

## Possible Benefits of Direct Oral Anticoagulants for the Electrophysiological Substrate Properties of Atrial Fibrillation: Can these New Agents have Antiatrial Fibrillation Actions?

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### Abstract

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia, and is associated with thromboembolic events. Previous studies also have shown a close relationship between AF and heart failure, and heart failure can be one of the most important risk factors for AF. Therefore, heart failure animal models have been established to investigate the structural and electrical remodeling for AF substrates and suggested that the structural and/or electrical remodeling caused by heart failure may play an important role in AF genesis. Several recent studies have demonstrated that Direct Oral Anticoagulants (DOACs) can directly modulate the mechanical and electrophysiological properties of the Left Atrium (LA) and Pulmonary Veins (PVs) and suggest that DOACs may have a beneficial effect of anti-AF actions via preventing AF progression in addition to their anti-thrombotic action. Therefore, DOACs may affect the natural course of AF progression causing a transition from a paroxysmal to persistent form. Although, many clinical studies need to be conducted to evaluate the additional effects of DOACs, it would have a great impact on clinical practice. In this manuscript, I will focus on recent studies regarding: The effects of thrombin, factor Xa, and its inhibitors on tissue inflammation and fibrosis. The beneficial effects of thrombin inhibitors on the AF substrate in a heart failure animal model. The role of the PV myocardium on AF arrhythmogenesis in a heart failure animal model. The beneficial effects of DOACs on the electrophysiological properties of the atrium and PVs.

Finally, I will discuss about the significant impact of AF progression and the possible benefits of DOACs on the clinical outcomes of catheter ablation of AF and the future direction of clinical research to evaluate the beneficial effects of DOACs on AF substrates.

**Keywords:** Atrial electrical remodeling; Atrial fibrillation; Atrial fibrosis; Factor Xa inhibitors; Thrombin inhibitor

### Introduction

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia in adults, frequently encountered in clinical practice, and is associated with cranial and extra-cranial thromboembolic events with an increased mortality [1]. A hypercoagulable state during AF caused by increased circulating levels of the fibrinolytic degradation products, Plasminogen Activator Inhibitor-1 (PAI-1) and thrombin-antithrombin complex have been reported in the previous reports [2,3]. Due to both the hypercoagulability and blood stasis during poorly contractile fibrillating atria, AF patients frequently demonstrated a spontaneous echo contrast and/or thrombus formation inside the cardiac chamber. Oral anticoagulant therapy including conventional Vitamin K Antagonist (VKA), warfarin, and several newly developed non-VKAs, Direct Oral Anticoagulants (DOACs), such as the selective direct thrombin (factor IIa) inhibitor, dabigatran or direct factor Xa inhibitors, apixaban, rivaroxaban, and edoxaban can reduce the incidence of AF related-thromboembolic events.

Reports from recent randomized controlled trials investigating non-valvular AF populations demonstrated the superior or non-inferior efficacy and overall safety of the DOACs over warfarin [4-9]. On the other hand, previous studies have shown a close relationship between AF and heart failure, and heart failure can be one of the most important risk factors for AF [10]. AF can also worsen the cardiac contractile function and induce heart failure [1,11]. Therefore, heart failure animal models have been established to investigate the structural and electrical remodeling for AF substrates. Allesie et al. suggested that the structural and/or electrical remodeling caused by heart failure may play an important role in AF genesis [12].

### Effects of Thrombin, Factor Xa, and Its Inhibitors on Tissue Inflammation and Fibrosis

Previous studies demonstrated that both thrombin and factor Xa promote tissue inflammation via the Protease Activated Receptor (PAR)-1 [13,14]. In a human study, Bukowska et al. reported that factor Xa enhanced proinflammatory signaling in human atrial tissue, upregulating PAR-2, phosphorylated extracellular signal-related kinase, Intracellular Adhesion Molecule (ICAM)-1, interleukin-8, and

PAI-1. These actions were enhanced by rapid atrial pacing simulating the remodeling process of AF and were suppressed by inhibitors of PAR-1 or PAR-2. Furthermore, both thrombin and factor Xa also promote tissue fibrosis [14]. Howell et al. and Chambers and Laurent reported that inhibitor of thrombin possess antifibrotic actions [15,16]. Furthermore, the correlation between atrial fibrosis and AF maintenance has been reported. Basic and clinical studies suggest the importance of atrial fibrosis as a major contributor to AF maintenance [12,17-19]. According to these data, thrombin and factor Xa are suggested to play significant roles in the progression of the AF substrate. Therefore, both thrombin and factor Xa inhibitors could have an anti-AF action.

