Sequencing and titrating approach of therapy in heart failure with reduced ejection fraction following the 2021 European Society of Cardiology guidelines: an international cardiology survey

Sequencing and Titrating Approach of Therapy in Heart Failure with Reduced Ejection Fraction Following the 2021 ESC guidelines: an International Cardiology Survey.

Charles Fauvel, MD[1,2]; (….) Nathan Mewton MD PhD[21]

1. *Cardiovascular medicine department, Wexner Medical Center, The Ohio State University, Columbus, Ohio*
2. *Cardiology Department, Rouen University Hospital, France*
3. *Xxx*
4. *xxx*
5. *Ziekenhuis Oost-Limburg A.V., Genk, Belgium*
6. *Hasselt University, Diepenbeek/Hasselt, Belgium*
7. *Xxx*
8. *Xxx*
9. *Xx*
10. *Città della Salute e della Scienza di Torino, Hospital Department of Medical Sciences, University of Turin, Italy*
11. *Heart Failure Department and Clinical Investigation Center Inserm 1407, Louis Pradel Cardiovascular Hospital, Hospices Civils de Lyon, Claude Bernard University Lyon 1, France.*

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Corresponding author:

Pr Nathan Mewton, MD PhD

Heart Failure Department, Clinical Investigation Center

Inserm 1407 & CarMeN 1060

Hospices Civils de Lyon, Université Claude Bernard Lyon 1

Tel: +33 472 35 71 70

Mail: nathan.mewton@chu-lyon.fr

Twitter handle: @mewton_nathan

INTRODUCTION

Four major therapeutic classes of drugs have shown to reduce morbidity and mortality in patients with heart failure and reduced ejection fraction (HFrEF): renin-angiotensin system blockers (i.e., angiotensin-converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB]) or angiotensin-receptor neprilysin inhibitor (ARNi), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i). (1)

A major change of the 2021 Heart Failure (HF) European Society of Cardiology (ESC) guidelines was that each of the four aforementioned therapeutic classes should be prescribed to all patients with HFrEF regardless of any notion of efficiency hierarchy during an arbitrary 4-weeks timeline for titration. (1) This was in contrast with all previous ESC guidelines, where it was recommended to start with a combination of BB and ACEi/ARB followed by an up-titration to the maximally tolerated dose before starting MRA if a patient with a left ventricular ejection fraction (LVEF) below than 35% remained symptomatic. (2) These guidelines were mostly based on a "historical approach" that followed the order of results from randomized controlled trials published over the last 30 years.

However, in recent years, SGLT2i has emerged as a major drug class to reduce morbidity and mortality in HFrEF patients (3). With four major classes to introduce, several questions concerning the sequencing, titration, and optimal timing of all these drugs remain unanswered. Several international heart failure experts have recently proposed different sequencing and titrating approaches according to their expertise (4,5) or statistical modeling of major heart failure randomized trials (6). However, there are no evidence-based randomized clinical trial data to support either simultaneous initiation of low-doses of quadruple therapy versus sequential use of these four classes in HFrEF patients. There are

1 also no data on the perception and/or implementation of these new guidelines in the general
2 cardiology community. Our main objective was to get the opinion of the most popular
3 sequencing approach among the general cardiology community through the collection of
4 answers from a broad range of cardiologists. We designed an international web-based survey
5 asking about views and experience with sequencing, titrating and opinions on HF drugs one
6 year after the publication of the 2021 ESC Heart Failure guidelines.

METHODS

Set up and validation of the survey

This survey was an investigator-initiated survey initially designed and drafted in English within the heart failure working group of the French Society of Cardiology which is closely affiliated with the Heart Failure Association (HFA) of the ESC. The survey was conceived, optimized, revised, and approved by several groups of cardiologists: board members of the Heart Failure group from the French Society of Cardiology, the Young Cardiologist Community from the French Society of Cardiology, alumni of the Zürich Post-Graduate Course in Heart Failure task and task force members from the European Society of Cardiology Academy.

N.M. made the final editing of the survey and implemented it on SurveyMonkey.com (Momentive, Waterford, NY, USA). The survey material compromised of 24 individual questions is available in the supplementary appendix of this manuscript.

There were no conflicts of interest to declare upon drafting and implementing this survey. No industry or organizational support was involved at any moment in this process.

