ESC European Society of Cardiology

European Journal of Cardiovascular Nursing (2022) **22**, 33–42
https://doi.org/10.1093/eurjcn/zvac036

ORIGINAL RESEARCH

An inevitable or modifiable trajectory towards heart failure in high-risk individuals: insights from the nurse-led intervention for less chronic heart failure (NIL-CHF) study

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Received 29 July 2021; revised 4 April 2022; accepted 5 April 2022; online publish-ahead-of-print 20 August 2022

Aims We extended follow-up of a heart failure (HF) prevention study to determine if initially positive findings of improved cardiac recovery were translated into less *de novo* HF and/or all-cause mortality (primary endpoint) in the longer term.

Methods and results The Nurse-led Intervention for Less Chronic HF (NIL-CHF) study was a single-centre randomized trial of nurse-led prevention involving cardiac inpatients without HF. At 3 years, 454 survivors (aged 66 ± 11 years, 71% men and 68% coronary artery disease) had the following: (i) a normal echocardiogram (128 cases/28.2%), (ii) structural heart disease (196/43.2%), or (iii) left ventricular diastolic dysfunction/left ventricular systolic dysfunction (LVDD/LVSD: 130/28.6%). Outcomes were examined during median 8.3 (interquartile range 7.8–8.8) years according to these hierarchal groups and change in cardiac status from baseline to 3 years. Overall, 109 (24.0%) participants had a *de novo* HF admission or died while accumulating 551 cardiovascular-related admissions/3643 days of hospital stay. Progressively worse cardiac status correlated with increased hospitalizations ($P < 0.001$). The mean rate (95% confidence interval) of cardiovascular admissions/days of hospital stay being 0.09 (0.05–0.12) admissions/0.33 (0.13–0.54) days vs. 0.27 (0.20–0.34) admissions/2.20 (1.36–3.04) days per annum for those with a normal echocardiogram vs. LVDD/LVSD at 3 years. With progressively higher event rates, the adjusted hazard ratio for a *de novo* HF admission and/or death associated with a structural abnormality (24.5% of cases) and LVDD/LVSD (36.2%) at 3 years was 1.57 (0.82–3.01; $P = 0.173$) and 2.07 (1.05–4.05; $P = 0.035$) compared with a normal echocardiogram (10.9%). Mortality also mirrored the direction/extent of cardiac status/trajectory.

Conclusions These data suggest the positive initial effects of NIL-CHF intervention on cardiac recovery contributed to better long-term outcomes among patients at high risk of HF. However, prevention of HF remains challenging.

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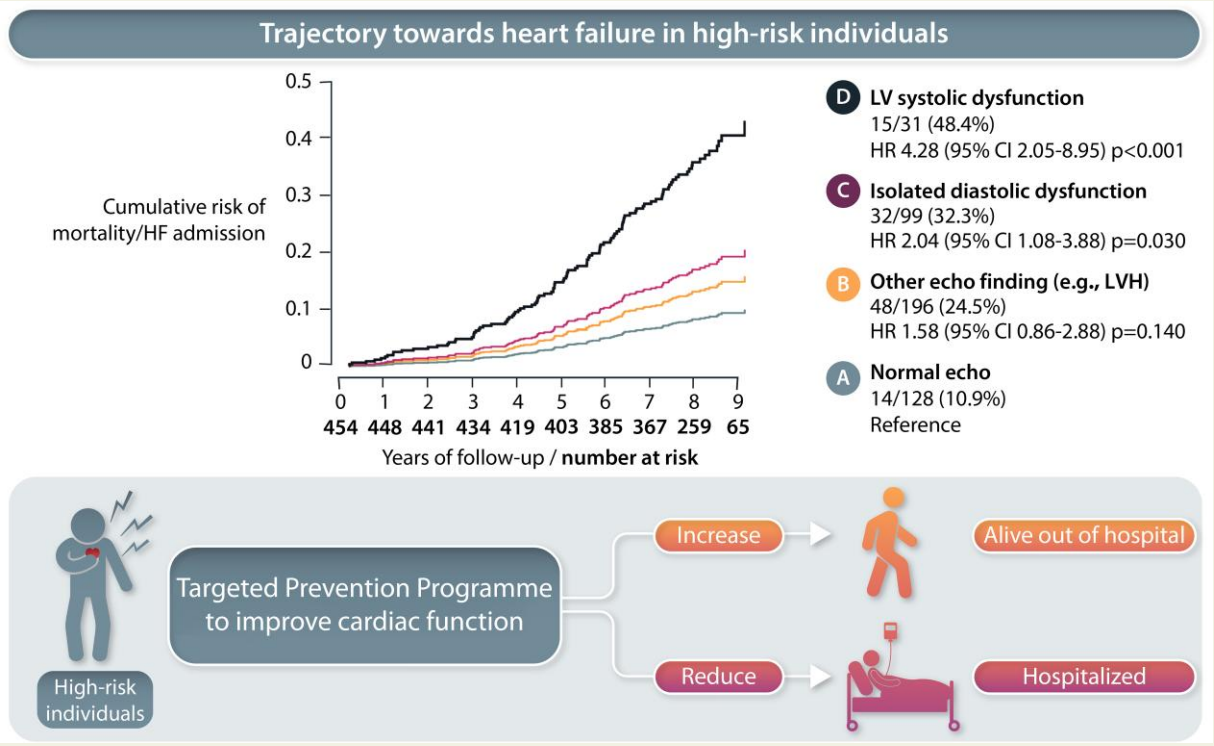
Graphical Abstract



Intervention to improve cardiac structure and function contributed to better long-term outcomes among patients at high-risk of HF.

