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Combination Therapy of Renin Angiotensin System Inhibitors and Bepridil is Useful for Maintaining Sinus Rhythm in Patients With Atrial Fibrillation

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Abstract

Background. The present study evaluated the effect of treatment renin angiotensin system inhibitors (RAS-I) for maintaining sinus rhythm after conversion from persistent atrial fibrillation. As the efficacy of RAS-I in atrial fibrillation is unclear, our study evaluated conversion to and maintenance of sinus rhythm by combination therapy with RAS-I and bepridil in patients in atrial fibrillation.

Methods. Bepridil was administered to 125 consecutive patients with paroxysmal and persistent atrial fibrillations. Two groups of patients were compared: The bepridil group was treated with bepridil alone, the RAS-I group with bepridil plus angiotensin II receptor blockers or angiotensin converting enzyme inhibitors. The primary end point was length of time to first recurrence of atrial fibrillation.

Results. Maintenance of sinus rhythm was achieved in 25 patients (45%) in the bepridil group and 44 patients (63%) in the RAS-I group (persistent and paroxysmal atrial fibrillations). The difference between the bepridil group and the RAS-I group was significant ($p < 0.05$). Maintenance of sinus rhythm was achieved in 9 of 25 patients (36%) in the bepridil group, and in 22 of 35 patients (62%) in the RAS-I group with persistent atrial fibrillation. The difference between the bepridil group and the RAS-I group was significant ($p < 0.05$). Bepridil plus RAS-I was particularly effective at preventing the recurrence of atrial fibrillation in patients with left ventricular dysfunction (left ventricular ejection fraction < 50%).

Conclusions. Combination therapy with RAS-I and bepridil may be useful for maintenance of sinus rhythm.

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Key Words

■ **Angiotensin II (receptor blockers)** ■ **Ventricular function (left ventricular dysfunction)**
■ **Antiarrhythmia agents (antiarrhythmic therapy)**
■ **Atrial fibrillation**

INTRODUCTION

Atrial fibrillation (AF) is the most frequent form of arrhythmia in clinical practice, affecting 6% of people aged over 65 years.[1] AF is associated with increased risk of stroke, death, and heart failure.[2,3]

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Recent large trials have shown that rhythm-control therapy does not offer any prognostic advantage over rate-control therapy in patients with persistent AF.[4,5] However, some of these findings have been questioned. The clinical recurrence of AF after cardioversion results from a biological phenomenon known as remodeling which progressively and irreversibly alters the electrical and structural properties of the atrial tissue and cardiac cells.[6,7] Moreover, in the setting of heart failure or left ventricular hypertrophy, AF is associated with atrial dilation and increased fibrosis. These phenomena can result in AF becoming resistant to antiarrhythmic drugs. However, stroke and heart failure are considered preventable if AF is treated from an early stage and is cured.

Recent reports have demonstrated that bepridil showed useful conversion effects in patients with persistent and paroxysmal AF and was highly effective for maintaining sinus rhythm (SR) after pharmacological or electrical cardioversion.[8,9] Electrical and structural remodeling in the atria is important in causing recurrent persistent AF. In this regard, angiotensin II receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACE-I) prevent the promotion of AF by suppressing structural remodeling.

The present study evaluated conversion to and maintenance of SR by combination therapy with RAS-I and bepridil for paroxysmal or persistent AF.

SUBJECTS AND METHODS

Study population

Maintenance of SR and clinical characteristics were retrospectively examined. The study population consisted of 125 consecutive patients with paroxysmal or persistent AF treated with bepridil between June 1998 and July 2006. The patients were 70 men and 55 women with mean age of 66 ± 21 years. Two groups of patients were compared: in the bepridil group, bepridil was the only antiarrhythmic ($n = 56$), whereas the RAS-I group was treated with bepridil plus either ARB ($n = 40$) or ACE-I ($n = 29$). Bepridil was administered at a dose of 100–200 mg/day. Candesartan was administered at a dose of 8 mg/day (21 patients) and losartan was administered at a dose of 50 mg/day (19 patients). Enalapril was administered at a dose of 5 mg/day (15 patients) and lisinopril was administered at a dose of 10 mg/day (14 patients).

The primary end point was length of time to first recurrence of AF. In this study, paroxysmal AF was defined as self-terminating AF within 48 hr and persistent AF as non-self-terminating AF lasting more than 48 hr and requiring pharmacological or electrical conversion to restore SR. Patients with chronic AF were excluded. Patients were also excluded with acute myocardial infarction within the previous month, cardiac surgery within 3 months, hyperthyroidism, pregnancy, bronchial asthma, and sinus bradycardia. Lone AF was defined as no cardiac disease (hypertension, heart failure, ischemic heart disease, valvular disease and cardiomyopathy).

Measurements

The beginning of the follow-up for this study was considered to be the day of administration of bepridil. Conversion and maintenance of SR after pharmacological or electrical cardioversion were evaluated, with the primary end point being length of time to first recurrence of AF. Electrocardiography (ECG) parameters including heart rate, PQ interval, QT interval, and QTc were measured before and after bepridil administration. ECG was recorded at 2 weeks or 1-month follow-up visits. Transthoracic echocardiography was performed to examine left atrial dimension (LAD) and left ventricular ejection fraction (LVEF). The incidence of adverse complications was also evaluated.

Statistical analysis

Results are presented as mean ± SD. p values < 0.05 were considered statistically significant. The Kaplan-Meier method was used to analyze the time to recurrence of AF during the follow-up period.

RESULTS

Patient characteristics

The baseline characteristics of the two groups are presented in **Table 1**. Mean age did not differ significantly between the two groups: 66 ± 11 years in the bepridil group, and 67 ± 12 years in the RAS-I group. Duration of AF was 730 ± 922 days in the bepridil group, and 688 ± 812 days in the RAS-I group (NS). Duration of medication was 503 ± 412 days in the bepridil group, and 478 ± 442 days in the RAS-I group (NS). The ejection fraction was 62 ± 14% in the bepridil group, and 56 ± 12% in the RAS-I group; so was significantly higher in the bepridil group than in the RAS-I group ($p = 0.03$). No significant difference

Table 1 Baseline characteristics of patients with atrial fibrillation

	Bepridil group (n=56)	RAS-I group (n=69)
Age (yr)	66±11	67±12
Sex (male/female)	30/26	40/29
Duration of AF (day)	730±922	688±812
Duration of medicine (day)	503±412	478±442
Ejection fraction (%)	62±14*	56±12*
Left atrial dimension (mm)	42±7	45±11
Dosage of bepridil (mg)	160±52	150±49

Continuous values are±SD. *$p<0.05$.
RAS-I = renin angiotensin system inhibitor; AF = atrial fibrillation.

between the two groups was noted for LAD or bepridil dosage.

Maintenance of SR (persistent and paroxysmal AFs)

The maintenance of SR in patients with persistent AF and paroxysmal AF is presented in **Fig. 1**. White bars depict maintenance of SR and black bars demonstrate recurrence of AF. SR was maintained in 25 of 56 patients (45%) in the bepridil group, and in 44 of 69 patients (63%) in the RAS-I group. The difference between the bepridil group and the RAS-I group was significant ($p = 0.05$). Maintenance of SR in patients with persistent AF is demonstrated in **Fig. 2—left**. SR was maintained in 9 of 25 patients (36%) in the bepridil group, and in 22 of 35 patients (62%) in the RAS-I group. The difference between the bepridil group and RAS-I group was significant ($p = 0.04$). The maintenance of SR with paroxysmal AF is demonstrated in **Fig. 2—right**. SR was maintained in 16 of 31 patients (52%) in the bepridil group, and in 22 of 34 patients (65%) the RAS-I group.

