

Atrial Fibrillation and Renal Disease

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Abstract

Co-occurrence of atrial fibrillation and renal dysfunction in general population is described in many epidemiological studies. Major issue is optimal anticoagulation in patients with atrial fibrillation and renal disease warranting balance between risks of ischemic stroke and hemorrhages. The second issue is catheter ablation of AF patients with renal dysfunction. Both issues are discussed in this paper.

Introduction

The association of impaired renal function with atrial fibrillation (AF) is well established. It is also known that stroke is major life threatening complication of AF and renal disease. Aim of this brief review is discussion of two major topic areas. Firstly, we review safety and efficacy of anticoagulation therapy for patients suffering from both AF and renal insufficiency. Secondly, last studies on impact of impaired renal function on long-term outcome after catheter ablation of atrial fibrillation are discussed.

Oral Anticoagulation with Warfarin in Patients with AF and Impaired Renal Function

Oral anticoagulation with warfarin is an effective therapy to reduce the risk for stroke related to atrial fibrillation in a majority of patients. However, impact of renal insufficiency on the therapy with warfarin in these patients was not considered for a long time. First single-center study including 29 pts with end-stage renal disease reported in 2003 association between bleeding and use of warfarin. In this study an annual hemorrhages rate of 11% in patients who were not on anticoagulation, 16% in those treated with antiplatelet therapy, and 26% in those on oral anticoagulation were observed. Of note, in 10 out of 13 patients on warfarin had a major bleeding. The international normalized ratio (INR) was higher than intended (no values specified in the article), but none of the bleeding complications with oral anticoagulation was fatal.¹ However, another retrospective analysis performed in 123 patients from the US Renal Data System provided opposite results. Patients who started their hemodialysis in 1996 and were subsequently hospitalized for atrial fibrillation

found a significantly lower cumulative 3-year all-cause mortality in patients on warfarin (33%) as compared to 56% in those without oral anticoagulation.²

The algorithm for individual risk assessment of oral anticoagulation in patients with glomerular filtration rate (GFR) < 60 mL/min and atrial fibrillation was proposed 2009. It was based on CHADS₂ score and risk factors for bleeding such as previous hemorrhages, liver diseases, etc. However, the authors acknowledged that the consideration of bleeding risk cannot simply be calculated by a scoring system but rather needs the input of the treating physician, who is competent in evaluating the complex medical conditions typical of renal insufficiency.³

An interesting study conducting literature search of Medline through Ovid (1966 to January 2009) and of EMBASE through Ovid (1980 to January 2009) was published 2009.⁵ The Medical Subject Heading terms “atrial fibrillation,” “warfarin,” and “bleeding” were combined with “end-stage renal disease,” “dialysis,” and “kidney failure.” This study proposed controversial approach for decision about use of warfarin in patients with AF and end stage renal disease. The authors suggested that patients < 65 years of age, with normal echocardiograms, and without or with well controlled hypertension, and without diabetes will likely derive little benefit from OAC. In contrast, patients with uncontrolled hypertension, concurrent use of antiphospholipid antibodies, previous severe hemorrhage, a history of treatment noncompliance, frequent falls, calciphylaxis, or severe malnutrition should be considered relatively contraindicated for the use of OAC due to the high risk of subsequent hemorrhage.⁴

A comprehensive literature search, published in 2011, confirmed lack of relevant information: although, rates of major bleeding episodes in anticoagulated hemodialysis patients with AF are high, no large randomized trials assessing the real risk/benefit of full-intensity anticoagulation in such patients were performed.⁵

Published in August 2012 Danish cohort study performed on register data of 132,372 patients with non-valvular AF provided

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confused results. Among these patients a total of 3587 patients (2.7%) had non-end-stage chronic kidney disease, and 901 (0.7%) required renal-replacement therapy. Warfarin treatment was associated with a significantly decreased risk of stroke or systemic thromboembolism overall and among patients requiring renal-replacement therapy. However warfarin was not revealed to decrease risk among patients with non-end-stage renal disease. Regarding risk of bleeding in this cohort, the authors found that risk of bleeding was higher among patients with non-end-stage renal disease and among those requiring renal-replacement therapies than among patients without renal disease. Moreover, treatment with warfarin, aspirin, or both incrementally increased this risk.⁶

Thus, up till now the balance between risk of stroke and bleeding during warfarin therapy should be estimated in every patient, with AF and renal disease, by discretion of experienced physician.

