Original article

International Normalized Ratio and Mortality Risk in Acute Heart Failure and Nonvalvular Atrial Fibrillation Patients Receiving Vitamin K Antagonists

Enrique Santas,[a] Gema Miñana,[a,b] Jana Gummel,[a] Roxana Farcasan,[a] Ana Payá,[a] Raquel Heredia,[a] Vicent Bodí,[a,b] Anna Mollar,[a] Vicente Bertomeu-González,[c,d,e] Francisco Javier Chorro,[a,b,c] Juan Sanchis,[a,b,c] Josep Lupón,[c,f,g] Antoni Bayés Genís,[c,f,g] and Julio Núñez[a,b,c,]*

[a] *Servicio de Cardiología, Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain*
[b] *Departamento de Medicina, Universitat de València, Valencia, Spain*
[c] *Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain*
[d] *Servicio de Cardiología, Hospital Universitario San Juan, San Juan de Alicante, Alicante, Spain*
[e] *Departamento de Medicina, Universidad Miguel Hernández, Alicante, Spain*
[f] *Servicio de Cardiología, Unidad de Insuficiencia Cardiaca, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain*
[g] *Departamento de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain*

A B S T R A C T

Introduction and objectives: Heart failure patients with nonvalvular atrial fibrillation (NVAF) on treatment with vitamin K antagonists (VKA) often have suboptimal international normalized ratio (INR) values. Our aim was to evaluate the association between INR values at admission due to acute heart failure and mortality risk during follow-up.
Methods: In this observational study, we retrospectively assessed INR on admission in 1137 consecutive patients with acute heart failure and NVAF who were receiving VKA treatment. INR was categorized into optimal values (INR = 2-3, n = 210), subtherapeutic (INR < 2, n = 660), and supratherapeutic (INR > 3, n = 267). Because INR did not meet the proportional hazards assumption for mortality, restricted mean survival time differences were used to evaluate the association among INR categories and the risk of all-cause mortality.
Results: During a median [interquartile range] follow-up of 2.15 years [0.71-4.29], 495 (43.5%) patients died. On multivariable analysis, both patients with subtherapeutic and supratherapeutic INR showed higher risks of all-cause mortality, as evidenced by their restricted mean survival time differences at 5 years' follow-up: –0.50; 95%CI, –0.77 to –0.23 years; $P < .001$; and –0.40; 95%CI, –0.70 to –0.11 years; $P = .007$, respectively, compared with INR 2-3.
Conclusions: In acute heart failure patients on treatment with VKA for NVAF, INR values out of normal range at admission were independently associated with a higher long-term mortality risk.

© 2018 Sociedad Española de Cardiología. Published by Elsevier España, S.L.U. All rights reserved.

Razón internacional normalizada y mortalidad de los pacientes con insuficiencia cardiaca y fibrilación auricular tratados con antagonistas de la vitamina K

R E S U M E N

Introducción y objetivos: Los pacientes con insuficiencia cardiaca en tratamiento con antagonistas de la vitamina K (AVK) por fibrilación auricular no valvular (FANV) a menudo presentan valores alterados de la razón internacional normalizada (INR). El objetivo es evaluar la asociación entre la INR al ingreso por insuficiencia cardiaca y el riesgo de mortalidad en el seguimiento.
Métodos: Estudio observacional retrospectivo en el que se evaluó la INR al ingreso de 1.137 pacientes consecutivos con insuficiencia cardiaca aguda en tratamiento con AVK por FANV. Esta se categorizó en: INR en rango óptimo (INR = 2-3, n = 210), infraterapéutica (INR < 2, n = 660) o supraterapéutica (INR > 3, n = 267). La asociación independiente entre INR y mortalidad se evaluó mediante cálculo restringido de las diferencias en tiempos de supervivencia media, dado que la INR no cumple la condición de proporcionalidad de riesgos de mortalidad.
Resultados: Tras una mediana de 2,15 [0,71-4,29] años, fallecieron 495 pacientes (43,5%). En el análisis multivariable, tanto la INR infraterapéutica como la supraterapéutica se asociaron con un mayor riesgo de mortalidad, con unas diferencias en tiempos de supervivencia media a 5 años de –0,50 años

---

* Corresponding author: Servicio de Cardiología, Hospital Clínico Universitario de Valencia, Avda. Blasco Ibáñez 17, 46010 Valencia, Spain.
E-mail address: yulnunez@gmail.com (J. Núñez).

(IC95%,–0,77 a –0,23; p < 0,001) y –0,40 años (IC95%, –0,70 a –0,11; p = 0,007) con respecto a los pacientes con INR 2-3.

Conclusiones: La INR fuera de rango óptimo al ingreso de los pacientes con insuficiencia cardiaca aguda en tratamiento con AVK por FANV se asocia de manera independiente con un mayor riesgo de mortalidad en el seguimiento a largo plazo.

Abbreviations

CV: cardiovascular
INR: international normalized ratio
NVAF: nonvalvular atrial fibrillation
RMST: restricted mean survival time
VKA: vitamin K antagonist

INTRODUCTION

Atrial fibrillation and heart failure are closely associated, both clinically and pathophysiologically.[1] Atrial fibrillation is the most common arrhythmia in patients with heart failure and is associated with an increased risk of thromboembolic events, worse functional class, and worse prognosis.[2] Because of the risk of stroke or systemic embolism, the vast majority of heart failure patients with nonvalvular atrial fibrillation (NVAF) need long-term oral anticoagulant therapy.[3] Nevertheless, and despite recent evidence in favor of direct oral anticoagulants,[4,5] a large proportion of patients with heart failure and NVAF in Spain are treated with vitamin K antagonists (VKAs). Management of oral anticoagulant therapy in the setting of heart failure, however, is difficult because of multiple drug interactions, concomitant liver or kidney failure, and greater international normalized ratio (INR) instability.[6,7] This is particularly true during acute decompensated heart failure, as heart failure patients often have INR values outside the optimal therapeutic range.[8]

INR was also recently associated with mortality risk in patients with acute heart failure who were not receiving anticoagulants.[9] Pathophysiologic mechanisms that could explain the importance of INR in heart failure include tissue hypoxia, liver dysfunction, and the degree of neurohormonal activation. The prognostic value of INR in patients on VKA therapy, however, is unknown. The aim of this study was to assess the association between INR and long-term mortality risk in patients with acute heart failure and NVAF being treated with a VKA.

