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Impact of Nurse-Led, Multidisciplinary Home-Based Intervention on Event-Free Survival Across the Spectrum of Chronic Heart Disease

Composite Analysis of Health Outcomes in 1226 Patients From 3 Randomized Trials

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Background—We sought to determine the overall impact of a nurse-led, multidisciplinary home-based intervention (HBI) adapted to hospitalized patients with chronic forms of heart disease of varying types.

Methods and Results—Prospectively planned, combined, secondary analysis of 3 randomized trials (1226 patients) of HBI were compared with standard management. Hospitalized patients presenting with heart disease but not heart failure, atrial fibrillation but not heart failure, and heart failure, as well, were recruited. Overall, 612 and 614 patients, respectively, were allocated to a home visit 7 to 14 days postdischarge by a cardiac nurse with follow-up and multidisciplinary support according to clinical need or standard management. The primary outcome of days-alive and out-of-hospital was examined on an intention-to-treat basis. During 1371 days (interquartile range, 1112–1605) of follow-up, 218 patients died and 17917 days of hospital stay were recorded. In comparison with standard management, HBI patients achieved significantly prolonged event-free survival (90.1% [95% confidence interval, 88.2–92.0] versus 87.2% [95% confidence interval, 85.1–89.3] days-alive and out-of-hospital; $P=0.020$). This reflected less all-cause mortality (adjusted hazard ratio, 0.67; 95% confidence interval, 0.50–0.88; $P=0.005$) and unplanned hospital stay (median, 0.22 [interquartile range, 0–1.3] versus 0.36 [0–2.1] days/100 days follow-up; $P=0.011$). Analyses of the differential impact of HBI on all-cause mortality showed significant interactions (characterized by U-shaped relationships) with age ($P=0.005$) and comorbidity ($P=0.041$); HBI was most effective for those aged 60 to 82 years (59%–65% of individual trial cohorts) and with a Charlson Comorbidity Index Score of 5 to 8 (36%–61%).

Conclusions—These data provide further support for the application of postdischarge HBI across the full spectrum of patients being hospitalized for chronic forms of heart disease.

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Key Words: case management ■ heart diseases ■ mortality ■ outcome assessment (health care) ■ patient readmission ■ secondary prevention

There is an increasing pressure to develop cost-effective strategies to mitigate persistently high levels of rehospitalization and premature mortality associated with chronic heart disease. Beyond pharmacological agents and devices, disease management programs are integral to applying flexible, guideline-based management, coordinating care, and providing individualized support.^{1,2} However, the evidence to support their application across the full spectrum of heart disease remains incomplete and fragmented. For example, although the overall evidence supporting short-term cardiac rehabilitation³ and chronic heart failure (CHF) management⁴ programs is extensive and mostly favorable, there is a paucity of research to support programs designed to prevent progressive cardiac

dysfunction in patients who survive an acute coronary syndrome⁵ or to optimize outcomes in those with atrial fibrillation (AF).^{6,7} Moreover, a diverse range of disease management techniques have been tested. Ideally, the same form of disease management program adapted to the individual patient profile would be tested across a diverse range of cardiac patients receiving high levels of standard care to determine its overall potential to improve health outcomes in the real-world setting.

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Clinical Perspective on p 1877

In the absence of a single definitive trial, we conducted 3 contiguous trials examining the benefits of the same model

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of care (nurse-led, multidisciplinary, home-based intervention [HBI]) to prevent secondary events in hospitalized patients spanning the continuum of heart disease. In each trial, we postulated that the benefits of HBI would transcend a patient's specific cardiac needs and would be more responsive to their wider clinical and psychosocial needs with improvements in all-cause health outcomes. We now report on a prospectively planned, composite analysis of study outcomes from these trials. A priori, we postulated that, in the overall setting of chronic heart disease, HBI is superior to standard care in preventing recurrent hospitalization and premature mortality on an all-cause basis in patients with any form of chronic heart disease.

Methods

Study Design and Patients

Baseline and outcome data were combined from 3 trials targeting hospitalized patients with: (1) a range of chronic heart disease states (most presented with acute coronary syndrome) but not CHF (n=611) enrolled in the Nurse-led Intervention for Less Chronic Heart Failure (NIL-CHF) Study⁸; (2) chronic AF but not CHF (n=335) enrolled in the Standard versus Atrial Fibrillation Specific Management Strategy (SAFETY) Trial⁹; and (3) CHF (n=280) enrolled in the Which Heart Failure Intervention Is Most Cost-effective & Consumer Friendly in Reducing Heart Failure Hospital Care (WHICH?) Trial.¹⁰ All 3 trials were registered via www.anzctr.org.au (12608000022369, 12610000221055, and 12607000069459, respectively) and conducted with appropriate ethics approval.

Detailed descriptions of each study design^{5,11,12} and subsequent outcomes⁸⁻¹⁰ (including extended follow-up of the WHICH? Cohort)¹³ were published between 2011 and 2015. Each adhered to CONSORT guidelines for conducting pragmatic health service interventions.¹⁴ Applying the same methods of recruitment, profiling, and follow-up, with only minor differences in clinical management specific to the target patient population, data were derived from 1226 patients recruited from 6 tertiary referral hospitals across 5 Australian states with a combined follow-up of 4517 person-years (see Table 1).

A blinded, computer-generated randomized protocol was implemented by an independent data management team via telephone for each study with a predetermined, block randomization sequence for individual study sites. Stratification for reduced versus preserved ejection fraction in the WHICH? Trial of patients with CHF and nominated rhythm versus rate control in the SAFETY Trial of patients with AF were applied. Overall, 612 and 614 patients were allocated to HBI and standard management, respectively.

Study Data

All patients were comprehensively profiled during their index admission by using the same framework of profiling and data entry. This included sociodemographic status, past medical history (including details specific to their primary reason for trial inclusion), clinical profile, in-hospital management, and planned post-discharge care.