### **Beneficial effects of thrombin inhibitors on the Atrial Fibrillation (AF) substrate in a heart failure animal model**

Jumeau et al. reported the beneficial effects of chronic treatment with direct thrombin inhibitors (over 4 weeks with 25 mg/kg/day of dabigatran etexilate or 6 mg/kg/day of S35972) on the AF progression of AF in a rat heart failure model after coronary ligation induced ischemia-reperfusion injury [20]. This heart failure model established by the authors revealed enhanced thrombogenesis, electrical remodeling with prolonged AF episodes, and structural remodeling with atrial fibrosis and hypertrophy. Direct thrombin inhibitors decreased the upregulation of the Connective Tissue Growth Factor (CTGF), Brain Natriuretic Peptide (BNP),  $\beta$ -myosin Heavy Chain (MHC), and PAI-1. In a rat atrial preparation, thrombin exposure for 7 days directly enhanced the expression of BNP,  $\beta$ -MHC, and PAI-1, a signal transducer and activator of transcription 3 (Stat3). An inhibitor of PAR-1 and Rho-associated Protein Kinase (ROCK) signaling diminishes these actions. According to the author's findings, activated thrombin significantly contributes to promote electrical and structural remodeling in the heart failure model via thrombin/PAR-1 signaling and direct thrombin inhibitors can suppress the AF progression independent of their anticoagulant action. Therefore, the authors suggested that direct thrombin inhibitors can be a novel potential therapeutic application for electrical and structural remodeling in the course of AF progression.

### **Role of the Pulmonary Vein (PV) myocardium on Atrial Fibrillation (AF) arrhythmogenesis in a heart failure animal model**

Chang et al. demonstrated the involvement of the Pulmonary Vein (PV) myocardium in atrial arrhythmogenesis in the setting of a high rate pacing induced rabbit heart failure model [21,22]. The authors demonstrated that the PV myocardium from a rabbit heart failure model had enhanced spontaneous activity, a higher incidence of the early and delayed after depolarizations, and a decrease in conduction velocity as compared to that from the LA. Dysregulated sodium and calcium homeostasis, and enhanced calcium sparks promote arrhythmogenesis of PV cardiomyocytes in this heart failure model, which may play an important role in the development of AF. Therefore, the authors suggested that the PV myocardium can be more arrhythmogenic compared than the LA, and can play an important role in the AF genesis in the heart failure model.

