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ORIGINAL RESEARCH ARTICLE

Design of a multicentre randomized controlled trial to assess the safety and efficacy of dose titration by specialized nurses in patients with heart failure. ETIFIC study protocol

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Abstract

Aims Heart failure (HF) is associated with many hospital admissions and relatively high mortality, rates decreasing with administration of beta-blockers (BBs), angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor antagonists. The effect is dose dependent, suboptimal doses being common in clinical practice. The 2012 European guidelines recommend close monitoring and dose titration by HF nurses. Our main aim is to compare BB doses achieved by patients after 4 months in intervention (HF nurse-managed) and control (cardiologist-managed) groups. Secondary aims include comparing doses of the other aforementioned drugs achieved after 4 months, adverse events, and outcomes at 6 months in the two groups.

Methods We have designed a multicentre (20 hospitals) non-inferiority randomized controlled trial, including patients with new-onset HF, left ventricular ejection fraction ≤40%, and New York Heart Association class II–III, with no contraindications to BBs. We will also conduct qualitative analysis to explore potential barriers to and facilitators of dose titration by HF nurses. In the intervention group, HF nurses will implement titration as prescribed by cardiologists, following a protocol. In controls, cardiologists will both prescribe and titrate doses. The study variables are doses of each of the drugs after 4 months relative to the target dose (%), New York Heart Association class, left ventricular ejection fraction, N-terminal pro B-type natriuretic peptide levels, 6 min walk distance, comorbidities, renal function, readmissions, mortality, quality of life, and psychosocial characteristics.

Conclusions The trial seeks to assess whether titration by HF nurses of drugs recommended in practice guidelines is safe and not inferior to direct management by cardiologists. The results could have an impact on clinical practice.

Keywords Up-titration; Nursing or nurse; Heart failure

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Introduction

The prevalence of heart failure (HF), estimated to be approximately 2% in the general population and ≥10% in over 70 year olds,[1] is increasing in Europe, and HF is already the leading cause of hospital admission in over 65 year olds.[2] All this has a great impact on healthcare systems and on the quality of life of patients and their caregivers.

To reduce hospitalizations and premature death due to HF and improve symptoms and prognosis, clinical practice

guidelines (CPGs)[1] recommend (Class 1, Level of Evidence A) the administration of beta blockers (BBs), angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) in HF patients with New York Heart Association (NYHA) functional class II–IV and left ventricular ejection fraction (LVEF) $\leq$40%, except in the presence of contraindications. However, it is necessary to titrate these drugs to reach the target dose, implying the need for closer monitoring of the clinical status and laboratory results of patients.[3]

Although the prescription of the aforementioned drugs has improved in recent times, dose titration is often not carried out in accordance with the CPGs. A recent observational study conducted by the HF group of the European Society of Cardiology (2011–2013) in 21 European and Mediterranean countries found that 33.7, 32.4, and 35.1% of patients were in the process of titration of ACEIs, ARBs, and BBs, respectively, while the target dose of BBs, ACEIs, ARBs, and MRAs was only reached in 17.5, 29.3, 24.1, and 30.5% of patients. What is more, the reason why the BB target dose was not reached was not documented in 29.2% of patients.[4]

More recently, similar results have been obtained in Spain,[5] with 30.3, 30, 34.6, and 26.7% patients found to be in the process of titration of ACEIs, ARBs, BBs, and MRAs, respectively, the target dose of these drugs being reached in just 16.2, 23.3, 13.2, and 23.5% of patients. Further, the reason why the target dose was not reached was unknown in 27.8, 25.7, 28.5, and 50.1% of patients on ACEIs, ARBs, BBs, and MRAs, respectively. It is likely that the difficulty of maintaining close monitoring of patient clinical status is a key factor underlying the lack of optimal titration of these drugs in practice, and hence new approaches are required to improve the situation, involving other doctors or nurses to oversee the process.

The specific recommendations on dose titration in the 2012 European Society of Cardiology (ESC) CPGs include that nurses specialized in HF collaborate in this process, becoming involved with patient education, follow-up face-to-face or over the telephone, monitoring of blood test results, and titration of ACEIs/ARBs, BBs, MRAs, and diuretics.[3] The 2011 ESC/HF Association standards for HF care[6] underline that the two main responsibilities of this type of nurse are the education of patients and their family, and the optimization of drugs (titration/prescription of drugs, depending on the country), recommending that such nurses have immediate access to cardiologists if advice is needed.

Jaarsma *et al.* in their study on HF management programmes in Europe[7] found that:

> *'Dose titration by nurses was mainly protocol-led and included diuretics (78%), beta-blockers (76%), angiotensin converting enzyme-inhibitors (74%), angiotensin II receptor blockers (59%), aldosterone receptor antagonists (53%), and potassium supplements (26%).'*

They also observed that most nurses involved in caring for HF patients are trained and have experience in cardiology.

Blue and McMurray[8] noted the emerging role of specialized HF nurses and that this role was becoming mainstream in Sweden, the Netherlands, and the UK. They indicated that the responsibilities that should be taken on by such nurses are determined by their training, including supervised practice, perception of their role by managers and the healthcare team, the existence of protocols, and of medical and legal support, and auditing of standards of practice.

Numerous meta-analyses on HF programmes demonstrate that multidisciplinary teams, closely monitoring patients, providing education, and optimizing treatment, significantly reduce rates of readmissions.[1] Further, nurses are the health professionals most closely involved, according to the meta-review of 15 meta-analyses by Savard *et al.*[9] A considerable number of these meta-analyses mentioned dose titration by HF nurses. In the clinical trials included, nurses titrated ACEIs, ARBs, BBs, K, diuretics, MRAs, and digoxin,[10–21] assessed the dose reached,[13,14,19,20] and initiated treatment following a protocol.[10,12,14,15,17] Hardly any similar research has been conducted in Spain. Notably, the meta-analysis of Yu *et al.*[22] concluded that dose titration by cardiology nurses, following algorithms and with support from a cardiologist, is the most promising approach to improve outcomes.

