Effects of Angiotensin Converting Enzyme Inhibitors and Statins on Endothelial Function, Inflammation, and Coagulation in Patients with Hypertension and Atrial Fibrillation

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ABSTRACT

Introduction: The renin-angiotensin-aldosterone system has been reported to affect the endothelial function, prothrombotic and hypercoagulable state, and maintenance of atrial fibrillation (AF). Whether angiotensin converting enzyme inhibitors (ACEIs) and statins improve the prothrombotic condition of patients with hypertension and AF is unclear.

Materials & Methods: Patients with hypertension and AF were divided into four groups: Group I (N=15; M:F, 10:5; age, 49±6 years) received no ACEI or statin, group II (N=17; M:F, 11:6; age, 48±6 years) received cilazapril 5 mg without statin, group III (N=18; M:F, 9:9; age, 49±7 years) received cilazapril 5 mg and atorvastatin 10 mg, and group IV (N=16; M:F, 10:6; age, 45±3 years) received cilazapril 5 mg and atorvastatin 40 mg. Serum markers of endothelial function (von Willebrand factor [vWF]), inflammation (quantitative and high-sensitivity C-reactive protein, erythrocyte sedimentation rate), and coagulation (fibrinogen, fibrinogen degradation product, d-dimer) were measured at baseline and 6 months.

Results: There were no thromboembolism cases in any group during the 6-month follow up. There were no significant differences in the levels of each marker at baseline. There were no significant changes in vWF at 6 months in group I and II; however, it was significantly reduced at 6 months (172±43%, vs. 110±41%, p=0.001) in group III. vWF and fibrinogen levels were significantly reduced at 6 months in group IV (184±52% vs. 150±68%, p=0.021 and 331±73 mg/dL vs. 275±57 mg/dL, p=0.047, respectively). Other markers were not changed significantly in any group.

Conclusion: High doses of statin and ACEI may have a beneficial effect on endothelial function and coagulation, which may contribute to the reduction of thromboembolism risk in patients with hypertension and AF.

Key Words: atrial fibrillation, thromboembolism, angiotensin converting enzyme inhibitor, statin
Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia associated with a substantial risk of stroke and thromboembolism. Although the mechanism of stroke and thromboembolism in AF patients is incompletely understood, the increased risk is mainly due to the embolization of thrombus formed within the left atrial appendage. There is increasing evidence that the increased risk of stroke and thromboembolism in AF patients is facilitated by increased thrombogenesis, with changes in the left atrial wall, a prothrombotic or hypercoagulable state (including abnormalities of hemostasis, thrombosis, and platelet and endothelial function), and AF-related inflammation, leading to the fulfillment of Virchow's triad.

The renin-angiotensin-aldosterone system and inflammation have been reported to affect the endothelial function, prothrombotic and hypercoagulable state, and maintenance of AF. It is not certain whether angiotensin converting enzyme inhibitors (ACEIs) and statins improve the prothrombotic condition in hypertension patients and reduce thromboembolism in patients with persistent and permanent AF.

Material and Methods

All patients enrolled had hypertension, more than one known risk factor for thromboembolism, and no prior history of taking ACEIs, angiotensin receptor blockers, or statins. The enrolled patients were randomly assigned to four groups. Group I (N=15; M:F, 10:5; age, 49±6 years) received no ACEI or statin, group II (N=17; M:F, 11:6; age, 48±6 years) received cilazapril 5 mg without statin, group III (N=18; M:F, 9:9; age, 49±7 years) received cilazapril 5 mg and atorvastatin 10 mg, and group IV (N=16; M:F, 10:6; age, 45±3 years) received cilazapril 5 mg and atorvastatin 40 mg.

Serum markers of endothelial function (von Willebrand factor (vWF)), inflammation (quantitative and high sensitive C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)), and coagulation (fibrinogen, fibrinogen degradation product (FDP), d-dimer) were measured at baseline and 6 months. Blood samples were obtained by atraumatic venipuncture in the morning, after fasting for >12 hours. Blood was drawn without stasis into a tube preloaded with trisodium citrate. vWF was measured by the enzyme-linked immunosorbent assay technique using commercial reagents (R & D systems, MN, USA). CRP was measured by the latex agglutination method (quantitative CRP, Behring nephelometer analyzer; high-sensitivity CRP, Olympus AU 5400). Measurements of fibrinogen, FDP, and d-dimer were performed with chromogenic assay (Sysmex CA1500, Sysmex Corporation, Kobe, Japan).

All patients received antithrombotic therapy according to the American College of Cardiology/American Heart Association guideline. Drugs for heart rate control were prescribed equally among all groups. Those who received anti-inflammatory drugs such as steroids were excluded. Previously established and widely accepted epidemiologic risk factors for thromboembolism including old age (≥65 years), hypertension, diabetes mellitus, heart failure, and history of embolism were investigated, and echocardiographic parameters including left ventricular ejection fraction (LVEF) and left atrial dimension were measured. Left ventricular dysfunction was defined as LVEF less than 40%. Exclusion criteria were recent (<6 months) myocardial infarction or acute coronary syndrome, stroke, infection or inflammatory disease, surgery, malignancy, thyrotoxicosis, and renal or liver impairment.

