ESC European Society of Cardiology

European Journal of Heart Failure (2022)
doi:10.1002/ejhf.2743

RESEARCH ARTICLE

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

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Received 22 August 2022; revised 26 September 2022; accepted 16 November 2022

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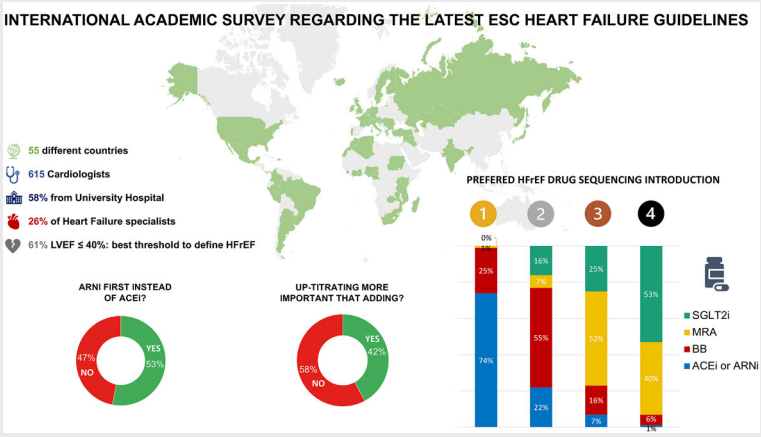
Aims In symptomatic patients with heart failure and reduced ejection fraction (HFrEF), recent international guidelines recommend initiating four major therapeutic classes rather than sequential initiation. It remains unclear how this change in guidelines is perceived by practicing cardiologists versus heart failure (HF) specialists.

Methods and results An independent academic web-based survey was designed by a group of HF specialists and posted by email and through various social networks to a broad community of cardiologists worldwide 1 year after the publication of the latest European HF guidelines. Overall, 615 cardiologists (38 [32–47] years old, 63% male) completed the survey, of which 58% were working in a university hospital and 26% were HF specialists. The threshold to define HFrEF was ≤40% for 61% of the physicians. Preferred drug prescription for the sequential approach was angiotensin-converting enzyme inhibitors or angiotensin receptor–neprilysin inhibitors first (74%), beta-blockers second (55%), mineralocorticoid receptor antagonists third (52%), and sodium–glucose cotransporter 2 inhibitors (53%) fourth. Eighty-four percent of participants felt that starting all four classes was feasible within the initial hospitalization, and 58% felt that titration is less important than introducing a new class. Age, status in training, and specialization in HF field were the principal characteristics that significantly impacted the answers.

Conclusion In a broad international cardiology community, the 'historical approach' to HFrEF therapies remains the preferred sequencing approach. However, accelerated introduction and uptitration are also major treatment goals. Strategy trials in treatment guidance are needed to further change practices.

Graphical Abstract



The latest European guidelines for heart failure with reduced ejection fraction (HFrEF) patients recommend initiating four major therapeutic classes rather than the sequential initiation from the previous guidelines. Without any evidence from randomized controlled trials, the perception and the practical approach to these guidelines by practicing cardiologists remain unclear. We found that left ventricular ejection fraction (LVEF) ≤40% remains the most frequent threshold to define HFrEF and the 'historical' approach to HFrEF drug titration remains the most popular sequencing approach. However, most participants felt that starting all four classes was feasible within the initial hospitalization and that titration is less important than introducing a new class. This is the first and largest survey providing real-world data on HFrEF drug introduction and titration after the latest European heart failure guidelines. Even if the 'historical' sequencing approach remains dominant, starting all four classes in a short-time period was perceived as feasible. Strategy trials in treatment guidance are now needed to demonstrate the safety and define the best treatment implementation approach.
ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Keywords Guideline • Heart failure • Pharmacology • Treatment

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]

The 2021 European Society of Cardiology (ESC) heart failure (HF) guidelines moved away from the traditional hierarchical approach to the treatment of heart failure and suggested that the four pillars of treatment should be prescribed to all patients with HFrEF at any encounter would this be during hospitalization or an outpatient visit.[1] A similar concept has been embraced more recently, albeit with some differences, by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[2] The previous guideline recommendations 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. The Heart Failure Association (HFA) of the ESC has suggested a treatment approach based on patient phenotypes while others have proposed different sequencing and titrating approaches according to their expertise[4,5] or statistical modelling of major HF 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 also no data on the perception and/or implementation of these new guidelines in the general cardiology community. Our main objective was to get the opinion of the most popular sequencing approach among the general cardiology community through the collection of answers from a broad range of cardiologists. We designed an international web-based survey asking about views and experience with sequencing, titrating and opinions on HF drugs 1 year after the publication of the 2021 ESC HF guidelines.