Distribution of the survey

After validation, the survey was published on the SurveyMonkey platform and shared via mail to the mailing list of the French Heart Failure and Cardiomyopathy group and the French Young Cardiologist in Training group of the French Society of Cardiology. The survey was also sent to the mailing lists of the ESC Academy and the Zurich Postgraduate Course in Heart Failure network and several members of the Heart Failure Association board. The link for the survey was posted on several social networks.

The survey was available for one month (from the 15th of March to the 16th of April 2022) on the web platform. Three successive invitations were sent to all networks within this time frame.

Statistical Analysis

Categorical variables are expressed as percentages (%) while continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) when appropriate. For multigroup comparison, analysis of variance (ANOVA) was used in the case of continuous variables whereas the chi-square test was used in the case of categorical variables. For intergroup comparison, categorical variables were compared with the chi-square test or Fisher's exact test when appropriate, whereas the Student t-test or Mann-Whitney/Wilcoxon test was used for continuous variables after having evaluated the type of the distribution using the Shapiro-Wilk test.

The following four prespecified subgroup analyses were systematically performed: gender (i.e., male versus female), age (≤ 30 years old, between 30 and 50 years old, and ≥ 50 years old), HF self-declared specialist versus non-specialists, non-graduated (i.e, a medical student or trainee) versus graduated (i.e., medical doctor). Statistical analysis was performed with R (*R Project for Statistical Computing, Vienna, Austria, version 4.0.2*), using bilateral tests with $p<0.05$ considered statistically significant.

RESULTS

Main characteristics of participants

Six hundred and fifteen cardiologists from 55 different countries completed the survey between March 15th and April 16th, 2022. The median time spent to fill this survey was 5'57'' minutes. Among the participants who completed the survey, >95% answered all the questions. The characteristics of the participants are presented in **Table 1**. Participants were 38 [32, 47] years old, majority were males (n=389, 63%), mainly from Europe (n=433, 71%). The largest group of participants were practicing in an university hospital (n=358, 58%). The proportion of HF specialists was 27% (n=167) and 26% (n=159) of participants had attended at least one ESC Heart Academy course.

LVEF threshold to define HFrEF

For most participants (n=371, 61%), a LVEF ≤ 40% was the accepted threshold to define HFrEF and start medical therapy and 11% more considered a threshold of ≤35%. Only 15% accepted a threshold ≤50% and 2.6% a LVEF threshold ≤60% (**Figure 1**). In the subgroup analysis, three-quarters of the HF specialists accepted the LVEF ≤ 40% as a cut-off to define HFrEF versus only 56% among non-HF specialists (p=0.002). Among physicians aged ≥ 50 years, only 52% chose the thresholds of 40% to define HFrEF (p=0.01) whereas there were no significant differences in accepting LVEF ≤ 40% as HFrEF between genders or between medical or trainees versus fully qualified doctors.

In a naïve HFrEF treatment patient: ARNi or ACEi/ARBs first?

More than half of the participants (n=327, 53%) would initiate medical HFrEF therapy with an ARNi instead of ACEi/ARBs. This result was consistent across all subgroups (**Figure 2**) except for students/trainees and physicians aged ≤ 30 years, where the majority would start with an ACEI/ARB (59% and 51%, respectively).

Is titration more important than adding another HF drug class?

A majority of physicians (n=358, 58%) responded that adding another HFrEF drug class is more important than up-titrating those already started. This result was consistent among all subgroups except physicians aged ≥ 50 years (p=0.049) (**Figure 3**).

HFrEF treatment sequencing and up-titration

Regarding the order of HF drug introduction, the "historical approach" appeared to be the most common one starting with ACEi or ARNi first (n=421, 74%), BB second (n=328, 55%), MRA third (n=317, 52%), and SGTL2i (n=318, 53%) fourth. Of note, only 16% of the participants would start SGLT2i as second line agent. These results are presented in **Figure 4** and were consistent across all subgroups (**Appendix, figure 1**).

A broad majority of participants (n=518, 84%) felt that it is possible to start all four drug classes during the initial hospitalization, without any differences between subgroups. The most realistic time interval to reach the maximal up-titration of all four HF drugs was one month for 44% (n=271) of participants, followed by 6 months for 31% (n=192), 15 days for 18% (n=112), and one week for 6.3% (n=39). Again, there were no significant differences in the subgroup analysis.

