Usefulness of upstream therapy with renin-angiotensin system inhibitors for prevention of new-onset atrial fibrillation in patients with heart failure

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Background: The preventive effects of renin-angiotensin system inhibitors for suppression of new-onset atrial fibrillation (AF) are unclear. In the present study, we evaluated the effect of angiotensin receptor blocker (ARB)/angiotensin converting enzyme inhibitor (ACEI) on the incidence of new-onset AF in patients with heart failure (HF).

Methods: The study subject consisted of 525 patients with history of hospitalization due to HF without documented AF and they were all followed-up under standard pharmacological therapies for HF. The incidence and predicting factors for new-onset AF were evaluated by univariate and multivariate analyses.

Results: During the observation period of 16 ± 10 months, 57 patients exhibited new onset AF. When compared with patients with and without new-onset AF in the univariate analysis, minimum level of serum brain natriuretic peptide (BNP) was higher, and incidence of use of ARB/ACEI was lower. In the multivariate analysis, higher minimum level of serum BNP, LVEF (left ventricular ejection fraction) <35% and no use of ARB/ACEI were the independent predicting factors for new-onset AF. In Kaplan-Meier analysis, the incidence of AF was lower in patients with ARB/ACEI use than in patients without ARB/ACEI use (P = 0.0093).

Conclusion: In patients with history of hospitalization due to HF, the use of ARB/ACEI was considered effective for prevention of new-onset AF.

Key words: atrial fibrillation, heart failure, upstream therapy, renin-angiotensin system, renin-angiotensin system inhibitors

Introduction

Atrial fibrillation (AF) is one of the most common tachyarrhythmias observed in the clinical practice.1-3 Although there are several reports of congenital or inherited AF,4,5 most of AF will appear as a result of the construction of arrhythmogenic substrate which is promoted by the interaction between triggering premature atrial contraction and structural degeneration of atrial tissue.6,7 The latter is understood as the structural remodeling for AF substrate and is characterized by extracellular matrix proliferation and intercellular fibrosis.8 In experimental studies, these structural changes were exaggerated by sympathetic and angiotensin stimulations and they were reportedly suppressed by the use of renin-angiotensin system inhibitors, i.e., angiotensin receptor blocker (ARB) or angiotensin converting enzyme inhibitors (ACEI).6-17 Because these agents also suppressed the AF inducibility, they were considered as "upstream therapy" for AF.18 Although retrospective observation of patients expected the suppressive effect of ARB/ACEI for AF occurrence in patients with heart failure (HF),19,20 a few recent mega-trials which set the AF suppression as the primary end point, i.e., GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-Atrial Fibrillation), J-Rhythm II and ANTI-PAF (antagonist in paroxysmal atrial fibrillation) studies, failed to prove the efficacy of ARB for AF prevention at least in the secondary prevention of AF in patients.10,14,15,21-23

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for the already constructed AF substrate, so that the efficacy of the upstream therapy, if there is any, should be evaluated in an earlier phase of construction of the AF substrate. In the present study, we have evaluated the new-onset AF episode during long-term observation in patients with HF to clarify the risk factors for new-onset AF and the role of ARB/ACEI as the upstream therapy for new-onset AF.

Methods

Study population
This study was designed as a retrospective cohort study. The study population consisted of 688 consecutive patients with congestive heart failure who were admitted to our institute during the 12-year period from 1996 to 2008. The mean age was 67 ± 13 years, and 240 patients were female. Through the continuous electrocardiogram (ECG) monitoring, the presence of AF was screened and 163 patients with spontaneous episodes of AF were excluded from further observation in this study. The clinical characteristics of the remaining 525 patients are summarized in Table 1. The underlying heart diseases were ischemic heart disease in 262, dilated cardiomyopathy in 123, hypertrophic cardiomyopathy in 19, valvular heart disease in 67, and various other diseases in 54 patients. These were diagnosed based on the findings from the cardiac catheterization, echocardiogram, cardiac magnetic resonance imaging, etc.

Therapeutic strategy for HF
Therapeutic strategy for HF basically followed the guidelines24,25 of acute and chronic HF therapy in each era but nonadherence occasionally occurred on an individual patient basis. This study did not provide any therapeutic intervention in the choice of therapeutic strategy.

Patient observation
At the time of admission, standard investigations including 12-lead ECG, chest x-ray, echocardiography, and blood analysis were performed for all patients. After achieving a stable condition, these evaluations were repeated prior to the patients being discharged, and all patients were followed up as outpatients under stable therapies for at least for 6 months. During the hospitalization, their serum level of brain natriuretic peptide (BNP) was measured, once a week, and the minimum level of serum BNP was also used as a parameter for prediction of new-onset AF. During the observation period, the appearance of new-onset AF was picked up by a routine 12-ECG recording in the outpatient clinic, once every few months, and a Holter ECG recording, once a year. After 2005, portable ECG recorders, i.e., cardiophone (Nihon Koden, Tokyo) were