Nevertheless, despite the proven efficacy of specific HF programmes, it is very difficult to assess the effectiveness of each component of such interventions, given the multifactorial nature of the interventions, complexity and heterogeneity of studies, and variations in the characteristics of patients, training and experience of nurses, countries, and their health systems. Specifically, in our case, it is difficult to ascertain the contexts in which dose titration by HF nurses can be safe and effective.

Regarding randomized trials focused on drug optimization, we should mention the study by Rao and Walsh[19] in the UK, in which specialist HF nurses titrated ACEIs and BBs, the authors concluding that the intervention, whether in hospital or at home, was more effective if carried out by specialized health professionals. In the USA, Ansari *et al.*[12] compared different organizational strategies to increase prescribing of BBs and the doses used in accordance with CPGs and concluded that the involvement of a facilitator nurse was a successful strategy.

The nurses who perform dose titration tend to be specialists in cardiology or in HF, and sometimes are case managers or advanced practice nurses, with specific training in HF. Most have access to cardiologists for advice and protocols to follow.

Other observational studies, some multicentre in design,[23,24] also describe the role of HF nurses in titrating or initiating ACEIs and BBs,[23] showing that different combinations of drugs can be managed by this type of trained nurses with high levels of efficacy and safety.[23] The Danish study recommends setting process quality indicators, assessing areas for improvement and continuous training.[24] Other recently published research, a post-hoc study in Germany,[25] has indicated

improvements in the prescribing of ACEIs/ARBs and BBs and the dosages used in a programme coordinated by nurses.

In Spain, a study carried out by Comín *et al.*[26] in an HF unit set a clear basis for our current project, their goal being to compare titration of BBs by HF nurses and cardiologists. The results of this pilot evaluation suggested that assigning this task to the nurses was safe and even more effective than using cardiologists specialized in HF, higher doses of BBs being reached in patients under the nurses' care without a higher rate of adverse events. However, the study had certain limitations including the relatively small sample size (n = 98), the fact it was based on a convenience sample, the lack of randomization, and the consideration of only one drug.

To sum up, a review of the literature confirms that drug adjustment by HF nurses is a widespread practice, and there are CPGs on assigning this role to nurses. The high prevalence of HF, its health and social impact, the benefit in clinical outcome with these drugs, current deficiencies in dose optimization with respect to CPGs, and the small number of randomized clinical trials in this field warrant the development of a multicentre randomized trial to generate high-quality evidence on the efficacy and safety of dose titration by specialist HF nurses. This practice may be a cost-effective option, facilitating the universal provision of this type of care in an unfavourable economic climate.

Hypothesis

Primary hypothesis

The titration of BBs, as recommended by CPGs, by a specialist nurse (intervention group) in HF patients with LVEF ≤40% would be at least as effective and safe as the same process carried out by a cardiologist (control group). Specifically, in the 4 months after initiation of the intervention, the mean relative dose (% compared with the target dose recommended in CPGs[1]) of BBs reached in the intervention group (specialist HF nurse) would not be lower than that in the control group (cardiologist specialized in HF).

Secondary hypotheses

The titration of ACEIs, ARBs, and RMAs, as recommended in CPGs, performed in the same patients over the same period, would be at least as effective (mean relative dose) in the intervention group as in the control group.

The titration of BBs, ACEIs, ARBs, and RMAs would be safe, with no associated increase in the rate of adverse events.

Beneficial effects of titration of these drugs would be at least as great in the intervention group as in controls, considering improvements in LVEF, NYHA class, N-terminal pro B-type natriuretic peptide, 6 min walk distance, and the Minnesota Living with HF Questionnaire (MLHFQ) and Euro-Qol-5D (EQ-5D) scores, at 6 months after inclusion in the study (2 months after the end of the intervention). Further, there would be no significant differences in hospital admissions or mortality between the groups. The differences would vary as a function of demographic, socioeconomic, and clinical characteristics as well as prognostic variables and level of self-care.

Objectives

Primary objective

To compare the mean relative dose of BBs reached in patients in the intervention (HF nurse) and control (cardiologist) groups at 4 months after starting titration

Secondary objectives

To compare, in a similar way, the mean relative doses of ACEIs, ARBs, and MRAs reached in patients

To compare the percentage of adverse events in the two groups attributable to dose changes, over the 4 months of titration, by drug group, BBs, ACEIs, ARBs, and MRAs

To compare the rates of mortality and readmissions in the two groups for the 6 months after starting the titration, and to compare the mean LVEF, NYHA class, N-terminal pro B-type natriuretic peptide, 6 min walk distance, and MLHFQ and EQ-5D scores

To identify variables that condition outcomes

Study Design

This will be a multicentre randomized controlled trial in which participants, HF patients with an LVEF ≤40%, will be randomly allocated to one of two parallel groups and followed up for 6 months (*Figure 1*).