Keywords Heart failure • Secondary prevention • Mortality • Disease management

Novelty

- Clinical trajectory towards heart failure is not inevitable, and favourable cardiac trajectory underpins better long-term outcomes.
- Intensive management in younger patients with low levels of co-morbidity can adversely influence long-term outcomes.
- Assessment of conventional thresholds (i.e., to identify systolic and diastolic dysfunctions) in high-risk patients without evidence of syndrome heart failure can assist matching the right patient with the right intervention.

Introduction

As recently highlighted by an expert position statement from the European Society of Cardiology (ESC) Heart Failure Association,[1] the primary prevention of heart failure (HF) remains problematic.[2] For example, one of its major antecedents, hypertension, continues to affect 30–45% of adults in high-income countries.[3] Anti-hypertensive treatment (most notably neurohormonal antagonists) effectively halves the risk of developing HF and prolongs life.[4] Similarly, HF is a major complication of type 2 diabetes (the burden of which will continue to rise with high levels of sedentary behaviours, poor nutritional habits, and obesity).[3] Recent trials of sodium-glucose-contransporter-2 (SGLT2) inhibitors demonstrate the potential to prevent progression to HF among those with diabetes.[5] Many of those who do develop the syndrome HF will present firstly with an acute coronary syndrome due to underlying coronary artery disease (CAD).[2,3] Such individuals are more likely to present with left ventricular systolic dysfunction (LVSD)—the prognostic implications of which [at least measured by left ventricular ejection fraction (LVEF)][6,7] are still being explored. In the absence of CAD, older individuals affected by largely uncontrolled hypertension and diabetes typically present with HF associated with a structural abnormality [typically left ventricular hypertrophy (LVH)] that may already be associated with prognostically significant left ventricular diastolic dysfunction (LVDD).[1–3] Many of these individuals (particularly those with significant LVDD and/or LVSD) are at high risk for subsequent premature mortality.[6–8]

Overall, therefore, there are many pathways to HF and its prevention poses many challenges. One of these challenges is preventing progression to HF (and premature mortality) in those already presenting with advanced forms of heart disease but still to develop the syndrome. Unfortunately, there remains a paucity of direct evidence to support health service interventions designed to prevent such progression in high-risk individuals. In the STOP trial, a collaborative care model guided by brain-natriuretic peptide (BNP) screening in the community was effective in preventing asymptomatic left

ventricular dysfunction but not HF.[9] Similarly, in the Nurse-led Intervention for Less Chronic HF (NIL-CHF) study,[10] we also observed significantly better cardiac recovery on echocardiography at 3 years [35.8 vs. 24.9%, odds ratio 1.44, 95% confidence interval (CI) 1.08 to 1.92, P = 0.011] and reduced hospital stay among a high-risk cohort of patients randomized to a nurse-led, multi-disciplinary programme of home/clinic visits. However, we were unable to demonstrate any impact of the study intervention on the composite primary endpoint of *de novo* HF admission or all-cause mortality.[10]

Study aims and hypothesis

In this prospectively planned analysis of the NIL-CHF study cohort (once additional 5-year follow-up of the cohort was completed), we aimed to explore the long-term implications of observed differences in the initial trajectory of change in cardiac structure and function; some of which appeared to be positively mediated by the study intervention. We specifically tested the hypothesis that among a high-risk patient population without evidence of the syndrome HF at baseline, progressively worse cardiac dysfunction (as opposed to echocardiographic evidence of recovery) from baseline to 3 years, would be associated with a higher incidence of the primary endpoint of a *de novo* HF admission or all-cause mortality in the longer term. We also hypothesized that these individuals would experience a higher rate of cardiovascular-related hospitalization and hospital stay.

Methods

A detailed description of the original rationale and design of the NIL-CHF study[11] and the intention-to-treat primary endpoint analyses according to group assignment[10] have been published previously. The study conformed to Consolidated Standards of Reporting Trials guidelines for pragmatic trials.[12] All participants provided written informed consent to participate—including long-term surveillance for subsequent hospital episodes and mortality. The study was approved by the Alfred Ethics Committee (262/07) and conforms to the Declaration of Helsinki.[13]

Study setting

Study recruitment and initial follow-up were conducted at the 390-bed tertiary-referral, Alfred Hospital in Melbourne, Australia. All patients were subject to specialist cardiac services and additional cardiac rehabilitation and referral to allied healthcare where appropriate. Australia has a hybrid public–private healthcare system that provides ready access to high-level primary to hospital care, specialist services, and evidence-based treatments. All study participants were recruited from the cardiology unit between June 2008 and July 2010 with capture of subsequent hospitalization and mortality data extended to mid-2018.

Study cohort

As described previously,[10] all elective and emergency patients admitted to the cardiology unit of the hospital aged ≥45 years were systematically screened for study eligibility. Participants were recruited if they were discharged to home with any chronic cardiovascular condition requiring active treatment except CHF (defined by guidelines that remain consistent with current recommendations).[14,15] To further exclude the possibility of CHF, potential participants were screened for a CHF post-index admission and subject to a detailed clinical review and echocardiogram at 30 days. Overall, 611 participants met the study criteria and were included in the initial primary endpoint, intention-to-treat analyses.[10]

Figure 1 shows the criteria used to identify the specific of participants included in the current analysis and key outcomes according to the trajectory of cardiac dysfunction documented from baseline to 3 years according to group assignment. During the first phase of 3-year follow-up, 41 participants (6.8%) died. Subsequently, there were 116 participants [comprising 79 men (aged 66.7 ± 11.7 years) and 37 women (aged 63.1 ± 11.2 years)] who were still alive at 3 years post-randomization but declined to attend their scheduled clinical reassessment. On an adjusted basis, there was no difference between those survivors who attended the 3-year NIL-CHF clinic according to their age ($P = 0.598$), sex ($P = 0.463$), group allocation ($P = 0.188$), or cardiac status ($P = 0.974$) assessed at 1-month post-index admission. As reported previously,[10] the study intervention group experienced higher levels (1.6-fold more likely compared with standard care) of cardiac recovery (from baseline to 3 years; see *Figure 1*).

