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Effectiveness of out-patient based acute heart failure care: a pilot randomised controlled trial

Wong, KYK

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Corresponding Author:	Kenneth Y.K. Wong, MA, DM (Oxon), FRCP, FESC,FACC Lancashire Cardiac Centre Blackpool, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Lancashire Cardiac Centre
Corresponding Author's Secondary Institution:	
First Author:	Kenneth Y.K. Wong, MA, DM (Oxon), FRCP, FESC,FACC
First Author Secondary Information:	
Order of Authors:	Kenneth Y.K. Wong, MA, DM (Oxon), FRCP, FESC,FACC
	Dyfrig A. Hughes, BPharm MSc PhD MRPharmS FFRPS FBPhS FLSW
	Maciej Debski, MD, PhD
	Nang Latt, MBBS, MRCP
	Omar Assaf, MB BCh
	A. Abdelrahman, MBBS, MRCP
	Rebecca Taylor, MSc
	Victoria Allgar, PhD CStat
	Loie McNeill, BA, CGMA
	Stuart Howard, BA, BSc
	S.Y.S. Wong, MA (Oxon), MBBS (Lond), FRCP
	Robert Jones, BEd (Hons)
	Christopher Cassidy, MB ChB, FRCP
	Alison Seed, MD
	Gavin Galasko, BM BCh MA DM (Oxon) FRCP
	A. L. Clark, MA, MD,FRCP
	Gershan Davis, FRCP FRACP FESC FSCCT FHEA
	A Montasem, BSc, MSc, PhD, CPsychol
	Chim C. Lang, BMSc (hons)., MD., FRCP, FACC
	Paul R Kalra, MA MB BChir MD FRCP
	Ross Campbell, PhD
	Gregory Y.H. Lip, MD

	J.G.F. Cleland, MD, PhD
Order of Authors Secondary Information:	
Abstract:	Objectives: Acute heart failure (AHF) hospitalisation is associated with 10% mortality. Outpatient based management (OPM) of AHF appeared effective in observational studies. We conducted a pilot randomised controlled trial (RCT) comparing OPM with standard inpatient care (IPM). Methods: We randomised patients with AHF, considered to need IV diuretic treatment for >2 days, to IPM or OPM. We recorded all-cause mortality, and the number of days alive and out-of-hospital (DAOH). Quality of life, mental well-being and Hope scores were assessed. Mean NHS cost savings and 95% central range (CR) were calculated from bootstrap analysis. Follow-up: 60 days. Results: Eleven patients were randomised to IPM and thirteen to OPM. There was no statistically significant difference in all-cause mortality during the index episode (1/11 vs 0/13) and up to 60 days follow-up (2/11 vs 2/13) [p=0.86]. The OPM group accrued more DAOH {47 [36,51] vs 59 [41,60], p=0.13}. Two patients randomised to IPM (vs 6 OPM) were readmitted [p=0.31]. Hope scores increased more with OPM within 30 days but dropped to lower levels than IPM by 60 days. More out-patients had increased total well-being scores by 60 days (p=0.04). OPM was associated with mean cost savings of £2,658 (95% CR 460 - 4,857) per patient. Conclusions: Patients with acute HF randomised to OPM accrued more days alive out of hospital (albeit not statistically significantly in this small pilot study). OPM is favoured by patients and carers and is associated with improved mental well-being and cost savings.
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April 14, 2021

Prof. Patrizio Lancellotti, MD, PhD
Editor-in-Chief
Acta Cardiologica

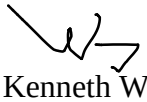
Dear Professor Lancellotti,

We are pleased to submit our manuscript: "**Effectiveness of out-patient based acute heart failure care: A pilot randomised controlled trial**" for consideration of publication as an Original Article at *Acta Cardiologica.* This small pilot randomised controlled trial demonstrated that patients with acute heart failure randomised to out-patient management accrued more days alive out of hospital without increase in mortality. Out-patient management is favoured by patients and carers and is associated with improved mental well-being and cost savings. We hope the Editors and Readers of *Acta Cardiologica* will find our manuscript interesting and relevant, especially in the COVID-19 pandemic era. Further, the results underpin the rationale for a large multicentre randomised controlled trial for which we are applying for a research grant from the UK NIHR to perform. Thus the present pilot study paper is likely to be quoted often.

The authors declare 1) the paper is not under consideration elsewhere; 2) none of the paper's contents have been previously published; 3) all authors have read and approved the manuscript; 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. No conflict of interest, financial or others exists for any of the authors.

We thank the editorial board for taking the time to consider our manuscript.

Yours Sincerely,



Dr Kenneth Wong MA (Oxon), DM (Oxon), FRCP (Lond), PGCME (HYMS), FHEA, FESC, FACC
Department of Cardiology, Lancashire Cardiac Centre,
Blackpool Teaching Hospitals NHS Foundation Trust
Blackpool, United Kingdom
Phone- +44-1253-957783
dr.wong@nhs.net

Online Supplement

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Methods

Sample size –this is a pilot study so formal sample size calculation is not required. In the feasibility study, we aimed to recruit 100 patients over 12-24 months to demonstrate feasibility (of recruiting, randomizing) and inform effect size for a multicentre RCT. In the end, after 12 months, 105 patients were contacted about the study and screened, but only 24 patients were consented and randomised, having satisfied all the inclusion and exclusion criteria.

Clinical outcomes

Details regarding the Pre-specified secondary endpoints -

1. Rehospitalisation for HF within 60 days of randomisation - Note that a further readmission for an in-patient would be in addition to their index HF episode, a readmission for an out-patient may be within the initial index episode but after discharge for in-patient care. Thus, the endpoint Days alive out of hospital (DAOH) took care of the complexities of deciding whether a patient "crossed over" or was readmitted.
2. Death from any cause within 60 days of randomisation
3. Cardiovascular death within 60 days of randomisation,
4. Symptom resolution/ oedema reduction to no more than a "trace of ankle oedema" or "back to usual" in patients known to have refractory leg oedema)/achievement of "dry weight" (usual weight when not fluid-overloaded).
5. Duration of diuretic treatment
6. Patient-centred secondary endpoints included patient and carer satisfaction ("family and friend test"), Quality of life assessment, measured using EQ5D-5L, the Short

Warwick-Edinburgh Mental Wellbeing scale (SWEMWBS) and the Adult State Hope Scale.

7. Cost effectiveness

Cost effectiveness analysis was performed using the Trust's patient level costing models from financial years 2018/19 and 2019/20 to calculate total treatment costs. This takes into account of length of stay, staff time (doctors/nurses/allied healthcare professionals), lab tests, radiology and other diagnostic tests and medicine/device therapy etc. Where patient level costs were unavailable, e.g. for Community visits, we used a national average cost.

The quality of our patient-level costing data is excellent. We received a Cost Assessment Tool score of 86% from NHS Improvement. The Cost Assessment Tool takes into account of a range of metrics including Data Quality, Costing Allocation Methods, Governance and Information Gaps.

£83 per day was the estimated cost of home visits and community centre; £59 for <4 hour utilisation of the hospital "frusemide lounge" (Cardiac Day Ward).

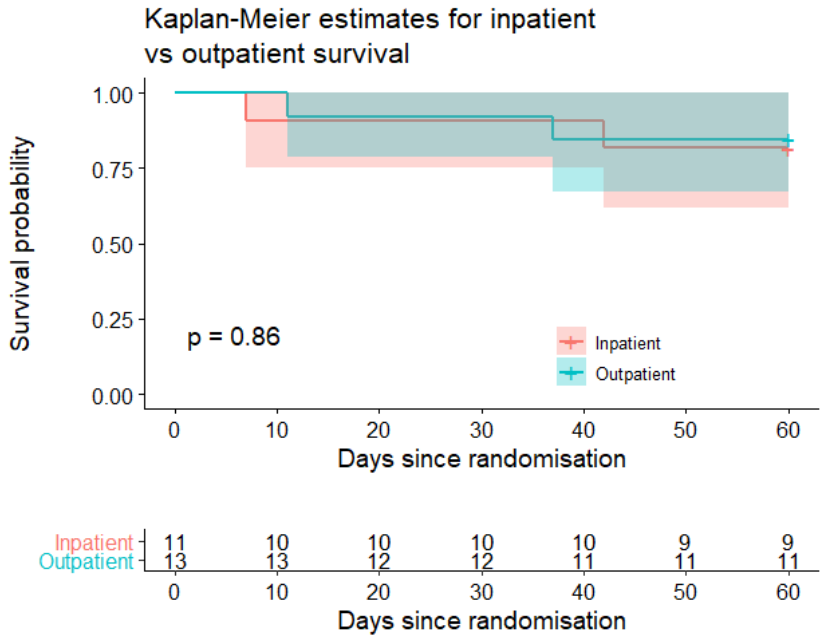
Typically, the cost of medical ward vs cardiology ward vs CCU vs ICU vs HDU (per day) is £214 per day (medical), £162 per day (cardiac), CCU £522 per day, ICU/HDU £787 per day at our Trust. Follow up visit in Cardiac clinic costs £128. £253 is the average cost of an A&E attendance.

Responses to the EQ-5D-5L were mapped to the 3L valuation set [26], and quality-adjusted life years (QALYs) measured based on the trapezium rule. Incremental costs and QALYs were calculated in an exploratory analysis of cost-effectiveness. A bootstrap analysis with 10,000 replicates was performed to estimate the 95% central ranges (CR) in total costs and QALYs, and their differences [27].

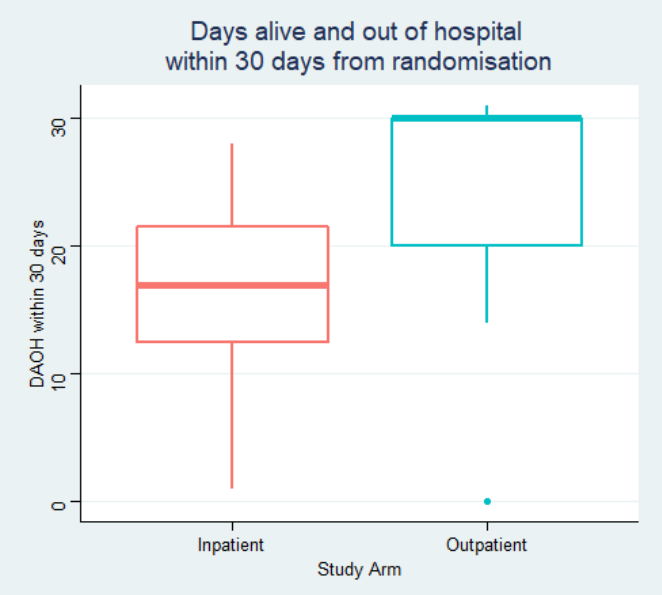
Results [Supplementary Results and Supplementary Figures and tables]

Kaplan-Meier survival analysis assessed the impact of OPM on all-cause mortality. The censor date was at least 60 days after the completion of the last patients' treatment.

Supplementary Figure 1: Out-patient based therapy for AHF was not associated with worse survival (log rank test p=0.86)

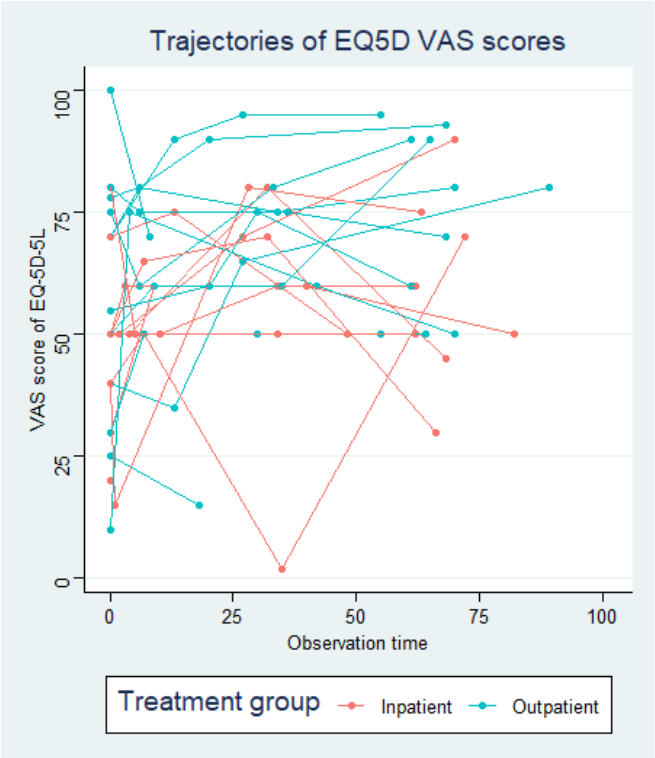


Supplementary Figure 2**: Out-patient based AHF treatment was effective at increasing the number of full days alive out of hospital during 30 day follow-up**

