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The Effects of Beta-Adrenergic Antagonists in Patients With Heart Failure

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University of Auckland, 1997
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I was principal investigator of the Echocardiography Substudy of this main trial (Chapters 6 and 7). This involved preparation of the echocardiography protocol, coordination of the substudy, measurement of the echocardiograms, data handling and subsequent statistical analysis. All statistical analyses for the echo substudy were carried out by myself, under the supervision of Greg Gamble. I would like to pay special tribute to the echocardiographers at the hospitals in this substudy. Their meticulous imaging of their patients was a key factor in the success of the study. I would also like to acknowledge all the patients involved in these studies whose patience allowed detailed and sometimes time-consuming echoes to be performed.

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Publications

The following papers have been published from this thesis:

Chapter 2


Chapter 3


Chapter 4


Chapter 5


Chapter 6

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Chapter 8
List of Abbreviations

Abbreviations used frequently throughout this thesis are listed below:

ACE  Angiotensin Converting Enzyme
BBPP  Beta-Blocker Pooling Project
BHAT  Beta-Blocker Heart Attack Trial
CONSENSUS  Cooperative North Scandinavian Enalapril Survival Study
EDVI  End-Diastolic Volume Index
EF  Ejection Fraction
ESVI  End-Systolic Volume Index
ICD  International Classification of Diseases
LV  Left Ventricle
NYHA  New York Heart Association
SD  Standard deviation
SE  Standard error of the mean
SOLVD  Studies of Left Ventricular Dysfunction
SVI  Stroke Volume Index
WMSI  Wall Motion Score Index
Abstract

Background

Congestive heart failure is a common clinical syndrome, the incidence and prevalence of which appear to be increasing. Mortality and morbidity remain high despite major advances in the understanding of the pathophysiology and management of heart failure over recent years. Consequently there is a need for further therapies which can improve the outlook for patients with heart failure. The beta-blockers have traditionally been contraindicated in patients with heart failure. However, there is a strong rationale for using these agents in addition to the ACE inhibitors. The aims of this thesis were several fold. Firstly, to determine the magnitude of the problem which heart failure represents in New Zealand. Secondly, to determine the effects of beta-blockers, on LV size and function, symptoms, and exercise tolerance in patients with heart failure due to ischaemic heart disease. Finally, to conduct a systematic overview to determine the effects of beta-blockers on total mortality in patients with heart failure.

Methods

Data were obtained from the New Zealand Health Information Service regarding hospitalisations and deaths due to heart failure in New Zealand. A randomised, placebo-controlled trial of the effects of carvedilol, a vasodilator beta-blocker, was carried out in 20 hospitals in Australia and New Zealand. In this study patients with heart failure due to ischaemic heart disease were randomised to either carvedilol or placebo in addition to their usual treatment.
An echocardiographic substudy was carried out in 10 of the 20 centres. The aims of this substudy were to determine the effects of carvedilol on left ventricular size and function, using quantitative 2D-echocardiography. Finally, the effects of beta-blockers on total mortality was examined in a systematic overview.

Results

The data regarding heart failure in New Zealand showed that each year there were an average of 8000 hospital admissions each year of 5000 patients with heart failure. In addition, there were at least 850 deaths each year directly related to heart failure. The cost associated with the hospital admissions was estimated at NZ$50 million per year, or 1% of the total health budget in New Zealand.

The ANZ carvedilol study demonstrated firstly, that carvedilol is well tolerated in patients with heart failure due to ischaemic heart disease. Left ventricular ejection fraction improved compared with placebo treated patients and left ventricular size was reduced when assessed by M-mode echocardiography. Despite these improvements in left ventricular function, symptoms and exercise tolerance were unchanged. However, there was a reduction in a combined end-point of death or hospital readmission in the carvedilol group compared with placebo. The 2D-echocardiography substudy demonstrated that carvedilol reduced both end-diastolic and end-systolic volumes and prevented the progressive LV dilatation which occurred in the placebo group. These
changes occurred with the improvement in LV ejection fraction which had previously been reported. In addition to these favourable effects on LV size and function, left ventricular regional wall motion was improved.

The overview of 24 randomised trials involving 3141 patients showed that beta-blocker therapy reduced total mortality by 31% compared with control.

Conclusions
Firstly, the NZ data has confirmed that heart failure remains a major public health problem in New Zealand. The ANZ Carvedilol Trial has shown the carvedilol is safe and well tolerated in patients with heart failure due to ischaemic heart disease. Carvedilol improved left ventricular ejection fraction, reduced left ventricular volumes and improved left ventricular regional wall motion. In addition, carvedilol reduced death or hospital readmission but had little effect on symptoms or exercise tolerance. The results from the meta-analysis have shown that beta-blocker therapy reduced total mortality by approximately one-third. Such data support the use of beta-blockers in addition to ACE inhibitors in the treatment of patients with heart failure. However, further randomised, controlled trials are required to reliably determine the effects of beta-blockers in different patient subgroups, such as the elderly and those with more severe heart failure, as well as the effects on total mortality before such therapy can be recommended for widespread use in all patients with heart failure.
Introduction and Epidemiology of Heart Failure

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