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Original article

Impact of Variations in Kidney Function on Nonvitamin K Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Recent Acute Heart Failure

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ABSTRACT

Introduction and objectives: Renal impairment and fluctuations in renal function are common in patients recently hospitalized for acute heart failure and in those with atrial fibrillation. The aim of the present study was to evaluate the hypothetical need for dosage adjustment (based on fluctuations in kidney function) of dabigatran, rivaroxaban and apixaban during the first 6 months after hospital discharge in patients with concomitant atrial fibrillation and heart failure.

Methods: An observational study was conducted in 162 patients with nonvalvular atrial fibrillation after hospitalization for acute decompensated heart failure who underwent creatinine determinations during follow-up. The hypothetical recommended dosage of dabigatran, rivaroxaban and apixaban according to renal function was determined at discharge. Variations in serum creatinine and creatinine clearance and consequent changes in the recommended dosage of these drugs were identified during 6 months of follow-up.

Results: Among the overall study population, 44% of patients would have needed dabigatran dosage adjustment during follow-up, 35% would have needed rivaroxaban adjustment, and 29% would have needed apixaban dosage adjustment. A higher proportion of patients with creatinine clearance < 60 mL/min or with advanced age (≥ 75 years) would have needed dosage adjustment during follow-up.

Conclusions: The need for dosage adjustment of nonvitamin K oral anticoagulants during follow-up is frequent in patients with atrial fibrillation after acute decompensated heart failure, especially among older patients and those with renal impairment. Further studies are needed to clarify the clinical importance of these needs for drug dosing adjustment and the ideal renal function monitoring regime in heart failure and other subgroups of patients with atrial fibrillation.

Repercusiones en la posología de los anticoagulantes orales no antagonistas de la vitamina K por las variaciones de la función renal de los pacientes con fibrilación auricular e insuficiencia cardiaca aguda reciente

Palabras clave:
Anticoagulantes
Función renal
Posología
Insuficiencia cardiaca
Fibrilación auricular

RESUMEN

Introducción y objetivos: El deterioro de la función renal y las fluctuaciones de esta son frecuentes en los pacientes recientemente hospitalizados por insuficiencia cardiaca aguda que presentan fibrilación auricular. El objetivo de este estudio es evaluar la necesidad hipotética de ajustes de dosis (según las fluctuaciones de la función renal) de dabigatrán, rivaroxabán y apixabán durante los 6 meses siguientes al alta hospitalaria a los pacientes con fibrilación auricular e insuficiencia cardiaca concomitantes.

Métodos: Se llevó a cabo un estudio observacional en 162 pacientes con fibrilación auricular no valvular después de una hospitalización por insuficiencia cardiaca aguda descompensada a los que se practicaron determinaciones de creatinina durante el seguimiento. Se determinaron las

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posologías hipotéticas recomendadas de dabigatrán, rivaroxabán y apixabán según la función renal al alta. Se identificaron las variaciones aparecidas en la creatinina sérica y el aclaramiento de creatinina y los consiguientes cambios en las dosis recomendadas de estos fármacos durante 6 meses de seguimiento.

Resultados: De la población total del estudio, el 44% de los pacientes habría necesitado un ajuste de la posología de dabigatrán durante el seguimiento; el 35%, la de rivaroxabán y el 29%, la de apixabán. Hubo mayor proporción de pacientes con aclaramiento de creatinina < 60 ml/min o de edad avanzada (≥ 75 años) que habrían necesitado ajuste de la dosis durante el seguimiento.

Conclusiones: La necesidad de un ajuste de la posología de los anticoagulantes orales no antagonistas de la vitamina K durante el seguimiento es frecuente en los pacientes con fibrilación auricular después de una insuficiencia cardiaca aguda descompensada, sobre todo los de mayor edad y con deterioro de la función renal. Se necesitan nuevos estudios para esclarecer la importancia clínica de estas necesidades de ajuste de la dosis de los fármacos y la pauta idónea de seguimiento de la función renal de los pacientes con insuficiencia cardiaca y otros subgrupos de pacientes con fibrilación auricular.

Abbreviations

ADHF: acute decompensated heart failure
AF: atrial fibrillation
CrCl: creatinine clearance
NOACs: nonvitamin K oral anticoagulants
TTR: time in therapeutic range

INTRODUCTION

Renal impairment and fluctuations in renal function are common in patients with recent acute decompensated heart failure (ADHF) hospitalization,[1,2] and in those with atrial fibrillation (AF).[3] However, there have been no studies of the effect of these fluctuations occurring at different time points after hospital discharge on the need for dosage adjustment of nonvitamin K oral anticoagulants (NOACs). The aim of the present study was to evaluate the hypothetical need for dosage adjustment (based exclusively on fluctuations in kidney function) of dabigatran, rivaroxaban and apixaban during the first 6 months after hospital discharge in patients with concomitant AF and ADHF.

METHODS

Study Population and Design

We identified a cohort of 253 consecutive patients discharged from the *Hospital Clínico Universitario Virgen de la Arrixaca* (Murcia, Spain) with a concomitant diagnosis of AF and ADHF. Patients with contraindications for NOACs and those without serum creatinine measurement within 6 months of hospital discharge were excluded (Figure 1 of the supplementary material). Given that kidney function may improve during follow-up, patients with a contraindication to NOACs due to renal dysfunction and without other contraindications were included in the analyses. The final study population consisted of 162 patients and their baseline clinical characteristics were all recorded in detail. During the study period, clinical management decisions about each patient were made by the responsible cardiologist. The study was approved by the local ethics committee.

The CHA_2DS_2-VASc (congestive heart failure/left ventricular systolic dysfunction, hypertension, age ≥ 75 [doubled], diabetes, stroke [doubled]-vascular disease, age 65-74 and female sex) and HAS-BLED (noncontrolled hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [age > 65 years], drugs/ alcohol concomitantly) scores were calculated as assessment of stroke and bleeding risk.

To evaluate the impact of variations of kidney function on NOACs dosing adjustment, we calculated the hypothetical recommended dosing of NOACs based exclusively on kidney function estimate according to the recommendations of the European Heart Rhythm Association Practical Guide.[4] The last serum creatinine measured during the index hospitalization was used to define baseline renal function status. All serum creatinine measurements during the first 6 months following hospital discharge were collected to assess the fluctuations in renal function. Creatinine clearance (CrCl) was estimated using the Cockroft-Gault equation ([140 – age] × weight [Kg])/(serum creatinine [mg/dL] × 72) (× 0.85 for women). We identified a hypothetical need for dosage adjustment when the recommended dose of NOACs based on 1 kidney function estimation (or serum creatinine in the case of apixaban) differed from the previous one. We used Rosendaal's method to estimate the time in therapeutic range (TTR) of patients taking vitamin K antagonists. This method assumes a linear increase or decrease between 2 consecutive international normalized ratio (INR) determinations in order to estimate the time (as a proportion of the time of follow-up) in which the INR would have be in range (between 2.0 and 3.0).

Statistical Methods

Continuous variables are presented as the mean ± standard deviation or median [interquartile range], as appropriate, and categorical variables as a percentage. Differences in baseline characteristics were compared using the Student *t* test or Man Whitney U test for continuous variables, and the chi-square test for categorical