New Oral Anticoagulants in Patients with AF and Impaired Renal Function

The new oral anticoagulants for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban, apixaban).⁷

According to last update of European guidelines for the management of atrial fibrillation administration of dabigatran may be considered in reduced dose of 110 mg (150 mg in case of mild or no renal disease) in patients with moderate renal impairment with GFR 30-49 mL/min.⁸ The same issue recommends also dose reduction by administration of rivaroxaban to 15 mg (20 mg in case of preserved renal function) in patients with moderate renal impairment. However, European Heart Rhythm Association does not recommend use of all new anticoagulants in patients with severe or end stage renal disease (GFR < 30 mL/min).⁹

Compared to dabigatran and rivaroxaban, apixaban seems to have lower risk due to a reduced degree of renal excretion.⁷ Recently published analysis of the ARISTOTLE study including 18122 patients has shown that the new oral anticoagulant, apixaban, was better than warfarin in preventing the primary outcome, stroke or systemic embolism, in atrial-fibrillation patients, regardless of renal function. Thereby the authors found that patients with renal disease seemed to have the greatest reduction in major bleeding with apixaban. The incidence of major bleeding in patients with GFR of <50 mL/min in patients on apixaban was significantly lower than those on warfarin (hazard ratio 0.50; 95% CI 0.38-0.66) $p=0.005$.¹⁰ However, this study did not include hemodialysis patients.

In summary, no clinical trials on new oral anticoagulants including patients on dialysis or close to dialysis were performed until now. Therefore careful balancing of the clinical benefits and risks of each drug (and its dose adjustment) is required by each individual patient suffering AF and severe renal disease. Careful follow-up of renal function is also required in all patients with AF and impaired renal function.⁹

According to results ARISTOTLE study apixaban appears to be an option for patients with AF and moderate renal impairment (GFR > 30 mL/min). However, no comparative studies on risks from renal disease among patients on new oral anticoagulants were performed, so due to lack of evidence no preferable anticoagulant drug for patients with AF and renal disease can be recommended now.

Impact of Renal Impairment on Outcome After Catheter Ablation of Atrial Fibrillation

The role of renal impairment as predictor for AF recurrence after catheter ablation was investigated in relatively small number of single center studies.¹¹⁻¹³ All these studies provided similar results regarding poor outcome in patients with GFR < 60 mL/min. These results were also confirmed in our observation study included 702 patients with paroxysmal and not paroxysmal AF. In contrast to other study, majority of our patients had no or subclinical renal dysfunction (median GFR in our study was 88 mL/min with inter-quartile range (75-102) mL/min). We performed ROC analysis of GFR and found 68 mL/min to be optimal cut off point in our cohort. Hazard ratio adjusted by type of AF, left atrial size and presence of metabolic syndrome was 1.43 95% CI (1.05-1.95). We also performed separate analysis of outcome after repeated ablation procedure and again, GFR measured prior to index procedure was predictive for outcome after repeated procedure (adjusted hazard ratio = 1.35 95% (1.05-1.84)).¹⁴

Recently published retrospective study performed on 15423 patients with mean age of 72 years revealed impact of renal impairment on a year mortality after catheter ablation of AF (hazard ratio = 2.07 95% CI (1.66-2.58)).¹⁵ To our best knowledge, this is only one study investigating impact of renal impairment on mortality after catheter ablation in elderly.

New prospective study investigated impact of outcome after catheter ablation on renal function. The authors found very interesting results, in patients with mild to moderate renal dysfunction (GFR > 30 mL/min) arrhythmia freedom was associated with improvement of renal function over a 1-year follow-up. In subgroup analysis they found that in the subgroup belonging to the highest quartile of baseline GFR, GFR did not increase after successful ablation, whereas arrhythmia recurrence was associated with a significant decrease in GFR over 1 year. In subgroup of lowest quartile of baseline GFR, freedom of arrhythmia was associated with increase of GFR.¹⁶ These findings are in concordance with large prospective community-based observational cohort study including 235818 patients. Bidirectional association between AF and renal dysfunction (renal dysfunction increased the risk of new onset of AF, and AF increased the risk of development of renal disease) was reported. The authors concluded that: a) AF and chronic renal disease share risk factors and putative mechanisms, suggesting that common pathophysiological processes may drive both outcomes; b) possible common link between AF and chronic kidney disease is renin-angiotensin-aldosterone system activation.¹⁷

However, the major clinically relevant issue remains unresolved. Although impaired renal function predicts poor outcome after catheter ablation,¹¹⁻¹⁴ not all patients with impaired renal function have recurrence after catheter ablation of AF. Currently, it is important to establish algorithm allowing prediction of outcome after catheter ablation in patients with mild and moderate renal dysfunction. This issue should be investigated in new ongoing studies.