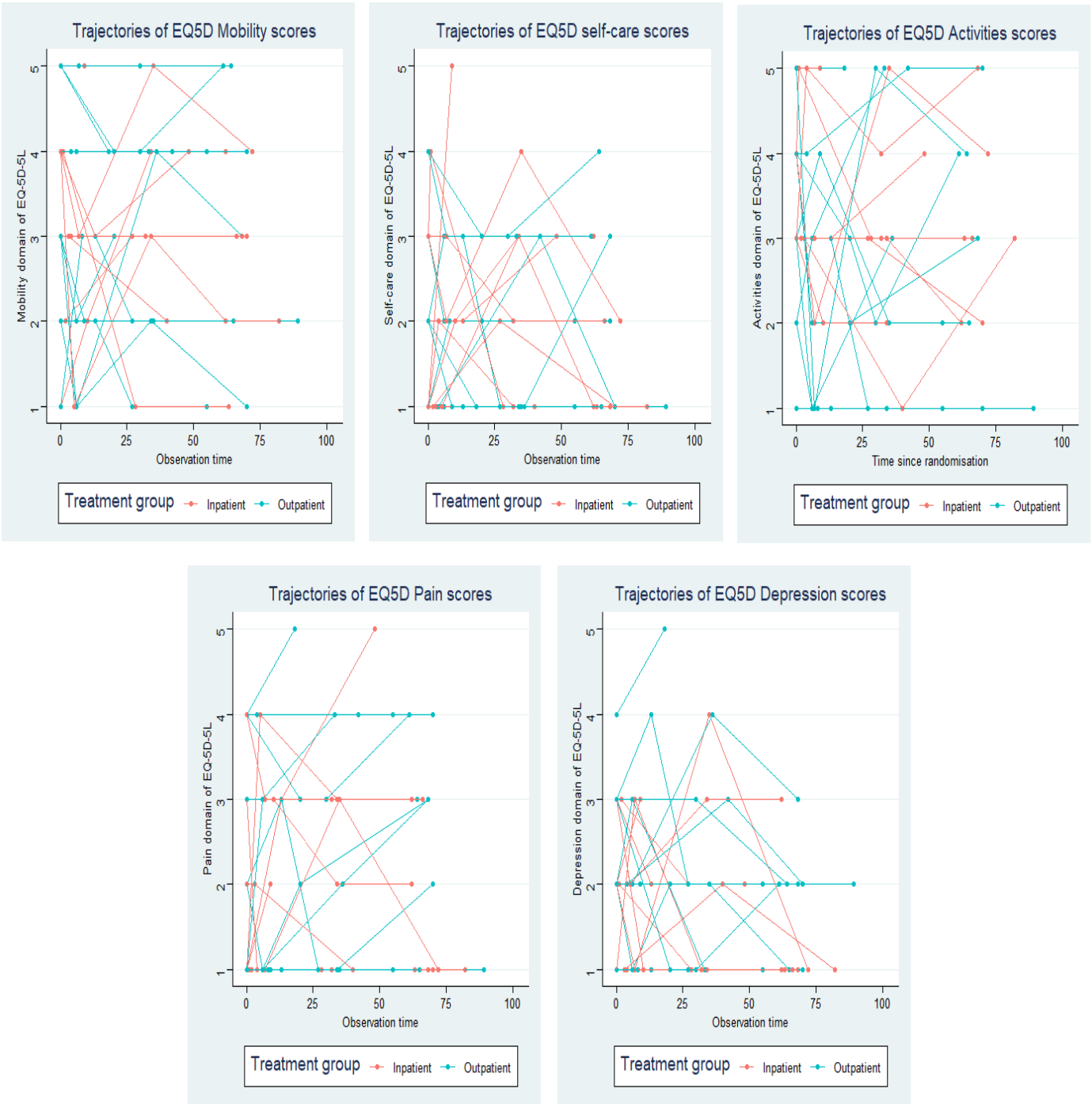


Supplementary Figure 3 [Online Supplement]: **EQ5D Visual Analogue Scale score trajectories across real time**

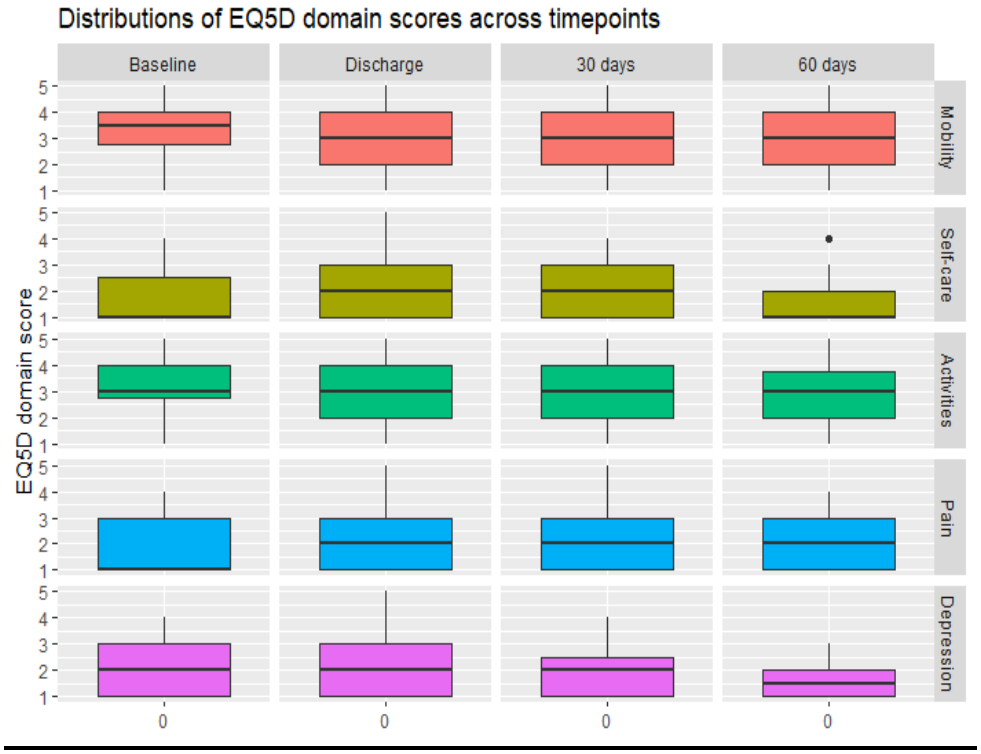
The visual analogue scale scores of the EQ5D plotted per patient across the duration of the study time. The blue trajectories (out-patients) are seen to generally climb more than the red trajectories (in-patients).



Supplementary Figure 4**: EQ5D domain score trajectories across real time**



Supplementary Figure 5**: Distribution of EQ5D domain scores across time points**



The trajectory plots and boxplots of distributions for all 5 individual EQ5D domains show no changes that are statistically significant: Wilcoxon tests of change from baseline to discharge (p=0.23, 0.50, 0.47, 0.51 and 0.81 respectively).

Supplementary Table 1 Patient and Carer satisfaction ("NHS Family and Friends Test")

	Discharge	30 days	60 days
Patient satisfied			
In-patient (n=10)	10/10	8/8	8/8
Out-patient (n=12)	12/12	10/10	11/11
Patient would choose again			
In-patient (n=10)	9/10	8/8	8/8
Out-patient (n=12)	12/12	10/10	10/11
Carer satisfied			
In-patient (n=7)	3/5	6/6	6/6
Out-patient (n=10)	10/10	6/6	9/9
Carer would choose again			
In-patient (n=7)	3/5	6/6	6/6
Out-patient (n=10)	10/10	6/6	9/9

100% patients in both arms were satisfied according to the "NHS Family and Friends Test" but interestingly 100% would choose OPM again but only 90% would choose Inpatient care. Similarly, 100% carers were satisfied in the OPM arm whilst 60% only were satisfied if the patient is randomised to inpatient care. 100% carers would choose OPM again, vs 60% IPM carers.

Supplementary Table 2 Does out-patient based therapy increase Hope score in patients with acute heart failure?

Hope	Hope (total) score -baseline		Increase in score from baseline to discharge		Increase in score from baseline to 30 days		Increase in score from baseline to 60 days	
In-patient	33 [27,40] (n=11)	P=0.69	0 [-5, 7] (n=9)	p=0.34	2 [-14, 5] (n=9)	p=0.43	6.5 [-4.3, 16] (n=8)	p=0.59
Out-patient	30 [23,42.5] (n=13)		5 [-1.5, 9] (n=12)		6.5 [-5, 8.8] (n=10)		2.5 [-7, 12.3] (n=10)	

Supplementary Table 3 Increases in Visual Analogue Scale scores of EQ5D

Comparing the VAS scores of the EQ5D tool across time points. "Increase in score" is calculated as the simple subtraction of the scores at the two time points, so that a negative result means the score decreased (lower score is indicative of worse overall health).

VAS score	VAS score at baseline		Increase in score from baseline to discharge		Increase in score from baseline to 30 days		Increase in score from baseline to 60 days	
Inpatient	50 [40, 50] (n=11)	P=0.25	2.5 [0, 10] (n=10)	p=0.65	10 [-20, 20] (n=9)	p=0.27	5 [-9, 31] (n=8)	p=0.28
Outpatient	70 [40, 78] (n=13)		10 [-20, 20] (n=12)		20 [6, 24] (n=10)		23 [10,33] (n=11)	

Supplementary Table 4: Comparison of changes in transformed SWEMWBS scores between baseline and discharge

Change was calculated as discharge score minus baseline score, so that a positive change represented an increase in score (higher score implies greater wellbeing). Scores were Normally distributed, even in this small sample (Shapiro-Wilk test p>0.23 at all time points) and thus comparisons were made using appropriate t-tests. Scores are presented as mean (SD). Comparisons within time points as well as across time points are shown as outpatients are found to have significantly poorer wellbeing than inpatients at the time of randomisation.

		Inpatients	Outpatients	
Raw scores	**Randomisation** *n_{IN}=10, n_{OUT}=12*	25.6 (4.5)	21.0 (5.1)	**p=0.034**
	Discharge *n_{IN}=10, n_{OUT}=12*	23.0 (5.2)	24.9 (5.1)	p=0.40
	30 days from rand. *n_{IN}=8, n_{OUT}=9*	24.8 (4.9)	27.1 (4.8)	p=0.35
	60 days from rand. *n_{IN}=8, n_{OUT}=11*	26.4 (6.1)	24.4 (6.6)	p=0.50
Change from randomisation	**Discharge** *n_{IN}=9, n_{OUT}=11*	-1.4 (5.6)	4.4 (4.9)	**p=0.026**
	30 days *n_{IN}=8, n_{OUT}=9*	-0.6 (4.2)	6.3 (5.4)	**p=0.010**
	60 days *n_{IN}=8, n_{OUT}=10*	0.2 (4.8)	5.3 (5.5)	p=0.053

IPM wellbeing scores at discharge were not significantly different compared with baseline. [25.6 vs 23.0, p=0.46]. OPM wellbeing scores at discharge were significantly increased. [Mean 21.0 vs 24.9, p=0.01].

IPM had higher initial wellbeing scores (25.6 vs 21.0, p=0.034).
On discharge, there was no longer significant difference (23.0 vs 24.9, p=0.40).
Thus, OPM scores increased significantly more than IPM (mean change 4.4 vs -1.4, p=0.026)

Achievement of target weight, oedema and symptom resolution

Diuretic treatment was delivered over 5.8 days (SD 2.8) for in-patients and 8.5 (SD 5.2) days for out-patients. There was no significant difference in target weight achieved (on discharge from treatment) in patients who survived to discharge visit [OPM 9/13 vs IPM 4/10*; P = 0.22 (Fisher's Exact test)]; oedema resolution to no more than a trace/back to normal [OPM 9/13 vs IPM 6/10; P = 0.69]; symptom resolution [OPM 10/13 vs IPM 7/10; P = 1]; composite end-point [i.e. any treatment target met out of the three types: OPM 13/13 vs IPM 7/10; P = 0.068]. One in-patient died suddenly before the discharge visit without achieving target weight loss, symptom/oedema resolution. Overall, out-patients lost more weight in this trial, in-patients mostly gained weight, based on only 14 patients (5 from each group had missing data) [Supplementary Table 5 Diuretic Dose and Weight Change].

Supplementary Table 5 Diuretic Dose and Weight Change

		In-patient (n=11)	Out-patient (n=13)	p-value
Weight loss (kg) [difference in weight between randomisation and discharge visit]		-0.2 [-0.7, 2.0]	3.1 [1.2, 7.8]	**0.044**
TOTAL duration of iv diuretic treatment from randomisation to discharge (including "weekend interruption" where no iv treatment was given), days		5.8 (2.8)	8.5 (5.2)	0.117
Median dose of IV diuretic	per day of IV treatment [IQR]	100 [60-123]	103 [80-120]	0.726
No of days of weekend interruption	{% who had weekend interruption in outpatient group}	0 [0-0] {0}	2 [0-2] {8/13, 62%}	-
Total dose of iv frusemide	from randomisation to discharge	720 [240-1160]	640 [400-820]	>0.99
Total dose of bumetanide	over weekend *	-	4 [0-5]	-

* 1 patient had 7.5mg bendofluazide over the weekend in the outpatient group (3 doses of 2.5mg)

Figures are presented either as: mean (standard deviation), as median [Q1, Q3], or as percentage

Appendices [Online Supplement]

Appendix 1

Measures of Hope, Well-being and Quality of Life

The Adult Hope Scale (AHS) relates to Snyder's cognitive model of hope. Snyder sees hope as "a positive motivational state that is based on an interactively derived sense of successful (a) agency (goal-directed energy), and (b) pathways (planning to meet goals)". In essence then, hope stems from being able to see the next step, then having the motivation and the know-how to get there. The Short Warwick-Edinburgh Mental Well-Being Scale (SWEMWBS) measures subjective mental well-being. It has been used to assess the impact of medical interventions on general well-being.

