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Evaluation of the impact of atrial fibrillation on rehospitalization events in heart failure patients in recent years

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ABSTRACT

Background: Although we have previously reported that the presence of paroxysmal atrial fibrillation (AF) is an independent risk factor for rehospitalization in patients with congestive heart failure (CHF) in a population from 1996 to 2002, the impact of AF configuration as a risk factor in a more recent population remains to be clarified.

Methods and results: 319 patients with CHF admitted to our institute in 2006–2007 were retrospectively evaluated. The patients were divided into 3 groups in accordance with their basic cardiac rhythm, i.e. sinus rhythm ($n = 210$), chronic AF ($n = 68$), and paroxysmal AF ($n = 41$). During the follow-up period of 19 ± 17 months, there was no significant difference in mortality or rehospitalization events among the 3 groups ($p = 0.542$). In the multivariate analysis, no administration of β-blockers was the only independent risk factor for rehospitalization due to CHF exacerbation.

Conclusions: The clinical impact of AF configuration as a risk factor of rehospitalization due to CHF exacerbation was considered to be decreased in recent years.

Introduction

Atrial fibrillation (AF) is one of the most common types of arrhythmia in clinical practice and it is considered to be responsible for substantial morbidity and mortality in some types of diseases [1–4]. Theoretically, the rapid ventricular rate during AF reduces the length of the diastolic phase and it results in a decrease in hemodynamic ventricular filling. The lack of atrial contraction also contributes to a reduction in the ventricular filling at the end of the diastolic phase. It has been reported that these changes reduce cardiac output by 20–40% depending on the basic situation [5–7]. Meta-analyses of several mega-trials, including SOLVD, CHARM, etc., have demonstrated the contribution of AF rhythm to a worse prognosis in patients with heart failure (HF) in comparison with sinus rhythm [8,9]. However, the more recent JCARE-CARD and AF-CHF studies have documented no significant difference between patients with and without AF, even in cases of HF when appropriate rate control and anticoagulation therapies were performed [10–13]. Although the reason for this discrepancy is unclear, several improvements in the modality of HF therapy in recent years, such as brain-natriuretic peptide (BNP)-guided therapy, β-blocker therapy, and renin–angiotensin system (RAS) suppression therapy may have reduced the impact of AF on the prognoses for HF patients [14]. Our institute has also reported similar findings. When retrospective observations of HF patients were performed in a patient population from 1996 to 1999, the rehospitalization event rate was higher in patients with AF than those without AF [15], but the difference became insignificant in a patient population from 1996 to 2002 [14]. Interestingly, the latter study exhibited a higher rehospitalization event rate in patients with paroxysmal AF than chronic AF or sinus rhythm. The results of the latter study might suggest that the impact of AF on HF patients depends not on the presence of AF but on a change in basic rhythm [14], but this concept was not confirmed in the sub-analysis of the AF-CHF study. Therefore, we planned to re-evaluate the impact of AF on HF patients in a more recent population in our institute reflecting more recent therapeutic modality of HF therapy. In the present study, the rehospitalization events of HF patients were evaluated in a recent population. Clinical parameters were retrospectively compared between the patients with and without rehospitalization events to clarify the clinical factors which determine the prognoses of HF patients.

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Methods

Patient population

The study population consisted of 319 consecutive patients with exacerbated HF diagnosed with congestive HF (CHF) for the first time, according to the Framingham criteria, admitted to Kitasato University Hospital from January 2006 to December 2007. Patients with permanent pacemaker implantation and patients who died on their first admission were excluded. The mean age was 70 ± 14 years and 116 were female. The clinical characteristics of the patients are summarized in Table 1. Clinical parameters were basically analyzed at the time of hospital discharge as the patient baseline characteristics for HF. The mean heart rate was calculated from the Holter electrocardiogram (ECG) recording or the trend data of consecutive ECG monitoring during admission. Findings on ultrasonic cardiography were recorded by trans-thoracic echocardiogram (Aplio, Toshiba Co. Ltd., Tokyo, Japan). The dimension of each chamber was measured in the left parasternum view, and the ejection fraction was calculated using the modified Simpson method. Structural heart disease was diagnosed by routine echocardiography and/or cardiac catheterization. The history of cardiac surgery included any type of surgical procedure, such as open chest or open heart surgery, and coronary interventions. Patients who underwent catheter ablation for AF such as pulmonary vein isolation were not included in the study population. All studies were performed with the approval of the Clinical Studies and Ethics Committee of Kitasato University Hospital.