METHODS

Study Group and Protocol

We studied a consecutive cohort of 2604 patients with a primary diagnosis of acute heart failure admitted to the cardiology ward of a tertiary care university hospital between January 2004 and December 2016. Acute heart failure was defined according to clinical practice guidelines.[10] Patients with acute decompensated heart failure resulting from new-onset or chronic heart failure were included. Of the 2604 patients in the registry, 1467 were excluded because *a)* they did not have a diagnosis of atrial fibrillation (n = 1262), *b)* they did not have a diagnosis of valvular atrial fibrillation according to the recommendations of the European Cardiology Society[3] (n = 157), or *c)* they were being treated with an anticoagulant other than a VKA (n = 48). The final sample thus consisted of 1137 patients.

A wide range of variables, including clinical, physical examination, biochemical, electrocardiographic, and echocardiographic variables, together with details of concomitant treatments, were recorded during the initial hospital stay. Treatment was individualized at the discretion of the attending cardiologist and in accordance with clinical practice guidelines applicable over the study period.

The study was performed in accordance with the principles set forth in the Declaration of Helsinki and was approved by ethics committee of the hospital.

INR Values

INR was measured during the first medical contact in the emergency department. A value of 2 to 3 was considered to be within the optimal therapeutic range. Patients were classified into 3 categories depending on their INR value: *a)* a therapeutic category (INR 2-3), *b)* a subtherapeutic category (INR < 2), and *c)* a supratherapeutic category (INR > 3).

Follow-up and Assignment of Events

Survival after hospital discharge was checked by reviewing the patients' electronic medical records. The researchers responsible for assigning the events did not have access to the patients' INR data. The primary endpoint was the association between INR and all-cause mortality during follow-up. The secondary endpoint was the association between INR and cause-specific mortality, categorized as *a)* cardiovascular vs noncardiovascular death) and *b)* death due to heart failure vs death due a cause other than heart failure. Cardiovascular death was defined using the criteria recommended by the American Heart Association and included sudden death attributable to heart failure, acute myocardial infarction, stroke, vascular bleeding, or peripheral artery disease, and death due to an unknown cause. In all other cases, the cause of death was considered to be noncardiovascular.[11]

Statistical Analysis

Continuous variables are expressed as means ± standard deviation or, when nonnormally distributed, as medians and interquartile range. Discrete variables are expressed as percentages. The baseline characteristics of patients in the INR categories were compared using analysis of variance. The Kruskal-Wallis test was used for nonparametric variables.

The proportional hazards assumption was tested for all the study variables in the 3 INR categories using scaled Schoenfeld residuals and log-log curves. A different method of analysis was used depending on whether the assumption of proportional hazards was met or not. In the first case, a Royston-Parmar model was used and in the second case, differences in restricted mean survival time (RMST) were calculated.[12] RMST is an alternative to the hazard ratio for situations in which the assumption of proportional hazards does not hold. RMST differences represent the years of life lost associated with a given study variable.[12,13] The

variables for which IRN did not meet the proportional hazards assumption were all-cause mortality, cardiovascular death, and death due to heart failure. The assumption was met for noncardiovascular death and death due to a cause other than heart failure. The maximum follow-up time in the RMST analysis was set at 5 years. Results are expressed as the difference in number of years up to the event.

All the variables in Table 1 were evaluated for their prognostic value. Backward elimination was used to simplify the final multivariate model. The optimal polynomial for the continuous variables was calculated during stepwise selection to ensure linearity with the event. Cumulative incidence curves were generated to analyze cause-specific mortality and differences were evaluated using the Gray test.[14] RMST adapted to competing risks was used in the multivariate analysis of cause-specific mortality.

A 2-tailed P value of less than .05 was considered significant for all analyses. The statistical analyses were performed by MedStats Consulting (Reading, Pennsylvania, United States) using STATA 15.1 (StataCorp LP; College Station, Texas, United States).

RESULTS

Baseline Patient Characteristics

The mean ± standard deviation age of the patients was 74 ± 10 years; 581 patients (51.1%) were women and 568 (50.2%) had already been hospitalized for heart failure. Most of the patients (n = 927, 81%) had an INR outside the therapeutic range. There were 210 patients (18.5%) in the therapeutic category (INR, 2-3),

