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Prevention of atrial fibrillation in patients with aortic valve stenosis with candesartan treatment after aortic valve replacement

Jordi S. Dahl [a,*], Lars Videbæk [a], Mikael K. Poulsen [a], Patricia A. Pellikka [b], Karsten Veien [a], Lars Ib Andersen [c], Torben Haghfelt [a], Jacob E. Møller [d]

[a] Department of Cardiology, Odense University Hospital, Denmark
[b] Division of Cardiovascular Diseases, Mayo Clinic Rochester, USA
[c] Department of Thoracic Surgery, Odense University Hospital, Denmark
[d] Department of Cardiology, Heart Center, Copenhagen University Hospital Rigshospitalet, Denmark

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ABSTRACT

Background: Accumulating data has suggested that treatment with Angiotensin-II receptor antagonists can prevent the new onset of atrial fibrillation (AF). The aim of this study was to evaluate whether treatment with candesartan on top of conventional treatment could prevent new onset AF in patients with aortic valve stenosis (AS) after aortic valve replacement.
Methods and results: The study was a single centre, consecutive; investigator initiated study using a prospective randomised blinded endpoint design. 91 patients with severe AS without known AF scheduled for aortic valve replacement (AVR) were randomised to candesartan 32 mg once daily on top of conventional treatment or conventional therapy immediately after AVR. Patients were examined with ECG 3, 6, 9 and 12 months after surgery, and Holter-ECG analysis after 3 and 12 months. Primary endpoint was episode of AF with a duration exceeding 30 s, on the ECG or Holter-ECG and/or patients hospitalised due to AF. 14 patients developed new onset AF during follow up. AF-free survival was significantly higher (94% vs 74%, $p = 0.02$) in patients treated with candesartan.
Conclusion: In patients with symptomatic severe AS undergoing AVR, treatment with candesartan may prevent the new onset of atrial fibrillation.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is often associated with reduced exercise capacity and increased cardiovascular risk. AF is frequently seen in patients with hypertension [1], where the risk of AF is especially increased in patients with left ventricular (LV) hypertrophy and left atrial (LA) dilatation [2]. Aortic valve stenosis (AS) is characterised by chronic LV and LA pressure overload. Due to direct effects on the myocardium and indirectly through activation of the renin angiotensin aldosterone system (RAAS), pressure overload leads to LV hypertrophy, LA dilatation and fibrosis and thus increasing the risk of AF.

Animal [3,4] and human [5] studies have shown that LA remodelling can be prevented by RAAS inhibition. In addition several previous studies have suggested that inhibition of the RAAS with ACE-inhibitors or Angiotensin-II-receptor antagonists can prevent the development of AF [6–10]. Most studies were retrospective primary prevention studies and AF was assessed as an ancillary variable. Lately, larger prospective trials in populations with low occurrence of severe LA and LV remodelling have failed to support the preventive effect of RAAS blockade [11,12]. The possible anti-arrhythmic effect of RAAS blockade is believed to be related to reverse LA and LV remodelling, regression in LA fibrosis and improved LV hemodynamics [13], suggesting that mainly patients with excessive LV and LA remodelling might benefit of RAAS blockade.

We have recently demonstrated that postoperative treatment with candesartan independently of blood pressure is associated with improved reverse LA and LV remodelling, in patients with severe AS [14]. The secondary endpoint of our study was to assess whether these structural changes prevented the development of AF. The aim of the present study was thus to assess the effect of RAAS blockade with candesartan in preventing the development of AF in patients in sinus rhythm that have undergone aortic valve replacement for aortic stenosis.

2. Methods

The study was a single centre, consecutive; investigator initiated study using a prospective randomised blinded endpoint design. The study was registered with the National Board of Health and the Danish Data Protection Agency and was approved by the local ethical committee. All patients gave written informed consent. ClinicalTrials.gov

* Corresponding author at: Department of Cardiology, Odense University Hospital, Sdr. Boulevard, 5000 Odense C, Denmark. Tel.: +45 65412615.
E-mail address: jordidahl@hotmail.com (J.S. Dahl).

