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Accumulation of risk markers predicts the incidence of sudden death in patients with chronic heart failure

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Abstract

Background: Sudden death is common in chronic heart failure (CHF). Risk stratification is the first step for primary prevention.
Aim: To evaluate the use of risk markers for estimating sudden death risk.
Methods and results: We prospectively examined 680 stable patients with CHF. Risk markers were evaluated using the Cox's proportional hazard model in a stepwise manner. Ejection fraction <30%, left ventricular end-diastolic diameter >60 mm, brain natriuretic peptide >200 pg/ml, non-sustained ventricular tachycardia, and diabetes were significantly associated with increased risk of sudden death. When the number of risk markers were included as co-variables, only "number of risk markers ≥3″ entered the model (hazard ratio 8.95, 95% confidence interval 4.57–17.52), while the effects of individual markers did not enter the model. The annual mortality from sudden death was 11% in patients with 3 or more risk markers and 1.4% in patients with 2 or less.
Conclusions: Rather than particular risk markers, the number of accumulated risk markers was a more powerful predictor for sudden death in patients with CHF. The number of risk markers could be useful for risk stratification of sudden death.

Keywords: Brain natriuretic peptide; Ejection fraction; Observational study; Risk markers; Heart failure

1. Introduction

Sudden death is common in patients with chronic heart failure (CHF) [1–3], and many patients die from the first ventricular arrhythmia without being resuscitated. The implantable cardioverter defibrillator (ICD) is a promising treatment for primary prevention of sudden death in patients with CHF. The MADIT II trial indicated that the ICD was superior to conventional therapy in patients with previous myocardial infarction and low left ventricular ejection fraction (EF ≤ 30%) in terms of all cause mortality [4]. However, a strategy for the primary prevention of sudden death has not been established in patients with CHF.

Risk screening is the first step for primary prevention of sudden death, and should use simple, easily performed measurements. Low EF is recognized as a strong risk marker for sudden cardiac death from ischaemic and non-ischaemic causes in CHF patients [5,6]. Moreover, Grimm et al. [6] reported that the combination of EF < 30% and non-sustained ventricular tachycardia (NSVT) substantially increased the predictive power. It is likely that combined and/or accumulated risk markers may provide more powerful risk stratification for sudden death. To test this hypothesis, we analyzed the database from a multi-center heart failure registry, CHART (*C*hronic *H*eart failure *A*nalysis and *R*egistry in *T*ohoku district).

2. Methods

2.1. Organization of the CHART study

The organization of the CHART study has been described previously [3,7]. Briefly, the CHART study is a multi-center

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prospective observational study, which included stable CHF patients who had organic heart disease and a previous history of hospitalization due to clinical congestive heart failure. The CHART study also included symptomatic patients who had not been hospitalized, if they had organic heart disease and EF < 50% or left ventricular diastolic diameter (LVDD) ≥ 55 mm. The CHART study was approved by the local ethics committees.

The underlying aetiology of CHF was divided into five categories, i.e., dilated cardiomyopathy (DCM), coronary artery disease (CAD), valvular heart disease (VHD), left ventricular hypertrophy (LVH), and other heart diseases. DCM included both primary and secondary non-ischaemic dilated cardiomyopathies. LVH included hypertensive heart disease and idiopathic hypertrophic cardiomyopathy. VHD was primary valvular heart diseases. Congenital or unclassified heart diseases were categorized as other heart diseases. The present analysis was performed in patients with CAD, DCM, LVH, and corrected VHD, excluding uncorrected VHD and other heart diseases.

Conventional echocardiographic measurements were required at the registration. BNP was measured by RIA using ShionoRIA® BNP (Shionogi, Tokyo, Japan). Non-sustained ventricular tachycardia (NSVT) was defined as 3 or more consecutive ventricular premature beats (RR ≤ 400 ms) that were not sustained for more than 30 s.