Methods

Set-up and validation of the survey

This survey was an investigator-initiated survey initially designed and drafted in English within the HF working group of the French Society of Cardiology, which is closely affiliated with the HFA of the ESC. The survey was conceived, optimized, revised, and approved by several groups of cardiologists: board members of the HF 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 HF task and task force members from the ESC Academy (online supplementary *Appendix S1*).

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 online supplementary *Table S1*.

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 HF 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 HF network and several members of the HFA board. The link for the survey was posted on several social networks.

The survey was available for 1 month (from 15 March 2022 to 16 April 2022) on the web platform. Three successive invitations were sent to all networks within this time frame (online supplementary *Appendix S1*).

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 for continuous variables whereas the chi-square test was used for categorical variables. For intergroup comparison, categorical variables were compared with the chi-square test or Fisher's exact test when appropriate, whereas the Student's *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 five pre-specified subgroup analyses were systematically performed: gender (i.e. male vs. female), age (<30, 30–50, and >50 years), HF self-declared specialist versus non-specialists, non-graduated (i.e. a medical student or trainee) versus graduated (i.e. medical doctor), and finally according to the continent of origin of the participants (i.e. Europe, America, Asia, Africa). 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

Overall, 615 cardiologists from 55 different countries completed the survey between 15 March 2022 and 16 April 2022. The median time spent to fill this survey was 5.57 min. Among the participants who completed the survey, >95% answered all the questions.

The characteristics of the participants are presented in *Table 1*. Participants had a mean age of 38 [32–47] years, the majority was male ($n = 389$, 63%), mainly from Europe ($n = 433$, 71%). The largest group of participants were practicing in a university hospital ($n = 358$, 58%). The proportion of HF specialists was 27% ($n = 167$)

Table 1 Main characteristics of the population ($n = 615$)

Variables	N	
Age, years	611	38 (32–47)
Age by class, years		
≤30		134 (22)
30–50		351 (57)
≥50		126 (21)
Male sex	613	389 (63)
Continent	614	
Africa		47 (7.7)
Asia		48 (7.8)
America (North, Central, South)		86 (14)
Europe		433 (71)
Location of practice	613	
University hospital		358 (58)
General hospital		137 (22)
Private hospital		73 (12)
Private practice		45 (7.3)
Subspeciality	614	
General cardiology		184 (30)
Heart failure specialist		167 (27)
Interventional cardiology		108 (18)
Cardiovascular imaging		60 (9.8)
Medical student or trainee		54 (8.8)
Intensive care		24 (4.2)
Others[a]		15 (2.4)
At least one ESC academy course attending	615	159 (26)

Values are given as *n* (%), or median (quartile 1–quartile 3).
ESC, European Society of Cardiology.
[a]Others included: four cardiologists from cardiac rehabilitation, three echocardiographers, two cardio-oncologists, one congenital heart disease cardiologist, and six non-cardiologists.

and 26% ($n = 159$) of participants had attended at least one ESC Heart Academy course.

Left ventricular ejection fraction 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 10.3% more considered a threshold of ≤35%. Only 15% accepted a threshold ≤50% and 2.7% 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 (*Figure 1*), and finally according to the continent of origin of the participants (online supplementary *Figure S1*).

In a naïve HFrEF treatment patient: ARNi or ACEi/ARB 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). Except for African participants (where a majority would not start with ARNi), this result was also consistent regarding the continent of origin (online supplementary *Figure S2A*).

Is titration more important than adding another heart failure drug class?

