Study identification

Official Title: Safety and Effectiveness of Drug up Titration by Nurses Specialized in Heart Failure (HF) Patients.

ClinicalTrials.gov Identifier: *NCT02546856.*

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Study protocol

The protocol of the 2 randomised groups, is briefly summarized:

HF-cardiologist group (control): Usual care provided at a HF Unit was planned. A HF-cardiologist was responsible for prescription and titration, also based on European Society of Cardiology guidelines and addenda[1,2] and control nurse for clinical evaluation and self-care education, similar to the HF-nurse group with the exception of the titration process. The number of visits depended on each hospital's organization.

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

HF-nurse group (intervention): The protocol was based on the European Heart Failure (HF) Guidelines.[1,2] HF-nurse requirements were 400-hour HF training and at least 2 years of experience. HF-nurses worked in a team with a HF-cardiologist. Initial drug prescription and expected rate of titration was made by the cardiologist, while the titration process planning was made by HF-nurse. Weekly or biweekly face to face visits were planned, and biweekly drug up-titration, alternating different drugs, was considered. Clinical and analytical evaluation and patient education prior to each increase were required. Dose adjustment of just one drug at each visit, safety checklist review and routine supervision by cardiologist were established. The titration process was tailored to each individual. Cardiologist availability for consultation or visit and early care for decompensation were also established. (See Tables)

1.McMurray JJV, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012 Eur Heart J 2012; 33:1787–1847.

2. McMurray JJ, Adamopoulos S, Anker SD,Auricchio A, BöhmM, Dickstein K, Falk V,Filippatos G, Fonseca C, Gomez SanchezMA, Jaarsma T, Køber L, Lip GYH,Maggioni AP, Parkhomenko A, PieskeBM, Popescu BA, Rønnevik PK, RuttenFH, Schwitter J, Seferovic P, Stepinska J,Trindade PT, Voors AA, Zannad F, ZeiherA. ESC guidelines for the diagnosis andtreatment of acute and chronic heartfailure 2012: Addenda. Eur Heart J [online] 2012 1-8. www.escardio.org/guidelines-surveys/es-guidelines/GuidelinesDocuments/Guidelines-Heart-Failure web-tables.pdf (15 May 2013).

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

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.

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	**Cardiologist**: (A) Agree / (D) Disagree-concern. Measure proposed, Solution yes/no
Name and Surname(s) /patient number: **Date**:	
Are BBs indicated? NYHA II-IV and LVEF ≤ 40%. Yes/No	A
Are BBs contraindicated? Asthma, 2nd or 3rd-degree AV block (in the absence of permanent pacemaker) Yes to some/ No to all	A
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	A A
Prescription, dosing, rate of titration and observations noted in patient health record? Yes/No	A
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	

Checklist for FOLLOW-UP VISITS: INCREASES IN BBs (adapted from 2012 ESC guidelines [3])	
HF nurse (*) Number of increases: 1st, 2nd Dose increase	**Cardiologist (**):1st/2ndincrease:**
Name and Surname(s) /patient number: **Date**:	Agree A /Disagree-concern D, measure proposed. Solution? yes/no
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	

(*) 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**

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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**

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