Evaluation of the sST2-guided optimization of medical treatments of patients admitted for heart failure, to prevent readmission: Study protocol for a randomized controlled trial

Corentin Curinier, Kamila Solecki, Anne Dupuy, Cyril Breuker, Manuela Lotierzo, Laetitia Zerkowski, Eran Kalmanovich, Mariama Akodad, Jérôme Adda, Pascal Battistella, et al.

► To cite this version:

Corentin Curinier, Kamila Solecki, Anne Dupuy, Cyril Breuker, Manuela Lotierzo, et al.. Evaluation of the sST2-guided optimization of medical treatments of patients admitted for heart failure, to prevent readmission: Study protocol for a randomized controlled trial. Contemporary Clinical Trials, 2018, 66, pp.45 - 50. 10.1016/j.cct.2018.01.007 . hal-01786998

HAL Id: hal-01786998

<https://hal.umontpellier.fr/hal-01786998>

Submitted on 9 Jan 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Evaluation of the sST2-guided optimization of medical treatments of patients admitted for heart failure, to prevent readmission: Study protocol for a randomized controlled trial

Corentin Curinier^{a,*}, Kamila Solecki^a, Anne-Marie Dupuy^b, Cyril Breuker^{c,d,e,f}, Manuela Lotierzo^b, Laetitia Zerkowski^d, Eran Kalmanovich^a, Mariama Akodad^a, Jérôme Adda^a, Pascal Battistella^a, Audrey Castet-Nicolas^c, Nils Kuster^b, Sandra Marques^{a,b,c,d,e,f}, Sonia Soltani^a, Marine Chettouh^a, Anne Verchere^c, Claire Belloc^c, Camille Roubille^{d,f}, Pierre Fesler^{d,f}, Grégoire Mercier^e, Jean-Paul Cristol^{b,f}, Yohan Audurier^c, François Roubille^{a,f}

^a Cardiology Department, University Hospital of Montpellier, Montpellier, France

^b Department of Biochemistry, Centre Ressources Biologiques de Montpellier, University Hospital of Montpellier, Montpellier, France

^c Pharmacy Department, University Hospital of Montpellier, Montpellier, France

^d Internal Medicine and Hypertension Department, Lapeyronie Hospital, Montpellier University, Montpellier, France

^e Economic evaluation unit at Montpellier teaching hospital, University of Montpellier, Montpellier, France

^f PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, 34295 Montpellier, Cedex 5, France

1. Background

The prevalence of heart failure (HF) in France is about 1–2% [1,2]. Although mortality decreased in the past two decades, it remains high, still estimated about 30% after 2 years of evolution [3,4]. Patients suffering from HF are frequently readmitted within the first month [5–8], leading to a heavy burden, with a cost of 2 billions euros in France [9], mainly driven by hospitalization (63%). Presently, about 25% of patients are readmitted within the first month and up to 50% within the first year [3,4].

It appears crucial to prevent readmissions. Rehabilitation could be of particular interest to achieve this purpose [10]. Various approaches have been proposed including close post-discharge nurse follow-up [11–13] by a multidisciplinary team [14]. Telemonitoring is still a subject of debate [15,16].

The cornerstone of HF management remains the optimization of recommended medical treatment including the drugs which have proved to improve survival: beta-blockers [17,18], angiotensin converting enzyme inhibitors (ACE-inhibitors) [14] or angiotensin receptor blockers (ARBs) [19], mineralocorticoid inhibitors [20], ivabradine [21] and sacubitril-valsartan [22] for patients with reduced left ventricular ejection fraction (LVEF). One of the main concern regarding the medical treatments is the titration of drugs. The natriuretic peptides could help [23,24] although not recommended by the European Society of Cardiology (gap of evidence) (ESC) [4] or by the American Heart

Association (AHA) - American College of Cardiology (ACC) to this purpose [25,26], because of the absence of clear and consistent evidence for improvement in mortality and cardiovascular outcomes. Nevertheless, the natriuretic peptides reflect only one of the pathophysiological aspects, advocating for other biomarkers. The sST2 (the truncated soluble form of the protein encoded by the suppression of tumorigenicity 2 gene) is considered a promising candidate [27]. Briefly, this biomarker belongs to the Interleukine-1 receptor family. The transmembrane form (ST2L), is expressed on the cell membrane of cardiomyocytes and fibroblasts; the soluble form (sST2), is secreted by the endothelial cells. The interleukin-33 (IL-33) is the common ligand [28]. This pathway has been reported to prevent hypertrophy, fibrosis and apoptosis in physiological conditions. However, in pathophysiological conditions, the sST2 increases and prevents the normal action of IL33 on the ST2L.

