Table 2. Baseline ECG Variables

	Responders (n=16)	Non-responders (n=24)	P-value
QRS duration (ms)	158±18	144±18	0.02
QRS axis			
LADEV	12 (75)	7 (29)	0.004
QRS patterns in pivotal leads			
I: R, Rs, qR (dominant leftward)	13 (81)	18 (75)	0.65
QS, rS, Qr, QR (dominant rightward)	3 (19)	6 (25)	
V1: rS, QS (dominant posterior)	14 (88)	18 (75)	0.35
R, Rs, RS, qR (dominant anterior)	2 (13)	6 (25)	

Data given as mean±SD or n (%).
ECG, electrocardiogram; LADEV, left axis deviation.

Table 3. Changes in ECG Variables After CRT

	Responders (n=16)	Non-responders (n=24)	P-value
ΔQRS (ms)	26±24	7±24	0.02
QRS axis shift			
LADEV → RADEV	11 (69)	3 (13)	<0.001
LADEV → Normal	0 (0)	1 (4)	0.42
LADEV → LADEV	1 (6)	3 (13)	0.53
QRS patterns in pivotal leads			
I: R, Rs, qR → QS, rS, Qr, QR (emergence of rightward force)	9 (56)	5 (21)	0.03
V1: rS, QS → R, Rs, RS, qR (emergence of anterior force)	12 (75)	11 (46)	0.07
Emergence of both rightward force in lead I and anterior force in V1	9 (56)	3 (13)	0.003

Data given as mean±SD or n (%).
ΔQRS, shortening of QRS duration after cardiac resynchronization therapy; RADEV, right axis deviation. Other abbreviations as in Tables 1,2.

ed according to the jet (0, none; 1, trivial; 2, mild; 3, moderate; 4, severe). Dyssymchrony was assessed by independent cardiologists who were blinded to other patient data.

CRT Device Implantation

CRT device implantation was performed transvenously. The LV lead was advanced to a lateral vein or, when it was unattainable, to a posterolateral or anterolateral vein. The right ventricular (RV) lead was implanted in the apex or septum at the discretion of the physicians. When indication for internal defibrillator existed, a combined device was implanted. CRT devices were then programmed at a standard atrioventricular delay with optimization using echocardiography. Medications were recorded immediately prior to implantation of the CRT device with titration of medications made at the discretion of the patients' outpatient physicians, who had no knowledge of this study.

Definition of CRT Responder

Patients were followed up in the device clinic at 1 month after CRT device implantation and then every 3 months. Patients were classified at 6 months as responders to CRT if they were alive and had no hospitalization for heart failure decompensation and a decrease in LV end-systolic volume by ≥15% compared with baseline assessments, as described previously.[5,11]

Statistical Analysis

Data are expressed as mean±SD for the continuous variables and as numbers and percentage for categorical variables. Comparisons of clinical characteristics and ECG variables were made using unpaired t-test in the case of continuous variables. Otherwise, a non-parametric Mann-Whitney U-test was used. Univariate and multivariate logistic regression analysis were used for identifying whether variables at baseline or after CRT were predictive of a positive response to CRT, including age, gender, etiology of heart failure, NYHA functional class, history of atrial fibrillation, LVEF, LV end-systolic volume, LV end-diastolic volume, medication, LV and RV pacing sites, presence of dyssynchrony, LV–RV delay, and ECG variables. Odds ratios (ORs) are presented with 95% confidence intervals (95% CIs). $P<0.05$ was considered statistically significant.

Results

Patient Characteristics

The subjects consisted of 30 men and 10 women with mean age 60±14 years. The underlying etiology of heart failure was ischemic heart disease in 10 patients and non-ischemic heart disease in 30 patients. At baseline, 28 patients were in NYHA functional class III and 8 patients were in class IV. Thirty-four patients had sinus rhythm and 6 patients had longstanding persistent atrial fibrillation, and QRS durations were 120–187 ms (mean 149±19 ms). The mean LVEF was 26±10%. The presence of dyssynchrony was observed in 21 patients. Implantation of the CRT device was successfully performed in all patients. A CRT device with a cardioverter defibrillator was implanted in 35 patients and a CRT pacemaker was implanted in 5 patients. The LV pacing lead was implanted in a lateral vein in 27 pa-

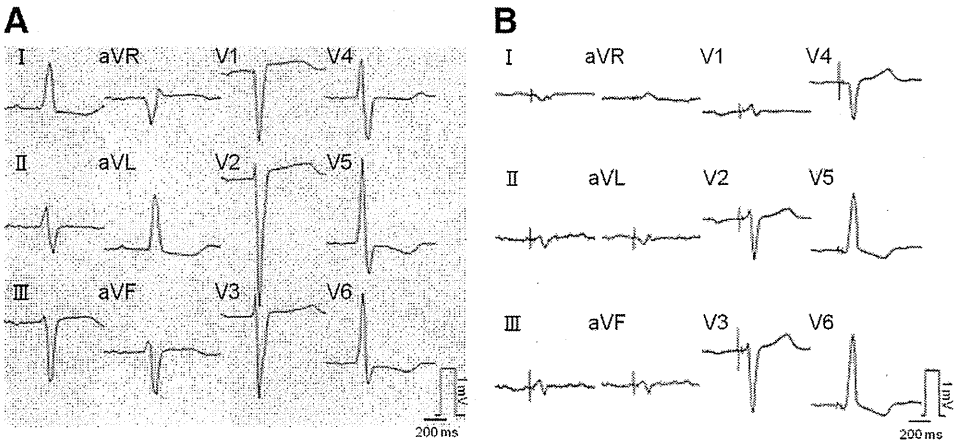

Figure 1. Representative electrocardiogram of a responder. (**A**) At baseline, QRS duration was 175ms. QRS axis was left axis deviation and QRS patterns were Rs in lead I (dominant leftward) and QS in V1 (dominant posterior). (**B**) After cardiac resynchronization therapy, QRS duration was 160ms and ΔQRS was 15ms. QRS axis changed from left axis deviation to right axis deviation and QRS patterns changed from Rs to QS in lead I (emergence of rightward force) and from QS to RS in V1 (emergence of anterior force).

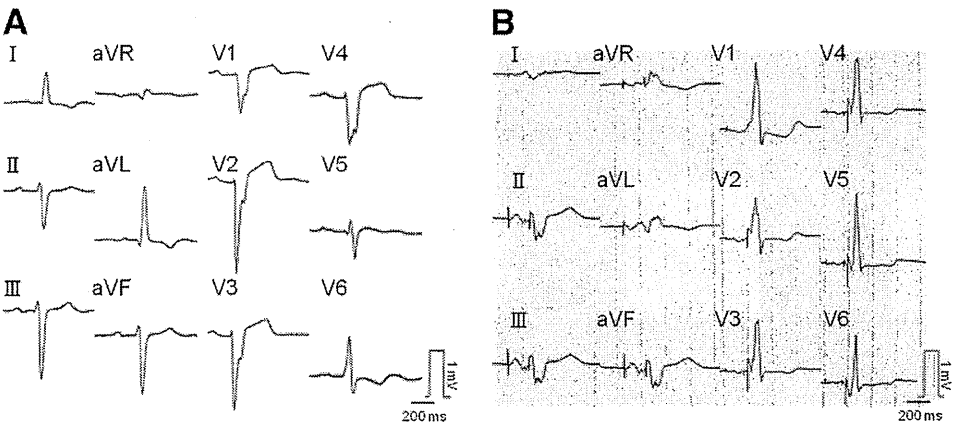

Figure 2. Representative electrocardiogram of another responder. (**A**) At baseline, QRS duration was 139ms. QRS axis was left axis deviation and QRS patterns were RS in lead I (dominant leftward) and QS in V1 (dominant posterior). (**B**) After cardiac resynchronization therapy (CRT), QRS duration was 136ms and ΔQRS was 3ms. QRS axis changed from left axis deviation to right axis deviation and QRS patterns changed from RS to QS in lead I (emergence of rightward force) and from QS to Rs in V1 (emergence of anterior force). This shows that QRS axis shift from left axis and the emergence of both rightward and anterior forces after CRT were useful to predict the response to CRT.

tients, in a posterolateral vein in 10 patients, and in an anterolateral vein in 3 patients. The RV pacing lead was implanted in the apex in 37 patients and in the septum in 3 patients.

Response to CRT

During the 6-month follow-up period, no patient died and 5 patients were hospitalized for heart failure decompensation. Among 40 patients, 16 (40%) responded to CRT based on the present criteria.

Responders vs. Non-Responders

The clinical characteristics of the responders and non-responders are summarized in **Table 1**. There were no significant differences in age, sex, etiology of heart failure, medications, NYHA functional class, LV function, presence of dyssynchrony, LV–RV delay, or pacing sites between the 2 groups. The baseline ECG variables of the 2 groups are given in **Table 2**. There were no significant differences in QRS patterns between the 2 groups, but responders were more likely to have a wider QRS duration (158±18 vs. 144±18ms, P=0.02) and a higher frequency of LADEV (75% vs. 29%, P=0.004) compared with non-responders.

The changes in ECG variables after CRT for the 2 groups are listed in **Table 3**. The shortening of QRS duration after CRT

(ΔQRS) was significantly greater in responders than in non-responders (26±24 vs. 7±24 ms, P=0.02). QRS axis shift from LADEV to RADEV was observed more frequently in responders than in non-responders (69% vs. 13%, P<0.001). In addition, the emergence of both rightward forces in lead I (R regression, Q emergence, S emergence) and anterior forces in V1 (R emergence, QS regression) was observed more frequently in responders than in non-responders (56% vs. 13%, P=0.003). Representative cases of responders are shown in **Figures 1,2**. In **Figure 1**, the shortening of QRS duration (QRS duration at baseline, 175 ms; QRS duration after CRT, 160 ms; ΔQRS, 15 ms), QRS axis shift from LADEV to RADEV, and the emergence of both rightward force in lead I and anterior force in V1 were observed after CRT. In **Figure 2**, the shortening of QRS duration was not significant (QRS duration at baseline, 139 ms; QRS duration after CRT, 136 ms; ΔQRS, 3 ms), but QRS axis shift from LADEV to RADEV and the emergence of both rightward force in lead I and anterior force in V1 were observed after CRT.

Predictors of Response to CRT

Multivariate logistic regression analysis identified the independent predictors of response to CRT at baseline or after CRT. Regarding the variables at baseline, LADEV remained as an independent predictor of response to CRT (OR, 6.24; 95% CI: 1.48–31.3, P=0.01). QRS duration, however, did not predict response to CRT. As for the variables after CRT, ΔQRS (OR, 1.05; 95% CI: 1.00–1.11, P=0.04) and QRS axis shift from LADEV to RADEV (OR, 14.5; 95% CI: 2.25–158, P=0.01) were independent predictors of response to CRT.

Receiver operating characteristic curve analysis was performed on ΔQRS to define an optimal cut-off for prediction of response to CRT. The optimal cut-off was identified as ΔQRS=7 ms, yielding a sensitivity of 81% and a specificity of 67% (**Figure 3**).

When we evaluated the baseline related variables of ΔQRS and QRS axis shift from LADEV to RADEV after CRT, ΔQRS ≥7 ms was associated with baseline QRS duration (OR, 1.07; 95% CI: 1.03–1.12, P<0.001), and QRS axis shift from LADEV to RADEV was not associated with baseline variables except for LADEV at baseline.

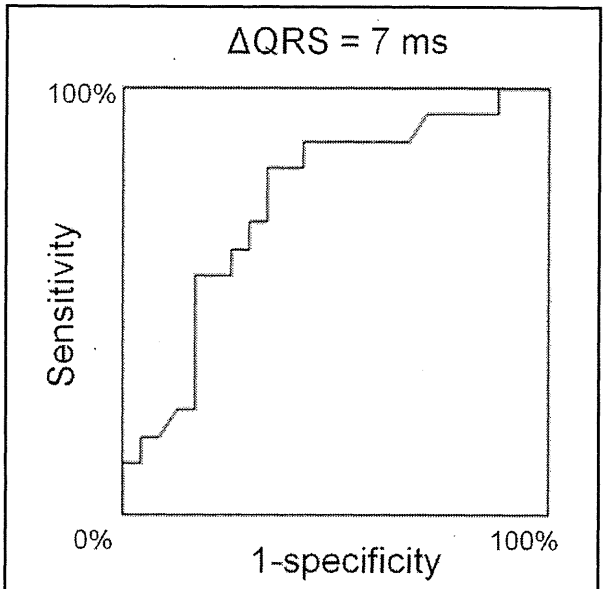

Figure 3. Receiver operating characteristic curve analysis indicating a sensitivity of 81% and a specificity of 67% at the optimal cut-off of 7 ms for ΔQRS. The area under the curve was 0.74.