Thirty-three percent of participants (n=199) reported that they optimise HFrEF treatment in 26 to 50% of cases, 25% of participants (n=152) in 51 to 75% of cases, 24% (n=144) in more

than 75% of cases, and 6.2% (n=38) less than 25% of cases. HF specialists considered optimizing treatment significantly more frequently compared to non-specialists (p=0.002). Importantly, 40% (n=246) of participants estimated that they achieve full up-titration in 26 to 50% of HFrEF patients and 35% (n=212) in 51 to 75% of cases. HF specialists estimated that they achieve full up-titration significantly more often than non-specialists: full up-titration in more than 50% of cases by 56% of specialists versus 37% of non-specialits (p<0.001).

Perception of HF drug classes efficiency

To the question "*if you had to choose only one HF drug class for a patient with HFrEF, which one would you choose?*", the majority of the physicians answered ACEi or ARNi (n=415, 68%), followed by BB in 22% (n=135), then SGLT2i (n=55, 9%) and finally MRA (n=8, 1%). The results by subgroups are summarized in **Figure 5**.

ARNis were considered as the most efficient HF drug for 39% (n=242) of participants, followed by ACEi (n=152, 25%), BB (n=144, 23%), SGTL2i (n=40, 6.5%), MRA (n=7, 1.1%). Regarding individual HF drug efficiency between subgroups of participants, there was a significant difference with students/trainees considering BB as the most efficient HF drug compared to others (p=0.025). They were no other statistical differences across the subgroups analyses.

MRA introduction with glomerular filtration rate < 30 mL/min.

Fifty-six percent of participants choose to introduce MRAs even if the GFR is < 30 mL/min, with a careful monitoring of serum potassium (**Figure 6**). In the subgroup analysis, students/trainees and physicians aged ≤ 30 yo were significantly more reluctant to introduce MRAs in this situation (44% and 48%, respectively). Conversely, HF specialists were

significantly more likely to start MRAs in this situation compared to non-specialists (69% versus 51%; p<0.001).

Major sides effects for each HFrEF drugs

Table 2 summarizes the most significant side-effects expected according to each HFrEF-targeted drugs (question 18 to 22 of the survey, **appendix table 1**). Cough was considered as the main side-effect of ACEi (n=231, 38%), symptomatic hypotension with ARNi (n=456, 75%), hyperkaliemia with MRA (n=507, 83%), bradycardia with BB (n=369, 59%) and urinary tract infection with SGLT2i (n=318, 52%).

DISCUSSION

This large international survey amongst more than 600 practicing cardiologists is the first and largest to provide real-world feedback on HF drug titration practice in patients with HFrEF among the cardiology community, following the publication of the latest European Society of Cardiology HF 2021 guidelines (**Graphical abstract**). The main findings from this survey are: i) a LVEF ≤40% is the preferred threshold to define HFrEF and initiate medical therapy; ii) the sequential "historical approach" of the HFrEF drugs introduction remains the preferred strategy; and iii) renin-angiotensin system inhibitors (RASi) are the preferred HF drug to start. Remarkably (and in contrast to current practice), prescribing an additional drug class was perceived as more important than titration of the individual classes, and a large majority of participants believed that all four classes could be prescribed at discharge after a first HF hospitalization.

LVEF threshold to define HFrEF

Most of participants considered that an LVEF ≤ 40% is the threshold to define HFrEF, which is aligned with the ESC and ACC/AHA guidelines. (1,7) The four major HF drug classes have a class I recommendation for HFrEF, and therefore an accurate definition of the LVEF threshold of HFrEF is important. (1) Furthermore, in the 2021 ESC HF Guidelines, patients with LVEF between 41 and 49% have been reclassified as "mildly reduced LVEF" and all four drug classes have been reclassified to class II of recommendation in this patient population. (1) Nevertheless, the Emperor-Preserved HF trial and Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trials (8) together with meta-analysis of the Paradigm and Paragon HF trials (9) suggest a reduction in HF hospitalizations and all-cause mortality with the use of SGLT2i and

ARNi up to the LVEF of 50 and 55% respectively. (8) As such, a redefinition of LVEF thresholds to define HFrEF up to LVEF of 55% might be warranted as the current threshold of 40% induces therapeutic inertia, which is clearly illustrated by this survey.

The comparison of very different thresholds and terms from different cardiology societies clearly emphasizes this controversy. Hudson *et al*, clearly show the differences in perception to define the boundary between HF with reduced and preserved LVEF (10). There is growing evidence that there is neuro-hormonal RAS and sympathetic nervous system activation up to 55%. (11,12) The 41-55% borderline interval between HFrEF and HFpEF probably induces therapeutic inertia, and our survey results clearly show that the 40% threshold is fixed in the cardiology community.