Fig. 3 shows the Kaplan-Meier estimates of the percentage of patients remaining free from recur-

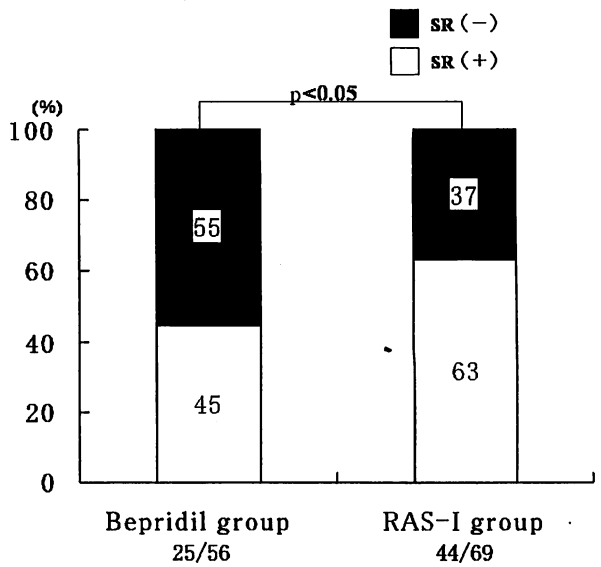

Fig. 1 Maintenance of sinus rhythm with persistent and paroxysmal atrial fibrillations
White bar shows the maintenance of sinus rhythm and *black bar* shows the recurrence of atrial fibrillation.
SR = sinus rhythm. Other abbreviation as in Table 1.

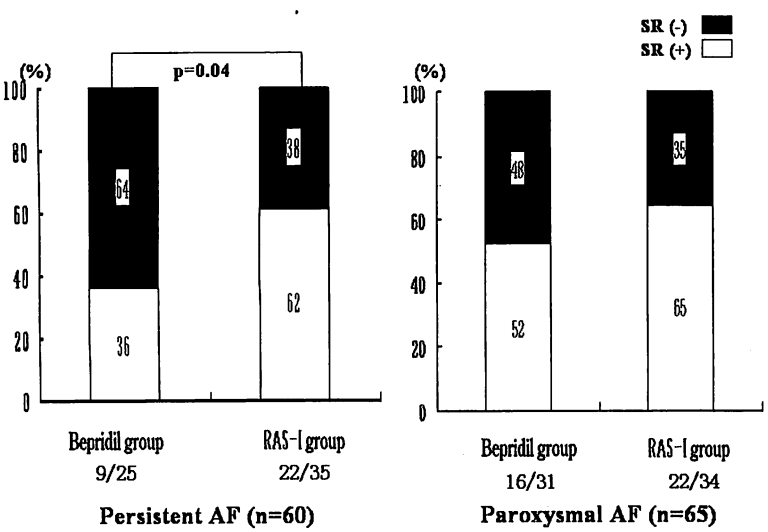

Fig. 2 Maintenance of sinus rhythm with persistent atrial fibrillation (*left*) and paroxysmal atrial fibrillation (*right*)
White bar shows the maintenance of sinus rhythm and *black bar* shows the recurrence of atrial fibrillation.
Abbreviations as in Table 1, Fig. 1.

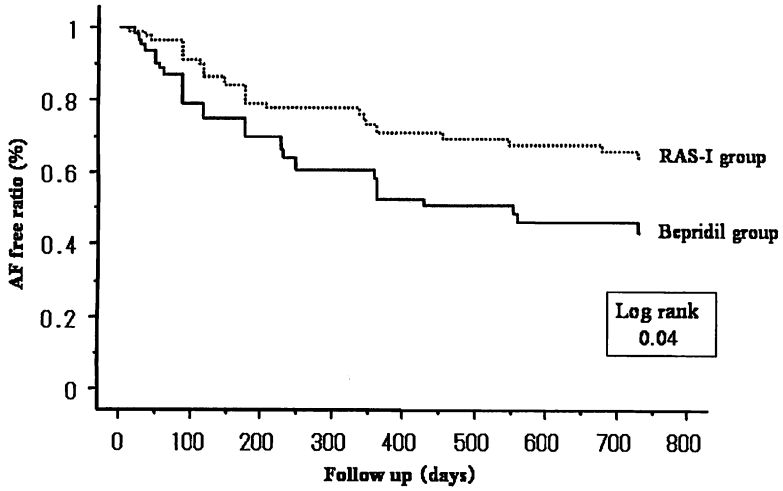

Fig. 3 Kaplan-Meier estimates of the percentage of patients remaining free from recurrence of persistent atrial fibrillation
X-axis shows days of follow up (day) after bepridil administration.
Abbreviations as in Table 1.

rence of persistent AF. The *X*-axis shows duration of follow up (days) after pharmacological or electrical conversion to restore SR. This analysis demonstrated a probability of 63% for maintaining SR for 24 months in the patients who received RAS-I, compared with 45% in those who did not ($p = 0.04$). **Table 2** shows maintenance of SR by the disease. Of those with lone AF, SR was maintained in 11 of 24 patients (46%) in the bepridil group, and 7 of 14 patients (50%) in the RAS-I group. There was no significant difference between the two groups. Of those with hypertension, SR was maintained in 4 of 12 patients (33%) in the bepridil group, and 16 of 37 patients (43%) in the RAS-I group (NS). Among those with ischemic heart disease, SR was maintained in 1 of 4 patients (25%) in the bepridil group, and 9 of 17 patients (53%) in the RAS-I group. Of those with heart failure, SR was maintained in 2 of 6 patients (33%) in the bepridil group, and 16 of 24 patients (66%) in the RAS-I group. However, in patients with heart failure and ischemic heart disease, bepridil plus RAS-I had a higher SR maintenance rate than bepridil alone.

Table 2 Maintenance of sinus rhythm in patients with various diseases

	Bepridil group	RAS-I group
Lone AF ($n=45$)	11/24 (46%)	7/14 (50%)
Hypertension ($n=52$)	4/12 (33%)	16/37 (43%)
Ischemic heart disease ($n=23$)	1/4 (25%)	9/17 (53%)
Heart failure ($n=34$)	2/6 (33%)	16/24 (66%)

Abbreviations as in Table 1.

Table 3 Maintenance of sinus rhythm with left ventricular dysfunction

Ejection fraction	Bepridil group ($n=56$)	RAS-I group ($n=69$)
60%-	13/27 (48%)	14/22 (63%)
50-59%	10/22 (45%)	11/17 (64%)
40-49%	2/7 (28%)	12/18 (66%)
-39%	0	7/12 (58%)

Left ventricular ejection fraction was divided into four groups, and compared with maintenance of sinus rhythm. In the RAS-I group, the maintenance of sinus rhythm was high regardless of left ventricular ejection fraction. Especially, the maintenance of sinus rhythm in patients with less than 50% (left ventricular ejection fraction) was higher than that of other groups.
Abbreviation as in Table 1.

Maintenance of SR with left ventricular dysfunction

The patients were divided into four groups by LVEF and SR maintenance rate was compared (**Table 3**). For patients with LVEF > 50%, no significant intergroup difference was found. However, in the RAS-I group, maintenance of SR was high regardless of LVEF.

Electrocardiography parameters

For PQ interval and the QRS duration, no significant difference was observed between the two groups before and after bepridil administration. In the bepridil group, QT interval and QTc increased

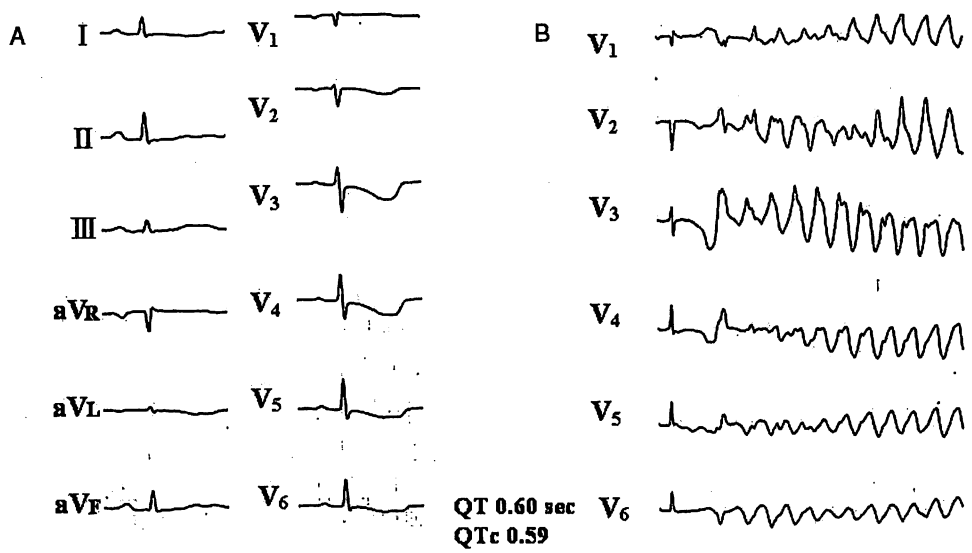

Fig. 4 Electrocardiograms
A: A 65-year-old woman patient was treated with bepridil only (200 mg/day). Before torsades de pointes was observed, QT interval was 0.60 sec.
B: We performed DC cardioversion. Torsades de pointes was termination. Serum potassium concentration was 3.2 mEq/*l*.

significantly from 0.40 to 0.43 sec ($p = 0.05$), and from 0.41 to 0.45 ($p = 0.01$). In the RAS-I group, QT interval and QTc increased significantly from 0.38 to 0.42 sec ($p = 0.01$) and QTc from 0.41 to 0.44 ($p = 0.05$).

