SCIENTIFIC LETTER

Raised B-type natriuretic peptide predicts implantable cardioverter-defibrillator therapy in patients with ischaemic cardiomyopathy

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Identification of patients with congestive heart failure (CHF) at risk for sudden cardiac death (SCD) remains a major problem. Implantable cardioverter-defibrillator (ICD) implantation constitutes an effective preventive strategy, both for primary and for secondary prevention of SCD.[1][2] Evidence regarding the benefit of ICD implantation in patients with advanced CHF is limited, however, as death caused by pump failure becomes more important in these patients and the projected life span is short. Improved risk stratification for identification of appropriate candidates for ICD implantation appears critical to ensure access of eligible patients to this lifesaving treatment and to spare inappropriate candidates the side effects. Cost effectiveness is critically dependent on identification of appropriate high-risk subgroups in patient groups with low left ventricular ejection fraction (LVEF).[1] The role of the B-type natriuretic peptides in predicting mortality in patients with CHF including SCD is increasingly being recognised.[3][4] The definition of SCD used in clinical trials does not rule out ischaemic or non-cardiac causes of death, however, as shown by an autopsy study.[5] The present study evaluated the hypothesis that raised N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations may predict ventricular tachyarrhythmia as a surrogate marker of SCD in patients with ischaemic CHF and an ICD device.

METHODS

NT-proBNP concentrations (Roche Diagnostics, Mannheim, Germany) were determined at ICD implantation in patients with ischaemic CHF (scintigraphic LVEF $\leqslant$ 30%) and were correlated with the results of ICD interrogation during the first postoperative year. Exclusion criteria were NT-proBNP measurement unavailable at the time of ICD implantation, acute cardiogenic shock, myocardial infarction, renal failure, operation within four weeks before ICD implantation, a combined ICD/cardiac resynchronisation therapy device, patients lost to follow up, and technical ICD defects after implantation. Appropriate ICD therapy comprised defibrillation (active ventricular tachycardia (VT) zones) and anti-tachycardia pacing to avoid missing critical episodes of ventricular tachyarrhythmia, as no homogeneous predefined ventricular fibrillation zones were available. Inappropriate therapy was for tachyarrhythmic episodes of supraventricular origin or slow VT evaluated by an electrophysiologist in our centre blinded to the study. Kaplan–Meier log rank analyses were performed for a range of potential cut-off NT-proBNP concentrations to determine the distribution of tachyarrhythmia-free survival time. The best discriminating NT-proBNP concentration was thus derived. Univariate and multivariate Cox regression analyses were performed to determine an association with ICD therapy.

RESULTS

Fifty patients with advanced ischaemic CHF (median New York Heart Association (NYHA) class 3, median LVEF 20%, median NT-proBNP concentration 1690 pg/ml) were identified who had received an ICD for primary (n = 34, MUSTT (Multicenter Unsustained Tachycardia Trial) criteria) or secondary prevention (n = 16, AVID (Antiarrhythmics Versus Implantable Defibrillators) criteria).[1][2] The follow-up period was restricted to one year (median 0.78 years with a median of four postoperative visits), as NT-proBNP concentrations are subject to change. Among 193 ICD interrogations, 34 (17.6%) showed appropriate ICD therapy (9 × shock for fast VT, 16 × shock for ventricular fibrillation and 9 × antitachycardia pacing for fast VT). The average annual rate of appropriate ICD therapies per interrogations was 22.6%. In the group of patients with ICD events (n = 16, 11 of whom had 2–4 events) NT-proBNP concentrations were significantly higher than in the remaining patients (5836 (4140) v 1654 (1431) pg/ml, p = 0.0023).

NT-proBNP concentration of 2536 pg/ml was identified as the optimal cut off for the prediction of ICD therapy during the first postoperative year, characterised by a sensitivity of 87.5% and a specificity of 88%. Patients stratified accordingly did not differ significantly in clinical and demographic parameters (table 1). ICD therapy was detected in significantly more patients with NT-proBNP concentrations above the cut-off concentration (14/18 v 2/32, p = 0.0005) and tachyarrhythmia-free survival was significantly worse (p < 0.0001) (fig 1). Univariate analysis identified raised NT-proBNP (p < 0.0001, relative risk (RR) 7.73, 95% confidence interval (CI) 2.92 to 20.45), no treatment with statins (p = 0.0103, RR 3.18, 95% CI 1.31 to 7.69), atrial fibrillation (p = 0.0256, RR 2.87, 95% CI 1.14 to 7.25) and indication for ICD implantation (secondary prevention) (p = 0.0341, RR 2.55, 95% CI 1.07 to 6.06) as significant predictors of ICD therapy. Drug, LVEF, sex, heart rate variability (standard deviation of all normal-to-normal RR intervals), NYHA functional class, QRS duration, serum creatinine concentration, age, blood pressure, heart rate and non-sustained VT had no influence. Multivariate analysis identified NT-proBNP as the only independent predictor of future ICD events (p < 0.0001, RR 11.07, 95% CI 3.57 to 34.30).