Sequencing and up-titration of four classes in HF patients

The latest HF guidelines suggest starting the 4 principal HF drug classes simultaneously (1), which is a significant change from the sequential step-by-step approach presented in all previous HF guidelines. (2) However, international experts in the field of HF and cardiology societies have proposed various sequencing approaches (4,5). One approach consisted of a 3-step approach starting with BB+SGLT2i followed by ARNi and finally MRA over 4 months. (4,5) In recent statistical modeling of individual data from pivotal HF randomized clinical trials, Shen *et al*. suggest that the "historical" sequence following the chronological order in which trials were conducted, with a cautious up-titration of each treatment, may not lead to the best outcome for patients with HFrEF. According to their statistical model, the optimal alternative sequence included SGLT2i and an MRA as the first two therapies allowing to decrease a virtual composite outcome of HF and cardiovascular death by 47 events per thousand patients in one year (6).

Additionally to these expert opinions and this complex statistical model, this survey is the first to provide real-life data across the spectrum of the cardiology community. The traditional "historical" sequencing remains the preferred approach rather than a new type of sequencing or starting all classes simultaneously. This could be related to personal habits, limited access to new therapies in specific countries, perception of each drug's efficiency, or the impact of previous 2016 guidelines being more embedded in the clinical practice than any other sequence. However, most participants considered a rapid introduction of all four drugs within the initial hospitalization followed by rapid up-titration within one month to be feasible. (4,5) Furthermore as presented by Marti *et al*., (13) there is a clear shift to targeting all the different pathological pathways activated in HFrEF by introducing a new class rather than titrating a single individual class to maximally tolerated dose. This opinion is also supported by the results of the ATLAS trial (14) where there was a moderate benefit in outcomes of low doses of lisinopril versus high doses.(15)

Subgroup Comparisons

Several interesting findings come from the subgroup analyses for each question. Responses were consistent among male and female responders. However, training stage, age, and specialization in the heart failure field significantly impact the answers. Young physicians and trainees were considerably more careful and respectful of traditional guidelines compared to older cardiologists. Senior cardiologists are more sensitive to titrating rather than introducing new HF drug classes. Being specialized in heart failure seems to be associated with bolder approaches in terms of drug introduction (ARNi and MRA) and time to titration.

Rather than expert opinion, evidence-based medicine is necessary.

The treatment strategy for patients with HFrEF is probably at a turning point. There have been huge advances in the medical and device armamentarium available to treat HFrEF. (1) Therefore, the question is less "How to find new therapies for HFrEF?" but more "How to best implement the existing therapies?" while maximizing efficacy, minimizing side effects, and taking into account the features of each patient (i.e., tolerance, comorbidities, HFrEF etiology, and phenotype). In addition, integration of the medico-economic aspect should also be considered.

Several open questions to address in clinical trials are raised in this context: Is a low dose of a fourth drug better than a full dose of three drugs? Should we start with one class rather than another or all simultaneously? Should we consider a combination rather than an add-on titration strategy, and if so, should we start with a dual or triple combination therapy? How long should titration take to ensure the patient's safety? Should titration be the same for all or should it be tailored to each patient, based on a goal-oriented treatment strategy using risk stratification? Should we go beyond LVEF alone to phenotype HFrEF patients and then adapt treatments? This survey might be an opportunity to initiate clinical trials to evaluate several strategies across the HFrEF spectrum.

Limitations.

We acknowledge several limitations. First, we only consider "typical" HFrEF patients without considering comorbidities (i.e., aging, chronic kidney disease, etc.) or treatment intolerance. However, this is in line with the expert opinion strategy previously proposed. (4,5) Secondly, the survey had an open-access, and therefore, we cannot affirm that all the responders were physicians and that the recipient could represent a biased selection of the most "updated" practicing cardiologists. Yet, the results are consistent. Third, this survey was built independently and was not endorsed by the Heart Failure Association of the European Society

of Cardiology. Still it was approved by several board members of the HFA, by several cardiologists from various countries in Europe, and it was endorsed by the French HF group from the French Society of Cardiology. Finally, this survey did not address the question of simultaneous introduction of all HF drugs together.