Study data

As described in more detail previously,[11] in addition to comprehensive baseline profiling at the index admission, trained study personnel conducted a detailed clinical examination, documented a 6-minute walk test (6MWT), and applied behavioural and psychometric profiling tools to determine each participant's physical to psychosocial status at 30-day and then 3-year post-index admission. The same study sonographer also performed a comprehensive echocardiogram (reviewed by the same consultant cardiologist) at these two critical timepoints.

Categories of cardiac dysfunction

For the current analyses, all data derived from the echocardiograms performed at day 30 and then 3 years post-index admission were coded (on a blinded basis) into the following three mutually exclusive, hierarchal categories of increasing cardiac dysfunction based on contemporary expert guidelines[16]:

(1) No evidence of a cardiac abnormality/dysfunction (*normal echocardiogram*);
(2) Any structural cardiac abnormality (*cardiac abnormality*)—including LVH defined by two-dimensional left ventricular interventricular septal thickness at end diastole, left ventricular posterior wall dimension at end diastole (threshold for both >1.1 cm), and/or the presence of septal hypertrophy but no evidence of concurrent LVSD/LVDD; or
(3) Singular or combined LVDD/LVSD—with LVDD defined as any moderate diastolic dysfunction (with pseudo normalization pattern and/or peak diastolic tissue velocity of ≤8 cm/s) or mild diastolic dysfunction with elevated filling pressure (*E*/*e*′ ratio ≥15)[17] in the absence of LVSD, and LVSD defined as a LVEF ≤45% with or without LVDD.

All study participants were further categorized according to their documented pattern of cardiac function/dysfunction from baseline to 3 years using the key criteria described above, in respect to:

(1) Evidence of any cardiac recovery whereby they moved down a category in respect to their cardiac structure (e.g. if at 3 years, they no longer presented with LVH and had no LVDD/LVSD) and/or function (e.g. if their LVEF increased from 39% to 52% and they were left with a cardiac abnormality or normal echocardiogram);
(2) No change/status quo based on their echocardiographic profile; or
(3) Evidence of cardiac decline/progressive dysfunction (e.g. if their LVEF decreased from 52 to 39%—*de novo* LVSD).

On this basis, in addition to the three main categories of progressively worse cardiac status (normal, structural abnormality, and LVSD/LVDD

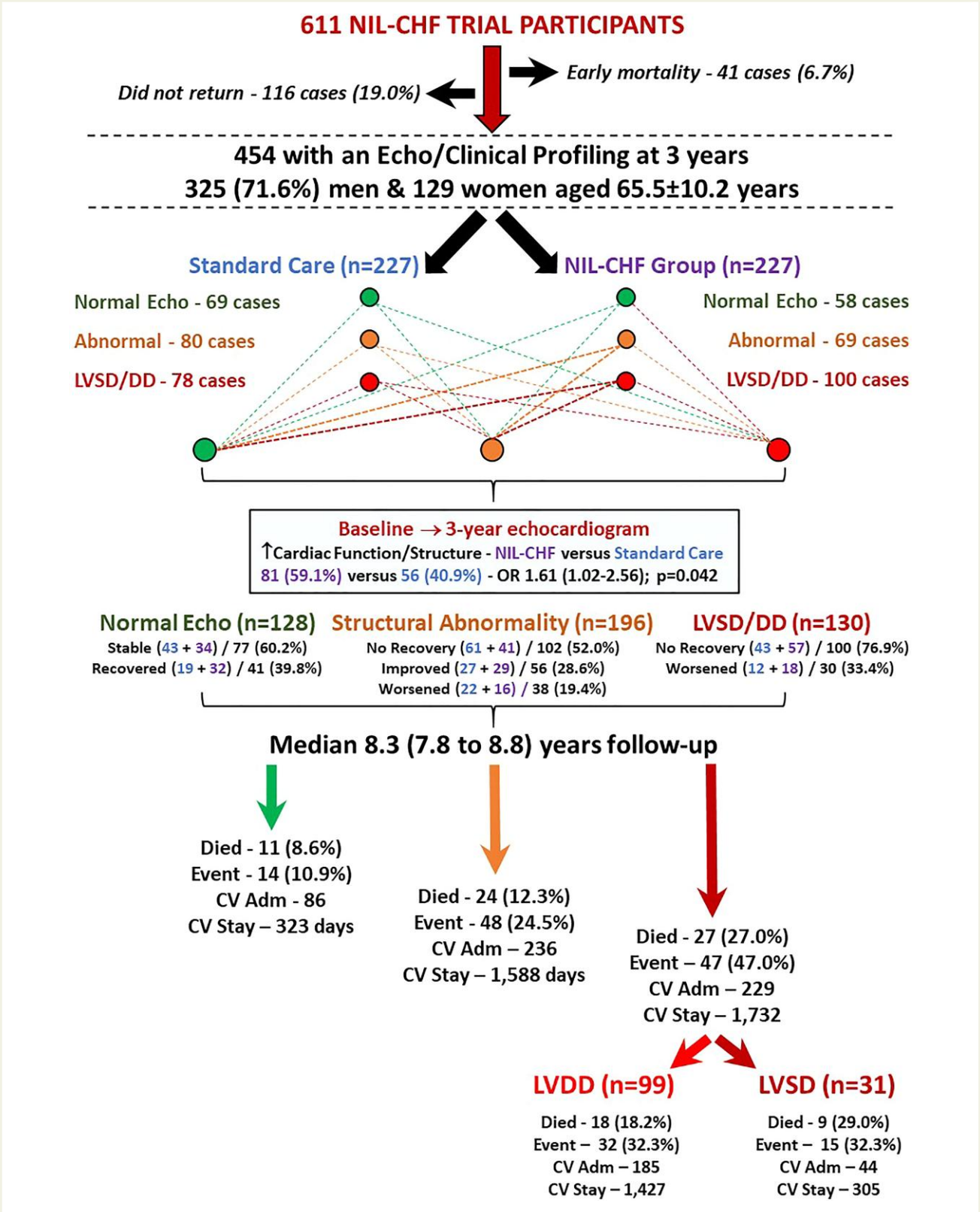


Figure 1 Study flow chart. 'Abnormal' refers to those with a structural abnormality but not LVDD/LVSD. CV, cardiovascular; LVDD/DD, left ventricular diastolic dysfunction; LVSD, left ventricular systolic dysfunction.

with or without a structural abnormality), a total of nine (3 × 3 pathways) different potential trajectories from baseline to 3 years were identified and assessed in outcome analyses.