The majority of physicians ($n = 358$, 58%) responded that adding another HFrEF drug class is more important than uptitrating those already started. This result was consistent among all subgroups except physicians aged ≥50 years ($p = 0.049$) (*Figure 3*) and for Asian and African participants (online supplementary *Figure S2B*).

HFrEF treatment sequencing and uptitration

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 (online supplementary *Figures S2C* and *S3*).

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 uptitration of all four HF drugs was 1 month for 44% ($n = 271$) of participants, followed by 6 months for 31% ($n = 192$), 15 days for 18% ($n = 112$), and 1 week for 6.3% ($n = 39$). Again, there were no significant differences in the subgroup analysis.

A total of 33% of participants ($n = 199$) reported that they optimize 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 uptitration in 26% to 50% of HFrEF patients and 35% ($n = 212$) in 51% to 75% of cases. HF specialists estimated that they achieve full uptitration significantly more often than non-specialists: full uptitration in more than 50% of cases by 56% of specialists versus 37% of non-specialists ($p < 0.001$).

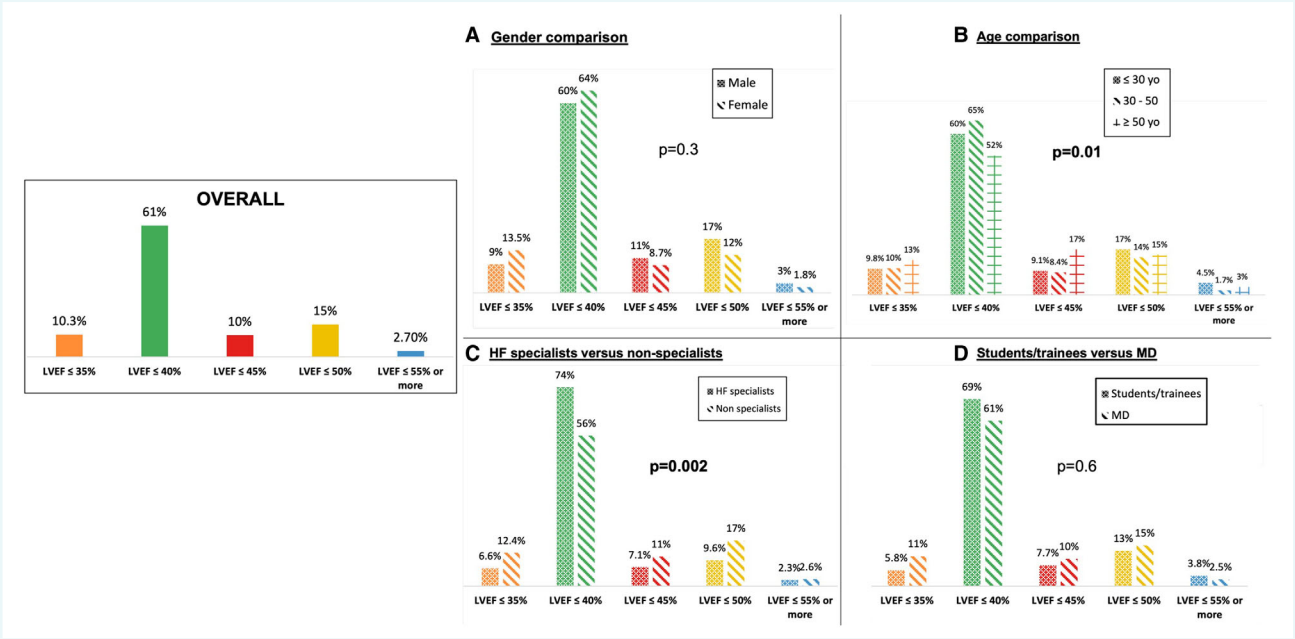


Figure 1 What is the accurate left ventricular ejection fraction (LVEF) threshold to define heart failure (HF) with reduced ejection fraction? MD, medical doctor.