Complications

A 65-year-old woman patient suffered torsades de pointes. She was treated with bepridil only (200 mg/day). Before torsades de pointes was observed, QT interval was 0.6 sec (**Fig. 4**). QT prolongation was observed in 6 patients. Bepridil were discontinued in 3 of these patients, but the remaining 3 continued to receive bepridil at a low dose (50−100 mg) ; QT interval was normalized in 3 cases. Liver dysfunction was observed in 3 patients ; bepridil was discontinued in these patients, and liver function normalized.

DISCUSSION

Main findings

The major findings of this retrospective study were as follows. Patients treated with bepridil plus RAS-I were more likely to remain in SR than patients treated with bepridil alone. The combination of bepridil plus RAS-I was effective at preventing the recurrence of AF in patients with left ventricular dysfunction (LVEF < 50 %). Bepridil was useful and safe in left ventricular dysfunction, providing the QT interval is carefully observed.

SR maintenance with bepridil

Bepridil was originally developed as an anti-anginal drug, but it blocks several ion channels, including sodium, potassium, and calcium channels.[10−13] In particular, its potassium channel blocking action prolongs action potentials, and this is expected to give rise to anti-arrhythmic properties in AF similar to those of amiodarone. The mechanism of SR maintenance remains unclear, but bepridil might prevent short-term remodeling in the atrium as well as reversing mid- to long-term remodeling.[14] In our study, SR was maintained in 69 of 125 patients (55 %) in whom it was initially restored by bepridil or cardioversion during an average follow-up of 24 months. SR was maintained over a mean follow-up of 18 months in 81 % of patients (70/86).[14] Because our study had a longer follow-up period and there were many patients with left ventricular dysfunction in our study, SR was maintained in a smaller proportion of patients. Nevertheless, our findings are comparable to those of previous studies. The relatively strong potassium channel blocking effect of bepridil often causes QT prolongation, which can result in torsades de pointes.[15] We consider that the maximum

appropriate dose of bepridil is 200 mg/day, and we continued careful follow-up including observation of QT interval and serum potassium concentration.

Effects of RAS-I on AF

The mechanism of SR maintenance remains unclear, but it is possible that RAS-I prevents atrium remodeling. Several reports describe ACE-I or ARB exerting anti-arrhythmic effects that prevent AF. Enalapril markedly reduces the risk of development of AF (by 78%) in patients with left ventricular dysfunction (SOLVD trials).[16] Trandolapril reduced the risk of development of AF (by 55%) in patients with left ventricular dysfunction due to acute myocardial infarction.[17] The mechanism of SR maintenance involves ACE-I treatment attenuating the susceptibility to AF by lowering atrial pressure and reducing left atrial enlargement. These studies were retrospective analyses. The LIFE study showed that new-onset AF was reduced by 33% more with losartan compared to atenolol, with similar blood pressure reduction for the two drugs.[18] Our study did not investigate blood pressure, but lowering of blood pressure could be an important part of the mechanism. The Val-HeFT study showed valsartan reduced new-onset AF by 37%.[19] However, the majority of these trials were post-hoc reports of randomized trials designed to assess outcomes other than AF. Thus, these data may be prone to multiple-testing errors and data-derived emphasis biases.

Prospective investigation of patients treated with amiodarone plus irbesartan found a lower rate of recurrence of atrial fibrillation than in patients treated with amiodarone alone.[20] Most of the benefit of irbesartan occurred during the first 2 months after conversion; after this point, the Kaplan-Meier curves appeared parallel. In our study, most of the benefit of RAS-I occurred during the first 6 months after conversion, after which the two curves also appeared parallel. This finding is similar to that of certain recent studies[17] and points to the importance of remodeling just after cardioversion. There are several possible biologic mechanisms by which RAS-I might reduce the development of AF. These trials demonstrated that RAS-I could prevent or modify atrial remodeling through other mechanisms, such as decreasing atrial stretch, lowering diastolic left ventricular pressure and subsequently left atrial pressure, preventing atrial fibrosis, modifying sympathetic tone, or modulating ion currents of refractoriness.

Maintenance of SR in patients with left ventricular dysfunction

A meta analysis showed that ACE-I and ARB appeared to be effective in the prevention of AF among patients with left ventricular dysfunction and clinical heart failure.[21] However, the studies evaluated did not ascertain difference in LVEF. We divided patients into four groups by LVEF and compared maintenance of SR. In the RAS-I group, SR maintenance rate was high regardless of LVEF and was particularly good in comparison to other treatment groups for patients with LVEF $< 50\%$.

Study limitations

This study was a retrospective analysis. As the patient groups may have had different characteristics, it is difficult to evaluate the efficacy of RAS-I from the present study. We are therefore currently performing a prospective study. Moreover, it is difficult to evaluate the maintenance of SR in asymptomatic patients with paroxysmal AF at 2 weeks or 1 month during follow up visits. However, in persistent AF, such follow-up is probably adequate to evaluate the maintenance of SR, because persistent AF was defined as non-self-terminating AF lasting more than 48 hr and requiring pharmacological or electrical conversion to restore sinus rhythm.

CONCLUSIONS

Patients treated with bepridil plus RAS-I had a lower rate of recurrence of AF than did those treated with bepridil alone. Moreover, bepridil plus RAS-I was effective at preventing the recurrence of AF in patients with left ventricular dysfunction.

要　約

レニン・アンジオテンシンシステム拮抗薬とベプリジルの併用は心房細動洞調律維持に有効

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箕浦　慶乃　浅野　拓　丹野　郁　小林　洋一

背　景: 最近の論文では持続性心房細動の除細動後の洞調律維持にレニン・アンジオテンシンシステム拮抗薬(RAS-I)が有効であると報告されている．ただ，心房細動に対するRAS-Iの有効性は明らかでない．今回我々はベプリジルとRAS-Iの併用が心房細動の洞調律維持に有効かどうか検討した．

方　法: 対象はベプリジルを内服している125例の発作性心房細動，持続性心房細動の患者である．ベプリジル単独群(56例)とベプリジルとRAS-I併用群(69例)の2群に分けて検討した．内服後の洞調律維持により評価した．

結　果: 全症例のうちベプリジル単独群では56例中25例(45％)で洞調律維持が可能であった．RAS-I併用群では69例中44例(63％)で洞調律維持が可能であり，RAS-I併用群のほうで有意に洞調律維持が可能であった($p<0.05$)．持続性心房細動ではベプリジル単独群で25例中9例(36％)で洞調律維持が可能であった．RAS-I併用群では35例中22例(62％)で洞調律維持が可能であり，RAS-I併用群のほうで有意に洞調律維持が可能であった($p<0.05$)．有意差は認められなかったが，心機能低下例(左室駆出率＜50％)においてRAS-I併用群のほうが洞調律維持がよかった．

結　論: ベプリジルとRAS-Iの併用は，持続性心房細動の除細動後の洞調律維持に有効であった．

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レニン・アンジオテンシン系阻害薬とベプリジルの併用療法は心房細動患者の洞調律維持に有用

要旨

背景：本試験の目的は、持続性心房細動から転換後の洞調律維持におけるレニン・アンジオテンシン系阻害薬（RAS-I）の治療効果を評価することであった。心房細動に対する RAS-I の有効性は明らかでない。そのため我々は今回、RAS-I とベプリジルの併用療法による心房細動の洞調律への転換をその維持を含めて検討した。