Setting

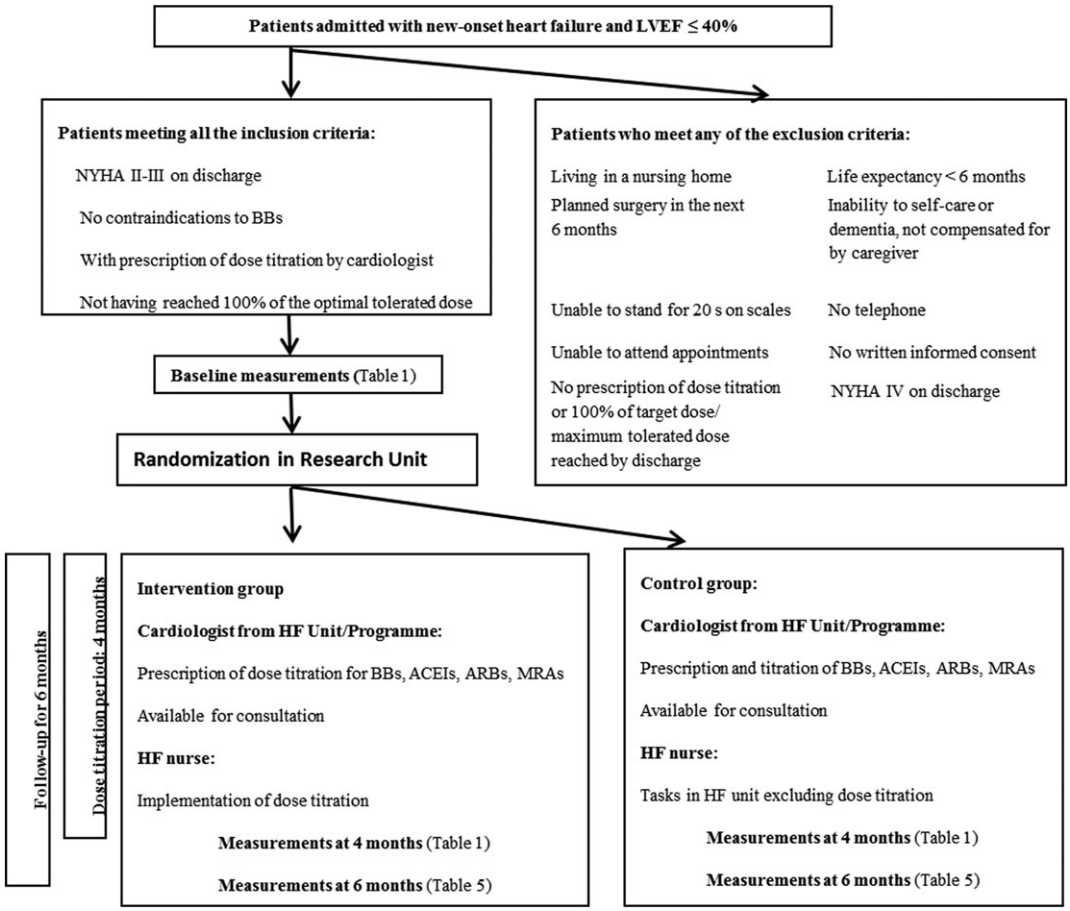
The trial will be conducted across 20 hospitals in nine different regions with different health services in Spain.

Study population

***Inclusion criteria*:**
Patients included will be

- Admitted for new-onset ('*de novo*') HF with signs and symptoms and structural changes visible on ultrasound or with another imaging technique

Figure 1 Study algorithm.



- With an LVEF ≤40%.
- Classified as NYHA class II–III on discharge
- With no contraindications to the prescription of BBs, considering those cited in CPGs[3]: asthma, and second- or third-degree AVB in the absence of a permanent pacemaker
- With titration prescribed by a cardiologist, but without having reached an optimal dose (100% of the target dose or maximum tolerated dose) before discharge
- With written informed consent

Patients with contraindications to drugs other than BBs may be included.

Exclusion criteria

Patients who meet any of the following criteria will be excluded:

- Living in a nursing home
- With a life expectancy <6 months
- With surgery scheduled, or to be performed, in the following 6 months (Patients will not be excluded for procedures to implant a cardiac resynchronization therapy device, cardioverter–defibrillator or pacemaker, minor surgery, or percutaneous transluminal coronary angioplasty)
- With inability to self-care or with severe dementia not compensated for by a competent caregiver (Memory Impairment Screen score ≤4)
- Unable to weigh themselves (stand on a scales for at least 20 s without leaning on the wall) and record the weight
- Without a telephone
- Under home care and unable to attend medical appointments.

Losses to follow-up

- Death during the period of intervention or follow-up
- Withdrawal of patient consent
- Clinical problems or difficulties attending appointments that hinder follow-up
- Failure to obtain essential clinical data

Sample size calculation

For the hypothesis that the relative dose of BBs reaches 52% by the end of the study[26] and using an equivalence margin of 7%, we would need 157 patients per group for

an alpha level of significance of 0.05 and a statistical power of 80% (beta of 0.80). For the hypotheses of similar mortality and readmissions after 6 months, assuming that up to 20% of patients may experience this type of event and using an equivalence margin of 5%, we would need at least 178 patients per group. For the hypothesis of similar adverse effects, assuming that up to 30% of patients may experience this type of effect at some point during titration[26] and using an equivalence margin of 5%, we would need at least 262 patients per group.

Hence, estimating that as many as 20% of patients will be lost to follow-up, we need to recruit a total of 314 patients per group to test the main hypotheses.

Data collection: patient recruitment

An active surveillance system will be set up to operate 3 days/week, enabling a hospital nurse to identify patients admitted for HF. Inclusion and exclusion criteria will be checked. Eligible patients will be invited to participate and included after they have given written informed consent.

Randomization

Once all the baseline measurements have been taken, randomization will be performed centrally. Recruitment and randomization will be performed in the hospital prior to discharge or at the most a week after that during the first consultation. The principal investigator will contact the Research Unit of Galdakao-Usansolo Hospital, where each patient will be assigned to one of the groups at a ratio of 1:1, using a block size of four patients and stratified by hospital.