Evaluation of the factors determining rehospitalization

Rehospitalization events due to exacerbation of CHF were retrospectively evaluated from the time of hospital discharge until December 2010. In the present study, we picked up the rehospitalization event due to exacerbation of CHF and the other causes of rehospitalization events, that include cardiopulmonary arrest, ventricular tachycardia/fibrillation, acute myocardial infarction, cerebral infarction, hemorrhagic episode, etc., were excluded. The event was counted when the main reason for the second hospitalization was the exacerbation of CHF. After the retrospective observation, the patients were divided into two groups with and without rehospitalization events. Clinical parameters were compared between the two groups by uni- and multi-variate analyses to clarify the factors determining rehospitalization events.

All patients were divided into three groups in accordance with the basic cardiac rhythm during their first hospitalization as follows: (1) a sinus rhythm (SR) group who exhibited no documentation of AF during their hospitalization ($n = 210$); (2) a chronic AF (CAF) group who exhibited continuous AF and were diagnosed as CAF during their hospitalization ($n = 68$); and (3) a paroxysmal AF (PAF) group who exhibited spontaneous changes between SR and AF and were diagnosed as PAF during their hospitalization ($n = 41$) [16]. The therapeutic strategy for AF in individual patients,

Table 1
Clinical characteristics and comparison of patients with and without rehospitalization.

	Total	Rehospitalization(+)	Rehospitalization(−)	*p*-Value
Age	69.7 ± 14.0	73.1 ± 12.5	68.2 ± 14.4	0.0059†
Male, no.(%)	203(63.6)	64(64.7)	139(63.2)	0.8014
Underlying cardiovascular disease of HF, no.(%)				
IHD	145(45.5)	50(50.5)	95(43.2)	0.2243
CM	39(12.2)	8(8.1)	31(14.1)	0.1295
VHD	59(18.5)	24(24.2)	35(15.9)	0.0761
HHD	23(7.2)	4(4.0)	19(8.6)	0.1420
Other	53(16.6)	13(13.2)	40(18.2)	0.2622
Complicating disorder, no.(%)				
HT	187(58.6)	65(65.7)	122(55.5)	0.0870
DM	117(36.7)	35(35.4)	82(37.3)	0.7421
Old CI	30(9.4)	8(8.1)	22(10.0)	0.5869
On admission				
NYHA(II:III:IV)	55:162:102	12:53:34	43:109:68	0.2660
On discharge				
Heart rate, bpm	75 ± 15	76 ± 18	74 ± 13	0.7412
LAD, mm	42.7 ± 11.4	46.1 ± 16.0	41.4 ± 8.4	0.0106*
LVDd, mm	53.3 ± 10.3	53.6 ± 11.5	53.1 ± 0.8	0.8819
LVEF, %	47.3 ± 14.4	44.6 ± 14.4	48.5 ± 14.3	0.0668
CTR, %	54.8 ± 7.6	56.4 ± 7.6	54.1 ± 7.4	0.0080†
BNP, pg/ml	137.3 ± 160.3	170.6 ± 16.2	121.0 ± 11.3	0.0034†
ECG rhythm group, no.(%)				
SR	210(65.8)	61(61.6)	149(67.7)	0.2870
PAF	41(12.9)	15(15.2)	26(11.8)	0.4105
CAF	68(21.3)	23(23.2)	45(20.5)	0.5752
Cardiac surgery, no.(%)	145(45.5)	47(47.5)	98(44.6)	0.6269
Medication use, no.(%)				
Statin	126(39.5)	32(32.3)	94(42.7)	0.0786
ACE inhibitors/ARB	288(90.3)	93(93.9)	195(88.6)	0.1390
β-Blocker	188(58.9)	49(49.5)	139(63.2)	0.0215*
Spironolactone	93(29.2)	27(27.3)	66(30.0)	0.6200
Digoxin	88(27.6)	26(26.3)	62(28.2)	0.7429
Amiodarone	15(4.7)	6(6.1)	9(4.1)	0.4420
Warfarin	123(38.6)	31(31.3)	92(41.8)	0.0745
TTR (%)	61.7 ± 9.7	61.5 ± 10.1	61.8 ± 9.7	0.7052