2.2. Data analysis

The mode of death was categorized as heart failure death, sudden death, or non-cardiac death. Sudden death was defined as sudden, unexpected death without worsening heart failure. It included witnessed sudden collapse and death, and unwitnessed deaths which were unexpected and which could not be explained by non-cardiac causes. The mode of death was determined by the individual investigators who were in charge of the patients.

The statistical comparison of incidence was performed using the χ^2-test. Differences in mean values were tested by analysis of variance (one-way) and multiple comparisons were performed by the Bonferroni method. Risk markers were evaluated with Cox's proportional hazard model using the stepwise method. The end point was sudden death. When patients died from heart failure or non-cardiac causes they were considered as censored cases at that time. The following co-variables were tested: age, sex, past history of heart failure hospitalization, underlying heart diseases, NYHA functional class III/IV, diabetes, hypertension, non-sustained ventricular tachycardia (NSVT), atrial fibrillation, drugs [angiotensin converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blocker (ARB), beta-blocker, digitalis, spironolactone], BNP, EF, and LVDD. BNP, EF, and LVDD were tested as continuous and binary forms. The binary forms of these parameters were primarily estimated according to the receiver operating characteristics (ROC) curve. Cox's regression analysis was computed using, "StatView5.0" (SAS, Cary, NC). The sudden death-free survival rate was estimated by Kaplan–Meier analysis.

Table 1
Baseline clinical data of patients

Number of cases	680
Age mean ± SD (median)	66 ± 14 (68)
Male (%)	469 (69)
Past hospitalization due to congestive heart failure (%)	464 (68)
NYHA III/IV (%)	128 (19)
CAD cases (%)	232 (34)
BNP pg/ml (median)	273 ± 383 (144)
LVDD mm (median)	57 ± 10 (57)
EF % (median)	42 ± 14 (41)
Diabetes (%)	147 (22)
Atrial fibrillation (%)	188 (29)
NSVT (%)	131 (19)
ACEI/ARB (%)	483 (71)
Beta-blocker	263 (39)
Spironolactone (%)	134 (20)
Digitalis (%)	273 (40)

CAD coronary artery disease, BNP brain natriuretic peptide, LVDD left ventricular diastolic diameter, EF ejection fraction, NSVT non-sustained ventricular tachycardia, ACEI/ARB angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Table 2
Risk markers associated with an increase in total mortality

Individual risk markers	Hazard ratio	95% confidence interval
Age (year)	1.03	1.02–1.05
NSVT	1.72	1.14–2.58
LVDD (mm)	1.04	1.02–1.06
Log BNP	2.17	1.45–3.24
Diabetes	2.57	1.72–3.85
NYHA III/IV	1.59	1.03–2.46
ACEI/ARB	0.53	0.35–0.80

Abbreviations same as Table 1.

3. Results

1017 cases were registered in the database. We excluded 230 patients with uncorrected VHD and 107 patients who did not receive the first follow-up after

Table 3
Risk markers associated with an increase in sudden death

	Hazard ratio	95% confidence interval
Individual risk markers		
NSVT	2.63	1.35–5.12
EF < 30%	2.31	1.14–4.68
LVDD > 60 mm	2.26	1.09–4.72
BNP > 200 pg/ml	2.20	1.10–4.38
Diabetes	2.21	1.10–4.45
Number of risk markers included		
Risk markers ≥ 3	8.95	4.57–17.52

Abbreviations same as Table 1.

