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# Candesartan, NT-proBNP and recurrence of atrial fibrillation after electrical cardioversion ☆

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**Abstract**

*Background:* Some small studies have suggested that low levels of brain natriuretic peptide (BNP) measured before electrical cardioversion for atrial fibrillation (AF) may be associated with maintenance of sinus rhythm after the procedure. We hypothesized that 1) plasma levels of N-terminal fragment of proBNP (NT-proBNP) measured before cardioversion were predictive of AF recurrence, 2) treatment with candesartan would influence the levels of NT-proBNP, and 3) restoration of sinus rhythm would reduce the levels of NT-proBNP.
*Methods:* We investigated 171 patients with persistent AF who underwent electrical cardioversion in a prospective, blinded, placebo-controlled clinical trial (Candesartan in the Prevention of Relapsing Atrial Fibrillation, CAPRAF). Plasma levels of NT-proBNP were measured at baseline and at the end of the study. Patients with congestive heart failure were excluded from the study.
*Results:* Baseline NT-proBNP levels were similar in patients with unsuccessful cardioversion ($n=22$), patients with successful cardioversion remaining in sinus rhythm ($n=40$) and patients with successful cardioversion who had a relapse of AF ($n=89$): median (interquartile range) 73.9 pmol/L (43.2, 145.6); 88.2 pmol/L (59.2, 147.5) and 90.0 pmol/L (55.3, 138.4), respectively. Maintenance of sinus rhythm was associated with a significant reduction in NT-proBNP levels, whereas NT-proBNP levels were not affected by treatment with candesartan.
*Conclusions:* Plasma NT-proBNP concentration measured before electrical cardioversion did neither predict cardioversion success nor relapse of AF in patients without heart failure. Treatment with candesartan did not affect the levels of NT-proBNP. Maintained sinus rhythm during follow-up was associated with a significant reduction in NT-proBNP levels.


*Keywords:* Atrial fibrillation; Cardioversion; Natriuretic peptide; Angiotensin receptor blockade

## 1. Introduction

On secretion from cardiomyocytes, the intracellular prohormone of brain natriuretic peptide (proBNP) is split into the biologically active brain natriuretic peptide (BNP) and the remaining inactive N-terminal fragment of proBNP (NT-proBNP). NT-proBNP has a longer plasma half-life than BNP, and may provide a better diagnostic resolution [1,2]. The main stimulus for cardiac NT-proBNP secretion is myocardial stretch [3]; however both hormonal activity (catecholamines, angiotensin II, endothelin) and hypoxia may modulate its secretion [4,5]. In heart failure, the ventricular myocardium is

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considered the main source of BNP and NT-proBNP. However, proBNP is also produced in the atrial wall [6], and elevated levels have been documented in patients with atrial fibrillation (AF) without left ventricular dysfunction [7,8]. Restoration of sinus rhythm has been shown to reduce plasma levels of BNP and NT-proBNP [9–13].

Some small studies have suggested that low levels of BNP measured before electrical cardioversion for AF may be associated with maintenance of sinus rhythm after the procedure [14–16]. In contrast, NT-proBNP level was found not to be a valid predictor for long-term success of sinus rhythm restoration after cardioversion in another small study, including only 34 patients [17].

Studies have indicated that treatment with angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 receptor blockers (ARBs) may reduce the incidence of AF in hypertensive patients [18,19], after myocardial infarction [20] and in patients with heart failure [21–23]. Some studies have also indicated that treatment with ACE inhibitors or ARBs may reduce the recurrence rate of AF after electrical cardioversion [24–26]. While treatment with ACE inhibitors and ARBs is associated with a reduction in NT-proBNP and BNP levels in patients with heart failure [27], data on the effect of these drugs in patients with AF without heart failure is limited.

We hypothesized that 1) plasma levels of NT-proBNP measured before cardioversion were predictive of AF recurrence, 2) treatment with candesartan would influence the levels of NT-proBNP, and 3) restoration of sinus rhythm would reduce the levels of NT-proBNP.

## 2. Materials and methods

The present study was a substudy of a double blind, placebo-controlled study (Candesartan in the Prevention of Relapsing Atrial Fibrillation, CAPRAF) [28]. Briefly, 171 patients with persistent AF were randomised to receive candesartan 8 mg once daily ($n=86$) or placebo ($n=85$) for 3 to 6 weeks before and candesartan 16 mg once daily or placebo for 6 months after electrical cardioversion. Patients with congestive heart failure were excluded from the study.

Blood samples for analysis of NT-proBNP were collected at baseline and at the end of the study. Patients who had a relapse of AF during 6 months follow-up had their blood sample taken at that time. NT-proBNP was measured in EDTA–plasma with the Elecsys proBNP sandwich immunoassay on Elecsys 2010 (Roche Diagnostics, Basel, Switzerland). The inter-assay coefficient of variation was 7%. Echocardiographic measurements were performed according to recommendations by the American Society of Echocardiography [29]. Approval was obtained from the Regional Ethics Committee, and all patients provided written informed consent.

### 2.1. Statistical analyses

Data are expressed as mean±SD for normally distributed continuous variables, and median values (25th, 75th percentiles) are given for continuous variables not normally distributed. Categorical variables are presented as frequencies (%). Continuous variables were compared by Students *t* test or the Mann–Whitney *U*-test depending on distribution. Categorical data were compared by the chi-square test or Fisher's exact test where appropriate. The impact of clinical variables on NT-proBNP levels was analysed using non-parametric bivariate correlations (Spearman; correlation coefficient denoted $r_s$). Logarithmic transformation of baseline NT-proBNP levels was used in linear regression models. The effect of treatment with candesartan on NT-proBNP levels was analysed with the Mann–Whitney *U*-test comparing the change from baseline to the end of study relative to baseline levels. A two-sided *p*-value of $<0.05$ was considered significant. SPSS 12.0.1 software was used for statistical calculations.

## 3. Results

Baseline characteristics of the study population are presented in Table 1. The duration of AF before randomisation was unknown in 95 patients (56%), and known in 76 patients (40 in the candesartan group and 36 in the placebo group; median 11 weeks and 10 weeks, respectively).

### 3.1. NT-proBNP levels before cardioversion

Plasma NT-proBNP levels were measured at baseline in 165 patients. The levels were significantly higher in patients with hypertension ($n=49$) than in patients without this condition ($n=116$): 116.1 pmol/L (92.5, 150.5) vs. 78.1 pmol/L (66.7, 90.4) ($p=0.002$). Women ($n=38$) had higher levels of

Table 1
Baseline characteristics of the study population

| | $n=171$ |
|---|---|
| *Medical history* | |
| Age (years) | 64±11 |
| Sex (woman/men) | 39/132 |
| Body mass index (kg/m$^2$) | 26±4 |
| Hypertension | 51 (29.8%) |
| Coronary heart disease | 16 (9.4%) |
| Diabetes | 12 (7.0%) |
| Chronic obstructive pulmonary disease | 12 (7.0%) |
| *Medication* | |
| Digitoxin | 22 (12.9%) |
| Beta-blockers | 62 (36.3%) |
| Calcium channel blockers | |
| – Verapamil | 59 (34.5%) |
| – Other | 18 (10.5%) |
| Statins | 23 (13.5%) |
| *Echocardiogram* | |
| Left atrial diameter (long axis view, mm) | 46.2±5.5 |
| Left atrial area (apical four-chamber view, cm$^2$) | 27.0±5.2 |
| Fractional shortening (%) | 29.9±7.3 |

Baseline characteristics of the study population. Values are given as number (%) of patients or mean values ± standard deviation.