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CLINICAL RESEARCH
Heart failure/cardiomyopathy

Standard vs. intensified management of heart failure to reduce healthcare costs: results of a multicentre, randomized controlled trial

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Aims To determine if an intensified form of heart failure management programme (INT-HF-MP) based on individual profiling is superior to standard management (SM) in reducing health care costs during 12-month follow-up (primary endpoint).

Methods and results A multicentre randomized trial involving 787 patients (full analysis set) discharged from four tertiary hospitals with chronic HF who were randomized to SM ($n = 391$) or INT-HF-MP ($n = 396$). Mean age was 74 ± 12 years, 65% had HF with a reduced ejection fraction (31.4 ± 8.9%) and 14% were remote-dwelling. Study groups were well matched. According to Green, Amber, Red Delineation of rIsk And Need in HF (GARDIAN-HF) profiling, regardless of location, patients in the INT-HF-MP received a combination of face-to-face (home visits) and structured telephone support (STS); only 9% ('low risk') were designated to receive the same level of management as the SM group. The median cost in 2017 Australian dollars (A$1 equivalent to ∼EUR €0.7) of applying INT-HF-MP was significantly greater than SM ($152 vs. $121 per patient per month; $P < 0.001$), However, at 12 months, there was no difference in total health care costs for the INT-HF-MP vs. SM group (median $1579, IQR $644 to $3717 vs. $1450, IQR $564 to $3615 per patient per month, respectively). This reflected minimal differences in all-cause mortality (17.7% vs. 18.4%; $P = 0.848$) and recurrent hospital stay (18.6 ± 26.5 vs. 16.6 ± 24.8 days; $P = 0.199$) between the INT-HF-MP and SM groups, respectively.

Conclusion During 12-months follow-up, an INT-HF-MP did not reduce healthcare costs or improve health outcomes relative to SM.

Keywords Heart failure • Nurse-led • Multidisciplinary management • Healthcare costs • Hospitalization • Mortality

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Introduction

Based on a robust evidence-base (Level 1A), the latest ESC guidelines recommend that patients with heart failure (HF) are enrolled in a multidisciplinary care management programme (MP) to reduce the risk of HF hospitalization and mortality.[1] Findings from contemporary systematic reviews and meta-analyses[2,3] suggest that there is a cogent argument for establishing such multidisciplinary care in the post-discharge setting via HF nurses and home visits; particularly to improve 'all-cause', as opposed to HF-specific, outcomes. Previously, we conducted a multicentre, head-to-head trial of home-based vs. specialist clinic-based HF management that applied the same nurse-led, multidisciplinary care.[4] Consistent with a broader analysis of this strategy across the spectrum of heart disease,[5] home-based management was superior in reducing hospital stay and prolonging survival in the longer-term[6]; and health economic analysis demonstrated it to be more cost-effective compared to specialist HF clinics.[7]

Despite their overall efficacy, however, HF-MPs are being challenged further to reduce high levels of morbidity and mortality. At the same time, an increasingly older and more clinically complex patient population are making greater demands on limited healthcare resources.[8,9] We postulated that an initial investment in more intensive management directed towards higher risk HF patients would yield cost-savings overall via less costly hospital stay in the medium-to-longer term. Therefore, we tested the hypothesis that 'a more intensive, nurse-led, post-discharge, multidisciplinary, HF management programme incorporating outreach home-based intervention enhanced by structured telephone support (STS) (INT-HF-MP) would be superior to standard management (SM) incorporating home-based care and STS for metropolitan and remote-dwelling patients, respectively, in reducing the total cost of healthcare during 12-month follow-up'.

Methods

Study design and participants

The Which Heart failure Intervention is most Cost-effective in reducing Hospital stay (WHICH? II) Trial was a multicentre, randomized trial that adheres to the CONSORT guidelines for a pragmatic trial[10] and the Declaration of Helsinki for ethical practice—(ANZCTR 12613000921785).

Participant recruitment commenced on August 28th 2013 from four tertiary hospitals in Adelaide, Melbourne and Sydney, Australia. The last participant was discharged from hospital in February 2016 and minimum 12-month follow-up completed in February 2017. Ethics approval was obtained from Central Northern Adelaide Health Service (HREC/13/TQEHLMH/99), Melbourne Health (HREC 2013.145), St Vincent's Hospital Sydney (HREC/13/SVH/313) and Prince of Wales Hospital, Sydney (HREC/13/SVH/313). All participants gave written informed consent. Participants were enrolled by registered nurses at each site. Patients aged ≥ 18 years admitted to participating hospitals were eligible if they had a cardiologist-confirmed diagnosis of chronic HF based on echocardiography and persistent exercise intolerance [New York Heart Association (NYHA) Class II–IV], a history of ≥1 admission for acute decompensated HF (including the index admission) and were being discharged to home. Patients were only excluded if they had a terminal condition and/or were unable to provide fully informed consent. Patients from non-English speaking background were included and supported by translation services when needed.