As regards HF, sST2 may be a potent predictor for survival [29–33]. Felker et al. showed that in patients with stable HF, when sST2 > 35 ng/L, all-cause mortality at 3 years, cardiovascular mortality and hospitalization for HF are doubled [34]. It has been reported to be a better risk predictor than natriuretic peptides [35]. Importantly sST2 is not influenced by renal function [33], age or body mass index [36].

Furthermore, sST2 levels vary quickly after the admittance [37], and a variation > 15.5% between admittance and discharge has been reported to be correlated with a better survival [38].

Abbreviations: HF, heart failure; ACE-inhibitor, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; AHA/ACC, American College of Cardiology/American Heart Association; ESC, European Society of Cardiology; ST2, Suppression of tumorigenicity-2; sST2, soluble ST2; ST2L, ST2 ligand (transmembrane form); IL-33, interleukin-33; NT-proBNP, N-terminal pro B-type natriuretic peptide; BNP, B-type natriuretic peptide; V, Visits; LV, Left ventricular

* Corresponding author.

E-mail address: corentin.curinier@ch-perpignan.fr (C. Curinier).

Fig. 1. Schematic design of the trial.

In this trial, we aim at evaluating the sST2-guided therapy as a help for the physician to optimize the recommended treatments.

2. Methods

2.1. Design

2.1.1. Aim of the study

The main aim is to evaluate the interest of sST2-guided medical treatment optimization of patients admitted for HF, in order to prevent readmission.

2.1.2. Design and setting of the study: see Fig. 1

STADE-HF will be a monocentric prospective biomedical interventional randomized open-label superiority trial aiming at evaluating the two strategies with two parallel arms: conventional therapy versus sST2-guided therapy. It will be carried out in the University Hospital of Montpellier. Owing to the type of intervention, blinding of investigators is not possible. However, the patients will be blinded to the intervention arm.

2.2. Characteristics of participants

The study will include adults (men and women), hospitalized for acute HF. The diagnosis of acute HF will be made according to the recommendations of the ESC [4], by searching typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) corroborated by high NT-proBNP ≥ 450 pg/ml, or by the necessity to administer diuretics without taking into account the level of LVEF. The patients are hospitalized either in cardiology or in internal medicine department.

Main exclusion criteria are cardiogenic shock, life-threatening conditions (< 7 days), previously ongoing clinical trial.

2.3. Intervention (see Fig. 2)

2.3.1. Two groups randomization

Informed consent form is obtained for each patient enrolled in the study. They are randomly assigned to one of the two following groups:

- Conventional treatment: sST2 is not known by the clinician

He manages the HF patients according to international guidelines especially the recent ESC guidelines [4], recommending to optimize treatments with maximum tolerated doses of every class of drugs as long as possible.

Fig. 2. Schematic protocol for adaptation of the treatment following the sST2 (available or not and depending on the level).

- sST2-guided therapy: sST2 assessed on day 4 is known by the clinician who adjusts HF treatment based on sST2 level (see Figs. 1 and 2)

We will use centralized stratified web-based randomization method. A computer program will generate randomization sequences with varying block sizes unknown to the investigators. A web-based randomization system will implement the randomization stratified on sex, age and glomerular filtration rate (below 30, between 30 and 60, and above 60 ml/min). The investigators will access to the website using a personal information number. The patients will be individually and randomly assigned to the two groups with a 1:1 ratio.

The intervention is 1) the assessment of sST2 and 2) the adaptation of the treatment taking into account the sST2 result.

The laboratory samples from the patients included in the study will be aliquoted and stored at -80°C . The collection will be declared and centralized in the laboratory of Biochemistry of the University Hospital of Montpellier. Blood tests performed on the day of inclusion will be in accordance with the European guidelines on heart failure: hemogram, ionogram, urea, creatinine, iron status and hepatic workup. These tests will be repeated during hospitalization according to clinical needs.

Venous blood will be collected in dry and EDTA tubes and immediately centrifuged (the samples are transported in a mean total delay of < 3 h (all inclusive until frozen).

NT-proBNP levels will be determined from serum by immuno-electrochemiluminescence assay on the Cobas8000/e602[®] immunochemistry system (Roche Diagnostics, Meylan, France).

