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EFFICACY AND SAFETY OF EDOXABAN IN PATIENTS WITH ATRIAL FIBRILLATION AND SEVERE CHRONIC KIDNEY DISEASE

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Abstract

Atrial fibrillation (AF) is an arrhythmia with high prevalence in the elderly and it is frequently associated with increased risk of mortality and morbidity from stroke and systemic thromboembolism. Edoxaban, an activated, highly selective, daily factor-Xa direct inhibitor, was approved in 2015 by the Food and Drug Administration and the EMA for the prevention of stroke and systemic embolies in patients with AF, and also for the treatment and prevention of recurrences in venous thromboembolism. The characteristic of edoxaban and other DOAC (direct oral anticoagulants) is safety with a significant reduction in hemorrhagic risk, especially intracranial bleeding. We analyzed retrospective data from 30 patients from June 2016 to November2018 who had documented AF with severe renal impairment (eGFR 15-29 mL/min). The AF patients were followed for the effectiveness outcome of thromboembolism (ischemic stroke and/or systemic embolism) and bleeding outcomes (composite of major bleeding, gastrointestinal bleeding, and intracranial hemorrhage), as well as bleeding requiring hospitalization. A secondary safety endpoint was total minor bleedings. During follow-up, we observed no major bleedings, systemic embolism, strokes, or cardiovascular deaths; only three minor hemorrhages. Our observational study confirms the results already present in literature, the AF patients with severe Chronic Kidney Disease (CKD) treated with edoxaban30 mg/die for stroke prevention, no major bleedings or thrombotic events were observed, but only some minor bleedings.

Keywords : *atrial fibrillation, edoxaban, renal failure*

Introduction

Atrial fibrillation is an arrhythmia with high prevalence in the elderly and it is frequently associated with increased risk of mortality and morbidity from stroke and systemic thromboembolism. In elderly patients, this arrhythmia is often associated with specific clinical conditions such as CKD, coronary artery disease, cognitive impairment and polypharmacy. For all these reasons, anticoagulant use is underutilized in the elderly (1). Edoxaban, an activated, highly selective, daily factor-Xa direct inhibitor, was approved in 2015 by the Food and Drug Administration and the EMA for the prevention of stroke and systemic embolies in patients with AF,and also for the treatment and prevention of recurrences in venous thromboembolism. The characteristic of edoxaban and other DOAC (direct oral anticoagulants) is safety with a significant reduction in hemorrhagic risk, especially intracranial bleeding ; in fact, the latest ESC guidelines recommend the use of DOACs to replace warfarin in most AF patients with CHA_2DS_2-VASc score ≥2. For edoxaban , the recommended dose is 60 mg/die, to be reduced to 30 mg /die in patients with creatinine clearances between 15-50 ml/min or with body weight ≤ 60 kg or with concomitant use of P-gp inhibitors (2) . Several studies indicate that the combination of end-stage renal failure and AF confers a significantly greater risk of both thromboembolic and hemorrhagic events that increase as kidney function worsens. There are little evidence on the effects of non-vitamin K oral anticoagulants in patients with severe CKD (3) . The aim of our observational study is to assess the clinical efficacy and safety of edoxaban30 mg/die in patients with Atrial Fibrillation (AF) and severe renal impairment, an estimated glomerular filtration rate (eGFR) of 15–29 mL/min.

Materials and methods

We analyzed retrospective data from 30 patients from June 2016 to November2018 who had documented AF with severe renal impairment (eGFR 15-29 mL/min). Population mean age was 70 years and 20% were female(20 males and 10 females).The inclusion criteria were patients with at least one episode of documented AF of any duration in the preceding12 months; a CHA_2DS_2-VASc score of ≥ 2; any type of NVAF; age > 65 years; and severe renal impairment with an eGFR between 15 and 29 mL/min, calculated using the Cockroft–Gault formula. Patients were classified as having paroxysmal AF (episodes of AF for < 7 days), persistent AF (duration 1 week to 1 year), or permanent AF (duration ≥ 1 year or failed electric cardioversion), as defined by the AF guidelines. The exclusion criteria were eGFR < 15 or > 29 mL / min ; a high risk of bleeding; use of dual antiplatelet therapy; moderate to severe mitral stenosis; other indications for anticoagulation different from AF; acute coronary syndrome or coronary revascularization; or stroke within 30 days.

Standard two-dimensional transthoracic echocardiographic examination was performed. Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction (LVEF) were measured using the modified Simpson's rule from the apical view. Follow-up, characterized by clinical examination and blood analysis, was performed at 3, 6, and 12 months. The AF patients were followed for the effectiveness outcome of thromboembolism (ischemic stroke and/or systemic embolism) and bleeding outcomes (composite of major bleeding, gastrointestinal bleeding, and intracranial hemorrhage), as well as bleeding requiring hospitalization. A secondary safety endpoint was total minor bleedings.

Results and Conclusions

During follow-up, we observed no major bleedings, systemic embolism, strokes, or cardiovascular deaths. Only three minor hemorrhages (two epistaxis and one hematuria, none of which required blood transfusion or hospital admission) observed. From the these three patients with minor hemorrhages , no differences observed in LVEF or left atrial dimension at echocardiography, body mass index, and the thrombotic and hemorrhagic risk profile.

The efficacy of OAC therapy for stroke prevention in CKD patients is not based on randomized prospective trials but the risk-benefit ratio is based on sub-analysis of clinical trials. In literature are present a results of an explorative study that

analyzed patients with AF and severe CKD treated with edoxaban 30 mg once daily that appears to be safe in patients with severe CKD (4) . No major bleeding or thrombotic events were observed. Some minor bleedings were observed.
Our observational study confirms the results already present in literature, the AF patients with severe CKD treated with edoxaban30 mg/die for stroke prevention, no major bleedings or thrombotic events were observed, but only some minor bleedings. Stroke prevention in AF patients with severe CKD remains a challenge due to high risk of stroke and bleeding. Prior to considering OAC therapy in elderly patients with severe CKD, a comprehensive assessment including the risks and benefits should be determined. More studies investigating comparative effectiveness and safety for edoxaban 30 mg once daily in patients with AF and severe CKD in comparison with other choices of antithrombotic treatment options are needed.

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