方法：ベプリジルを投与した発作性および持続性心房細動患者の連続 125 例を対象とした。ベプリジル単独を投与したベプリジル群、ベプリジルとアンジオテンシン II 受容体遮断薬またはアンジオテンシン変換酵素阻害薬のいずれかを投与した RAS-I 群の 2 群に患者を分けて比較した。主要評価項目は心房細動の初回再発までの時間の長さであった。

結果：持続性および発作性心房細動の全症例では、ベプリジル群の 25 例（45%）および RAS-I 群の 44 例（63%）で洞調律維持が可能であり、ベプリジル群と RAS-I 群で有意差が認められた（$p<0.05$）。持続性心房細動では、ベプリジル群の 25 例中 9 例（36%）および RAS-I 群の 35 例中 22 例（62%）で洞調律維持が可能であり、ベプリジル群と RAS-I 群で有意差が認められた（$p<0.05$）。ベプリジルと RAS-I の併用は左室機能不全（左室駆出率が 50%未満）患者における心房細動の再発予防に特に有効であった。

結論：RAS-I とベプリジルの併用療法は洞調律維持に有用となりうる。

キーワード

■アンジオテンシン II（受容体遮断薬）■心室機能（左室機能不全）

■抗不整脈薬（抗不整脈治療）

■心房細動

序論

心房細動（AF）は 65 歳以上の 6%の人が罹患し、実際の診療では頻度の最も高い不整脈の一形態である [1)]。AF は脳卒中、死亡、心不全のリスク増加と関連している [2,3)]。

最近の大規模試験は、持続性 AF 患者のリズムコントロール治療にはレートコントロール治療と比較して予後の優位性がないことを明らかにした [4,5]。ただし、これらの結果の中には疑問視されているものもある。心臓除細動後の AF の臨床的再発は、心房組織や心筋細胞の電気的および構造特性を徐々に不可逆的に変質させてゆくリモデリングとして知られる生物学的現象によって起こる [6,7]。さらに、心不全や左室肥大などの状態で AF が起こると心房拡張や線維化亢進を招き、この場合の AF は抗不整脈薬に反応しにくくなることがある。ただし、AF が初期段階で治療され治癒する場合の脳卒中および心不全は予防可能と考えられる。

最近の報告では、持続性および発作性 AF 患者においてベプリジルが有用な転換効果を示し、薬理学的または電気的カルディオバージョン後の洞調律(SR) 維持に非常に有効であることを明らかにした [8,9]。心房の電気的および構造的リモデリングは再発性持続性 AF の発症において重要である。この点については、アンジオテンシン II 受容体遮断薬（ARB）およびアンジオテンシン変換酵素阻害薬（ACE-I）が構造的リモデリングを抑制して AF の進行を予防する。

本試験では、発作性または持続性 AF における RAS-I とベプリジルの併用療法による SR への転換をその維持を含めて検討した。

対象と方法

対象集団

SR 維持および臨床的特徴を後ろ向きに検討した。1998 年 6 月から 2006 年 7 月の間にベプリジルを投与された発作性または持続性 AF の連続 125 例を対象とした。患者は 70 人が男性、55 人が女性で、平均年齢は 66±21 歳であった。抗不整脈薬のみを投与されたベプリジル群(56 例)、ベプリジルと ARB（40 例）または ACE-I(29 例）のどちらかを投与された RAS-I 群の 2 群の患者を比較した。ベプリジルは 100〜200mg/日の用量で投与された。カンデサルタンは 8 mg/日の用量で投与され（21 例)、ロサルタンは 50 mg/日の用量で投与された（19 例)。エナラプリルは 5 mg/日の用量で投与され（15 例)、リシノプリルは 10 mg/日の用量で投与された（14 例)。

主要評価項目は AF の初回再発までの時間の長さであった。本試験では、48 時間以内に自然停止した AF を発作性 AF と定義し、自然停止せず 48 時間以上持続し、SR の回復に薬理学的または電気的転換を要した AF を持続性 AF と定義した。慢性 AF の患者は除外した。前月中に急性心筋梗塞、３ヵ月以内の心臓手術、甲状腺機能亢進症、妊娠、気管支喘息、および洞性徐脈を認めた患者も除外した。心疾患（高血圧、心不全、虚血性心疾患、弁膜症および心筋症）がないものを孤立性 AF と定義した。

測定

ベプリジルの投与日を本試験のフォローアップの開始と見なした。薬理学的または電気的カルディオバージョン後の SR への転換とその維持を評価し、AF の初回再発までの時間の長さを主要評価項目とした。心拍数、PQ 間隔、QT 間隔、および QTc などの心電図（ECG）パラメータはベプリジルの投与前後に測定された。ECG は 2 週目または 1 ヵ月目のフォローアップ受診時に記録された。経胸壁心エコー法にて左房径（LAD）および左室駆出率（LVEF）を検討した。有害な合併症の発現率も評価した。

統計解析

結果は平均±標準偏差（SD）として表した。*P* 値が 0.05 未満であれば統計学的に有意と見なした。カプラン・マイヤー法を用いてフォローアップ期間中の AF 再発までの期間を検討した。

結果

患者特性

2 群のベースライン特性を**表 1** に示す。平均年齢はベプリジル群では 66±11 歳、RAS-I 群では 67±12 歳と 2 群間に有意差は認められなかった。AF の期間はベプリジル群では 730±922 日、RAS-I 群では 688±812 日（有意差なし）であった。投薬期間はベプリジル群では 503±412 日、RAS-I 群では 478±442 日（有意差なし）であった。駆出率はベプリジル群では 62±14%、RAS-I 群では 56±12%であり、RAS-I 群よりもベプリジル群の方が有意に高かった（$p = 0.03$）。LAD またはベプリジル投与量について 2 群間の有意差は認められなかった。

SR 維持（持続性および発作性 AF）

持続性 AF および発作性 AF 患者における SR 維持を**図 1** に示す。白い棒グラフは SR 維持を示し、黒い棒グラフは AF 再発を示す。ベプリジル群の 56 例中 25 例（45%）および RAS-I 群の 69 例中 44 例（63%）で SR は維持された。ベプリジル群と RAS-I 群で有意差が認められた（$p = 0.05$）。持続性 AF 患者における SR 維持を**図 2（左）**に示す。ベプリジル群の 25 例中 9 例（36%）および RAS-I 群の 35 例中 22 例（62%）で SR は維持された。ベプリジル群と RAS-I 群で有意差が認められた（$p = 0.04$）。発作性 AF における SR 維持を**図 2（右）**に示す。ベプリジル群の 31 例中 16 例（52%）および RAS-I 群の 34 例中 22 例（65%）で SR は維持された。

図 3 は、持続性 AF が再発しなかった患者割合を示したカプラン・マイヤー推定量である。X 軸は、薬理学的または電気的転換により SR を回復させた後のフォローアップの期間（日）を示す。この解析では、RAS-I 投与患者において SR が 24 ヵ月間維持する確率は 63%であったが、これに対して非投与患者では 45%であった（$p = 0.04$）。**表 2** は疾患ごとの SR 維持

を示す。孤立性 AF 患者では、ベプリジル群の 24 例中 11 例（46%）および RAS-I 群の 14 例中 7 例（50%）で SR は維持された。2 群間に有意差は認められなかった。高血圧患者では、ベプリジル群の 12 例中 4 例（33%）および RAS-I 群の 37 例中 16 例（43%）で SR は維持された（有意差なし）。虚血性心疾患の患者では、ベプリジル群の 4 例中 1 例（25%）および RAS-I 群の 17 例中 9 例（53%）で SR は維持された。心不全患者では、ベプリジル群の 6 例中 2 例（33%）および RAS-I 群の 24 例中 16 例（66%）で SR は維持された。しかし、心不全および虚血性心疾患の患者では、ベプリジルと RAS-I の併用の方がベプリジル単独よりも高い SR 維持率を示した。

左室機能不全における SR 維持

患者を LVEF ごとに 4 群に分けて SR 維持率を比較した（**表 3**）。LVEF が 50%を超える患者では有意な群間差は認められなかった。しかし、RAS-I 群では LVEF に関係なく高い SR 維持が認められた。