Both measures have been used in a variety of physical health populations, including patients with renal disease, fibromyalgia and amputees. Hope is predictive of subjective well-being and quality of life, which in turn predicts healthcare use and illness management [12].

Importantly, there is evidence suggesting that hope can predict outcome independent of depression. Everson et al. [18] examined the relationship between levels of hopelessness and all-cause and cause-specific mortality, and incidence of myocardial infarction (MI) and cancer in a population-based sample of middle-aged men. The large study included 2428 men, aged 42 to 60, from the Kuopio Ischemic Heart Disease study, a longitudinal study of psychosocial risk factors for ischemic heart disease and other outcomes. In 6 years of follow-up, 174 deaths (87 cardiovascular and 87 non-cardiovascular, including 40 cancer deaths and 29 deaths due to violence or injury), 73 incident cancer cases, and 95 incident MI had occurred. Men were rated low, moderate, or high in hopelessness if they scored in

the lower, middle, or upper 1/3 of scores on a 2-item hopelessness scale. Age-adjusted Cox proportional hazards models identified a dose-response relationship such that moderately and highly hopeless men were at significantly increased risk of all-cause and cause-specific mortality relative to men with low hopelessness scores. Indeed, highly hopeless men were at more than 3-fold increased risk of death from violence or injury compared with the reference group. These relationships were maintained after adjusting for biological, socioeconomic, or behavioural risk factors, perceived health, depression, prevalent disease, or social support. High hopelessness also predicted incident MI, and moderate hopelessness was associated with incident cancer. These findings indicate that hopelessness is a strong predictor of adverse health outcomes, independent of depression and traditional risk factors.

EQ-5D-5L

Consists of five items each with a different domain: mobility, self-care, activities, pain and depression. Each is scored from 1-5 where 5 is the worst (severe limitation/unable to do). According to NICE, the 5-level questionnaire is used because it provides greater sensitivity with smaller "floor and ceiling effect". We have used the 3 level (3L) cross-walk value set for England to calculate the health related QoL index while awaiting validation of the newer 5 level value set.

Value sets are used to transform the health profile into an index value that can be interpreted as a health utility; these range from -0.594 to 1.000 where a value below zero is taken to describe a health state whose quality is perceived to be "worse than death".

The visual analogue scale (VAS) helps us determine patients' perception of their own health, where 100 means the "best health you can imagine" and 0 is the worst.

EQ5D-5L Health Questionnaire: English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about	❑
I have slight problems in walking about	❑
I have moderate problems in walking about	❑
I have severe problems in walking about	❑
I am unable to walk about	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

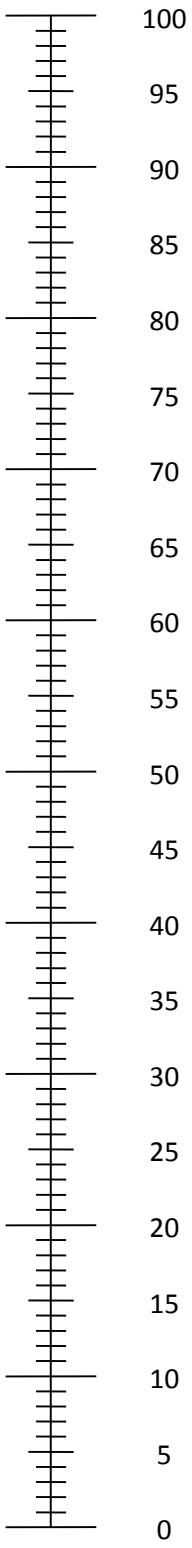
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Mark an X on the scale to indicate how your health is TODAY.
Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



The Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS)

Below are some statements about feelings and thoughts.

Please tick the box that best describes your experience of each over the last 2 weeks	None of the time	Rarely	Some of the time	Often	All of the time
STATEMENT					
I've been feeling optimistic about the future	1	2	3	4	5
I've been feeling useful	1	2	3	4	5
I've been feeling relaxed	1	2	3	4	5
I've been dealing with problems well	1	2	3	4	5
I've been thinking clearly	1	2	3	4	5
I've been feeling close to other people	1	2	3	4	5
I've been able to make up my own mind about things	1	2	3	4	5

The Adult State Hope Scale (Snyder et al., 1996)

Read each item carefully.

Using the scale shown below, please select the number that best describes *how you think about yourself right now* and put that number in the blank before each sentence.

Please take a few moments to focus on yourself and what is going on in *your life at this moment.*

Once you have this "here and now " set, go ahead and answer each item according to the following scale:

Definitely False	1
Mostly False	2
Somewhat False	3
Slightly False	4
Slightly True	5
Somewhat True	6
Mostly True	7
Definitely True	8

_____ 1. If I should find myself in a jam, I could think of many ways to get out of it

_____ 2. At the present time, I am energetically pursuing my goals

_____ 3. There are lots of ways around any problem that I am facing now

_____ 4. Right now, I see myself as being pretty successful

_____ 5. I can think of many ways to reach my current goals

_____ 6. At this time, I am meeting the goals that I have set for myself

Scoring information

Pathways subscale score: Add items 1, 3, and 5. Scores on this subscale can range from 3 to 24, with higher scores indicating higher levels of pathways thinking.

Agency subscale score: Add items 2, 4, and 6. Scores on this subscale can range from 3 to 24, with higher scores indicating higher levels of agency thinking.

Total hope score: Add the pathways and Agency subscales together. Scores can range from 6 to 48, with higher scores representing higher hope levels.

Development and validation of the State Hope Scale. Journal of Personality and Social Psychology, 70, 321–335.

Appendix 2

Frailty assessment

The Derby Frailty Index was initially developed as a Frailty identification tool (FIT) in 2013 which does not require additional training for staff. The tool was used to identify suspected frail patients for targeted further comprehensive geriatric assessment and interventions.

Frailty is suggested if one or more of the following criteria were met:

- Age >65 and a care home resident
- >75 with confusion, or falls or reduced mobility
- >84 with >4 co-morbidities.

The Rockwood clinical frailty scale is another simplified screening tool for assessing the degree of frailty. It is a 9-point ordinal scale which takes into account information about cognition, mobility, function and co-morbidities based on the history and physical examination to assign a frailty level from 1 to 9. This method is easier to administer and effectively estimates important outcomes including survival and institutionalisation. A frailty score of 5 or more indicates frailty, as used in other outcome research studies e.g. SENIOR-RITA. Category descriptions are given below:

1 Robust, active, energetic, well-motivated, fit, exercises regularly - Very fit

2 Without active disease but less fit that category 1- Well

3 Disease symptoms are well controlled compared with those in category 4 (Managing well)

4 Not frankly dependent, but commonly complains of being slow or is symptomatic of diseases - Apparently vulnerable

5 Limited dependence on others for IADLs - Mildly frail

6 Needs help for both IADLs and BADLs - Moderately frail

7 Completely dependent for all BADLs and IADLs - Severely frail

8 Completely dependent and approaching end of life,

(could not recover from even a minor illness) - Very severely frail

9 Life expectancy <6 months, but not otherwise frail - Terminally ill

IADLs- instrumental activities of daily living, e.g. banking, transportation, cooking, cleaning, medication management, shopping.

BADLs- basic activities of daily living, e.g. feeding, bathing, dressing, toileting ambulation

Supplementary References

References 1-25 are in the main paper [print version]

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Effectiveness of out-patient based acute heart failure care: A pilot randomised controlled trial

Short title: Acute Heart Failure IN or OUT pilot RCT

Key Words- Acute Heart Failure, Cost-effectiveness, Health Economics, Healthcare delivery, Heart failure

Conflict of interest- None declared

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ABSTRACT

Objectives: Acute heart failure (AHF) hospitalisation is associated with 10% mortality. Outpatient based management (OPM) of AHF appeared effective in observational studies. We conducted a pilot randomised controlled trial (RCT) comparing OPM with standard inpatient care (IPM).

Methods: We randomised patients with AHF, considered to need IV diuretic treatment for ≥2 days, to IPM or OPM. We recorded all-cause mortality, and the number of days alive and out-of-hospital (DAOH). Quality of life, mental well-being and Hope scores were assessed. Mean NHS cost savings and 95% central range (CR) were calculated from bootstrap analysis.

Follow-up: 60 days.

Results: Eleven patients were randomised to IPM and thirteen to OPM. There was no statistically significant difference in all-cause mortality during the index episode (1/11 vs 0/13) and up to 60 days follow-up (2/11 vs 2/13) [p=0.86]. The OPM group accrued more DAOH {47 [36,51] vs 59 [41,60], p=0.13}. Two patients randomised to IPM (vs 6 OPM) were readmitted [p=0.31]. Hope scores increased more with OPM within 30 days but dropped to lower levels than IPM by 60 days. More out-patients had increased total well-being scores by 60 days (p=0.04). OPM was associated with mean cost savings of £2,658 (95% CR 460 - 4,857) per patient.

*Conclusions***:** Patients with acute HF randomised to OPM accrued more days alive out of hospital (albeit not statistically significantly in this small pilot study). OPM is favoured by patients and carers and is associated with improved mental well-being and cost savings.

Introduction

Acute heart failure (AHF) is common and associated with significant morbidity and mortality [1, 2]. The risk of HF hospitalisation is currently augmented by the possibility of COVID-19 exposure. Higher mortality was observed in patients with underlying cardiovascular disease and multi-morbidity after COVID-19 infection. [3] If intravenous (IV) diuretic treatment can be safely delivered at home, and effectively reduce the need for inpatient management, or shorten hospital length of stay, this may also offer patients hope and improved mental wellbeing.

Evidence for the safety of parenteral diuretics out of hospital was suggested by observational studies [4, 5]. In a British Heart Foundation (BHF) sponsored study, involving 96 patients recruited over 2 years in 12 centres, specialist nurses were trained to administer IV diuretics out of hospital, to closely monitor the patients' response to treatment, and adjust dose as necessary. 79% of interventions achieved the desired outcome of avoiding hospital admission but only 63% achieved the target reduction in oedema and/or weight [6,7].

There is also the potential for reduction in hospital bed days with significant cost saving (about £2000 per patient). In addition, there are potential gains in terms of quality of life for patients if given a choice in their place of care, that in turn improves their sense of empowerment and ability to recover [8]. Surprisingly, the BHF observational study reported no deaths. This suggests selection bias, given that expected mortality is 7-11% for patients hospitalised with HF, according to the National HF audit. As such it remains uncertain as to whether these data are relevant for patients typically admitted for IV diuretics.

Our objective was to test the hypothesis that out-patient based management (OPM) has value over inpatient management (IPM) in reducing the number of overnight stays in hospital without compromising patient outcome. We conducted a pilot randomised controlled trial

(RCT) in order to inform the design of a larger multi-centre RCT of in-patient vs out-patient diuretic treatment of AHF.

Methods

Patients- We randomised patients with AHF, peripheral or pulmonary oedema (who no longer had a new requirement of supplementary oxygen) and who were considered to need at least two more days of IV diuretic treatment.

Patients had to have objective evidence of HF including one or all of the following: left ventricular ejection fraction <50% by any imaging modality; plasma brain natriuretic peptide (BNP) >100pg/mL within the previous two years (as per European Society of Cardiology (ESC) HF guideline 2016). The amended protocol (see below) also allows inclusion of patients with right ventricular impairment by "eyeball assessment" or tricuspid annulus plane systolic excursion (TAPSE) <16mm.

Patients were excluded if they had co-morbidities that warranted hospitalisation, e.g. atrial fibrillation with poor ventricular rate control (>140/min), significant bradycardia (<40/min), sepsis, significant anaemia (haemoglobin<80g/L), acute coronary syndrome or haemodynamically significant arrhythmia, symptomatic hypotension/ postural hypotension, creatinine > 250 umol/l, sodium <125 mmol/l, potassium <3 mmol/l, severe aortic stenosis with planned urgent in-patient surgery.

Patients were recruited from a community or inpatient setting.

Protocol amendment- At the beginning of the feasibility study, patients had to be recruited within 72 hours of presenting but we found that not to be feasible with a very low recruitment rate. We thus sought ethical permission to remove this requirement. The minor amendment to the protocol was approved and improved our recruitment rate without affecting our primary objective. The amended protocol also allows inclusion of patients with right ventricular impairment by "eyeball assessment" or tricuspid annulus plane systolic excursion (TAPSE) <16mm.

Patients were randomised to in patient management [(IPM), conventional care] or out-patient management [(OPM), at home, in the community centre or in the hospital "Furosemide lounge"]. Furosemide lounge is an ambulatory care unit within the hospital (Cardiac Day Case Unit), with facilities to administer IV diuretics, and is staffed by nurses and a doctor.

The place of care was selected based on logistical considerations, such as whether the patient could travel to the community centre or hospital "Furosemide lounge". Out-patients were given oral bumetanide to cover the weekends where IV treatment was not feasible, in accordance with the BHF observational study [6,7]. Treatments were allocated in a theoretical 1:1 ratio using mixed block randomisation. Blinding of patients and practitioners was impossible, though all parties were blinded to treatment allocation until after recruitment, consent and randomisation.

The IV furosemide dose was decided by the doctor / HF Nurse specialist. Monitoring of symptoms, blood pressure (BP), fluid status, renal function and electrolytes, medication optimisation and HF education continued as required in both IPM and OPM.