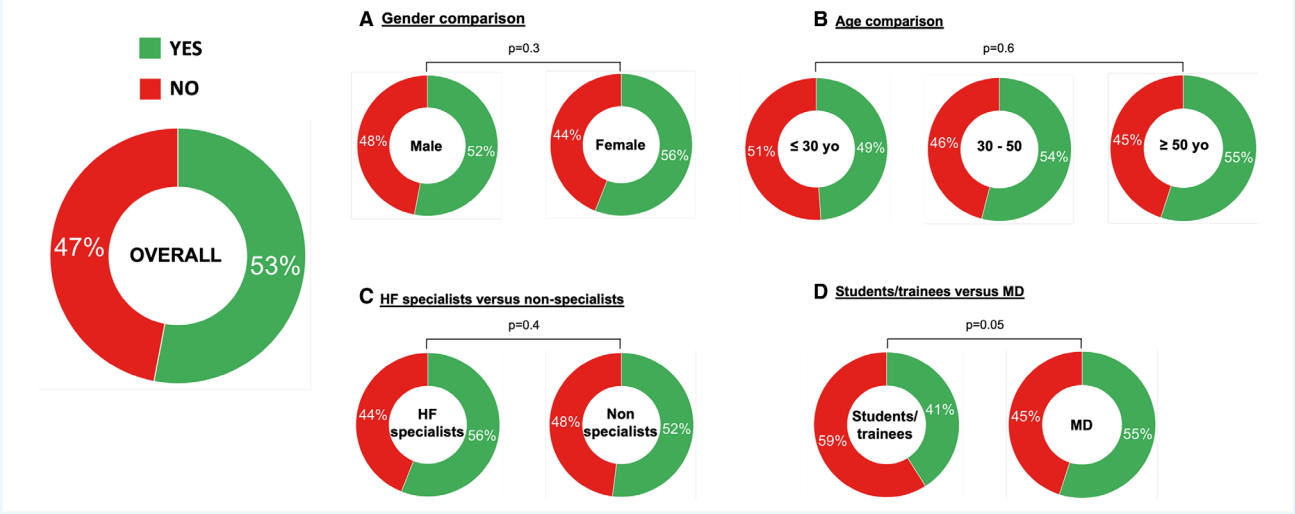


Figure 2 In a patient with primary heart failure (HF) with reduced ejection fraction, without prior HF drug treatment, do you start with angiotensin receptor–neprilysin inhibitors instead of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers? MD, medical doctor.

Perception of heart failure 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* and online supplementary *Figure S2D*.

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). There were no other statistical differences across the subgroups analyses.

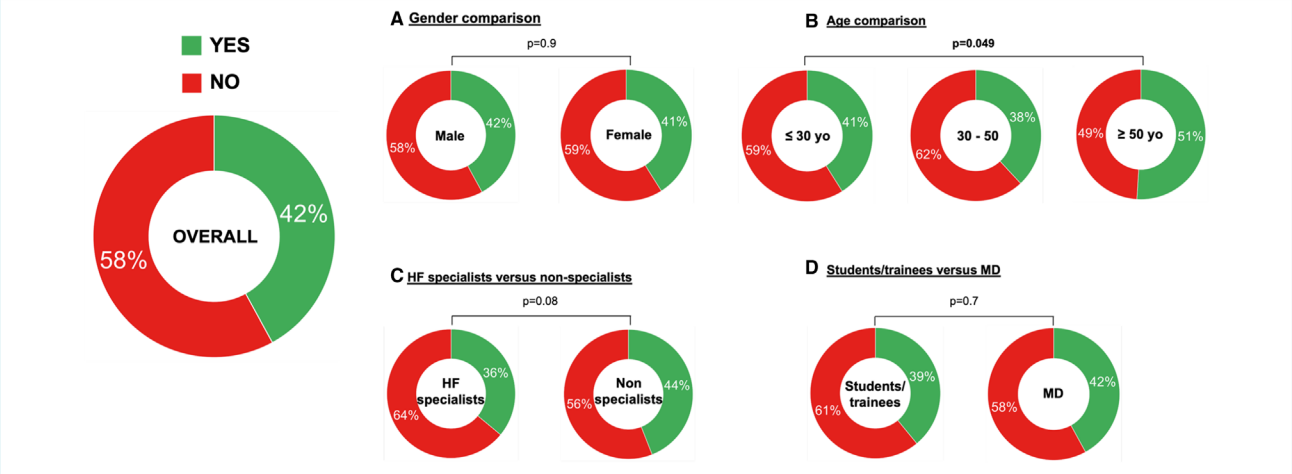


Figure 3 Is titration more important than adding another heart failure (HF) drug class? MD, medical doctor.