Clinical Management

No restrictions on the level of standard management (other than no structured home visits) were applied. Treating physicians were routinely sent a copy of the hospital discharge summary and information about the trial and group allocation. Postdischarge, patients had unrestricted access to outpatient management via >50 specialist physicians (predominantly cardiologists), routine follow-up provided by 941 primary care physicians, subsidized pharmacological treatment, and referral to allied healthcare services when required. Common elements of the HBI were as follows: (1) a home visit 7 to 14 days

posthospitalization conducted by a registered cardiac nurse with tertiary qualifications; (2) comprehensive automated reports derived from baseline and home profiling providing treating physicians with recommendations to address any treatment or management deficits; (3) coordination of multidisciplinary follow-up; (4) telephone follow-up by the cardiac nurse with both scheduled and patient-initiated contacts; (5) a strong focus on the 6 months postindex hospitalization to address residual risk with reapplication of home visits if a patient experienced an unplanned hospitalization; and (6) structured review and generation of a comprehensive report and recommendations for optimal long-term management once active study management was discontinued. Table 2¹⁵⁻²⁰ summarizes the specific features of postdischarge management for the 3 studies.

End Points

Health outcomes were collected via electronic health records by personnel masked to group allocation. Subsequent adjudication of the type and nature of recurrent hospitalizations were determined by each study's blinded end point committee. The primary end point for this composite analysis was event-free survival expressed as the proportion of actual versus maximal unplanned days-alive (a combined total of 1 648 560 days) and out-of-hospital (DAOH). For example, a patient who experienced 10 days of unplanned hospitalization and died on day 700 of 730 possible days follow-up achieved 690 of 730 DAOH (94.5% of maximal). The 2 components of this end point, all-cause deaths and days of unplanned hospitalization, were also examined separately. Hospitalization data (episodes and related overnight hospital stay) were also examined on an all-cause, unplanned, and cardiovascular-specific basis.

Statistical Analysis

Profiling and outcome data from the 3 studies were pooled and analyzed using SPSS v22.0. Discrete variables were summarized by frequencies and percentages and continuous variables by means (standard deviation) and medians (interquartile range) where appropriate. Between-group comparisons of health outcomes (including the primary end point) were assessed by Mann-Whitney *U* test. All efficacy analyses were undertaken on an intention-to-treat basis and blinded to group allocation. Multivariate analyses used the baseline variables listed in Table 3.^{21,22} Survival data were used to generate Kaplan-Meier survival curves and group comparisons analyzed with the log-rank test. A Cox proportional hazards model was constructed to derive adjusted hazard ratios (HRs) for independent correlates of all-cause mortality using a backward, stepwise approach. All predictors included in the Cox model were from baseline and were not time varying. We tested only for covariates of mortality, not management group, because covariates were from baseline, and random assignment to treatment group will ensure no systematic effects beyond chance. The assumption of proportional hazards was tested for the effect of treatment by using time-weighted score tests and the assumption was not rejected ($P>0.05$). Because of incomplete data for left ventricular ejection fraction (n=839) and cognitive function (n=1004), these 2 variables were initially excluded and then added to the final iteration to determine their impact on the explanatory variables. Patient hospital activity data (unplanned, all-cause, and cardiovascular related) were converted to the rate of hospitalizations and days of hospital stay per 100 days of follow-up. An exploration of the relative impact of HBI on being in the worst quintile of DAOH and experiencing a fatal event was conducted by including a condition×trial interaction in logistic regression models. We also explored the possibility that there was a differential intervention effect according to the age of the patient and their burden of disease (as measured by the Charlson Comorbidity Index Score²³); both were treated as continuous variables and tested by including a condition×age and condition×age² or condition×comorbidities and condition×comorbidities² interaction terms in the regression models. Quadratic terms were included to allow the possibility that there was a U- or J-shaped pattern of interventional effect. If the quadratic term was not statistically significant, it was dropped.

Table 1. Major Design Features of the NIL-CHF Study, SAFETY Trial, and WHICH? Trial

