Clinical Trial: Methods and Design

The Singapore Heart Failure Outcomes and Phenotypes (SHOP) Study and Prospective Evaluation of Outcome in Patients With Heart Failure With Preserved Left Ventricular Ejection Fraction (PEOPLE) Study: Rationale and Design

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ABSTRACT

Background: Heart failure (HF) with preserved ejection fraction (EF) accounts for a substantial proportion of cases of HF, and to date no treatments have clearly improved outcome. There are also little data comparing HF cohorts of differing ethnicity within the Asia-Pacific region.

Methods: The Singapore Heart Failure Outcomes and Phenotypes (SHOP) study and Prospective Evaluation of Outcome in Patients with Heart Failure with Preserved Left Ventricular Ejection Fraction (PEOPLE) study are parallel prospective studies using identical protocols to enroll patients with HF across 6 centers in Singapore and 4 in New Zealand. The objectives are to determine the relative prevalence, characteristics, and outcomes of patients with HF and preserved EF (EF ≥50%) compared with those with HF and reduced EF, and to determine initial data on ethnic differences within and between New Zealand and Singapore. Case subjects (n = 2,500) are patients hospitalized with a primary diagnosis of HF or attending outpatient clinics for management of HF within 6 months of HF decompensation. Control subjects are age- and gender-matched community-based adults without HF from Singapore (n = 1,250) and New Zealand (n = 1,073). All participants undergo detailed clinical assessment, echocardiography, and blood biomarker measurements at baseline, 6 weeks, and 6 months, and are followed over 2 years for death or hospitalization. Substudies include vascular assessment, cardiopulmonary exercise testing, retinal imaging, and cardiac magnetic resonance imaging.

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Conclusions: The SHOP and PEOPLE studies are the first prospective multicenter studies defining the epidemiology and interethnic differences among patients with HF in the Asia-Oceanic region, and will provide unique insights into the pathophysiology and outcomes for these patients. (*J Cardiac Fail 2013;19:156−162*)

Key Words: Heart failure, preserved ejection fraction, epidemiology, pathophysiology, outcomes.

Heart failure (HF) is a major and growing public health problem worldwide. It is estimated that in the United States of America, ∼6.6 million people >18 years old had HF in 2010. This number is expected to grow by an additional 3 million by 2030.[1] HF is associated with poor outcomes, with ∼50% of patients dying within 5 years.[2,3] Ethnic differences have been demonstrated among Americans in the Multiethnic Study of Atherosclerosis (MESA), where African-Americans had the highest risk of developing HF, followed by Hispanic, White, and Chinese-Americans (4.6, 3.5, 2.4, and 1.0 per 1,000 person-years, respectively), reflecting ethnic differences in the expression of cardiovascular risk factors.[4]

Singapore and New Zealand are located in the Asia-Pacific region with land areas of 682 km^2 and 286,000 km^2, respectively, and each with a population of ∼5 million. The life expectancy at birth is ∼80 years in both countries. The major ethnic groups found in Singapore are Chinese, Malay, and Indian, comprising, respectively, 74%, 13%, and 9% of the population, whereas in New Zealand, European, Māori, Asian, and Pacific Islander ethnicities constitute, respectively, 67%, 15%, 10%, and 7% of the population.

In Singapore, age-adjusted HF hospital admission rates rose by almost 40% from 1991 to 1998, accounting for 5% of all hospitalisations and 3% of all deaths in patients aged ≥65 years.[5] HF admission rates have continued to rise, accounting for >5,000 admissions in 2011. The average length of stay was 4−5 days and the average cost of treatment >S$2,000 for each inpatient episode. Despite a decline in age-adjusted mortality from 1991 to 1998,[5] the 5-year mortality remained high at 68%.[6] Ethnic differences in outcomes have been observed among patients enrolled in an HF management program at two centers in Singapore, with Indians and Malays possessing a worse prognosis than Chinese.[7] Although the greater burden of diabetes and consequent atherosclerotic vascular disease in Indians may explain their worse outcome, the reasons for the poorer prognosis in Malays are unclear.[7]

In New Zealand, there are ∼5,500 patients who are admitted 12,000 times for HF each year.[8] The average length of stay is 5 days, and overall costs associated with HF account for ∼2% of the total health budget.[9] Although a decline in mortality for patients with HF was observed during the 1990s in New Zealand, mortality for HF stagnated during the past decade, with current mortality rates remaining high (20% at 6 months and 30% at 12 months).[8] HF among Māoris occurs 10−15 years earlier and is associated with 8-fold higher rates of readmission and mortality compared with non-Māoris.[10] The reasons for these differences are uncertain.

These data demonstrate that HF is an important health problem in Singapore and New Zealand. There are notable but incompletely understood ethnic differences in the burden of HF, risk factors, and clinical outcomes for patients with HF in both countries. Furthermore, it has been increasingly recognized over the past 2 decades that HF can occur despite the presence of normal left ventricular (LV) ejection fraction (EF), constituting the syndrome of HF with preserved EF (HF-PEF). Epidemiologic studies in American and European populations have shown that the prevalence of HF-PEF among patients with HF averages 54% in these Western cohorts, with a range of 40%−71%.[11] Very little is known regarding the prevalence of HF-PEF in Asia-Pacific cohorts.[12−14] Earlier reports have varied regarding outcomes in patients with HF-PEF, with some often-cited studies suggesting that prognosis is as poor as in patients with HF with reduced EF (HF-REF).[15−17] However, a recent meta-analysis of >40,000 patients from 31 studies demonstrated lower mortality for patients with HF-PEF than HF-REF.[18] These conflicting results may be due to a variety of factors, including intrinsic differences in the patient populations recruited, variations in the definition of the syndrome of HF-PEF, and potential bias within the studies due to missing data (missing EF measurements). These data highlight the need for prospective longitudinal studies in large cohorts of HF with a carefully validated diagnosis of HF but unselected for EF or other potential biases. Such studies are needed to accurately determine the clinical characteristics, outcomes, and prognostic factors among patients with HF-PEF versus HF-REF. Identification of patients who are at higher risk of clinical events will allow targeted clinical trials of specific therapeutic interventions—an urgent need in HF-PEF because there is to date no therapy proven to improve mortality in HF-PEF.

Methods

This is a prospective observational study of representative samples of patients with validated HF in Singapore and New Zealand, compared with age-matched control subjects without HF, designed to address the following aims and hypotheses.

Primary Aims

1. To determine the proportion of patients with HF who have HF-PEF.
2. To determine the prognosis for patients with HF-PEF compared with patients with HF-REF.