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Oral anticoagulants in patients with chronic kidney disease and atrial fibrillation

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ABSTRACT

The aim of this study was to investigate the effects of new/direct oral anticoagulants (DOACs) on renal function parameters in chronic kidney disease patients with estimated glomerular filtration rate (eGFR) >30 mlmin-11.73m2.

A total of 40 chronic kidney disease patients with normal, mildly or moderately decreased renal function and non valvular atrial fibrillation were included (Group A) and were followed for 12 months. Dabigatran was started as 150 mg twice daily dose and rivaroxaban 20 mg once daily in patients with eGFR ≥ 50 mlmin-11.73m2. In patients with eGFR <50 and > 30 mlmin-11.73m2 dabigatran was started as 110 twice daily dose and rivaroxaban 15 mg once daily. Apixaban was started 2.5mg twice daily.

In group B there were 200 patients on warfarin for non valvular atrial fibrillation. Calculated HAS-BLED score was 2.8 (A) and 2.9 (B) and mean CHA2DS2VASc score was of 2.9 (A) and 3.1 (B). Changes in eGFR for up to12 months were evaluated. Treatment with warfarin caused a significant eGFR declined from 56±21 mlmin-11.73m2 to 51±19 (p<0.001), and 30% (62 of 200) of the patients had adverse events (31%). In patients on dabigatran and rivaroxaban, in both dosing regimens, and apixaban, eGFR (from 58±23 mlmin-11.73m2 to 58±19 mlmin-11.73m2 (p=0.01)) did not change, with significantly less adverse events (12% of patients). The results of our study suggest that therapy with new/direct oral anticoagulants (non-VKA oral anticoagulants) have a better bleeding risk profile and less decline in eGFR compared with vitamin K antagonists.

Key words: vitamin K antagonists, non-VKA oral anticoagulants, renal function

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in the population and affects about 2% of the European population. (1) Untreated patients are more prone to thrombosis. Stroke is a serious consequence of AF and oral anticoagulant therapy with vitamin K antagonist (VKAs) or four non-VKAs is indicated. Four non-VKAs have been found to be at least as effective and safer than VKAs for stroke prevention in patients with non-valvular AF. (2) When treated with vitamin K-antagonists (VKAs) like warfarin, patients are more prone to major bleeding and may have a worsening of renal function because vitamin K-dependent factors protect against vascular and renovascular calcification. (2) The anticoagulation therapy is intended to minimize ischemic stroke risk, yet puts the patient at risk for haemorrhagic stroke and other forms of major bleeding. With warfarin, the most important strategy used to reduce the risk of any bleeding is to maintain the therapeutic international normalized ratio (INR).

Non-VKA oral anticoagulants (DOACs) are easier to administer than VKAs because they can be given in fixed doses without routine coagulation monitoring. The DOACs include dabigatran, which inhibits thrombin, and apixaban, rivaroxaban and edoxaban, which inhibit factor Xa. (3)

We investigate effects and safety of new/direct oral anticoagulants (DOACs) on renal function parameters in CKD patients with estimated glomerular filtration rate (eGFR) >30 mlmin-11.73m2

MATERIALS AND METHODS

A total of 40 CKDp with normal, mildly or moderately decreased (estimated GFR > 30 mlmin-11.73m2) renal function with non valvular AF were included (Group A) and were followed for 12 months. In this group A, dabigatran was started as 150 mg twice daily dose (9 patients) and rivaroxaban 20 mg (9 patients) once daily in patients with eGFR ≥ 50 mlmin-11.73m2. In patients with eGFR <50 and > 30 mlmin-11.73m2, dabigatran was started as 110 twice daily dose (9 patients) and rivaroxaban 15 mg once daily (9 patients). Apixaban was started 2.5mg twice daily (4 patients). During the same period from 1 January 2015 through 1 January 2016 200 patients were on warfarin for non valvular AF (Group B). Biochemical Evaluation included a routine laboratory profile and in group B INR control. Estimated glomerular filtration (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. The HAS-BLED

bleeding score is used to determine the risk for bleeding in patients with AF: A score is calculated on the basis of: a) Hypertension (systolic blood pressure > 160 mm Hg), b) Abnormal renal or liver function, c) Stroke, d) Bleeding (major bleeding history, anaemia, or predisposition to bleeding), e) Labile INRs (unable to maintain a stable, therapeutic INR ≥ 60% of the time), f) Elderly (aged > 65 years), g) Drug use (i.e., antiplatelet agents or NSAIDs) (1 point each). A score ≥ 3 suggests increased risk of experiencing bleeding complications. (4) For all patients CHA2DS2VASc (congestive heart failure (C), hypertension (H), age>75 y (A), diabetes mellitus (D), stroke (S), vascular disease (VA), sex (S)) score was calculated too. Bleeding or worsening of renal function were categorized as adverse event (AE).