EDTA plasma will be used for quantitative determination of sST2 with ASPECT-PLUS[®] ST2 test on ASPECT Reader[®] instrument from Critical Diagnostics (San Diego, California distributed in France by Eurobio society). sST2 plasma concentrations will be measured with a

high sensitivity sandwich monoclonal lateral flow immunoassay. Plasma (35 µl) is loaded into the sample well where it flows through the anti ST2 antibody coated strip. Assay buffer is added to the second well (two drops). The cassette is then inserted into the ASPECT Reader for incubation, and ST2 concentration (ng/ml) is determined and reported by the reader within 20 min. Analytic measuring range goes up to 250 ng/ml and the limit of detection claimed by the manufacturer is < 12.5 ng/ml. Total CV for clinical ST2 level (32 ng/ml) was 14,2% as reported by the manufacturer. All other biochemistry parameters as urea, creatinine, sodium, iron and hepatic enzymes will be performed on Cobas 8000/c701® and ISE (Roche, Meylan, France).

sST2 and NT-pro-BNP were performed for all patients on the admission and/or inclusion day as well as on day four, discharge and one month consultation day. However, ST2 result on day 4 will be disclosed to clinicians exclusively for the ST2 group patients. Other sST2 values during the rest of the study will be disclosed to clinicians in both groups?.

2.3.2. Therapeutic adaptation according to the randomization group and ST2 results

In our previous study [29], the median sST2 value of our 180 patients with stable heart failure was 37 ng/ml. In the STADE HF study, this threshold value will allow us to discriminate two groups of patients, with the hypothesis that a sST2 value > 37 ng/ml would reflect an increased activity of pathophysiological processes involved in heart failure.

Therefore, for patients in the sST2 group, sST2 result on day 4 will be available to the clinician. If below 37 ng/ml, the clinician will take care of the patient according to his or her habits, in accordance with ESC guidelines on heart failure. On the contrary, if the sST2 result is above 37 ng/ml, the clinician should try to adapt the treatments of HF at best. A therapeutic optimization help sheet will be provided to the clinician. For each patient with sST2 result > 37 ng/ml, the clinician should specify 1) whether the various therapeutic classes of heart failure are indicated or not 2) the therapeutic adaptation (initiation or withdrawal of the drug, increase or decrease of the dosage). For this group of patients with high sST2 and therefore probably more active cardiomyopathy, the clinician should be as aggressive as possible in therapeutic titration, considering heart rate (for beta-blockers and i(f) current inhibitors), blood pressure (for ACE-inhibitors, ARBs, Nephilysin inhibitors and beta blockers), serum potassium and renal function (for Aldosterone receptor antagonists and Nephilysin inhibitors). The discussion between clinicians and pharmacists could be very interesting to achieve a treatment as personalized and complete as possible (Table 1).

For patients in conventional treatment group, management follows the usual way, according to ESC recommendations [4] and without knowing ST2 result. A medication reconciliation process is proposed to all patients (conventional treatment and sST2-guided therapy), at both admission and discharge day. Medication reconciliation is the process of comparing order of all medications the patient has been taking and should take at admission, transfer and discharge of hospitalization. During medication reconciliation process, the Best Possible Medication History, defined as the most comprehensive list of all medications taken by the patient including prescription and over the counter medication will be performed and recorded in medical record [39].

2.4. Follow up

The patients are evaluated by a physician (either a cardiologist or an internist): on admission – Visit (V) 1, on day 4 (V2), on discharge (V3) and on one month after discharge (V4). Cardiology consultation department phone number will be given to all patients. Cardiologist will provide consultation before one month whenever necessary.

In each department, clinical pharmacists will help for inclusion,

drug management and evaluation of patients. Treatments before admission, during hospitalization (day 4) and at discharge will be registered by medication reconciliation process.

At V 1 (Day 0), 2 (Day 4), 3 (Day of discharge) and 4 (one month after discharge) a physical examination, medication history, electrocardiogram (ECG), blood examination are performed.

At V 1 (Day 0) +/– V 4 (one month after discharge): Echocardiography is performed.

At 1 year, the evaluation is performed either during a routine visit, or by phone.

For a schematic presentation of the following, please see Figs. 1 and 2.

3. Subject discontinuation

Subjects may withdraw from the study at any time upon request, at the discretion of the investigator for safety or behavioral reasons, or due to the inability of the subject to comply with the required schedule of visits or procedures. Subjects withdrawn from the study are subsequently managed according to conventional practice. Every effort will be made to ensure follow-up for outcomes relevant to the trial objectives.