HF, heart failure; IHD, ischemic heart disease; CM, cardiomyopathy; VHD, valvular heart disease; HHD, hypertensive heart disease; HT, hypertension; DM, diabetes mellitus; CI, cerebral infarction; NYHA, New York Heart Association; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; CTR, cardiothoracic ratio; BNP, brain natriuretic peptide; ECG, electrocardiogram; SR, sinus rhythm; PAF, paroxysmal atrial fibrillation; CAF, chronic atrial fibrillation; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; TTR, time in therapeutic range.

* $p < 0.05$ between the patients with rehospitalization.

† $p < 0.01$ between the patients without rehospitalization.

including rhythm control, rate control, and anticoagulation therapy, was decided by plural experienced cardiologists. The clinical parameters, including rehospitalization and total death events, were compared among these 3 groups. In this case, rehospitalization was due to exacerbation of CHF as above, and total death was death due to all causes. To evaluate the effect of cardiac rhythm, in addition to the comparison between the three groups were compared the presence of any type of AF.

Statistical analysis

Continuous data are expressed as mean ± SD. Patient characteristics were compared using the chi-squared test and one-way analysis of variance test. The event-free rates among the groups were calculated using the Kaplan–Meier method, and differences among the groups were defined as a p-value of <0.05 (two-tailed) for all analyses. The Cox proportional hazards model was applied to evaluate differences in the occurrence of rehospitalization for CHF exacerbation among the groups after taking into account the effect of several potential confounders using the statistical software JMP (JMP 7.0, SAS Inc. Tokyo, Japan).

Results

Incidence and determinants of rehospitalization events

During the retrospective observation period of 12–61 months (19 ± 17 months), rehospitalization events were recorded in 99/319 patients. Table 1 shows the clinical characteristics of the patients with and without rehospitalization events. Among the parameters, the age was older, left atrial dimension (LAD) was larger, cardiothoracic ratio (CTR) was larger, and BNP level was higher in patients with rehospitalization events than those without events. The incidence of β-blocker prescription was lower in patients with rehospitalization events than those without events.

Table 2 exhibits the result of uni- and multivariate analyses of the clinical parameters as risk factors for rehospitalization events. The univariate analysis shows that significant risk factors for the rehospitalization events were higher age, higher minimum level of BNP, larger CTR, larger LAD, and no administration of β-blockers. In the multivariate analysis, no-administration of β-blockers was the only significant factor indicating that this is an independent risk factor for rehospitalization events.

Comparison of patients with different basic cardiac rhythms

Table 3 shows a comparison of the 3 sub-groups with different basic cardiac rhythms, i.e. SR, PAF, and CAF. In comparison with the SR group, the PAF group exhibited higher age, higher incidence of digoxin administration, and lower incidence of statin administration. In contrast, the CAF group exhibited higher prevalence of valvular heart disease, larger CTR, higher BNP level, larger LAD, higher incidence of digoxin administration, and lower incidence of statin administration in comparison with the SR group. The PAF group showed smaller LAD, smaller CTR, lower BNP level, and higher incidence of amidarone administration in comparison with the CAF group. The incidence of death or rehospitalization events did not show any significant differences among the 3 groups. Fig. 1 shows the Kaplan–Meier event-free curves of each group for rehospitalization and total death events. There was no significant difference in rehospitalization events among the 3 groups (Panel A). Although the SR group tended to exhibit better prognosis in terms of total deaths (Panel B), there was no significant difference among the 3 groups.

Discussion

Relationship between rehospitalization due to CHF exacerbation and AF burden

It has been considered that AF would be a risk factor for exacerbation of CHF [8,9]. Shortening of the diastolic phase and a lack of atrial contraction, which can both be observed in AF, reduce ventricular filling and will theoretically reduce cardiac output [5–7]. These hemodynamic changes may practically exacerbate the CHF in clinical patients, and earlier reports have documented the contribution of AF to worsening prognoses in patients with CHF [8,9]. However, more recent studies have demonstrated no significant difference in prognoses between CHF patients with and without AF when appropriate rate control and anticoagulation therapies were given [10–12]. This difference is considered to be explained by recent changes in the therapeutic modality for CHF patients. The use of β-blockers and/or RAS suppressing medicines

Table 2
Uni- and multi-variate analyses of the risk factors for the rehospitalization.