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Identifier: NCT00294775. The study design and effect of candesartan on regression of LV hypertrophy has previously been published [14]. In brief patients aged >18 years; with symptomatic severe AS (estimated aortic valve area <1 cm^2) planned for AVR at Odense University Hospital, Denmark during the period February 2006 to April 2008 were enrolled. Patients with LV ejection fraction <40%, s-creatinine >220 μmol/l, previous aortic valve surgery, planned additional valve repair/replacement, infective endocarditis, predominant aortic valve regurgitation, ongoing treatment with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker were excluded. During the study period 114 patients were enrolled and randomised. As predefined in the protocol, 18 patients with a history of documented atrial fibrillation were excluded from this study. Furthermore 5 patients died during surgery leaving 91 patients in the study, of which 83 finished the 12-month follow up period (n = 5 died, n = 2 severe disease, n = 1 withdraw consent).

Patients were randomly assigned in a 1:1 fashion to either candesartan on top of conventional treatment or conventional treatment, after written consent was obtained. Candesartan treatment was started the 2nd day after surgery or on the day the patient was discharged from the cardiothoracic intensive care unit, if systolic brachial blood pressure exceeded 120 mm Hg. Initial dose was 8 mg candesartan once daily and if tolerated, the dose was increased to a target dose of 32 mg once daily.

All patients were treated for arterial hypertension if resting brachial blood pressure exceeded 135/90 mm Hg at any controls. Blood pressure was measured twice from the right arm with a sphygmomanometer in the supine position after 30 minute rest; the average blood pressure was calculated. In the control arm calcium channel blockers, diuretics and beta blockers were used to achieve blood pressure lowering.

2.1. Assessment of atrial fibrillation

The day before surgery and at each follow up at the outpatient clinic (3, 6, 9 and 12 months after surgery) a 12-lead resting ECG was performed. ECGs were recorded continuously for 2 min in the supine position with a paper speed of 25 mm/s.

A 24-hour Holter ECG recording was performed 3 months after surgery, and repeated after 12 months where 48 h was recorded. The recording was performed with Reynolds Medical Tracker 3 and a Pathfinder 700 (Reynolds Medical Limited, England) for analysis. All ECGs were interpreted by the same experienced cardiologist. Patients were ECG monitored continually during the first four to 5 days after cardiac surgery to detect postoperative arrhythmias. Additionally a 48-hour Holter ECG was performed if patients presented with symptoms suggestive of AF between visits. An episode of irregular heart rhythm symptomatic or asymptomatic with no definite P-waves and with a duration exceeding 30 s was considered suggestive of AF according to guidelines [15]. When a patient had 2 or more episodes, AF was considered recurrent. If the arrhythmia terminated spontaneously, recurrent AF was designated paroxysmal; when sustained beyond 7 days it was designated persistent [15].

Episodes of AF were considered secondary to other conditions and were not registered as endpoint AF, in the setting of acute myocardial infarction (n = 0), pericarditis/pericardial effusion (n = 2), hyperthyroidism (n = 0), pulmonary embolism or infectious disease (N = 3). Episodes of AF occurring within 30 days of valve replacement were considered as postoperative AF and not recorded as an endpoint. In patients with postoperative AF it was attempted to cardiovert patients to sinus rhythm with either amiodarone or with electric cardioversion. If initiated amiodarone was continued for a total of 3 weeks. Treatment of AF (primary, postoperative and secondary), was decided by attending physicians not taking part of the present study.

2.2. Echocardiography

All echocardiograms were performed by the same experienced operator on a GE Vivid 5 ultrasound machine (GE Medical System, Horten, Norway), the day prior to surgery. Echocardiography was repeated 3, 6, and 12 months after surgery. Echocardiograms were stored digitally for later blinded analyses. Great care was taken to ensure random analyses of echocardiograms and complete blinding to randomization status and clinical variables in all cases.

Aortic valve area was estimated using quantitative Doppler using the continuity equation. Peak flow velocity across the valve was determined in the window where the highest velocity could be recorded using continuous wave Doppler with cursor as parallel as possible with the flow across the valve. Peak transvalvular gradient was estimated using the Bernoulli equation. Finally the peak systolic flow velocity in the outflow tract was estimated with pulsed wave Doppler.

LV mass was estimated according to the joint recommendations of the American (ASE) and European (EAE) associations of echocardiography using Devereux's formula (0.8*(1.04([LV internal diameter + posterior wall thickness + interventricular septal thickness]^3 − [LVID]^3) + 0.6 g) [16,17]). Diastolic LV wall thickness and dimensions were estimated from the average of 3 consecutive frozen 2-D images obtained in the parasternal long axis [17]. Relative wall thickness was calculated using the formula 2 × posterior wall thickness/LV internal diameter in diastole [18]. LVH was considered when LV mass index is >116 g/m^2 in men and in women when >100 g/m^2 [16].