3.1. Outcomes

Clinical outcomes are assessed by investigators to determine whether a protocol-specified outcome had occurred. The main clinical outcome is all-cause readmission within one month of discharge.

The secondary endpoints are:

- Heart failure-specific readmission rate at 1 month;
- Length of stay;
- Natriuretic peptides use;
- Total inpatient cost at 1 month;
- Biochemistry-related cost at 3 month.

3.2. Sample size

Regarding patients admitted for HF, the readmission rate at day 30 is about 25% in France [7], corresponding to approximately 2 million people in our region [40]. To our knowledge, there is no study available in the literature allowing specifically the estimation of the decrease of hospitalization due to a biomarker-guided strategy. Hence the hypothesis is based on results of studies assessing the effect of other interventions having a strong organizational component, such as transitional care interventions [41]. Based on the hypothesis of a 50% reduction of readmissions (rate of 12.5% versus 25%), with a type I error of 5% and a power (1-β) of 80%, the number of patients needed to include is of 136 per group. Taking into account the intermediary analyses and the loss to follow-up, 150 subjects per group will be included, making a total of 300.

3.3. Statistical analysis

The initial comparability of the two arms will be assessed by describing all characteristics at inclusion. The comparison of the two arms will be performed on the intention-to-treat population, i.e. all randomized patients will be included in the analysis in the arm they have been assigned to regardless of the intervention they have actually received. If important protocol deviations occur, a per-protocol analysis might be considered. In such case, the results of the per-protocol analysis will be compared with those of the intention-to-treat analysis. Regarding the primary analysis, the null-hypothesis of equal rates of 30-day all-cause readmission will be tested using logistic regression. All comparisons will be adjusted on the stratification variables (i.e. sex, age and glomerular filtration rate). The secondary outcomes will be

Table 1
Addendum for therapeutic optimization according with the guidelines.

Therapeutic class	Therapeutic class indicated ? (Column to be filled if LVEF <35 %)	Prescribed ?	Modification ?
Beta blocker	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
ACE-inhibitor	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
ARBs	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
Aldosterone Receptor Antagonists	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
Neprilysin inhibitor	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
Loop diuretics	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
I(f) current inhibition	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase
Digitalis glycosides	☐ Yes ☐ No	☐ Yes ☐ No	☐ Decrease ☐ Stop ☐ Introduction ☐ Increase

described using the measures of the empirical distributions. Qualitative outcomes will be compared using chi-square or Fisher test according to the sample sizes. Quantitative ones will be compared using Student or Wilcoxon-Mann-Withney test according to the observed distribution. *P*-values of the corresponding statistical tests comparing the intervention groups and associated 95% confidence intervals will be given.

Two interim analyses will be performed after availability of the results for the primary outcome (30-day readmission) for 100 and 200 randomized patients. The overall type I error rate will be controlled using the Haybittle-Peto method as follows:

- Overall two-sided type I error rate: 0.05
- Boundary for the two-sided *p*-value for accepting the null-hypothesis in the first interim analysis: 0.001
- Boundary for the two-sided *p*-value for accepting the null-hypothesis in the second interim analysis: 0.001
- Boundary for the two-sided *p*-value for accepting the null-hypothesis in the final analysis: 0.048.

We chose the Haybittle-Peto method because the same threshold is used at all interim analyses and because the final analysis is performed using a threshold very close to 0.05, which make it easier to read and understand. We chose to perform > 1 interim analysis because of the high uncertainty around our primary hypothesis, and < 3 because we believe it will be very unlikely to see any difference with < 100 patients.

The results of the interim analyses will be presented to the Data Safety and Monitoring Board who will advise the Steering Committee to either stop or continue the trial.

If the null hypothesis of superiority of ST2 on the readmission rate is

not rejected, our main conclusion will be that there is no significant difference between the two interventions. The remaining analysis of the secondary outcomes will then be exploratory.

3.4. Funding

No funding to declare for this trial. Eurobio will provide half of the assays for sST2 measurements. The Montpellier University Hospital will provide the costs for promotion and the department of cardiology will support all other costs.

3.5. Ethical considerations

The protocol of this trial was approved by the French institutional review board (Comité de Protection des Personnes de Montpellier, France) on September 21, 2016 (Reference number: 2016-A01148-43). The trial protocol was registered to ClinTrials (NCT02963272) on October 31, 2016.

All patients enrolled in the study will have signed informed consent.

4. Discussion

Many strategies have been proposed to prevent readmission in patients with HF, including the intervention of clinical pharmacists [42], a better network plan [11], a multidisciplinary follow-up [12,43], and telemedicine [44].