	Univariate	Multivariate		
	p-Value	Odds ratio	95%CI	p-Value
Age	0.0059	0.148	−0.062 to 0.003	0.0550
Gender(male)	0.8014	1.461	−0.240 to 0.618	0.3841
Presence of PAF	0.4105	0.004	...	0.6958
Presence of CAF	0.5752	0.001	...	0.7131
Presence of any type of AF	0.2870	0.001	...	0.7072
Valvular heart disease	0.0761	0.910	−0.482 to 0.397	0.8339
NYHA	0.1459	0.003	... to 0.321	0.8636
History of cardiac surgery	0.6269	0.590	−0.611 to 0.075	0.1296
HR, bpm	0.7412	1.276	−0.019 to 0.027	0.7463
Lowest BNP, pg/dl	0.0034	0.255	−0.004 to 0.001	0.2643
CTR, %	0.0080	0.381	−0.079 to 0.045	0.5874
LVEF, %	0.0668	7.228	0.003 to 0.057	0.0530
LAD, mm	0.0106	0.142	−0.081 to 0.004	0.0796
Non-administration of statin	0.0736	0.651	−0.576 to 0.139	0.2374
Non-administration of ACEI/ARB	0.1665	1.796	−0.350 to 1.079	0.4077
Non-administration of β-blocker	0.0199	0.614	−0.601 to 0.112	0.0178*
Non-administration of digoxin	0.7055	1.129	−0.342 to 0.445	0.7635

95%CI, 95% confidence interval; PAF, paroxysmal atrial fibrillation; CAF, chronic atrial fibrillation; AF, atrial fibrillation; NYHA, New York Heart Association; HR, heart rate; BNP, brain natriuretic peptide; CTR, cardiothoracic ratio; LVEF, left ventricular ejection fraction; LAD, left atrial dimension; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.

* $p < 0.05$.

Table 3
Clinical characteristics of the SR, PAF, and CAF groups.

	SR group (n = 210)	PAF group (n = 41)	CAF group (n = 68)
Age	68.2 ± 14.4	73.5 ± 14.1*	72.3 ± 11.8
Male, no.(%)	137(65.2)	24(58.5)	44(64.7)
Underlying cardiovascular disease of HF, no.(%)			
IHD	110(52.4)	15(36.6)	20(29.4)†
CM	31(14.7)	4(9.8)	4(5.9)
VHD	30(14.3)	7(17.1)	22(32.4)†
HHD	19(9.1)	4(9.8)	0(0)*,§
Other	20(9.5)	11(26.7)†	22(32.3)†
Complicating disorder, no.(%)			
HT	128(61.0)	23(56.1)	36(52.9)
DM	90(42.9)	11(26.8)	16(23.5)†
Old CI	20(9.5)	3(7.3)	7(10.3)
On admission			
NYHA, II:III:IV	40:100:70	9:20:12	6:42:20
On discharge			
Heart rate, bpm	73 ± 14	73 ± 12	79 ± 17*
LAD, mm	40.1 ± 7.2	40.5 ± 7.7	52.7 ± 17.4†,§
LVDd, mm	53.8 ± 10.4	51.6 ± 9.0	52.5 ± 10.8
LVEF, %	45.5 ± 14.9	50.5 ± 11.5	51.4 ± 13.4†
CTR, %	53.5 ± 6.6	53.0 ± 5.4	60.0 ± 9.1†,§
BNP, pg/ml	129.6 ± 166.8	109.9 ± 104.5	174.6 ± 164.1†,§
Medication use, no.(%)			
Statin	99(47.1)	10(24.4)†	17(25.0)†
ACE inhibitors/ARB	192(91.4)	35(85.4)	61(89.7)
β-Blocker	129(61.4)	23(56.1)	36(52.9)
Spironolactone	59(28.1)	11(26.8)	23(33.8)
Digoxin	35(16.7)	15(36.6)*	38(55.9)†
Amiodarone	10(4.8)	4(9.8)	1(1.5)‡
Warfarin	53(25.2)	21(51.2)†	49(72.1)†,‡
TTR (%)	61.1 ± 10.3	60.1 ± 8.7	63.1 ± 9.6
Death, no.(%)			
Total death	18(8.6)	5(12.2)	9(13.2)
CHF	8	1	2
VT/VF	3	2	3
Other	7	2	4
Rehospitalization due to CHF	61(29.1)	15(36.6)	23(33.8)