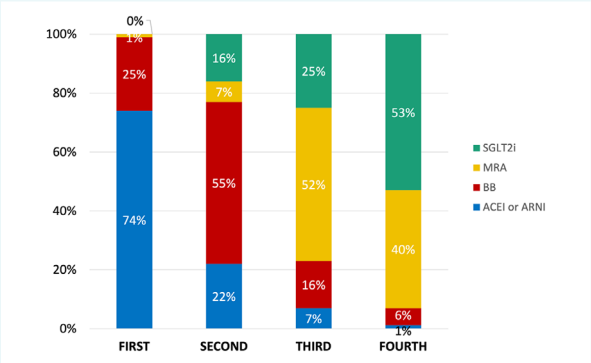


Figure 4 What would be your standard best heart failure drug sequencing (classify by order of introduction) ? ACEI, angiotensin-converting enzyme inhibitor; ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

MRA introduction with glomerular filtration rate <30 ml/min

A total of 56% of participants choose to introduce MRAs even if the glomerular filtration rate (GFR) is <30 ml/min, with a careful monitoring of serum potassium (*Figure 6*). In the subgroup analysis, students/trainees and physicians aged ≤30 years and African participants 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% vs. 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, online supplementary *Table S1*). Cough was considered as the main side-effect of ACEi (n = 231, 38%), symptomatic hypotension with ARNi (n = 456, 75%), hyperkalaemia with MRA (n = 507, 83%), bradycardia with BB (n = 360, 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 ESC HF 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 drug introduction remains the preferred strategy; and (iii) renin–angiotensin system inhibitors (RASi) are the preferred HF drug to start. However, most of the participants (84%) considered feasible to start the four foundation therapies together. 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.

Left ventricular ejection fraction threshold to define HFrEF

Most of participants considered that a LVEF ≤40% is the threshold to define HFrEF, which is aligned with the ESC and ACC/AHA guidelines.[1,2] 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

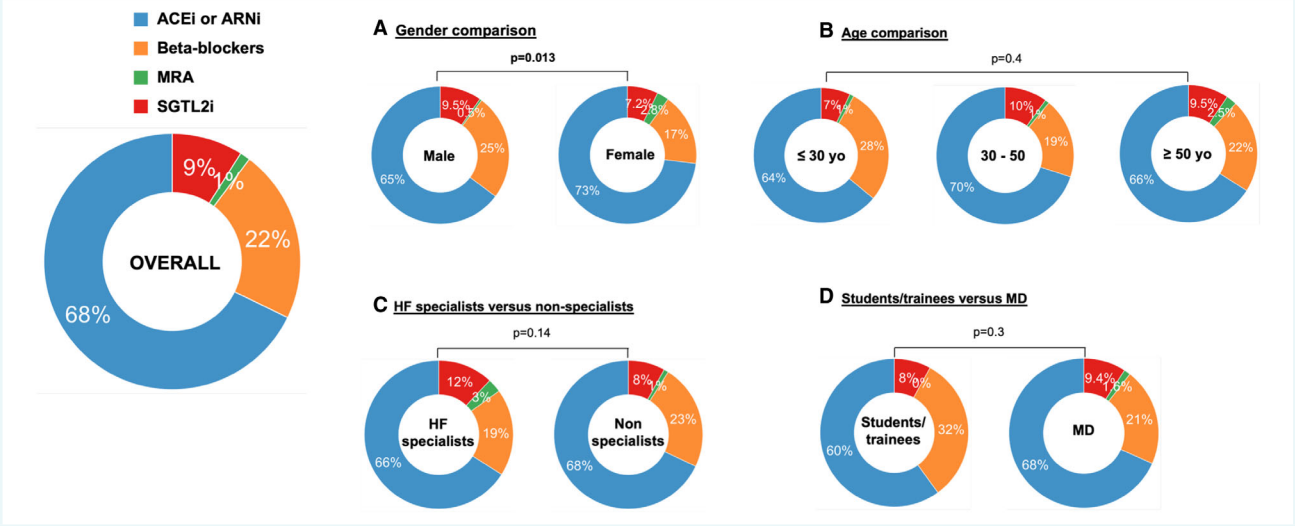


Figure 5 If you had to choose one heart failure (HF) drug class only for a patient with HF with reduced ejection fraction, which one would you choose? ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; MD, medical doctor; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