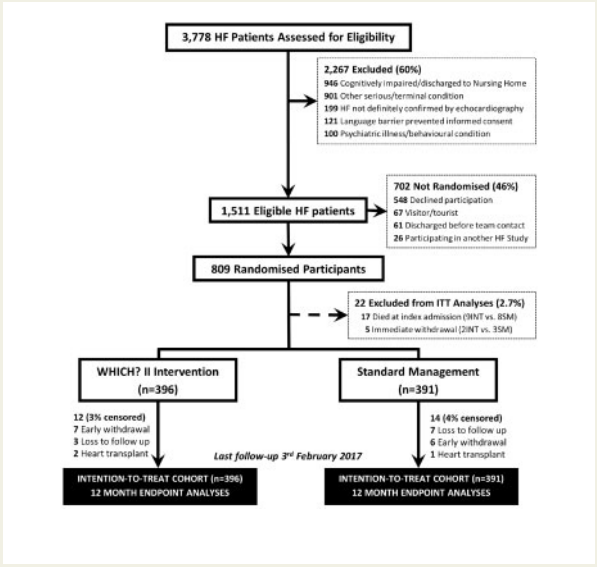

Figure 1 CONSORT flow-chart.

Group randomization

Blinded, computer-generated randomization was applied by an independent data management team via telephone. A pre-determined randomization sequence, with block groups for each study site and stratified according to presence of HF with reduced or preserved ejection fraction [HFrEF or HFpEF, respectively, based on a left ventricular ejection fraction (LVEF) <45% or ≥45%] and metropolitan-dwelling (<30 km and/or <45 min travel time to a patient's home) or remote-dwelling status, allocated 407 and 402 patients, respectively, to the INT-HF-MP and SM groups (see *Figure 1*).

Study data

All study data were collected via protocol-following registered nurses with standardized case-report forms (see Supplementary material online, *Appendix I*). This included comprehensive demographic and clinical profiling (including HF history and hospital management) via a combination of medical record review, patient interview and validated instruments. The latter comprised assessment of cognition, depressive symptoms, self-care abilities, physical strength, and level of (age-adjusted) multimorbidity via the Montreal Cognitive Assessment (MoCA) Tool,[11] two-item Arrol tool,[12] European Self-Care Behaviour Scale,[13] handgrip strength via a calibrated manometer (hydraulic hand dynamometer SH5001) and Charlson Comorbidity Index Score,[14] respectively. Brain natriuretic peptide (BNP) levels were also obtained initially using the Alere Heart Check Meter Kit (since discontinued by the manufacturer) and then the Alere Triage MeterPro immediately prior to index hospital discharge.

Post-discharge management

All patients were managed within the Australian healthcare system that provides free or subsidized (depending on income) access to high level management including primary and tertiary care, pharmacological treatment, devices and allied health services. The nature and intensity of post-discharge management depended on a patient's home location and group assignment (see *Figure 2*).

As per local guidelines,[15] SM was determined by each patient's home location. Those within reach of the hospital's pre-existing HF service

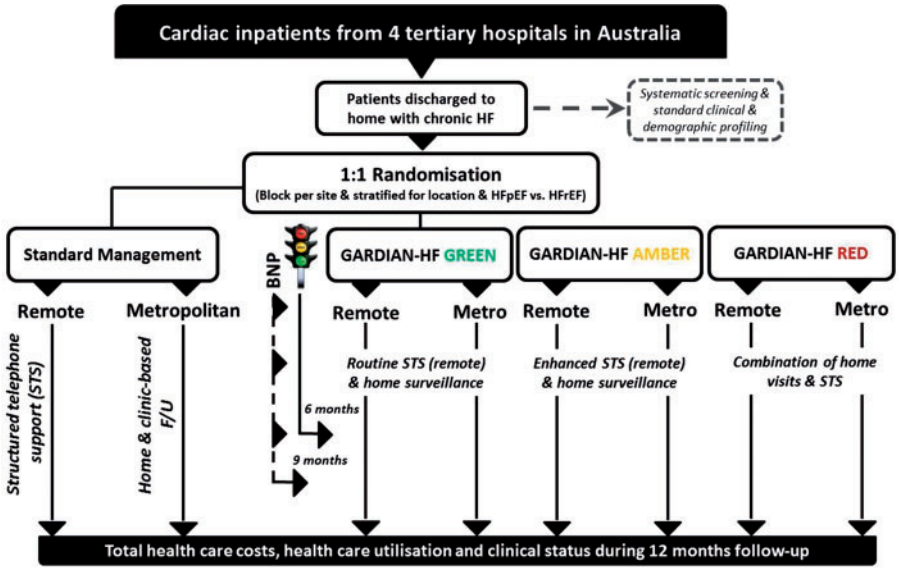

Figure 2 Study design and clinical management.