Discussion

Major Findings

There were 2 major findings in the present study. First, 40% of the patients with IVCD responded to CRT at 6 months after CRT. Second, variables of surface ECG at baseline or after CRT could predict response to CRT in patients with IVCD. LADEV at baseline, or ΔQRS and QRS axis shift from LADEV to RADEV after CRT predicted the probability of response to CRT.

CRT in Patients With IVCD

There have been few studies regarding the effects of CRT in patients with IVCD. Aranda et al reported that 19 patients with CRT had improved quality of life at 6 months after CRT, but had no improvement in NYHA functional class, 6-min walk distance, exercise time, or peak oxygen uptake compared with 16 patients without CRT.[12] Rickard et al found that improvements in NYHA functional class or LVEF after CRT were significantly less in patients with IVCD compared with patients with LBBB.[13] Wokhlu et al also found that NYHA functional class responders, defined those with a decrease by 0.5 point, comprised 33% of patients with IVCD, and LVEF responders, defined as those with an increase by ≥5%, comprised 39% of those patients.[14] These previous studies suggested that patients with IVCD did not respond to CRT. In the present study, 40% of the patients with IVCD responded to CRT. This response rate was lower compared with large major trials,[1–5] and the present study therefore also suggests that patients with IVCD derive less symptomatic and echocardiographic benefits from CRT. In contrast, the present response rate was higher than the Wokhlu et al response rate.[14] Given that the present study likely had a lower prevalence of ischemic heart disease and a wider QRS duration at baseline compared with that study, these differences at baseline could influence response to CRT. In addition, the presence of dyssynchony might be related to CRT response rate in the present study.

QRS Duration and Response to CRT

In the present study, baseline QRS duration and ΔQRS were significantly greater in responders than in non-responders, and multivariate logistic regression analysis showed that ΔQRS was a predictor of response to CRT in patients with IVCD.

Auricchio et al and Kass et al reported that baseline QRS duration >150 ms was predictive of hemodynamic improvement in the acute setting.[15,16] The COMPANION trial found that benefits in terms of reduction in mortality or hospitalization were maximal in patients with QRS duration >168 ms.[3] The CARE-HF trial also noted similar benefits in patients with QRS duration >150 ms.[5] It has been suggested that markedly prolonged baseline QRS duration predicts response to CRT. Some studies, however, have shown that baseline QRS duration may not be the optimal criterion for selecting patients for CRT, and that the quantification of dyssynchrony on echocardiography appears promising.[17–20] In contrast, some studies cast doubt on the utility of echocardiographic parameters in predicting response to CRT.[11,21]

There is growing evidence that ΔQRS is an independent predictor of response to CRT. Several studies suggest that ΔQRS is a better predictor of benefits from CRT than baseline QRS

duration.[22–26] Alonso et al showed that baseline QRS duration was similar between responders and non-responders, but QRS duration after CRT differed between the 2 groups: responders had a significant reduction, whereas non-responders did not have a reduction.[22] Lecoq et al reported that 73% of patients responded to CRT, and that ΔQRS was significantly greater in responders and was the only independent predictor.[23] The recent subanalysis of the PROSPECT Study also showed that the difference between Bi-V and pre-implantation QRS duration can predict positive outcomes after CRT.[26] On the basis of the known pathophysiology of electromechanical disorders, changes in QRS duration caused by CRT may reflect the quality of electrical resynchronization and the degree of correction of electromechanical abnormalities. Thus, it is timely to revisit the usefulness of baseline QRS duration for CRT device implantation.

Variable Ventricular Activation Pattern and Response to CRT

Although the relationship between QRS duration and response to CRT has been investigated, the pattern of ventricular activation sequence on ECG has not been fully analyzed as a predictor. In a recent study, Sweeney et al found that characterization of ventricular activation sequence on the ECG anticipated the probability of response to CRT in patients with LBBB.[10] They showed that ventricular activation fusion, which was QRS axis shift from LADEV to RADEV or increases in R-wave amplitudes in V1 through V2 on the ECG during CRT, predicted LV reverse remodeling.

Patients with IVCD have delayed activation of either some or all of the right, left, or both ventricles. Patients with IVCD may have less left-sided conduction delay than LBBB and therefore may not respond to CRT. In the present study, LADEV at baseline and QRS axis shift from LADEV to RADEV after CRT, indicating left to right activation reversal, were found more frequently in responders. Moreover, on analysis of QRS patterns, the emergence of both rightward forces in lead I and anterior forces in V1, indicating both left to right and posterior to anterior activation reversal, was found in responders. Therefore, the present study suggests that patients with IVCD who have left-sided electrical LV conduction delay and reversal of ventricular activation induced by CRT have the potential for response to CRT.

ECG Predictors in Patients With LBBB and IVCD

Regarding the ECG predictors of response to CRT, the LBBB activation pattern itself is considered to be beneficial.[12–14,26,27] In previous studies, in which LBBB patients comprised all or >90% of the cohorts, it has been shown that baseline QRS duration and ΔQRS are better predictors of response to CRT.[23,24,28,29] The recent study suggested that QRS axis shift from LADEV to RADEV is strongly associated with response to CRT in patients with LBBB.[10] Little is known, however, about the ECG predictors in patients with IVCD. In the present study, we found that ΔQRS and QRS axis shift from LADEV to RADEV were associated with response to CRT. The present results in patients with IVCD are similar to those of previous studies in patients with LBBB. Thus, the differences in the CRT response rate between LBBB and IVCD may be influenced by the degree of left-side electrical LV conduction delay and change in ventricular activation after CRT.

The present study is unique because it analyzed the response to CRT in patients with IVCD, a subject for which data are very limited. To our knowledge, this is the first study to identify predictors of response to CRT in patients with IVCD. The present study has clinical importance because it focuses on surface ECG, despite its apparent simplicity. There are no previous studies that have investigated these variables on surface ECG in patients with IVCD.

Clinical Implications

The response to CRT is significantly different between patients with LBBB and patients with non-LBBB, especially IVCD. The concept of CRT is mainly to minimize LV conduction delay, which reduces contractile asynchrony and improves LV mechanics by coordinating contraction of the interventricular septum and lateral left ventricle. In some cases of IVCD, however, LV conduction delay is not present in the lateral left ventricle even though there is wide QRS.[30] We believe that the simple marker of LADEV at baseline ECG is a clue for predicting response to CRT. Patient selection could be another factor that determines response to CRT, and we should also consider QRS morphology, including type of BBB, and axis deviation, in addition to QRS duration when determining the indication for CRT.

Study Limitations

The present study had some limitations. First, it was a retrospective cohort study. Second, the fact that data were collected at a single center allowed for the introduction of treatment bias, which could influence the outcome of therapy. Third, baseline QRS duration was wide in some of the present patients, but the definition of IVCD was consistent with the consensus described in the previous studies, and the QRS duration in the present study was similar to the previous studies showing the QRS duration in patients with IVCD.[12,13,31] Fourth, assessment of IVCD and changes in ventricular activation were not performed using other methods. Finally, because of the small number of patients studied, the current findings regarding ECG predictors of response to CRT need confirmation in large prospective studies.

Conclusions

The present study confirms the midterm benefits conferred by CRT. Among 40 patients with IVCD, 16 (40%) were considered as clinical responders at 6 months after CRT. Patients with IVCD may not respond to CRT, but the surface ECG variables, such as LADEV at baseline, or ΔQRS and QRS axis shift from LADEV to RADEV after CRT, can predict the likelihood of response to CRT. These findings suggest that left-side electrical LV conduction delay at baseline and reversal of ventricular activation after CRT on surface ECG could be important to predict the response to CRT in patients with IVCD.

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References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, et al; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation: Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; **346:** 1845–1853.
2. Arya A, Haghjoo M, Dehghani MR, Alasti M, Alizadeh H, Kazemi B, et al. Effect of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in patients with an implantable cardioverter-defibrillator. *Heart Rhythm* 2005; **2:** 1094–1098.
3. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350:** 2140–2150.
4. Linde C, Leclercq C, Rex S, Garrigue S, Lavergne T, Cazeau S, et al. Long-term benefits of biventricular pacing in congestive heart failure:

Results from the Multisite stimulation in cardiomyopathy (MUSTIC) study. *J Am Coll Cardiol* 2002; **40:** 111–118.
5. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, et al; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; **352:** 1539–1549.
6. Momomura S, Tsutsui H, Sugawara Y, Ito M, Mitsuhashi T, Fukamizu S, et al. Clinical efficacy of cardiac resynchronization therapy with an implantable defibrillator in a Japanese population: Results of the MIRACLE-ICD outcome measured in Japanese indication (MOMIJI) study. *Circ J* 2012; **76:** 1911–1919.
7. Verbeek XA, Vernooy K, Peschar M, Cornelussen RN, Prinzen FW. Intra-ventricular resynchronization for optimal left ventricular function during pacing in experimental left bundle branch block. *J Am Coll Cardiol* 2003; **42:** 558–567.
8. Ypenburg C, van Bommel RJ, Borleffs CJ, Bleeker GB, Boersma E, Schalij MJ, et al. Long-term prognosis after cardiac resynchronization therapy is related to the extent of left ventricular reverse remodeling at midterm follow-up. *J Am Coll Cardiol* 2009; **53:** 483–490.
9. Strik M, Ploux S, Vernooy K, Prinzen FW. Cardiac resynchronization therapy: Refocus on the electrical substrate. *Circ J* 2011; **75:** 1297–1304.
10. Sweeney MO, van Bommel RJ, Schalij MJ, Borleffs CJ, Hellkamp AS, Bax JJ. Analysis of ventricular activation using surface electrocardiography to predict left ventricular reverse volumetric remodeling during cardiac resynchronization therapy. *Circulation* 2010; **121:** 626–634.
11. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008; **117:** 2608–2616.
12. Aranda JM, Conti JB, Johnson JW, Petersen-Stejskal S, Curtis AB. Cardiac resynchronization therapy in patients with heart failure and conduction abnormalities other than left bundle branch-block: Analysis of the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). *Clin Cardiol* 2004; **27:** 678–682.
13. Rickard J, Kumbhani DJ, Gorodeski EZ, Baranowski B, Wazni O, Martin DO, et al. Cardiac resynchronization therapy in non-left bundle branch block morphologies. *Pacing Clin Electrophysiol* 2010; **33:** 590–595.
14. Wokhlu A, Rea RF, Asivatham SJ, Webster T, Brooke K, Hodge DO, et al. Upgrade and de novo cardiac resynchronization therapy: Impact of paced or intrinsic QRS morphology on outcomes and survival. *Heart Rhythm* 2009; **6:** 1439–1447.
15. Auricchio A, Stellbrink C, Block M, Sack S, Vogt J, Bakker P, et al. The effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. *Circulation* 1999; **99:** 2993–3001.
16. Kass DA, Chen CH, Curry C, Talbot M, Berger R, Fetics B, et al. Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. *Circulation* 1999; **99:** 1567–1573.
17. Mollema SA, Bleeker GB, van der Wall EE, Schalij MJ, Bax JJ. Usefulness of QRS duration to predict response to cardiac resynchronization therapy in patients with end-stage heart failure. *Am J Cardiol* 2007; **100:** 1665–1670.
18. Pitzalis MV, Iacoviello M, Romito R, Guida P, De Tommasi E, Luzzi G, et al. Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. *J Am Coll Cardiol* 2005; **45:** 65–69.
19. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002; **105:** 438–445.
20. Sakamaki F, Seo Y, Ishizu T, Yanaka S, Atsumi A, Yamamoto M, et al. Tissue Doppler imaging dyssynchrony parameter derived from the myocardial active wall motion improves prediction of responders for cardiac resynchronization therapy. *Circ J* 2012; **76:** 689–697.
21. Seo Y, Ito H, Nakatani S, Takami M, Naito S, Shiga T, et al. The role of echocardiography in predicting responders to cardiac resynchronization therapy. *Circ J* 2011; **75:** 1156–1163.
22. Alonso C, Leclercq C, Victor F, Mansour H, de Place C, Pavin D, et al. Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. *Am J Cardiol* 1999; **84:** 1417–1421.
23. Lecoq G, Leclercq C, Leray E, Crocq C, Alonso C, de Place C, et al. Clinical and electrocardiographic predictors of a positive response to cardiac resynchronization therapy in advanced heart failure. *Eur Heart J* 2005; **26:** 1094–1100.
24. Molhoek SG, Van Erven L, Bootsma M, Steendijk P, Van Der Wall EE, Schalij MJ. QRS duration and shortening to predict clinical response to cardiac resynchronization therapy in patients with end-stage heart failure. *Pacing Clin Electrophysiol* 2004; **27:** 308–313.
25. Bonakdar HR, Jorat MV, Fazelifar AF, Alizadeh A, Givtaj N, Sameie N, et al. Prediction of response to cardiac resynchronization therapy using simple electrocardiographic and echocardiographic tools. *Europace* 2009; **11:** 1330–1337.
26. Hsing JM, Selzman KA, Leclercq C, Pires LA, McLaughlin MG, McRae SE, et al. Paced left ventricular QRS width and ECG parameters predict outcomes after cardiac resynchronization therapy: PROSPECT-ECG substudy. *Circ Arrhythm Electrophysiol* 2011; **4:** 851–857.
27. Auricchio A, Prinzen FW. Non-responders to cardiac resynchronization therapy: The magnitude of the problem and the issues. *Circ J* 2011; **75:** 521–527.
28. Yeim S, Bordachar P, Reuter S, Laborderie J, O'Neill MD, Lafittle S, et al. Predictors of a positive response to biventricular pacing in patients with severe heart failure and ventricular conduction delay. *Pacing Clin Electrophysiol* 2007; **30:** 970–975.
29. Dupont M, Rickard J, Baranowski B, Varma N, Dresing T, Gabi A, et al. Differential response to cardiac resynchronization therapy and clinical outcomes according to QRS morphology and QRS duration. *J Am Coll Cardiol* 2012; **60:** 592–598.
30. Ploux S, Lumens J, Whinnett Z, Montaudon M, Strom M, Ramanathan C, et al. Noninvasive electrocardiographic mapping to improve patient selection for cardiac resynchronization therapy: Beyond QRS duration and left bundle branch block morphology. *J Am Coll Cardiol* 2013; **61:** 2435–2443.
31. Perrin MJ, Green MS, Redpath CJ, Nery PB, Keren A, Beanlands RS, et al. Greater response to cardiac resynchronization therapy in patients with true complete left bundle branch block: A PREDICT substudy. *Europace* 2012; **14:** 690–695.