Patient data were collected throughout the index episode (defined as the period from randomisation till hospital discharge for the IPM or from randomisation till the end of the IV diuretic treatment for the OPM) and for 60 days following randomisation. All patients gave fully informed and signed consent to participate in the study which was approved by the North West - Haydock Research Ethics Committee (reference number 17/NW/0645).

Clinical outcomes

The pre-specified primary safety outcome was all-cause mortality within the index episode. The clinical effectiveness outcome was the number of full days alive and out of hospital (DAOH) within 30 days after randomisation. Treatment on the day ward as an out-patient did not count as an in-patient day. DAOH (up to 60 days) was an exploratory effectiveness outcome. [9] DAOH is an endpoint recommended by the United Kingdom (UK) Heart Failure Research Investigator network, which considered this endpoint as more relevant, capturing all episodes of hospitalisation as well as mortality (instead of time to first event). This was also endorsed by the Patient Public Involvement (PPI) group as an endpoint that the PPI group felt to be meaningful. Two or more DAOH were considered to be clinically meaningful (during 30 days follow-up).

Pre-specified secondary endpoints included rehospitalisation for HF, death from any cause, cardiovascular death within 60 days of randomisation, symptom resolution/oedema reduction/achievement of "dry weight". Duration of diuretic treatment was recorded. Costs were assessed from an NHS perspective using the Trust's patient level costing models from

financial years 2018/19 and 2019/20. Where patient level costs were unavailable, e.g. for Community visits, we used a national average cost. [See online supplement for details].

Patient-centred secondary endpoints included patient and carer satisfaction (“family and friend test”), Quality of life assessment, measured using EQ5D-5L, the Short Warwick-Edinburgh Mental Wellbeing scale (SWEMWBS) [10] and the Adult State Hope Scale [11-14] which was validated as accurate in detecting fluctuations in hope.

Statistical methods:

The trial was reported in accordance with the CONSORT statement (http://consort-statement.org/). Analysis was performed on an intention-to-treat basis.

The baseline characteristics of the study cohort were summarised as percentages, mean (SD), or median [IQR], as appropriate. Tests of equivalence of group proportions, means or medians were conducted and considered statistically significant with $p<0.05$: it was understood that the small sample size made it difficult to discern true differences between groups. For categorical values, a chi-squared test was used unless expected cell counts were <5, in which case Fisher’s exact test was used. Equivalence of normally-distributed variables was tested using a t-test, and non-normal numeric variables using a Mann-Whitney (Wilcoxon) test.

Responses to the EQ-5D-5L were mapped to the 3L valuation set, and quality-adjusted life years (QALYs) measured based on the trapezium rule. Incremental costs and QALYs were calculated in an exploratory analysis of cost-effectiveness. A bootstrap analysis was performed with 10,000 replications, to estimate the 95% central ranges (CR) in total costs and QALYs, and their differences.

Patient and public involvement (PPI):

The Blackpool Victoria Hospital PPI group was convened after the start of this feasibility RCT. They showed considerable enthusiasm in supporting the study, and unanimously endorsed the meaningfulness of the exploratory clinical effectiveness outcome [number of full days alive and out of hospital (DAOH) within 30 days after randomisation]. Two or more DAOH were considered to be meaningful to members of the PPI group. This informed sample size calculations of the definitive multi-centre RCT. They also preferred 30 rather than 60 days follow-up to allow patients to take part in other interventional HF research studies after the end of their participation in the present study. They were not involved in the recruitment to and conduct of the study, but they will be involved in our plans to disseminate the study results to relevant wider patient communities. A draft of the paper was forwarded to the PPI members and their representative is our patient co-applicant of the NIHR grant for the multi-centre study. He has been given the task of choosing what information/results to share after publication, summarising our key findings in a lay summary in bullet points, and also produce a video to encourage patients to participate in the multi-centre definitive study.

Results

Of 24 patients enrolled, eleven were randomised to in-patient (IPM) and thirteen to out-patient care (OPM). [Figure 1] Baseline characteristics were summarised in Table 1.

During the 30 days following randomisation, patients randomised to IPM accrued a median of 17 (IQR 13 to 22) days alive out of hospital (DAOH) compared to 30 (IQR 20 to30) days for OPM (p=0.018), distribution shown in Online Supplement Figure 2). [Table 2]

There was no statistically significant difference in all-cause mortality during the index episode. Only one patient who was randomised to IPM, died (suddenly). Within 60 days of randomisation, 2 patients from each group died.

Secondary Clinical Endpoints

Two patients randomised to IPM were readmitted compared to 6 patients randomised to OPM within 60 days from randomisation [p=0.31]. Two patients randomised to OPM in the end "crossed over" i.e. did not have IV diuretics outside hospital. One patient was readmitted with HF/multi-organ failure the day after discharge, and deemed inappropriate for further IV diuretic treatment, the other patient crossed over to IPM due to delayed discharge because of subacute limb ischaemia. In OPM, there was one adverse event which was not study-related (day-case nose biopsy of ulcerative lesion). Table 2 summarised details of readmission/SAEs. No patient was readmitted more than once during the first 30 days after randomisation. Beyond 30 days 5 patients randomised to OPM experienced a new SAE (including 3 readmitted with HF) vs 2 IPM (1 HF death and 1 readmission due to HF).

Readmissions were common (3 assigned to OPM required two readmissions within 60 days- one patient had two HF readmissions, one was readmitted for non-HF reasons (NSTEMI and atypical chest pain respectively), one was readmitted for cholecystitis and then HF. Only one patient randomised to IPM required more than one readmission (cellulitis, HF).

Six of 13 (46%) randomised to OPM had serious adverse events (SAE)- delayed discharge, readmission for any reason or death, compared with 5/11 IPM (45%).

Target weight, oedema and symptom resolution

There was no significant difference in the composite end-point of target weight achieved (on discharge from treatment) in patients who survived to discharge visit /oedema

resolution/symptom resolution [OPM 13/13 vs IPM 7/10; P = 0.068]. One in-patient died suddenly before the discharge visit without achieving target weight loss, symptom/oedema resolution. [See online supplement for details].

Patient related outcome measures

All patients who completed the "Family and Friends Test" were satisfied, in both treatment groups, though one in-patient and carer commented that they would not choose the service again. Examples of comments from this validated feedback included "it was helpful to be at home to care for my wife" and "treatment very successful, helped avoid admission to hospital". Carer satisfaction was higher in the out-patient group (100% vs 60% in-patients) by discharge [Supplementary Table 1].

Out-patient Hope scores increased more than in-patient scores (a 5 point increase at discharge for out-patients compared to no change for in-patients, p=0.34, Supplementary Table 2); in-patients' mental well-being score was higher at baseline but more out-patients had increased total well-being scores by discharge and by the 30-day follow-up visit [Table 3]; and the VAS (visual analogue scale) scores of EQ5D improved more for out-patients than in-patients (Supplementary Table 3, Supplementary Figure 3).

However, by the end of the 60 follow-up, hope scores are increased less for outpatients than inpatients, with a corresponding drop in mental wellbeing scores, despite continued increase in quality of life score (EQ5D-VAS).

Cost-effectiveness (secondary endpoint)

The median length of stay was 3 days in the out-patient group (compared with 13 for in-patients), with no patient admitted to CCU, HDU or ITU or receiving

dialysis/haemofiltration. There was one extra A&E visit. There were no extra GP visits during the index episode for OPM, and the cost of extra visit for consultant /HF clinic (12 extra visits) was factored into the equation (£1536).

Mean total costs of IPM were £5,081 (95% CR 3199 to 6963), compared with £2,423 (95% CR 1394 to 3451) for OPM. OPM thus saved £2,658 (95% CR 460 to 4857) per patient [Figure 2]. OPM was associated with 0.0425 QALYs (95% CR 0.0284 to 0.0566), versus 0.0394 (95% CR 0.0240 to 0.0548) for IPM, a difference of 0.0031 QALYs (95% CR -0.0179 to 0.0242). Given this small and non-significant increment in QALY, this exploratory analysis suggests OPM may be cost-effective, based on cost minimisation.

Discussion

This small pilot RCT demonstrates that patients with AHF randomised to out-patient based therapy accrued significantly more days alive out of hospital (30 vs 17 days for patients randomised to standard in-patient care) without increase in mortality. This was associated with mean cost savings of £2,658 per patient and could lead to significant savings for the NHS if rolled out nationally. Patients with HF are high frequency service users, accounting for 1 million bed days per year and 5% of all adult emergency hospital admissions [1].

In the current COVID-19 pandemic, it can be argued that it may be safer for patients with AHF to be managed at home. [15] Thirteen fewer days in hospital would be appreciated by many patients, as evidenced in the “Family-and-Friends test”/ patient satisfaction survey in the present study. There were no safety signals in terms of excess mortality, but a large multicentre RCT is urgently required to justify large investments in development of out-patient based AHF therapy. Despite the fact that all previous studies examining safety of OPM were observational, there is already significant expansion of such services in the UK.

[16,17] We feel it may be premature for rapid expansion of outpatient based AHF services without definitive evidence of efficacy and safety in a large multi-centre RCT.

Hopelessness, defined as having negative expectations about oneself and the future, is associated with worse prognosis in middle aged men in the Kuopio Ischemic Heart Disease study [18]. Conversely, hope defined as a positive psychology construct, comprises of state hope (which is one's goal directed thinking in any given moment and situation), and trait hope (that is a person's disposition or general way of goal directed thinking and hence more stable). [19] Hope has been linked with positive health outcomes in chronically ill populations [20,21], but there is little research in this regard in cardiovascular disease populations including heart failure. We measured State Hope using the Adult State Hope Scale as we were interested in changes at different time points. There were improvements in the Out-patient group score compared to in-patients at the point of discharge and at the first thirty days. These changes were similar in score to the only other study using the State Hope scale in cardiovascular patients [22] (mean change from 30.6 at baseline to 35.75 at 8 weeks, $p<0.005$). Dunn et al's pilot study in 2018 used an emotional support intervention in patients with ischaemic heart disease [22]. By contrast, the mean hope score for >400 normal students is 37.2 [11] The initial increase in hope in our present feasibility study diminished within 60 days, possibly as a result of increased readmissions. Trait hope was not assessed so the dispositional effects on state Hope cannot be excluded.

The present feasibility study signals that AHF may be successfully treated with IV diuretics on an out-patient basis, and that patients may enjoy a better quality of life and report an increased mental well-being and hope.

Though limited in significance due to a small sample size and imbalance between randomised group characteristics, these results are encouraging and informed the design of a larger, multicentre RCT.

Frailty and its associated high risk of major adverse health outcomes are well documented. The Derby Frailty Index [23] was initially developed as a Frailty identification tool which does not require additional training for staff. The Rockwood clinical frailty scale is another simplified screening tool for assessing the degree of frailty. It takes into account information about cognition, mobility, function and co-morbidities to assign a frailty level from 1 to 9. This method effectively estimates important outcomes including survival and institutionalisation [24]. We found both methods of frailty assessment feasible in the present study. Patients randomised to IPM were slightly more frail, but not clinically or statistically significantly. A mean Rockwood score 5 or 6 suggested mild or moderate frailty which in practice would identify patients as frail indicating comprehensive geriatric assessment so there would be no clinical significance in that difference in score. Further exploration of frailty in a larger RCT may help refine exclusion criteria for OPM. In practice, whilst many of the relatively frail patients might have their preferred place of care in the community, relatives might find the prospect rather daunting and this should be taken into account.

Limitations

The small sample size limits generalisation of this pilot single centre RCT. Nevertheless, even with 24 patients it was possible to demonstrate significantly more DAOH in patients randomised to OPM. We found it was not feasible to ask outpatients to measure their urine output. We also found patients' estimate of dry weight rather inaccurate. However, the use of

the pre-specified composite endpoint of symptom/oedema resolution/target weight achievement helps overcome this limitation.

From an economic evaluation perspective, our study aimed to primarily identify relevant items of resource use associated with each arm, and the feasibility of collecting such data. We collected relevant data associated with each patient in each arm, such as hospitalisation, GP visits. The exploratory cost-effectiveness analysis indicated that OPM might be a cost-effective alternative to IPM based on cost minimisation. A definitive RCT with an integrated economic evaluation would provide a more robust estimate of cost-effectiveness to inform the NHS.

Last but not least, moderate level of hope is prevalent amongst patients with AHF. A recent AHF survey showed <30% have clinical psychology service to support their heart failure service. [25] Only 19% of respondents are aware they have clinical psychology service; whilst 6% are not sure if they have clinical psychology service. Our study highlights the need for business planning for more clinical psychologists who can help us deliver excellent whole person care in patients with HF. More research is urgently required to test other strategies tailored to maintain hope in the longer term beyond 30 days. This pilot RCT provides preliminary evidence that there is benefit to a patient's mental health and quality of life in being able to receive treatment out of hospital.

This small pilot RCT demonstrated that patients with acute HF randomised to OPM accrued significantly more DAOH without increase in mortality. OPM is favoured by patients and carers and is associated with improved mental well-being.

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Supplementary Table 2 Does out-patient based therapy increase hope score in patients with acute heart failure?