received follow-up care from experienced HF nurses who applied multidisciplinary, home-based intervention (minimum of one home visit within 7–14 days) post-index discharge, including access to specialist cardiology support and referral to additional support (e.g. pharmacist review and exercise programs). Those living remotely ($n = 113$) received STS via the National Heart Foundation of Australia's National Health Information Service—Call Centre utilized in the previously reported CHAT Study.[16] In order to protect the integrity of SM, minimal contact or monitoring of the activities by the HF-MP teams was applied.

As part of the study intervention, those allocated to the INT-HF-MP were initially profiled prior to hospital discharge according to the Green, Amber, Red Delineation of rIsk And Need tool[17] adapted to HF (GARDIAN-HF—see Supplementary material online, *Figure S1* and *Table S1*), to determine their level of risk of premature mortality or recurrent hospitalization (based on patterns of outcome in the WHICH? Trial).[4] A critical component of this profiling is the detection of ongoing clinical instability [automatically classified as high risk (Red) requiring proactive management]. All metropolitan-dwelling patients received a 7–14 day home-visit. Those remote-dwelling patients designated GARDIAN-HF Red also received a home visit (mean 270 km) and the remainder a phone-call review at 7–14 days (see Supplementary material online, *Table S2*). GARDIAN-HF status was updated at the 7–14 day review, and automated reports sent to each patient's healthcare team. As shown in *Figure 3* a combination of repeat home visits and STS (via an automated GARDIAN-ANGEL system to flag alerts and communications with the HF Nurse) were then applied according to GARDIAN-HF Status (see Supplementary material online, *Figures S2* and *S3*). Due to a combination of patient requests (to reduce phone contact) and high clinical vigilance, levels of STS were similar for Red and Amber GARDIAN-HF designated patients. GARDIAN-HF status was reassessed at 6 months (noting minimal probability of reclassification downwards). For those aged <75 years, the same methods used at baseline (where possible) were reapplied to obtain BNP levels at 3, 6, and 9 months, with automated clinical alerts and recommendations for treatment titration if the BNP remained elevated (>600 pg/mL). During 12 month follow-up, only 7% of patients subject to incremental STS demonstrated no signs of clinical instability; those designated GARDIAN-HF Red Status the most labile (see Supplementary material online, *Figure S4*) and requiring either urgent review (12% of contacts) or an emergency intervention (1%—Supplementary material online, *Figure S5*).

Study endpoints

All data were evaluated by study investigators masked to group allocation. The primary endpoint was total healthcare costs during 12-month follow-up. These were calculated in 2017 Australian dollars (A$1 is equivalent to ~EUR €0.7). As described in Supplementary material online, *Appendix II*, they comprised three key cost components: (i) hospital care (including non-admitted emergency department visits, unplanned and elective hospital admissions, rehabilitation, palliative care, and outpatient reviews/procedures); (ii) community care (including primary care visits, allied health care and nursing home stay); and (iii) HF-specific management that, in the INT-HF-MP group reflected the additional costs of applying extra home visits and STS to remote and metropolitan-dwelling patients, respectively, in addition to serial BNP monitoring among patients aged <75 years. Major secondary endpoints were: (i) the pattern of all-cause rehospitalization and related hospital stay with further delineation of unplanned vs. elective, cardiovascular-disease (CVD) related and HF-related hospitalization; (ii) all-cause mortality, (iii) event-free survival as expressed by the number of days alive and out-of-hospital (DAOH), and (iv) change in generic (EuroQol 5-dimensions/5-levels questionnaire, EQ-5D-5L)[18] and HF-specific (Kansas City Cardiomyopathy Questionnaire, KCCQ)[19] health-related quality of life from baseline to 12 months.