The main aim of STADE-HF trial is to evaluate the interest of sST2 biomarker to guide the management of patients admitted for HF, in order to reduce the rate of readmission. Other secondary endpoints will provide hypotheses-generating results. More precisely, sST2 biomarker

has been shown to predict remodeling [45], and therefore could reflect to some extent the activity of the HF process. Indeed, HF could be the result of various pathophysiological pathways, on which treatments could be more or less effective depending on the prominent one. Briefly, the higher the sST2, more likely is the impact of drugs with putative antiremodeling impact, such as mineralocorticoid receptors antagonists in patients admitted for myocardial infarction and presenting LV remodeling [46,47], or beta-blockers in patients with HF [37].

Guidelines are mainly based on general recommendations, without specific consideration of genetic background, renal or hepatic function, or other comorbidities. This systematic approach lacks customization, and could probably explain some negative results, as distinct backgrounds or pathophysiological pathways could overlap, leading to biased results.

A large amount of data emphasizes the interest of natriuretic peptides for the follow-up and eventually the adaptation of HF patients treatment, especially to regulate fluid overload [48]. Nevertheless, there are only few data on adaptation of chronic treatments. Importantly, in our preliminary study [29], sST2 provided additional information to NT-proBNP, suggesting that it should be able to integrate the information value (but independently for age, body mass index or renal function) and should then appear as a candidate to replace and not be added.

The main originality of our approach is to adapt the use of recommended drugs not on the base of a systematic approach, but considering the disease itself, and by the pathophysiological aspects (HF with a high potential fibrotic activity or not). The first days of hospitalization for acute heart failure are generally marked by the predominance of congestive signs, requiring significant depletion with the use of intravenous diuretics. After a few days, the patient generally reaches a period of relative stability, allowing sST2 measurement and the adaptation of recommended drugs.

This personalized management appears more appealing from a pathophysiological point-of-view. To our knowledge, this is the first time that this kind of approach is evaluated in HF patients.

5. Limits

- 1) The trial will include only few patients in one cardiological and internal medicine center.
- 2) We chose to provide only few results for sST2 and we cannot be sure that other results could provide better information.
- 3) Optimization of the treatment of HF. In a real-life trial, we aimed at urging the physicians in charge to implement the guidelines. It well-established that about 60–70% of the patients do not receive recommended drugs in the real-life cohorts, for various reasons. In our study, in the intensive-managed arm, a specific flowchart had to be filled by experienced senior physicians to explain why the recommended drug is not prescribed and to optimize treatments. We will report the percentages of modifications, but this could be a bias, as individual behaviors are likely.
- 4) The design relies on the potent capacity of currently used medications to prevent the remodeling and even reverse the fibrotic process, which remains highly hypothetical.
- 5) The sST2 threshold is a bit arbitrary and is better established in chronic patients. This pilot study will provide important data to better design a larger multicentric prospective trial.

6. Trial status

Until now, no patient has been included in the trial. All the legal authorizations have been obtained in 2016.

Ethics approval and consent to participate

Comité de Protection des Personnes, Montpellier, France:

registration number: N° ID-RCB: 2016-A01148-43, on 21 September 2016.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Half of the reagents necessary for the ST2 assay will be offered by the Eurobio France laboratory.

Authors' contributions

CC participated in the design of the study, will recruit patients and participate in the therapeutic optimization, and wrote the article.

KS participated in the design of the study, will recruit patients and participate in the therapeutic optimization, and wrote the article.

CB will participate in the therapeutic optimization and in medication reconciliation process, and wrote the article.

EK will recruit patients and participate in the therapeutic optimization.

MA will recruit patients and participate in the therapeutic optimization.

JA will recruit patients and participate in the therapeutic optimization.

PB will recruit patients and participate in the therapeutic optimization.

CAN will participate in the therapeutic optimization and in medication reconciliation process, and wrote the article.

NK will analyze the data.

SM participated in the design of the study, will recruit patients.

SS participated in the design of the study, will recruit patients.

MC participated in the design of the study, will recruit patients.

AV will analyze the data.

CB participated in the design of the study and the establishment of the eCRF.

CR will recruit patients and participate in the therapeutic optimization, and wrote the article.

PF will recruit patients and participate in the therapeutic optimization.

GM participated in the design of the study and will analyze the data.

JPC participated in the design of the study, will perform the dosages and wrote the article.

YA will participate in the therapeutic optimization and in medication reconciliation process, and wrote the article.