Supplementary Table 3 EQ5D VAS score comparison

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Supplementary Figure 1 [Online Supplement]: Out-patient based therapy for AHF was not associated with worse survival

Supplementary Figure 2 [Online Supplement]: Out-patient based AHF treatment was effective at increasing the number of full days alive out of hospital during 30 day follow-up

Supplementary Figure 3 [Online Supplement]: Trajectories of EQ5D-VAS scores

Supplementary Figure 4 [Online Supplement]: EQ5D domain score trajectories across real time

Supplementary Figure 5 [Online Supplement]: Distribution of EQ5D domain scores across time points

Figure 1 Participant Flow Diagram

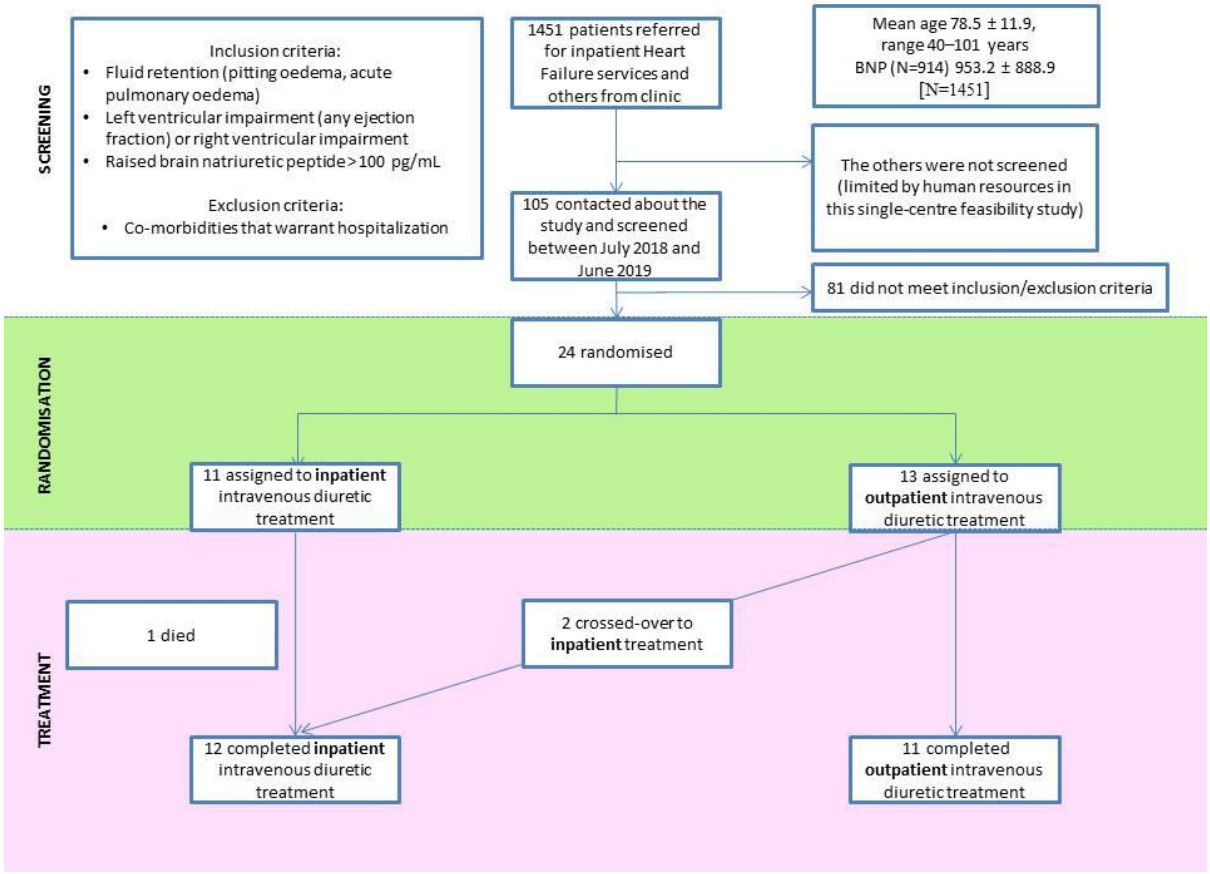

Figure 2 Cost savings with Out-patient based treatment

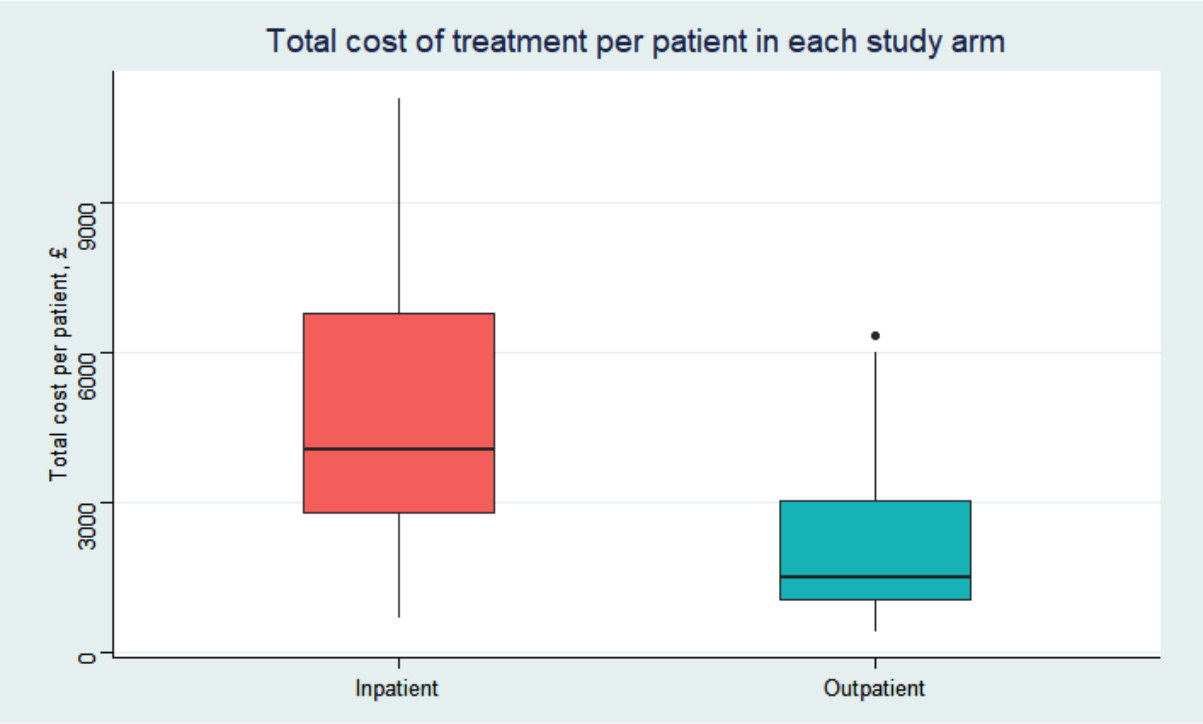

Table 1 Baseline Characteristics

		In-patient (n=11)	Out-patient (n=13)	p
Sex	*Female*	7 (63.6%)	3 (23.1%)	0.095
Age	*at randomisation*	81.8 (10.4)	70 (16.0)	0.052
BMI	*kg/m²*	28 (7)	37.1 (8)	**0.01**
Weight	*kg*	73.6 (20.9)	108.5 (31.9)	**0.005**
HF status	*Peripheral Oedema*	90.9%	92.3%	0.90
	Pulmonary oedema	27.3%	30.77%	0.85
	Both	18.2%	23.1%	0.77
NYHA	*Class II*	0	2 (15.4%)	0.07
	Class III	11 (100%)	8 (61.5%)	
	Class IV	0	3 (23.1%)	
Degree of peripheral oedema	*None*	1 (9%)*	0	0.080
	Mild		2 (15.4%)	
	Moderate	7 (64%)	11 (84.6%)	
	Severe	3 (27%)	0	
BNP	*[missing data-2 from each group]*	357 [251, 470],	360 [264, 699]	>0.99
LV systolic function on echocardiography	*EF 55% or more*	5 (45.5%)	5 (38.5%)	>0.99
	Impaired (<55%)	6 (54.5%)	8 (61.5%)	
IHD Aetiology		18.2%	7.7%	0.44
Arrhythmia		63.6%	23.1%	0.1
DCM		0	7.7%	-
Hypertension		54.54%	46.15%	1
Valvular		45.45%	38.46%	0.68
Number of comorbidities		3.8±2.7	5±2.9	0.3
Rockwood frailty score	at randomisation	5.6 (1.2)	5.4 (1.6)	0.67
Premorbid Rockwood frailty score		5.0 (1.2)	4.8 (1.3)	0.76
Derby frailty index	*Number (%) Frail*	6 (54.5%)	6 (46.2%)	0.99

Receiving “end of life”/palliative care		1 [9.09%] Severe MR - patient did not want surgery.	1 [7.7%] AS deemed not fit for AVR or TAVI by MDT	>0.99
Systolic BP	mmHg	145 (21.2)	137 (25)	0.43
Diastolic BP	mmHg	75 (14)	75 (17.8)	0.96
Hb	g/L	119 (16.7)	119.7 (17.3)	0.92
Albumin	g/L	36 [34,40]	36 [34,39]	0.97
Sodium	mmol/L	138 (2.4)	137.6 (2.8)	0.44
Potassium	mmol/L	4.4 (0.7)	4.1 (0.54)	0.3
Urea	mmol/L	11.35 (4.4)	10.2 (5.1)	0.55
Creatinine	umol/L	119.5 (37)	113.7 (48)	0.75
Already on IV diuretic		6 (54.4%)	10 (76.9%)	0.39
No. of days on IV diuretic pre-randomisation		2.3(3.4)	3.3(3.8)	0.5
ACEi	*(none on ARB in both groups)*	45.45%	23.1%	0.24
Sacubitril / valsartan		0	23.1%	-
Beta blocker		63.6%	76.9%	0.47
MRA		0	30.8%	-
Ivabradine		0	7.7%	-
Digoxin		18.2%	7.7.%	0.43
Iron Deficiency anaemia (IDA)		27.3%	38.46%	0.56
IV replacement therapy for IDA	*(in last 12 months)*	18.2%	15.4%	0.44
Smoker	*Non-smoker*	7 (63.6%)	5 (38.5%)	0.527
	Ex-smoker	3 (27.3%)	6 (46.2%)	
	Smoker	1 (9.1%)	2 (15.4%)	

*pulmonary oedema only

ACEi=Angiotensin Converting Enzyme Inhibitor; ARB= Angiotensin Receptor Blocker; AS= aortic stenosis; BMI=body mass index; BNP=Brain Natriuretic Peptide; BP=blood pressure; DCM=dilated cardiomyopathy; Hb=haemoglobin; HF=heart failure; IDA= Iron Deficiency anaemia; IHD=ischaemic heart disease; IV=intravenous; LV=left ventricular; MR= mitral regurgitation; NYHA=New York Heart Association;

[Descriptive statistics are presented either as: mean (SD), as median [Q1, Q3], or as N (percentage)]

Table 2 Clinical Effectiveness and Safety endpoints

		In-patient (n=11)	Out-patient (n=13)	p-value
Number of full days out of hospital per patient within 30 days of randomisation {min, max}		17 [13,22] min-max {1, 28}	30 [20, 30] min-max {0, 31}	**0.018**
Number of full days out of hospital per patient within 60 days of randomisation {min, max}		47 [36, 51] min-max {1, 58}	59 [41, 60] min-max {0, 61}	0.13
Hospital length of stay per patient during index episode, days		13 [7, 14.5]	3 [2, 7]	**0.004**
Number of patients readmitted within 60 days from randomisation		2	6	0.31
SAE (A&E attendance, delayed discharge, readmission within 60 days , death)	*No.of patients with at least 1 SAE*	5/11	*6/13*	>0.99
	During Index episode ()	2(pacemaker implant delayed discharge , MI leading to death)	*2 (cross-over/ readmitted with HF/multi-organ failure; delay discharge due to subacute limb ischaemia)*	>0.99
	Between discharge and 30 days of randomisation	2(HF; Cellulitis)	*3 (HF X1 , MI , Cholecystitis)*	>0.99
	31-60 days of randomisation	2 (HF readmission, HF Death)	*5 (HFx3 , atypical chest pain, elective leg amputation)*	0.68
	Total SAEs From Index to 60 days of randomisation	6	*10*	N/A
HF Readmissions	*During Index episode*	Not applicable	*1*	
	Between discharge and 30 days of randomisation	1	*1*	>0.99
	31-60 days of randomisation	*1*	*3*	0.71
Total HF admissions *From Index to 60 days of randomisation*		*2*	*5*	0.52
Non-HF readmissions	*During Index episode*	Not applicable	0	
	Between discharge and 30 days of	1 -Joint infection (wrist inflammation/cellulitis)	2 -NSTEMI - cholecystitis	>0.99

	randomisation			
	31-60 days of randomisation	0	2 (atypical chest pain, Elective leg amputation)	0.54
Total Non HF admissions *From Index to 60 days of randomisation*		1	4	0.42
Deaths	*Index episode*	1 (non HF related)	0	0.93
	Between discharge and 30 days of randomisation	0	1 HF death	>0.99
	31-60 days of randomisation	1 HF death	1 HF death	>0.99
Total Deaths *From Index to 60 days of randomisation*		2	2	>0.99

**** Index episode-before inpatient discharge or discharge visit after end of diuretic treatment for outpatients***

HF= heart failure; SAE=Serious Adverse Event

Figures are presented either as: mean (standard deviation), as median [Q1, Q3], or as percentage

Table 3 Mental Well-being (SWEMWBS) score comparison

TRANSFORMED SWEMWBS	In-patient	Out-patient	P value
Mean score at baseline	25.6 (4.46)	21.0 (5.08)	**0.03**
Number of patients whose score increased from baseline to discharge	4	8	0.36
Number of patients whose score increased from baseline to 30 days	3	8	**0.050**
Number of patients whose score increased from baseline to 60 days	3	9	**0.040**

Measurements of the transformed (Normalised) SWEMWBS scores were taken at baseline, discharge and at 30 days and 60 days post randomisation. The table shows the mean score at baseline and the number of patients whose wellbeing levels increased over treatment

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Blackpool Teaching Hospitals
NHS Foundation Trust

REGIONAL CARDIAC CENTRE
DIVISION OF CARDIAC SERVICES

Lancashire Cardiac Centre
Whinney Heys Road
Blackpool
Lancashire
FY3 8NR

DR K WONG – CONSULTANT CARDIOLOGIST

Editor, Acta Cardiologica

6th December 2022

Dear Editor,

Thank you for accepting our paper for publication following the submission of “editable version of the paper”. On behalf of my team of coauthors, I look forward to reviewing the proof of the paper.