Statistical analyses

All analyses were performed, in blinded fashion, according to a prospectively planned Statistical Analysis Plan (see Supplementary material online, *Appendix III*) by the trial statistician. Health outcome data from the original

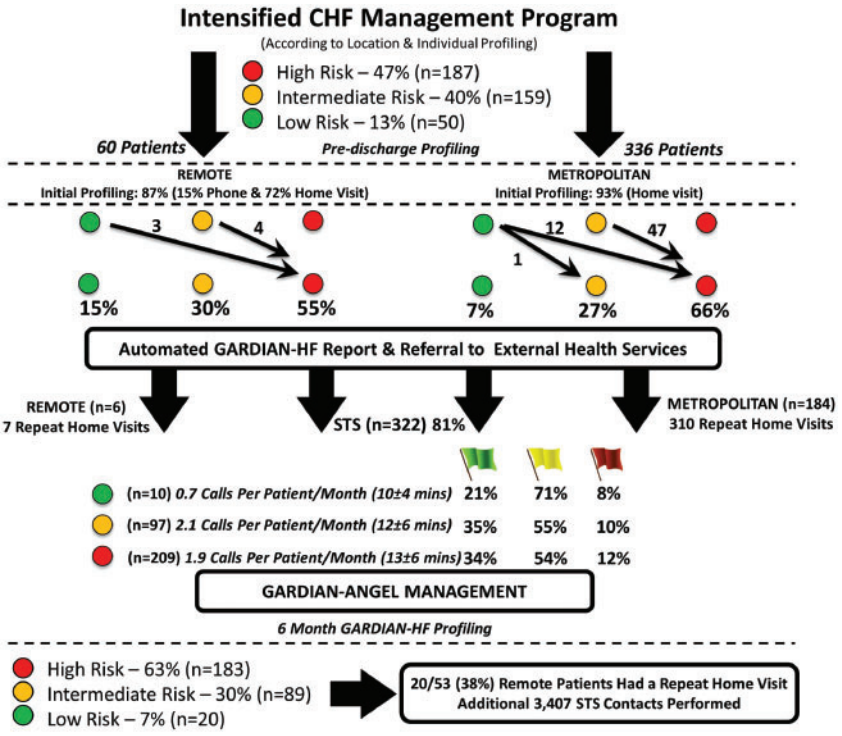

Figure 3 Pattern of intensified management according to GARDIAN-HF.

WHICH? Trial[4] were used to inform study power calculations. A total of 400 participants in each group provided >85% power (2-sided alpha 0.05) to detect a >15% group differential in total healthcare cost and all-cause hospital stay. Data for all four sites were pooled. Discrete variables were summarized by frequencies and percentages and continuous variables by standard measures of central tendency and dispersion using mean ± standard deviation (SD) and medians [inter-quartile range (IQR)]. All efficacy analyses were undertaken on a full analysis set basis. Total healthcare costs, the number of recurrent admissions and days of hospital stay were compared between groups using adjusted negative binomial regression after adjusting for length of follow up (events per participant per month) and stratification criteria (HF type and home location). Kaplan-Meier survival analyses were used to examine all-cause mortality, with a log-rank test used for between group comparisons. The fraction of maximum possible vs. actual DAOH (all forms of hospitalization) was compared with the Mann–Whitney *U* test. Other between group comparisons were assessed by Student's *t*-tests (normally distributed continuous data), Mann–Whitney *U* test (non-normally distributed continuous data) and χ^2 test [with calculation of odd ratios (OR) and 95% confidence intervals (CI)] where appropriate.

Results

Baseline profile

As shown in *Figure 1*, a total of 787/809 patients formed the full analysis set (following early death and withdrawal) and were randomized to the INT-HF-MP ($n = 396$) or SM ($n = 391$). Overall, *Table 1* shows that this was a typically older cohort (aged 74 ± 12 years), of whom, 41% were female. Factors likely to complicate HF management included low education levels (76%), living alone (40%) or having a non-English speaking background (20%). Geographically, 14% of patients lived remotely from specialist health services (range 30 to 1154 km). The majority of patients, most of whom (80%) presented as NYHA Class III/IV, had a history of hypertension (76%) and/or coronary artery disease (61%) and had been treated for HFrEF (65%) or HFpEF (35%) for an average of 47 months. Of the 253 patients (32%) with a secondary diagnosis of HF, ischaemic heart disease (28%), arrhythmias (19%—primarily AF) and respiratory disease (10%) accounted for half these presentations. Levels of multimorbidity were high with >50% of patients affected by concurrent mild cognitive impairment, anaemia, atrial fibrillation, moderate-to-severe renal impairment and/or depressive symptoms. Overall, the mean (age-adjusted) Charlson Comorbidity Index Score was 6.9 ± 2.4. Following a median of 6 (IQR 4 to 11) days index hospitalization, the majority were assessed as NYHA Class II (72%) and were prescribed an appropriate combination of pharmacotherapy comprising diuretics (90%), beta-blockers (81%) and renin-angiotensin-aldosterone system (RAAS) blockade (70%) relevant to their HF type/expert recommendations[1] and individual tolerance to such therapy. Overall, the two groups were very well matched according to their baseline profile (see *Table 1*).