心電図パラメータ

PQ 間隔および QRS 期間について、ベプリジル投与前後で 2 群間の有意差は認められなかった。ベプリジル群では、QT 間隔および QTc は 0.40 秒から 0.43 秒（p ＝0.05）および 0.41 秒から 0.45 秒(p ＝0.01）に有意に増加した。RAS-I 群では、QT 間隔および QTc は 0.38 秒から 0.42 秒(p ＝0.01)および 0.41 秒から 0.44 秒(p ＝0.05)に有意に増加した。

合併症

65 歳の女性患者がトルサード ド ポアントを発現した。本患者にはベプリジルのみ (200 mg/日) が投与された。トルサード ド ポアントを認める前の QT 間隔は 0.6 秒であった (**図 4**)。QT 延長は 6 例に認められた。このうち 3 例ではベプリジルは中止されたが、残りの 3 例ではベプリジルの投与は低用量（50～100 mg）で継続され、QT 間隔は正常化した。肝機能障害が 3 例で認められた。この 3 例ではベプリジルが中止されると肝機能は正常化した。

考察

主要な結果

本後ろ向き試験の主要な結果は以下のとおりである。ベプリジルと RAS-I を併用投与した患者はベプリジル単独を投与した患者よりも SR を維持する可能性が高かった。ベプリジルと RAS-I の併用は左室機能不全患者（LVEF が 50%未満）の AF 再発予防に有効であった。QT 間隔を注意深く観察する条件であれば、ベプリジルは左室機能不全に対して有用で安全であった。

ベプリジルによるSR維持

ベプリジルは抗狭心症薬として当初開発されたが、ナトリウム、カリウム、カルシウムチャネルなどのいくつかのイオンチャネルを遮断する[10-13]。特に、そのカリウムチャネル遮断作用が活動電位を延長し、これがアミオダロンの作用と同様にAFにおいて抗不整脈作用を引き起こすと予想される。SR維持の機序はいまだ明らかでないが、ベプリジルは心房の短期的なリモデリングを予防するだけでなく、中長期的な逆リモデリングを生じさせる可能性もある[14]。本試験では、平均24ヵ月のフォローアップ期間中にベプリジルまたはカルディオバージョンによって当初回復した125例中69例（55%）でSRが維持された。86例中70例（81%）では、平均18ヵ月間のフォローアップ期間中にSRは維持された[14]。本試験はフォローアップ期間が長く、多くの左室機能不全患者が含まれていたため、SRを維持した患者割合は少なかったが、それでも今回の結果は過去の研究結果と同等である。ベプリジルの比較的強いカリウムチャネル遮断効果がQT延長を頻繁に引き起こし、その結果としてトルサード ド ポアントを起こす可能性がある[15]。我々は、ベプリジルの最大適正投与量は200 mg/日であると考え、QT間隔および血清カリウム濃度の観察を含む注意深いフォローアップを継続した。

RAS-IがAFに及ぼす効果

SR維持の機序はいまだ明らかでないが、RAS-Iは心房リモデリングを阻止する可能性がある。いくつかの報告は、ACE-IまたはARBの発揮する抗不整脈効果がAFを予防することを記述している。エナラプリルは左室機能不全患者のAF発現のリスク(78%）を著明に低下させている（SOLVD試験）[16]。トランドラプリルは急性心筋梗塞による左室機能不全患者におけるAF発現のリスクを(55%）低下させた[17]。このSR維持の機序には、心房圧を低下させて左房拡大を抑制することによってAF感受性を軽減するACE-I治療が関係している。これらの試験はレトロスペクティブ分析であった。LIFE試験では、ロサルタンの方がアテノロールと比較して初発AFを33%以上減少させたが、2剤の血圧低下は同等であった[18]。本試験は血圧を検討しなかったが、機序の重要な部分に血圧の低下が含まれている可能性がある。Val-HeFT試験ではバルサルタンが初発AFを37%減少させた[19]。ただし、これらの試験の多くはAF以外の転帰評価を目的とした無作為化試験の事後報告であった。したがって、これらのデータは多重検定の誤りやデータに由来する強調バイアスを生じやすい可能性がある。

アミオダロンとイルベサルタンを併用投与した患者の前向き研究では、アミオダロン単独を投与した患者よりも心房細動の低い再発率が示された[20]。イルベサルタンの恩恵の多くは転換後最初の2ヵ月間に現れ、この時点より後のカプラン･マイヤー曲線は平行であった。本試験では、RAS-Iの恩恵のほとんどは転換後最初の6ヵ月間に現れ、その後の2曲線もやはり平行であった。この結果は最近のある試験と類似し[17]、カルディオバージョン直後のリモデリングの重要性を示している。RAS-IがAFの発現を減少させうるいくつかの生物学的機序の候補がある。これらの試験は、RAS-Iが心房伸展を抑制する、左室拡張期圧を

低下させ続いて左房圧を低下させる、心房線維化を防ぐ、交感神経緊張を修飾する、または不応性のイオン電流を調節するなどのその他の機序を介して心房リモデリングを予防ないし修飾しうることを明らかにした。

左室機能不全患者における SR 維持

あるメタアナリシスは、ACE-I および ARB が左室機能不全ならびに臨床的心不全患者における AF の予防に有効なようであることを示した[21]。しかし、そこで評価した試験は LVEF の差を確認していなかったため、我々は患者を LVEF ごとに 4 群に分けて SR 維持を比較した。RAS-I 群の SR 維持率は LVEF に関係なく高く、LVEF が 50%未満の患者ではその他の治療群と比較して特に良好であった。

試験の限界

本試験はレトロスペクティブ分析であった。患者群の特性が異なっていた可能性があるため、本試験から RAS-I の有効性を評価するのは難しい。そのため前向き試験を現在実施中である。さらに、無症候性発作性 AF 患者ではフォローアップ期間の 2 週または 1 ヵ月受診時に SR 維持を評価することが難しい。しかし、自然停止せず 48 時間以上持続し、洞調律の回復に薬理学的または電気的転換を要した AF と定義した持続性 AF における SR 維持の評価には、このようなフォローアップはまず間違いなく適切であると考えられる。

結論

ベプリジルと RAS-I を併用投与した患者は、ベプリジルを単独投与した患者よりも AF 再発率が低かった。さらに、ベプリジルと RAS-I の併用は左室機能不全患者の AF 再発予防にも有効であった。

ナンバリング
①
心房細動に対する RAS-I の有用性

②
表 1　心房細動患者のベースライン特性

③
ベプリジル群
（56 例）
RAS-I 群
(69 例)

④
年齢（歳）
性別（男／女）
AF の期間（日数）
投薬期間（日数）
駆出率（%）
左房径（mm）
ベプリジルの投与量（mg）

⑤
連続値は±SD。*p＜0.05。
RAS-I＝レニン・アンジオテンシン系阻害薬、AF=心房細動。

⑥
ベプリジル群　　RAS-I 群
25/56 例　　44/69 例

⑦
図 1　持続性および発作性心房細動における洞調律維持
*白い棒グラフ*は洞調律維持を示し、*黒い棒グラフ*は心房細動再発を示す。
SR＝洞調律。その他の略語は表 1 のとおり。

⑧
持続性 AF（60 例）
発作性 AF（65 例）

⑨
図 2　持続性心房細動（左）および発作性心房細動（右）における洞調律維持
*白い棒グラフ*は洞調律維持を示し、*黒い棒グラフ*は心房細動再発を示す。
略語は表 1、図 1 のとおり。

①AF 無発症率（%）
②フォローアップ（日）
③ログランク検定

④

図 3　持続性心房細動が再発しなかった患者割合のカプラン･マイヤー推定量

X 軸はベプリジル投与後のフォローアップの日数（日）を示す。
略語は表 1 のとおり。

⑤

表 2　各種疾患ごとの洞調律維持。

⑥

孤立性 AF(45 例)
高血圧（52 例）
虚血性心疾患（23 例）
心不全（34 例）

略語は表 1 のとおり。

⑦

表 3　左室機能不全における洞調律維持

⑧

駆出率

⑨

左室駆出率を 4 群に分け、洞調律維持を比較した。RAS-I 群の洞調律維持は左室駆出率に関係なく高かった。特に、50%未満（左室駆出率）患者の洞調律維持はその他の群よりも高かった。
略語は表 1 のとおり。

①

QT 0.60 秒
QTc 0.59

②

図 4　心電図

*A：*ベプリジルのみ（200 mg/日）を投与された 65 歳女性患者。トルサード ド ポアントを認める前の QT 間隔は 0.60 秒であった。
*B：*直流（DC）カルディオバージョン実施例。トルサード ド ポアントが停止点であった。

血清カリウム濃度は 3.2 mEq/*l*であった。

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Combination Therapy of Renin Angiotensin System Inhibitors and Bepridil is Useful for Maintaining Sinus Rhythm in Patients With Atrial Fibrillation

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Abstract

Background. The present study evaluated the effect of treatment renin angiotensin system inhibitors (RAS-I) for maintaining sinus rhythm after conversion from persistent atrial fibrillation. As the efficacy of RAS-I in atrial fibrillation is unclear, our study evaluated conversion to and maintenance of sinus rhythm by combination therapy with RAS-I and bepridil in patients in atrial fibrillation.