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RAPID COMMUNICATION

Appropriate Duration of Driving Restrictions After Inappropriate Therapy From Implantable Cardiac Shock Devices

– Interim Analysis of the Nippon Storm Study –

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Background: Little is known regarding the appropriate duration for driving restrictions after inappropriate implantable cardiac shock device (ICSD) therapy.

Methods and Results: We evaluated the Nippon Storm Study data, and found that inappropriate ICSD therapy occurred in 114 (7.6%) patients during a median follow-up of 464 days. Among those patients, 25 experienced further inappropriate ICSD therapy during a subsequent median follow-up of 380 days. Time-dependent recurrence of inappropriate ICSD therapy occurred in 19 (76%) patients within 180 days.

Conclusions: The interval for driving restrictions after inappropriate ICSD therapy can be reduced. (*Circ J* 2014; **78:** 1989–1991)

Key Words: Cardiac resynchronization therapy; Driving restriction; Implantable cardioverter defibrillator

Implantable cardiac shock devices (ICSDs), including implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy devices with a defibrillator (CRT-Ds), have become an established therapeutic option for reducing the risk of sudden cardiac death.[1–5] With the increase in both the implantation of an ICD and CRT-D, the number of patients with an ICSD who drive a vehicle has grown. In 2003, a Joint Committee of the Japanese Circulation Society, Japanese Heart Rhythm Society and Japanese Association for Thoracic Surgery published a statement regarding the driving restrictions for patients suffering from syncope caused by a cardiac arrhythmia,[6] and patients were advised not to drive for 12 months after inappropriate ICSD therapy. Because of recent advances in detection algorithms, the occurrence of inappropriate shock therapies has decreased. However, sufficient data concerning the incidence of inappropriate ICSD therapy is lacking for a large Japanese population.

The purpose of this study was to investigate the incidence of both the first and subsequent inappropriate ICSD therapy, and to propose the appropriate duration for driving restrictions after inappropriate ICSD therapy in Japanese patients with an ICSD.

Methods

The details of the overall study design of the Nippon Storm Study have been published.[7] Briefly, patient registration was conducted from 48 Japanese ICSD centers (**Appendix**), using a web site registration (JCDTR: Japanese cardiac defibrillator therapy registration). The clinical background of the eligible patients was collected. All centers followed the consensus guidelines for implantation of an ICSD. We performed an interim analysis of the Nippon Storm Study regarding inappropriate ICSD therapy, which includes antitachycardia pacing and/or shocks. Follow-up data, including the incidence of a second

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Table. Baseline Characteristics of the Registered Patients Undergoing Implantation of an ICSD (n=1,570)

Clinical characteristics	
Age, years	62±14
Sex, male (%)	1,223 (78)
Indication for ICSD (%)	
Primary prevention	735 (47)
Secondary prevention	835 (53)
Type of ICSD (%)	
ICD	1,064 (68)
CRT-D	506 (32)
Etiology of underlying heart disease (%)	
Ischemic heart disease	493 (31)
Dilated cardiomyopathy	357 (23)
Hypertrophic cardiomyopathy	205 (13)
Brugada syndrome	142 (9)
Arrhythmogenic RV cardiomyopathy	28 (2)
Long QT syndrome	25 (2)
Other	320 (20)
NYHA classification (%)	
I	648 (41)
II	498 (32)
III	371 (24)
IV	53 (3)
LVEF (%)	43±19

CRT-D, cardiac resynchronization therapy devices with defibrillator; ICD, implantable cardioverter defibrillator; ICSD, implantable cardiac shock device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; RV, right ventricular.

inappropriate ICSD therapy, were also collected.

Statistical Analysis

The results are expressed as frequencies and percentages for categorical variables and the median or mean±SD for numerical variables. Event-free survival curves were calculated according to the Kaplan-Meier method.

Results

Patient Registry

Data collection including the registration of new ICSD patients began in October 2010 and data accumulation for the Registry was terminated in July 2012. A total of 1,570 patients were enrolled.

Baseline Characteristics of Registered Patients

The baseline characteristics of the 1,570 ICSD patients are outlined in **Table**. At the time of the implantation, the mean age was 62±14 years. A total of 1,223 (78%) study subjects were male. As for the indications for an ICSD, 735 (47%) of the study subjects received an ICSD for primary prevention and 835 (53%) for secondary prevention. An ICD was implanted in 1,064 (68%) patients and CRT-D applied to 506 (32%). Regarding the underlying heart disease, 493 (31%) patients with ischemic heart disease and 357 (23%) with dilated cardiomyopathy were included. The mean left ventricular ejection fraction was 43±19%.

Incidence of Inappropriate ICSD Therapy

Of the 1,570 patients, follow-up data were available for 1,504; 66 enrolled patients were lost to follow-up before their first

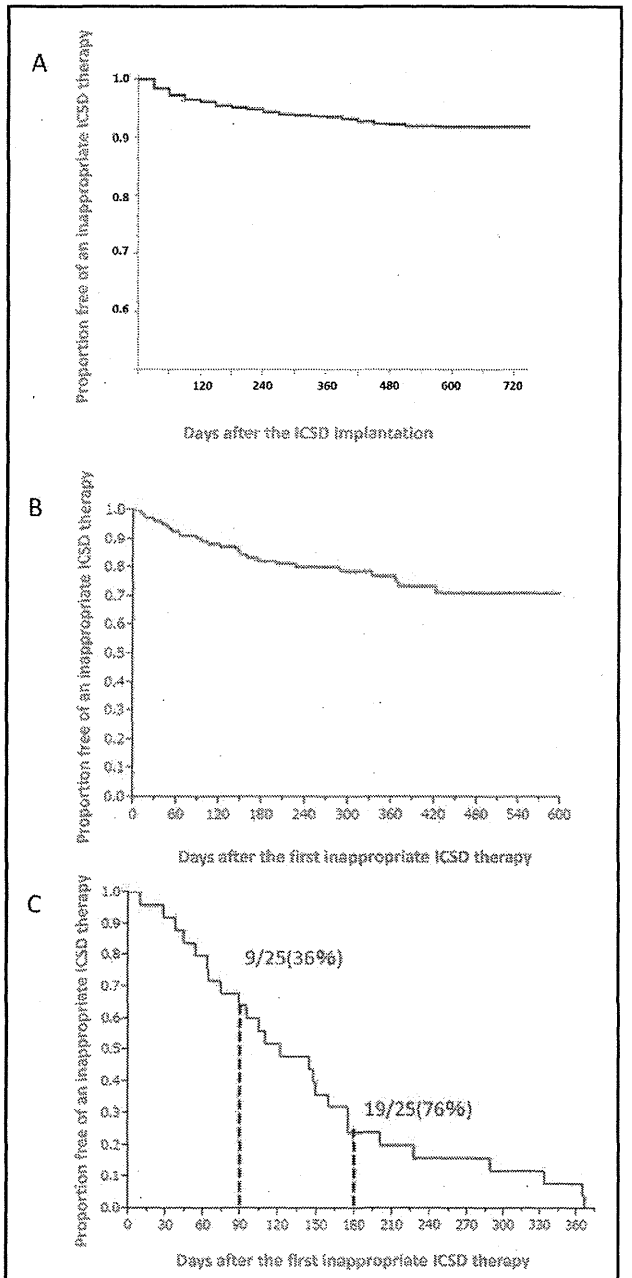

Figure. (**A**) Cumulative free probability of inappropriate ICSD therapy. The annual incidence of the first inappropriate ICSD therapy was 6.7%. (**B**) Cumulative free probability of a second inappropriate ICSD therapy. Among 114 ICSD patients with an inappropriate therapy, 25 patients experienced recurrence during a subsequent median follow-up of 380 days. (**C**) Time-dependent recurrence of an inappropriate ICSD therapy. Another inappropriate ICSD therapy occurred in 9 (36%) patients within 90 days and in 19 (76%) patients within 180 days. ICSD, implantable cardiac shock device.

visit and therefore were not part of this analysis. The interim analysis of the Nippon Storm Study revealed that inappropriate ICSD therapy occurred in 114 (7.6%) patients during a mean follow-up of 467±169 days (**Figure A**). The median time to the first inappropriate ICSD therapy was 108 days (interquartile range, 43–234 days). The annual incidence of the first inappropriate ICSD therapy in this cohort of 1,504 patients was

6.7%. Shock deliveries induced neither fatal arrhythmia nor hemodynamic incapacitation. Atrial fibrillation or atrial tachycardia was the most common trigger for inappropriate therapy (**Figure S1A**); 62 (55%) patients received only antitachycardia pacing and inappropriate shocks occurred in 52 (45%) of them (**Figure S1B**).

Recurrence of Inappropriate ICSD Therapy

Among the 114 patients with a first inappropriate ICSD therapy, 25 (22%) received a second inappropriate ICSD therapy during a mean follow-up of 380±194 days (**Figure B**). The time-dependent recurrence of inappropriate ICSD therapy was within 90 days in 9 (36%) patients and within 180 days in 19 (76%) (**Figure C**).

Discussion

Several studies have investigated the risk associated with driving for patients with an ICSD[8–10] and based on those reports, guidelines for driving restrictions in patients with an ICSD have been published in some countries.[11,12] The Consensus Statement published by the European Heart Rhythm Association recommends driving restrictions for 6 months after inappropriate ICSD therapy,[11] whereas in the United States, the duration of he driving restriction after inappropriate ICSD therapy is not mentioned specifically, but patients are recommended not to resume driving until the cause of the inappropriate therapy is corrected.[12] The present study revealed that the time-dependent recurrence of inappropriate ICSD therapy was within 90 days in 9 (36%) patients and within 180 days in 19 (76%) patients. Based on that data, the annual risk of recurrent inappropriate ICSD therapy is calculated as 19.3% with a driving restriction of 90 days after inappropriate ICSD therapy and 13.6% with a driving restriction of 180 days after inappropriate ICSD therapy. According to several Western guidelines,[11,13] private automobile drivers with a 22% or lower risk of "sustaining an annual risk of sudden cardiac incapacitation (SCI)" should be allowed to drive. Even if all the inappropriate ICSD therapies lead to an SCI, this level of yearly risk of inappropriate ICSD therapy is considered to be within a socially acceptable level. Moreover, on the assumption that ICSD patients drive for 1 h every day, the annual traffic accident rate because of inappropriate ICSD therapies is presumed to be 0.85% with driving restriction of 180 days and 1.21% with 90-day restriction after inappropriate ICSD therapy even if all the inappropriate ICSD therapies lead to an SCI. The former value is less than the Japanese annual traffic accident rate in 2010 of 0.90%.[14]

Conclusions

The interim analysis of the Nippon Strom Study revealed that driving restrictions after an inappropriate ICSD therapy can be reduced.