Conclusions:

The anticoagulation in AF patients having renal dysfunction remains difficult clinical issue, however new oral anticoagulants like apixaban seem to be a promising drug therapy for this cohort of patients. The use of new oral anticoagulants after pulmonary vein isolation in patients with renal dysfunction is not evidenced and should be intensively investigated. Renal dysfunction is independent

predictor for poor outcome after catheter ablation. New studies for stratification of patients with renal dysfunction regarding outcome after catheter ablation of AF are needed.

References:

1. Vazquez E, Sanchez-Perales C, Garcia-Cortes MJ, Borrego F, Lozano C, Guzman M, Gil JM, Liebana A, Perez P, Borrego MJ, Perez V: Ought dialysis patients with atrial fibrillation be treated with oral anticoagulants? *Int J Cardiol* 87: 135– 139, 2003
2. Abbott KC, Trespalacios FC, Taylor AJ, Agodoa LY. Atrial fibrillation in chronic dialysis patients in the United States: Risk factors for hospitalization and mortality. *BMC Nephrol* 2003; 4:1– 10,
3. Reinecke H, Brand E, Mesters R, Schäbitz WR, Fisher M, Pavenstädt H, Breithardt G. Dilemmas in the management of atrial fibrillation in chronic kidney disease. *J Am Soc Nephrol*. 2009; 20:705-711
4. Sood M, Komenda P, Sood AR., Rigatto C, MD, Buetti J. The Intersection of Risk and Benefit: Is Warfarin Anticoagulation Suitable for Atrial Fibrillation in Patients on Hemodialysis? *Chest*. 2009; 136:1128-1133
5. Marinigh R, Lane DA, Lip GH. Severe Renal Impairment and Stroke Prevention in Atrial Fibrillation. *J Am Coll Cardiol*. 2011; 57:1339-1348
6. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012; 367:625–635
7. Poulsen BK, Grove EL, Husted SE. New oral anticoagulants: a review of the literature with particular emphasis on patients with impaired renal function. *Drugs*. 2012; 72:1739-1753.
8. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012; 33: 2719–2747
9. Heidbuchel H, Verhamme P, Alings M, Antz , Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013; 15: 625–651.
10. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012; 33:2821–30.
11. Naruse Y, Tada H, Sekiguchi Y, Machino T, Ozawa M, Yamasaki H, Igarashi M, Kuroki K, Itoh Y, Murakoshi N, Yamaguchi I, Aonuma K. Concomitant chronic kidney disease increases the recurrence of atrial fibrillation after catheter ablation of atrial fibrillation: A mid-term follow-up. *Heart Rhythm* 2011; 8:335–341.
12. Tokuda M, Yamane T, Matsuo S, Ito K, Narui R, Hioki M, Tanigawa S, Nakane T, Yamashita S, Inada K, Shibayama K, Miyayama S, Yoshida H, Miyazaki H, Date T, Yokoo T, Yoshimura M. Relationship between renal function and the risk of recurrent atrial fibrillation following catheter ablation. *Heart*
13. Chao TF, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Suenari K, Li CH, Chen SA. Associations between renal function, atrial substrate properties and outcome of catheter ablation in the pts with paroxysmal atrial fibrillation. *Circ J* 2011; 75:2326–2332
14. Berkowitsch A, Kuniss M, Greiss H, Wójcik M, Zaltsberg S, Lehinant S, Erkapic D, Pajitnev D, Pitschner HF, Hamm CW, Neumann T. Impact of impaired renal function and metabolic syndrome on the recurrence of atrial fibrillation after catheter ablation: a long term follow-up. *Pacing Clin Electrophysiol*. 2012;35:532-543
15. Piccini JP, Sinner MF, Greiner MA, Hammill BG, Fontes JD, Daubert JP, Ellinor PT, Hernandez AF, Walkey AJ, Heckbert SR, Benjamin EJ, Curtis LH. Outcomes of Medicare Beneficiaries Undergoing Catheter Ablation for Atrial Fibrillation. *Circulation* 2012; 126:2200–2207
16. Takahashi Y, Takahashi A, Kuwahara T, Okubo K, Fujino T, Takagi K, Nakashima E, Kamiishi T, Hikita H, Hirao K, Isobe M. Renal function after catheter ablation of atrial fibrillation. *Circulation*. 2011 Nov 29;124:2380–2387.
17. Watanabe H, Watanabe T, Sasaki S, Nagai K, Roden DM, Aizawa J, Close bidirectional relationship between chronic kidney disease and atrial fibrillation: The Niigata preventive medicine study. *American Heart Journal* 2009;158: 629–636