Table 1
Patients' Baseline Characteristics by INR Category

	INR 2–3 (n = 210)	INR < 2 (n = 660)	INR > 3 (n = 267)	P
Age, y	75 ± 9	74 ± 11	74 ± 9	.704
Men	117 (55.7)	317 (48.0)	122 (45.7)	.036
First admission for HF	103 (49.0)	367 (55.6)	98 (36.7)	.002
Hypertension	170 (80.9)	519 (78.6)	203 (76.0)	.191
Diabetes mellitus	91 (43.3)	239 (36.2)	106 (39.7)	.517
Dyslipidemia	109 (51.9)	313 (47.4)	114 (42.7)	.044
Active smoking	12 (5.7)	89 (13.4)	20 (7.5)	.773
Ischemic heart disease	62 (29.5)	158 (23.9)	79 (29.6)	.834
Valvulopathy[*]	45 (21.4)	107 (16.2)	91 (34.1)	<.001
Severe aortic stenosis	20 (9.5)	50 (7.6)	38 (14.2)	.007
Severe mitral insufficiency	17 (8.1)	45 (6.8)	30 (11.2)	.082
HR, bpm	102.2 ± 30.5	115.4 ± 32.5	101.1 ± 29.3	.298
SBP, mmHg	139.9 ± 27.4	143.1 ± 31.4	142.7 ± 32.1	.717
QRS > 120 ms	67 (31.9)	179 (27.1)	76 (28.5)	.467
LBBB	35 (17)	110 (17)	52 (19)	.574
Pleural effusion	118 (56.2)	311 (47.1)	140 (52.4)	.549
Peripheral edema	166 (79)	430 (65)	173 (65)	.002
Hemoglobin, g/dL	12.4 ± 1.9	12.8 ± 1.9	12.3 ± 1.9	.558
Sodium, mEq/L	139 ± 4.3	139 ± 4.3	137.4 ± 5.2	<.001
NT-proBNP, pg/mL	4116 [4916]	4069 [3.859]	4970 [5288]	.005
CA 125, IU/mL	75 [118]	56 [101]	76 [127]	.051
H-S troponin T, pg/mL	64 [41]	61 [49]	73 [47]	.001
Total cholesterol, mg/dL	154 ± 41	162 ± 41	157 ± 42	.834
GGT, IU/L	80 ± 76	78 ± 76	78 ± 71	.214
Total bilirubin, mg/dL	1.0 ± 0.4	0.9 ± 0.4	1.1 ± 0.4	.203
Serum creatinine, mg/dL	1.30 ± 0.57	1.21 ± 0.52	1.32 ± 0.56	.235
Urea, mg/dL	61.6 ± 29.7	57.4 ± 31.1	67.9± 34.9	.006
GFR, mL/min/1.73 m²	60.6 ± 24.9	63.3 ± 25.5	56.9± 22.7	.043
AST, IU/L	30 ± 15	35 ± 40	31 ± 16	.476
LVEF, %	52.9 ± 15.3	51.7 ± 14.5	54.4 ± 13.5	.034
LVEF < 40%	50 (23.8)	152 (23.0)	40 (15.0)	.013
Left atrium, mm	47.1 ± 8	45.1 ± 8	48.9 ± 8	.082
LVTDD, mm	55.4 ± 9.6	55.8 ± 9.9	55.6 ± 10.1	.236
DT, ms	194 ±54	198 ± 63	193 ± 52	.937
SPAP, mmHg	48 ± 16	45 ± 13	49 ± 13	.020
TAPSE, mm	17 ± 3.0	17 ± 2.9	17 ± 2.7	.329

AST, aspartate aminotransferase; CA 125, carbohydrate antigen 125; DT, deceleration time; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; HF, heart failure; HR, heart rate; H-S, high-sensitivity; INR, international normalized ratio; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NT-ProBNP, N-terminal probrain natriuretic peptide; LVTDD, left ventricular telediastolic diameter; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid anular plane systolic excursion.
Values are expressed as No. (%), mean ± standard deviation, or median [interquartile range].
    * The term *valvulopathy* refers to severe valve disorders and does not include rheumatic mitral stenosis or the presence of a prosthetic heart valve.

660 (58.0%) in the subtherapeutic category (INR < 2), and 267 (23.5%) in the supratherapeutic category (INR > 3).

The patients' baseline characteristics are shown by INR group in Table 1. INR values outside the therapeutic range, in particular, subtherapeutic values, were associated with various clinical, biochemical, and echocardiographic variables that are typically associated with poor prognosis in heart failure. Notably, there were no differences between the 3 groups for biochemical liver function parameters. Supratherapeutic INR values were more common in patients with preserved left ventricular ejection fraction than with reduced left ventricular ejection fraction (Table 1).

INR and All-Cause Mortality

Over a median follow-up period of 2.15 (0.71-4.29) years, 495 patients (43.5%) died. Crude mortality rates were higher in patients with INR values outside the therapeutic range (Table 2). According to the Kaplan-Meier survival analysis, thus, the risk of all-cause mortality was higher in patients an INR value lower than 2 and in particular in those with an INR value above 3 (log rank test, P = .014) (Figure 1).

The multivariate analysis of RMST differences confirmed an independent association between INR on admission to hospital and an increased risk of all-cause mortality: $RMST_{INR < 2} = -0.50$ years (95% confidence interval [95%CI], −0.77 to −0.23) ($P < .001$) and $RMST_{INR > 3} = -0.40$ years (95%CI, −0.70 to −0.11) ($P = .007$) (Table 3). The Harrell C statistic was 0.771. The survival curves adjusted for all-cause mortality are shown by INR category in Figure 2. These curves were estimated from the multivariate RMST model and include the interaction between INR and time. On comparison of patients in the subtherapeutic and therapeutic

categories, the strength of the association between subtherapeutic values and risk of all-cause mortality decreased over time and lost its significance in the second year. The association in the supratherapeutic group, by contrast, remained relatively constant over time but was only significant from the third month up to the third year (Figure 3). The modeling of time-dependent hazard ratios is presented in Table 1 of the supplementary material. When INR was established as a continuous variable in the multivariate model, both subtherapeutic and supratherapeutic INR values were found to be associated with an increased risk of all-cause mortality ($P < .001$) (Figure of the supplementary material).

INR and Cardiovascular Death

Of the 495 deaths recorded, 378 (76.4%) were attributable to cardiovascular causes. The crude rates for the specific causes of death by INR category are shown in Table 2.