FR participated in the design of the study, will recruit patients participate in the therapeutic optimization and wrote the article.

All authors read and approved the final manuscript

Acknowledgements

Reagents used in this study as ST2 were provided by Eurobio France. We thank the “CHU de Montpellier, Centre des Ressources Biologiques, Collection Liquides biologiques, Hôpital Lapeyronie, F-34295, Montpellier, France”.

References

[1] A. Mosterd, A.W. Hoes, Clinical epidemiology of heart failure, *Heart* 93 (9) (2007 Sep 1) 1137–1146.

[2] C. de Peretti, C. Pérel, P. Tuppin, M.C. Iliou, Prevalence and functional status of coronary heart diseases and heart failure in the adult population in France: contribution of the “disabilities and health” cross-sectional surveys, *Bull. épidémiologique hebdomadaire*. 13 (2013 Dec).

[3] E.M. Antman, J. Bax, R.A. Chazal, M.A. Creager, G. Filippatos, J.L. Halperin, et al., Updated clinical practice guidelines on heart failure: an international alignment, *J. Am. Coll. Cardiol.* 68 (13) (2016 Sep 27) 1474–1475.

[4] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, Cleland JGF, Coats AJS, et al., ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, *Eur. Heart J.* 37 (27) (2016) 2129–2200.

[5] M. Gheorghiade, W.T. Abraham, N.M. Albert, B.H. Greenberg, C.M. O’connor, L. She, et al., Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure, *JAMA* 296 (18) (2006 Nov 8) 2217–2226.

[6] J. Chen, S.-L.T. Normand, Y. Wang, H.M. Krumholz, National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998–2008, *JAMA* 306 (15) (2011 Oct 19) 1669–1678.

[7] A. Gabet, Y. Juilliére, A. Lamarche-Vadel, M. Vernay, V. Olié, National trends in rate of patients hospitalized for heart failure and heart failure mortality in France, 2000–2012, *Eur. J. Heart Fail.* 17 (6) (2015 Jun 1) 583–590.

[8] C. Pérel, F. Chin, P. Tuppin, Taux de patients hospitalisés pour insuffisance cardiaque en 2008 et évolutions en 2002–2008, *Bulletin épidémiologique hebdomadaire* 41 (2012 Jan 10) 466.

[9] J. Merlière, C. Couvreur, L. Smadja, A. Jolivet, Caractéristiques et trajet de soins des insuffisants cardiaques du Régime général. point de repère. n°38, (2012 Aug 1).

[10] P.A. Ades, S.J. Keteyian, G.J. Balady, N. Houston-Miller, D.W. Kitzman, D.M. Mancini, et al., Cardiac rehabilitation exercise and self-care for chronic heart failure, *JACC Heart Fail.* 1 (6) (2013 Dec 1) 540–547.

[11] E. Lambrinou, F. Kalogirou, D. Lamnisos, P. Sourtzi, Effectiveness of heart failure management programmes with nurse-led discharge planning in reducing re-admissions: a systematic review and meta-analysis, *Int. J. Nurs. Stud.* 49 (5) (2012 May) 610–624.

[12] D.S.F. Yu, D.R. Thompson, D.T.F. Lee, Disease management programmes for older people with heart failure: crucial characteristics which improve post-discharge outcomes, *Eur. Heart J.* 27 (5) (2006 Mar) 596–612.

[13] S. Stewart, M.J. Carrington, T.H. Marwick, P.M. Davidson, P. Macdonald, J.D. Horowitz, et al., Impact of home versus clinic-based management of chronic heart failure: the WHICH? (Which heart failure intervention is most cost-effective & consumer friendly in reducing hospital care) multicenter, Randomized Trial, *J. Am. Coll. Cardiol.* 60 (14) (2012 Oct 2) 1239–1248.

[14] K. Swedberg, J. Kjekshus, Effects of enalapril on mortality in severe congestive heart failure: results of the cooperative north Scandinavian Enalapril Survival Study (CONSENSUS), *Am. J. Cardiol.* 62 (2) (1988 Jan 1) 60A–66A.

[15] S.C. Inglis, R.A. Clark, R. Dierckx, D. Prieto-Merino, J.G.F. Cleland, Structured telephone support or non-invasive telemonitoring for patients with heart failure, *Cochrane Database Syst. Rev.* 10 (2015 Oct 31) CD007228.