LV ejection fraction was estimated using Simpsons Biplane method. Longitudinal LV systolic function was assessed using peak systolic mitral annular motion assessed with tissue Doppler imaging with the Doppler sample volume placed in the septal, lateral, anterior, inferior, and posterior mitral valve annulus.

Mitral inflow was assessed in the apical four-chamber view using pulsed-wave Doppler with the sample volume paced at the tips of mitral leaflets during diastole. From the mitral inflow profile, the E- and A-wave peak velocities and deceleration time were measured. Doppler tissue imaging of the mitral annulus, was used in the aforementioned sampling sites to measure the early diastolic e′ velocity from each site.

LA volume was assessed using the area length method [16] from the apical four and two-chamber views. Measurements were obtained in end-systole from the frame preceding mitral valve opening, and the volume was indexed for body surface area. Severe LA dilatation was considered when LA volume index is ≥40 ml/m^2 [16].

2.3. Plasma N-terminal pro-brain natriuretic peptide

Blood samples were collected immediately following the echocardiogram, where the subject had been resting recumbent for at least 30 min. Samples were collected in ethylenediamine tetra-acetic acid tubes. These were then centrifuged and plasma samples stored at −80 °C for later analysis. N-terminal pro-brain natriuretic peptide (NT-proBNP) was determined using an ELECSYS® proBNP immunoassay (Roche Diagnostics GmbH Mannheim Germany).

2.4. Statistics

Data are presented as mean ± standard deviation or number and percentages. Differences between groups were tested by Student's t-tests for unpaired data once normality was demonstrated and categorical variables using Fisher's exact test. Due to a non-Gaussian distribution NT-pro BNP is presented as median and inter-quartile range, and differences between groups were tested with a Wilcoxon rank test.

Finally, uni- and multivariable Cox-regression analyses were constructed to assess the relationship between new onset atrial fibrillation at 12 months and randomization status after adjustment for possible confounders. A p value<0.05 was considered significant. STATA/SE version 9.0 (StataCorp LP, Texas, USA) software was used for statistical analysis.

3. Results

Characteristics of 91 patients enrolled in the study, are presented in Table 1. No differences were seen between groups, except higher preoperative heart failure class in the candesartan group (NYHA 2.2 ± 0.6 vs 2.0 ± 0.8, p = 0.05), the proportion of patients with heart failure class 3/4 symptoms and performance on 6 minute walk test however was not significantly different (332 ± 10 vs. 349 ± 112 m, p = 0.55). No patients were treated with class IC antiarrythmic drugs or digoxine at baseline and there was no difference in the use of beta-blockers and calcium channel blockers between groups (Table 2). During follow up half of patients were treated with beta-blockers with no difference between groups (48% vs 50%, p = 1.00 at 6 months, 40% vs 41%, p = 1.00 at 12 months) Table 2.

In the candesartan group systolic blood pressure decreased −6.3 ± 27 mm Hg compared with −0.1 ± 21 mm Hg in the conventional management group, p = 0.25. After 12 months no difference in systolic blood pressure was seen (143 ± 23 vs. 147 ± 19 mm Hg, p = 0.48) Table 2.

Table 1
Characteristics of patients.

	Candesartan	Standard	p-value
	n = 46	n = 45	
Age, y	72 ± 8	71 ± 11	0.86
Male gender	29 (63%)	29 (64%)	1.00
Hypertension	21 (46%)	18 (40%)	0.67
Diabetes	7 (15%)	5 (11%)	0.76
Coronary heart disease	11 (24%)	8 (18%)	0.61
Peripheral artery disease	6 (13%)	3 (7%)	0.49
Stroke	4 (9%)	3 (7%)	1.00
Symptoms			
6 min walk test (m)	332 ± 140	349 ± 112	0.55
NYHA	2.2 ± 0.6	2.0 ± 0.8	0.05
NYHA 3–4	14 (30%)	10 (22)	0.48
Chest pain	24 (52%)	22 (49%)	0.83
Surgery			
EURO score	5.8 ± 2.0	5.4 ± 1.9	0.34
CABG	16 (35%)	14 (31%)	0.82
Mechanical prosthesis	7(15%)	10 (22%)	0.43
Valve size	23.6 ± 2.0	23.8 ± 2.0	0.65
Postoperative atrial fibrillation	21 (46%)	18 (40%)	0.67