The cumulative risk of cardiovascular death was higher in patients with nontherapeutic INR values (Gray test, $P = .063$) and was particularly high in those with values above 3 (Figure 4). After the multivariate adjustment, however, although both subtherapeutic and supratherapeutic INR values were associated with a higher risk of cardiovascular death, the association was somewhat stronger for subtherapeutic values (differences in RMST at 5 years: $RMST_{INR < 2} = -0.39$ years (95%CI, −0.68 to −0.11); $P = .007$, and $RMST_{INR > 3} = -0.26$ years (95%CI, −0.57 to 0.05) years; $P = .098$) (Table 3).

The survival curves for the secondary endpoints are shown in Figure 5. The association between the risk of cardiovascular death and subtherapeutic INR values was stronger in the early follow-up period, as is also reflected in the time-dependent hazard ratios (Table 1 of the supplementary material). Compared with INR

Table 2

Crude Incidence Rates (per 100 Person-Years) and 95% Confidence Intervals (CIs) for All-Cause and Cause-Specific Mortality by INR Category

Criterion	Incidence rate		
	INR 2-3	INR < 2	INR > 3
All-cause mortality	13.85 (11.09-17.29)	18.25 (16.21-20.54)	21.01 (17.83-24.75)
CV death	11.01 (8.58-14.12)	13.59 (11.85-15.59)	16.45 (13.67-19.8)
Non-CV death	2.84 (1.74-4.64)	4.66 (3.69-5.89)	4.55 (3.20-6.48)
Death due to HF	7.28 (5.36-9.89)	8.59 (7.23-10.21)	8.81 (6.84-11.35)
Death due to a cause other than HF	6.57 (4.76-9.07)	9.66 (8.21-11.37)	12.19 (9.83-15.12)

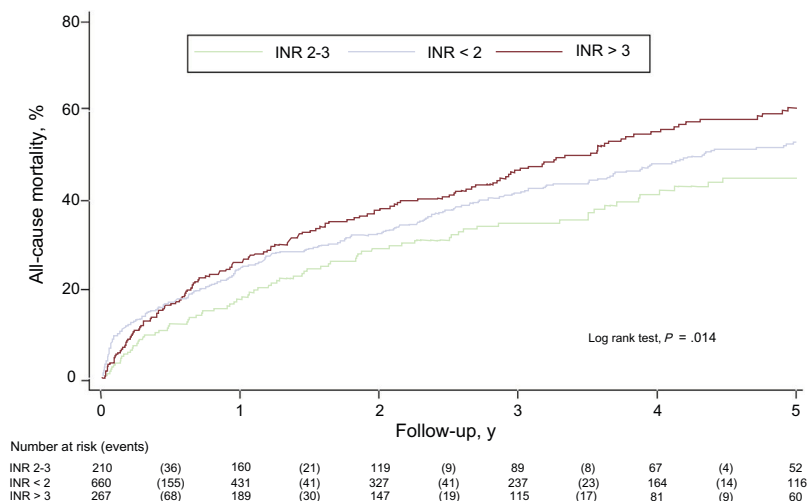CV, cardiovascular; HF, heart failure; INR, international normalized ratio.

Figure 1. Kaplan-Meier all-cause mortality curves by international normalized ratio (INR) category.

Table 3
Risk Estimates (Differences in Mean Survival Times) in the Different Analyses of Primary and Secondary Endpoints in Subtherapeutic (INR < 2) and Supratherapeutic (INR > 3) Categories Compared With INR 2–3

Criterion	Mean survival time, y (95%CI)			Differences in mean survival time, y (95%CI)	
	INR 2-3	INR < 2	INR > 3	INR < 2-INR 2-3	INR > 3-INR 2-3
All-cause mortality[a]	3.56 (3.34-3.79)	3.07 (2.92-3.21)	3.16 (2.96-3.36)	−0.50 (−0.77 to −0.23); P < .001	−0.40 (−0.70 to −0.11); P = .007
CV death[b]	3.81 (3.57-4.04)	3.42 (3.25-3.58)	3.55 (3.34-3.76)	−0.39 (−0.68 to −0.11); P = .007	−0.26 (−0.57 to 0.05); P = .098
Non-CV death[c]	4.67 (4.51-4.82)	4.5 (4.38-4.62)	4.51 (4.35-4.68)	−0.17 (−0.35 to 0.02); P = .085	−0.15 (−0.37 to 0.07); P = .181
Death due to HF[d]	4.21 (3.99-4.42)	3.89 (3.74-4.05)	4.17 (3.98-4.35)	−0.31 (−0.57 to −0.05); P = .018P	−0.04 (−0.31 to −0.23); P = .775
Death due to a cause other than HF[e,5]	4.21 (3.98-4.44)	3.96 (3.8-4.11)	3.72 (3.49-3.96)	−0.25 (−0.52 to 0.02); P = .068	−0.48 (−0.81 to −0.16); P = .004