	Inclusion Criteria	Exclusion Criteria	Indicative Cohort Profile		Major Outcome Measures
NIL-CHF Study ^{5,8}	<ul style="list-style-type: none"> All elective and emergency patients admitted to the cardiology unit of a tertiary hospital with specialist cardiac services in Melbourne, Australia, between June 2008 and July 2010. All cardiac inpatients aged ≥ 45 y were screened for study eligibility. Patients must present with a cardiovascular diagnosis requiring active treatment. Eligible patients must live within a 40-km radius of the hospital Eligible patients must be English speaking. 	<ul style="list-style-type: none"> Patients with a congenital condition, surgically repairable, or significant valve disease. Patients with a terminal condition at the time of the index admission. Cases of preexisting CHF arising from the index admission. Randomly assigned patients were excluded from end point analyses if they experienced a CHF-related admission within 30 days of hospital discharge. 	Mean age: 66 (11) Female: 29% Live alone: 39% Obese: 34% Smoker: 18% Hypertension: 62% Type 2 diabetes mellitus: 26% Anemia: N/A Renal Impairment: 16% Depressive symptoms: 24% Cognitive impairment: 49% Charlson Comorbidity Score: 4.7 (2.8) Median (IQR) index stay, days: 4 (2–7)		Primary: De novo CHF-related hospitalization or all-cause mortality during 3- to 5-y follow-up. Secondary: Rate of emergency, cardiovascular-related and all-cause hospitalization, and days of hospital stay. Cardiac function from baseline to 3 y according to 5 prespecified criteria consistent with expert guidelines: <ul style="list-style-type: none"> No evidence of a cardiac abnormality Systolic dysfunction Diastolic dysfunction A combination of systolic and diastolic dysfunction Any other cardiac abnormality including left ventricular hypertrophy Event-free survival from death or unplanned hospitalization.
SAFETY Trial ^{9,12}	<ul style="list-style-type: none"> Patient recruitment commenced on June 2, 2010 from sites in Adelaide, Melbourne and Canberra, Australia Patients admitted to the cardiac units of participating hospitals were eligible to participate if they had a diagnosis of chronic AF. Eligible patients were living independently within a 40-km radius of the hospital and were able to provide informed consent. 	<ul style="list-style-type: none"> Patients with a primary diagnosis of valvular heart disease, scheduled catheter ablation procedure, preexisting diagnosis of HF, alcohol-induced AF, or a terminal condition/malignancy requiring palliative care. 	Mean age: 72 (11) Female: 48% Live alone: 39% Obese: 43% Smoker: 14% Hypertension: 72% Type 2 diabetes mellitus: 29% Anemia: 14% Renal impairment: 35% Depressive symptoms: 36% Cognitive impairment: 65% Charlson Comorbidity Score: 4.9 (2.6) Median (IQR) index stay, days: 3 (1–5)		Primary: Days-alive and out-of-hospital (unplanned) during minimum 2 y follow-up. Secondary: All-cause mortality. Rate of emergency, cardiovascular-related and all-cause hospitalization, and days of related hospital stay.
WHICH? Trial ^{10,11}	<ul style="list-style-type: none"> Patient recruitment commenced on June 1, 2008 from sites in Adelaide, Brisbane and Sydney, Australia Patients admitted to the cardiac units of participating hospitals were eligible to participate if they were aged ≥ 18 y, discharged to home with a cardiologist-confirmed diagnosis of CHF (based on echocardiography), persistent moderate to severe symptoms (NYHA Class II–IV) and a recent history of ≥1 admission for acute HF. 	<ul style="list-style-type: none"> Patients who lived outside a 30-km radius of the hospital were excluded. Patients who were unable to perform informed consent, and who were non-English speaking were excluded. Patients were excluded if they had a terminal condition. 	Mean age: 71(14) Female: 27% Live alone: 55% Obese: N/A Smoker: 69% Hypertension: 63% Type 2 diabetes mellitus: 39% Anemia: 39% Renal impairment: 61% Depressive symptoms: 35% Cognitive impairment: 40% Charlson Comorbidity Score: 6.4 (2.4) Median (IQR) index stay, days: 7 (4–11)		Primary: Unplanned hospitalization or mortality during 12–18 mo of follow-up (dichotomous event-free survival and expressed as days-alive and out-of-hospital). Secondary: Rate of emergency, cardiovascular-related, HF-related and all-cause hospitalization, and days of related hospital stay. Longer-term survival and health care activity during minimum 3-y follow-up.

AF indicates atrial fibrillation; CHF, chronic heart failure; HF, heart failure; and NYHA, New York Heart Association.

Table 2. Characteristics of Clinical Management in the NIL-CHF Study, SAFETY Trial, and WHICH? Trial

	Study Intervention	Standard Care
NIL-CHF Study ^{5,8}	<ul style="list-style-type: none"> • Management was explicitly guided by expert guidelines for the secondary prevention of heart disease.¹⁵ • Short-term cardiac rehabilitation was offered to patients discharged from hospital with an ACS. • Comprehensive home visit at 7–14 days after index hospital discharge supplemented by comprehensive clinical profiling (including echocardiography and functional testing) at a nurse-led clinic at 30–35 days postdischarge. • Based on initial profiling, an individualized management plan based on the Green Amber and Red Delineation of risk And Need (GARDIAN) tool¹⁶ was used to generate an initial report and recommendations for clinical support and management and sent to the patient's primary care and specialist physician. A cardiac nurse then implemented that plan (with a strong focus on preventing progressive cardiac dysfunction) via a combination of repeat home visits, telephone follow-up, and multidisciplinary support. • At 18 mo and 36 mo, a repeat visit to the nurse-led clinic for follow-up clinical profiling and review of management goals relative to expert secondary prevention guidelines¹⁵ was conducted. • Follow-up by the cardiac nurse with multidisciplinary support applied between 18 and 36 mo. • A final report and recommendations for longer-term clinical support and management was sent to the patient's primary care and specialist physician at 36 mo. 	<ul style="list-style-type: none"> • Management was broadly guided by expert guidelines for the secondary prevention of heart disease.¹⁵ • Short-term cardiac rehabilitation was offered to patients discharged from hospital with an ACS. • Vicarious management applied by the cardiologists based at the Heart Center of a specialist tertiary referral hospital and the patient's primary care physician. • Clinical profiling (with structured reports of findings sent to the patient's healthcare team) conducted at 30–35 days and 36 mo postindex hospital discharge.
SAFETY Trial ^{9,12}	<ul style="list-style-type: none"> • Management was explicitly guided by expert guidelines for the management of chronic forms of AF.¹⁷ • Comprehensive home visit at 7–14 days postdischarge supplemented by 24-h ECG Holter monitoring and detailed profiling for thromboembolic events and progressive cardiac dysfunction before the home visit.¹⁸ • Based on initial profiling, an individualized management plan based on the GARDIAN tool¹⁶ was used to generate an initial report and recommendations for clinical support and management and sent to the patient's primary care physician and cardiologist. A cardiac nurse then implemented that plan (with a strong focus on optimal AF management) via a combination of repeat home visits, telephone follow-up, and multidisciplinary support. • Repeat 24-h ECG Holter monitoring applied at 12 mo. • At 12 and 24 mo, a visit to a nurse-led clinic for follow-up clinical profiling and review of management goals relative to expert guidelines for AF¹⁷ and secondary cardiac prevention¹⁵ was conducted. • Follow-up by the cardiac nurse with multidisciplinary support applied between 12 and 24 mo. • A final report and recommendations for longer-term clinical support and management for optimal AF was sent to the patient's primary care and cardiologist at 24 mo. 	<ul style="list-style-type: none"> • Management was broadly guided by expert guidelines for the management of AF.¹⁷ • Vicarious management applied by the patient's cardiologist and primary care physician. • Comparative 24-h ECG Holter monitoring conducted at 12 mo. • Clinical profiling (with structured reports of findings sent to the patient's healthcare team) conducted at 12 and 24 mo postindex hospital discharge.
WHICH? Trial ^{10,11}	<ul style="list-style-type: none"> • Management was explicitly guided by expert guidelines for the management of CHF.^{19,20} • Comprehensive home visit at 7–14 days postdischarge supplemented by detailed profiling of multimorbidity (including anemia, renal dysfunction, depression, and cognitive impairment) and ability to self-care before the home visit. • Based on initial profiling, an individualized management plan was used to generate an initial report and recommendations for clinical support and management and sent to the patient's primary care physician and cardiologist. A HF nurse then implemented that plan (with a strong focus on optimal HF management) via a combination of repeat home visits, telephone follow-up, and multidisciplinary support (including specialist HF clinic visits) up to 18 mo. • At 12–18 mo, a home visit for follow-up clinical profiling and review of management goals relative to expert guidelines for CHF management^{19,20} was conducted. • A final report and recommendations for longer-term clinical support and management for optimal CHF management was sent to the patient's primary care physician and cardiologist at 12–18 mo. 	<ul style="list-style-type: none"> • Management was explicitly guided by expert guidelines for the management of CHF.^{19,20} • The same principles and structure of management as HBI was applied via a specialist, outpatient HF clinic at each participating hospital. • No home visits were applied.

