Original Article

A Randomised, Placebo-controlled Trial of Carvedilol in Early Familial Dilated Cardiomyopathy

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Background: **Screening of asymptomatic relatives of patients with dilated cardiomyopathy (DCM) has identified a population of individuals with left ventricular dilatation and/or minimally impaired contraction who are believed to have early disease. A proportion of these individuals with early disease progress to overt cardiomyopathy, however to our knowledge there have been no studies that have examined the impact of early intervention on disease progression.**

Methods: **We evaluated 424 asymptomatic relatives in 110 families of probands with DCM and identified 102 individuals (24%) with suspected "early disease" (EDCM). Thirty-two EDCM subjects were randomised into a six-month placebo-controlled trial of the β-blocker, carvedilol. Transthoracic echocardiography and plasma nt-proBNP levels were measured at baseline and repeated at six months. The primary trial endpoint was change in left ventricular end-systolic diameter after six months. Subjects completing six months of blinded trial therapy were offered open-label carvedilol and then observed over an extended period with repeated clinical evaluation and echocardiography.**

Results: **At baseline, left ventricular dimensions, systolic function and plasma nt-proBNP levels were similar in carvedilol and placebo groups. There were no significant changes observed in these parameters in either treatment group after six months, however reductions in end-diastolic diameter (% predicted) were observed in carvedilol-treated subjects ($P = 0.002$) during an open-label median follow-up of 32 months (range: 13–56 months).**

Conclusions: **In an asymptomatic population of individuals with EDCM, treatment with carvedilol for six months had no effect on echocardiographic left ventricular dimensions or systolic function, however longer-term treatment may reverse left ventricular remodelling (Australian Clinical Trials Registry N012605000204640).**

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Introduction

Familial dilated cardiomyopathy (DCM) is a genetically heterogenous disorder with nearly 40 chromosomal loci and disease-associated genes reported to date [1]. Because mutations in known disease genes account for only a minority of cases, physicians rely on clinical evaluation in most families. Studies that have systematically screened asymptomatic family members in DCM kindreds have found a subgroup of individuals with left ventricular dilatation and/or minimally depressed systolic function [2–4]. Longitudinal studies of these individuals have demonstrated that they face a substantial risk of progression to symptomatic DCM [5]. Identification of family members at risk provides the opportunity for early intervention but there are currently no data to support either pharmacological treatment or wait-and-see approaches for pre-symptomatic individuals.

The third-generation β-blocker, carvedilol, has been shown to reverse left ventricular enlargement, increase left ventricular ejection fraction, reduce hospitalisation and improve survival in patients with mild, moderate and severe heart failure [6–9]. In a recently published study, Chandar and colleagues reported that administration of carvedilol to heterozygous LMNA knockout mice from 12 weeks of age prevented the development of DCM in this model of genetically inherited DCM [10]. This finding suggests that pre-emptive treatment of individuals genetically predisposed to DCM may prevent or retard progression to clinically overt disease. To our knowledge, the effects

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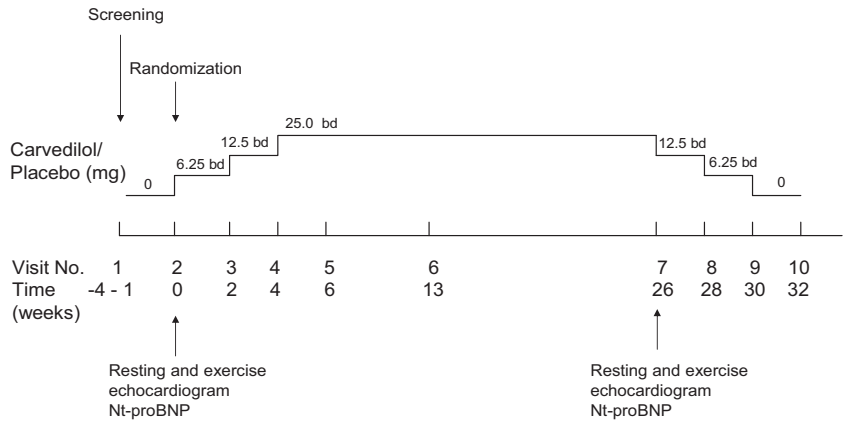