CV, cardiovascular; HF, heart failure; INR, international normalized ratio; LVEF, left ventricular ejection fraction; NT-ProBNP, N-terminal probrain natriuretic peptide.
[a] Model adjusted for age, first admission for HF, branch block, Charlson comorbidity index, heart rate, urea, systolic blood pressure, hemoglobin, and NT–proBNP.
[b] Model adjusted for age, first admission for HF, branch block, LVEF < 40%, Charlson comorbidity index, heart rate, urea, systolic blood pressure, hemoglobin, and NT-proBNP.
[c] Model adjusted for age, LVEF < 40%, Charlson comorbidity index, heart rate, systolic blood pressure, and hemoglobin.
[d] Model adjusted for age, first admission for HF, branch block, LVEF < 40%, Charlson comorbidity index, heart rate, urea, systolic blood pressure, hemoglobin, and NT-proBNP.
[e] Model adjusted for age, LVEF < 40%, Charlson comorbidity index, heart rate, urea, systolic blood pressure, and hemoglobin.
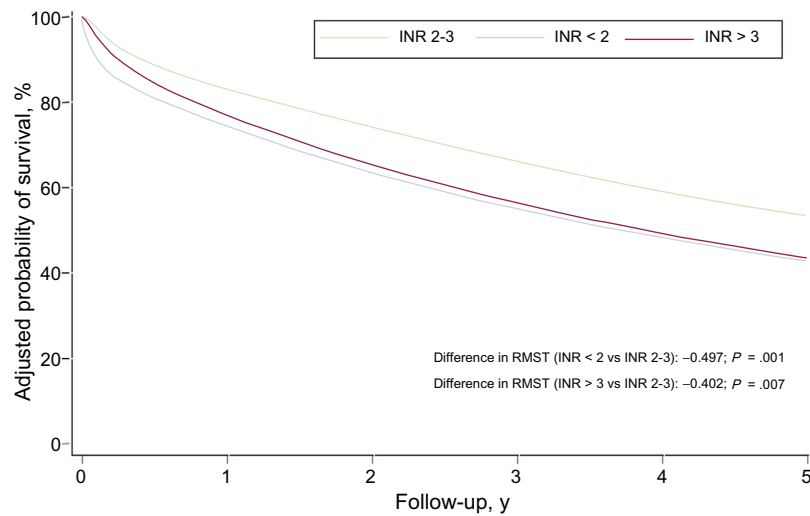

Difference in RMST (INR < 2 vs INR 2-3): −0.497; P = .001
Difference in RMST (INR > 3 vs INR 2-3): −0.402; P = .007

Figure 2. Adjusted survival curves for all-cause mortality by international normalized ratio (INR) category. RMST, restricted mean survival time.
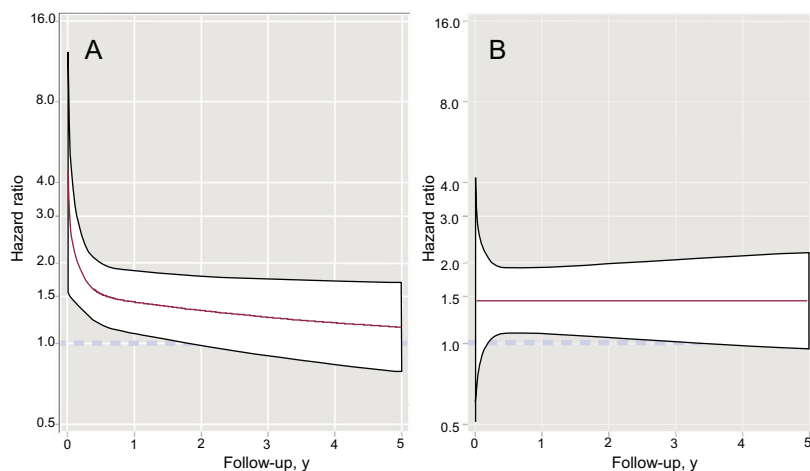

Figure 3. Estimated all-cause mortality risk according to time. A, INR < 2 vs. 2–3. B, INR > 3 vs. 2–3. INR, international normalized ratio.
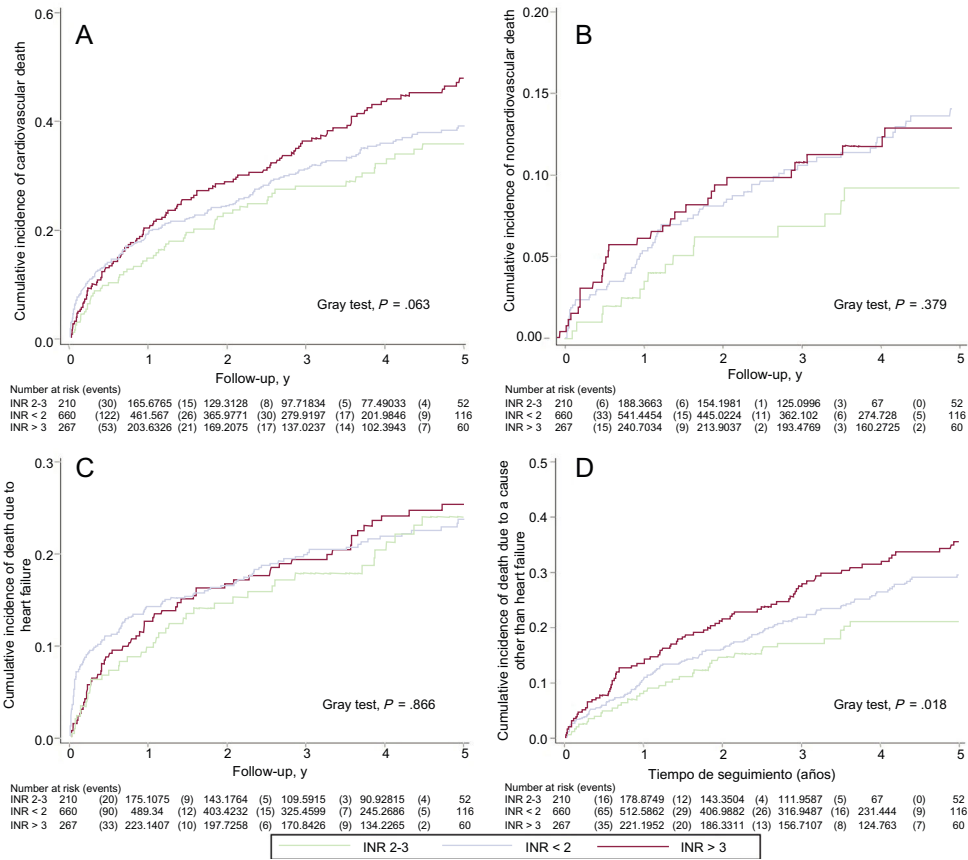
Figure 4. Cumulative indicence. A: cardiovascular death. B: noncardiovascular death. C: death due to heart failure. D: death due to a cause other than heart failure. INR, international normalized ratio.