ACS indicates acute coronary syndrome; AF, atrial fibrillation; CHF, chronic heart failure; HBI, home-based intervention; and HF, heart failure.

Table 3. Baseline Characteristics According to Group Assignment and Sex (n=1226)

	Home-Based Intervention		Standard Management	
	Men (n=394)	Women (n=218)	Men (n=415)	Women (n=199)
Sociodemographic profile				
Age, y	67 (12)	72 (11)	68 (12)	71 (12)
Living alone*	152/393 (39%)	111/218 (51%)	147/412 (36%)	111/198 (56%)
<12 y education*	209/391 (54%)	134/217 (62%)	223/411 (54%)	128/197 (65%)
Risk factors*				
Obese (body mass index ≥ 30 kg/m ²)	128/364 (35%)	80/199 (40%)	128/369 (35%)	65/173 (38%)
Abdominal obesity	239/337 (71%)	140/168 (83%)	233/317 (74%)	121/149 (81%)
Hypertension (BP $\geq 130/80$ mm Hg)	214/379 (57%)	124/210 (59%)	222/384 (58%)	105/185 (57%)
Meeting exercise guidelines	173/392 (44%)	75/218 (34%)	172/408 (42%)	60/195 (31%)
Current smoker	87/393 (22%)	19/218 (9%)	73/412 (18%)	31/195 (16%)
High-risk alcohol use	88/387 (23%)	14/214 (7%)	91/408 (22%)	12/194 (6%)
Total cholesterol ≥ 4 mmol/L	125/319 (39%)	110/173 (64%)	131/312 (42%)	87/152 (57%)
High-density lipoprotein ≤ 1 mmol/L	174/302 (58%)	39/160 (24%)	162/299 (54%)	42/143 (29%)
Low-density lipoprotein ≥ 2 mmol/L	136/273 (50%)	85/152 (56%)	137/272 (50%)	80/138 (58%)
Clinical profile				
Systolic BP, mm Hg	130 (20)	133 (23)	131 (21)	130 (21)
Diastolic BP, mm Hg	74 (14)	73 (14)	75 (14)	70 (13)
Heart rate, beats/min*	81 (27)	86 (28)	80 (23)	87 (30)
Left ventricular ejection fraction*	50 (17)	56 (14)	53 (17)	60 (15)
Type 2 diabetes mellitus	123 (31%)	57 (26%)	133 (32%)	53 (27%)
Renal dysfunction (eGFR < 60 mL·min ⁻¹ ·1.73m ⁻²)*	100/383 (26%)	78/210 (37%)	122/388 (31%)	69/189 (37%)
Anemia (sex-specific)*	143/380 (38%)	83/210 (40%)	147/386 (38%)	61/190 (32%)
Charlson Comorbidity Index Score	5.0 (2.9)	5.2 (2.5)	5.1 (2.7)	5.0 (2.5)
Depressive symptoms*	155/390 (40%)	89/218 (41%)	142/407 (35%)	77/195 (40%)
Mild cognitive impairment*	166/330 (50%)	85/176 (48%)	180/342 (53%)	87/156 (56%)
In-hospital management				
Median length of stay	4.5 (2.0–8.0)	4.0 (2.0–8.0)	4.0 (2.0–8.0)	4.0 (2.0–8.0)
Median days in specialist/intensive care	3.0 (0–6.0)	2.0 (0–4.3)	2.0 (0–6.0)	2.0 (0–5.0)
Coronary revascularization	96 (24%)	25 (12%)	110 (27%)	23 (12%)
Primary discharge diagnosis				
Acute coronary syndrome	81 (21%)	32 (15%)	84 (20%)	31 (16%)
Acute heart failure	72 (18%)	37 (17%)	65 (16%)	30 (15%)
Stable coronary artery disease	63 (16%)	19 (9%)	57 (14%)	20 (10%)
Atrial Fibrillation	59 (15%)	56 (26%)	66 (16%)	60 (30%)
Discharge pharmacotherapy				
Lipid-lowering agent	291 (74%)	143 (66%)	302 (73%)	130 (65%)
Antiplatelet therapy	282 (72%)	142 (65%)	290 (70%)	123 (62%)
Angiotensin blockade	272 (69%)	152 (70%)	303 (73%)	128 (64%)
β -Blocker	232 (59%)	108 (50%)	240 (58%)	98 (49%)
Diuretic	145 (37%)	101 (46%)	148 (36%)	89 (45%)
Nitrate therapy	135 (34%)	65 (30%)	140 (34%)	62 (31%)
Antiarrhythmic agent	135 (34%)	87 (40%)	131 (32%)	104 (52%)
Anticoagulant	102 (26%)	75 (34%)	132 (32%)	63 (32%)

Data are presented as mean (SD), median (IQR), or number of patients (%). Depressive symptoms determined by positive response to a 2-item Arroll tool²¹ and mild cognitive impairment score is < 26 on the Montreal Cognitive Assessment tool.²² BP indicates blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; and SD, standard deviation.

*Data not available for all randomly assigned patients.