Acknowledgments

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Disclosures

This manuscript represents original work that has not been published and is not being considered for publication elsewhere in whole or in part in any language except as an abstract. All co-authors have read and approved the submission of the manuscript.

Conflict of Interests and Statement

There was no financial support from a specific company for this study except from the Japan Arrhythmia Device Industry Association (JADIA) or any conflict of interest, and no specific unapproved usage of any compound or product occurred.

References

1. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; **352:** 225–237.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350:** 2140–2150.
3. Moss AJ. What we have learned from the family of multicenter automatic defibrillator implantation trials. *Circ J* 2010; **74:** 1038–1041.
4. Miyoshi T, Kamiya CA, Katsuragi S, Ueda H, Kobayashi Y, Horiuchi C, et al. Safety and efficacy of implantable cardioverter-defibrillator during pregnancy and after delivery. *Circ J* 2013; **77:** 1166–1170.
5. Momomura S, Tsutsui H, Sugawara Y, Ito M, Mitsuhashi T, Fukamizu S, et al; MOMIJI Study Investigators. Clinical efficacy of cardiac resynchronization therapy with an implantable defibrillator in a Japanese population: Results of the MIRACLE-ICD outcome measured in Japanese indication (MOMIJI) study. *Circ J* 2012; **76:** 1911–1919.
6. Aizawa Y, Ikeguchi S, Okabe F, Ogawa S, Kasanuki S, Katoh T, et al. Joint committee statement about driving restriction in patients with syncope related to cardiac arrhythmia. *J Arrhythmia* 2003; **19:** 502–512 (in Japanese).
7. Kurita T, Noda T, Nitta T, Furushima H, Shimizu A, Ohe T, et al. Nippon Storm Study design. *J Arrhythmia* 2012; **28:** 277–279.
8. Akiyama T, Powell JL, Mitchell LB, Ehlert FA, Baessler C. Resumption of driving after life-threatening ventricular tachyarrhythmia. *N Engl J Med* 2001; **345:** 391–397.
9. Albert CM, Rosenthal L, Calkins H, Steinberg JS, Ruskin JN, Wang P, et al; TOVA Investigators. Driving and implantable cardioverter defibrillator shocks for ventricular arrhythmias: Results from the TOVA study. *J Am Coll Cardiol* 2007; **50:** 2233–2240.
10. Kawata H, Noda T, Kurita T, Yamagata K, Yamada Y, Okamura H, et al. Clinical effect of implantable cardioverter defibrillator replacements: When should you resume driving after an implantable cardioverter defibrillator replacement? *Circ J* 2010; **74:** 2301–2307.
11. Vijgen J, Botto G, Camm J, Hiojet C, Jung W, Le Heuzey J, et al. Consensus statement of the European Heart Rhythm Association: Updated recommendations for driving by patients with implantable cardioverter defibrillators. *Europace* 2009; **11:** 1097–1107.
12. Epstein AE, Baessler CA, Curtis AB, Estes NA, Gersh BJ, Grubb B, et al. Addendum to 'Personal and Public Safety Issues Related to Arrhythmias That May Affect Consciousness: Implications for Regulation and Physician Recommendations. A medical/scientific statement from the American Heart Association and the North American Society of Pacing and Electrophysiology': Public safety issues in patients with implantable defibrillators. A Scientific statement from the American Heart Association and the Heart Rhythm Society. *Circulation* 2007; **115:** 1170–1176.
13. Simpson C, Dorian P, Gupta A, Hamilton R, Hart S, Hoffmaster B, et al. Canadian Cardiovascular Society Consensus Conference: Assessment of the cardiac patient for fitness to drive: Drive subgroup executive summary. *Can J Cardiol* 2004; **20:** 1314–1320.
14. National Police Agency [Japan]. Annual report for traffic road accidents in 2010. www.npa.go.jp (accessed May 10, 2014).

Supplementary Files

Supplementary File 1

Appendix

Figure S1. (A) Cause of inappropriate ICSD therapy.

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Original Article

Efficacy and safety of novel anticoagulant dabigatran in clinical practice for Japanese patients with non-valvular atrial fibrillation

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ABSTRACT

Background: There is little evidence of the efficacy and safety of dabigatran in Japanese patients with non-valvular atrial fibrillation (NVAF).

Methods and Results: We evaluated 300 consecutive patients with NVAF (68 ± 11 years old, 209 men, 180 paroxysmal) who received 220 mg/day (203 patients) or 300 mg/day dabigatran (97 patients) at our hospital. Most patients (84%) had lower $CHADS_2$ (congestive heart failure, hypertension, age > 75 years, diabetes, stroke/transient ischemic attack) scores of 0 (n=60), 1 (n=114), or 2 (n=78) and lower HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition) scores of 0 (n=39), 1 (n=114), or 2 (n=103). The estimated creatinine clearance was 77 ± 24 mL/min, which was inversely correlated to age (r^2=0.48, $p < 0.0001$). Activated partial thromboplastin time was 42 ± 9 s but was not dependent on sampling time. During follow-up of 263 ± 160 days, an ischemic stroke occurred in 1 patient (0.3%), but no systemic embolism was observed. Some adverse events were reported for 70 (23%) patients, such as dyspepsia (n=42, 14%) or minor bleeding complications (n=11, 4%) resulting in discontinuation of dabigatran for 39 patients. However, no major complications were observed, and no patient died from adverse events or because of cardiovascular or stroke events.

Conclusions: Dabigatran is safe and useful for the prevention of ischemic strokes in Japanese NVAF patients, but additional care should be taken for elderly patients.

1. Introduction

The prevalence of atrial fibrillation (AF) increases with age, and Japan has one of the fastest aging populations in the world. Warfarin is highly effective in reducing the risk of stroke in patients with AF. However, warfarin is subject to several shortcomings, such as its narrow therapeutic window, need for frequent coagulation monitoring, slow onset and offset of action, and numerous drug and food interactions [1,2]. Moreover, there are no net clinical benefits of warfarin for patients with non-valvular AF (NVAF) and lower $CHADS_2$ (congestive heart failure, hypertension, age > 75 years, diabetes, stroke/transient ischemic attack) scores of 0–1 [3]. Therefore, physicians have often been hesitant to prescribe anticoagulation therapy for NVAF patients with lower $CHADS_2$ scores.

Dabigatran is a novel oral anticoagulant that is a potent, direct, competitive, and reversible inhibitor of thrombin. The RE-LY, a randomized evaluation trial of long-term anticoagulation therapy and its sub-analysis, demonstrated that dabigatran (220 or 300 mg/day) has many clinical advantages for anticoagulation in patients with NVAF as compared with warfarin [4–7]. Therefore, dabigatran has been approved in many countries for the prevention of strokes in patients with NVAF [8,9]. However, there is little clinical evidence for its use in Japanese AF patients [10–12]. Furthermore, severe bleeding complications after dabigatran administration have been reported in some Japanese patients [13]. Thus, the aim of this study was to clarify the efficacy and safety of anticoagulation with dabigatran in Japanese patients with NVAF.

2. Methods

2.1. Patients

This study involved 300 consecutive NVAF patients who received dabigatran from April 2011 to August 2012 at the Department of

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Cardiovascular Medicine of National Cerebral and Cardiovascular Center. Dabigatran was prescribed at 220 mg/day (203 patients: 68%) or 300 mg/day (97 patients: 32%). The primary physician of the patient determined the dosage. We retrospectively analyzed the clinical characteristics and short-term efficacy and safety after dabigatran therapy in these patients.

2.2. Definition of stroke, hemorrhage, and renal function

Stroke was defined as the sudden onset of a focal neurological deficit in a location consistent with the territory of a major cerebral artery, and categorized as ischemic, hemorrhagic, or unspecified. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented by imaging, surgery, or autopsy. Intracranial hemorrhage included hemorrhagic stroke and subdural or subarachnoid hemorrhage [4].

Major bleeding was defined as a decrease in hemoglobin≥2 g/dL, a transfusion of ≥2 units of whole blood or packed red blood cells, or symptomatic bleeding in a critical area or organ. Minor bleeding was defined as clinically overt bleeding that did not meet the criteria for major bleeding. Estimated creatinine clearance (eCCr) was calculated using Cockcroft–Gault equations [14].

$$\text{eCCr} = \frac{(140-\text{age}) \times \text{body weight(kg)} \times [0.85 \text{ if female}]}{72 \times \text{serum creatinine(mg/dL)}}$$

Deteriorating renal function was defined as an eCCr decrease to < 30 mL/min or at the discretion of the primary physician to discontinue dabigatran due to the eCCr decrease.

2.3. $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED Scores

We assessed stroke risk using the $CHADS_2$ and CHA_2DS_2-VASc scores [15,16]. The $CHADS_2$ score assigns 1 point each for congestive heart failure (CHF), hypertension (HT), age≥75 years, and diabetes mellitus (DM) and 2 points for a history of stroke or transient ischemic attack (TIA) [15]. The CHA_2DS_2-VASc score assigns 1 point each for CHF, HT, age 65–74 years, DM, vascular disease, female sex; and 2 points for age≥75 years, and a history of stroke or TIA [16]. The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (≥75 years), drugs/alcohol) score is used to assess the risk for cerebral and systemic bleeding, scoring HT, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile international normalized ratio, elderly (≥75 years), and drugs/alcohol (1 point each) [15]. If a HAS-BLED score is ≥3, a patient is considered to have a measurable risk of bleeding [9,17].

2.4. Radiofrequency catheter ablation procedure

The patients for whom radiofrequency (RF) catheter ablation was indicated for AF received dabigatran at least 30 days before RF catheter ablation. The Supplemental Methods describe the RF ablation procedure in detail. Periprocedural anticoagulation was based on a predetermined algorithm. Dabigatran was discontinued the evening prior to the day of RF ablation, and continuous heparin infusion of 10,000–15,000 U/day was administered until 3 h before the RF ablation procedure, and resumed after hemostasis until 24 h after the procedure. Dabigatran was resumed about 24 h after RF ablation at the same dose as that administered before the procedure.

2.5. Activated partial thromboplastin time measurement

Activated partial thromboplastin time (APTT) was measured several times after dabigatran administration. Primary physician decided when to collect blood sample. We investigated the relationship between APTT and its sampling time in each dabigatran dose. The APTT measurement was repeated at almost the same time during follow-up, and these APTT values were compared for reproducibility.

2.6. Follow-up

Patients visited our institute, another hospital, or their primary physician within 2–4 weeks of dabigatran being first prescribed; if no bleeding or other adverse events were observed, patients were followed up at least every 3 months.

2.7. Statistical analysis

Data are expressed as mean ± SD. Data were analyzed by unpaired *t*-test if they were normally distributed. The χ^2 test was used to analyze the independence of the 2 classification criteria in the qualitative data. The comparison of the APTT values of each patient was analyzed using the paired *t*-test, followed by the

Table 1
Patient characteristics.

	Dabigatran Total (n=300)	Dabigatran 220 mg/day (n=203)	Dabigatran 300 mg/day (n=97)	p-value
Age, years	68 ± 11	72 ± 8	59 ± 9	< 0.0001
≥75, n (%)	88 (29)	86 (42)	2 (2)	< 0.0001
Sex, n (M/F)	209/91	128/75	81/16	0.0003
Weight (kg)	64 ± 11	61 ± 10	70 ± 12	< 0.0001
Serum Cr (mg/dL)	0.83 ± 0.16	0.83 ± 0.17	0.83 ± 0.14	ns
eCCr (mL/min)	77 ± 24	68 ± 19	95 ± 24	< 0.0001
AF, n: (paroxysmal/persistent)	180/120	123/80	57/40	ns
Previous stroke or TIA, n (%)	41 (14)	33 (16)	8 (8)	0.06
LA diameter (mm)	41 ± 7	41 ± 7	41 ± 8	ns
Structural heart disease, n (%)	81 (27)	64 (32)	17 (18)	0.01
Congestive heart failure, n (%)	53 (18)	41 (20)	12 (12)	ns
Hypertension, n (%)	179 (60)	133 (66)	46 (47)	0.0028
Diabetes mellitus, n (%)	45 (15)	33 (16)	12 (12)	ns
Drugs for peptic ulcer, n (%)	155 (52)	102 (50)	53 (55)	ns
Concomitant use of anti-platelet agent, n (%)	27 (9)	26 (13)	1 (1)	0.0009
Previous medication use				
Warfarin, n (%)	121 (40)	89 (44)	32 (33)	0.07
Anti-platelet agent, n (%)	16 (5)	10 (5)	6 (6)	ns
Follow-up period (days)	263 ± 160	264 ± 161	259 ± 159	ns

Cr=Creatinine, AF=atrial fibrillation, LA=left atrium, TIA=transient ischemic attack, eCCr=estimated creatinine clearance, ns=not significant.