Study endpoints

The composite primary endpoint was *de novo* HF-related hospitalization or all-cause mortality during the median follow-up period of 8.3 (interquartile range 7.8–8.8) years from the index hospital admission to the extended census timepoint. The secondary endpoint of interest was all cardiovascular-related admissions and related hospital stays. All deaths and cardiovascular-related admissions from the index admission were identified (with cross-verification to original outcome data) using individual outcome data captured by the Centre for Victorian Data Linkage.[18] This state-wide resource captures all public hospital admissions according to International Classification of Diseases (ICD), Tenth Revision, Clinical Modification coding.[19] It also captures the date of death of any individual admitted to hospital. Any admission associated with an ICD coding of I11.0, I13.0, I13.2, I50, and I97.1 was identified as a specific HF admission and any coding inclusive of I00–I99 any cardiovascular-related admission.

Statistical analysis

Although the original study was powered to address the primary endpoint at 3 years, event rates were much lower than anticipated with probable type II error.[10] Given the smaller cohort size and exclusion of cases, this study was not designed/powered to further examine the impact of the study intervention; the current analyses focusing on the distribution of events occurring within the pre-specified echocardiographic groups described above. Standard methods for describing and comparing continuous and grouped data, including mean (± standard deviation) and median (interquartile range) values for normally and non-Gaussian distributed continuous variables and proportions for categorical data collected at baseline (index admission/NIL-CHF clinic 1 month later) and then 3-year post-index admission, were applied. These same methods were used to compare change in clinical and functional status between baseline and 3 years according to cardiac status assessed by echocardiogram. This included analyses of the rate (per year of follow-up) of cardiovascular-related and HF admissions/related hospital stay using one-way analysis of variance followed by post-hoc Dunnett's test for specific group comparisons. The Kaplan–Meier method followed by a backward, stepwise Cox proportional hazards regression model was then used to determine the independent correlates of the composite primary endpoint of an HF admission or all-cause death during extended study follow-up. All baseline demographic, clinical (including index admission and treatment), management group, and functional profiling data are summarized in *Table 1*, plus equivalent data collected at 3 years, along with the pre-specified echocardiographic categories were firstly examined (event-free vs. event) on a univariate basis. Variables were entered into the model if the univariate *P*-value was <0.1 and retained at the same multivariate threshold of significance. The assumption of proportional hazards was confirmed by visual inspection. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26.0 software (SPSS Inc.). The significance was accepted at the standard level of $P < 0.05$ (two-sided).

Results

Study cohort

Overall, 325 men (71.6%, mean age 64.4 ± 10.0 years) and 129 women (68.3 ± 10.1 years) at their index admission, who completed echocardiographic and clinical assessments at 3 years, were studied. *Table 1* summarizes the cohort's characteristics at baseline and their cardiac status assessed at 30 days according to their subsequent cardiac status reassessed at 3 years (according to the three pre-specified categories of cardiac function). Overall, there were key differences in the demographic (more women in the LVDD/LVSD vs. normal echocardiogram group) and risk factor profile (fewer smokers vs. more hypertensive and overweight individuals in the structural abnormality and LVDD/LVSD groups) of individuals according to their 3-year cardiac profile. Similarly, there were gradients (from less in the 'normal echo' group to higher in those with LVDD/LVSD) evident in respect to baseline diabetes, renal dysfunction, and levels of comorbidity, but minimal differences in respect to CAD. There were similar gradients in the baseline length and acuity of their index hospital stay (higher in those with greater cardiac dysfunction documented at 3 years), while the balance of prescribed neurohormonal modulating agents was similar across all three groups. Overall, 51 participants had completely recovered their cardiac structure/function (from day 30 to 3 years), contributing to 128 participants (28.2%) with a normal echocardiogram reported at 3 years. Of the 196 participants with a structural abnormality (43.2%), 56 vs. 38 participants had LVDD or LVSD and a normal echocardiogram at 30 days (baseline). Finally, of the 130 participants in the LVDD/LVSD group (28.6%), 30 had evidence of progressive cardiac dysfunction between 30 days and 3 years post-index admission.