The only changes to the previous edition (revised 130922),which was deemed satisfactory by the peer reviewer are

(1) an update of the following reference (another paper of mine which has now been published in full) and its related text in the present paper-

25. Abdullah Abdullah, Suzanne YS Wong, Robbie Jones, Kenneth YK Wong. Outpatient-based acute HF care calls for development of clinical psychology service for whole-person care provision. Br J Cardiol 2022;29:141–4

“Last but not least, moderate level of hope is prevalent amongst patients with AHF. A recent AHF survey showed <30% have clinical psychology service to support their heart failure service. [25]”

The above is how the penultimate paragraph of the present manuscript should read.

(2) Affiliation of Prof Gregory Lip-
Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

The final version 061222 has been uploaded and is editable.

Yours sincerely,

Dr Kenneth Wong MA(Oxon), DM (Oxon), FRCP (Lond), PGCME (HYMS), FHEA, FESC, FACC

Consultant Cardiologist with special interest in Heart Failure and Imaging,

Heart Failure and Imaging Research Lead,

Department of Cardiology, Lancashire Cardiac Centre, Blackpool.

Honorary affiliation-Liverpool Centre for Cardiovascular Science, UK

01253-300000,

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Effectiveness of out-patient based acute heart failure care: A pilot randomised controlled trial

Short title: Acute Heart Failure IN or OUT pilot RCT

Wong K.Y.K. MA(Oxon), DM (Oxon), FRCP (Lond), PGCME (HYMS), FHEA, FESC, FACC[1,2],

Hughes D.A. [3] BPharm MSc PhD MRPharmS FFRPS FBPhS FLSW,

Debski M. [1], MD, PhD

Latt N. [1], MBBS, MRCP

Assaf O. [1] MB BCh

Abdelrahman A. [1], MBBS, MRCP

Taylor R. [1], MSc

Allgar V. PhD CStat [4],

McNeill L. [1], BA, CGMA

Howard S. [1], BA, BSc

Wong S.Y.S. [1] MBBS, FRCP,

Jones R.[1], BEd (hons).

Cassidy C. J. [1] MB ChB, FRCP

Seed A. [1] MD

Galasko G. BM BCh MA DM (Oxon) FRCP [1]

Clark A. [4], MA, MD, FRCP

Davis G.K. [6], DGM Dip Card MD MSc (Med Ed) MSc (Med L'dship) FRCP FRACP FESC FSCCT FHEA

Montasem A [6] MSc, PhD, CPsychol

Lang C.C. BMSc (hons)., MD., FRCP (Edin)., FRCP (Lond)., FACC [7],

Kalra P.R. MA MB BChir MD FRCP [8]

Campbell R. [9], PhD

Lip G.Y.H. [10], MD

Cleland J.G.F. [9] MD, PhD

Correspondence:

Dr Kenneth Wong MA(Oxon), DM (Oxon), FRCP (Lond), PGCME (HYMS), FHEA, FESC, FACC

Department of Cardiology, Lancashire Cardiac Centre,

Blackpool Teaching Hospitals NHS Foundation Trust

Blackpool, United Kingdom

Phone- +44-1253-957783

Dr.Wong@nhs.net

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Author Affiliations

1. Blackpool Teaching Hospitals NHS Foundation Trust
2. Liverpool Centre for Cardiovascular Science, UK
3. Centre for Health Economics and Medicines Evaluation, Bangor University, UK
4. Hull York Medical School
5. Worcerstershire Acute Hospital NHS Trust
6. School of Medicine, University of Central Lancashire, Preston, UK
7. University of Dundee
8. Portsmouth Hospitals University NHS Trust
9. University of Glasgow

10.Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

ABSTRACT

Objectives: Acute heart failure (AHF) hospitalisation is associated with 10% mortality. Outpatient based management (OPM) of AHF appeared effective in observational studies. We conducted a pilot randomised controlled trial (RCT) comparing OPM with standard inpatient care (IPM).

Methods: We randomised patients with AHF, considered to need IV diuretic treatment for ≥2 days, to IPM or OPM. We recorded all-cause mortality, and the number of days alive and out-of-hospital (DAOH). Quality of life, mental well-being and Hope scores were assessed. Mean NHS cost savings and 95% central range (CR) were calculated from bootstrap analysis.

Follow-up: 60 days.

Results: Eleven patients were randomised to IPM and thirteen to OPM. There was no statistically significant difference in all-cause mortality during the index episode (1/11 vs 0/13) and up to 60 days follow-up (2/11 vs 2/13) [p=0.86]. The OPM group accrued more DAOH {47 [36,51] vs 59 [41,60], p=0.13}. Two patients randomised to IPM (vs 6 OPM) were readmitted [p=0.31]. Hope scores increased more with OPM within 30 days but dropped to lower levels than IPM by 60 days. More out-patients had increased total well-being scores by 60 days (p=0.04). OPM was associated with mean cost savings of £2,658 (95% CR 460 - 4,857) per patient.

*Conclusions***:** Patients with acute HF randomised to OPM accrued more days alive out of hospital (albeit not statistically significantly in this small pilot study). OPM is favoured by patients and carers and is associated with improved mental well-being and cost savings.

Introduction

Acute heart failure (AHF) is common and associated with significant morbidity and mortality [1, 2]. The risk of HF hospitalisation is currently augmented by the possibility of COVID-19 exposure. Higher mortality was observed in patients with underlying cardiovascular disease and multi-morbidity after COVID-19 infection. [3] If intravenous (IV) diuretic treatment can be safely delivered at home, and effectively reduce the need for inpatient management, or shorten hospital length of stay, this may also offer patients hope and improved mental wellbeing.

Evidence for the safety of parenteral diuretics out of hospital was suggested by observational studies [4, 5]. In a British Heart Foundation (BHF) sponsored study, involving 96 patients recruited over 2 years in 12 centres, specialist nurses were trained to administer IV diuretics out of hospital, to closely monitor the patients' response to treatment, and adjust dose as necessary. 79% of interventions achieved the desired outcome of avoiding hospital admission but only 63% achieved the target reduction in oedema and/or weight [6,7].

There is also the potential for reduction in hospital bed days with significant cost saving (about £2000 per patient). In addition, there are potential gains in terms of quality of life for patients if given a choice in their place of care, that in turn improves their sense of empowerment and ability to recover [8]. Surprisingly, the BHF observational study reported no deaths. This suggests selection bias, given that expected mortality is 7-11% for patients hospitalised with HF, according to the National HF audit. As such it remains uncertain as to whether these data are relevant for patients typically admitted for IV diuretics.

Our objective was to test the hypothesis that out-patient based management (OPM) has value over inpatient management (IPM) in reducing the number of overnight stays in hospital without compromising patient outcome. We conducted a pilot randomised controlled trial

(RCT) in order to inform the design of a larger multi-centre RCT of in-patient vs out-patient diuretic treatment of AHF.

Methods

Patients- We randomised patients with AHF, peripheral or pulmonary oedema (who no longer had a new requirement of supplementary oxygen) and who were considered to need at least two more days of IV diuretic treatment.

Patients had to have objective evidence of HF including one or all of the following: left ventricular ejection fraction <50% by any imaging modality; plasma brain natriuretic peptide (BNP) >100pg/mL within the previous two years (as per European Society of Cardiology (ESC) HF guideline 2016). The amended protocol (see below) also allows inclusion of patients with right ventricular impairment by "eyeball assessment" or tricuspid annulus plane systolic excursion (TAPSE) <16mm.

Patients were excluded if they had co-morbidities that warranted hospitalisation, e.g. atrial fibrillation with poor ventricular rate control (>140/min), significant bradycardia (<40/min), sepsis, significant anaemia (haemoglobin<80g/L), acute coronary syndrome or haemodynamically significant arrhythmia, symptomatic hypotension/ postural hypotension, creatinine > 250 umol/l, sodium <125 mmol/l, potassium <3 mmol/l, severe aortic stenosis with planned urgent in-patient surgery.

Patients were recruited from a community or inpatient setting.

Protocol amendment- At the beginning of the feasibility study, patients had to be recruited within 72 hours of presenting but we found that not to be feasible with a very low recruitment rate. We thus sought ethical permission to remove this requirement. The minor amendment to the protocol was approved and improved our recruitment rate without affecting our primary objective. The amended protocol also allows inclusion of patients with right ventricular impairment by "eyeball assessment" or tricuspid annulus plane systolic excursion (TAPSE) <16mm.

Patients were randomised to in patient management [(IPM), conventional care] or out-patient management [(OPM), at home, in the community centre or in the hospital "Furosemide lounge"]. Furosemide lounge is an ambulatory care unit within the hospital (Cardiac Day Case Unit), with facilities to administer IV diuretics, and is staffed by nurses and a doctor.

The place of care was selected based on logistical considerations, such as whether the patient could travel to the community centre or hospital "Furosemide lounge". Out-patients were given oral bumetanide to cover the weekends where IV treatment was not feasible, in accordance with the BHF observational study [6,7]. Treatments were allocated in a theoretical 1:1 ratio using mixed block randomisation. Blinding of patients and practitioners was impossible, though all parties were blinded to treatment allocation until after recruitment, consent and randomisation.

The IV furosemide dose was decided by the doctor / HF Nurse specialist. Monitoring of symptoms, blood pressure (BP), fluid status, renal function and electrolytes, medication optimisation and HF education continued as required in both IPM and OPM.

Patient data were collected throughout the index episode (defined as the period from randomisation till hospital discharge for the IPM or from randomisation till the end of the IV diuretic treatment for the OPM) and for 60 days following randomisation. All patients gave fully informed and signed consent to participate in the study which was approved by the North West - Haydock Research Ethics Committee (reference number 17/NW/0645).

Clinical outcomes

The pre-specified primary safety outcome was all-cause mortality within the index episode. The clinical effectiveness outcome was the number of full days alive and out of hospital (DAOH) within 30 days after randomisation. Treatment on the day ward as an out-patient did not count as an in-patient day. DAOH (up to 60 days) was an exploratory effectiveness outcome. [9] DAOH is an endpoint recommended by the United Kingdom (UK) Heart Failure Research Investigator network, which considered this endpoint as more relevant, capturing all episodes of hospitalisation as well as mortality (instead of time to first event). This was also endorsed by the Patient Public Involvement (PPI) group as an endpoint that the PPI group felt to be meaningful. Two or more DAOH were considered to be clinically meaningful (during 30 days follow-up).

Pre-specified secondary endpoints included rehospitalisation for HF, death from any cause, cardiovascular death within 60 days of randomisation, symptom resolution/oedema reduction/achievement of "dry weight". Duration of diuretic treatment was recorded. Costs were assessed from an NHS perspective using the Trust's patient level costing models from

financial years 2018/19 and 2019/20. Where patient level costs were unavailable, e.g. for Community visits, we used a national average cost. [See online supplement for details].

Patient-centred secondary endpoints included patient and carer satisfaction (“family and friend test”), Quality of life assessment, measured using EQ5D-5L, the Short Warwick-Edinburgh Mental Wellbeing scale (SWEMWBS) [10] and the Adult State Hope Scale [11-14] which was validated as accurate in detecting fluctuations in hope.

Statistical methods:

The trial was reported in accordance with the CONSORT statement (http://consort-statement.org/). Analysis was performed on an intention-to-treat basis.

The baseline characteristics of the study cohort were summarised as percentages, mean (SD), or median [IQR], as appropriate. Tests of equivalence of group proportions, means or medians were conducted and considered statistically significant with $p<0.05$: it was understood that the small sample size made it difficult to discern true differences between groups. For categorical values, a chi-squared test was used unless expected cell counts were <5, in which case Fisher’s exact test was used. Equivalence of normally-distributed variables was tested using a t-test, and non-normal numeric variables using a Mann-Whitney (Wilcoxon) test.

Responses to the EQ-5D-5L were mapped to the 3L valuation set, and quality-adjusted life years (QALYs) measured based on the trapezium rule. Incremental costs and QALYs were calculated in an exploratory analysis of cost-effectiveness. A bootstrap analysis was performed with 10,000 replications, to estimate the 95% central ranges (CR) in total costs and QALYs, and their differences.