Wilcoxon signed-rank test. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Patient Characteristics

Table 1 lists the baseline characteristics of the patients in this study. The mean age was 68 ± 11 years; patients aged 70–75 years were the most numerous in the sample (Fig. 1a). There were 209 male patients. On average, the patients receiving 300 mg/day dabigatran were younger and heavier than those on 220 mg/day dabigatran were (59 ± 9 vs. 72 ± 8 years old; $p < 0.0001$, and 70 ± 12 vs. 61 ± 10 kg; $p < 0.0001$, respectively). Nearly all patients aged > 75 years (98%) received 220 mg/day dabigatran. Sixty percent ($n = 180$) of AF was paroxysmal and the remaining 40% ($n = 120$) was persistent. Forty-one patients (14%) had suffered a prior stroke or TIA.

The averaged left atrium diameter was 41 ± 7 mm. Eighty-one patients (27%) had structural heart disease such as cardiomyopathy ($n = 14$) and ischemic heart disease ($n = 21$), and 53 patients (18%) had CHF. One hundred seventy-nine patients (60%) had HT, and 45 (15%) had DM. The frequency of age≥75 years; female sex; and number of patients with structural heart disease, HT, and concomitant use of an anti-platelet agent were significantly greater in the patients on 220 mg/day dabigatran than those on 300 mg/day dabigatran were (Table 1).

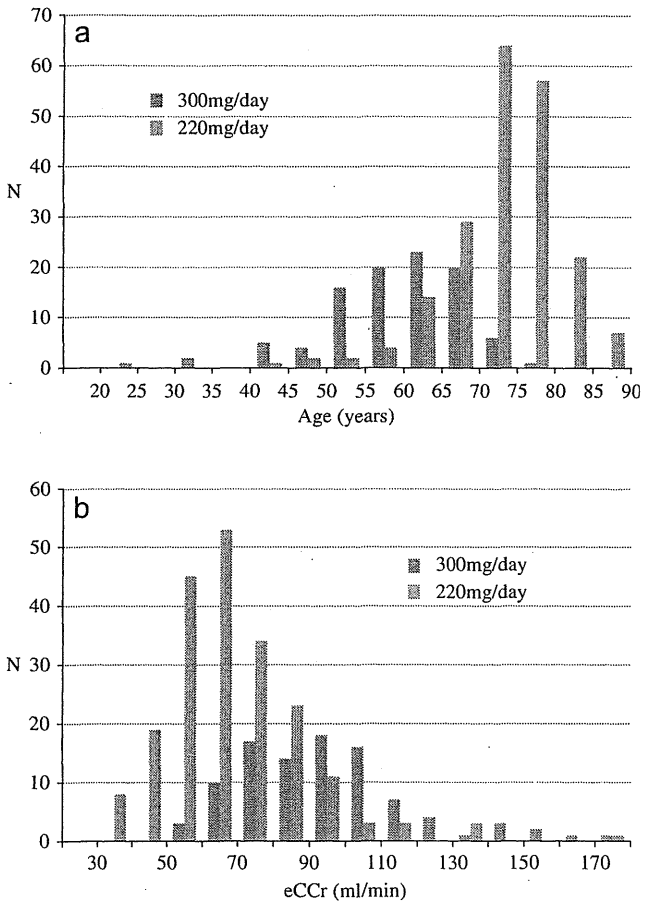

Fig. 1. (a) Relationship between age and number of patients who received dabigatran (red=300 mg/day, blue=220 mg/day). Fig. 1 and (b) Relationship between eCCr and number of patients who received dabigatran (red=300 mg/day, blue=220 mg/day). eCCr=estimated creatinine clearance.

One hundred twenty-one patients (40%) switched from warfarin to dabigatran and 16 patients (5%) switched from their anti-platelet agent to dabigatran for anticoagulant therapy. An anti-platelet agent was prescribed concomitantly with dabigatran in 27 patients (9%) mainly due to ischemic heart disease. The frequency of concomitant use of an anti-platelet agent was higher in elderly patients (≥75 years old) as compared with younger patients (13 of 88; 15% vs. 14 of 212; 7%, respectively; $p = 0.02$). RF catheter ablation was performed in 73 patients (24%).

Table 2 displays the distribution of the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores. The $CHADS_2$ score was 0 in 60 patients (20%), 1 in 114 (38%), 2 in 78 (26%), and ≥3 in 48 (16%); thus, the mean score was 1.5 ± 1.2. The CHA_2DS_2-VASc score was 0 in 26 patients (9%), 1 in 61 (20%), 2 in 65 (22%), and ≥3 in 148 (49%). The mean CHA_2DS_2-VASc score was 2.6 ± 1.7. The HAS-BLED score was 0 in 39 patients (13%), 1 in 114 (38%), 2 in 103 (34%), and ≥3 in 44 (15%). The mean HAS-BLED score was 1.5 ± 1.0.

The $CHADS_2$, CHA_2DS_2-VASc, and HAD-BLED scores were higher for patients receiving 220 mg/day dabigatran than those receiving 300 mg/day dabigatran.

3.2. Thromboembolic events

Ischemic stroke occurred in one 60-year-old male patient (Table 3) with persistent AF after RF ablation. The patient had received 220 mg/day dabigatran for 1 month before the RF procedure. His eCCr was 91 mL/min and his $CHADS_2$ score was 1 (DM). Vision disturbance due to left occipital lobe infarction occurred 1 day after the RF procedure. Dabigatran was increased from 220 mg/day to 300 mg/day after the event. His neurological symptoms improved during the follow-up period. No stroke events occurred in the remaining patients during follow-up of 263 ± 160 days; no patient experienced systemic embolism during the follow-up period.

3.3. Adverse events and discontinuation

Adverse events by dabigatran were observed in 70 (23%) patients (Table 3). No major complications, including intracranial hemorrhage, occurred during the follow-up period. Minor bleeding complications occurred in 11 patients (4%), including 1 patient with gastrointestinal bleeding. Forty-two (14%) patients had

Table 2
$CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores.

	Dabigatran Total (n=300)	Dabigatran 220 mg/day (n=203)	Dabigatran 300 mg/day (n=97)	p-value
$CHADS_2$ score, mean	1.5 ± 1.2	1.8 ± 1.3	0.9 ± 0.8	< 0.0001
0; n (%)	60 (20)	25 (12)	35 (36)	< 0.0001
1; n (%)	114 (38)	74 (36)	40 (41)	ns
2; n (%)	78 (26)	60 (30)	18 (19)	0.04
≥3; n (%)	48 (16)	44 (22)	4 (4)	0.0001
CHA_2DS_2-VASc score, mean	2.6 ± 1.7	3.1 ± 1.6	1.4 ± 1.2	< 0.0001
0; n (%)	26 (9)	1 (0.5)	25 (26)	< 0.0001
1, n (%)	61 (20)	27 (13)	34 (35)	< 0.0001
2; n (%)	65 (22)	47 (23)	18 (19)	ns
3; n (%)	74 (25)	59 (29)	15 (15)	0.01
4; n (%)	40 (13)	35 (17)	5 (5)	0.004
≥5; n (%)	34 (11)	34 (17)	0 (0)	< 0.0001
HAS-BLED score, mean	1.5 ± 1.0	1.9 ± 0.9	0.9 ± 0.8	< 0.0001
0, n (%)	39 (13)	5 (2)	34 (35)	< 0.0001
1; n (%)	114 (38)	70 (34)	44 (45)	0.07
2; n (%)	103 (34)	86 (42)	17 (18)	< 0.0001
≥3, n (%)	44 (15)	42 (21)	2 (2)	< 0.0001

Table 3
Thromboembolic event, adverse events, and discontinuation of dabigatran.

	Dabigatran Total (n=300)	Dabigatran 220 mg/day (n=203)	Dabigatran 300 mg/day (n=97)	p-value
Thromboembolic event, n	1 (0.3)	1 (0.5)	0 (0)	0.49
Adverse events, n (%)	70 (23)	52 (26)	18 (19)	0.18
Major bleeding, n (%)	0 (0)	0 (0)	0 (0)	–
Minor bleeding, n (%)	11 (4)	9 (4)	2 (2)	0.31
Dyspepsia, n (%)	42 (14)	32 (16)	10 (10)	0.20
Swallowing difficulty, n (%)	5 (2)	3 (1)	2 (2)	0.71
Deteriorating renal function, n (%)	4 (1)	4 (2)	0 (0)	0.16
Diarrhea, n (%)	3 (1)	2 (1)	1 (1)	0.97
Rash, n (%)	3 (1)	2 (1)	1 (1)	0.97
Itching, n (%)	2 (1)	1 (0.5)	1 (1)	0.59
Discontinuation, n (%)	65 (22)	40 (20)	25 (26)	0.23
Temporal use for RF ablation, n (%)	23 (8)	7 (3)	16 (16)	<0.0001
Side effects, n (%)	39 (13)	30 (15)	9 (9)	0.19

RF=radiofrequency.

dyspepsia such as upper abdominal pain, abdominal pain, and abdominal discomfort. None died from adverse events or cardiovascular and stroke events. There was no significant difference in the frequency of adverse events between patients receiving 220 mg/day and 300 mg/day dabigatran.

Sixty-five patients discontinued dabigatran, with 39 patients (60%) discontinuing it due to adverse events such as dyspepsia (n=21), deteriorating renal function (n=4), minor bleeding (n=3), swallowing difficulty (n=2), or rash (n=2). Due to the prolongation of APTT (65 s and 59 s each), dabigatran was discontinued for another 2 patients at the discretion of their primary physicians. Of these 41 patients, 26 (63%) subsequently switched to warfarin, 8 patients to rivaroxaban, and 4 patients to aspirin. One patient died from malignant mesothelioma during the follow-up period. The remaining 23 patients discontinued dabigatran because they used it temporarily for RF ablation. The follow-up period (dabigatran prescription period) of these 23 patients was 190 ± 92 days. There was no significant difference in the frequency of discontinuation between patients receiving 220 mg/day and 300 mg/day dabigatran.

Drugs for peptic ulcer were prescribed for 155 of the 300 patients (52%): 128 patients (43%) received a proton pump inhibitor and 17 patients (6%) received an H_2-blocker. In 42 patients with dyspepsia, drugs for peptic ulcer were prescribed in 28 patients (67%), of whom 24 received a proton pump inhibitor and 2 received an H_2-blocker. The drugs for peptic ulcer were effective in curing the dyspepsia in 9 patients (proton pump inhibitor in 8 patients, H_2-blocker in 1 patient).

3.4. Dabigatran and renal function

The averaged serum creatinine was 0.83 mg/dL, and there was no difference between patients who received 220 mg/day and 300 mg/day dabigatran. However, as the patients on 300 mg/day dabigatran were heavier and younger, their mean eCCr was higher than that in those who received 220 mg/day dabigatran (95 ± 24 vs. 68 ± 19 mL/min; p<0.0001). An eCCr<50 mL/min was observed in 26 of 203 patients (13%) who received 220 mg/day dabigatran, whereas the eCCr of all 97 patients who received 300 mg/day dabigatran was >50 mL/min (p=0.0002) (Fig. 1b).

Fig. 2 illustrates the relationship between eCCr and age, where the eCCr was inversely correlated to the age of patients (r^2=0.484, p<0.0001). The eCCr at 141 ± 125 days after dabigatran administration could be calculated again in 235 of the 300 patients. We decided to discontinue dabigatran in 3 patients because their eCCr fell to <30 mL/min after dabigatran administration (Table 4). The baseline eCCr of these 3 patients was 62.2, 38.6, and 48.8 mL/min, respectively, decreasing to 28.5, 28.3, and 29.5 mL/min, respectively, during follow-up. Another 72-year-old man discontinued dabigatran at the discretion of his primary physician because his eCCr decreased to 36.7 mL/min from 51.4 mL/min. These 4 patients had all received 220 mg/day dabigatran.