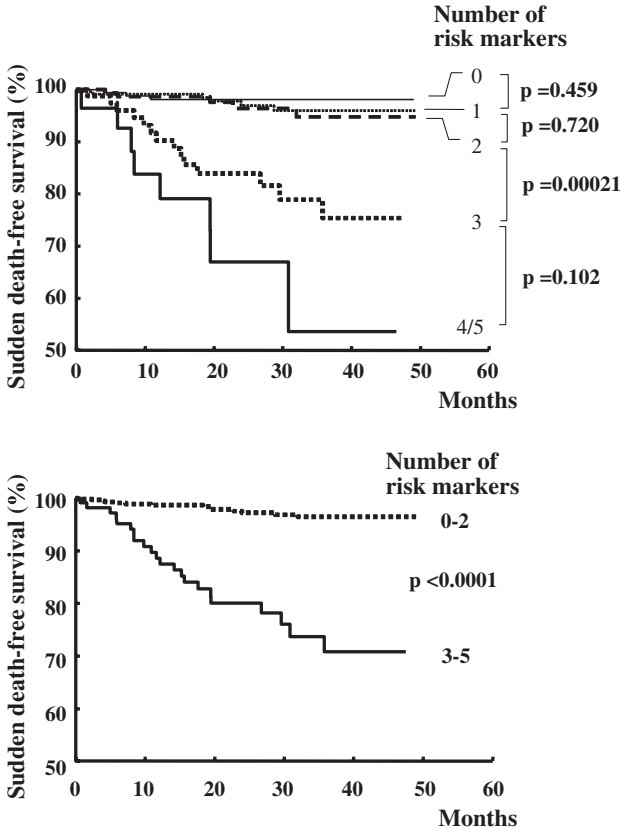

Fig. 1. Kaplan–Meier analysis for sudden death-free survival in patients grouped by the number of risk markers. Patients with 2 or less risk markers had a low event rate, but the event rate substantially increased in patients with 3 or more risk markers. The number of cases are shown in Table 4.

registration. We therefore analyzed data for 680 patients. Registration started in February 2000, and ended in March 2004. The follow-up was tentatively discontinued at the same time for data analysis. Table 1 summarizes the baseline clinical characteristics of the patients. Most patients (68%) had experienced a previous hospitalization due to clinically defined heart failure. The other patients who had not been hospitalized due to heart failure, had a similar history and degree of cardiac dysfunction (mean age 66±13 years, 34% had CAD, EF was 39±11%, and LVDD was 58±8 mm.

During the mean follow-up period of 26 months, we observed 103 deaths (61 cardiac and 42 non-cardiac). As shown in Table 2, age, NSVT, LVDD, Log BNP, diabetes, NYHA III/IV, and ACEI/ARB use were significantly associated with total mortality by Cox's regression analysis using stepwise methods.

Cardiac deaths comprised 25 heart failure deaths and 36 sudden deaths. Using ROC curves (data not shown), the cut off value for EF was estimated as 30%, for BNP as 200 pg/ml, and for LVDD as 60 mm. Cox's regression analysis with stepwise methods showed that EF<30%, LVDD>60 mm, BNP>200 pg/ml, NSVT and diabetes entered the model, but continuous forms of EF, LVDD, and BNP did not. The hazard ratios are shown in Table 3. In addition, after including the number of risk markers as a co-variable, only "number of risk markers ≥3″ was significantly associated with an increase in the risk of sudden death (hazard ratio 8.95, 95% confidence interval 4.57–17.52). No other individual risk markers entered the model. The upper panel of Fig. 1 shows the Kaplan–Meier analysis for patients grouped according to the number of risk markers. Only two patients had 5 risk markers, and they were merged into one group with patients who had 4 risk markers. The sudden death-free survival rate was significantly lower in patients with ≥3 risk markers, and appeared to decrease with an increased number of risk markers. The lower panel of Fig. 1 shows that there was a substantial difference in the sudden death-free survival rate between patients with 0–2 and those with 3–5 risk markers.

Fig. 2 shows the sudden death-free survival rate in patients grouped according to EF and the number of other risk markers. There was no difference in the probability of sudden death between patients with EF<30% and 0–1 other risk markers and those with EF≥30% and 0–2 other risk markers (the total number of risk markers <3). Furthermore, there was no difference in the probability of sudden death between patients with EF<30% and 2–4 other risk markers and those with EF≥30% and 3–4 other risk markers (the total number of risk markers ≥3).

