 trial23 (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.24 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.25

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.

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