Changes in eGFR for up to12 months were evaluated. The study was approved by local ethic committee and provided written informed consent to participate. We used STATISTIKA 10, 2011 software, statistically significant if p<0.001.

RESULTS

In Group A (age 64-95 (71±15 years), body mass index (BMI) 36.4±5.1 kg/m2) the duration of hypertension was 10±5 years, the duration of AF was 3±2 years, eGFR 58±23 mlmin-11.73m2. In Group B the duration of hypertension was 13±5 years, the duration of AF was 5±4 years, eGFR 55±21 mlmin-11.73m2.

HAS-BLED score was 2,8 and 2.9 and mean CHA2DS2VASc score was of 2.9 and 3.1 for Group A and Group B. Treatment with warfarin caused a significant eGFR declined from 56±21 mlmin-11.73m2 to 51±19 (p<0.001), and 30% (66 of 220) of patients had AE (30%: gastrointestinal bleeding Forrest I and II in 15%, intracranial haemorrhage in 10 %, epistaxis and local haematoma in 5%). Patients transfered to the Intensive Care Unit had INR > 3.5 and had interaction between warfarin and antibiotics such as trimethoprim/sulfamethoxazole and/or with nonsteroidal anti-inflammatory drug (NSAID).

Patients with poor international normalized ratio control in group B (time in therapeutic range or TTR<65) had a faster decline in eGFR. However, the 12-month administration of DOACs caused a non-significant decrease in eGFR. In patients on dabigatran (18 patients) and rivaroxaban (18 patients) in both doses and apixaban (4 patients) eGFR (from 58±23 mlmin-11.73m2 to 58±19 mlmin-11.73m2 (p=0.01)) did not change, with significantly less AE (12% patients: 2 with mildly gastrointestinal bleeding and 1 with local hematoma).

DISCUSSION

Chronic kidney disease (CKD) has not been included in common stroke risk stratification schemes like the CHA2DS2VASc score, but is important predictor of thromboembolism and raises the risk of systemic thromboembolism in patients with AF. Until recently, vitamin K antagonists (VKAs) were the only available oral anticoagulants evaluated for long-term treatment of patients with CKD and AF. (5) We should be looking regularly at kidney function and at other modifiable risk factors that heighten stroke risk in these patients, because 80% of patients self-treat pain with NSAID and antibiotics which doubles the risk of bleeding. (6,7) Strategies to reduce bleeding include correcting modifiable characteristics (e.g. alcohol use and hypertension) and gastroprotection. (8) No one on DOAKs showed signs of hemodynamic instability and severe bleeding. Only in two cases, one on dabigatran (2x150mg) and one on apixabane the patient's endoscopy revealed a peptic ulcer (Forrest III), most likely aggravated by NSAID use. After the endoscopy, the patients were treated with proton pump inhibitor, and did not have any further signs of bleeding. The effects of DOACs may be prolonged in patients with underlying CKD. Therefore, important questions to ask a patient having GI bleeding on DOACs include the timing of their last DOAC ingestion and whether they have any underlying renal disorders. In patients having bleeding while taking dabigatran, a reversal agent, idarucizumab, is now available in the US and Europe and here in Croatia in Hospital Merkur. (9)

The current indications for this reversal agent include: the need for emergency surgery or life-threatening bleeding. The decision to use a reversal agent must be made on a case by case basis with the help of a multi-disciplinary treatment team. (9) Andexanet alfa, a reversal agent for rivaroxaban and apixaban (and edoxaban), is in late stage clinical trials. (10)

CONCLUSION

The results of our study suggest that therapy with DOACs have a better bleeding risk profile and less decline in eGFR compared with vitamin K antagonists.

Further randomized clinical trials could be beneficial in improving both renal and cardiovascular outcomes especially within non-valvular atrial fibrillation CKD patients on DOAKs with coexistent acute coronary syndrome or coronary stenting. Multidisciplinary meeting in necessary in this patients.

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