J Cardiol 2007 Dec; 50(6): 343–350

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

Mitsuharu KAWAMURA, MD
Hiroyuki ITO, MD
Tatsuya ONUKI, MD
Fumito MIYOSHI, MD
Yoshino MINOURA, MD
Taku ASANO, MD
Kaoru TANNO, MD, FJCC
Youichi KOBAYASHI, MD

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.

J Cardiol 2007 Dec; 50(6): 343–350

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]

昭和大学医学部 第三内科: 〒142−8666 東京都品川区旗の台 1−5−8
The Third Department of Internal Medicine, Showa University School of Medicine, Tokyo
Address for correspondence: KAWAMURA M, MD, The Third Department of Internal Medicine, Showa University School of Medicine, Hatanodai 1−5−8, Shinagawa-ku, Tokyo 142−8666; E-mail: mitsu-0709@fiberbit.net
Manuscript received May 29, 2007; revised August 23, 2007; accepted August 29, 2007

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-

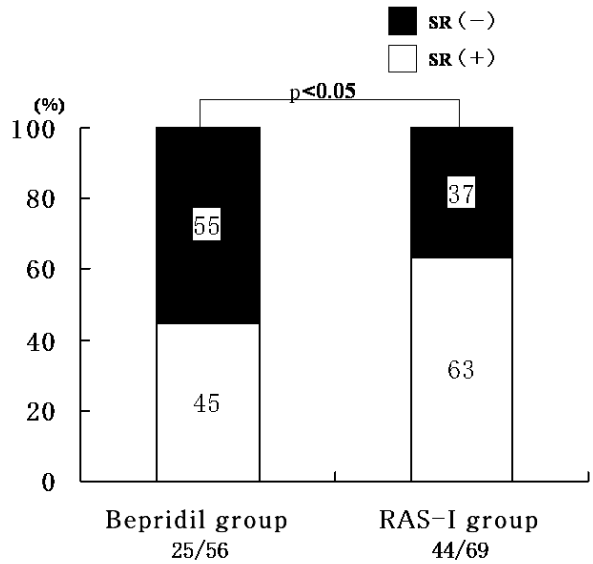

Fig. 1 Maintenance of sinus rhythm with persistent and paroxysmal atrial fibrillations
White bar shows the maintenance of sinus rhythm and *black bar* shows the recurrence of atrial fibrillation.
SR = sinus rhythm. Other abbreviation as in Table 1.

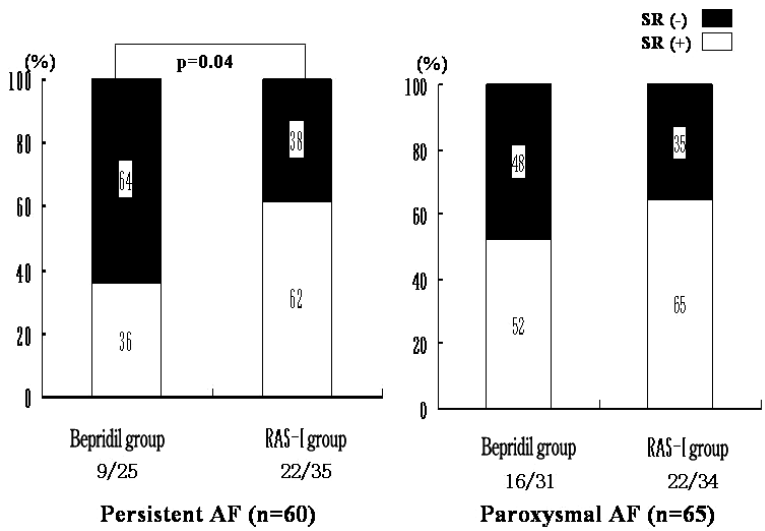

Fig. 2 Maintenance of sinus rhythm with persistent atrial fibrillation (*left*) and paroxysmal atrial fibrillation (*right*)
White bar shows the maintenance of sinus rhythm and *black bar* shows the recurrence of atrial fibrillation.
Abbreviations as in Table 1, Fig. 1.