Intervention group protocol

The intervention (*Figures 2–5*) will be carried out in accordance with the CPG recommendations.[1,3]

The titration period will be 4 months, with follow-up to 6 months. Its process will be guided by the following advised measures:

a) Drug prescription as well as the rate of titration of each patient will be made by the cardiologist at the beginning of the process and an HF nurse will be responsible for implementing the titration process.
b) To consider possible biweekly increases[3]
c) To consider alternating increases of different drugs (American Heart association Heart Failure 2013 CPGs[27]).
d) To plan weekly visits or at the most every two weeks from the intervention nurse.
e) To plan approximately two to three dose increases of BBs and ACEIs/ARBs and one of MRA
f) The dose increase of MRA will be made after finishing ACEI/ARB titration
g) Analysis of renal function and ions will be made prior to each dose increase of ACEIs/ARBs and MRA
h) In every visit, just one drug dose increase will be made
i) All dose increases will be made in face to face visits after clinical evaluation protocol.
j) The titration process will be tailored to the needs of each individual. The 4 month period is not mandatory but indicative.
k) At baseline and before each dose increase, a safety checklist based on ESC 2012 guidelines (addenda) will be used, this covering the most common problems and possible solutions, and when to seek advice or refer a patient. This checklist will be reviewed both by the HF nurse as well as the cardiologist
l) The cardiologist will always be available for consultation.
m) A further period of 3–4 weeks will be established to assess effects and adverse events.
n) Patients will be treated promptly in the event of decompensation.

This period of 4 months has the potential to also prevent readmissions, because a more intensive monitoring is carried out during the period considered vulnerable (3 months after admission); it takes advantage of frequent educational visits of patient and family after admission and could provide the clinical benefits of drug optimization earlier to patients

Control group protocol

Patients in this group will receive the usual care provided by HF units or programmes. A cardiologist will be in charge of the prescription and all decisions related to dose titration, while an HF nurse will be responsible for patient clinical assessment, ensuring patients receive appropriate care in the event of decompensation and education for patients and their families.

The characteristics of usual care in each of the participating hospitals will be assessed using questionnaires, prior to starting the trial. In hospitals in which usual organization of care for HF patients involves internal medicine specialists or primary-care doctors, these doctors will be included in the follow-up for both groups (intervention and control). In any case, management of the titration process will be the responsibility of the cardiologist.

The Safety of the intervention will be strengthened by various different measures, including requiring extensive training (400 h) and experience (at last 2 years) in the case of the HF nurses, and the prescription and titration

Figure 2 Control and intervention protocol.

CONTROL GROUP PROTOCOL: Usual Care in the HF Units or Programmes (The characteristics of the usual care will be assessed using questionnaires)

CARDIOLOGIST: prescription and drug dosing decisions

HF NURSE: clinical assessment, patient and family education and ensuring patients receive appropriate care in the event of decompensation

General practitioner or internal medicine specialist: in centres where such doctors are part of the team, they may perform follow-up or manage decompensation

INTERVENTION GROUP PROTOCOL: Period of titration, 4 months; follow-up, 6 months

CARDIOLOGIST: 1. Initial prescription **(ESC 2012 guidelines[1,3])**

Drug Name:	Initial dose and frequency:	Target dose and frequency:	Titration schedule Dose and increase time	MONITOR
BB:……	**…… mg /…..h**	**…..mg /….h**	**Dose increase: … Every …….days Alternate with ACEIs**	Symptomatic hypotension, HR, AV block, sinus node dysfunction, worsening of HF
ACEI/ARB: ……	**….. mg /…..h**	**…..mg /….h**	**Dose increase: …… Every …….days Alternate with BBs**	Symptomatic hypotension, creatinine, GFR, K, coughing
MRA:…….	**….. mg /….h**	**….mg/….h**	**Dose increase: …… When: ……**	Creatinine, GFR, K

CARDIOLOGIST: 2. REGULAR review of the nurse checklist | **CARDIOLOGIST: 3. Available for answering queries, consultations or management of decompensation**

HF NURSE appointment schedule: Weekly/fortnightly until completion of titration, then fortnightly/monthly. **Example:** For 2 increases of BBs/ACEIs-ARBs and one of MRAs

1st consultation Baseline	2nd consultation	3rd consultation	4th consultation	5th consultation	6th consultation	7th consultation	8th consultation	Final consultation
Tasks: 1-2-3-4-4c-5-6-7-8	**Tasks:** 3-3b-5b-6-7	**Tasks:** 2b- 3-4c-6-7-8	**Tasks:** 2b-3-4b-6-7-8	**Tasks:** 2b- 3-4c- 6-7-8	**Tasks:** 2b-3-4b-6-7-8	**Tasks:** 2b- 3-4c- 6-7-8	**Tasks:** 2b-3-4b-4 d-6-7-8	**Tasks:** 3,4 b, 5-6-7-8
ACEI/ARB			**Dose increase:**		**Dose increase:**			
BB		**Dose increase:**		**Dose increase:**	(4)			
MRA							**Dose increase:**	

(1) Review patient discharge report and case history (patient interview and health record**).**

(2) Review initial checklist: Review ACEIs/ARBs, BBs, MRAs: Indications, contraindications, special precautions, allergies.

Check the records for ACEIs/ARBs, BBs, MRAs: Name, initial and target dose, dose titration schedule: dose and increase time. Alternate titration of drugs.

Review drug interactions: Hypotensive drugs, bradycardia-inducing drugs and other drugs that may interact with renal function or K levels.

(2b) Review checklist for dose increases: review standard problems and solutions, consult/refer, increase dose if appropriate

(3) Conduct clinical assessment and record findings: signs and symptoms, BP, HR, weight, volume status.