Table 4 summarizes the predictive performance of "number of risk markers" for sudden death compared to that of individual risk markers. Number of risk markers ≥3

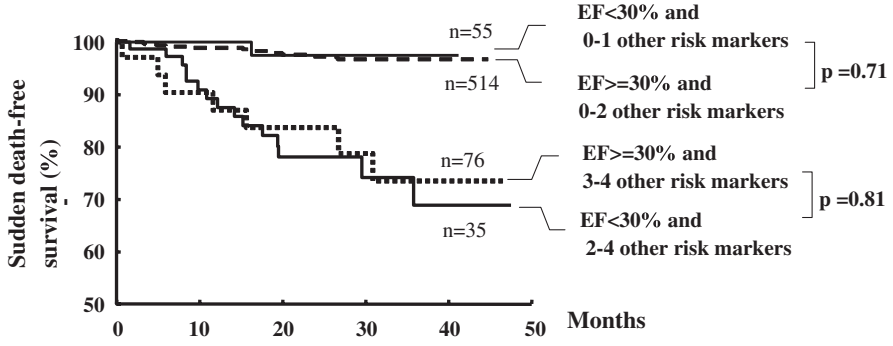

Fig. 2. Kaplan–Meier analysis for sudden death in patients who were grouped by a combination of low EF and the number of other risk markers. The incidence of sudden death was dependent on the total number of the risk markers including low EF.

Table 4
Predictive performance of the risk markers for sudden death

	Number of cases	Number of sudden deaths	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Risk markers						
EF < 30%	131	16	0.44	0.82	0.12	0.96
LVDD > 60 mm	242	23	0.64	0.66	0.10	0.97
BNP > 200 pg/ml	264	22	0.61	0.62	0.08	0.97
NSVT (+)	131	17	0.47	0.82	0.13	0.97
Diabetes	147	13	0.36	0.79	0.09	0.96
Number of risk markers						
Number of risk markers ≥ 4	28	8	0.22	0.97	0.29	0.96
Number of risk markers ≥ 3	111	22	0.61	0.86	0.20	0.98
Number of risk markers ≥ 2	269	27	0.75	0.62	0.10	0.98
Number of risk markers ≥ 1	505	33	0.92	0.27	0.07	0.98
Number of risk markers ≥ 0	680	36	–	–	–	–

Abbreviations same as Table 1.

had relatively good sensitivity and specificity as a predictor of sudden death in the patients examined.

4. Discussion

4.1. Accumulated risk markers predict the risk of sudden death

EF < 30%, LVDD > 60 mm, BNP > 200 pg/ml, NSVT, and diabetes entered the model. After including the number of risk markers as co-variables, only "number of risk markers ≥ 3" entered the model. The main effects of the individual risk markers did not enter the model. Kaplan–Meier analysis showed that the incidence of sudden death was quite low when the number of risk markers was 2 or less, and it substantially increased when the number was 3 or more. Kaplan–Meier analysis showed that EF < 30% may not affect the incidence of sudden death when patients are grouped according to the number of accumulated risk markers.

The risk markers identified in the present study have already been recognized as predictors for sudden death in patients with CHF [6]. BNP has also been reported as a significant predictor for sudden death in patients with CHF [8]. However, the prognostic power of the combined/accumulated risk markers is unclear. In patients with myocardial infarction, Richards et al. [9] reported that combined assessment of EF and BNP provided substantially better risk stratification than that provided by either alone. In patients with CHF, we also reported that high BNP was associated with an increased risk of sudden death when EF was reduced [3]. In patients with DCM, Grimm et al. [6] reported that the combination of EF < 30% and NSVT was associated with an 8.2-fold risk of major arrhythmic events compared to patients with EF ≥ 30% and no NSVT. The present study also indicated that combined risk markers are more important than isolated ones.

It is reasonable to assume that the incidence of sudden death will increase with the accumulation of significant risk markers, the present study demonstrated that the incidence of sudden death increased with the number of risk markers. That is, the cumulative incidence of sudden death substantially increased when patients accumulated 3 risk markers. The incidence of sudden death was 1.4% at 1 year and 2.8% at 2 years when the number of risk markers was 2 or less, but increased to 11.0% at 1 year and 20.0% at 2 years when the number of risk markers was 3 or more.