Trajectories of change in cardiac structure and function

Based on a comparison of their echocardiographic profile at 30 days and 3 years, 107 participants (23.6%) were found to have evidence of cardiac recovery. Alternatively, 279 (61.5%) were found to be stable, while 68 (15.0%) participants had evidence of progressive dysfunction (comprising 38 and 30 participants found to have a structural abnormality and LVDD/LVSD at 3 years, respectively). As shown in *Figure 1*, those assigned to the study intervention were 1.6-fold more likely to demonstrate any form of cardiac recovery compared with standard care ($P = 0.042$). Three in five participants were found to have the same cardiac function/dysfunction at both time points, including 77 (17.0%) with normal echocardiogram, 102 (22.5%) categorized with structural abnormality, and 100 (22.0%) with unchanged LVSD/LVDD. Overall, cardiac recovery (as opposed to cardiac decline) was characterized by more positive changes in 6MWT [mean Δ 32.3 m (95% CI 15.3 to 49.2) vs. 9.6 m (95% CI −18.5 to +37.6)] and a lesser change in systolic blood pressure [mean Δ 4.8 mmHg (95% CI 1.2 to 8.4) vs. 9.3 mmHg (95% CI 4.9 to 13.7)] that reflected more positive changes in respect to LVEF [mean Δ 4.1% (95% CI 2.2 to 6.0) vs. 0.4% (95% CI −1.8 to +2.5); $P = 0.01$] and left ventricular mass index (LVMI) [mean Δ −10.7 g/m^2 (95% CI −5.3 to −14.2) vs. −0.5 g/m^2 (95% CI +1.8 to −7.6); $P < 0.001$]. Unfortunately, we were unable to clearly identify the distinctive phenotype of participants in the cardiac recovery vs. decline group (based on multivariate analyses) that had contributed to their cardiac status at 3-year follow-up (*Table 2*).

Health outcomes

During complete follow-up (baseline to extended study census), 73 (16.1%), 62 (13.7%), and 109 (24.0%) of the 454 participants had at

Table 1 Cohort characteristics

	Echocardiographic assessment at 3-year post-index admission		
	Normal echo (*N* = 128)	**Structural abnormality (*N* = 196)**	**LVDD/LVSD (*N* = 130)**
Demographic profile (baseline profile)			
Age (years)	61.4 ± 9.6	66.0 ± 9.7	68.8 ± 10.2
Men	89 (69.5%)	156 (79.6%)	80 (61.5%)
Living alone	48 (37.5%)	70 (35.7%)	46 (35.4%)
<12 years education	59 (46.1%)	75 (38.5%)	51 (39.5%)
Risk factor profile (baseline profile)			
History of smoking	31 (24.2%)	29 (14.8%)	17 (13.1%)
Hypertension (BP >130/80 mmHg)	70 (54.7%)	122 (63.9%)	80 (61.5%)
Overweight (BMI ≥ 25 kg/m^2)	86 (67.2%)	162 (83.9%)	100 (76.9%)
Total cholesterol (≥4.0 mmol/L)	53 (41.7%)	84 (44.2%)	52 (40.3%)
Clinical profile			
Coronary artery disease	87 (68.0%)	129 (65.8%)	92 (70.8%)
Coronary revascularization	44 (34.4%)	63 (32.1%)	42 (32.3%)
Diabetes mellitus	22 (17.2%)	55 (28.1%)	37 (28.5%)
Depressive symptoms	32 (25.2%)	39 (19.9%)	25 (19.4%)
eGFR <60 mL/min/1.73 m^2	8 (6.3%)	28 (14.5%)	30 (23.1%)
Charlson index of co-morbidity score	3.2 ± 1.8	4.6 ± 2.3	5.2 ± 2.6
Index admission			
Length of stay (days)	5.4 ± 9.0	6.9 ± 12.3	8.0 ± 10.8
ICU/CCU stay (days)	3.2 ± 4.1	3.5 ± 4.6	4.8 ± 6.6
Post-discharge management			
NIL-CHF intervention	66 (51.6%)	86 (43.9%)	75 (57.7%)
Angiotensin blockade	88 (68.8%)	145 (74.0%)	88 (67.7%)
Beta-blocker	66 (51.6%)	93 (47.4%)	71 (54.6%)
Anti-platelet	101 (78.9%)	158 (80.6%)	111 (85.4%)
Calcium channel blocker	17 (13.3%)	53 (27.0%)	25 (19.2%)
Diuretic	11 (8.6%)	25 (12.8%)	35 (26.9%)
Oral hypoglycaemic agent	17 (13.3%)	48 (24.5%)	27 (20.8%)
Status 30 days post-index admission			
Normal echocardiogram	77 (60.2%)	38 (19.4%)	12 (9.2%)
LVMI (g/m^2)	93.0 ± 18.3	115.3 ± 24.1	112.5 ± 27.4
LVH/structural abnormality	13 (10.2%)/29 (22.7%)	95 (49.0%)/102 (52.0%)	49 (37.7%)/18 (13.8%)
E/*e*′ ratio	10.0 ± 3.0	11.1 ± 3.2	16.6 ± 6.9
LVDD	20 (15.6%)	41 (21.2%)	87 (66.9%)
LVEF (%)	63.6 ± 7.0	62.1 ± 9.1	56.9 ± 12.3
LVSD	3 (2.3%)	19 (9.8%)	35 (26.9%)
Functional/structural recovery	51 (39.8%)	56 (28.6%)	N/A
Functional/structural worsening	N/A	38 (19.4%)	30 (23.1%)

Results are presented as mean ± SD, median (interquartile range), or *n* (%).
BP, blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; ICU/CCU, intensive care unit.

least one HF admission, died or both (the composite primary endpoint), respectively. Concurrently, the cohort accumulated 551 cardiovascular-related admissions and 3643 days of hospital stay. Of these, 163 (29.6%) admissions and 1775 (48.7%) days of hospital stay were HF related. There were significant differences ($P < 0.001$ for all comparisons across groups and $P < 0.05$ for between group comparisons, except rate of HF stay) in these outcomes according to a participant's cardiac status at 3 years—the lowest to highest rates of morbidity occurring in those with normal function vs. LVDD/LVSD recorded at this timepoint. Specifically, the mean rate

of cardiovascular admissions/days of related hospital stay was 0.09 (95% CI 0.05 to 0.12) admissions/0.33 (95% CI 0.13 to 0.54) days, 0.15 (95% CI 0.12–0.18) admissions/1.19 (95% CI 0.57 to 1.83) days, and 0.27 (95% CI 0.20 to 0.34) admissions/2.20 (95% CI 1.36 to 3.04) days per annum among those assessed with normal, a structural abnormality and LVDD/LVSD at 3 years, respectively. A similar gradient was observed in relation to HF-related hospitalization/days of related stay with 0.01 (95% CI 0.00 to 0.03) admissions/0.15 (95% CI 0.00 to 0.32) days, 0.04 (95% CI 0.03 to 0.06) admissions/0.61 (95% CI 0.03 to 1.18) days, and 0.11 (95% CI 0.07 to 0.15) admissions/1.15 (95% CI 0.57 to 1.73) days per annum among those assessed with normal, a structural abnormality, and LVDD/LVSD at 3 years, respectively (see *Figure 1* for a summary outcomes).