(3b) Assess: Coughing if on ACEIs. Gynecomastia if on spironolactone

(4) Record lab test results: Cr and GFR, K. **(4b) Assess results**: Cr, GFR, K, Na **(4c) Issue lab test request form**: Cr, GFR, K, Na**.**

(4d) Request complete blood tests at 12 weeks

(5) Perform ECG **(5b)** Perform extra ECG if HR < 50 bpm.

(6) Provide education: understanding signs and symptoms of HF and their monitoring, causes, flexible recommendations on diuretics and when and how to seek advice/ medical attention, diet…

(7) Assess and discuss self-care: Measurements of BP, HR, and weight; self-care booklet; taking all medications correctly. **(7b) Self-care scale**

(8) Provide/explain: appointment schedule, list of drugs

(9) Underline possibility of contact over the phone or face-to-face in the event of worsening, to ensure early care

HF: heart failure; BB: beta blockers; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blockers; MRA: mineralocorticoid receptor antagonists. BP: Blood Pressure. HR: Heart Rate. AV block: Atrioventricular block.GF: Glomerular Filtration. K: Potassium. Na: Sodium. ECG: Electrocardiogram

Figure 3 Checklist for titration: ACEIs/ARBs.

CHECKLIST FOR STARTING TITRATION: ACEIs/ARBs (adapted from 2012 ESC guidelines[3])

HF nurse review Indications, contraindications and precautions checked by the nurse as an extra level of safety, similar to the monitoring of allergies	**Cardiologist**: (A) Agree / (D) Disagree-concern. Measure proposed, Solution yes/no
Name and Surname(s) /patient number: **Date**:	
Are ACEIs indicated? NYHA II-IV and LVEF ≤ 40%. Yes/No	A
Are ACEIs contraindicated? Angioedema, bilateral renal artery stenosis, severe aortic stenosis, risk of pregnancy/pregnancy Yes to some/ No to all	A
ACEIs precautions/specialist advice needed? Plasma creatinine (Cr) >2.5 mg/dl, GFR<30 ml/min/1.73 m^2.	A
Serum potassium (K) > 5 mmol/l (mEq/l), asymptomatic severe hypotension (SBP < 90 mmHg) Yes to some /No to all	A
Prescription, dosing, rate of titration and observations noted in patient health record? Yes/No	A
Baseline BP, creatinine and K levels noted in patient health record Yes/No	
Dose increases and monitoring planned? (*) Yes/No	
Education provided to patient and family? Yes/No	
Patient understanding of drug regimen and adherence checked? Yes/No	

Checklist for FOLLOW-UP VISITS: INCREASES IN ACEIs/ARBs (adapted from 2012 ESC guidelines [3])

HF nurse (*) Number of increases: 1st, 2nd Dose increase	**Cardiologist (**):1st/2nd increase:** Agree A /Disagree-concern D, measure proposed. Solution? yes/no
Name and Surname(s) /patient number: **Date**:	
Laboratory tests completed? Cr, GFR, K, Na Yes/No	
Worsening of renal function? Yes /No	
Cr> 30% of baseline : yes/no Cr> 50% of baseline: yes /no Cr > 3 mg, GFR < 25 ml/min/1.73 m^2: Yes/No	
Recorded and doctor notified? Yes /No	
Standard solution tried? Review nephrotoxic medication, K supplements or K-sparing agents	
Reduce diuretics if no signs of congestion Reduce ACEI/ARB dose by half,	
Seek specialist advice, request further tests Yes / No; Which?	
Increase in creatinine? > 100% Yes /No **3.5** mg Yes/No **GFR < 20** ml/min/1.73 m^2**:** Yes/No	
Discontinue ACEIs/ARBs Seek urgent advice from the specialist	
K => 5,5 Recorded and doctor notified? Yes /No	
Standard solution tried? Same as for worsening of renal function yes/no. low potassium diet Yes / No; Which?	
K=>6	
Standard solution tried? Same as before, seek urgent specialist advice, ECG, discontinue medication Yes /No; Which?	
Clinical assessment made of volume status? Euvolaemic? Yes/No	
If hyper-hypovolaemic, possible causes reviewed? ¿ Diuretic dose/diet adjusted? Other factors? Yes/No; measure used:	
Symptomatic low BP? Yes/No	
Standard solution tried? : Consider other hypotensive drugs, reduce/ discontinue nitrates, Ca-antagonists...	
Decrease the dose of diuretics, if no signs of congestion, Manage timing of hypotensive drugs, seek advice Yes/No; which?	
New-onset cough (without expectoration or fluid overload)? Yes /No Recorded and doctor notified? Yes /No	
Patient educated/understands: a) desired effects yes/no, b) adverse effects yes/no, c) avoiding NSAIDs not prescribed by a physician and salt substitutes high in K yes/no, d) when and how to seek advice/medical attention Yes/No	
Medication adherence checked? Yes /No Education reinforced and measures taken to support adherence if appropriate? Yes/No	
New **dose**? Yes /no. **Dose increased?** Yes /No, if no, reason: Maximum dose increase made: doubling of the previous dose? Yes /No	
Time since previous dose increase ≥ 2 weeks? Yes /No **Dose reduction:** Yes /No; Reason	

(*) The HF nurse completes the checklist prior to every dose increase
(**) The HF cardiologist reviews the checklists (completed by the nurse**) of all patients under titration every other week**

NYHA: New York Heart Association. LVEF: left ventricular ejection fraction. Cr Creatinine. GF Glomerular Filtration. K: Potassium. SBP: systolic blood pressure. ECG: Electrocardiogram.