Patient and public involvement (PPI):

The Blackpool Victoria Hospital PPI group was convened after the start of this feasibility RCT. They showed considerable enthusiasm in supporting the study, and unanimously endorsed the meaningfulness of the exploratory clinical effectiveness outcome [number of full days alive and out of hospital (DAOH) within 30 days after randomisation]. Two or more DAOH were considered to be meaningful to members of the PPI group. This informed sample size calculations of the definitive multi-centre RCT. They also preferred 30 rather than 60 days follow-up to allow patients to take part in other interventional HF research studies after the end of their participation in the present study. They were not involved in the recruitment to and conduct of the study, but they will be involved in our plans to disseminate the study results to relevant wider patient communities. A draft of the paper was forwarded to the PPI members and their representative is our patient co-applicant of the NIHR grant for the multi-centre study. He has been given the task of choosing what information/results to share after publication, summarising our key findings in a lay summary in bullet points, and also produce a video to encourage patients to participate in the multi-centre definitive study.

Results

Of 24 patients enrolled, eleven were randomised to in-patient (IPM) and thirteen to out-patient care (OPM). [Figure 1] Baseline characteristics were summarised in Table 1.

During the 30 days following randomisation, patients randomised to IPM accrued a median of 17 (IQR 13 to 22) days alive out of hospital (DAOH) compared to 30 (IQR 20 to30) days for OPM (p=0.018), distribution shown in Online Supplement Figure 2). [Table 2]

There was no statistically significant difference in all-cause mortality during the index episode. Only one patient who was randomised to IPM, died (suddenly). Within 60 days of randomisation, 2 patients from each group died.

Secondary Clinical Endpoints

Two patients randomised to IPM were readmitted compared to 6 patients randomised to OPM within 60 days from randomisation [p=0.31]. Two patients randomised to OPM in the end "crossed over" i.e. did not have IV diuretics outside hospital. One patient was readmitted with HF/multi-organ failure the day after discharge, and deemed inappropriate for further IV diuretic treatment, the other patient crossed over to IPM due to delayed discharge because of subacute limb ischaemia. In OPM, there was one adverse event which was not study-related (day-case nose biopsy of ulcerative lesion). Table 2 summarised details of readmission/SAEs. No patient was readmitted more than once during the first 30 days after randomisation. Beyond 30 days 5 patients randomised to OPM experienced a new SAE (including 3 readmitted with HF) vs 2 IPM (1 HF death and 1 readmission due to HF).

Readmissions were common (3 assigned to OPM required two readmissions within 60 days- one patient had two HF readmissions, one was readmitted for non-HF reasons (NSTEMI and atypical chest pain respectively), one was readmitted for cholecystitis and then HF. Only one patient randomised to IPM required more than one readmission (cellulitis, HF).

Six of 13 (46%) randomised to OPM had serious adverse events (SAE)- delayed discharge, readmission for any reason or death, compared with 5/11 IPM (45%).

Target weight, oedema and symptom resolution

There was no significant difference in the composite end-point of target weight achieved (on discharge from treatment) in patients who survived to discharge visit /oedema

resolution/symptom resolution [OPM 13/13 vs IPM 7/10; P = 0.068]. One in-patient died suddenly before the discharge visit without achieving target weight loss, symptom/oedema resolution. [See online supplement for details].

Patient related outcome measures

All patients who completed the "Family and Friends Test" were satisfied, in both treatment groups, though one in-patient and carer commented that they would not choose the service again. Examples of comments from this validated feedback included "it was helpful to be at home to care for my wife" and "treatment very successful, helped avoid admission to hospital". Carer satisfaction was higher in the out-patient group (100% vs 60% in-patients) by discharge [Supplementary Table 1].

Out-patient Hope scores increased more than in-patient scores (a 5 point increase at discharge for out-patients compared to no change for in-patients, p=0.34, Supplementary Table 2); in-patients' mental well-being score was higher at baseline but more out-patients had increased total well-being scores by discharge and by the 30-day follow-up visit [Table 3]; and the VAS (visual analogue scale) scores of EQ5D improved more for out-patients than in-patients (Supplementary Table 3, Supplementary Figure 3).

However, by the end of the 60 follow-up, hope scores are increased less for outpatients than inpatients, with a corresponding drop in mental wellbeing scores, despite continued increase in quality of life score (EQ5D-VAS).

Cost-effectiveness (secondary endpoint)

The median length of stay was 3 days in the out-patient group (compared with 13 for in-patients), with no patient admitted to CCU, HDU or ITU or receiving

dialysis/haemofiltration. There was one extra A&E visit. There were no extra GP visits during the index episode for OPM, and the cost of extra visit for consultant /HF clinic (12 extra visits) was factored into the equation (£1536).

Mean total costs of IPM were £5,081 (95% CR 3199 to 6963), compared with £2,423 (95% CR 1394 to 3451) for OPM. OPM thus saved £2,658 (95% CR 460 to 4857) per patient [Figure 2]. OPM was associated with 0.0425 QALYs (95% CR 0.0284 to 0.0566), versus 0.0394 (95% CR 0.0240 to 0.0548) for IPM, a difference of 0.0031 QALYs (95% CR -0.0179 to 0.0242). Given this small and non-significant increment in QALY, this exploratory analysis suggests OPM may be cost-effective, based on cost minimisation.

Discussion

This small pilot RCT demonstrates that patients with AHF randomised to out-patient based therapy accrued significantly more days alive out of hospital (30 vs 17 days for patients randomised to standard in-patient care) without increase in mortality. This was associated with mean cost savings of £2,658 per patient and could lead to significant savings for the NHS if rolled out nationally. Patients with HF are high frequency service users, accounting for 1 million bed days per year and 5% of all adult emergency hospital admissions [1].

In the current COVID-19 pandemic, it can be argued that it may be safer for patients with AHF to be managed at home. [15] Thirteen fewer days in hospital would be appreciated by many patients, as evidenced in the “Family-and-Friends test”/ patient satisfaction survey in the present study. There were no safety signals in terms of excess mortality, but a large multicentre RCT is urgently required to justify large investments in development of out-patient based AHF therapy. Despite the fact that all previous studies examining safety of OPM were observational, there is already significant expansion of such services in the UK.

[16,17] We feel it may be premature for rapid expansion of outpatient based AHF services without definitive evidence of efficacy and safety in a large multi-centre RCT.

Hopelessness, defined as having negative expectations about oneself and the future, is associated with worse prognosis in middle aged men in the Kuopio Ischemic Heart Disease study [18]. Conversely, hope defined as a positive psychology construct, comprises of state hope (which is one's goal directed thinking in any given moment and situation), and trait hope (that is a person's disposition or general way of goal directed thinking and hence more stable). [19] Hope has been linked with positive health outcomes in chronically ill populations [20,21], but there is little research in this regard in cardiovascular disease populations including heart failure. We measured State Hope using the Adult State Hope Scale as we were interested in changes at different time points. There were improvements in the Out-patient group score compared to in-patients at the point of discharge and at the first thirty days. These changes were similar in score to the only other study using the State Hope scale in cardiovascular patients [22] (mean change from 30.6 at baseline to 35.75 at 8 weeks, $p<0.005$). Dunn et al's pilot study in 2018 used an emotional support intervention in patients with ischaemic heart disease [22]. By contrast, the mean hope score for >400 normal students is 37.2 [11] The initial increase in hope in our present feasibility study diminished within 60 days, possibly as a result of increased readmissions. Trait hope was not assessed so the dispositional effects on state Hope cannot be excluded.

The present feasibility study signals that AHF may be successfully treated with IV diuretics on an out-patient basis, and that patients may enjoy a better quality of life and report an increased mental well-being and hope.

Though limited in significance due to a small sample size and imbalance between randomised group characteristics, these results are encouraging and informed the design of a larger, multicentre RCT.

Frailty and its associated high risk of major adverse health outcomes are well documented. The Derby Frailty Index [23] was initially developed as a Frailty identification tool which does not require additional training for staff. The Rockwood clinical frailty scale is another simplified screening tool for assessing the degree of frailty. It takes into account information about cognition, mobility, function and co-morbidities to assign a frailty level from 1 to 9. This method effectively estimates important outcomes including survival and institutionalisation [24]. We found both methods of frailty assessment feasible in the present study. Patients randomised to IPM were slightly more frail, but not clinically or statistically significantly. A mean Rockwood score 5 or 6 suggested mild or moderate frailty which in practice would identify patients as frail indicating comprehensive geriatric assessment so there would be no clinical significance in that difference in score. Further exploration of frailty in a larger RCT may help refine exclusion criteria for OPM. In practice, whilst many of the relatively frail patients might have their preferred place of care in the community, relatives might find the prospect rather daunting and this should be taken into account.

Limitations

The small sample size limits generalisation of this pilot single centre RCT. Nevertheless, even with 24 patients it was possible to demonstrate significantly more DAOH in patients randomised to OPM. We found it was not feasible to ask outpatients to measure their urine output. We also found patients' estimate of dry weight rather inaccurate. However, the use of

the pre-specified composite endpoint of symptom/oedema resolution/target weight achievement helps overcome this limitation.

From an economic evaluation perspective, our study aimed to primarily identify relevant items of resource use associated with each arm, and the feasibility of collecting such data. We collected relevant data associated with each patient in each arm, such as hospitalisation, GP visits. The exploratory cost-effectiveness analysis indicated that OPM might be a cost-effective alternative to IPM based on cost minimisation. A definitive RCT with an integrated economic evaluation would provide a more robust estimate of cost-effectiveness to inform the NHS.

Last but not least, moderate level of hope is prevalent amongst patients with AHF. A recent AHF survey showed <30% have clinical psychology service to support their heart failure service. [25] Only 19% of respondents are aware they have clinical psychology service; whilst 6% are not sure if they have clinical psychology service. Our study highlights the need for business planning for more clinical psychologists who can help us deliver excellent whole person care in patients with HF. More research is urgently required to test other strategies tailored to maintain hope in the longer term beyond 30 days. This pilot RCT provides preliminary evidence that there is benefit to a patient's mental health and quality of life in being able to receive treatment out of hospital.

This small pilot RCT demonstrated that patients with acute HF randomised to OPM accrued significantly more DAOH without increase in mortality. OPM is favoured by patients and carers and is associated with improved mental well-being.

Tables and Figure Legends

Table 1 Baseline Characteristics

Table 2 Clinical Effectiveness and Safety endpoints

Table 3 Mental Well-being (SWEMWBS) score comparison

Figure 1 Participant Flow Diagram

Figure 2 Cost savings with Out-patient based treatment

Supplementary Table 1 Patient and Carer satisfaction ("NHS Family and Friends Test")

Supplementary Table 2 Does out-patient based therapy increase hope score in patients with acute heart failure?

Supplementary Table 3 EQ5D VAS score comparison

Supplementary Table 4 Comparison of changes in transformed SWEMWBS scores between baseline and discharge

Supplementary Table 5 Diuretic Dose and Weight Change

Supplementary Figure 1 [Online Supplement]: Out-patient based therapy for AHF was not associated with worse survival

Supplementary Figure 2 [Online Supplement]: Out-patient based AHF treatment was effective at increasing the number of full days alive out of hospital during 30 day follow-up

Supplementary Figure 3 [Online Supplement]: Trajectories of EQ5D-VAS scores

Supplementary Figure 4 [Online Supplement]: EQ5D domain score trajectories across real time

Supplementary Figure 5 [Online Supplement]: Distribution of EQ5D domain scores across time points