Figure 5. Adjusted survival curves. A: cardiovascular death. B: noncardiovascular death. C: death due to heart failure. D: death due to a cause other than heart failure. INR, international normalized ratio; RMST, restricted mean survival time.
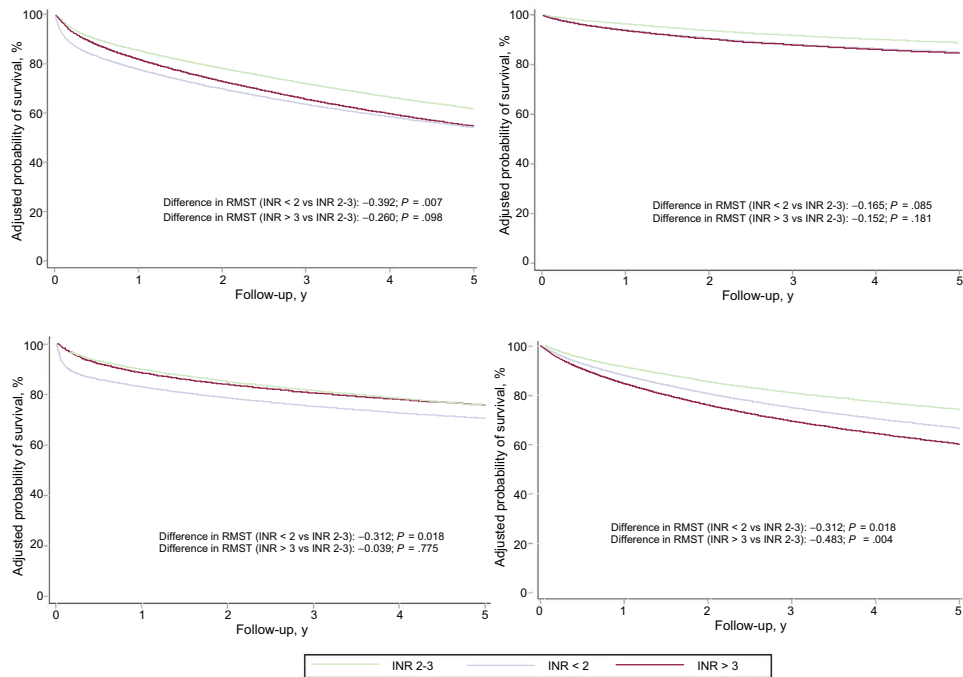
values in the therapeutic range, supratherapeutic values were associated with a sustained increased risk, but this did not reach statistical significance.

The crude rates for cause-specific mortality were low (Table 2 of the supplementary material). No significant differences were observed for death attributable to ischemic stroke, acute myocardial infarction, hemorrhagic stroke, or sudden death, although there were a higher number of deaths due to hemorrhagic stroke and sudden deaths in patients with INR values above 3. The cause of death was unknown in 84 patients (16%).

INR and Noncardiovascular Death

In total, 117 deaths (23.6%) did not have a cardiovascular cause. The incidence of noncardiovascular death was higher in the subtherapeutic and supratherapeutic categories (Table 2), but the differences with patients in the therapeutic category were not significant (Gray test, $P = .379$) (Figure 4).

Because the assumption of proportional hazards was met for this criterion, the prognostic values of the different INR categories are presented as single hazard ratios in Table 4. The results confirm the lack of association between INR and the risk of noncardiovascular death identified in the RMST analysis (Table 3).

The number of deaths due to bleeding was very low (Table 2 of the supplementary material) and no differences were observed in cumulative risk between the 3 INR categories (Gray test, $P = .949$).

INR and Death Due to Heart Failure

A total of 230 deaths were attributed to heart failure (46.5%). Although the crude incidence rate was higher in patients with nontherapeutic INR values (Table 2), no significant differences were observed for cumulative risk between the 3 categories (Gray test, $P = .866$) (Figure 4).

The category associated with the highest risk of mortality due to heart failure was the subtherapeutic category, which was mostly attributable to early events. In the multivariate RMST analysis, only patients with subtherapeutic INR values had an increased risk of death due to heart failure: $RMST_{INR < 2} = -0.31$ years (95%CI, −0.57 to −0.05) ($P = .018$) (Table 3 and Figure 5). The time-dependent hazard ratios (Table 1 of the supplementary material) showed a pronounced and significant increase in risk in the subtherapeutic category, but this decreased rapidly and lost its significance after the third month of follow-up.

INR and Death Due to a Cause Other Than Heart Failure

There were marked differences between the 3 INR groups in terms of the cumulative incidence of death due to causes other than heart failure, with the highest rate observed in the supratherapeutic category (Gray test, $P = .018$) (Figure 4).

In the multivariate analysis (Table 3), patients with supratherapeutic INR values had a considerably increased risk of death due to a cause other than heart failure compared with patients with values in the therapeutic range: $RMST_{INR > 3} = -0.48$ (95%CI, −0.81 to −0.16) ($P = .004$) (Figure 5). The assumption of proportional hazards was also met for this criterion and the prognostic values of the different INR categories are thus shown as a single hazard ratio in Table 4, supporting the results of the RMST analysis.