[16] A. Pandor, P. Thokala, T. Gomersall, H. Baalbaki, J.W. Stevens, J. Wang, et al., Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation, *Health Technol. Assess Winch Engl.* 17 (32) (2013 Aug) 1–207 (v–vi).

[17] A. Hjalmarson, S. Goldstein, B. Fagerberg, H. Wedel, F. Waagstein, J. Kjekshus, et al., Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group, *JAMA* 283 (10) (2000 Mar 8) 1295–1302.

[18] M. Packer, A.J. Coats, M.B. Fowler, H.A. Katus, H. Krum, P. Mohacs, et al., Effect of carvedilol on survival in severe chronic heart failure, *N. Engl. J. Med.* 344 (22) (2001 May 31) 1651–1658.

[19] C.B. Granger, J.J.V. McMurray, S. Yusuf, P. Held, E.L. Michelson, B. Olofsson, et al., Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-alternative trial, *Lancet Lond. Engl.* 362 (9386) (2003 Sep 6) 772–776.

[20] B. Pitt, F. Zannad, W.J. Remme, R. Cody, A. Castaigne, A. Perez, et al., The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators, *N. Engl. J. Med.* 341 (10) (1999 Sep 2) 709–717.

[21] K. Swedberg, M. Komajda, M. Böhm, J.S. Borer, I. Ford, A. Dubost-Brama, et al., Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study, *Lancet Lond. Engl.* 376 (9744) (2010 Sep 11) 875–885.

[22] J.J.V. McMurray, M. Packer, A.S. Desai, J. Gong, M.P. Lefkowitz, A.R. Rizkala, et al., Angiotensin-neprilysin inhibition versus enalapril in heart failure, *N. Engl. J. Med.* 371 (11) (2014 Sep 11) 993–1004.

[23] R.W. Troughton, C.M. Frampton, H.-P. Brunner-La Rocca, M. Pfisterer, L.W.M. Eurlings, H. Erntell, et al., Effect of B-type natriuretic peptide-guided treatment of chronic heart failure on total mortality and hospitalization: an individual patient meta-analysis, *Eur. Heart J.* 35 (23) (2014 Jun 14) 1559–1567.

[24] P. Jourdain, G. Jondeau, F. Funck, P. Gueffet, A. Le Hellico, E. Donal, et al., Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study, *J. Am. Coll. Cardiol.* 49 (16) (2007 Apr 24) 1733–1739.

[25] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey, M.H. Drazner, et al., ACCF/AHA guideline for the management of heart failure, *Circulation* 128 (16) (2013) e240–327.

[26] C.W. Yancy, M. Jessup, B. Bozkurt, J. Butler, D.E. Casey, M.M. Colvin, et al., ACCF/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the management of heart failure: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America, *Circulation* 136 (6) (2017) e137–e161 (CIR.0000000000000509).

[27] B. Dieplinger, T. Mueller, Soluble ST2 in heart failure, *Clin. Chim. Acta* 443 (2015 Mar 30) 57–70.

[28] D.A. Pascual-Figal, J.L. Januzzi, The biology of ST2: the international ST2 consensus panel, *Am. J. Cardiol.* 21157 (Suppl3B-7B) (2015 Apr) (2015 Apr 2).

[29] A.M. Dupuy, C. Curinier, N. Kuster, F. Huet, F. Leclercq, J.M. Davy, et al., Multi-marker strategy in heart failure: combination of ST2 and CRP predicts poor outcome, *PLoS One* 11 (6) (2016) e0157159.

[30] D.A. Pascual-Figal, J. Ordoñez-Llanos, P.L. Tornel, R. Vázquez, T. Puig, M. Valdés, et al., Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction, *J. Am. Coll. Cardiol.* 54 (23) (2009 Dec 1) 2174–2179.

[31] E.O. Weinberg, M. Shimp, S. Hurwitz, S. Tominaga, J.-L. Rouleau, R.T. Lee, Identification of serum soluble ST2 receptor as a novel heart failure biomarker, *Circulation* 107 (5) (2003 Feb 11) 721–726.

[32] J.L. Januzzi, W.F. Peacock, A.S. Maisel, C.U. Chae, R.L. Jesse, A.L. Baggish, et al., Measurement of the interleukin family member ST2 in patients with acute dyspnea: results from the PRIDE (pro-brain natriuretic peptide investigation of dyspnea in the emergency department) study, *J. Am. Coll. Cardiol.* 50 (7) (2007 Aug 14) 607–613.

[33] A. Bayes-Genis, Y. Zhang, B. Ky, ST2 and patient prognosis in chronic heart failure, *Am. J. Cardiol.* 115 (7 Suppl) (2015 Apr 2) (64B–9B).