Tachyarrhythmia-free survival remained significantly worse in a subgroup analysis with this NT-proBNP cut-off

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Table 1 Patient characteristics

Parameter	NT-proBNP (pg/ml)	
	≤2536 (n=32)	>2536 (n=18)
Age (years)	57.7 (7.6)	60.3 (8.7)
Men	26/32 (81.3%)	16/18 (88.9%)
NYHA class	2.6 (0.5)	2.7 (0.7)
LVEF by scintigraphy (%)	21.1 (4.3)	19.1 (7.4)
Serum creatinine (μmol/l)	97.2 (26)	97.2 (18)
Sinus rhythm	27/32 (84.4%)	14/18 (77.8%)
QRS duration (ms)	137.4 (34.0)	135.6 (27.8)
Heart rate variability (SDNN) (ms)	146.7 (37.9)	142.1 (31.4)
NSVT	24/32 (75%)	14/18 (77.8%)
Heart rate (beats/min)	67.3 (13.5)	70.2 (15.1)
Systolic blood pressure (mm Hg)	112.7 (15.5)	114.4 (22.1)
Diastolic blood pressure (mm Hg)	72.5 (11.7)	73.2 (11.3)
ACE/ATIIR inhibitor	30/32 (93.8%)	14/18 (77.8%)
β blocker	28/32 (87.5%)	12/18 (66.7%)
Statins	25/32 (78.1%)	11/18 (61.1%)
Spironolactone	22/32 (68.8%)	10/18 (55.6%)
Digitalis	18/32 (56.3%)	13/18 (72.2%)
Diuretics	26/32 (81.3%)	15/18 (83.3%)
Follow up (years)	0.72 (0.23)	0.69 (0.23)
ICD for secondary prevention	8/32 (25%)	8/18 (44.4%)
Death or heart transplant	1/32 (3.1%)	4/18 (22.2%)

Continuous and categorical variables were compared by Student's *t* test and the χ^2 test, respectively. All differences were non-significant. ACE, angiotensin-converting enzyme; ATIIR, angiotensin II type 1 receptor; ICD, implantable cardioverter-defibrillator; NSVT, non-sustained ventricular tachycardia; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SDNN, standard deviation of all normal-to-normal RR intervals.

concentration (p = 0.0001 in the primary prevention group, n = 34, and p = 0.0005 in the secondary prevention group, n = 16). In both subgroups NT-proBNP was the only independent predictor of ICD therapy (p = 0.0058, RR 7.74, 95% CI 1.81 to 33.17, and p = 0.024, RR 13.06, 95% CI 1.40 to 121.59, respectively).

DISCUSSION

Our study identified raised NT-proBNP concentrations in a high-risk group of patients with advanced ischaemic CHF as the only independent predictor of appropriate ICD therapy. This finding underscores the data from a previous study in
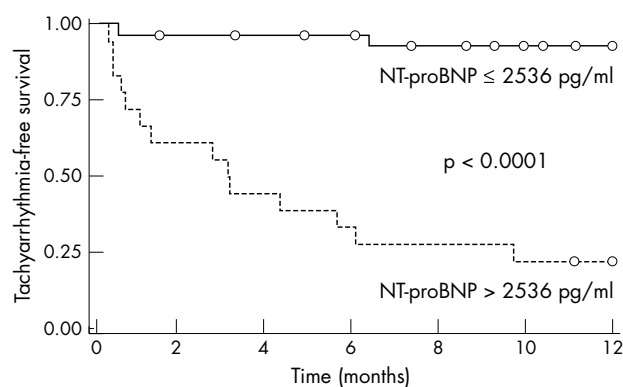

Figure 1 Event-free survival (Kaplan–Meier analysis) is shown for the two patient groups stratified according to N-terminal pro-brain natriuretic peptide (NT-proBNP) cut-off concentration of 2536 pg/ml. Detection of appropriate implantable cardioverter-defibrillator (ICD) therapy was a censored event; otherwise, follow up extended until completion of the first postoperative year. Open circles represent patients without an ICD event.

which log BNP was identified as a significant predictor of SCD.[4] Our study used a different assay system (NT-proBNP instead of BNP) and has two major advantages. Firstly, we used appropriate ICD therapy instead of the vague clinical definition of SCD, which cannot exclude non-arrhythmogenic death.[5] Secondly, the NT-proBNP cut-off concentration identified in our study is about 10-fold higher than a reasonable threshold (250 pg/ml) for the diagnosis of CHF in patients with normal renal function, enabling meaningful risk stratification of patients, unlike the very low BNP cut-off concentration in the previous study (130 pg/ml), comprising the great majority of patients with CHF.[4] Furthermore, our NT-proBNP cut-off concentration appears safe, as only two of 50 patients (4%) who fell below the cut off had ICD therapy.

Our data suggest that the use of NT-proBNP may improve candidate selection for ICD implantation. We regard the results from our pilot study as hypothesis generating and not as the basis for clinical decision making. We believe, however, that our study may provide the rationale to conduct a prospective clinical multicentre trial to validate our findings in a larger patient group combining serial measurements of NT-proBNP with a longer follow up.

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