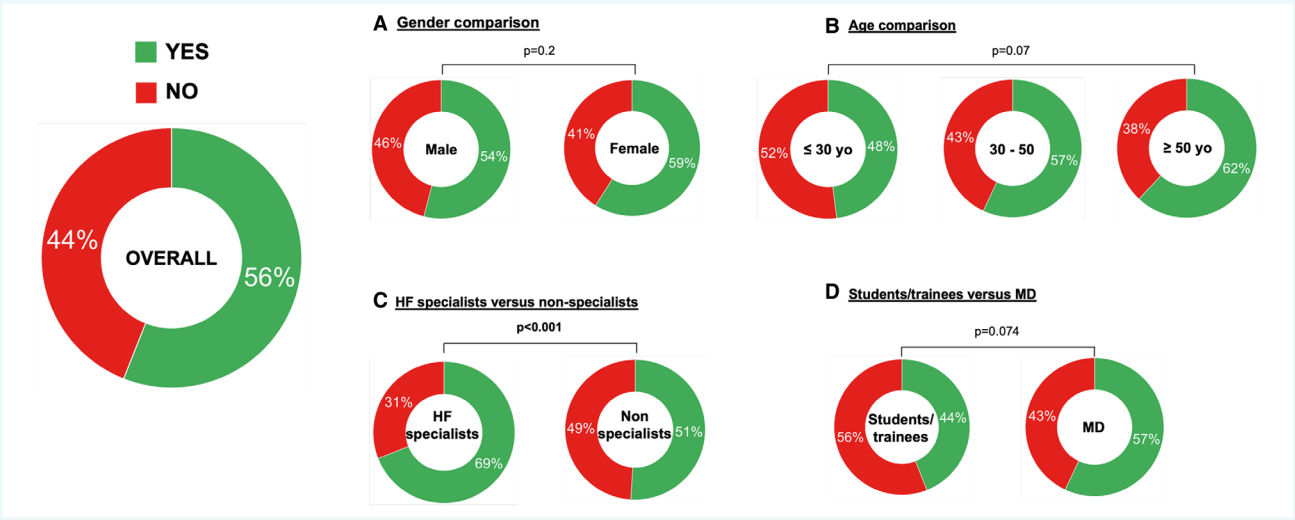


Figure 6 Do you introduce a mineralocorticoid receptor antagonist in heart failure (HF) patients with glomerular filtration rate <30 ml/min, with careful kalaemia monitoring? MD, medical doctor.

recommendation in this patient population.[1] However, the universal definition of HF suggests that amongst patients with a LVEF >40%, those with HF with improved ejection fraction should receive the treatments indicated for patients with HFrEF.[7] Nevertheless, the EMPEROR-Preserved and DELIVER trials[8,9] together with meta-analysis of the PARADIGM-HF and PARAGON-HF trials[10] 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 and Pettit[11] clearly show the differences in perception to define the boundary between HF with reduced and preserved LVEF. There is growing evidence that the neuro-hormonal renin–angiotensin system and sympathetic nervous system activation fades with increasing LVEF with a cut-off at 50% for the mortality benefit.[12–14] The 41–55% borderline interval between HFrEF and HF with preserved ejection fraction probably induces therapeutic inertia, and our survey results clearly show that the 40% threshold is fixed in the cardiology community.