Table 1 Baseline profile

	All (*n* = 787)	INT-HF-MP (*n* = 396)	SM (*n* = 391)
Sociodemographic profile			
Age (years)	74 ± 12	74 ± 11	74 ± 12
Female	325 (41%)	164 (41%)	161 (41%)
Living alone	314 (40%)	167 (42%)	147 (38%)
Remote dwelling	113 (14%)	60 (15%)	53 (14%)
<12 years of education	602 (76%)	295 (74%)	307 (79%)
English not first language	154 (20%)	83 (21%)	71 (18%)
Risk profile			
BMI (kg/m^2)—*n* = 786	29.8 ± 7.0	29.9 ± 7.4	29.6 ± 6.5
Current smoker	119 (15%)	57 (14%)	62 (16%)
Type 2 diabetes	348 (44%)	166 (42%)	182 (47%)
Hypertension	598 (76%)	298 (75%)	300 (77%)
Heart failure profile			
Duration of HF (months)	23 (IQR 9–61)	24 (IQR 9–65)	22 (IQR 8–58)
LVSD	509 (65%)	259 (65%)	250 (64%)
(LVEF %)	31.4 ± 8.9	31.4 ± 9.1	31.4 ± 8.7
NYHA class III/IV	222 (28%)	111 (28%)	111 (28%)
Elevated BNP—*n* = 761	389 (51%)	195 (50%)	194 (52%)
Prior HF admission (12 months)	472 (60%)	228 (58%)	244 (62%)
Clinical profile			
Systolic BP (mm/Hg)	135 ± 27	134 ± 27	136 ± 27
Diastolic BP (mm/Hg)	76 ± 16	76 ± 16	76 ± 16
Heart rate (beats/min)	86 ± 24	86 ± 24	85 ± 23
Acute pulmonary oedema	254 (32%)	126 (32%)	128 (33%)
Coronary artery disease	479 (61%)	226 (57%)	253 (65%)
Depressive symptoms	512 (65%)	247 (62%)	265 (68%)
eGFR <60 ml/min/1.73 m^2—*n* = 786	471 (60%)	242 (61%)	229 (59%)
Mild cognitive impairment—*n* = 576	330 (57%)	177 (60%)	153 (54%)
Anaemia (sex-specific)—*n* = 786	416 (53%)	212 (54%)	204 (52%)
Atrial fibrillation	428 (54%)	208 (53%)	220 (56%)
Cerebrovascular disease	169 (21%)	78 (20%)	91 (23%)
Sleep disorders	132 (17%)	68 (17%)	64 (16%)
Charlson Comorbidity Score	6.9 ± 2.4	6.8 ± 2.4	6.9 ± 2.4
CRT/ICD	150 (19%)	77 (19%)	73 (19%)
In-hospital management			
Principal diagnosis of HF	534 (68%)	268 (68%)	266 (68%)
Length of stay (days)	6 (IQR 4–11)	6 (IQR 4–11)	7 (IQR 4–11)
Critical care (days)	3 (IQR 0–7)	3 (IQR 0–7)	2 (IQR 0–7)
Pharmacotherapy			
Diuretic	709 (90%)	360 (91%)	349 (89%)
Beta-blocker	634 (81%)	322 (81%)	312 (80%)
RAAS blockade	553 (70%)	276 (70%)	277 (71%)
Anti-platelet	412 (52%)	214 (54%)	198 (51%)
Anti-coagulant	368 (47%)	190 (48%)	178 (46%)
Nitrate	235 (30%)	119 (30%)	116 (30%)
Digoxin	187 (24%)	93 (24%)	94 (24%)
Anti-arrhythmic agent	105 (13%)	52 (13%)	53 (14%)

There were no statistical differences between INT-HF-MP and SM groups, except for the comparison of history of coronary artery disease ($P = 0.028$).
Anaemia, haemoglobin (g/L) <130 males <120 females; BMI, body mass index; BNP, b-type natriuretic peptide; BP, blood pressure; CHF, chronic heart failure; eGFR, estimated glomerular filtration rate; Elevated BNP, >600 pg/mL; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NYHA, New York Heart Association; CRT, cardiac resynchronization therapy; ICD, implantable cardiac defibrillator; RAAS, renin-angiotensin-aldosterone system.