Table 2 Characteristics of change in cardiac status

	Changes in echocardiographic status from baseline to 3 years		
	Cardiac recovery (*N* = 107)	**Stable (*N* = 279)**	**Cardiac decline (*N* = 68)**
Baseline echo status			
Normal echo	N/A	77 (27.3%)	50 (73.5%)
Lone LVSD	17 (16.3%)	13 (4.6%)	N/A
Lone LVDD	53 (51.0%)	68 (24.1%)	N/A
LVSD/LVDD	5 (4.8%)	22 (7.8%)	N/A
Structural abnormality	29 (27.9%)	102 (36.2%)	18 (26.5%)

Reflective of this pattern of outcome, compared with those with normal cardiac function at 3 years, when adjusting for all parameters assessed at baseline and 3 years (including baseline cardiac function), those found to have a structural abnormality (adjusted HR 1.57, 95% CI 0.82 to 3.01; $P = 0.173$) and LVDD/LVSD (adjusted HR 2.07, 95% CI 1.05 to 4.05; $P = 0.035$) at 3 years, were progressively more likely to experience a *de novo* HF admission or die during prolonged follow-up (see *Figure 2*). As further shown in *Figure 3*, these trends reflected markedly different trajectories when comparing this outcome among these three key groups and according to differential patterns of cardiac recovery (associated with less events overall) vs. cardiac stability (gradient of events reflective of 3-year status)