DISCUSSION

The main finding in this study is that an INR value outside (above or below) the optimal therapeutic range in patients with acute heart failure and NVAF on VKA therapy on admission to hospital is independently associated with an increased risk of mortality during long-term follow-up.

Heart failure and atrial fibrillation often coexist as they share risk factors and pathophysiologic mechanisms.[15] The presence of heart failure significantly increases the risk of thromboembolic events in patients with atrial fibrillation and is itself an indication for long-term oral anticoagulant therapy.[3] It is not easy, however, to manage oral anticoagulant therapy in patients with heart failure and atrial fibrillation.[7,16] Several factors limit effective control, such as polypharmacy, frequent rehospitalization, renal or hepatic dysfunction, and hemostatic alterations linked to heart failure[7–9,17] and in particular acute heart failure.[7]

In the present series, over 80% of patients had an altered INR value on hospital admission. Possible explanations include factors that may have a negative effect on VKA metabolism, such as hepatic ischemia and/or tissue hypoxia due to reduced hepatic flow in patients with congestion.[18] INR values in patients with heart failure have also been correlated with degree of systemic inflammation[8] and hemodilution associated with systemic venous congestion.[19] The data from our study partly support the above hypotheses. In our series, altered INR values were significantly associated with elevated levels of certain biomarkers, including carbohydrate antigen 125 and N-terminal probrain natriuretic peptide. We found no association, however, between altered INR values and liver function marker levels.

The pathophysiologic mechanisms underlying the association between INR on hospital admission and risk of mortality are largely unknown. It is noteworthy, however, that the factors mentioned above as potential causes of altered INR values are all negative pathophysiologic and prognostic factors in heart failure. Nevertheless, the persistence of the association between altered INR and mortality after adjustment for confounders in the multivariate analysis, together with the strength of this association in the early

Table 4

Risk Estimates for Different Analyses Meeting the Proportional Hazards Assumption for Subtherapeutic (INR < 2) and Supratherapeutic (INR > 3) Categories Compared With INR 2–3

Criterion	Variable	sHR (95%CI)	P	Overall value, P	Harrell C statistic
Non-CV death[a]	INR 2-3	1		.362	0.666
	INR < 2	1.48 (0.86-2.56)	.160		
	INR > 3	1.44 (0.79-2.64)	.234		
Death due to causes other than HF[b]	INR 2-3	1		.016	0.659
	INR < 2	1.38 (0.96-1.98)	.084		
	INR > 3	1.75 (1.19-2.59)	.005		

95%CI, 95% confidence interval; CV, cardiovascular; HF, heart failure; INR, international normalized ratio; LVEF, left ventricular ejection fraction; sHR, subhazard ratio.

[a] Model adjusted for age, LVEF < 40%, Charlson comorbidity index, heart rate, systolic blood pressure, and hemoglobin. Includes CV death as a competing event.

[b] Model adjusted for age, LVEF < 40%, Charlson comorbidity index, heart rate, urea, systolic blood pressure, and hemoglobin. Includes death due to HF as a competing event.

phases of follow-up, suggest a possible causative link. In a recent study of 294 patients with acute heart failure who were not on anticoagulant therapy, Okada et al.[9] observed that altered INR values on admission were independently associated with lower survival at 1-year of follow-up. As in our study, these values were also associated with a worse neurohormonal activation profile. It should be noted, however, that the patients in our series were all on VKA therapy, and as such, INR was not only a biomarker, but also a modifiable treatment goal within each patient's anticoagulant management program.

Our exploratory analysis did not identify any clear associations between INR values and specific causes of death within the different INR categories, although it did reveal some interesting associations. Patients in the subtherapeutic category (INR < 2), for example, had a greater risk of dying of heart failure. Clinical deterioration and advanced disease in heart failure patients have been linked to increased drug interactions and decreased treatment adherence. Both of these situations have been associated with poor prognosis in heart failure[20] and could partly explain our findings. Patients in the supratherapeutic category (INR > 3) had a higher risk of dying of a cause other than heart failure. Although the reasons for this association are speculative, INR values above 3 were more common in patients with preserved left ventricular ejection fraction. As is known, heart failure with preserved ejection fraction is a multifactorial syndrome characterized by complex interactions between cardiovascular disorders and different comorbidities,[21] and patients are more likely to develop other diseases and die of causes other than heart failure.[22] At the same time, valvulopathy was more common in the supratherapeutic category, which could also partly explain the higher mortality in this subgroup.

A recent study showed that a patient-specific tailored oral anticoagulant therapy intervention significantly improved control in heart failure patients.[23] It is not known, however, what effect good control of oral anticoagulant therapy has on mortality risk in this setting.

One option that does not require INR monitoring is to use direct anticoagulants. Landmark clinical trials comparing direct anticoagulants and VKAs in patients with NVAF have included over 25 000 patients with heart failure, 13 251 of whom were treated with direct anticoagulants.[5] In the subgroup of heart failure patients, direct oral anticoagulants reduced the incidence of stroke or systemic embolism and major and intracranial bleeding, but had a neutral effect on all-cause and cardiovascular mortality.[4] Detection of altered INR on hospital admission could help identify a subgroup of patients in whom direct anticoagulants could be particularly beneficial compared with VKAs. More evidence, however, is needed as different criteria have been used to define heart failure and none of the trials have studied patients with acute decompensated heart failure.

INR did not meet the assumption of proportional hazards for its association with mortality risk. Analysis of RMST differences has been recommended as a suitable alternative for evaluating differences in survival attributable to a study variable over a given period, and its use is increasing.[12,13] The findings of our study show that, following multivariate adjustment for confounders, subtherapeutic and supratherapeutic INR values were respectively associated with a 6-month and 5-month reduction in mean 5-year survival compared with values in the therapeutic range. Risk attributable to INR on admission, however, was greater in the early follow-up period, particularly for patients with a value of less than 2. The association between supratherapeutic values and mortality risk, by contrast, remained more constant during long-term follow-up. More studies are needed to explain the pathophysiologic mechanisms behind these findings and to understand their implications for treatment.