Methods. Bepridil was administered to 125 consecutive patients with paroxysmal and persistent atrial fibrillations. Two groups of patients were compared: The bepridil group was treated with bepridil alone, the RAS-I group with bepridil plus angiotensin Ⅱ receptor blockers or angiotensin converting enzyme inhibitors. The primary end point was length of time to first recurrence of atrial fibrillation.

Results. Maintenance of sinus rhythm was achieved in 25 patients (45%) in the bepridil group and 44 patients (63%) in the RAS-I group (persistent and paroxysmal atrial fibrillations). The difference between the bepridil group and the RAS-I group was significant ($p < 0.05$). Maintenance of sinus rhythm was achieved in 9 of 25 patients (36%) in the bepridil group, and in 22 of 35 patients (62%) in the RAS-I group with persistent atrial fibrillation. The difference between the bepridil group and the RAS-I group was significant ($p < 0.05$). Bepridil plus RAS-I was particularly effective at preventing the recurrence of atrial fibrillation in patients with left ventricular dysfunction (left ventricular ejection fraction < 50%).

Conclusions. Combination therapy with RAS-I and bepridil may be useful for maintenance of sinus rhythm.

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Key Words

■ **Angiotensin Ⅱ (receptor blockers)** ■ **Ventricular function (left ventricular dysfunction)**
■ **Antiarrhythmia agents (antiarrhythmic therapy)**
■ **Atrial fibrillation**

INTRODUCTION

Atrial fibrillation (AF) is the most frequent form of arrhythmia in clinical practice, affecting 6% of people aged over 65 years.[1] AF is associated with increased risk of stroke, death, and heart failure.[2,3]

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Recent large trials have shown that rhythm-control therapy does not offer any prognostic advantage over rate-control therapy in patients with persistent AF.[4,5] However, some of these findings have been questioned. The clinical recurrence of AF after cardioversion results from a biological phenomenon known as remodeling which progressively and irreversibly alters the electrical and structural properties of the atrial tissue and cardiac cells.[6,7] Moreover, in the setting of heart failure or left ventricular hypertrophy, AF is associated with atrial dilation and increased fibrosis. These phenomena can result in AF becoming resistant to antiarrhythmic drugs. However, stroke and heart failure are considered preventable if AF is treated from an early stage and is cured.

Recent reports have demonstrated that bepridil showed useful conversion effects in patients with persistent and paroxysmal AF and was highly effective for maintaining sinus rhythm (SR) after pharmacological or electrical cardioversion.[8,9] Electrical and structural remodeling in the atria is important in causing recurrent persistent AF. In this regard, angiotensin II receptor blockers (ARB) and angiotensin converting enzyme inhibitors (ACE-I) prevent the promotion of AF by suppressing structural remodeling.

The present study evaluated conversion to and maintenance of SR by combination therapy with RAS-I and bepridil for paroxysmal or persistent AF.

SUBJECTS AND METHODS

Study population

Maintenance of SR and clinical characteristics were retrospectively examined. The study population consisted of 125 consecutive patients with paroxysmal or persistent AF treated with bepridil between June 1998 and July 2006. The patients were 70 men and 55 women with mean age of 66 ± 21 years. Two groups of patients were compared: in the bepridil group, bepridil was the only antiarrhythmic ($n = 56$), whereas the RAS-I group was treated with bepridil plus either ARB ($n = 40$) or ACE-I ($n = 29$). Bepridil was administered at a dose of 100–200 mg/day. Candesartan was administered at a dose of 8 mg/day (21 patients) and losartan was administered at a dose of 50 mg/day (19 patients). Enalapril was administered at a dose of 5 mg/day (15 patients) and lisinopril was administered at a dose of 10 mg/day (14 patients).

The primary end point was length of time to first recurrence of AF. In this study, paroxysmal AF was defined as self-terminating AF within 48 hr and persistent AF as non-self-terminating AF lasting more than 48 hr and requiring pharmacological or electrical conversion to restore SR. Patients with chronic AF were excluded. Patients were also excluded with acute myocardial infarction within the previous month, cardiac surgery within 3 months, hyperthyroidism, pregnancy, bronchial asthma, and sinus bradycardia. Lone AF was defined as no cardiac disease (hypertension, heart failure, ischemic heart disease, valvular disease and cardiomyopathy).

Measurements

The beginning of the follow-up for this study was considered to be the day of administration of bepridil. Conversion and maintenance of SR after pharmacological or electrical cardioversion were evaluated, with the primary end point being length of time to first recurrence of AF. Electrocardiography (ECG) parameters including heart rate, PQ interval, QT interval, and QTc were measured before and after bepridil administration. ECG was recorded at 2 weeks or 1-month follow-up visits. Transthoracic echocardiography was performed to examine left atrial dimension (LAD) and left ventricular ejection fraction (LVEF). The incidence of adverse complications was also evaluated.

Statistical analysis

Results are presented as mean ± SD. p values < 0.05 were considered statistically significant. The Kaplan-Meier method was used to analyze the time to recurrence of AF during the follow-up period.

RESULTS

Patient characteristics

The baseline characteristics of the two groups are presented in **Table 1**. Mean age did not differ significantly between the two groups: 66 ± 11 years in the bepridil group, and 67 ± 12 years in the RAS-I group. Duration of AF was 730 ± 922 days in the bepridil group, and 688 ± 812 days in the RAS-I group (NS). Duration of medication was 503 ± 412 days in the bepridil group, and 478 ± 442 days in the RAS-I group (NS). The ejection fraction was 62 ± 14% in the bepridil group, and 56 ± 12% in the RAS-I group; so was significantly higher in the bepridil group than in the RAS-I group ($p = 0.03$). No significant difference

Table 1 Baseline characteristics of patients with atrial fibrillation

	Bepridil group (n=56)	RAS-I group (n=69)
Age (yr)	66±11	67±12
Sex (male/female)	30/26	40/29
Duration of AF (day)	730±922	688±812
Duration of medicine (day)	503±412	478±442
Ejection fraction (%)	62±14*	56±12*
Left atrial dimension (mm)	42±7	45±11
Dosage of bepridil (mg)	160±52	150±49

Continuous values are±SD. *$p<0.05$.
RAS-I = renin angiotensin system inhibitor; AF = atrial fibrillation.

between the two groups was noted for LAD or bepridil dosage.

Maintenance of SR (persistent and paroxysmal AFs)

The maintenance of SR in patients with persistent AF and paroxysmal AF is presented in **Fig. 1**. White bars depict maintenance of SR and black bars demonstrate recurrence of AF. SR was maintained in 25 of 56 patients (45%) in the bepridil group, and in 44 of 69 patients (63%) in the RAS-I group. The difference between the bepridil group and the RAS-I group was significant ($p=0.05$). Maintenance of SR in patients with persistent AF is demonstrated in **Fig. 2—left**. SR was maintained in 9 of 25 patients (36%) in the bepridil group, and in 22 of 35 patients (62%) in the RAS-I group. The difference between the bepridil group and RAS-I group was significant ($p=0.04$). The maintenance of SR with paroxysmal AF is demonstrated in **Fig. 2—right**. SR was maintained in 16 of 31 patients (52%) in the bepridil group, and in 22 of 34 patients (65%) the RAS-I group.