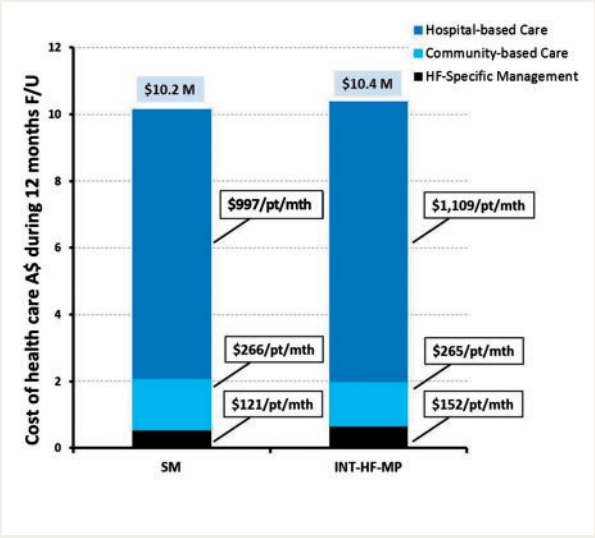

Figure 4 Healthcare costs according to group: Values are expressed in $A as median per patient per month. F/U, follow-up.

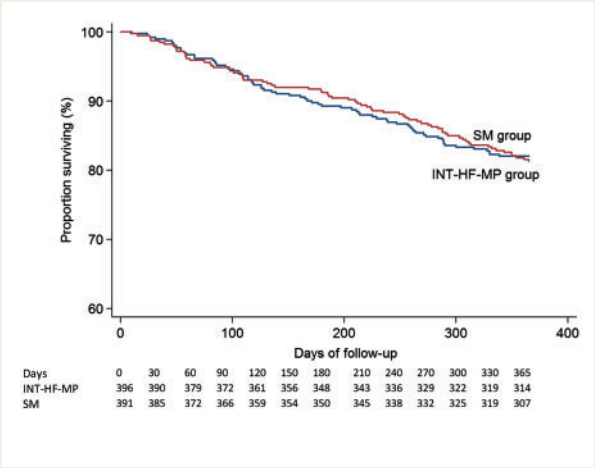

Figure 5 All-cause survival according to group.

Healthcare costs

Total healthcare costs for the two groups combined was >A$20 million during 12 months follow-up. *Figure 4* compares the total cost and three specific components of healthcare during 12-month follow-up for the two groups (see Supplementary material online, *Table S3*). The overall cost of applying HF-specific management per patient per month was greater for the INT-HF-MP compared to SM group (median $152, IQR $132 to $164 vs. $121, IQR $121 to $121, respectively; $P < 0.001$). For the primary endpoint, during 323 ± 94 days follow-up, the INT-HF-MP group accumulated total healthcare costs of $1579 (IQR $644 to $3717) per patient per month. This compared to a slightly lower cost of $1450 (IQR $564 to $3615) per patient per month during 326 ± 91 days of follow up in the SM group ($P = 0.336$). Accordingly, there were no differences in the cost of hospital-based ($1109, IQR $198 to $3069 vs. $997, IQR $153 to $3002 per patient per month; $P = 0.445$) or community-based healthcare costs ($265, IQR $214 to $317 vs. $266, IQR $219 to $334; $P = 0.893$) for the INT-HF-MP and SM groups, respectively. Additionally, irrespective of randomization strategy, there was a significant difference in the hospital-based costs between those with HFpEF and HFrEF, but not in respect to community-based healthcare or HF-specific management costs (see Supplementary material online, *Table S4*).

Survival and hospitalization

During 12-month follow-up, a total of 142 (18%) patients died; comprising 89/396 (23%), 52/303 (17%), and 1/88 (1.1%) patients initially categorized as Red, Amber, or Green respectively according to GARDIAN-HF criteria. According to group allocation, 70/396 (17.7%) patients in the INT-HF-MP group vs. 72/391 (18.4%) patients in the SM group ($P = 0.848$) died (*Figure 5*). Overall, the study cohort accumulated 2,204 hospital events comprising 485 non-admitted emergency department visits, 374 (944 length of stay days) elective admissions and 1178 (9909 days) unplanned admissions, in addition to 145 (2621 days) and 22 (384 days) admissions, respectively, related to rehabilitation and palliative care (see Supplementary material online, *Figure S6*). According to initial GARDIAN-HF status, patients categorized as Red, Amber, and Green accumulated a mean of 20, 18, and 5.4 days of all-cause hospital stay. *Table 2* compares the pattern of recurrent hospitalization and related stay according to group assignment. Overall, 251 (63%) INT-HF-MP patients compared to 222 (57%) SM patients had ≥1 unplanned hospitalization. There were no significant differences between the rate of unplanned, CVD-related, HF-specific and total hospitalization and related hospital stay between the two groups. Based on equivalent levels of mortality and hospital stay, there was also no significant difference between groups in respect to all-cause DAOH (304 ± 100 vs. 309 ± 96 days, representing 84.9% vs. 86.1% of actual/maximal DAOH in the INT-HF-MP vs. SM groups, respectively; $P = 0.493$). Importantly, the pattern of survival and hospitalization according to group assignment was similar for all four study sites.