SR, sinus rhythm; PAF, paroxysmal atrial fibrillation; CAF, chronic atrial fibrillation; HF, heart failure; IHD, ischemic heart disease; CM, cardiomyopathy; VHD, valvular heart disease; HHD, hypertensive heart disease; HT, hypertension; DM, diabetes mellitus; CI, cerebral infarction; NYHA, New York Heart Association; LAD, left atrial dimension; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; CTR, cardiothoracic ratio; BNP, brain natriuretic peptide; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; TTR, time in therapeutic range; CHF, congestive heart failure; VT, ventricular tachycardia; VF, ventricular fibrillation.

* $p < 0.05$ vs. SR group.
† $p < 0.01$ vs. SR group.
‡ $p < 0.05$ vs. PAF group.
§ $p < 0.01$ vs. PAF group.

[angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)] has improved the prognoses of CHF patients [17–20], while the use of various new biomarkers, such as BNP, has enabled stricter control of CHF in clinical practice [21,22]. These improvements may have reduced the contribution of AF to worse prognoses, and as a result, the difference between patients with and without AF may have become insignificant in recent years. In contrast, our previous report documented a unique finding. The result was that no significant difference was observed in rehospitalization and total death events between SR and CAF patients in the study population of CHF patients in 1996–2002, while only PAF patients with CHF exhibited worse prognoses than the others [14]. Because it was a retrospective observation of CHF patients under continuous CHF therapies, the result is understandable when we consider that not the presence of AF but rather a change in basic rhythm is a risk for CHF exacerbation. However, as this phenomenon could not be confirmed by other reports, we re-evaluated the same concept in a more recent population in this study. The result was that, similar to other recent reports, no significant difference could be found among the patients with SR, PAF, and CAF in a CHF population. The precise mechanism of this change is unclear but may be explained by changes in adherence to the therapeutic guidelines for CHF therapies that have occurred in recent years, at least at our institute. At the time of the previous report, i.e. 1996–2002, the latest CHF therapies such as BNP-guided therapy and use of β-blockers, ACE inhibitors, or ARBs, were already used, but adherence may have been limited. When we compared the clinical characteristics of the study populations in 2 different time periods at our institute, because the method of patient selection and the analyzed parameters were different between the 2 studies, the comparison was incomplete but has revealed one possible reason. Although the total population and subgroups with SR or CAF exhibited increase in the use of β-blockers, ACE inhibitors, or ARBs, the subgroup with PAF exhibited differences only in New York Heart Association class populations and BNP levels on discharge. At least in PAF subgroups, more strict observance of BNP-guided therapy in the more recent CHF population might have decreased the impact of PAF on the worse prognosis in CHF patients. However this lower BNP level might possibly result from better left ventricular ejection fraction in the more recent population. So that the interpretation should be concluded carefully, but there was no correlation between BNP level and left ventricular ejection fraction at least in this population [14].

Risk factors for rehospitalization due to CHF exacerbation

The prediction of CHF exacerbation is an important issue in clinical management of CHF patients. As discussed above, AF prevalence