In conclusion, in an investigator-initiated survey on the sequencing and titration of HFrEF drugs in a broad cardiology community, the sequential "historical approach" for HFrEF drug introduction remains dominant and RASi are the preferred HF drug to start. Interestingly, prescription of all four classes together prevails largely over titration of individual classes and a large majority of participants think that all four classes can be prescribed at the discharge after a first heart failure hospitalization. Prospective observational and randomized clinical strategy trials are needed to define the optimal optimization protocol.

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CONFLICT OF INTEREST.

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DATA AVAILABILITY STATEMENT.

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REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Aug 27;ehab368.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 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 J Heart Fail. 2016;18(8):891–975.
3. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Oct 8;383(15):1413–24.
4. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. Eur J Heart Fail. 2021 Jun;23(6):882–94.
5. McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. Circulation. 2021 Mar 2;143(9):875–7.
6. Shen L, Jhund PS, Docherty KF, Vaduganathan M, Petrie MC, Desai AS, et al. Accelerated and personalized therapy for heart failure with reduced ejection fraction. Eur Heart J. 2022 Apr 25;ehac210.
7. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022 May 3;145(18):e895–1032.
8. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Aug 27;
9. Solomon SD, Vaduganathan M, L Claggett B, Packer M, Zile M, Swedberg K, et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation. 2020 Feb 4;141(5):352–61.
10. Hudson S, Pettit S. What is “normal” left ventricular ejection fraction? Heart. 2020 Sep;106(18):1445–6.
11. Vergaro G, Aimo A, Prontera C, Ghionzoli N, Arzilli C, Zyw L, et al. Sympathetic and renin-angiotensin-aldosterone system activation in heart failure with preserved, mid-range

and reduced ejection fraction. Int J Cardiol. 2019 Dec 1;296:91–7.
12. Jimenez-Marrero S, Moliner P, Rodríguez-Costoya I, Enjuanes C, Alcoberro L, Yun S, et al. Sympathetic activation and outcomes in chronic heart failure: Does the neurohormonal hypothesis apply to mid-range and preserved ejection fraction patients? Eur J Intern Med. 2020 Nov;81:60–6.
13. Marti CN, Fonarow GC, Anker SD, Yancy C, Vaduganathan M, Greene SJ, et al. Medication dosing for heart failure with reduced ejection fraction - opportunities and challenges. Eur J Heart Fail. 2019 Mar;21(3):286–96.
14. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999 Dec 7;100(23):2312–8.
15. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet. 2020 Jul 11;396(10244):121–8.

FIGURES TITLES AND LEGENDS.

Structured graphical abstract.

Abbreviations: LVEF: left ventricular ejection fraction, HFrEF: Heart Failure with reduced Ejection Fraction, SGLT2i: sodium-glucose cotransporter 2 inhibitors, MRA: mineralocorticoid receptor antagonism, BB: beta-blockers, ACEi: angiotensin-converting enzyme inhibitor, ARNi: angiotensin-receptor neprilysin-inhibitor.

Figure 1. What is the accurate LVEF threshold to define HFrEF?

Abbreviations: LVEF: left ventricular ejection fraction, HF: heart failure, MD: medical doctor.

Figure 2. In a patient with primary HFrEF, without prior HF drug treatment, do you start with ARNi instead of ACEi or ARBs?

Abbreviations: HF: heart failure, MD: medical doctor.

Figure 3. Is titration more important than adding another HF drug class?

Abbreviations: HF: heart failure, MD: medical doctor.

Figure 4. What would be your standard best HF drug sequencing (classify by order of introduction)?

Abbreviations: SGLT2i: sodium-glucose cotransporter 2 inhibitors, MRA: mineralocorticoid receptor antagonism, BB: beta-blockers, ACEi: angiotensin-converting enzyme inhibitor, ARNi: angiotensin-receptor neprilysin-inhibitor.

Figure 5. If you had to choose one HF drug class only for a patient with HFrEF, which one would you choose?

Abbreviations: SGLT2i: sodium-glucose cotransporter 2 inhibitors, MRA: mineralocorticoid receptor antagonism, BB: beta-blockers, ACEi: angiotensin-converting enzyme inhibitor, ARNi: angiotensin-receptor neprilysin-inhibitor, HF: heart failure, MD: medical doctor.

Figure 6. Do you introduce MRA in HF patients with GFR < 30 mL/min, with careful kaliemia monitoring?

Abbreviations: MRA: mineralocorticoid receptor antagonism, HF: heart failure, MD: medical doctor

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