| Table 1. Clinical characteristics and comparison of patients with and without new-onset AF |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Total                          | With new-onset AF   | Without new-onset AF | P-value         |
| Number of patients             | 525               | 57               | 468             | 0.8709          |
| Age (years)                    | 66 ± 13           | 66 ± 13          | 66 ± 13         | 0.7391          |
| Gender (Female : Male)         | 183 : 342         | 21 : 36          | 162 : 306       | 0.5096          |
| On discharge                   |                  |                  |                 |                 |
| LVEF (%)                       | 41 ± 13           | 39 ± 13          | 41 ± 13         | 0.0722          |
| LVDD (mm)                      | 60 ± 10           | 62 ± 10          | 60 ± 10         | 0.1631          |
| LAD (mm)                       | 42 ± 6            | 42 ± 6           | 42 ± 6          | 0.7116          |
| Minimum level of serum BNP (pg/ml) | 177 ± 183   | 216 ± 175        | 172 ± 184       | 0.0204*          |
| Medication use, no. (%)        |                  |                  |                 |                 |
| ARB/ACEI                       | 435 (83%)         | 39 (68%)         | 396 (85%)       | 0.0022*          |
| β blocker                      | 263 (50%)         | 22 (39%)         | 241 (52%)       | 0.0659          |

AF, atrial fibrillation; HF, heart failure; IHD, ischemic heart disease; CM, cardiomyopathy; VHD, valvular heart disease; LVEF, left ventricular ejection fraction; LVDD, left ventricular end-diastolic dimension; LAD, left atrial dimension; BNP, brain natriuretic peptide; ARB, angiotensin-receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

*Indicates P < 0.05 between patients with and without new-onset AF.
upstream therapy for new-onset AF prevention

used to document AF in selected patients. In the patients with new-onset palpitation, an additional Holter ECG recording was performed to document AF. In this study, only electrocardiographically documented AF was counted as new-onset AF. When considerable cardiac events, such as rehospitalization due to exaggeration of HF, or patients' transferred to other hospitals occurred, such cases were excluded from further observation in the present study.

Evaluation of the clinical parameters as risk factors for new-onset AF

Clinical parameters, that is, age, gender, underlying cardiovascular disease of HF, left ventricular ejection fraction (LVEF), left ventricular diastolic dimension, left atrial dimension, BNP level, administration of ARB/ACEI and β-blocker, were compared between patients groups with and without new-onset AF during the observation period. Univariate and multivariate analyses were performed to evaluate each parameter as the predicting factor for the appearance of new-onset AF. In univariate analysis, each parameter was treated with continuous values. In the multivariate analyses, the cut-off point of LVEF was set at 35% in accordance with that in various clinical mega-trials. All studies were performed with the approval of the Clinical Studies and Ethics Committee of Kitasato University Hospital.

Statistics

All values are expressed as the mean ± standard deviation. The statistical analyses were performed with chi-square test. For the comparison between two groups, t-test and chi-square test was performed. The Cox proportional hazards model was applied to evaluate differences of background for the new-onset AF. The Kaplan-Meier test and the Wilcoxon's rank sum test were applied to evaluate the difference of administration of ARB/ACEI for new-onset AF. P values of <0.05 were considered to indicate statistically significant differences. We used the statistical software JMP (JMP 6.0, SAS inc. Tokyo, Japan).

Results

Incidence of new-onset AF during the observation period

During the observation period of 16 ± 10 months, new-onset AF was documented in 57 patients (11%). Table 1 shows a comparison of clinical characteristics of the patients with and without new-onset AF in the univariate analysis. The patients with new-onset AF exhibited higher level of "minimum serum BNP" during hospitalization and lower incidence of the use of ARB/ACEI in comparison with the patients without new-onset AF.

Multivariate analysis of clinical parameters for the prediction of new-onset AF

Table 2 exhibits a result of the multivariate analysis of the clinical parameters for the prediction of new-onset AF during the observation. As a result, higher minimum level of serum BNP, LVEF <35% and no use of ARB/ACEI were independent predicting factors for new-onset AF in HF patients.

Figure 1 exhibits cumulative event curves for new onset AF in patients with and without ARB/ACEI use. The incidence of new-onset AF was higher in patients without ARB/ACEI use than those with ARB/ACEI use.

Table 2. Uni- and multi-variate analyses of the prediction of new-onset AF

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>95%CI</td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>0.974</td>
<td>0.548-1.733</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>1.102</td>
<td>0.623-1.950</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0.754</td>
<td>0.352-1.618</td>
</tr>
<tr>
<td>Minimum level of serum BNP (pg/ml) on discharge</td>
<td>0.001</td>
<td>0.998-1.002</td>
</tr>
<tr>
<td>LVEF &lt;35%</td>
<td>0.485</td>
<td>0.276-0.853</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>1.004</td>
<td>0.956-1.050</td>
</tr>
<tr>
<td>Nonadministration of ARB/ACEI</td>
<td>2.538</td>
<td>1.376-4.683</td>
</tr>
<tr>
<td>Nonadministration of β blocker</td>
<td>1.820</td>
<td>1.031-3.211</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; 95%CI, 95% confidence interval; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; ARB, angiotensin-receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