Figure 1 Participant Flow Diagram

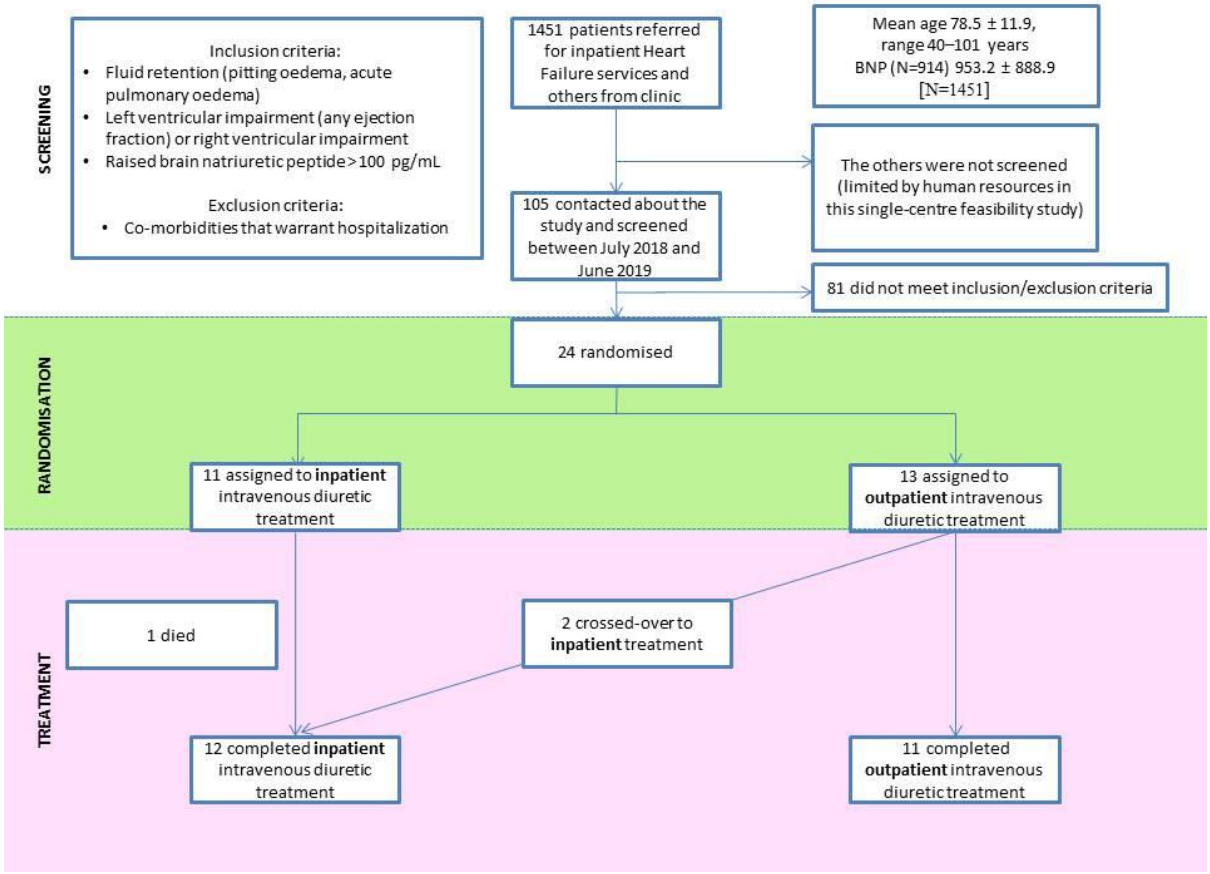

Figure 2 Cost savings with Out-patient based treatment

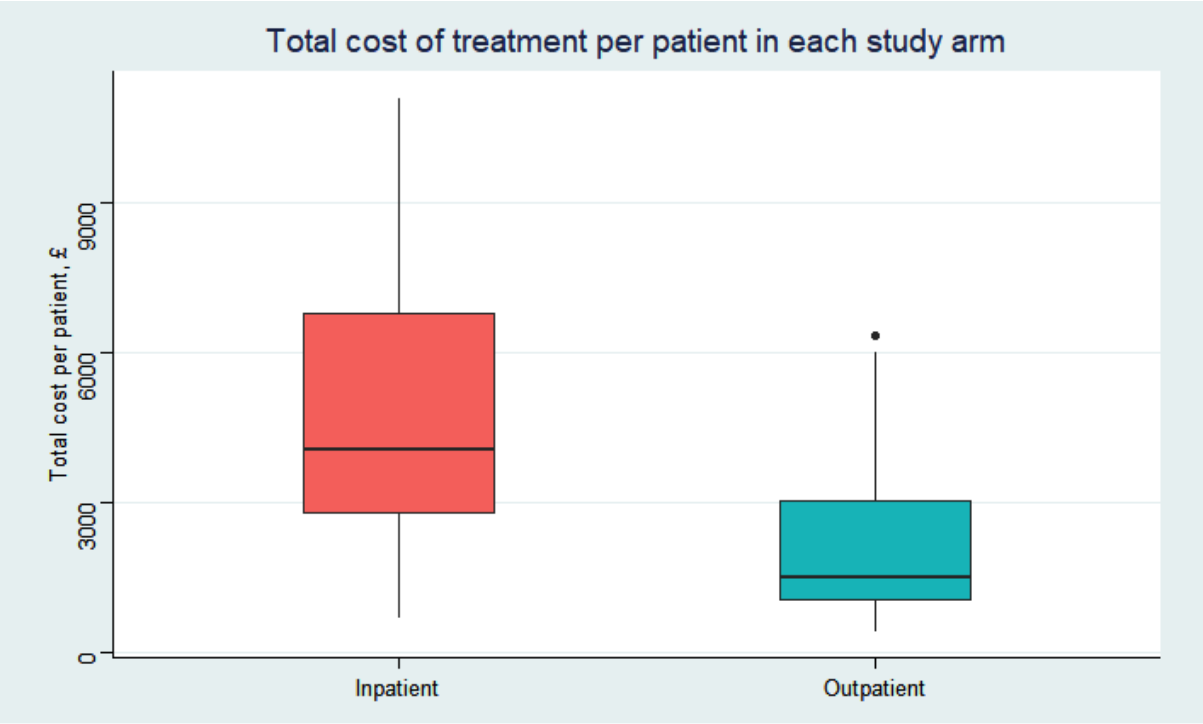

Table 1 Baseline Characteristics

		In-patient (n=11)	Out-patient (n=13)	p
Sex	*Female*	7 (63.6%)	3 (23.1%)	0.095
Age	*at randomisation*	81.8 (10.4)	70 (16.0)	0.052
BMI	*kg/m²*	28 (7)	37.1 (8)	**0.01**
Weight	*kg*	73.6 (20.9)	108.5 (31.9)	**0.005**
HF status	*Peripheral Oedema*	90.9%	92.3%	0.90
	Pulmonary oedema	27.3%	30.77%	0.85
	Both	18.2%	23.1%	0.77
NYHA	*Class II*	0	2 (15.4%)	0.07
	Class III	11 (100%)	8 (61.5%)	
	Class IV	0	3 (23.1%)	
Degree of peripheral oedema	*None*	1 (9%)*	0	0.080
	Mild		2 (15.4%)	
	Moderate	7 (64%)	11 (84.6%)	
	Severe	3 (27%)	0	
BNP	*[missing data-2 from each group]*	357 [251, 470],	360 [264, 699]	>0.99
LV systolic function on echocardiography	*EF 55% or more*	5 (45.5%)	5 (38.5%)	>0.99
	Impaired (<55%)	6 (54.5%)	8 (61.5%)	
IHD Aetiology		18.2%	7.7%	0.44
Arrhythmia		63.6%	23.1%	0.1
DCM		0	7.7%	-
Hypertension		54.54%	46.15%	1
Valvular		45.45%	38.46%	0.68
Number of comorbidities		3.8±2.7	5±2.9	0.3
Rockwood frailty score	at randomisation	5.6 (1.2)	5.4 (1.6)	0.67
Premorbid Rockwood frailty score		5.0 (1.2)	4.8 (1.3)	0.76
Derby frailty index	*Number (%) Frail*	6 (54.5%)	6 (46.2%)	0.99

Receiving “end of life”/palliative care		1 [9.09%] Severe MR - patient did not want surgery.	1 [7.7%] AS deemed not fit for AVR or TAVI by MDT	>0.99
Systolic BP	mmHg	145 (21.2)	137 (25)	0.43
Diastolic BP	mmHg	75 (14)	75 (17.8)	0.96
Hb	g/L	119 (16.7)	119.7 (17.3)	0.92
Albumin	g/L	36 [34,40]	36 [34,39]	0.97
Sodium	mmol/L	138 (2.4)	137.6 (2.8)	0.44
Potassium	mmol/L	4.4 (0.7)	4.1 (0.54)	0.3
Urea	mmol/L	11.35 (4.4)	10.2 (5.1)	0.55
Creatinine	umol/L	119.5 (37)	113.7 (48)	0.75
Already on IV diuretic		6 (54.4%)	10 (76.9%)	0.39
No. of days on IV diuretic pre-randomisation		2.3(3.4)	3.3(3.8)	0.5
ACEi	*(none on ARB in both groups)*	45.45%	23.1%	0.24
Sacubitril / valsartan		0	23.1%	-
Beta blocker		63.6%	76.9%	0.47
MRA		0	30.8%	-
Ivabradine		0	7.7%	-
Digoxin		18.2%	7.7.%	0.43
Iron Deficiency anaemia (IDA)		27.3%	38.46%	0.56
IV replacement therapy for IDA	*(in last 12 months)*	18.2%	15.4%	0.44
Smoker	*Non-smoker*	7 (63.6%)	5 (38.5%)	0.527
	Ex-smoker	3 (27.3%)	6 (46.2%)	
	Smoker	1 (9.1%)	2 (15.4%)	

*pulmonary oedema only

ACEi=Angiotensin Converting Enzyme Inhibitor; ARB= Angiotensin Receptor Blocker; AS= aortic stenosis; BMI=body mass index; BNP=Brain Natriuretic Peptide; BP=blood pressure; DCM=dilated cardiomyopathy; Hb=haemoglobin; HF=heart failure; IDA= Iron Deficiency anaemia; IHD=ischaemic heart disease; IV=intravenous; LV=left ventricular; MR= mitral regurgitation; NYHA=New York Heart Association;

[Descriptive statistics are presented either as: mean (SD), as median [Q1, Q3], or as N (percentage)]

Table 2 Clinical Effectiveness and Safety endpoints

		In-patient (n=11)	Out-patient (n=13)	p-value
Number of full days out of hospital per patient within 30 days of randomisation {min, max}		17 [13,22] min-max {1, 28}	30 [20, 30] min-max {0, 31}	**0.018**
Number of full days out of hospital per patient within 60 days of randomisation {min, max}		47 [36, 51] min-max {1, 58}	59 [41, 60] min-max {0, 61}	0.13
Hospital length of stay per patient during index episode, days		13 [7, 14.5]	3 [2, 7]	**0.004**
Number of patients readmitted within 60 days from randomisation		2	6	0.31
SAE (A&E attendance, delayed discharge, readmission within 60 days , death)	*No.of patients with at least 1 SAE*	5/11	*6/13*	>0.99
	During Index episode ()	2(pacemaker implant delayed discharge , MI leading to death)	*2 (cross-over/ readmitted with HF/multi-organ failure; delay discharge due to subacute limb ischaemia)*	>0.99
	Between discharge and 30 days of randomisation	2(HF; Cellulitis)	*3 (HF X1 , MI , Cholecystitis)*	>0.99
	31-60 days of randomisation	2 (HF readmission, HF Death)	*5 (HFx3 , atypical chest pain, elective leg amputation)*	0.68
	Total SAEs From Index to 60 days of randomisation	6	*10*	N/A
HF Readmissions	*During Index episode*	Not applicable	*1*	
	Between discharge and 30 days of randomisation	1	*1*	>0.99
	31-60 days of randomisation	*1*	*3*	0.71
Total HF admissions *From Index to 60 days of randomisation*		*2*	*5*	0.52
Non-HF readmissions	*During Index episode*	Not applicable	0	
	Between discharge and 30 days of	1 -Joint infection (wrist inflammation/cellulitis)	2 -NSTEMI - cholecystitis	>0.99

	randomisation			
	31-60 days of randomisation	0	2 (atypical chest pain, Elective leg amputation)	0.54
Total Non HF admissions *From Index to 60 days of randomisation*		1	4	0.42
Deaths	*Index episode*	1 (non HF related)	0	0.93
	Between discharge and 30 days of randomisation	0	1 HF death	>0.99
	31-60 days of randomisation	1 HF death	1 HF death	>0.99
Total Deaths *From Index to 60 days of randomisation*		2	2	>0.99

**** Index episode-before inpatient discharge or discharge visit after end of diuretic treatment for outpatients***

HF= heart failure; SAE=Serious Adverse Event

Figures are presented either as: mean (standard deviation), as median [Q1, Q3], or as percentage

Table 3 Mental Well-being (SWEMWBS) score comparison

TRANSFORMED SWEMWBS	In-patient	Out-patient	P value
Mean score at baseline	25.6 (4.46)	21.0 (5.08)	**0.03**
Number of patients whose score increased from baseline to discharge	4	8	0.36
Number of patients whose score increased from baseline to 30 days	3	8	**0.050**
Number of patients whose score increased from baseline to 60 days	3	9	**0.040**

Measurements of the transformed (Normalised) SWEMWBS scores were taken at baseline, discharge and at 30 days and 60 days post randomisation. The table shows the mean score at baseline and the number of patients whose wellbeing levels increased over treatment

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Contributorship Statement

Author Contributions

Wong K.Y.K. [1,2] designed the study, contributed to consent, assessment and management of patients in the trial, data collection, data analysis and interpretation, and writing the paper. He is responsible for the overall content as guarantor.

Hughes D.A.[3] performed the exploratory cost-effectiveness analysis.

Debski M. [1] contributed to consent, assessment and management of patients in the trial, data collection and data analysis and writing.

Latt N. [1] contributed to data collection and data analysis, and submission of abstracts which were published in Heart Suppl 2020.

Assaf O. [1] contributed to data collection for the study, in particular, cost-effectiveness data.

Abdelrahman A. [1] contributed to consent, assessment and management of patients in the trial, and data collection.

Taylor R. [1] performed most of the statistical analysis and writing of the results of the paper.

Allgar V. [4] contributed to the statistical design of the study and generated randomisation schedule blinded to investigators and patients.

McNeill L. [1] contributed to the collection and analysis of the cost-effectiveness data and critically reviewed the manuscript.

Howard S. [1] contributed to the analysis of the cost-effectiveness data and critically reviewed the manuscript.

Wong S.Y.S. [1] contributed to the design of the study and critically reviewed the manuscript.

Jones R.[1] is the patient public involvement group representative and critically reviewed the manuscript.

Cassidy C. J.[1] contributed to the design of the study and is a Safety Committee member.

Seed A. [1] contributed to the design of the study and critically reviewed the manuscript.

Galasko G. [1] contributed to the design of the study and is a Safety Committee member.

Clark A. [4] contributed to the design of the study and critically reviewed the manuscript.

Wilson D. [5] critically reviewed the manuscript.

Davis G.K. [6] critically reviewed the manuscript.

Montasem A [6] critically reviewed the manuscript.

Lang C.C. [7] critically reviewed the manuscript.

Kalra P.R. [8] critically reviewed the manuscript.

Campbell R. [9] critically reviewed the manuscript.

Lip G.Y.H. [2, 10] critically reviewed the manuscript.

Cleland J.G.F. [9] contributed to the design of the study and critically reviewed the manuscript.