Table 2 Most important side-effects expected according to each heart failure with reduced ejection fraction-targeted drug

ACEi, *n* (%)	
Cough	231 (38)
Symptomatic hypotension	178 (29)
Worsening renal function	128 (21)
Hyperkalaemia	42 (7)
Angioedema	33 (5)
ARNi, *n* (%)	
Symptomatic hypotension	456 (75)
Worsening renal function	86 (14)
Hyperkalaemia	52 (9)
Angioedema	16 (2)
MRA, *n* (%)	
Hyperkalaemia	507 (83)
Worsening renal function	81 (13)
Symptomatic hypotension	22 (4)
BB, *n* (%)	
Bradycardia	360 (59)
Symptomatic hypotension	97 (16)
Worsening renal function	72 (12)
None	61 (10)
Bronchitis exacerbation	21 (3)
SGLT2i, *n* (%)	
Urinary tract infection	318 (52)
None	140 (23)
Ketoacidosis	69 (11)
Worsening renal function	50 (8)
Symptomatic hypotension	36 (6)

ACEi, angiotensin-converting enzyme inhibitor; ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; HF, heart failure; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Sequencing and uptitration of four classes in heart failure patients

The latest HF guidelines suggest starting the four principal HF drug classes simultaneously,[1] which is a significant change from the sequential step-by-step approach presented in all previous HF guidelines.[15] However, international experts in the field of HF and cardiology societies have proposed various sequencing approaches.[4,5] In recent statistical modelling of individual data from pivotal HF randomized clinical trials, Shen *et al.*[6] suggest that the 'historical' sequence following the chronological order in which trials were conducted, with a cautious uptitration 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 1000 patients in 1 year. However, it must be considered that really naïve patients rarely exist in clinical practice as the majority of patients presenting with HF symptoms already receive some of the foundation therapy for HF because of their background conditions.

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 clinical practice than any other sequence. However, most participants considered a rapid introduction of all four drugs within the initial hospitalization followed by rapid uptitration within 1 month to be feasible.[4,5] Furthermore, 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.[16] This opinion is also supported by the results of the ATLAS trial[17] where there was a moderate benefit in outcomes of low doses versus high doses of lisinopril,[18] by a recent analysis of the Swedish HF registry that demonstrated that using more HF drugs at lower doses is more effective than titrating only one class to full dose,[19] and finally by a retrospective analysis of the BIOSTAT-CHF and ASIAN-HF registries showing that achieving lower BB and ACEi/ARB dose is associated with higher reduction of death and HF hospitalization than the highest dose of one.[20] Interestingly, and contrary to the answers presented here, this study also showed that uptitrating BB to 100% of the maximal dose was associated with greater all-cause mortality reduction than uptitrating ACEi/ARB to 100%.

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, the continent of origin, and specialization in the HF 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 HF seems to be associated with bolder approaches in terms of drug introduction (ARNi and MRA) and uptitration. Compared to non-HF specialists, HF specialists introduce MRA in patients with GFR <30 ml/min significantly more and they tend to implement HF therapies and achieve full uptitration in shorter delays. Finally, African participants are less likely prompt to introduce ARNi instead of ACEi or ARBs in a naïve-treatment HFrEF patient or MRA in case of GFR <30 ml/min. Moreover, a majority of Asian and African participants think that titrating is more important than adding a new HF drug class. Although we cannot say for sure, these results are probably related to greater difficulty in accessing innovative therapies.

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 aetiology, 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.

There is considerable effort put into the preparation and the writing of revised guidelines every 5 years. These guidelines summarize the most recent findings from clinical trials and are issued with levels of recommendation resulting from a thorough analysis of the literature and the consensus of key experts in the field of HF. These guidelines set the headlines of diagnosis and therapies for HF. Then, the national professional societies should integrate these guidelines, adapt, and pragmatically implement them according to healthcare system capabilities in order to apply them in daily practice.

Limitations

We acknowledge several limitations. First, we only considered '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 HFA of the ESC. 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.

Conclusion

In an investigator-initiated survey on the sequencing and titration of HFrEF drugs in a broad cardiology community, the sequential 'historical approach' to 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 HF hospitalization. Prospective observational and randomized clinical strategy trials are needed to define the optimal optimization protocol.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgement

We acknowledge all the cardiologists who attended this survey across the world.