Results are expressed as mean ± standard deviation. Comparison of serum markers between groups were analyzed using the paired t-test and analysis of variance. All statistical calculations were performed using commercially available statistical package software (SPSS version 12.0; IBM Corporation, IL, USA). A P value <0.05 was considered statistically significant.

Results

Clinical and demographic characteristics of the study population are shown in Table 1. There were no significant changes at 6 months or between-group differences in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels at baseline and 6 months (Figure 1).
Markers of Endothelial Dysfunction

The vWF (factor 8-related antigen) level was significantly decreased from baseline to 6 months in groups III and IV which received statin (group III, 172% to 110%, p<0.001; group IV, 184% to 125%, p=0.021). There were no significant changes in the vWF (ristocetin cofactor) level at 6 months or between-group differences at baseline and 6 months (Figure 2).

Markers of Inflammatory Activity

There were no significant changes at 6 months or between-group differences in ESR and CRP (quantitative and highsensitivity) levels at baseline and 6 months (Figure 3).

Coagulation Markers

Fibrinogen levels were significantly decreased in group IV (331±73 mg/dL vs. 275±57 mg/dL, p=0.047). However, there were no significant changes in the other coagulation markers (Figure 4).

Discussion

Endothelial dysfunction may lead to increased endothelial adhesiveness to leukocytes and the production of procoagulant and vasoactive molecules, cytokines, and growth factors. The vWF is a multifunctional plasma protein that plays a very important role in hemostasis following vascular injury. Circulating platelets adhere to the injured site and initiate the process of thrombosis, and subendothelial vWF mediates platelet adhesion to the injured site. The vWF is secreted not only from the vascular endothelium but also from the atrial endocardium in response to vascular injury and vascular disease. Raised plasma levels of vWF were reported to be associated with widespread endothelial damage/dysfunction, atherothrombosis, left atrial endothelial damage, and left atrial appendage thrombosis. Thrombomodulin (TM), a transmembrane spanning protein which can also be cleaved from the membrane to circulate in a soluble form, is one of the major anticoagulant components of the endothelial surface. Thrombin bound to TM consequently loses its procoagulant and proinflammatory functions. It cannot cleave fibrinogen or activate platelets and factor XIII. The present study results suggest that markers of endothelial dysfunction, especially the vWF, are associated with known epidemiologic risk factors for thromboembolism in Korean AF patients. Furthermore, ACEI and statin use could improve the endothelial function after 6 months, regardless of the statin dose. There is an apparent link between thrombogenesis and
An established index of inflammation is interleukin-6 (IL-6), which is a circulating cytokine produced by monocytes, macrophages, T-lymphocytes, and endothelial cells. IL-6 can induce a prothrombotic state by increasing the expression of fibrinogen, tissue factor, factor VIII, and von Willebrand factor, as well as by activating endothelial cells and increasing platelet production. Elevated CRP levels have been reported in AF patients, reflecting an inflammatory state, which could promote the persistence of AF. Although the CRP level was increased and correlated with some known risk factors for thromboembolism in previous studies, the use of ACEI or statin did not affect these markers or composite endpoint even with high doses. These results suggested the lesser role of inflammation in terms of thromboembolic risks in Korean AF patients.

The level of hemostatic activation may also reflect the underlying mechanism of thromboembolism, especially pronounced in cardioembolic stroke. Fibrin D-dimer assay is based on the production of cross-linked fibrin by thrombin, making it a sensitive marker of fibrin turnover, and allows the recognition of activated coagulation. Coagulation markers were substantially increased and associated with some risk factors for thromboembolism, and the use of high-dose atorvastatin at 40 mg could reduce fibrinogen levels after 6 months. Further well-controlled studies are required to evaluate the clinical effect of this dose and treatment duration.

There were no remarkable lipid profile changes even after 6 months of treatment with high-dose statin therapy. This result may have been associated with patient compliance. The mechanism of the pleiotropic effect of statins which involves an improvement in endothelial function and coagulation is unclear.

While the benefits of antithrombotic therapy in preventing stroke in AF patients are being increasingly recognized, further developments in thromboprophylaxis are needed, especially as warfarin confers the inconvenience of regular monitoring of
Figure 2. Von Willebrand factor (%) at baseline and 6 months (factor 8-related antigen (A), ristocetin cofactor (B)).

Figure 3. Levels of inflammation markers (erythrocyte sedimentation rate (A), quantitative C-reactive protein (B), high-sensitivity C-reactive protein (C)) at baseline and 6 months.

Figure 4. Levels of coagulation markers (fibrinogen (A), fibrinogen degradation product (B), fibrin D-dimer (C)) at baseline and 6 months.
prothrombin time (PT) and the benefits of aspirin are inconsistent. Current clinical practice for prevention of thromboembolic stroke in AF patients is limited not only by the low efficacy of antiplatelet therapy but also by the hemorrhagic complications and the inherent need for PT monitoring with warfarin therapy.18

In conclusion, the present study showed some beneficial effects of ACEI and high-dose statin on endothelial function and coagulation. The use of these drugs in addition to the conventional treatment with anticoagulation drugs may be useful for the prevention of thromboembolic events in high-risk patients or for secondary prevention of thromboembolism. The present study findings should be verified in further randomized controlled studies.

References