Fig. 3 shows the Kaplan-Meier estimates of the percentage of patients remaining free from recur-

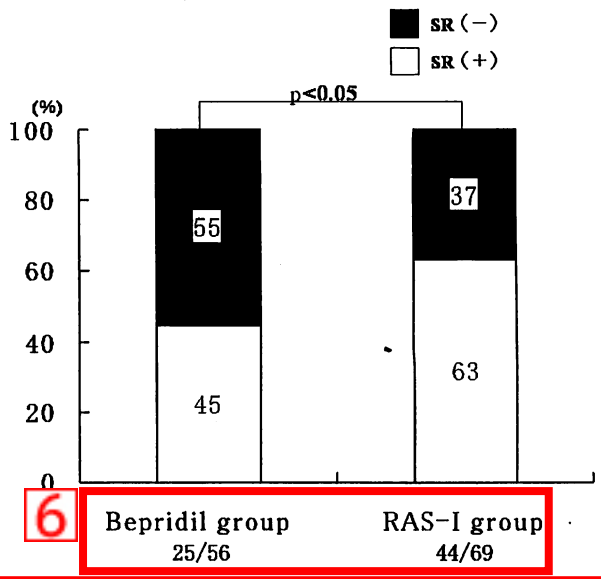

Fig. 1 Maintenance of sinus rhythm with persistent and paroxysmal atrial fibrillations
White bar shows the maintenance of sinus rhythm and *black bar* shows the recurrence of atrial fibrillation.
SR = sinus rhythm. Other abbreviation as in Table 1.

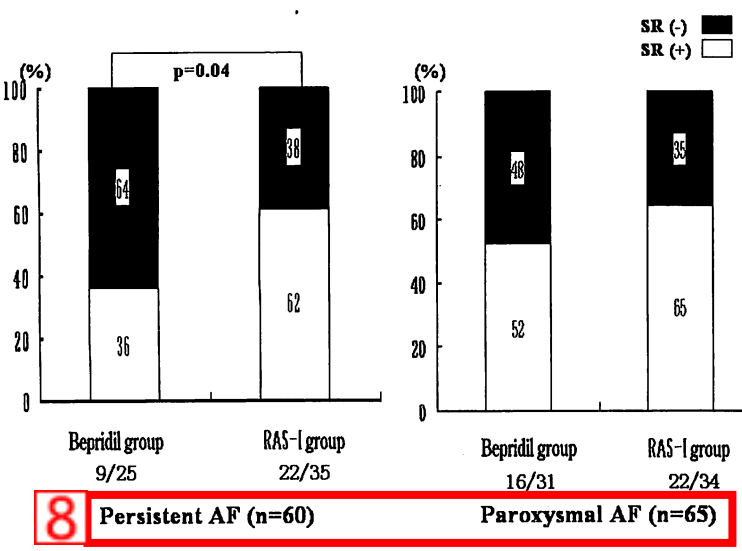

Fig. 2 Maintenance of sinus rhythm with persistent atrial fibrillation (*left*) and paroxysmal atrial fibrillation (*right*)
White bar shows the maintenance of sinus rhythm and *black bar* shows the recurrence of atrial fibrillation.
Abbreviations as in Table 1, Fig. 1.

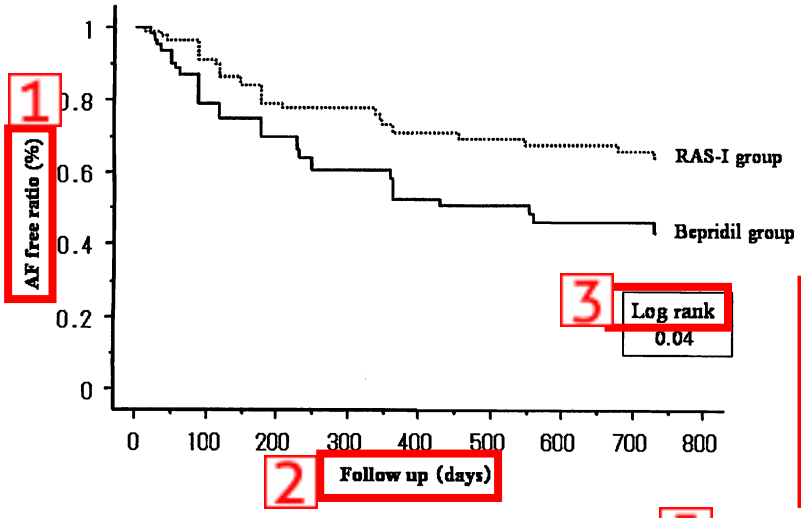

Fig. 3 Kaplan-Meier estimates of the percentage of patients remaining free from recurrence of persistent atrial fibrillation
X-axis shows days of follow up (day) after bepridil administration.
Abbreviations as in Table 1.

rence of persistent AF. The *X*-axis shows duration of follow up (days) after pharmacological or electrical conversion to restore SR. This analysis demonstrated a probability of 63% for maintaining SR for 24 months in the patients who received RAS-I, compared with 45% in those who did not ($p = 0.04$). **Table 2** shows maintenance of SR by the disease. Of those with lone AF, SR was maintained in 11 of 24 patients (46%) in the bepridil group, and 7 of 14 patients (50%) in the RAS-I group. There was no significant difference between the two groups. Of those with hypertension, SR was maintained in 4 of 12 patients (33%) in the bepridil group, and 16 of 37 patients (43%) in the RAS-I group (NS). Among those with ischemic heart disease, SR was maintained in 1 of 4 patients (25%) in the bepridil group, and 9 of 17 patients (53%) in the RAS-I group. Of those with heart failure, SR was maintained in 2 of 6 patients (33%) in the bepridil group, and 16 of 24 patients (66%) in the RAS-I group. However, in patients with heart failure and ischemic heart disease, bepridil plus RAS-I had a higher SR maintenance rate than bepridil alone.

Table 2 Maintenance of sinus rhythm in patients with various diseases

	Bepridil group	RAS-I group
Lone AF ($n=45$)	11/24 (46%)	7/14 (50%)
Hypertension ($n=52$)	4/12 (33%)	16/37 (43%)
Ischemic heart disease ($n=23$)	1/4 (25%)	9/17 (53%)
Heart failure ($n=34$)	2/6 (33%)	16/24 (66%)

Abbreviations as in Table 1.

Table 3 Maintenance of sinus rhythm with left ventricular dysfunction

Ejection fraction	Bepridil group ($n=56$)	RAS-I group ($n=69$)
60%-	13/27 (48%)	14/22 (63%)
50-59%	10/22 (45%)	11/17 (64%)
40-49%	2/7 (28%)	12/18 (66%)
-39%	0	7/12 (58%)

Left ventricular ejection fraction was divided into four groups, and compared with maintenance of sinus rhythm. In the RAS-I group, the maintenance of sinus rhythm was high regardless of left ventricular ejection fraction. Especially, the maintenance of sinus rhythm in patients with less than 50% (left ventricular ejection fraction) was higher than that of other groups.
Abbreviation as in Table 1.

Maintenance of SR with left ventricular dysfunction

The patients were divided into four groups by LVEF and SR maintenance rate was compared (**Table 3**). For patients with LVEF > 50%, no significant intergroup difference was found. However, in the RAS-I group, maintenance of SR was high regardless of LVEF.