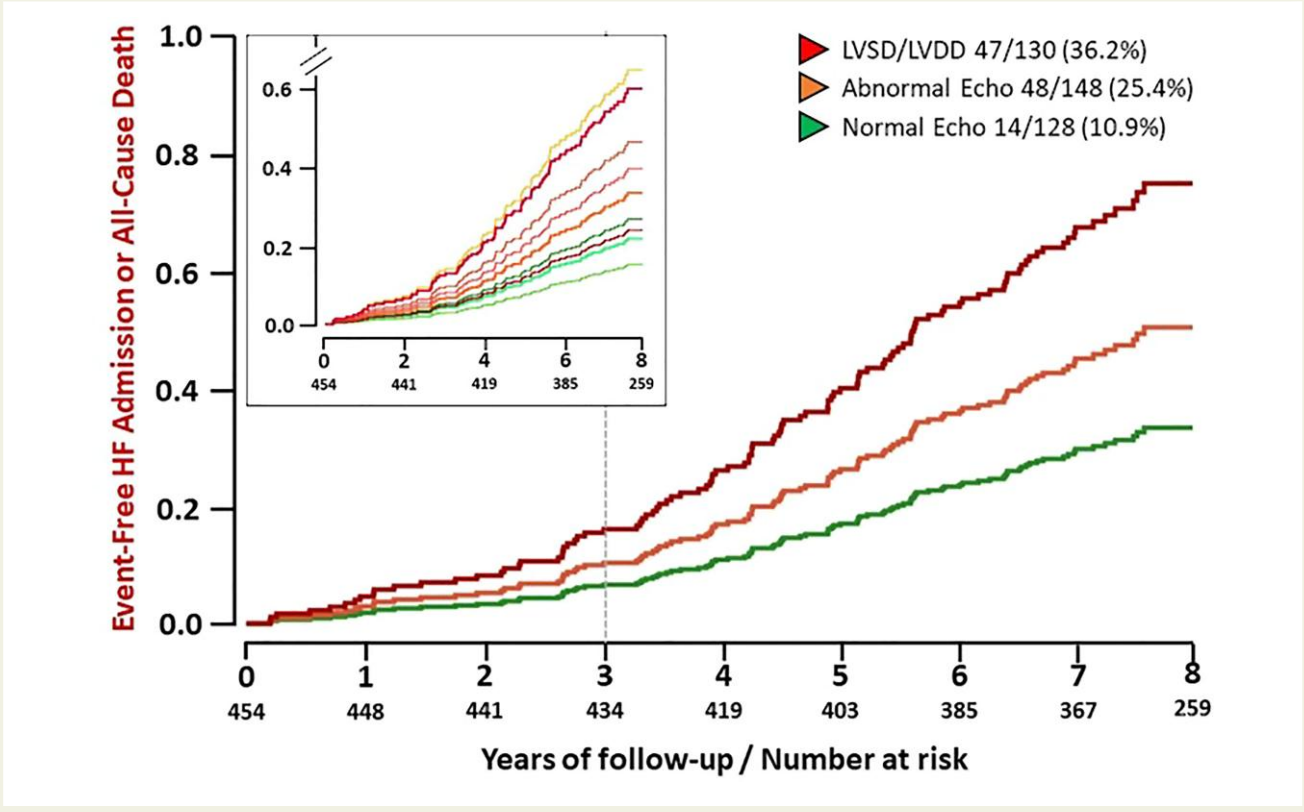


Figure 2 Event-free survival according to cardiac status at 3 years. The risk of a heart failure admission or all-cause death was also significantly correlated with progressive age (hazard ratio 1.05, 95% confidence interval 1.02–1.08 per year; $P = 0.002$), sex (hazard ratio 2.00, 95% confidence interval 1.22–3.27 men vs. women; $P = 0.006$), smoking status (hazard ratio 2.42, 95% confidence interval 1.38–4.27 smoker at baseline vs. rest; $P = 0.002$), length of index hospital stay (hazard ratio 1.02, 95% confidence interval 1.00–1.03 per day; $P = 0.017$), Charlson index of co-morbidity at baseline (hazard ratio 1.16, 95% confidence interval 1.05–1.28 per unit score; $P = 0.004$), and eGFR at 3 years (hazard ratio 0.98, 95% confidence interval 0.97–0.99 per unit increase; $P = 0.004$). The box insert shows the equivalent plots for the nine possible categories of no change/change according to cardiac status at baseline vs. 3 years; the lowest risk being among those who had a normal echo at both time points (light green line) and the highest among those with left ventricular diastolic dysfunction/left ventricular systolic dysfunction (deep red line) at both time points plus those who transitioned from structural heart disease to left ventricular diastolic dysfunction/left ventricular systolic dysfunction (yellow line).

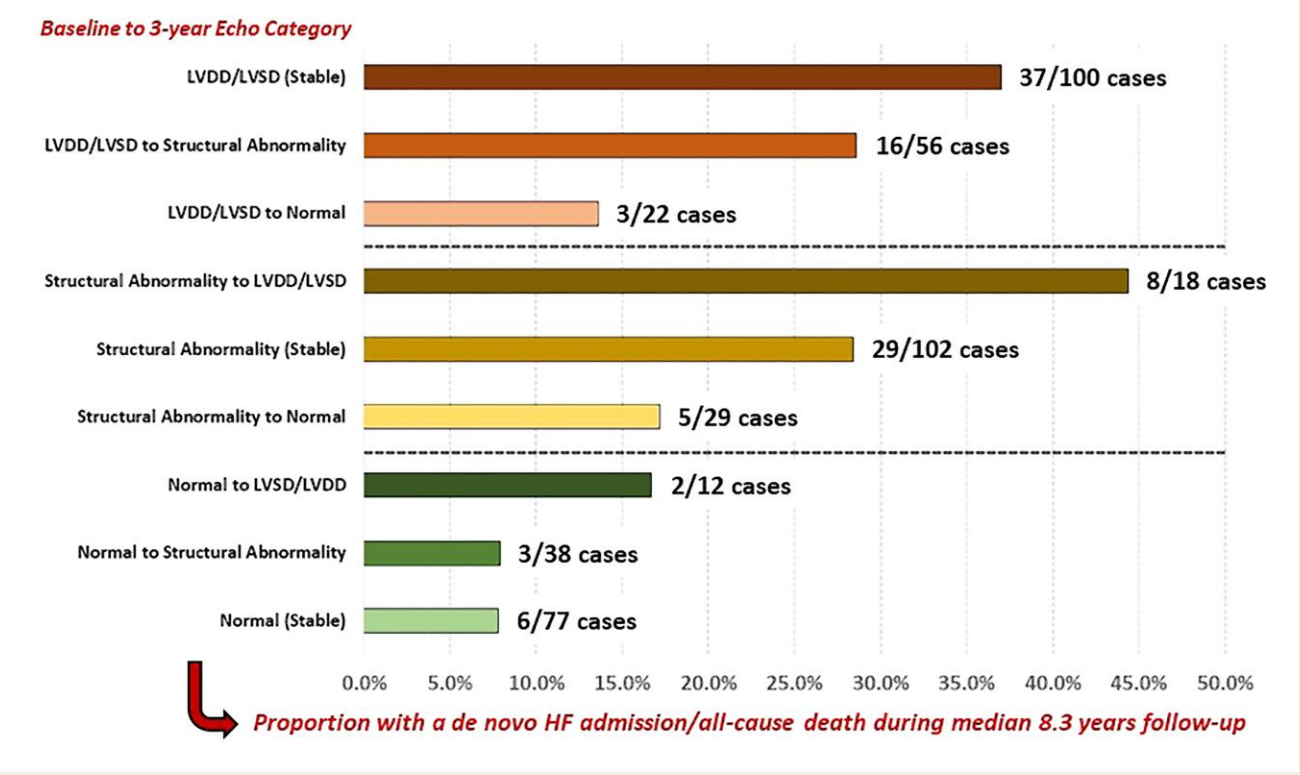


Figure 3 Event-free survival according to trajectory of cardiac status.

or evidence of worsening cardiac structure/function (associated with more events overall).

Discussion

Long-term follow-up of a typical cohort of cardiac inpatients exposed to high-quality care yet to develop HF, revealed that 15% were subsequently admitted to hospital with the syndrome and 24% experienced the composite endpoint of a *de novo* HF admission or death. Consistent with the nature of the study and timing of clinical assessments, nearly all such events occurred between 3- and 8-year post-index admissions. Those with evidence of structural heart disease and/or a combination of LVDD/LVSD were 1.5- to 2.0-fold more likely to experience such an event compared with those with normal cardiac structure/function at 3 years. Being in such a favourable clinical position was not necessarily predetermined 3 years earlier. Consistent with the original reported,[10] the intensive and structured nurse-led intervention was associated with a 1.6-fold increased likelihood of any cardiac recovery from baseline to 3 years. However, such cardiac recovery and possible pathways in this study cohort (noting the exclusion of those who died or did not return for echocardiographic assessment) was not confined to the intervention group. As suggested by *Figures 1* and *3*, each of the nine different permutations for cardiac recovery, status quo, or decline appeared to convey a different survival trajectory: the least malignant being among those with a favourable cardiac trajectory.