Because the main effect of individual risk markers did not enter the model after including the number of risk markers as a co-variable, the incidence of sudden death should be closely related to accumulation of risk markers, not to particular risk markers. Low EF appeared to be the single most important risk factor for sudden death in patients with ischaemic CHF [5] and DCM [6]. In the present study, however, the main effect of EF < 30% did not enter the model after including the number of risk markers as co-variables. Thus, EF < 30% may not have a particular power for predicting sudden death. We speculate that low EF is a powerful risk marker because the other risk markers tend to be present in patients with a low EF.

4.2. Predictive performance of the accumulated risk markers for sudden death

Accumulated number of risk markers ≥ 3 appeared to have good predictive performance with a relatively high positive predictive value (PPV = 0.20) and the highest negative predictive value (NPV = 0.98), which are good characteristics for a screening test for sudden death. The predictive performance of EF < 30% was relatively poor with a low PPV (0.12) and the lowest NPV (0.96).

Risk screening is the first step for the primary prevention of sudden death in patients with CHF. The screening test needs to be easily applicable to most patients. Reduced EF (< 30%) has been used for risk stratification [5] and ICD criteria [10], mainly because many randomized trials for sudden death including MADIT II, DEFINITE [4,11–13] have used it for entry criteria. However, the present study

suggests that reduced EF itself does not have a particularly good predictive performance. In clinical practice, a multi-faceted screening method is required in order to identify high-risk patients. We believe that the number of accumulated risk markers would be a suitable indicator for screening sudden death risk in patients with CHF.

4.3. Limitations

The present study has several limitations that need to be addressed. The main limitation was the relatively small size of the study (680 patients, 36 sudden deaths). The other critical point is the selection of the cut off values for EF, LVDD, and BNP. Previously, statistical values (mean, median, quartile, mean/standard deviation) and the ROC curve have been used for determining optimal cut off values. We used the ROC curve. However, there is no gold standard for determining cut off values, and a cut off value derived from the ROC curve may not necessarily be optimal in a multivariate setting. To confirm validity of the risk markers in a multivariate setting, the stepwise method was performed after including EF <25%, <30%, <35%, LVDD >55, >60 , >65 mm, BNP >100, >200, >300 pg/ml as co-variables. This showed that EF<30%, LVDD>60 mm, and BNP>200 pg/ml entered the model, and the other values did not. However, we do not think that the risk markers and cut off values used in the present study are definitive. They need to be refined qualitatively and/or quantitatively in future studies. We defined NSVT as 3 or more consecutive ventricular premature beats with a heart rate>150 bpm. This was a more rigorous criterion than that used in recent clinical trials (heart rate>100–120 bpm).

The endpoint was sudden unexpected death, and included both witnessed immediate death (<1 h) and non-witnessed unexpected death which could not be explained by non-cardiac causes according to the Utstein guidelines [14]. Neither was accompanied by worsening heart failure. We did not use non-invasive tests, such as T wave alternans [15,16], heart rate variability [17,18], heart rate turbulence [19], late potential [20] and QT dispersion [21]. These tests may have power to predict sudden death in patients with CHF, although they have problems in terms of applicability. The study population included a number of different heart diseases although the underlying heart disease did not enter the model.

In summary, reduced EF (<30%), dilated LVDD (>60 mm), high BNP (>200 pg/ml), NSVT, and diabetes, were significantly associated with an increased risk of sudden death in patients with CHF. Rather than particular risk markers, the number of accumulated risk markers was strongly associated with an increased risk of sudden death. Patients with 3 or more risk markers showed a substantial increase in sudden death mortality compared to patients with 2 or less risk markers. Reduced EF was one of the risk markers, but did not have a particular power for predicting sudden death in patients with CHF.

In conclusion, the number of accumulated risk markers was a powerful predictor for sudden death in patients with CHF. It provides multi-faceted risk stratification and should be useful for risk screening for sudden death in patients with CHF.

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Appendix A

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