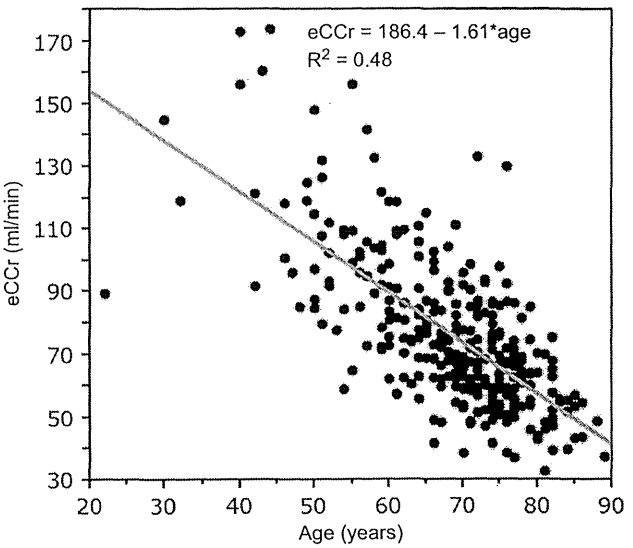

Fig. 2. Relationship between age and eCCr. The eCCr was inversely correlated to age (p<0.0001). eCCr=Estimated creatinine clearance.

Table 4
Patients for whom dabigatran was discontinued due to decrease in eCCr.

#	Age (years)	Sex	Dabigatran (mg/day)	Follow-up (days)	$CHADS_2$	eCCr (mL/min) (baseline)	eCCr (mL/min) (on dabigatran)
1	60	F	220	369	3	62.2	28.5
2	76	F	220	376	3	38.6	28.3
3	88	M	220	404	6	48.8	29.5
4	72	M	220	42	2	51.4	36.7

3.5. Dabigatran and APTT

The APTT could be evaluated in 233 patients and the mean APTT was 42 ± 9 s. There was no significant difference in mean APTT values between patients on 220 mg/day and 300 mg/day dabigatran (42 ± 9 s vs. 41 ± 9 s). Fig. 3 illustrates the relationship between the APTT and eCCr values. APTT was inversely correlated to eCCr (r^2=0.04, p=0.0087).

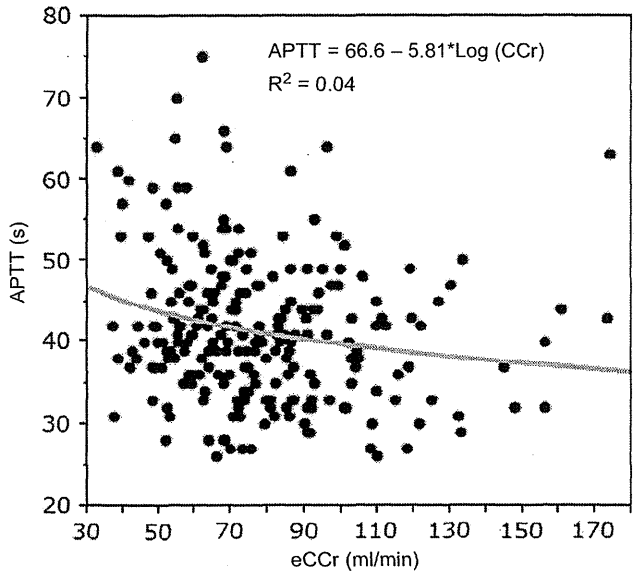

Fig. 3. Relationship between APTT values and eCCr. The APTT was inversely correlated to the eCCr. APTT=Activated partial thromboplastin time, eCCr=estimated creatinine clearance.

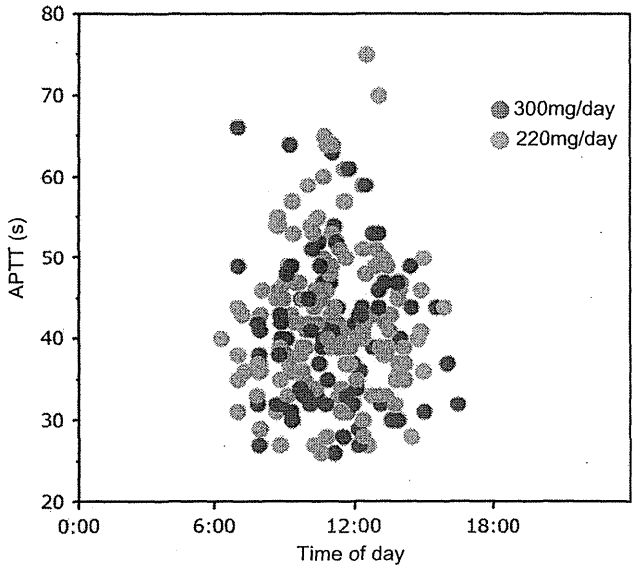

Fig. 4. Relationship between APTT values and sampling time (time of day). The APTT was not dependent on the time of day for each dabigatran dose (blue=220 mg/day, red=300 mg/day). APTT=Activated partial thromboplastin time.

Fig. 4 depicts the relationship between APTT and its sampling time at each dabigatran dose. There was a wide distribution in the APTT values among patients at each dabigatran dose, and the APTT was not dependent on the sampling time because patients were not permitted to change the time they took the dabigatran. The mean APTT measured on another day (41 ± 9 s) was almost the same as that recorded at the first use of dabigatran: 41 ± 9 s. There was no statistical difference ($p=0.41$) between the first and second APTT measurements. The day-to-day difference of the APTT values of each patient was not substantial (Supplemental Figure), indicating that the APTT values were highly reproducible.

Patients with minor bleeding events had greater APTT values as compared to those without minor bleeding events, but this was not statistically significant (mean, 48 ± 12 s vs. 41 ± 9 s; $p=0.052$).

4. Discussion

4.1. Main findings

We obtained several findings from this study. First, dabigatran is safe for the prevention of stroke in clinical practice for Japanese NVAF patients. Second, careful monitoring of laboratory data, including the eCCr, is necessary, especially in elderly patients and/or those with renal dysfunction because deteriorating renal function may occur during anticoagulation treatment using dabigatran. Third, the APTT values varied greatly but had high reproducibility; therefore, the APTT may be a suitable parameter for screening bleeding risk.

4.2. Advantages of dabigatran

Although patients with $CHADS_2$ scores of 0 or 1 face a certain degree of stroke risk, the bleeding risk with warfarin may outweigh the benefit [3]. On one hand, sub-analysis of the RE-LY indicated that dabigatran is more effective and safer for AF patients with lower CHADS2 scores (0 or 1) as compared to warfarin [5]. The European AF guidelines propose that when anticoagulation for AF is recommended, a direct thrombin inhibitor (dabigatran) or a factor Xa inhibitor should be considered based on their net clinical benefit rather than adjusted-dose warfarin for most patients with NVAF [9]. The sub-analysis of the RE-LY demonstrated that the efficacy and safety profiles of dabigatran for Japanese AF patients were almost the same as that for the entire study population in the RE-LY [10]. Based on the RE-LY, the Japanese Circulation Society recently released a statement recommending the use of dabigatran for patients with a $CHADS_2$ score of 1, whereas the use of warfarin remained within consideration for a CHADS2 score of 1 [18]. No major bleeding event occurred in this study. Therefore, dabigatran is safe for the prevention of ischemic stroke for Japanese NVAF patients in clinical practice as well.

4.3. Utility of APTT

Although it has been reported that the APTT is correlated with the anticoagulant effect of dabigatran at lower plasma concentrations, it does not denote an accurate quantitative value of the anticoagulant effect at higher concentrations [19,20]. In addition, the time to peak concentration of dabigatran is affected by factors such as age, sex, and renal function [21,22], and there is a wide distribution in the APTT values among patients receiving dabigatran, as shown in this study (Fig. 4). This study, however, demonstrated the reproducibility of the APTT values of each patient. In addition, we demonstrated that the APTT value is not greatly affected by sampling time. Although it may be difficult to use APTT as a marker of anticoagulant efficacy for dabigatran, it might be useful for screening bleeding risk among patients receiving dabigatran [11]. In this study, the APTT value was higher in patients with minor bleeding as compared with those with no bleeding. Therefore, APTT, which can be measured comparatively easily in outpatient settings, might be a useful marker for bleeding complication.

4.4. Shortcomings of dabigatran

There is no specific antidote to reverse the effects of dabigatran. Major gastrointestinal bleeding and dyspepsia were more common with dabigatran than with warfarin in the RE-LY [4]. Drugs for peptic ulcer, including proton pump inhibitors, were more frequently prescribed in this study than in the RE-LY (52% vs. 15%, respectively), and only 1 patient suffered minor gastrointestinal

bleeding in this study. Therefore, drugs for peptic ulcer may be useful for the prevention of gastrointestinal bleeding. Drugs for peptic ulcer were effective for our patients with dyspepsia to some extent, so they may also be useful for curing dyspepsia during dabigatran treatment.

4.5. The relationship between dabigatran and renal function

Dabigatran is often described as an anticoagulant that does not require routine coagulation monitoring because its pharmacokinetics are predictable [23]. However, many patients with AF are aged, and the elderly often have comorbidities such as DM, which are important risk factors for the deterioration of renal function [24]. In addition, advanced age itself is a risk factor for renal dysfunction [25]. In this study, the eCCr was inversely correlated with age (Fig. 2). Moreover, the elderly often have vascular diseases, e.g., ischemic heart disease, as comorbidities and require treatment with anti-platelet agents. Eikelboom et al. reported that the risk of bleeding increased with age, decreased CCr, and with concomitant use of anti-platelet agents [26]. In addition, gastrointestinal bleeding, which is one complication of dabigatran treatment, is not always accompanied by epigastric symptoms [27]. Therefore, fixed-dose dabigatran without monitoring may lead to a higher risk of bleeding. We recommend that laboratory data, including renal function, hematological value, and APTT, be monitored in particular in elderly patients who possess the risk factors for deterioration of renal function, such as DM and/or concomitant use of an anti-platelet agent, and/or higher HAS-BLED scores.

4.6. The relationship between dabigatran and RF ablation

There is some evidence for the efficacy and safety of dabigatran in patients undergoing RF ablation for AF. Lakkireddy et al. compared the efficacy and safety of dabigatran and warfarin in periprocedural anticoagulation in patients undergoing RF ablation for AF [28]. They reported that periprocedural use of dabigatran significantly increased the risk of thromboembolic and bleeding complications as compared with uninterrupted warfarin therapy. In contrast, Kaseno et al. reported that the periprocedural use of dabigatran was useful and safe in Japanese patients [12]. In this study, ischemic stroke occurred in 1 patient as a periprocedural complication of RF ablation. Therefore, it is necessary to investigate the efficacy and safety of dabigatran in RF ablation with a large patient sample and identify appropriate strategies for periprocedural anticoagulation.

4.7. Study limitations

We performed this study to evaluate the efficacy and safety of dabigatran in Japanese patients with NVAF; therefore, we did not compare it with warfarin. This study was retrospective and nonrandomized, and involved a small sample at a single cardiovascular center. In addition, the follow-up period was short. Further investigations are necessary to demonstrate the efficacy and safety of dabigatran. As the mean $CHADS_2$ score in this study was relatively low (1.5 ± 1.2 points), the efficacy and safety of dabigatran in clinical use are uncertain in patients with high $CHADS_2$ scores.

5. Conclusions

In clinical practice, dabigatran is useful and safe for the prevention of ischemic stroke in Japanese NVAF patients. Monitoring of laboratory data is necessary in patients receiving dabigatran, especially for elderly patients who have renal dysfunction and/or high HAS-BLED scores.

Conflict of interest statement

Drs. Shimizu and Ogawa received lecture fees from Bayer, Boehringer Ingelheim, and Sanofi. Dr. Kamakura received lecture fees from Bayer and Boehringer Ingelheim. Dr. Aiba received lecture fees from Boehringer Ingelheim. Dr. Ogawa received research funds from Bayer, and scholarship funds from Boehringer Ingelheim and Sanofi.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.joa.2013.04.010.