Figure 4 Checklist for titration: BB

CHECKLIST FOR STARTING TITRATION: BBs (adapted from 2012 ESC guidelines[3])	
HF nurse review Indications, contraindications and precautions checked by the nurse as an extra level of safety, similar to the monitoring of allergies **Name and Surname(s)** /patient number: **Date**: **Are BBs indicated**? NYHA II-IV and LVEF ≤ 40%. Yes/No **Are BBs contraindicated**? Asthma, 2nd or 3rd-degree AV block (in the absence of permanent pacemaker) Yes to some/ No to all **BBs precautions/specialist advice needed?** NYHA IV, recent/current HF exacerbation, persistent signs of congestion - try euvolaemia, AV block, HR <60 bpm, hypotension < 90 mmHg. Other bradycardia-inducing drugs: verapamil, diltiazem (discontinue), digoxin, amiodarone, ivabradine Yes to some /No to all **Prescription, dosing, rate of titration and observations** noted in patient health record? Yes/No **Baseline BP, HR, no 2nd or 3rd-degree AV block, no asthma** noted in patient health record Yes/No **Dose increases and monitoring planned?** (*) Yes/No **Education provided to** patient and family? Yes/No **Patient understanding of drug regimen and adherence checked?** Yes/No	**Cardiologist**: (A) Agree / (D) Disagree-concern. Measure proposed, Solution yes/no A A A A A
Checklist for FOLLOW-UP VISITS: INCREASES IN BBs (adapted from 2012 ESC guidelines [3])	
HF nurse (*) Number of increases: 1st, 2nd Dose increase **Name and Surname(s)** /patient number: **Date**: **BP, HR. if HR <50 bpm, ECG, changes in weight/ fluid status:** performed/assessed? Yes /No **HR < 50 bpm?** Yes /No IF HR < 50 bpm, AV block, sinus node dysfunction? Yes /No Recorded and doctor notified? Yes /No **Standard solution tried?** Review other bradycardia-inducing drugs, digoxin, amiodarone, ivabradine If HR < 50 bpm and worsening of symptoms, reduce the BB dose by half Yes / No; Which? **Clinical assessment made of volume status?** Euvolaemic? Yes/No **If hyper-hypovolaemic, possible causes reviewed?** ¿ Diuretic dose/diet adjusted? Other factors? If hypervolaemia is not resolved with other measures (diuretics, others), reduce BB dose by half Yes/No; measure used: **Symptomatic low BP?** Yes/No Standard solution tried? : Consider other hypotensive drugs, reduce/ discontinue nitrates, Ca-antagonists... Decrease the dose of diuretics, if no signs of congestion, Manage timing of hypotensive drugs, seek advice Yes/No; which? **Patient educated/understands**: a) desired effects yes/no,, b) adverse effects yes/no, c) when and how to seek advice/medical attention Yes/No **Medication adherence checked?** Yes /No Education reinforced and measures taken to support adherence if appropriate? Yes/No New **dose**? Yes/No. **Dose increased?** Yes /No, if no, reason: Maximum dose increase made: doubling of the previous dose? Yes /No Time since previous dose increase ≥ 2 weeks? Yes /No **Dose reduction:** Yes /No; Reason	**Cardiologist (**):1st/2ndincrease:** Agree A /Disagree-concern D, measure proposed. Solution? yes/no
(*) The HF nurse completes the checklist prior to every dose increase **(**) The HF cardiologist reviews the checklists (**completed by the nurse**) of all patients under titration every other week**	
NYHA: New York Heart Association. LVEF: left ventricular ejection fraction. Cr Creatinine. GF Glomerular Filtration. K: Potassium. SBP: systolic blood pressure. ECG: Electrocardiogram.	

schedule for each patient always being decided by a cardiologist, who notes these in the patient medical record. Further, the cardiologists will review the checklists (*Figures 3–5*) to be completed by the nurse, and any problems and the ways they are resolved will be recorded.

The cardiologist and, as appropriate, the patient's general practitioner or an internal medicine specialist will be available to answer any queries and to see the patient if this is necessary in the opinion of the HF nurse. Any adverse events will be recorded, and the causes of serious events will be assessed by the cardiologist in charge in each hospital. In

Figure 5 Checklist for titration: MRA

CHECKLIST FOR STARTING TITRATION: MRAs (adapted from 2012 ESC guidelines[3])

HF nurse review Indications, contraindications and precautions checked by the nurse as an extra level of safety, similar to the monitoring of allergies	**Cardiologist**: (A) Agree / (D) Disagree-concern. Measure proposed, Solution yes/no
Name and Surname(s) /patient number: **Date**:	
Are MRAs indicated? NYHA II-IV and LVEF≤ 35% despite ACEIs/ARBs and BBs, ischaemic heart disease. Yes/No	A
Are MRAs contraindicated? Eplerenone-strong CYP3A4 inhibitors, e.g., ketoconazole, itraconazole, nefazodone, telithromycin, clarithromycin, ritonavir, or nelfinavir, Yes to some/ No to all	A
MRA precautions /specialist advice needed? Plasma creatinine (Cr) >2.5 mg/dl, GFR< 30 ml/min/1.73 m2. Serum potassium (K) > 5 mmol/l (mEq/l) Yes to some /No to all	A A
Pharmacological interactions reviewed: K supplements, K-sparing diuretics (amiloride, triamterene, and combinations with furosemide nonsteroidal anti-inflammatory drugs, trimethoprim/trimethoprim-sulfamethoxazole, salt substitutes high in K Yes /No	A
Prescription, dosing, rate of titration and observations noted in patient health record? Yes/No	
Baseline creatinine and K levels noted in patient health record Yes/No	
Dose increases and monitoring planned? (*) Yes/No	
Education provided to patient and family? Yes/No	
Patient understanding of drug regimen and adherence checked? Yes/No	