Conflict of interest: C.F. reports consulting fees from Janssen, outside of the submitted work. W.M. reports payment or honoraria for lectures from Novartis, Abbott, Medtronic, Boehringer, AstraZeneca, Viphor, outside of the submitted work. C.I.S. reports consulting fees from Novartis, Medtronic, AstraZeneca, Bayer and Merck, and payment or honoraria for lectures from Servier, Medtronic, Novartis, AstraZeneca, Bayer and Merck. A.Z.M. reports payment or honoraria for lectures from Novartis, Boehringer Ingelheim, AstraZeneca. A.B. reports payment or honoraria for lectures from Novartis, Boehringer Ingelheim, AstraZeneca and Bayer and participation in Advisory Board for Bayer, AstraZeneca and Boehringer Ingelheim. M.T. reports payment or honoraria for lectures from Novartis, AstraZeneca, Boehringer Ingelheim, BerlinChemie, Pfizer, Novo Nordisk. L.F.T. reports payment or honoraria for lectures from Medtronic and Abbott and participation in a Data Safety Monitoring Board for Medtronic. N.J. reports travel grants from the HFA and ESC, payment or honoraria for lectures from Servier, AstraZeneca, Boehringer Ingelheim, Bayer, BerlinChemie, Teva Pharmaceutical industries, Pfizer, Krka, Sanofi Genzyme, and support for attending meetings/congresses from Servier, Teva Pharmaceutical Industries, Pfizer and Abbott. A.S. reports consulting fees from Abbott, Medtronic, Biosense Webster and honoraria for lectures from Abbott, Medtronic and EHRA. M.A. is consultant for Biosense Webster and Boston Scientific, clinical proctor for Medtronic and has received educational support from Abbott. D.M. reports honoraria for presentations from Bayer, Novartis and AstraZeneca. T.B. reports consulting fees from Boehringer Ingelheim and Amgen. F.B. reports payment for lectures from Vifor, Novartis, Bayer, Boehringer Ingelheim, AstraZeneca, and support for attending meetings from Vifor. N.L. reports consulting fees from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Novartis, MSD, Amicus Therapeutics, Pfizer, Recordati-Bouchara, payment or honoraria for lectures from AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Novartis, MSD, Amicus Therapeutics, Pfizer, Recordati-Bouchara, payment for expert testimony from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, and support for attending meeting from AstraZeneca, MSD, Actelion-Janssen, Novartis. T.D. reports grants from Novartis, Bayer and Vifor, consulting fees from Novartis, Bayer and Vifor, payment or honoraria for lectures from Novartis, Bayer, Vifor, support for attending meetings from Novartis, Bayer and Vifor. N.G. reports consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, Novartis, Vifor and Roche Diagnostics. L.S. reports consulting

fees from AstraZeneca, Novartis, Vifor and Bayer, payment for honoraria for lectures from Boehringer Ingelheim, AstraZeneca, payment or honoraria for lectures from Boehringer Ingelheim and AstraZeneca, support for attending meetings from Sanofi and AstraZeneca. T.P. reports grants from Servier, consulting fees from AstraZeneca, Novartis, Bayer, Pfizer-BMS, Siemens Healthcare, General Electric, payment or honoraria for lectures from AstraZeneca, Novartis, Bayer, Pfizer-BMS. A.C.S. reports payment or honoraria for lectures from Novartis, AstraZeneca, Boehringer Ingelheim, Vifor, Bayer, Sanofi. G.R. reports participation in a data safety monitoring board for Vifor DSMB and MitraClip independent study. F.R. reports grants from Air Liquide and Abbott, consulting fees from Abbott, Air Liquid, Bayer and Pfizer, payment or honoraria for lecture from AstraZeneca, Servier, Boehringer Ingelheim, Vifor, Bayer, Pfizer, Novartis, Servier, Novo Nordisk, Air Liquid, Abbott, support for attending meeting from Novartis, Boehringer Ingelheim, leadership of fiduciary role in Boehringer Ingelheim, Vifor, Novartis. N.M. reports consulting fees from Bayer, payment or honoraria for lectures from Boehringer Ingelheim, AstraZeneca, Vifor, Novartis, Amgen, support for attending meetings from AstraZeneca. All other authors have nothing to disclose.

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