References

[1] Barnes GD, Froehlich JB. Anticoagulation: where we are and where we need to go. J Thromb Thrombolysis 2009;28:220–3.
[2] Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361:2342–52.
[3] Singer DE, Chang Y, Fang MC, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009;15:297–305.
[4] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
[5] Oldgren J, Alings M, Darius H, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the $CHADS_2$ score: a subgroup analysis of the RE-LY trial. Ann Intern Med 2011;155:660–7.
[6] Healey JS, Eikelboom J, Douketis J, et al. Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation 2012;126:343–8.
[7] Nagarakanti R, Ezekowitz MD, Oldgren J, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation 2011;123:131–6.
[8] Wann LS, Curtis AB, Ellenbogen KA, et al. ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on Dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2011 2011;123:1144–50.
[9] Camm AJ, Lip GY, De Caterina R, et al. focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012 2012;33:2719–47.
[10] Hori M, Connolly SJ, Ezekowitz MD, et al. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation—sub-analysis in Japanese population in RE-LY trial. Circ J 2011;75:800–5.
[11] Suzuki S, Otsuka T, Sagara K, et al. Dabigatran in clinical practice for atrial fibrillation with special reference to activated partial thromboplastin time. Circ J 2012;76:755–7.
[12] Kaseno K, Naito S, Nakamura K, et al. Efficacy and safety of periprocedural dabigatran in patients undergoing catheter ablation of atrial fibrillation. Circ J 2012;76:2337–42.
[13] Uchiyama S, Ibayashi S, Matsumoto M, et al. Dabigatran and factor Xa inhibitors for stroke prevention in patients with nonvalvular atrial fibrillation. J Stroke Cerebrovasc Dis 2012;21:165–73.
[14] Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
[15] Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
[16] Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137:263–72.
[17] Lip GY, Frison L, Halperin JL, et al. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol 2011;57:173–80.
[18] Ogawa S, Hori M. Urgent statement on antithrombotic therapy of atrial fibrillation. Circ J 2011;75:2719–21.
[19] Lauer A, Ciancherti FA, Van Cott EM, et al. Anticoagulation with the oral direct thrombin inhibitor dabigatran does not enlarge hematoma volume in experimental intracerebral hemorrhage. Circulation 2011;124:1654–62.

[20] van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemostasis 2010;103:1116–27.
[21] Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemostasis 2011;9:2168–75.
[22] Stangier J, Stähle H, Rathgen K, et al. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor dabigatran in healthy elderly subjects. Clin Pharmacokinet 2008;47:47–59.
[23] Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 2008;47:285–95.
[24] Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383–93.
[25] Walker WG, Neaton JD, Cutler JA, et al. Renal function change in hypertensive members of the Multiple Risk Factor Intervention Trial. Racial and treatment effects. MRFIT Res Group. JAMA 1992;268:3085–91.
[26] Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363–72.
[27] Jaszewski R. Frequency of gastroduodenal lesions in asymptomatic patients on chronic aspirin or nonsteroidal antiinflammatory drug therapy. J Clin Gastroenterol 1990;12:10–3.
[28] Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol 2012;59:1168–74.

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Impact of Left Ventricular Diastolic Dysfunction on Outcome of Catheter Ablation for Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy

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Background: The relationship between outcome of radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) and the severity of left ventricular (LV) diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM) remains unknown.

Methods and Results: Twenty-two HCM patients (12 female, aged 65±11 years) with paroxysmal (n=5; 23%) or persistent (n=17; 77%) AF were enrolled. LV diastolic function was evaluated according to the ratio of the mitral inflow early filling velocity to the velocity of the early medial mitral annular ascent (E/e') measured on pulsed wave and tissue Doppler assessments in all patients. Pulmonary vein isolation was performed in all patients. A second procedure was performed in 3 patients. During a follow-up of 21±12 months, sinus rhythm was maintained in 13 of 22 patients (59%). E/e' was significantly higher in the patients with AF recurrence than in those without (18±7 vs. 11±3; P<0.01). On Kaplan-Meier analysis the prevalence of AF recurrence was significantly higher in patients with E/e' ≥15 (n=6) than in those with E/e' <15 (n=16; P<0.01). On multivariate Cox regression analysis the only significant and independent predictor for AF recurrence was E/e' (hazard ratio, 1.16; 95% confidence interval: 1.01–1.37, P=0.03).

Conclusions: LV diastolic dysfunction evaluated using E/e' was associated with difficulty of rhythm control after RFCA in patients with HCM and AF.

Key Words: Atrial fibrillation; Diastolic dysfunction; Hypertrophic cardiomyopathy; Radiofrequency catheter ablation

Atrial fibrillation (AF) is the most common tachyarrhythmia in patients with hypertrophic cardiomyopathy (HCM). AF is often poorly tolerated and is associated with significant clinical deterioration in these patients.[1–3] Maintenance of sinus rhythm (SR) is desirable in patients with HCM. Several studies have shown that radiofrequency catheter ablation (RFCA) of severely symptomatic AF is both a feasible and safe approach in patients with HCM.[4–7] The presence and severity of left ventricular (LV) diastolic dysfunction increase the risk of AF recurrence after RFCA in patients without structural heart disease.[8] In patients with HCM, severe LV diastolic dysfunction is common due to the thickened and non-compliant ventricular chambers. The relationship between the outcome of RFCA for AF in patients with HCM and the severity of LV diastolic dysfunction, however, has not been fully investigated. The purpose of this study was to evaluate the impact of LV diastolic dysfunction, as measured on ultrasonography, on the outcome of RFCA for AF in patients with HCM.

Editorial p????

Methods

Subjects

Twenty-four consecutive Japanese patients with HCM undergoing RFCA of paroxysmal or persistent AF at the National Cerebral and Cardiovascular Center from 2009 to 2012 were reviewed. The diagnosis of HCM was based on the presence of myocardial hypertrophy in the absence of local or systemic

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Table 1. Patient Characteristics

Variable	Total (n=22)	AF recurrence (n=9)	Without AF recurrence (n=13)	P-value
Age (years)	65±11	67±8	64±12	0.52
Female	12 (54.5)	6 (66.7)	6 (46.2)	0.90
Paroxysmal AF	5 (22.7)	2 (22.2)	3 (23.1)	0.96
Persistent AF	17 (77.3)	7 (77.8)	10 (76.9)	0.96
Duration of AF (months)	80±53	107±56	62±45	0.052
Family history of HCM	4 (18.2)	2 (22.2)	2 (15.4)	0.68
Use of AAD	15 (68.2)	5 (55.6)	10 (76.9)	0.29
Echocardiography				
Middle LV thickness (mm)	13±4	12±4	14±5	0.28
LVDd (mm)	45±6	47±2	44±2	0.30
LVDs (mm)	30±7	32±2	28±2	0.26
LVEF (%)	57±14	54±13	59±14	0.48
E	65±18	60±14	68±20	0.31
e'	5±2	4±1	7±2	0.0009
E/e'	14±6	18±7	11±3	0.002
MR (>moderate)	5 (22.7)	2 (22.2)	3 (23.1)	0.96
LVOTO (>30 mmHg)	3 (13.6)	3 (33.3)	0 (0.0)	0.03
LA diameter (mm)	48±6	49±5	46±6	0.20
LA volume (ml)†	98±38	115±41	86±33	0.08
RFCA				
Pulmonary vein isolation	22 (100)	9 (100)	13 (100)	NS
CTIA	10 (45.5)	2 (22.2)	8 (61.5)	0.12
Second procedure	3 (13.6)	1 (11.1)	2 (15.4)	0.22
Follow-up period (months)	21±12	22±14	20±11	0.72

Data given as mean±SD or n (%). †Measured on 3-D electrophysiologic mapping. AAD, anti-arrhythmic drug; AF, atrial fibrillation; CTIA, cavo-tricuspid isthmus ablation; E, mitral inflow early filling velocity; e', velocity of early medial mitral annular ascent; HCM, hypertrophic cardiomyopathy; LA, left atrium; LV, left ventricle; LVDd, left ventricular dimension at end-diastole; LVDs, left ventricular dimension at end-systole; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; RFCA, radiofrequency catheter ablation.

etiology. Paroxysmal and persistent AF were defined according to the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.[9] Two patients in whom LV diastolic dysfunction was not evaluated on ultrasonography were excluded. Consequently, 22 HCM patients were enrolled in this study. All patients provided informed consent. All patients were on oral anticoagulant therapy maintaining a target international normalized ratio of 2–3. Transesophageal echocardiography was performed to exclude any left atrial thrombi prior to the procedure in all patients.

Echocardiography

Comprehensive 2-D and Doppler echocardiography were performed in each patient using commercially available instruments before RFCA.[10,11] SR was maintained at the time of echocardiography in 15 of 22 patients. When echocardiography was performed during AF, all echocardiographic parameters were measured with an average of 3 consecutive beats. LV outflow tract (LVOT) gradient was measured with continuous-wave Doppler in the apical 3-chamber view. LVOT obstruction (LVOTO) was defined as a gradient >30 mmHg.[12] LV diastolic function was evaluated as the ratio of the mitral inflow early filling velocity to the velocity of the early medial mitral annular ascent (E/e'), measured on pulsed wave and tissue Doppler.[13]

RFCA

The RFCA was performed under sedation with i.v. propofol. All anti-arrhythmia medication, except for amiodarone, was discontinued for at least 5 half-lives before the procedure in all patients. Two standard catheters were positioned: a 6-F catheter (St. Jude Medical, Minnetonka, MN, USA) at the His bundle region via a femoral vein, and another 6-F catheter (Japan Lifeline, Tokyo, Japan) in the coronary sinus via the right cervical vein. The transseptal procedure was performed using fluoroscopic landmarks, and 2 SL0 sheaths (St. Jude Medical) and an 8.0-F Preface sheath (Biosense Webster, Irwindale, CA, USA) were advanced into the left atrium (LA). After the transseptal procedure, a single bolus of 4,000 U heparin was given. A continuous infusion with heparinized saline was performed to maintain an activated clotting time of 300–350 s. Two 7-F decapolar circular catheters (Lasso, Biosense-Webster, Diamond Bar, CA, USA) and a 3.5-mm open irrigated tip ablation catheter (Navistar Thermocool, Biosense Webster) were inserted into the LA. We performed 3-D electroanatomical mapping (CARTO system, Biosense Webster) of the LA. Mapping was complete when all regions of the LA had been systematically sampled and when a sufficient density of points had been acquired to determine the LA chamber. After reconstruction of the LA, the volume of the LA chamber was automatically analyzed with the CARTO system. Each pulmonary vein (PV) ostium was identified on PV venography and tagged on the 3-D electroanatomical map. Two decapolar circular mapping catheters were placed inside

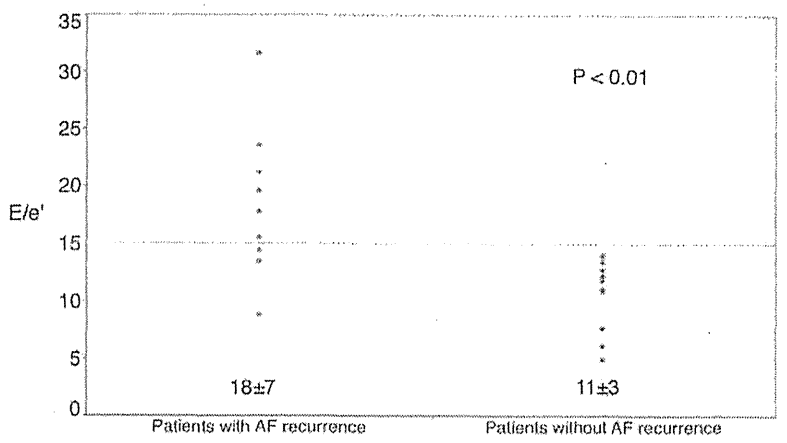

Figure 1. E/e' vs. presence of atrial fibrillation (AF) recurrence. E/e' was significantly higher in the patients with AF recurrence than in those without (P<0.01). E, mitral inflow early filling velocity; e', velocity of early medial mitral annular ascent.

the ipsilateral superior and inferior PV. The circumferential ablation lines, using a 3.5-mm tip irrigated catheter targeting a maximum temperature of 43°C, maximum power of 25–30 W, and infusion rate of 17 ml/min, were created at a distance from the PV ostia. The endpoint of the PV isolation was defined as the establishment of bidirectional conduction block between the LA and PV at least 30 min after successful PV isolation. Cavo-tricuspid isthmus ablation was performed at the operator's discretion.

Post-Procedure Care and Follow-up

After the first procedure, all patients received a follow-up every 1–3 months in the outpatient clinic. Follow-up included 12-lead electrocardiogram, 24-h Holter monitoring and assessment of the current condition. Anti-arrhythmic agents were resumed when there was evidence that AF recurred during the early unstable period after the procedure. AF recurrence was defined as sustained AF lasting >1 min. AF recurrence within a 2-month period after the procedure was considered transient, and a 2-month period was applied as a blanking period. Following the blanking period, repeat RFCA was carried out in the event of a recurrence of AF or atrial tachycardia. PV isolation was assessed and further ablation delivered as necessary.