Checklist for FOLLOW-UP VISITS: INCREASES IN MRAs (adapted from 2012 ESC guidelines[3])

HF nurse (*) Number of increases: 1st, 2nd Dose increase	**Cardiologist (**):1st/2nd increase:**
Name and Surname(s) /patient number: **Date**:	Agree A /Disagree-concern D, measure proposed. Solution? yes/no
Laboratory tests completed? Cr, GFR, K, Na Performed ≥after 1-4-8-12 weeks after start/ dose increase Yes/No	
Worsening of renal function? Yes /No Creatinine>2.5 mg, yes/no GFR<30 ml/min/1.73 m^2: yes /no Recorded and doctor notified? Yes /No	
Standard solution tried? Review nephrotoxic medication, K supplements or K-sparing agents Reduce diuretics if hypovolaemic Reduce MRA dose by half, Seek specialist advice, request further tests Yes / No; Which?	
Elevated creatinine? 3.5 mg Yes /No **GFR < 20** ml/min/1.73 m^2**:** Yes/No Discontinue MRA Seek urgent advice from the specialist	
K => 5,5 Yes /No Recorded and doctor notified? Yes /No	
Standard solution tried? Same as for worsening of renal function yes/no. low potassium diet yes /no Yes / No; Which?	
K=>6 **Standard solution tried?** Same as before, seek urgent specialist advice, ECG, discontinue medication Yes /No; measure used:	
Clinical assessment made of volume status? Euvolaemic? Yes/No	
If hyper-hypovolaemic, possible causes reviewed? Yes/No ¿ Diuretic dose/diet adjusted? Other factors? Yes/No; Which?	
Gynecomastia if on spironolactone: doctor notified? Yes/No	
Patient educated/understands: a) desired effects yes/no,, b) adverse effects yes/no, c) avoiding NSAIDs not prescribed by a physician and salt substitutes high in K yes/no d) when and how to seek advice/medical attention yes/no	
Medication adherence checked? Yes /No Education reinforced and measures taken to support adherence if appropriate? Yes/No	
New **dose**? Yes /no. **Dose increased?** Yes /No, if no, reason:	
Time since previous dose increase ≥ 4 weeks? Yes /No **Dose reduction:** Yes /No; Reason	

(*) The HF nurse completes the checklist prior to every dose increase

(**) The HF cardiologist reviews the checklists (completed by the nurse**) of all patients under titration every other week**

NYHA: New York Heart Association. LVEF: left ventricular ejection fraction. Cr Creatinine. GF Glomerular Filtration. K: Potassium. SBP: systolic blood pressure. ECG: Electrocardiogram.

addition, there will be a committee within the research team to oversee the safety of the research.

Variables and measurements

The primary endpoint variable is the dose (mean relative dose: % relative to the target dose recommended in CPGs[1]) of BBs reached 4 months after starting titration. One hundred percent BB target dose is considered: bisoprolol 10 mg o.d., nebivolol 10 mg o.d., and carvedilol 25–50 mg b.i.d.

Secondary outcomes include:

- The doses (mean relative dose: % relative to target dose recommended in the GPS[1]) of ACEIs, ARBs, and MRAs reached in the same period. One hundred percent target dose is considered: ACEI: enalapril 10–20 mg b.i.d., ramipril 5 mg b.i.d., lisinopril 20–35 mg o.d., captopril 50 mg t.i.d., trandolapril 4 mg o.d.; ARB II: candesartan 32 mg o.d., valsartan 160 mg b.i.d., losartan 150 mg o.d.; MRA: eplerenone 50 mg o.d., and spironolactone 25–50 mg o.d. Other variables considered: Reasons for not reaching target dose and number of visits.
- Any adverse events described as a problem in the CPGs:[3] symptomatic hypotension, HR $<$ 50, second or third. AVB, worsening renal function (Cr $>$ 50% of baseline; Cr $>$ 3 mg/dL, GFR $<$ 25 mL/min/1.73 m^2, cough, worsening of HF signs and symptoms. Serious adverse events are considered: drug withdrawal, hospital admissions, and mortality linked to dose changes
- Potential effects of the intervention at 6 months of follow-up on the following variables: LVEF, NYHA class (I–IV), Nt-pro-BNP, 6 min walk distance,[28] quality of life measured blindly using self-report questionnaires (MLHFQ[29] and EQ-5D[30]) validated for the Spanish population, number of readmissions, and mortality.

We will also collect data on other variables that may have an influence on outcomes (*Table 1*), namely, baseline demographic, the Memory impairment screen,[31] Lawton and Brody questionnaire,[32] Charlson index,[33] and other clinical characteristics and the European HF Self-care Behaviour Scale score.[34] (Description of test on Supporting Information, *Appendix S1*)

Statistical analysis

The analyses will be performed on an intention-to-treat basis and by protocol, comparing the percentage of patients who reach specified levels of titration in the two groups.

Both Student's *t*-test (or the non-parametric Wilcoxon test if continuous data are not normally distributed) and the χ^2 test (or Fisher's exact test) will be used to compare baseline sociodemographic and clinical characteristics of patients in the two groups. Means with standard deviations and medians with interquartile ranges will be calculated for the relative doses of BBs, ACEIs, ARBs, and MRAs assessed at 4 months after starting titration.

Factors that may be predictive of relative dose levels will be identified. For this, associations of clinical and sociodemographic factors and the intervention group with relative doses values will be assessed using Student's *t*-tests/Wilcoxon tests (for continuous variables) and χ^2 tests (for categorical variables). All variables with a P value $<$0.20 will be included as explanatory variables in a multivariate model, with relative dose as the response variable. Generalized linear models will be used for this modelling.