Electrocardiography parameters

For PQ interval and the QRS duration, no significant difference was observed between the two groups before and after bepridil administration. In the bepridil group, QT interval and QTc increased

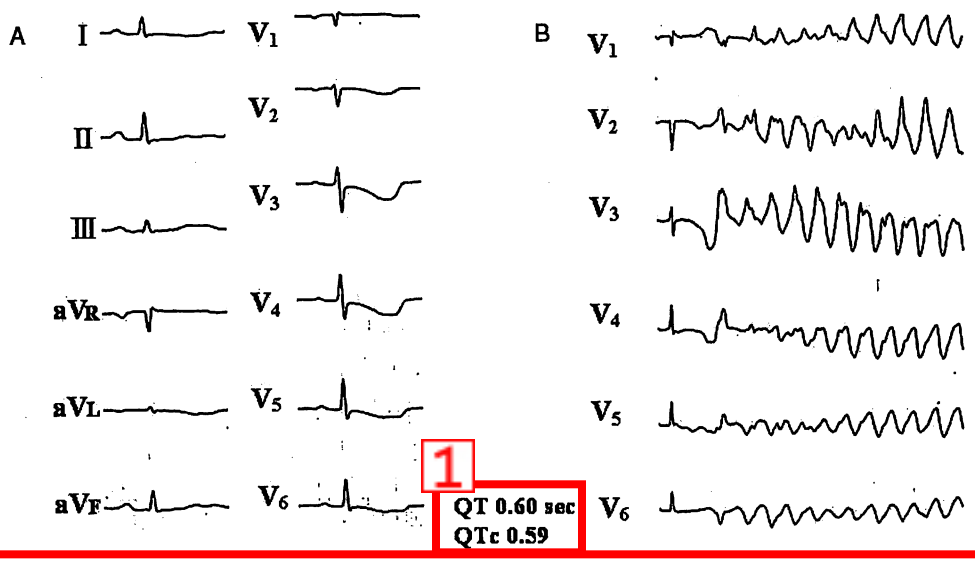

Fig. 4 Electrocardiograms
A: A 65-year-old woman patient was treated with bepridil only (200 mg/day). Before torsades de pointes was observed, QT interval was 0.60 sec.
B: We performed DC cardioversion. Torsades de pointes was termination. Serum potassium concentration was 3.2 mEq/*l*.

significantly from 0.40 to 0.43 sec ($p = 0.05$), and from 0.41 to 0.45 ($p = 0.01$). In the RAS-I group, QT interval and QTc increased significantly from 0.38 to 0.42 sec ($p = 0.01$) and QTc from 0.41 to 0.44 ($p = 0.05$).

Complications

A 65-year-old woman patient suffered torsades de pointes. She was treated with bepridil only (200 mg/day). Before torsades de pointes was observed, QT interval was 0.6 sec (**Fig. 4**). QT prolongation was observed in 6 patients. Bepridil were discontinued in 3 of these patients, but the remaining 3 continued to receive bepridil at a low dose (50−100 mg) ; QT interval was normalized in 3 cases. Liver dysfunction was observed in 3 patients ; bepridil was discontinued in these patients, and liver function normalized.

DISCUSSION

Main findings

The major findings of this retrospective study were as follows. Patients treated with bepridil plus RAS-I were more likely to remain in SR than patients treated with bepridil alone. The combination of bepridil plus RAS-I was effective at preventing the recurrence of AF in patients with left ventricular dysfunction (LVEF < 50 %). Bepridil was useful and safe in left ventricular dysfunction, providing the QT interval is carefully observed.

SR maintenance with bepridil

Bepridil was originally developed as an antianginal drug, but it blocks several ion channels, including sodium, potassium, and calcium channels.[10−13] In particular, its potassium channel blocking action prolongs action potentials, and this is expected to give rise to anti-arrhythmic properties in AF similar to those of amiodarone. The mechanism of SR maintenance remains unclear, but bepridil might prevent short-term remodeling in the atrium as well as reversing mid- to long-term remodeling.[14] In our study, SR was maintained in 69 of 125 patients (55 %) in whom it was initially restored by bepridil or cardioversion during an average follow-up of 24 months. SR was maintained over a mean follow-up of 18 months in 81 % of patients (70/86).[14] Because our study had a longer follow-up period and there were many patients with left ventricular dysfunction in our study, SR was maintained in a smaller proportion of patients. Nevertheless, our findings are comparable to those of previous studies. The relatively strong potassium channel blocking effect of bepridil often causes QT prolongation, which can result in torsades de pointes.[15] We consider that the maximum

appropriate dose of bepridil is 200 mg/day, and we continued careful follow-up including observation of QT interval and serum potassium concentration.

Effects of RAS-I on AF

The mechanism of SR maintenance remains unclear, but it is possible that RAS-I prevents atrium remodeling. Several reports describe ACE-I or ARB exerting anti-arrhythmic effects that prevent AF. Enalapril markedly reduces the risk of development of AF (by 78%) in patients with left ventricular dysfunction (SOLVD trials).[16] Trandolapril reduced the risk of development of AF (by 55%) in patients with left ventricular dysfunction due to acute myocardial infarction.[17] The mechanism of SR maintenance involves ACE-I treatment attenuating the susceptibility to AF by lowering atrial pressure and reducing left atrial enlargement. These studies were retrospective analyses. The LIFE study showed that new-onset AF was reduced by 33% more with losartan compared to atenolol, with similar blood pressure reduction for the two drugs.[18] Our study did not investigate blood pressure, but lowering of blood pressure could be an important part of the mechanism. The Val-HeFT study showed valsartan reduced new-onset AF by 37%.[19] However, the majority of these trials were post-hoc reports of randomized trials designed to assess outcomes other than AF. Thus, these data may be prone to multiple-testing errors and data-derived emphasis biases.

Prospective investigation of patients treated with amiodarone plus irbesartan found a lower rate of recurrence of atrial fibrillation than in patients treated with amiodarone alone.[20] Most of the benefit of irbesartan occurred during the first 2 months after conversion; after this point, the Kaplan-Meier curves appeared parallel. In our study, most of the benefit of RAS-I occurred during the first 6 months after conversion, after which the two curves also appeared parallel. This finding is similar to that of certain recent studies[17] and points to the importance of remodeling just after cardioversion. There are several possible biologic mechanisms by which RAS-I might reduce the development of AF. These trials demonstrated that RAS-I could prevent or modify atrial remodeling through other mechanisms, such as decreasing atrial stretch, lowering diastolic left ventricular pressure and subsequently left atrial pressure, preventing atrial fibrosis, modifying sympathetic tone, or modulating ion currents of refractoriness.

Maintenance of SR in patients with left ventricular dysfunction

A meta analysis showed that ACE-I and ARB appeared to be effective in the prevention of AF among patients with left ventricular dysfunction and clinical heart failure.[21] However, the studies evaluated did not ascertain difference in LVEF. We divided patients into four groups by LVEF and compared maintenance of SR. In the RAS-I group, SR maintenance rate was high regardless of LVEF and was particularly good in comparison to other treatment groups for patients with LVEF $< 50\%$.

Study limitations

This study was a retrospective analysis. As the patient groups may have had different characteristics, it is difficult to evaluate the efficacy of RAS-I from the present study. We are therefore currently performing a prospective study. Moreover, it is difficult to evaluate the maintenance of SR in asymptomatic patients with paroxysmal AF at 2 weeks or 1 month during follow up visits. However, in persistent AF, such follow-up is probably adequate to evaluate the maintenance of SR, because persistent AF was defined as non-self-terminating AF lasting more than 48 hr and requiring pharmacological or electrical conversion to restore sinus rhythm.

CONCLUSIONS

Patients treated with bepridil plus RAS-I had a lower rate of recurrence of AF than did those treated with bepridil alone. Moreover, bepridil plus RAS-I was effective at preventing the recurrence of AF in patients with left ventricular dysfunction.

要　約

レニン・アンジオテンシンシステム拮抗薬とベプリジルの併用は心房細動洞調律維持に有効

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背　景: 最近の論文では持続性心房細動の除細動後の洞調律維持にレニン・アンジオテンシンシステム拮抗薬(RAS-I)が有効であると報告されている．ただ，心房細動に対するRAS-Iの有効性は明らかでない．今回我々はベプリジルとRAS-Iの併用が心房細動の洞調律維持に有効かどうか検討した．

方　法: 対象はベプリジルを内服している125例の発作性心房細動，持続性心房細動の患者である．ベプリジル単独群(56例)とベプリジルとRAS-I併用群(69例)の2群に分けて検討した．内服後の洞調律維持により評価した．

結　果: 全症例のうちベプリジル単独群では56例中25例(45%)で洞調律維持が可能であった．RAS-I併用群では69例中44例(63%)で洞調律維持が可能であり，RAS-I併用群のほうで有意に洞調律維持が可能であった($p<0.05$)．持続性心房細動ではベプリジル単独群で25例中9例(36%)で洞調律維持が可能であった．RAS-I併用群では35例中22例(62%)で洞調律維持が可能であり，RAS-I併用群のほうで有意に洞調律維持が可能であった($p<0.05$)．有意差は認められなかったが，心機能低下例(左室駆出率<50%)においてRAS-I併用群のほうが洞調律維持がよかった．

結　論: ベプリジルとRAS-Iの併用は，持続性心房細動の除細動後の洞調律維持に有効であった．

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