Results

Cohort Profile

Between June 1, 2008 and March 31, 2011, 1226 of 10382 cardiac inpatients at participating hospitals were eligible for study entry, randomly assigned to a study group, and followed for study outcomes (Figure 1). Median follow-up of 1371 days (interquartile range, 1112–1605) across the 3 studies was completed by March 31, 2014. Reflective of the increasing severity of disease across this family of trials, multimorbidity, as measured by the mean (age-adjusted) Charlson Comorbidity Index Score²³ was 4.7, 4.9, and 6.2 in the NIL-CHF, SAFETY, and WHICH? Trial cohorts. The HBI and standard management groups were well matched for sociodemographic characteristics and clinical profile according to sex (Table 3). The most common primary discharge diagnoses were AF (20%), acute coronary syndrome (19%), and acute HF (17%); the majority being admitted for a cardiovascular-related diagnosis (Figure 2). Women comprised 34% of patients and were on average 4 years older than men. Overall, patients had high levels of antecedent risk for secondary events and noncardiovascular multimorbidity complicating their clinical management. Pharmacological management included appropriately prescribed levels of antiplatelet/coagulant agents, lipid-lowering, angiotensin blockade, β -blockade, diuretics, and antiarrhythmic agents (Table 3).

Primary End Point: Days Alive and Out of Hospital

Based on favorable outcome data with respect to both survival and hospital stay (see Survival Profile and Hospitalizations below), the HBI group accumulated more DAOH (737 852 of a maximal 821 707 days) than those allocated to standard management (723 527 of 826 853 days). Specifically, HBI patients experienced a mean of 1210 (standard deviation, 463) DAOH

equating to 90.1% (95% confidence interval [CI], 88.2–92.0) days event free. In comparison, standard management patients experienced 1184 (standard deviation, 494) DAOH equating to 87.2% (95% CI, 85.1–89.3) days event free ($P=0.02$).

Survival Profile

Overall, 94 of 612 (15%) patients allocated to HBI died in comparison with 124 of 614 (20%) patients allocated to standard management. HBI was associated with significantly prolonged survival (unadjusted HR, 0.75; 95% CI, 0.57–0.98; $P=0.032$; Figure 3). The effect was even stronger (HR, 0.67; 95% CI, 0.50–0.88; $P=0.005$) after adjusting for age (HR, 1.04; 95% CI, 1.02–1.05 per year; $P<0.001$); age-adjusted Charlson Comorbidity Index Score (HR, 1.22; 95% CI, 1.16–1.28 per unit score; $P<0.001$), AF (HR, 2.02; 95% CI, 1.46–2.79; $P=0.006$), being treated for hypertension (HR, 0.67; 95% CI, 0.51–0.88; $P=0.004$), prescribed a diuretic (HR, 2.96; 95% CI, 2.12–4.13; $P<0.001$), and index length of stay (HR, 1.03; 95% CI, 1.03–1.04 per day; $P<0.001$). When added in a separate model, left ventricular ejection fraction (HR, 0.97; 95% CI, 0.96–0.98 per unit increment) was also correlated with survival without substantially altering the original model.

Hospitalizations

The HBI group accumulated 7469 days of hospital stay from 1336 unplanned hospitalizations in comparison with 10448 days from 1412 unplanned hospitalizations in the standard management group. Adjusting for duration of follow-up, the HBI group accumulated significantly fewer cardiovascular admissions and accumulated significantly fewer days of hospital stay across all 3 categories of hospital activity (unplanned, cardiovascular related, and total all-cause; see Table 4).

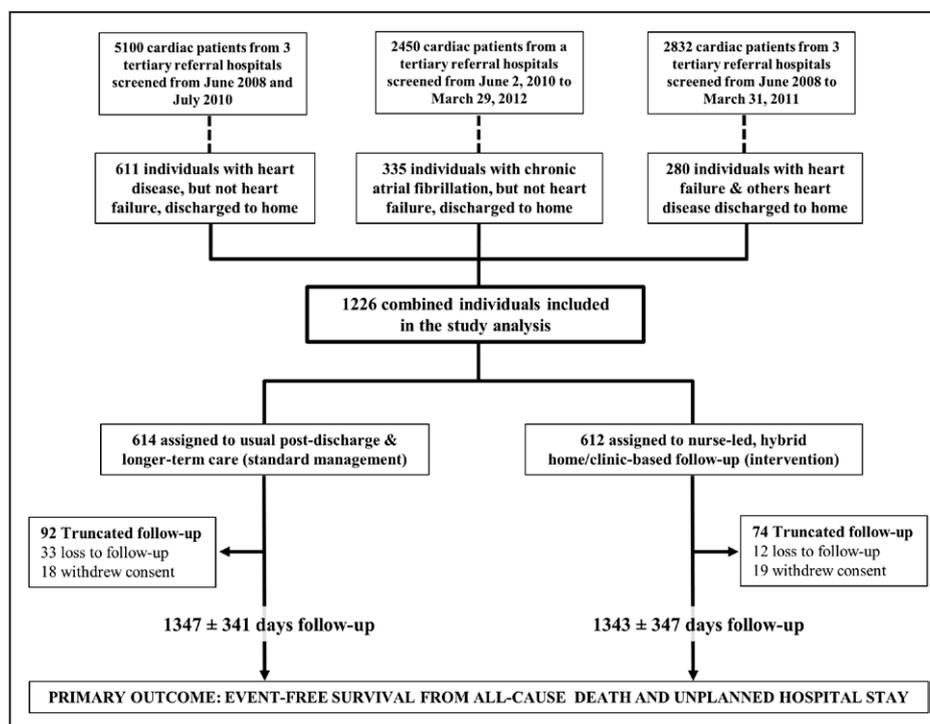


Figure 1. Combined study flow-chart.