The importance of maintaining or achieving a 'normal echocardiographic profile' (noting increasing evidence that the conventional thresholds for identifying systolic[6,7] and diastolic dysfunction[8] may need to be revisited) in such high-risk patients is clearly difficult—with only 28% of cases remaining low risk. The remaining cases (at a ratio of ~1.5:1) continued to be at high risk, including higher rates of cardiovascular admissions overall, due to underlying cardiac structural disease (typically LVH) and/or a combination of LVDD and LVSD (the latter having the worse outcomes overall). Our current findings reinforce the need to match the right patient with the right intervention, while confirming that a trajectory towards the syndrome of HF and premature mortality is not inevitable.

As recently highlighted by a report from the SCREEN-HF study[20] focusing on BNP level screening in a high-risk community cohort and a very large study of the prognostic importance of observed change in LVEF in patients being investigated or managed with heart disease,[21] there is no easy way to clearly delineate who will (or will not) develop HF and/or die prematurely. This remains a fundamental issue in clinical practice, whereby the cost-effective application of structured surveillance of potentially costly and time-consuming investigative tools remains poorly understood and under-valued.

The fundamental challenge for the original NIL-CHF study intervention was to improve upon high levels of standard care (including expert cardiology management and cardiac rehabilitation at one of Australia's premiere cardiologic institutions) and long-term preventative therapies. As evidenced by the recently announced primary endpoint analyses of the prospective angiotensin receptor-neprilysin inhibitor (ARNI) vs ACE inhibitor trial to determine superiority in reducing heart failure events after MI trial of ARNI vs. ACE inhibitor therapy post-myocardial infarction,[22] improving upon current strategies to prevent HF remains elusive (despite newer neurohormonal

modulating therapies proving to be so effective once the syndrome has developed[23]). As with the NIL-CHF intervention focusing on hospitalized patients, in the St Vincent's Screening TO Prevent Heart Failure of 1347 primary care patients,[9] an intensive preventative strategy focusing on those with underlying cardiovascular dysfunction (detected by elevated BNP levels) was associated with a significant reduction (8.7 vs. 5.3%; $P = 0.003$) in the proportion of individuals with left ventricular dysfunction but was not proven to prevent *de novo* HF; with low incidence/likely type II error in both trials. In the current analyses, we found strong evidence that key changes in modifiable risk factors including tobacco smoking, physical inactivity, body mass index, diabetes, and renal function influenced outcomes (further analyses are ongoing). This is in accord with recent ESC position guidelines with increasing focus on patients with metabolic disease-related morbidity.[24,25]

Despite the lack of definitive data, the goal of preventing progression to HF (and therefore repetitive and costly admissions and premature mortality), even in well-managed individuals with pre-existing heart disease, appears both desirable and achievable (particularly given the chain of evidence supporting the application of our original intervention to enhance cardiac recovery). As noted, among our cohort of initially surviving patients, a significant portion (15%) demonstrated worsening cardiac function, and this left them at higher risk of subsequently being admitted to hospital with HF and/or died (only 1 in 10 of such individuals having a 'normal heart' at 3 years post-index admission). As noted, selecting those most at risk of developing the syndrome remains highly important. Consistent with the preventative impact of SGLT2 inhibitors among those diagnosed with diabetes,[5] the proportion of such cases in our two high-risk groups was 28% (vs. 17% in those with a normal echocardiogram). So does the application of the right management programme. Since the completion of the NIL-CHF study, we have demonstrated the potential adverse impact of intensive management in younger individuals with low levels of co-morbidity[26] and have also demonstrated the need to consider the impact of environmental/seasonal factors in triggering cardiac events.[27] When combined with these new insights, there is a clear potential to revisit the NIL-CHF strategy and who might benefit most to alter their likely trajectory towards HF and a premature death.

Limitations

Our findings need to be interpreted with some caution. This was a single-centre study undertaken in an academic cardiology hospital within the Australian healthcare system. Consistent with low initial event rates, study participants had ready access to high standards of treatment and management including cardiac rehabilitation[28] and telephone coaching to target,[29] and gold-standard pharmacotherapy.[4] Our analyses were confined to those who were still alive at 3 years post-index admission and still engaged with the study. As opposed to the initial set of analyses, for pragmatic reasons, we focused on cardiovascular- and HF-related admissions using individual linkage to a validated administrative source without independent verification of the presence of HF. Moreover, our capacity (from a study power perspective) to examine outcome analyses relied on the distribution of cardiac function/dysfunction and we were unable to directly examine any potential long-term benefits of the study intervention (we can only infer these from the positive impact on cardiac recovery) and medical and pharmacological management beyond 3 years. We were also unable to properly examine the prognostic importance of the nine different cardiac trajectories identified within our cohort.

Conclusions

As originally reported,[10] compared with high-quality, standard care, an intensive nurse-led intervention tested in the NIL-CHF study was ineffective in preventing the composite endpoint *de novo* HF and all-cause mortality in a high-risk group of cardiac inpatients. However, it was associated with more improved cardiac function. During extended follow-up of those study participants comprehensively profiled at baseline and 3 years post-index admission, it was difficult to determine if this directly translated into better outcomes. However, these data provide strong evidence that a clinical trajectory towards HF is not inevitable and that more targeted prevention programmes may subsequently achieve (preventing HF) what appears to be an elusive goal.[30] As such, with some contemporary modifications (including the application of proven pharmacotherapies),[4] the same NIL-CHF study intervention applied to a higher risk cohort (specifically those with evidence of a structural abnormality and/or LVDD/LVSD but not normal cardiac function) may well prove to be effective in minimizing the composite endpoint of a *de novo* HF admission or all-cause mortality.

Acknowledgements

The authors thank the NIL-CHF study cohort for their participation in the study.

Funding

S.S. is supported by the National Health and Medical Research Council (NHMRC) of Australia (GNT1135894). The NIL-CHF study was funded by NHMRC of Australia Project Grant (GNT472662).

Conflict of interest: None declared.

Data availability

De-identified aggregated data that are supporting the findings of this study are available from the corresponding author, upon reasonable request.

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