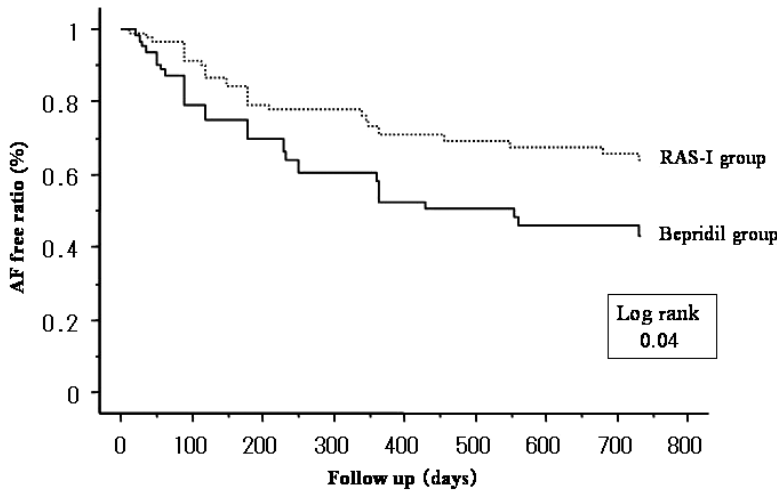

Fig. 3 Kaplan-Meier estimates of the percentage of patients remaining free from recurrence of persistent atrial fibrillation
X-axis shows days of follow up (day) after bepridil administration.
Abbreviations as in Table 1.

