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Review article

Oral anticoagulant management for stroke prevention in patients with atrial fibrillation and severe renal dysfunction

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Abstract Direct oral anticoagulants replaced vitamin K antagonist for the stroke prevention in almost all patients with atrial fibrillation except in patients with grade V renal failure and patients on dialysis. All of the DOACs are metabolized partly by kidneys. Vitamin K antagonists are used for the stroke prevention in patients with severe renal failure and on-dialysis. The use of vitamin K antagonists in patients with preterminal renal failure can accelerate renal calcification and even decline renal function. In the published meta-analysis of 11 observational studies with patients with AF and terminal renal failure, warfarin did not decrease stroke and mortality, but increased a major bleeding. Increase use of apixaban for the stroke prevention in AF patients with end stage kidney disease, was associated to less stroke, mortality and major bleeding compare to warfarin. Doses of apixaban 2.5 mg BID, rivaroxaban 10 mg OD and edoxaban 15 mg OD, had a similar kinetic as classical doses in patients with normal renal function. A physician who deal with these patients must know pharmacokinetic characteristics of various anticoagulation drugs . The availability of antidote for anti Xa oral anticoagulant drugs can promote the use of DOAC. When we choose the anticoagulation drag for patient with pre-terminal renal failure we must repeatedly measure creatinine clearance. We must educate patients about circumstances which can promote acute renal. We also need to know that any combination of anticoagulant drags with antiplatelet drags are more dangerous in patients with renal failure, than in patients with normal kidney function.

Key words stroke, end stage kidney disease, direct oral anticoagulants, vitamin K antagonists

Stroke prevention in patients with atrial fibrillation and terminal renal failure are great challenge. Patients with atrial fibrillation are prone to development of chronic renal failure and vice versa patients with renal failure are prone to development atrial fibrillation.[1] In the last decade, direct oral anticoagulants practically replaced vitamin K antagonist for the stroke prevention in almost all patients with atrial fibrillation except in patients with grade V renal failure and patients on dialysis. Big randomized trials with direct anticoagulant drugs for the stroke prevention in atrial fibrillation exclude patients with severe renal failure and according to limited data reduced dose of rivaroxaban, apixaban and edoxaban are recommended for the patients with renal creatinine clearance above 15 ml/min. [2] Patients with severe renal failure and on dialysis are susceptible to both ischemic and hemorrhagic events which makes the prevention of stroke in patients with atrial fibrillation very complex. All of the direct oral anticoagulants are metabolized at least partly by kidneys. Apixaban is less dependent on renal function and dabigatran is very much dependent. On the other hand, rivaroxaban is used once daily with higher maximum plasma value and it is also not suitable for patients with severe renal failure.

For a long period of time, vitamin K antagonists are used for the stroke prevention in patients with severe renal failure and on-dialysis. However, the use of vitamin K antagonists in patients with preterminal renal failure can accelerate renal calcification and even decline renal function. Unpredictable level of anticoagulation, with a lot of factors which can influence on it, in this very sensitive population of patients makes use of vitamin K antagonists very difficult. In the recently published meta-analysis of 11 observational studies with more than 6000 patients with AF and terminal renal failure, warfarin did not decrease stroke and mortality, but increased a major bleeding.[3] However, proper randomized trials on the use of oral anticoagulants in AF patients with end stage renal failure are lacking and the results of the observational trials should be interpreted with caution.

The first experience of dabigatran and rivaroxaban use for the stroke prevention in patients with AF and end stage renal failure indicated higher hospitalization and death rate for bleeding in patients treated with DOACs relative to warfarin.[4] It was becoming clear that the choice for the right anticoagulation management in end stage kidney disease very difficult and the new drug and approach is needed.

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In the last few years increase use of apixaban for the stroke prevention in AF patients with end stage kidney disease has been recorded at least in United States. In the large Medicare cohort study use of apixaban extent the 26% of all AF patients with end stage renal disease. Both doses of apixaban were used and higher dose were associated to less stroke, mortality and major bleeding compare to warfarin.[2] However, this was retrospective study and the strong bias might influence the results.
According to pharmacokinetic studies, doses of apixaban 2.5 mg BID, rivaroxaban 10 mg OD and edoxaban 15 mg OD, had a similar kinetic as classical doses of these drugs in patients with normal renal failure.[5,6,7] Dialysis decrease the level of apixaban around 5%.[7] Nevertheless, similar pharmacokinetic profile does not necessary mean the same efficacy and safety summery in patients with end stage renal failure and dedicated studies are needed.