Health-related quality of life

Baseline EQ-5D-5L scores were similar between the two groups. Among survivors with repeat scores at 12 months (270 INT-HF-MP and 258 SM patients), mean change in EQ-5D-5L scores were not significantly different (0.01, 95% CI -0.03 to 0.04 vs. 0.03 95% CI 0.0 to 0.07; $P = 0.221$). Similarly, baseline HF-specific health-related quality of life KCCQ scores and the changes from baseline to 12 months were similar between the two groups in all indices measured except for a greater improvement in KCCQ Self-efficacy subscale in INT-HF-MP patients (35, 95% CI 32 to 39 vs. 29, 95% CI 26 to 33; $P = 0.023$) from baseline to 12-month (see Supplementary material online, *Table S5*).

Discussion

Despite a substantial investment in profiling patient risk and then applying a combination of home visits and STS (regardless of location)

Table 2 Comparison of hospital events

	INT-HF-MP (*n* = 396)	SM (*n* = 391)	Group comparisons
Study follow-up			
Mean days of follow-up	323 ± 94	326 ± 91	*P* = 0.986
Unplanned admissions	595 | 5344 days	583 | 4565 days	
Episodes/participant	1.5 ± 1.9	1.5 ± 2.1	*P* = 0.915
Days/participant	13.5 ± 21.3	11.7 ± 19.3	*P* = 0.204
Median days of stay per event	12 (IQR 6 to 30)	13 (IQR 5 to 28)	*P* = 0.587
CVD-related admissions	424 | 3241 days	425 | 2859 days	
Episodes/participant	1.1 ± 1.5	1.1 ± 1.7	*P* = 0.880
Days/participant	8.2 ± 14.2	7.3 ± 14.4	*P* = 0.440
Median days of stay per event	10 (IQR 4 to 19)	9 (IQR 4 to 21)	*P* = 0.765
HF (primary) admissions	213 | 2006 days	182 | 1486 days	
Episodes/participant	0.5 ± 1.0	0.5 ± 1.0	*P* = 0.298
Days/participant	5.1 ± 11.5	3.8 ± 10.2	*P* = 0.198
Median days of stay per event	12 (IQR 6 to 21)	8 (IQR 4 to 19)	*P* = 0.228
All admissions	778 | 5820 days	774 | 5033 days	
Episodes/participant	2.0 ± 2.3	2.0 ± 2.8	*P* = 0.934
Days/participant	14.7 ± 21.7	12.9 ± 20.1	*P* = 0.221
Median days of stay per event	12 (IQR 5 to 26)	11 (IQR 4 to 27)	*P* = 0.462
Rehabilitation	70 | 1306 days	75 | 1315 days	
Episodes/participant	0.2 ± 0.4	0.2 ± 0.5	*P* = 0.649
Days/participant	3.3 ± 10.8	3.4 ± 10.0	*P* = 0.930
Median days of stay per event	14 (IQR 7 to 27)	19 (IQR 12 to 30)	*P* = 0.082
Palliative care	12 | 242 days	10 | 142 days	
Episodes/participant	0.03 ± 0.19	0.03 ± 0.16	*P* = 0.701
Days/participant	0.6 ± 5.1	0.4 ± 3.2	*P* = 0.417
Median days of stay per event	24 (IQR 4 to 29)	7 (IQR 4 to 23)	*P* = 0.393
Non-admitted ED visits	249	236	
Episodes/participant	0.6 ± 1.3	0.6 ± 1.1	*P* = 0.766

Follow-up was censored for death and lost to follow-up.

and supported by BNP monitoring where appropriate, compared to less intensive and costly HF management (representing the current gold-standard), there was no difference in the primary endpoint of total healthcare costs during 12 months follow-up. This outcome reflected a lack of expected impact on the pattern of recurrent hospitalization (of any type) and associated stay and survival by the study intervention. If anything, nearly all study endpoints tended to favour SM; comprising HF nurse home visits for metropolitan-dwelling patients and STS for regional dwelling patients (regardless of risk status). Incremental management, as applied in the mainly high risk 396 patients assigned to INT-HF-MP was not insubstantial; comprising an additional 72 home visits to remote dwelling patients (noting the logistical difficulty of applying repeat home visits in this cohort living up >1000 km away), 7208 STS contacts (>10% of which prompted additional management) and 421 BNP surveillance tests over and above SM. Nevertheless, beyond the primary and secondary endpoint comparisons, there were minimal clinical differences between survivors at 12 months (see Supplementary material online, *Table S6*).