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

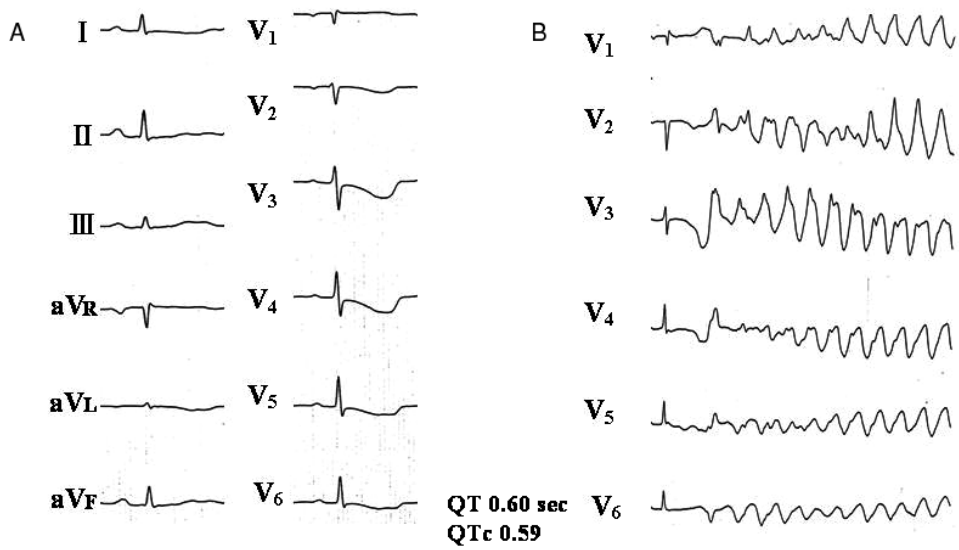

Fig. 4 Electrocardiograms

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

河村　光晴　伊藤　啓之　小貫　龍也　三好　史人
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．

J Cardiol 2007 Dec; 50(6): 343–350

References

1) Kannel WB, Abbott RD, Savage DD, McNamra PM: Epidemiologic features of atrial fibrillation : The Framingham study. N Engl J Med 1982; **306**: 1018−1022
2) Kannel WB, Wolf PA, Benjamin EJ, Levy D: Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: Population-based estimates. Am J Cardiol 1998; **82**: 2N−9N
3) Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ: Epidemiology and natural history of atrial fibrillation: Clinical implications. J Am Coll Cardiol 2001; **37**: 371−378
4) Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators: A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; **347**: 1825−1833
5) Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ; Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group: A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002; **347**: 1834−1840
6) Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA: Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. Circulation 1995; **92**: 1954−1968
7) Daoud EG, Marcovitz P, Knight BP, Goyal R, Man KC, Strickberger SA, Armstrong WF, Morady F: Short-term effect of atrial fibrillation on atrial contractile function in humans. Circulation 1999; **99**: 3024−3027
8) Fujiki A, Tsuneda T, Sugao M, Mizumaki K, Inoue H: Usefulness and safety of bepridil in converting persistent atrial fibrillation to sinus rhythm. Am J Cardiol 2003; **92**: 472−475
9) Yoshida T, Niwano S, Inuo K, Saito J, Kojima J, Ikeda K, Hara H, Izumi T: Evaluation of the effect of bepridil on paroxysmal atrial fibrillation: Relationship between efficacy and the f-f interval in surface ECG recordings. Circ J 2003; **67**: 11−15
10) DiBianco R, Alpert J, Katz RJ, Spann J, Chesler E, Ferri DP, Larca LJ, Costello RB, Gore JM, Eisenman MJ: Bepridil for chronic stable angina pectoris: Results of a prospective multicenter, placebo-controlled, dose-ranging study in 77 patients. Am J Cardiol 1984; **53**: 35−41
11) Anno T, Furuta T, Itoh M, Kodama I, Toyama J, Yamada K: Electromechanical effects of bepridil on rabbit isolated hearts. Br J Phamacol 1984; **81**: 41−47
12) Wang JC, Kiyosue T, Kiriyama K, Arita M: Bepridil differentially inhibits two delayed rectifier K^+ currents, I_{kr} and I_{ks}, in guinea-pig ventricular myocytes. Br J Phamacol 1999; **128**: 1733−1738
13) Harder DR, Sperelakis N: Bepridil blockade of Ca^{2+}-dependent action potentials in vascular smooth muscle of

dog coronary artery. J Cardiovasc Pharmacol 1981; **3**: 906−914
14) Nakazato Y, Yasuda M, Sasaki A, Iida Y, Kawano S, Nakazato K, Tokano T, Mineda Y, Sumiyoshi M, Nakata Y, Daida H: Conversion and maintenance of sinus rhythm by bepridil in patients with persistent atrial fibrillation. Circ J 2005; **69**: 44−48
15) Yasuda M, Nakazato Y, Sasaki A, Kawano Y, Nakazato K, Tokano T, Daida H: Clinical evaluation of adverse effects during bepridil administration atrial fibrillation and flutter. Circ J 2006; **70**: 662−666
16) Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, Guerra PG, Ducharme A: Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the Studies Of Left Ventricular Dysfunction (SOLVD) trials. Circulation 2003; **107**: 2926−2931
17) Pedersen OD, Bagger H, Kober L, Pedersen C: Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. Circulation 1999; **100**: 376−380
18) Wachtell K, Lehto M, Gerdts E, Olsen MH, Hornestam B, Dahlöf B, Ibsen H, Julius S, Kjeldsen SE, Lindholm LH, Nieminen MS, Devereux RB: Angiotensin Ⅱ receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: The Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 2005; **45**: 712−719
19) Maggioni AP, Latini R, Carson PE, Singh SN, Barlera S, Glazer R, Masson S, Ceré E, Tognoni G, Cohn JN; Val-HeFT Investigators: Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: Results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 2005; **149**: 548−557
20) Madrid AH, Bueno MG, Rebollo JM, Marín I, Peña G, Bernal E, Rodriguez A, Cano L, Cano JM, Cabeza P, Moro C: Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation: A prospective and randomized study. Circulation 2002; **106**: 331−336
21) Healey JS, Baranchuk A, Crystal E, Morillo CA, Garfinkle M, Yusuf S, Connolly SJ: Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: A meta-analysis. J Am Coll Cardiol 2005; **45**: 1832−1839