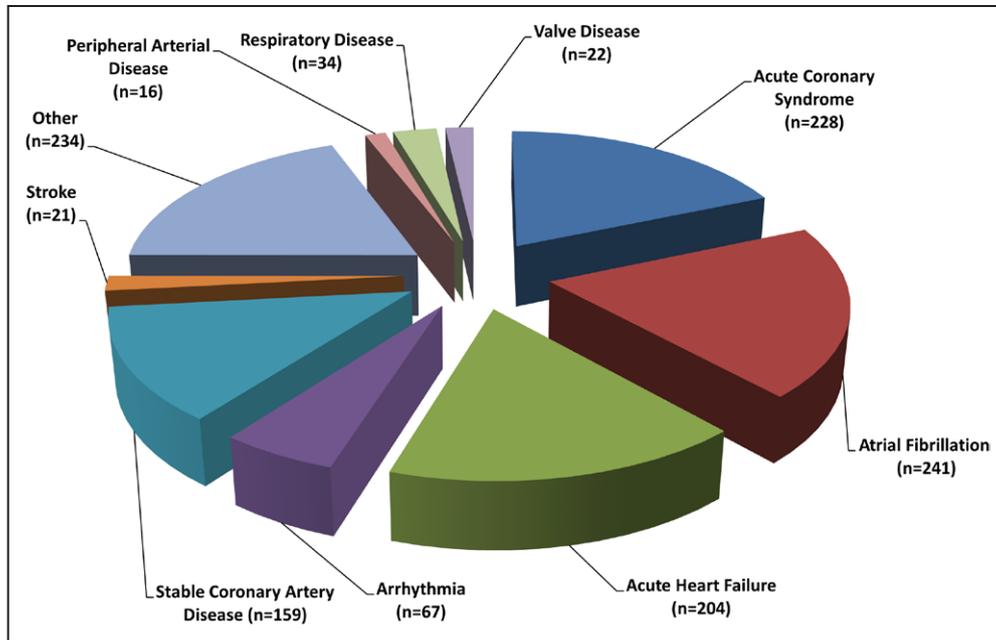


Figure 2. Primary cause of index hospitalization.

Differential Impact of HBI

For the worst quintile of DAOH (greatest number of days lost to hospital stay and death), the omnibus test of the trial×condition interaction did not reach statistical significance ($P=0.055$). There were no significant differences in the intervention effect between the WHICH? and SAFETY trials ($P=0.928$), and the intervention effects were comparable (odds ratio, 0.50; 95% CI, 0.28–0.88 in SAFETY and odds ratio, 0.49; 95% CI, 0.30–0.78 in WHICH?). However, there was a difference between the NIL-CHF Study and WHICH? ($P=0.026$) and the SAFETY Trial ($P=0.049$), and the intervention effect was smaller overall in NIL-CHF (odds ratio, 1.12; 95% CI, 0.64–1.97).

For all-cause mortality, the omnibus test of the trial×condition interaction was not statistically significant ($P=0.208$). Examining the specific contrasts between trials also revealed no statistically significant differences (WHICH? versus SAFETY, $P=0.946$; WHICH? versus NIL-CHF, $P=0.085$; SAFETY versus NIL-CHF, $P=0.168$). For lowest quintile of DAOH, the condition×age² interaction was significant ($P=0.045$), revealing a U-shaped relationship (see Figure 4). HBI had a significant, beneficial effect for adults who were 59 to 81 years old; this age range was predominant in WHICH? (58%), SAFETY (62%), and NIL-CHF (64%). For extent of comorbidity, the direction of the effect was the same U-shaped relation as for age. However, the condition×comorbidities²

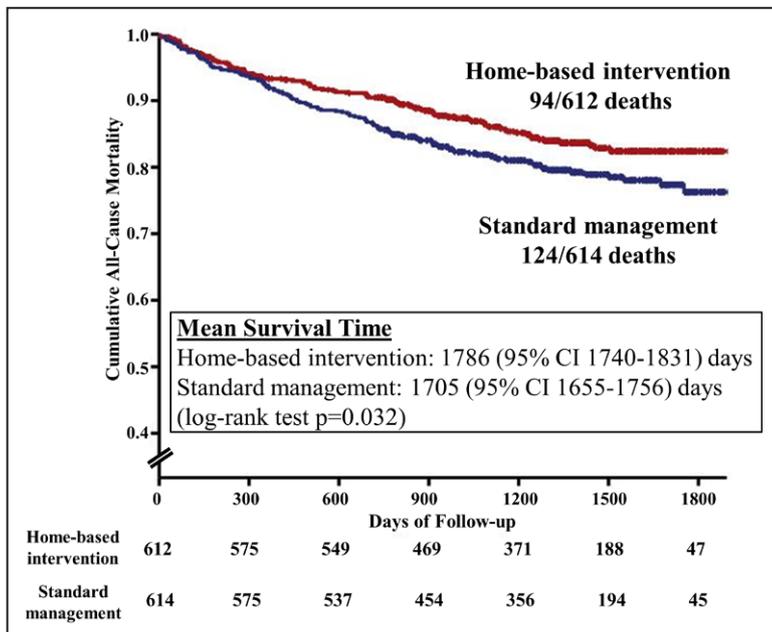


Figure 3. Kaplan–Meier (all-cause) survival plots. Nurse-led, multidisciplinary home-based intervention (518 censored observations) and standard management (490 censored observations). CI indicates confidence interval.

Table 4. Group Comparison of Hospital Outcomes

	Home-Based Intervention (n=612)	Standard Management (n=614)	Median (IQR) Rate per 100 Days Follow-up	P Value
Total follow-up (days)	747 827	737 090		
Median (IQR) follow-up, days	1321 (922–1571)	1295 (868–1587)		0.568
Unplanned admissions, days of stay	1336 (7649)	1412 (10448)		
Median (IQR) admissions per patient	1 (0–3)	1 (0–3)	0.08 (0–0.32) vs 0.12 (0–0.35)	0.083
Median (IQR) stay (days) per patient	3 (0–14)	4 (0–18)	0.22 (0–1.33) vs 0.36 (0–2.10)	0.011
Cardiovascular admissions, days of stay	735 (3334)	842 (4488)		
Median (IQR) admissions per patient	0 (0–2)	1 (0–3)	0 (0–0.16) vs 0.07 (0–0.19)	0.047
Median (IQR) stay (days) per patient	0 (0–6)	1 (0–7)	0 (0–0.55) vs 0.11 (0–0.76)	0.039
All admissions, days of stay	1868 (9975)	2017 (13563)		
Median (IQR) admissions per patient	2 (1–4)	2 (1–5)	0.15 (0.05–0.42) vs 0.18 (0.06–0.52)	0.117
Median (IQR) stay (days) per patient	6 (1–20)	7 (1–25)	0.49 (0.07–2.10) vs 0.67 (0.11–3.10)	0.017