Figure 1. *Study design: double-blind, placebo-controlled phase.*

of carvedilol or any other medical intervention have not been assessed in asymptomatic individuals with evidence of early familial dilated cardiomyopathy (EDCM). We hypothesised that carvedilol would reverse left ventricular remodelling in early dilated cardiomyopathy (EDCM). Here we report a randomised, placebo-controlled clinical trial of the β-blocker, carvedilol in subjects identified as having EDCM based on family screening of probands with DCM.

Methods

Study Population

One hundred-ten probands with a family history of dilated cardiomyopathy (DCM) were identified during 2001–2006 from the population of in-patients and outpatients attending the Cardiology Department at St Vincent's Hospital and also by referral from collaborating physicians throughout Australia. Eligible subjects with EDCM were identified by echocardiographic screening of asymptomatic relatives of probands with DCM. Criteria for EDCM were: (1) absence of heart failure symptoms and (2) left ventricular end-diastolic diameter (LVEDD) ≥112% predicted with fractional shortening (FS) ≥25%, or (3) normal LVEDD (<112% predicted) with impaired fractional shortening (<25%), and (4) absence of other primary or secondary cardiac structural, conduction, or rhythm disorders. Exclusion criteria were as follows: past history of cardiac disease, history of exposure to environmental risk factors for dilated cardiomyopathy including heavy alcohol consumption, cardiotoxic or illicit drugs, prior or current treatment with β-blockers, medical contraindications to β-blockers (airflow limitation with 15% or greater reversibility, resting heart rate less than 50 beats per minute, or blood pressure less than 80/50 mmHg), age less than 16 years, pregnancy and inability to comply with the trial protocol. All study subjects provided informed written consent and protocols were approved by the institutional Human Research Ethics Committee.

Trial Design

The trial design consisted of an initial double-blind phase of carvedilol versus placebo conducted over six months. This was then followed by an open-label extension of active carvedilol therapy. The trial was approved by the St Vincent's Hospital Human Research Ethics Committee (Approval no. H02/045) and registered by the Australian Clinical Trials Registry (ACTRN012605000204640). The trial design is shown in Fig. 1.

Double-blind, placebo controlled phase: This phase was conducted over seven study visits. Eligible subjects with EDCM were identified at an initial screening visit and invited by one of the investigators to participate in the clinical trial. Study medications were provided by Roche Products Australia and were distributed by the clinical trials pharmacist at St Vincent's Hospital. Subjects were sequentially assigned medication packs that contained either carvedilol or matching placebo according to a randomisation schedule generated by Roche Products Australia. Participants and investigators were blinded to treatment group during recruitment, data acquisition and data analysis. One to four weeks after an initial screening visit, trial subjects were randomised to receive carvedilol ($n = 16$) or matching placebo ($n = 16$) commencing at 6.25 mg bd. Doses were doubled at two-weekly intervals as tolerated aiming for a maintenance dose of 25 mg bd by Week 6. If the target dose was not achieved by Week 6, additional titration visits were scheduled at two-weekly intervals until Week 12. Thereafter, all subjects were maintained on the achieved dose of study medication until the final study visit at six months. The development of intolerable β-blocker-related side effects including fatigue and dizziness, sustained bradycardia less than 50 beats per min, sustained hypotension with systolic blood pressure less than 100 mmHg or symptoms and signs of heart failure were considered indications for study withdrawal. All 32 participants completed the trial protocol and all endpoint analyses.

Open-label extension: After completion of the six months double-blind phase, trial subjects were offered ongoing treatment with active carvedilol therapy. In those that