*Indicates P < 0.05.
Discussion

This study evaluating new-onset AF in patients with HF exhibited several interesting points. First, ECG documented new-onset AF was observed in 57 of 525 patients (11%) during the observation period of 16 ± 10 months. Second, higher minimum level of serum BNP, LVEF <35% and no use of ARB/ACEI were independent predicting factors for new-onset AF during the observation. Third, the cumulative events of new-onset AF were significantly higher in patients without ARB/ACEI use or higher minimum level of serum BNP. Predicting factors for new-onset AF in patients with HF is one of the common underlying diseases for the occurrence of AF. Higher atrial pressure will cause atrial wall stretch and it will result in increase of triggering premature atrial contractions and extracellular matrix synthesis, which are understood as the atrial remodeling for AF substrate. Therefore, pharmacological intervention aiming the prevention of progression of such atrial remodeling is expected to be effective especially in its earlier phase. In this study, we focused on the appearance of new-onset AF in patients with a history of HF, and documented several important clinical factors that predict the future appearance of new-onset AF. It may be reasonable that more severe HF will have greater chance of the appearance of arrhythmia including AF because the myocardial remodeling will be promoted more rapidly by more severe hemodynamic disturbance in patients with HF. Noteworthy, our present study documented another predicting factor for new-onset AF in the parameters of therapeutic interventions, i.e., no use of ARB/ACEI. Because it was one of the independent predicting factors in the multivariate analysis, this result indicates the possibility of ARB/ACEI therapy for the effective prevention of new-onset AF at least in the population of our present study.

Because the therapeutic strategy was not randomized in the present study, neither was the use or no use of individual medicines randomized. The main reason of nonadherence to the therapeutic guideline for HF therapy in the point of the use of ARB/ACEI was low blood pressure especially in earlier events among the patients in the present study. This may result in selection bias of the patients as more severe HF patients to the patient group of no use of ARB/ACEI. However, because the result has been led through the multivariate analysis, efficacy of ARB/ACEI as the upstream therapy for prevention of new-onset AF may possibly be interpreted from the results in the present study.

Usefulness of the upstream therapy for AF in HF

It has been reported that various stimulations in
pathological condition of HF will lead myocardial remodeling for further functional disorders including arrhythmias.\(^{28,29}\) In experimental studies, the stimulation of AT1 receptor of angiotensin II has been shown to cause cellular hypertrophy, degeneration as well as extracellular matrix proliferation and fibrosis, and then they all result in promotion of arrhythmogenic substrate for AF.\(^{13}\) Several investigators have reported that such myocardial remodeling and increase in AF inducibility could be suppressed by ARBs, and they have suggested possible effect of ARB as the upstream therapy for AF even in clinical cases. The meta-analysis of several studies have also exhibited possible effect of ARB/ACEI as the upstream therapy for AF at least in HF patients, but a few recent studies setting their primary endpoint as AF suppression, i.e., GISSI-AF, J-Rhythm II, ANTI-PAF, failed to prove their efficacy.\(^{10,14,15,21-23}\) Probably, the latter indicates that upstream therapy using ARB does not have strong impact on the secondary prevention of AF, but the its efficacy on the primary prevention of AF is unknown. Because we could exhibit possible effect of ARB/ACEI as the upstream therapy for new-onset AF, the understanding of the upstream therapy may have to be reconsidered.

One would say that ARB/ACEI therapy in HF population is fundamental therapy for HF but not the optional therapy aiming upstream therapy for AF, which is additional disorder in HF patients. However, the upstream therapy, in a broad sense, will include the optimal therapy for the underling heart disease, so that the use of ARB/ACEI can be considered as upstream therapy for AF. Furthermore, suppression of AF might also be involved as the mechanisms of better prognosis of HF patients under the treatment with ARB/ACEI.

Considering the effect of upstream therapy for AF, not only the new-onset AF, but also increase in the frequency of AF or change of paroxysmal AF to chronic AF should be counted as the parameters. However, the sensitivity or specificity of these parameters of AF are strongly dependent on the quality of continuous ECG monitoring, which usually cannot be achieved in the outpatient clinic. To evaluate these parameters, a prospective study utilizing portable ECG recorder, such as the transsthelephonic electrocardiogram, a "Cardiophone" (Nihon Koden), should be designed in the future.

**Limitations**

The present study has a few limitations as follows. First, the number of patients, especially the number of event cases, was limited. Second, because the observations were performed in retrospectively; therefore, the therapies were not randomized. Third, because we counted only ECG documented AF as the new-onset AF, the new-onset AF might be underestimated. Finally, because ARB/ACEI and \(\beta\)-blockers are known to improve the prognoses of HF patients, the direct effects of these medicines for prevention of new-onset AF could not be concluded separately from their indirect effects that might appear through the improvement of HF.

**Conclusions**

We evaluated the new-onset AF during long-term observation of patients with HF. In the multivariate analysis, LVEF < 35\%, a higher minimum level of serum BNP and no use of ARB/ACEI were independent predicting factors for new-onset AF. ARB/ACEI therapy was considered as a possibly an effective upstream therapy in patients with HF.

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**References**