[34] G.M. Felker, M. Fiuzat, V. Thompson, L.K. Shaw, M.L. Neely, K.F. Adams, et al., Soluble ST2 in ambulatory patients with heart failure: association with functional capacity and long-term outcomes, *Circ. Heart Fail.* 6 (6) (2013 Nov) 1172–1179.

[35] J. Lassus, E. Gayat, C. Mueller, W.F. Peacock, J. Spinar, V.-P. Harjola, et al., Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: the Multinational Observational Cohort on Acute Heart Failure (MOCA) study, *Int. J. Cardiol.* 168 (3) (2013 Oct 3) 2186–2194.

[36] S.U. Rehman, T. Mueller, J.L. Januzzi Jr., Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure, *J. Am. Coll. Cardiol.* 52 (18) (2008 Oct 28) 1458–1465.

[37] S. Manzano-Fernández, J.L. Januzzi, F.J. Pastor-Pérez, J.C. Bonaque-González, M. Boronat-García, D.A. Pascual-Figal, et al., Serial monitoring of soluble interleukin family member ST2 in patients with acutely decompensated heart failure, *Cardiology* 122 (3) (2012 Jul 24) 158–166.

[38] S. Boissot, J. Beede, S. Isakson, A. Chiu, P. Clopton, J. Januzzi, et al., Serial sampling of ST2 predicts 90-day mortality following destabilized heart failure, *J. Card. Fail.* 14 (9) (2008 Nov) 732–738.

[39] C. Breuker, O. Abraham, L. di Trapanie, T. Mura, V. Macioce, C. Boegner, et al., Patients with diabetes are at high risk of serious medication errors at hospital: interest of clinical pharmacist intervention to improve healthcare, *Eur. J. Intern. Med.* 38 (2016 Dec 19) 38–45.

[40] C.M. Duflos, K. Solecki, L. Papinaud, V. Georgescu, F. Roubille, G. Mercier, The intensity of primary care for Heart Failure Patients: a determinant of readmissions? The CarPaths study: a French region-wide analysis, *PLoS One* 11 (10) (2016) e0163268.

[41] C. Feltner, C.D. Jones, C.W. Cené, Z.-J. Zheng, C.A. Sueta, E.J.L. Coker-Schwimmer, et al., Transitional care interventions to prevent readmissions for persons with heart failure: a systematic review and meta-analysis, *Ann. Intern. Med.* 160 (11) (2014 Jun 3) 774–784.

[42] S.L. Koshman, T.L. Charrois, S.H. Simpson, McAlister FA, R.T. Tsuyuki, Pharmacist care of patients with heart failure: a systematic review of randomized trials, *Arch. Intern. Med.* 168 (7) (2008 Apr 14) 687–694.

[43] A. Takeda, S.J.C. Taylor, R.S. Taylor, F. Khan, H. Krum, M. Underwood, Clinical service organisation for heart failure, *Cochrane Database Syst. Rev.* 9 (2012 Sep 12) CD002752.

[44] G. Hindricks, N. Varma, Remote monitoring and heart failure: monitoring parameters, technology, and workflow, *Eur. Heart J.* 37 (41) (2016 Nov 1) 3164–3166.

[45] H.K. Gaggin, J. Szymonifka, A. Bhardwaj, A. Belcher, B. De Berardinis, S. Motiwala, et al., Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure, *JACC Heart Fail.* 2 (1) (2014 Feb) 65–72.

[46] Weir RAP, A.M. Miller, Murphy GEJ, S. Clements, T. Steedman, Connell JMC, et al., Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodeling after acute myocardial infarction, *J. Am. Coll. Cardiol.* 55 (3) (2010 Jan 19) 243–250.

[47] H.K. Gaggin, S. Motiwala, A. Bhardwaj, K.A. Parks, J.L. Januzzi, Soluble concentrations of the interleukin receptor family member ST2 and β -blocker therapy in chronic heart failure, *Circ. Heart Fail.* 6 (6) (2013 Nov) 1206–1213.

[48] R. Berger, D. Moertl, S. Peter, R. Ahmadi, M. Huelsmann, S. Yamuti, et al., N-terminal pro-B-type natriuretic peptide-guided, intensive patient management in addition to multidisciplinary care in chronic heart failure a 3-arm, prospective, randomized pilot study, *J. Am. Coll. Cardiol.* 55 (7) (2010 Feb 16) 645–653.