Limitations

This study has several limitations. First, as an observational, single-center study, its results may have been influenced by several biases and aspects inherent to daily practice. Second, we were missing data on time in therapeutic range on admission and on subsequent INR levels, meaning that we have no information on level of anticoagulant therapy control beyond the acute episode. Third, assignment of specific causes of death in observational studies is complicated and has evident limitations.[11] In this regard, the low incidence of deaths attributable to certain cardiovascular events, together with the presence of deaths due to unknown causes, makes it difficult to draw any firm conclusions about specific causes of death attributable to INR. Finally, INR was not measured at the same time as other variables (eg, echocardiographic variables).

CONCLUSIONS

INR values below or above optimal therapeutic values in patients with heart failure and NVAF on hospital admission for acute decompensated heart failure are independently associated with an increased risk of mortality during long-term follow-up.

CONFLICTS OF INTEREST

None declared.

WHAT IS KNOWN ABOUT THE TOPIC?

– The prognostic value of INR values in patients on VKA therapy who experience acute decompensated heart failure is unknown.

WHAT DOES THIS STUDY ADD?

– Overall, 81% of patients with heart failure and NVAF on VKA therapy had an INR value outside the therapeutic range during acute decompensated heart failure.
– Subtherapeutic and supratherapeutic INR values are independently associated with an increased risk of mortality during follow-up.

SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.rec.2018.07.010.

REFERENCES

1. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa. Temporal associations and differences in preserved versus reduced ejection fraction. *Circulation.* 2016;133:484–492.
2. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail.* 2017;5:565–574.
3. Kirchhof P, Benussi S, Kotecha D, et al. Guía ESC 2016 sobre el diagnóstico y tratamiento de la fibrilación auricular. *Rev Esp Cardiol.* 2017;70:50e1-e84.
4. Savarese G, Giugliano RP, Rosano GMC, et al. Efficacy and safety of novel oral anticoagulants in patients with atrial fibrillation and heart failure. A meta-analysis. *JACC Heart Fail.* 2016;4:870–880.

5. Xiong Q, Lau Y, Senoo K, Lane DA, Hong K, Lip GY. Non-vitamin K antagonist oral anticoagulants in patients with concomitant atrial fibrillation and heart failure: a systematic review and meta-analysis of randomized trials. *Eur J Heart Fail.* 2015;17:1192–1200.

6. Eapen ZJ, Mi X, Qualls LG, et al. Adherence and persistence in the use of warfarin after hospital discharge among patient with heart failure and atrial fibrillation. *J Card Fail.* 2014;20:23–30.

7. Ferreria JP, Girerd N, Alshalash S, Konstam MA, Zannad F. Antihrombotic therapy in heart failure patients with and without atrial fibrillation: updates and challenges. *Eur Heart J.* 2016;37:2455–2464.

8. Del Campo M, Roberts G. Changes in warfarin sensitivity during decompensated heart failure and chronic obstructive pulmonary disease. *Ann Pharmacother.* 2015;49:962–968.

9. Okada A, Sugano Y, Nagai T, et al. Prognostic value of prothrombin time international normalized ratio in acute decompensated heart failure. A combined marker of hepatic insufficiency and hemostatic abnormality. *Circ J.* 2016;80:913–923.

10. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2016;37:2129–2200.

11. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA Key data elements and definitions for cardiovascular endpoint events in clinical trials. *Circulation.* 2015;132:302–361.

12. Royston P, Parmar MK. The use of restricted mean survival time to estimate the treatment effect in randomized clinical trials when the proportional hazards assumption is in doubt. *Stat Med.* 2011;30:2409–2421.

13. Kim DY, Uno H, Wei LJ. Restricted mean survival time as a measure to interpret clinical trial results. *JAMA Cardiol.* 2017;2:1179–1180.

14. Fine J, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496–509.

15. Verma A, Kalman JM, Callans DJ. Treatment of patients with atrial fibrillation and heart failure with reduced ejection fraction. *Circulation.* 2017;135:1547–1563.

16. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT$_2$R$_2$ score. *Chest.* 2013;144:1555–1563.

17. Visser LE, Bleumink GS, Trienekens PH, Vulto AG, Hoffman A, Stricker BH. The risk of overanticoagulation in patients with heart failure on coumarin anticoagulants. *Br J Haematol.* 2004;127:85–89.

18. Self T, Reaves A, Oliphant C, Richardson AM, Sands CW. Does heart failure exarcebation increase response to warfarin? Critical review of the literature. *Curr Med Res Opin.* 2006;22:2089–2094.

19. Wheeler AP, Rice TW. Coagulopathy in critically ill patients. *Chest.* 2010;137:185–194.

20. Fitzgerald AA, Powers JD, Ho PM, et al. Impact of medication nonadherence on hospitalizations and mortality in heart failure. *J Card Fail.* 2011;17:664–669.

21. Sarwar CMS, Butler J, Anker SD. The Syndrome of Heart Failure with Preserved Systolic Function. *Rev Esp Cardiol.* 2017;70:232–233.

22. Santas E, Valero E, Mollar A, et al. Burden of Recurrent Hospitalizations Following an Admission for Acute Heart Failure: Preserved Versus Reduced Ejection Fraction. *Rev Esp Cardiol.* 2017;70:239–246.

23. Gotsman I, Ezra O, Hirsh B, et al. A patient-specific tailored intervention improves INR time on therapeutic range and INR variability in heart failure patients. *Am J Med.* 2017;130:982–989.