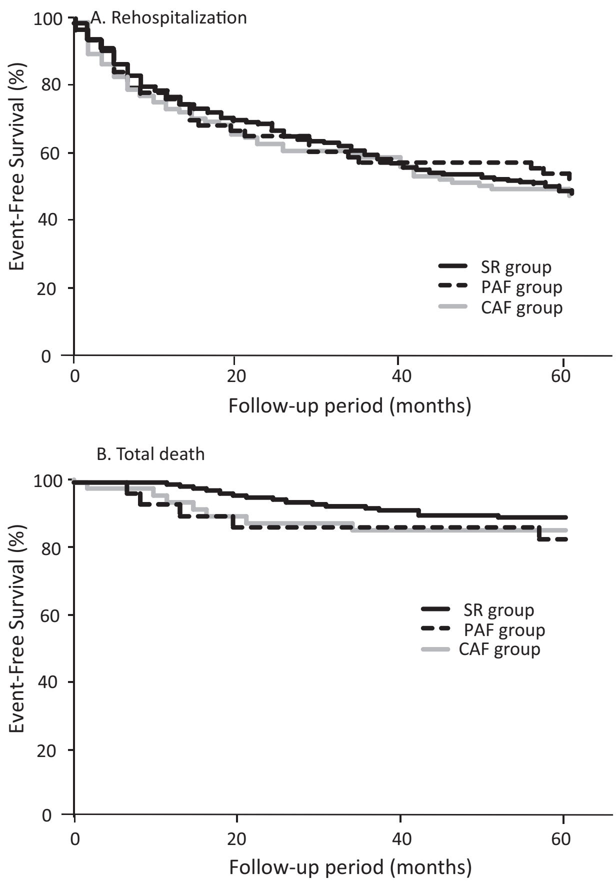

Fig. 1. Kaplan–Meier event-free curves for rehospitalization and total death events in groups with different cardiac rhythms. This figure shows Kaplan–Meier event-free curves for rehospitalization (Panel A) and total death (Panel B) in the 3 sub-groups. There was no significant difference among the 3 groups for these events. SR, sinus rhythm; PAF, paroxysmal atrial fibrillation; CAF, chronic atrial fibrillation.

was considered to be a risk for CHF worsening in earlier reports [1–4,8,9], but its impact should be considered as small or insignificant by referring to more recent reports [10–13]. Referring to our own data, not CAF, but rather PAF, may be a risk for CHF exacerbation [14], although its importance has decreased following the introduction of therapeutic procedures with higher adherence to the recommended guidelines.

Kubler et al. reported that lowering the BNP level by less than 20% during hospitalization would be a predictor for rehospitalization [23]. However, in our study population, this parameter was not significant for prediction of rehospitalization ($p = 0.307$, data not shown). Because we employ BNP < 200 pg/ml as one of the criteria for hospital discharge in our institute, we also evaluated BNP > 200 pg/ml as a predictor for clinical events, but it was not significant either. BNP is a good marker to evaluate the response of the patient's heart to CHF treatment, but the BNP level at hospital discharge may not reach its lowest level because the term of hospitalization is limited. Additionally, BNP may reflect the condition of not only the left ventricle, but also the right ventricle or the atria. Therefore, BNP at the time of hospital discharge may not be a simple independent predictor of future events.

Other reports demonstrated that no use of β-blockers, ACE inhibitors, or ARBs was a risk factor for rehospitalization [17,18,24–26]. Similar to these reports, we found that no use of β-blockers was the only independent predictor for rehospitalization events in the present study, but no use of ACE inhibitors or ARBs was not. The precise mechanism for the latter result is unclear, but it was probably due to the limited population of patients not receiving ACE inhibitors or ARBs (9.7%) in this study. Referring to the guidelines for CHF treatment, the use of β-blockers or RAS-suppressing medicines should be important and probably essential to prevent future events.

Limitations

There are a few limitations in this study. First, the study was carried out at a single center in both a retrospective and nonrandomized fashion. The acquired data may be biased depending on the clinical status and judgment of each patient. Second, there were some differences in clinical backgrounds in the 3 subgroups with different cardiac rhythms. The differences may have influenced the results of comparisons among the 3 groups even though the results showed no difference in prognoses. Third, because the observation was set retrospectively, therapies were not randomized, there are some missing data which could be useful to understand the patients' conditions, such as catecholamine level, so that the differences in therapies resulted in some bias. Finally, although the detection of AF itself was carefully performed by continuous monitoring, asymptomatic AF cannot be ruled out completely.

Conclusions

At least in the recent population, the presence or absence of AF did not affect the rehospitalization events due to CHF exacerbation in patients with history of CHF. The clinical impact of AF configuration as a risk factor of rehospitalization due to CHF exacerbation was considered to be decreased in recent years. This may be due to improved adherence, especially the usage of β-blockers, to recommended therapies for CHF patients.

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