IQR indicates interquartile range.

interaction did not reach statistical significance ($P=0.083$). For all-cause mortality, the condition \times age² interaction was significant ($P=0.005$), revealing a U-shaped relationship. HBI had a significant, beneficial effect for adults who were 60 to 82 years old, an age range also predominant in WHICH? (59%), SAFETY (63%), and NIL-CHF (65%). For extent of comorbidity, the condition \times comorbidities² interaction was also significant ($P=0.041$) and also displayed a U-shaped relationship. HBI had a significant, beneficial effect when the Charlson Comorbidity Index Score ranged from 5 to 8. This range was predominant in WHICH? (61%) and was common in SAFETY (45%) and NIL-CHF (36%).

Discussion

We combined outcome data from 3 closely related trials to examine the impact of HBI delivered by cardiac nurses with multidisciplinary support across the spectrum of heart disease. Historically, this model of care is reserved for those with CHF. However, as postulated, our composite findings suggest that HBI consistently prolongs DAOH in comparison with standard management across the full spectrum of chronic heart disease. DAOH represents a realistic and patient-focused outcome because it does not rely on a single event, but rather reflects the entirety of the patient's journey in terms of major outcomes.²⁴ Moreover, it has particular relevance to interventions seeking to prolong life while avoiding recurrent and often costly rehospitalization. Accordingly, positive findings were derived from a significant reduction in unplanned hospital stay and prolonged survival during study follow-up. Absolute differences between groups were clinically compelling. These positive differences were monitored over 2 to 5 years follow-up in contrast to the frequent reporting of short-term outcomes in those exposed to a secondary prevention program.^{3,4} For all-cause mortality, the number needed to treat to avert 1 additional death via the application of HBI was 21 patients. At the same time, HBI was associated with close to 600 fewer days of hospital stay per 100 patients. Overall, these unique data provide a strong case for extending the application

of this model of care more widely to those hospitalized with any form of chronic heart disease.

The benefits of home-based models of care, with their ability to improve the contextual profiling of affected patients to strengthen factors shown to improve health outcomes are now well described.^{8–10} Benefits include addressing often unknown issues such as cognitive impairment and clinical instability via an individualized, case management approach and improving self-care behaviors. Accordingly, across the 3 trials, there was evidence (albeit not definitive) of greater levels of healthcare engagement, more patient-initiated contacts, greater preservation of cardiac function through better blood pressure control, and more proactive up-titration of gold-standard therapies.^{8–10} The model of care applied in this instance was initially developed and successfully applied²⁵ in patients with a broad range of chronic disease states before being specifically adapted for those with CHF; the subsequent trial report was the first to demonstrate both prolonged survival and reduced risk of recurrent hospitalization in this patient population.²⁶ Since then, the literature has consistently demonstrated that an in-person, multidisciplinary approach is superior to other modes of management (including remote management strategies) to improve health outcomes in CHF, and this is likely to be the case for all forms of chronic heart disease.^{2,4,15,17,19} Based on the totality of evidence, expert guidelines have recommended the application of multidisciplinary, face-to-face programs of management for those hospitalized with CHF,²⁰ resulting in a global network of such programs. However, there has been a paucity of research and evidence to demonstrate that such an approach is beneficial more widely across the spectrum of chronic heart disease. These data, therefore, address an important gap in the literature and evidence base.

Beyond questioning the relevance of data derived from Australia (characterized by high standards of subsidized health care), it is worth considering whether a blanket approach to applying HBI is truly warranted. For example, in the recent Young@Heart Study,²⁷ applying HBI in a wealthier cohort of cardiac patients with greater access to a specialist Cardiologist, men but not women appeared to benefit from