A number of issues arising from these findings require commentary. Firstly, as part of pre-specified analyses, we determined that the pattern of healthcare costs and outcomes in the two groups was consistent across all four study sites and regardless of when a participant was randomized into the study; the latter indicating a lack of interventional 'fatigue' over time. A critical component of the study intervention was GARDIAN-HF profiling (to direct a combination of home visits and STS regardless of patient location). Based on initial profiling (during index admission) there was a clear gradient in subsequent hospitalization and survival from Green to Red status; indicating clear potential to attenuate elevated risk of poor outcomes via the study intervention. A consistent feature of systematic reviews and meta-analyses of the evidence underpinning the application of HF-MPs has been the superiority of nurse-led, multidisciplinary management applied via home visits.[2,3] This was applied as SM in this trial. Whilst we've previously demonstrated the incremental benefits of this approach relative to a purely specialist HF clinic approach (via the original WHICH? Trial[4,6,7]), it appears clear that face-to-face programs are superior to those applying remote management (i.e. STS alone).[3] It is certainly possible that the addition of STS as part of the study intervention (despite our best intentions and a dedicated communications and alert protocol—the GARDIAN-ANGEL system) interfered

with standard face-to-face management. Another strong possibility is that we reached a 'threshold effect' of management, whereby additional support, surveillance and advice (with the prospect of invoking the previously described phenomenon of a counter-productive 'clinical cascade' effect[20]) counter-balanced any potential benefits of more intensive intervention. The fact that this was a particularly old and fragile HF patient cohort with substantive multimorbidity (with significantly longer length of stay per episode) may be relevant to the observed lack of interventional effect. In a recent analysis of the overall benefits of nurse-led, home-based intervention in all forms of chronic heart disease,[5] we did observe the potential for worse outcomes when this model of care was applied to older individuals with high levels of multimorbidity. Given the high prevalence of AF in this cohort (around 50%) it is worth noting that many therapeutic options (e.g. CRT) are not known to be effective in affected individuals.[1] Keeping in mind that health goals may differ between age groups, it is necessary to determine how we might implement new interventions by adjusting previously successful modes of management, rather than simply conceding to poor quality of care in this increasingly common and challenging patient population.[8,9] Pending the outcome of longer-term follow-up of this cohort, according to group assignment, it will be critical to understand who might still benefit from the study intervention.

There are few trials that have purposefully compared the same type of HF management but modified the intensity of its application; a notable exception being the three-armed (one control group vs. HF nurse-led management applied in a moderately or intensive fashion) COACH Study conducted by Jaarsma *et al.*[21] Moreover, there is a paucity of trials purposefully applying a 'hybrid' approach (i.e. combining home visits and STS). Although our trial cohort is markedly older with greater multimorbidity (an expected difference given the two studies being a decade apart), the COACH Study also failed to find any benefits from applying HF management in a more intensive manner.[21] The challenge of further enhancing the cost-efficacy of current HF-MPs, particularly in the setting of negative trials of remote monitoring techniques relative to SM[22,23] remains unanswered.

As a pragmatic health services intervention trial undertaken in one health system, there are some limitations to interpreting the veracity and wider applicability of study findings. The patients, clinicians and majority of research personnel involved in the trial were not (completely) blinded to group assignment; with potential loss of blinding for endpoint adjudication if clinical reports indicated group assignment. We relied on administrative data-sets and cross-referencing to patient and clinician reports to verify study outcomes. We also purposefully avoided monitoring or measuring the intensity and nature of SM; relying upon our detailed understanding of the HF-MP being applied at each site and excluding the application of home visits and STS to regional-dwelling patients and metropolitan-dwelling patients, respectively, and the lack of routine access to BNP monitoring. This study was also conducted in Australia and the cost-dynamics of management may be different elsewhere. However, given the size, scope, and consistency of study findings across four different hospitals and HF services, they are likely to be relevant to other healthcare settings; particularly when hospital costs remain the major component of HF-related expenditure in high income countries.[24]

In conclusion, as part of one of the largest and most comprehensive studies of its kind, we compared gold-standard HF management with a more intensified version of the same that particularly targeted those patients most at risk of recurrent hospitalization and premature mortality. Despite accurately identifying such patients (and applying a more costly and intensive form of HF management), this investment failed to deliver better health outcomes and lower cost; at least during 12 months follow-up.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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