Statistical Analysis

Data were analyzed using JMP 9.0e (SAS Institute, Cary, NC, USA). Numeric data are expressed as the mean±SD. Chi-squared test or Student's t-test was used when appropriate to test for statistical difference. P<0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to identify the value of E/e' predictive of AF recurrence. Event rate curves were plotted according to the Kaplan-Meier method and were analyzed with the log-rank test. Univariate Cox regression analysis was performed to identify predictors of subsequent AF recurrence. The hazard ratio (HR) and 95% confidence interval (95% CI) were defined. To confirm their independent predictive value, variables with P<0.05 were tested in a multivariate model.

Results

Patient Characteristics

Patient clinical characteristics are listed in Table 1. Persistent AF was found in 17 patients (77.3%). Longstanding persistent AF was not included in this study. The mean duration of AF was 80±53 months. The mean of the LA diameter was 48±6 mm and the mean LA volume measured on 3-D mapping was 98±38 ml.

Procedure Outcome

All PV were successfully isolated in all patients. The mean procedure time was 244±60 min and the total duration of the RF applications was 39±12 min. Cavo-tricuspid isthmus ablation was performed in 10 patients (45.5%). No patients received linear lesions in the LA or a complex fractionated atrial electrogram ablation. In 3 patients, a second procedure was performed for recurrence of AF. Recovered PV conduction was found and successfully eliminated with RFCA.

Effect of Recurrence

From 21±12 months after the last procedure, maintenance of SR was observed in 13 of 22 patients (59%; Table 1). There were no significant differences between patients with and without AF recurrence with respect to age, gender, type of AF, family history of HCM, use of anti-arrhythmic drugs, or follow-up period (Table 1). The duration of AF tended to be longer in the patients with AF recurrence than in those without (P=0.052). There were also no significant differences on echocardiography between patients with and without AF recurrence except for E/e', e' and number of patients with LVOTO (>30 mmHg). Compared with the patients without AF recurrence, E/e' and number of patients with LVOTO (>30 mmHg) were significantly higher in those with an AF recurrence (18±7 vs. 11±3; P=0.002 and 3 vs. 0; P=0.03, respectively). E' was significantly lower in those with AF recurrence (3.6±1.2 vs. 6.5±2.0; P=0.0009).

There was no significant difference in the number of cavo-tricuspid isthmus ablations during the initial RFCA and the second procedure between the patients with and without AF recurrence. LA volume measured on 3-D electroanatomical mapping tended to be larger in the patients with AF recurrence than in those without (115±41 vs. 86±33; P=0.08).

LV Diastolic Dysfunction and Outcome of RFCA

Comparison of E/e' between the patients with and without AF recurrence is shown in Figure 1. E/e' was significantly higher

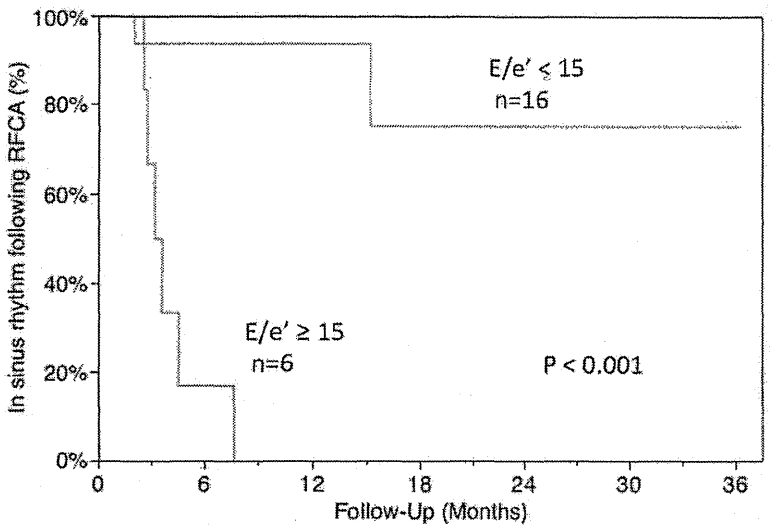

Figure 2. Kaplan-Meier curve of the maintenance of sinus rhythm following radiofrequency catheter ablation (RFCA). Patients with E/e' ≥15 had a significantly higher risk of atrial fibrillation recurrence than those with E/e' <15 (log-rank, P<0.001). E, mitral inflow early filling velocity; e', velocity of early medial mitral annular ascent.

Table 2. Predictors of AF Recurrence

	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
E/e'	1.19 (1.07–1.33)	0.002	1.16 (1.01–1.37)	0.03
Duration of AF (months)	1.02 (1.00–1.03)	0.02	1.01 (0.99–1.03)	0.40
LA volume (ml)†	1.02 (1.00–1.03)	0.04	1.00 (0.98–1.02)	0.28
LA diameter (mm)	1.14 (1.00–1.33)	0.05		
LVOTO (>30 mmHg)	3.99 (0.83–15.1)	0.08		
CTIA	0.50 (0.11–1.92)	0.32		
Second procedure	0.77 (0.04–4.28)	0.80		

†Measured on 3-D electrophysiologic mapping. Abbreviations as in Table 1.

in the patients with AF recurrence than in those without. In all 13 patients without AF recurrence, E/e' was <15. In contrast, in 6 of 9 patents (67%) with AF recurrence, E/e' was >15. On ROC curve analysis, the optimal threshold of E/e' for predicting AF recurrence was 15 (sensitivity, 67%; specificity, 100%). The area under the ROC curve was 0.88. Figure 2 shows the results of Kaplan-Meier analysis of the maintenance of SR following RFCA. Patients with E/e' ≥15 had a significantly higher risk of AF recurrence than those with E/e' <15 (log-rank, P<0.001).

Predictors of Long-Term Outcome

The results of Cox regression analysis are shown in Table 2. On univariate Cox regression analysis, E/e', duration of AF and LA volume measured on 3-D electroanatomical mapping were significant predictors of AF recurrence. On multivariate Cox regression analysis E/e' was the only predictor of AF recurrence following RFCA (HR, 1.16; 95% CI: 1.01–1.37, P=0.03).

Discussion

Main Findings

The major findings of the present study are as follows: (1) E/e' was significantly higher in patients with AF recurrence than in those without; (2) patients with E/e' ≥15 had a significantly higher risk of AF recurrence than those with E/e' <15; and (3) E/e' was the only predictor of AF recurrence following RFCA in the patients with HCM. To the best of our knowledge, this is the first report to describe the relationship between LV diastolic dysfunction and outcome of RFCA for AF in patients with HCM.

LV Diastolic Dysfunction and AF Recurrence

In the present study, we examined the correlation between LV diastolic dysfunction, estimated as E/e', and outcome for AF in HCM patients. In patients with HCM, the mitral variables of E/A ratio and deceleration time of early filling velocity have weak to no correlations with LV filling pressures.[14,15] But E/e' correlated reasonably well with LV pre-A pressure during SR,[15] which mean that E/e' is a good parameter of LV diastolic function even in patients with HCM. E/e' was significantly higher and e' was significantly lower in patients with AF recurrence. The lower e' reflects impaired myocardial relaxation. Severely impaired myocardial relaxation should elevate LA pressure, manifested as higher E/e'.[16,17] Elevated LA pressure might result in continuous atrial remodeling after RFCA, which might explain why a higher recurrence was noted.

Patients with LV diastolic dysfunction and AF have a lower LA voltage and higher recurrence rate of AF after RFCA.[8,18,19] In contrast, SR was maintained in 13 of 16 patients (82%) with mild or moderate LV diastolic dysfunction (E/e' <15). In those patients, the LA pressure might not be so high and the LA remodeling might not progress very much after RFCA for AF. The present results are in accordance with the previous reports showing that the presence and severity of LV diastolic dysfunction increased the risk of AF in patients with preserved LV systolic function.[20-22]

Several studies have demonstrated that RFCA of severely symptomatic AF is both a feasible and safe approach in patients with HCM.[4-7] Di Donna et al found that the most important independent predictors of AF recurrence following RFCA consisted of age, functional status and LA volume.[4] In that study, however, the relationship between the outcome of RFCA for AF and the severity of the LV diastolic dysfunction was not examined. Bunch et al showed that AF control following RFCA was less likely in patients with more advanced LV diastolic dysfunction.[7] In the present study, LV diastolic dysfunction was graded as normal (grade 0), abnormal relaxation (grade I), pseudonormalization (grade II), restrictive (grade III), or irreversible advanced restrictive (grade IV). Although the grade of diastolic dysfunction was inversely related to the rate of AF control, this relationship did not reach statistical significance. Also, echocardiographic variables utilized to assess LV diastolic function were not associated with a reduced likelihood of AF control. The severity of LV diastolic dysfunction was not assessed in some patients due to AF during echocardiography, which might result in exclusion of the patients with severe LV diastolic dysfunction and weakening of the inverse relationship between the severity of LV diastolic dysfunction and the rate of AF control.

Clinical Implication

According to the ESC guidelines for the management of AF, RFCA for symptomatic AF refractory to pharmacological control in patients with HCM is a class IIa indication.[23] At the same time, the ESC guidelines note that severe LV diastolic dysfunction is at high risk for recurrence. The appropriate candidates for RFCA in patients with HCM and AF have not been defined. We showed that outcome after RFCA was favorable in patients with mild or moderate LV diastolic dysfunction (E/e' <15). This suggests that HCM patients with mild or moderate LV diastolic dysfunction (E/e' <15) and AF might be good candidates for RFCA.

Study Limitations

This study had several limitations. First, this study was a retrospective study. Second, we could have underestimated the recurrence rate after RFCA for AF because asymptomatic AF recurrence could have been missed. Third, echocardiography was performed during AF in 7 of 22 patients. Although echocardiography during AF can be inaccurate, E/e' is useful in the estimation of LV filling pressure even in patients with AF.[24,25] There were no changes in LV diastolic parameters on tissue Doppler imaging following electrical cardioversion in patients with persistent AF,[26] which means that these parameters were used equally in the patients with SR and AF. Fourth, this was an analysis of a small number of patients and a small number of events. Further examination is required with a larger number of patients to confirm the present results.

Conclusions

LV diastolic dysfunction evaluated on E/e' was linked to the possibility of rhythm control after RFCA in the patients with HCM and AF. Patients with mild or moderate LV diastolic dysfunction (E/e' <15) might be good candidates for RFCA in those with HCM and AF.

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Disclosures

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References

1. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: A longitudinal study. *J Am Coll Cardiol* 1990; **15:** 1279–1285.
2. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001; **104:** 2517–2524.
3. Maron BJ, Olivotto I, Spirito P, Casey SA, Bellone P, Gohman TE, et al. Epidemiology of hypertrophic cardiomyopathy-related death: Revisited in a large non-referral-based patient population. *Circulation* 2000; **102:** 858–864.
4. Di Donna P, Olivotto I, Delcrè SDL, Caponi D, Scaglione M, Nault I, et al. Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: Impact of age, atrial remodelling, and disease progression. *Europace* 2010; **12:** 347–355.
5. Kilicaslan F, Verma A, Saad E, Themistoclakis S, Bonso A, Raviele A, et al. Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Heart Rhythm* 2006; **3:** 275–280.
6. Gaita F, Di Donna P, Olivotto I, Scaglione M, Ferrero I, Montefusco A, et al. Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2007; **99:** 1575–1581.
7. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM, et al. Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008; **19:** 1009–1014.
8. Hu YF, Hsu TL, Yu WC, Huang SH, Tsao HM, Tai CT, et al. The impact of diastolic dysfunction on the atrial substrate properties and outcome of catheter ablation in patients with paroxysmal atrial fibrillation. *Circ J* 2010; **74:** 2074–2078.
9. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, et al. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: Recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: A report of the HRS Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the EHRA, a registered branch of the ESC and the ECAS; and in collaboration with the ACC, the AHA, the APHRS, and the STS. Endorsed by the governing bodies of the ACCF, the AHA, the ECAS, the EHRA, the STS, the APHRS, and the HRS. *Heart Rhythm* 2012; **9:** 632–696.
10. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; **18:** 1440–1463.
11. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009; **10:** 165–193.
12. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: A report of the ACCF/AHA Task Force on Practice Guidelines. *Circulation* 2011; **124:** e783–e831, doi:10.1161/CIR.0b013e318223e2bd.
13. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr* 2009; **10:** 165–193.