Practical approach of anticoagulation management in patients with severe renal failure

A physician who deal with these patients must to continuously and carefully assessed the ischemic and bleeding risk in their patients. Monitoring of these patients are of an extreme importance. One must now pharmacokinetic characteristics of various anticoagulation drugs and how and when to monitor its anticoagulation level. Dabigatran should be avoided in patients with renal clearance under 30 ml/min in any dose. It is not known whether rivaroxaban dose of 10 mg once daily can be used in patients with end stage renal failure and this dose should be tried in the careful clinical setting. If vitamin K antagonists were chosen for stroke prevention in end stage renal failure patients, meticulous INR monitoring should be done with more often measurement of INR in any new circumstances. The first observational and pharmacokinetic data with apixaban use in these patients are promising. The choice to use 2.5 BID or 5 mg BID in patients on dialysis may depend whether ischemic or bleeding risk is prevalent. The availability of antidote for anti Xa oral anticoagulant drugs can further promote the use of these drags in end stage kidney disease in the future.
When we must choose the anticoagulation drag for patient with pre-terminal renal failure we must repeatedly measure creatinine clearance and always count at least ±10 ml/min. We must educate patients about circumstances which can promote acute renal failure, such as febrile state, diarrhea, vomiting, use of non-steroid anti-inflammatory drags etc. Any combination of anticoagulant drags with antiplatelet drags are much more dangerous in patients with renal failure than in patients with normal kidney function and this must be kept in mind.
The basic facts which can be useful for the anticoagulation management in patients with severe renal dysfunction are presented in table 1. [3]

Table 1. The basic facts for the management of anticoagulation in patients with severe renal failure.[3]

Renal clearance of different anticoagulant drugs
CrCl calculation (Corcoft-Gault formula)
Frequently monitoring of renal function (CrCl/10=months)
Appropriate dose of anticoagulants
Dynamic nature of renal function (±10-20 ml/min)
Interactions with other drugs (EHRA guidelines)
Education of patients and doctors

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Sažetak

Oralna antikoagulantna terapija za prevenciju moždanog udara kod pacijenata sa atrijalnom fibrilacijom i teškom bubrežnom disfunkcijom

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Direktni oralni antikoagulansi zamenili su antagoniste vitmina K u terapiji prevencije moždanog udara kod skoro svih pacijenta sa atrijalnom fibrilacijom, sem kod pacijenata sa 5. stadijumom bubrežne slabosti i kod pacijenata na dijalizi. Svi direktni oralni antikoagulnsi se delom izlučuju preko burega. Antagonisti vitamina K su se koristili za prevenciju moždanog udara kod pacijenata sa teškom bubrežnom slabošću i kod pacijenta na dijalizi. Upotreba antagonista vitamina K kod pacijenta sa preterminalnom bubrežnom slabošću može da izazove pojavu kalcifikacija i da pogorša bubrežnu slabost. U objavljenim meta-analizama 11 opservacionih studija sa pacijentima koji imaju AF i terminalnu bubrežnu slabost, varfarin nije smanjio stopu moždanog udara i smrtnosti, ali je povećao stopu velikih krvarenja. Povećana upotreba apiksabana za prevenciju moždanog udara kod pacijenata koji imaju atrijalnu fibrilaciju i terminalnu bubrežnu slabost, je povezana sa manje moždanih udara, manjom smrtnošću i manje velikih krvarenja u odnosu na varfarin. Doze apiksabana 2.5 mg, rivaroksabana 10 mg i endoksabana 15 mg, imaju sličnu kinetiku kao klasične doze kod pacijenata sa normalnom bubrežnom funkcijom. Lekari treba dobro da poznaju farmakokinetiku svih antikoagulantnih lekova. Takođe, dostupnost antidota za anti Xa direktne oralne antikoagulantne lekove promoviše njihovu upotrebu. Kada uvodimo oralnu antikoagulantnu terapiju kod pacijenata sa preterminalnom bubrežnom slabošću moramo više puta da određujemo vrednosti klirensa kreatinina. Moramo i da upoznamo naše pacijente sa stanjima, koja mogu da dovedu do akutne burežne slabosti. Takođe, treba da znamo, da je svaka kombinacija antikogulantnih lekova sa antitrombocitnim lekovima opasnija za pacijente sa bubrežnom slabošću, nego za one koji imaju normalnu funkciju bubrega.

Ključne reči: *Moždani udar, atrijana fibrilacija,terminalna bubrežna slabost, direktni oralni antikoagulantni lekovi, antagonisti vitamina K*