### **Beneficial effects of doacs on the electrophysiological properties of the atrium and Pulmonary Veins (PVs)**

Recently, several investigators have reported the direct actions of DOACs on the electrophysiological characteristics of the atrium and PVs. Spronk et al. investigated the effects of hypercoagulability and its suppression of AF remodeling using several animal models [23]. In isolated rat atria preparations, the authors found that thrombin enhances the expression of the pro-fibrotic factor, transforming growth factor  $\beta$ 1, and pro-inflammatory substance monocyte chemoattractant protein-1, and also increases the incorporation of 3H-proline, suggesting an increased collagen synthesis by fibroblasts. All these actions were inhibited by dabigatran and a PAR-1 blocker. Using a thrombomodulin gene mutation mouse with hypercoagulability, the authors found that the AF duration was prolonged and the collagen deposition in the atrium was increased. In a goat model with persistent AF established by high rate pacing, the factor Xa inhibitor, nadroparin reduced the thrombin production and complexity of the atrial activation quantified as the maximal activation times the difference per AF beat, and the unipolar electrogram fractionation index. Therefore, the authors suggested that PAR inhibition independent from the antithrombotic action is a promising target for the development of novel upstream therapies for AF. Chang et al. demonstrated that thrombin enhanced the triggered activity (delayed after depolarizations or burst firing) of rabbit PV preparations [24]. Furthermore, thrombin increased the diastolic tension and decreased the Action Potential Duration (APD) and contractility of the Left Atrium (LA). These actions of thrombin were inhibited by dabigatran, a PAR-1 blocker (BMS 200261), and a nitric oxide synthase inhibitor (L-NAME). PVs treated with dabigatran showed slower spontaneous activity with a reduced ion channel protein expression, calmodulin kinase II, sodium calcium exchanger, and Cav 1.2 than that of the control PVs. Furthermore, thrombin did not affect the electrophysiological and mechanical properties in dabigatran-treated PVs or the LA. Therefore, the authors suggested that thrombin can enhance the arrhythmogenesis of the PVs and LA, and dabigatran can have anti-AF actions. Chang et al also reported that rivaroxaban increased the diastolic tension of an LA preparation and decreased the APD of the LA cardiomyocyte from rabbits, but increased the L-type calcium current and ultra-rapid delayed rectifier potassium current [25]. Therefore, the authors suggested that rivaroxaban at clinically relevant concentrations (100 nM) directly affects ionic currents in LA myocytes.

### **Significant impact of Atrial Fibrillation (AF) progression and the possible benefits of DOACs on the clinical outcomes of catheter ablation of AF**

Over the past 20 years, basic and clinical studies have reported the importance of arrhythmogenic thoracic veins including the PVs and non-PV areas for the initiation and maintenance of AF. The efficacy and safety of curative catheter ablation techniques including the isolation of arrhythmogenic thoracic veins and elimination of ectopies initiating AF for paroxysmal AF has been reported [26-31]. Previous studies have demonstrated a strong correlation between low voltage areas detected by electro anatomical mapping systems and the distribution of atrial fibrosis evaluated by delayed-enhanced MR image [17,18]. Furthermore, the poor outcomes of PV isolation for non-paroxysmal and long-lasting persistent AF patients with extensive low voltage areas in atria have been reported. Therefore, extensive atrial fibrosis may correlate with the AF progression and may have a

significant impact on the poor efficacy of catheter ablation. Furthermore, Rolf et al. reported the necessity of an extensive ablation strategy targeting the low voltage areas distributed in the extra-PV area in addition to the PV isolation with better clinical outcomes compared with that of PV isolation only [19]. Therefore, the anti-fibrotic actions on the atrium by DOACs can be a potential therapeutic approach to suppress AF progression causing electrical and structural remodeling and for improving the efficacy of catheter ablation.

### Future direction of clinical research to evaluate the beneficial effects of DOACS on Atrial Fibrillation (AF) substrates

Currently, there is no clinical study to confirm the hypothesis that DOACs, but not VKA can suppress the AF progression including electrical, mechanical, and structural remodeling. According to recent studies, echocardiography, 3D voltage analyses, and delayed-enhanced MRI can quantify the mechanical, electrical, and structural remodeling developing the AF substrate. Therefore, a prospective or retrospective study can be conducted to compare the AF progression in matched AF patients treated with VKA and DOAC therapy using these imaging modalities. Furthermore, a longitudinal analysis can be performed to observe any beneficial actions on electrical, mechanical, and structural remodeling after the administration of DOAC therapy in the same patients. It would be very interesting to observe the difference in the anti-AF action between the patients treated with direct thrombin and Xa inhibitors. Considering the ethical issues, a major concern would appear for a randomized and prospective study comparing a placebo, VKA, and DOAC therapy to evaluate the efficacy of DOACs to modulate the AF progression.

### Conclusion

Several recent studies [14,20,23-25] have demonstrated that DOACs can directly modulate the mechanical and electrophysiological properties of the LA and PVs and suggest that DOACs may have a beneficial effect of anti-AF actions via preventing AF progression in addition to their anti-thrombotic action. Therefore, DOACs may affect the natural course of AF progression causing a transition from a paroxysmal to persistent form. Although, many clinical studies need to be conducted to evaluate the additional effects of DOACs, it would have a great impact on clinical practice.

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