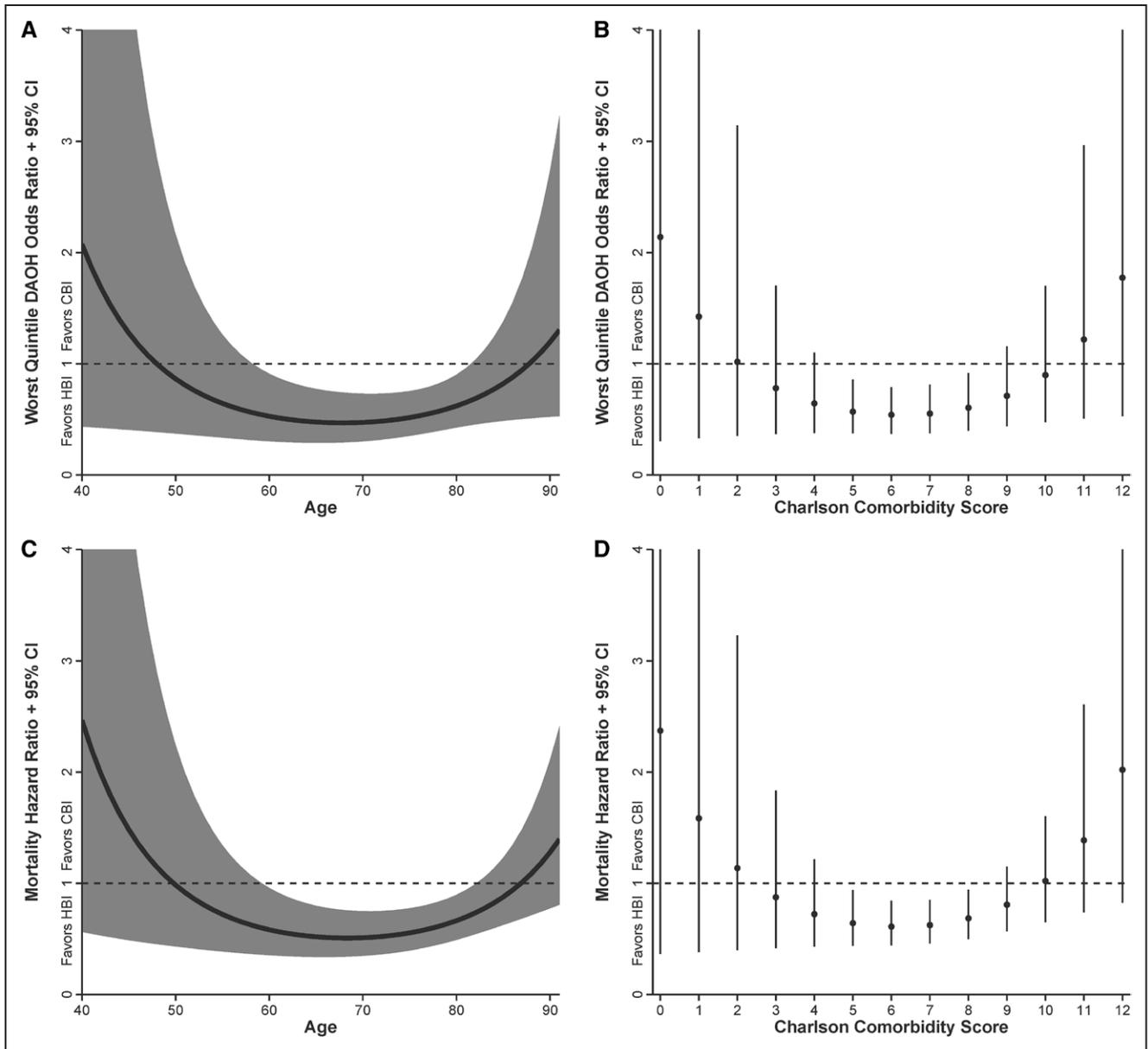


Figure 4. Interaction between age and Charlson Comorbidity Score and impact of HBI on the risk of being in the worst quintile of DAOH (A and B) or dying (C and D). CBI indicates clinic-based intervention (standard management); CI, confidence interval; DAOH, days-alive and out-of-hospital; and HBI, home-based intervention.

HBI; the latter potentially attributable to suboptimal application of HBI at 1 study site.²⁷ Beyond health system factors, the relative impact of HBI will undoubtedly vary according to clinical acuity and risk of premature mortality and recurrent hospital stay. Exploratory analyses of the interaction between HBI and a patient's age and comorbidity clearly showed a U-shaped response with respect to DAOH and survival alone, those at either end of the spectrum demonstrating an increased propensity to have more events when exposed to HBI. The potential to identify who benefits most from HBI and therefore to apply it on a more selective basis should not, however, detract from the overall benefits observed by this composite analysis; in particular, when one considers the unique advantage of HBI in being patient centered and detecting otherwise unknown clinical instability.^{4,28} The Green Amber

Red Delineation of Risk and Need (GARDIAN) tool¹⁶ was designed to achieve the former and is being used to guide the intensity of disease management according to the level of need in current trials of HBI in the setting of CHF. It is certainly possible that high levels of standard management alone, including traditional outpatient care, deliver the best health outcomes in younger patients with less complex clinical needs. Alternatively, the danger of not transitioning to a potentially more effective HBI over time is tempered by the natural history of heart disease toward more progressive, multiorgan disease and poor health outcomes in the long term.^{8,29} With an increasingly ageing cardiac patient population in whom multimorbidity and rehospitalizations are becoming more common,³⁰ our positive findings with respect to HBI, as a reflection of the overall benefits of applying successful

programs involving a home-based³¹ or transitional care³² approach to chronic heart disease management, are likely to become more clinically relevant over time.

Beyond previously identified trial limitations, including nonblinding of patients and health workers, a number of specific issues require comment. First, despite the purposeful nature of our program of research and efforts to standardize trial methodology,¹⁴ there were potentially important differences in the application of clinical management in each trial. One trial (the NIL-CHF Study)⁸ was conducted in a single tertiary center. The applicability of our findings (both negative and positive) from studies conducted within the Australian healthcare system requires careful consideration in terms of their generalizability. Nevertheless, our analyses of who benefits most from HBI remain ongoing and we are yet to undertake economic analyses to determine whether there is a cost threshold at which HBI might be applied. Finally, our composite findings are also yet to be tested via a single appropriately powered, prospective study.

In conclusion, across 3 contiguous clinical trials applying the same form of nurse-led, multidisciplinary, HBI adapted to the target patient population, this model of care was associated with more DAOH than standard management. These data support the wider application of HBI to optimize the immediate and longer-term postdischarge management of patients with a broad spectrum of heart disease states.

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Disclosures

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CLINICAL PERSPECTIVE

These data have important clinical implications for the application of disease management across the full spectrum of heart disease to prolong survival without provoking the competing risk of recurrent hospitalization. In combining 3 contiguous trials of the same form of management adapted to clinical profile (from younger individuals surviving an acute coronary event to older individuals hospitalized with more advanced forms of atrial fibrillation and chronic heart failure), we were able to tackle an important gap in the evidence base. Overall, we demonstrated that, in comparison with high levels of standard management, a nurse-led, multidisciplinary, home-based intervention was associated with both prolonged survival and reduced hospital stay over the longer term. Given that in clinical practice disease management programs are typically applied according to a single cardiac diagnosis (most notably chronic heart failure), overall, these data support the wider application of this approach to any patient discharged home from the hospital with a form of chronic heart disease; particularly in older individuals with multimorbidity. On this basis, there is scope to extend preexisting health services applying this kind of approach to the full spectrum of heart disease on a cost-effective basis. This would involve modifications in screening and referral protocols (to identify eligible patients), more health resources to accommodate an increased case load, and critical adjustments to patient profiling and needs assessments to adapt this strategy on an individual basis.