Adverse events will be assessed 4 months after starting the titration. As for relative dose levels, explanatory variables that predict the occurrence of adverse events will be identified. Subsequently, logistic regression and Cox proportional hazard models will be developed. Again, all variables with a P value $<$0.20 will be included as explanatory variables, and in this case, adverse events will be the response variable.

To assess the discriminatory power of the models, the area under the receiver operating characteristic curve will be calculated. A value above 0.80 will be considered to indicate that a model has good discriminating power. All the statistical analyses will be performed in R v 3.0, with statistical significance set at $P < 0.05$.

Ethical considerations

The study has been approved by the Clinical Research Ethics Committee of the Basque Country (CREC Euskadi). We will request written informed consent from patients prior to their inclusion. Data will be processed to ensure that no information can be associated with identifiable individuals and stored on password-protected database (Organic Act 15/1999, 13-12, on Protection of Personal Data). The research conforms to the ethical standards of the Declaration of Helsinki, the Geneva Declaration, the Belmont Report, and Good Clinical Practices from the FDA, and the submission conforms to the International Committee of Medical Journal Editors: Uniform Requirements for Manuscripts Submitted to Biomedical Journals: writing and editing for biomedical publication (Haematologica 2005; 89:264).

Discussion

Despite the fact that dose titration by HF nurses is recommended in CPGs and is widespread in some countries, there is no strong evidence supporting this practice in the

Table 1 Variables and measurements ETIFIC project

	Baseline	4 months	6 months
Demographic variables: age, sex, socioeconomic variables: level of education	X		
Psychosocial variables in patients >70 years old:			
Cognitive assessment (Memory Impairment Screen score)	X		
Level of dependence (Lawton Instrumental Activities of Daily Living Scale score)	X		
Social support of a family member or caregiver	X		
Functional capacity: Ability to stand for 20 s on scales to weigh oneself	X		
6 min walk distance	X		X
Cardiovascular risk factors (history): high blood pressure, dyslipidaemia, smoking, alcohol consumption, diabetes, weight, height, body mass index (kg/m^2)	X		
Other clinical characteristics:			
Blood pressure, heart rate	X	X	
New York Heart Association class	X	X	X
Left ventricular ejection fraction	X		X
Ischaemic heart disease, history of ischaemic heart disease	X		
Pacemaker, cardiac resynchronization therapy device, automatic implantable defibrillator	X	X	X
First, second, third-degree AV block	X	X	
Atrial fibrillation/atrial flutter	X	X	
Charlson comorbidity index adjusted for age	X		X
Laboratory tests: urea, creatinine, glomerular filtration, Na, K, haemoglobin	X	X	
glycated haemoglobin (if diagnosed with diabetes mellitus)	X		
Nt-proBNP/BNP (on discharge/when back to dry weight)	X		X
European Heart Failure Self-care Behaviour Scale and flexible diuretic dosing regimen	X	X	
Primary outcome variable: relative dose of BBs	X	X	
Secondary outcome variables: relative dose of ACEIs, relative dose of ARBs, relative dose of MRAs	X	X	
Reason for not reaching 100% of target dose BBs, ACEIs/ARBs, MRAs		X	
Health-related quality of life: MWHFQ, EQ-5D	X		X
Number of consultations made		X	
Adverse events		X	
BB titration: worsening of HF signs and symptoms, heart rate <50 bpm, AV block, symptomatic hypotension	X	X X	
ACEI/ARB titration: symptomatic hypotension, worsening of renal function, hyperkalemia	X		
RMA titration: worsening of renal function, hyperkalemia	X		
Serious adverse events: need for drug withdrawal, readmissions, and death linked to dose adjustment (causes of admission and death will assessed).		X	
Number of readmissions for HF. Number of deaths			X
Worsening of renal function: creatinine >50% of baseline, or >3 mg/dL, or glomerular filtration rate <25 mL/min/1.73 m^2			
Hyperkalemia: moderate, K > 5.5 mmol/L, severe, K ≥ 6 mmol/L			

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; AV block, atrioventricular block; BB, beta blockers; EQ-5D, Euro-Qol EQ-5D questionnaire; HF, heart failure; K, potassium; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonists; Na, sodium; Nt-proBNP, N-terminal pro B-type natriuretic peptide.

literature. To our knowledge, this is the first multicentre randomized controlled trial designed to compare the efficacy and safety of dose titration by HF nurses with the gold standard, namely, direct management by the HF unit cardiologist. It is hoped that this research will fill the gap in the literature, providing high-quality evidence in relation to the recommendations in current CPGs.[3]

Although limited to a single country, the trial is to be carried out in nine health services under different management and in 20 public hospitals which differ in their organization of care for patients with HF, training, and experience. If the results of the trial are positive, this protocol may serve as a model in other countries where nurses are not yet involved in dose titration, or in countries with restrictive legislation governing nursing, and also to strengthen training for nurses, because it includes medical prescription of the titration schedule, supervision of checklists, a list of possible solutions for the most common problems, and the main criteria for referral.[3]

Limitations

Limitations of the study that should be recognized include the difficulty of recruiting new-onset patients with LVEF ≤40%, losses to follow-up, associated with patient age, difficulties attending appointments, and concurrent illnesses. On the other hand, a 20% margin has been added to the sample size estimated to be required to test the main hypotheses, and the participation of 20 hospitals in the study means that we are likely to achieve our target sample size. Given differences in training and clinical experience between professionals and across the hospitals participating, we will adjust for these variables in the multivariate analysis.

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Conflict of interest

None declared.

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Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Appendix S1. Description of test.

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