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RESEARCH ARTICLE

Physician perceptions, attitudes, and strategies towards implementing guideline-directed medical therapy in heart failure with reduced ejection fraction. A survey of the Heart Failure Association of the ESC and the ESC Council for Cardiology Practice

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Aims Recent guidelines recommend four core drug classes (renin–angiotensin system inhibitor/angiotensin receptor–neprilysin inhibitor [RASi/ARNi], beta-blocker, mineralocorticoid receptor antagonist [MRA], and sodium–glucose cotransporter 2 inhibitor [SGLT2i]) for the pharmacological management of heart failure (HF) with reduced ejection fraction (HFrEF). We assessed physicians' perceived (i) comfort with implementing the recent HFrEF guideline recommendations; (ii) status of guideline-directed medical therapy (GDMT) implementation; (iii) use of different GDMT sequencing strategies; and (iv) barriers and strategies for achieving implementation.

Methods and results A 26-question survey was disseminated via bulletin, e-mail and social channels directed to physicians with an interest in HF. Of 432 respondents representing 91 countries, 36% were female, 52% were aged <50 years, and 90% mainly practiced in cardiology (30% HF). Overall comfort with implementing quadruple therapy was high (87%). Only 12%

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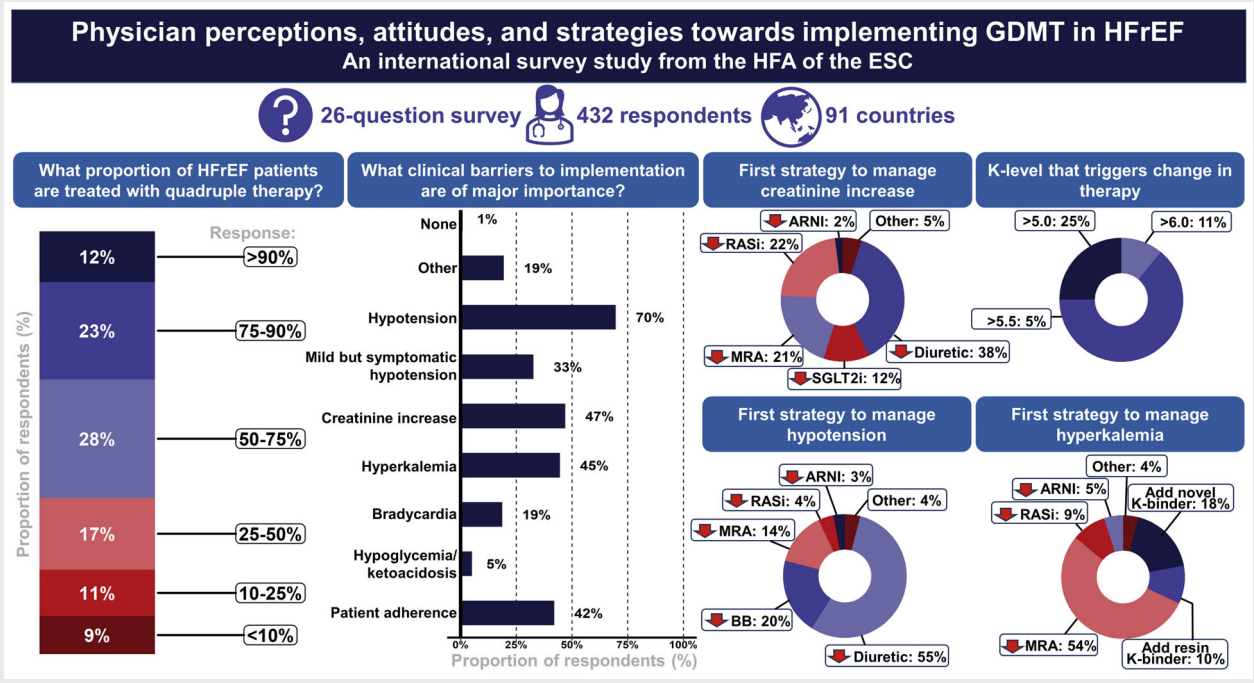
estimated that >90% of patients with HFrEF without contraindications received quadruple therapy. The time required to initiate quadruple therapy was estimated at 1–2 weeks by 34% of respondents, 1 month by 36%, 3 months by 24%, and ≥6 months by 6%. The average respondent favoured traditional drug sequencing strategies (RASi/ARNi with/followed by beta-blocker, and then MRA with/followed by SGLT2i) over simultaneous initiation or SGLT2i-first sequences. The most frequently perceived clinical barriers to implementation were hypotension (70%), creatinine increase (47%), hyperkalaemia (45%) and patient adherence (42%).

Conclusions Although comfort with implementing all four core drug classes in patients with HFrEF was high among physicians, a majority estimated implementation of GDMT in HFrEF to be low. We identified several important perceived clinical and non-clinical barriers that can be targeted to improve implementation.

Graphical Abstract



Physician perceptions of current state of and strategies to improve implementation of guideline-directed medical therapy (GDMT) in patients with heart failure with reduced ejection fraction (HFrEF). ARNI, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; ESC, European Society of Cardiology; HFA, Heart Failure Association; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Keywords Heart failure with reduced ejection fraction • Guideline-directed medical therapy • Treatment implementation

Introduction

Guideline-directed medical therapy (GDMT) reduces cardiovascular mortality and morbidity, as well as improves quality of life, in patients with heart failure (HF) and reduced ejection fraction (HFrEF).[1,2] However, adequate implementation of GDMT remains a major unmet need in clinical practice. Beyond clinical inertia, factors contraindicating therapy and/or linked with low tolerability, such as hypotension, impaired renal function, hyperkalaemia and polypharmacy might at least partially explain the poor implementation of GDMT often observed in HFrEF patients.[3–5]

Until 2021 international HF guidelines recommended a sequential approach to initiation and up-titration of HFrEF medications which reflected the chronological order these treatments were tested in landmark trials.[6,7] In contrast, the most recent updates of international HF guidelines recommend a parallel approach to initiation of the 'four pillars' of HFrEF pharmacological management—renin–angiotensin system inhibitors (RASi)/angiotensin receptor–neprilysin inhibitors (ARNi), beta-blockers, mineralocorticoid receptor antagonists (MRA), and sodium–glucose cotransporter 2 inhibitors (SGLT2i)—with treatment optimization according to the patient profile.[8–10] Therefore, there is no proposed sequence for drug initiation, although several alternative approaches might be adopted.[11–14]

Physicians' use of and attitudes to different sequencing strategies are central to their implementation in clinical practice. Moreover, a better understanding of physicians' perceived barriers to treatment and preferred strategies to deal with these barriers might offer important insights regarding how to foster the implementation of GDMT in HFrEF.

Therefore, the Heart Failure Association (HFA) of the European Society of Cardiology (ESC) performed an international survey among physicians with an interest in HF (HF specialists, other cardiologists and non-cardiologists) to assess: (i) physicians' comfort with implementing the recent HFrEF guideline recommendations; (ii) perceived extent of and time required for GDMT implementation in patients with HFrEF; (iii) perceived use of and attitudes towards different GDMT sequencing strategies; and (iv) perceived barriers to (and strategies to improve) implementation.

Methods

Survey preparation

This survey was designed and endorsed by the HFA of the ESC, and the full set of questions is reported in online supplementary *Table S1*. The final approved questionnaire consisted of 26 questions regarding (1) characteristics of the survey respondents (e.g. main area of clinical practice, number of patients with HFrEF evaluated per month, in-hospital vs. outpatient setting, years of experience, age, sex, and country), (2) the perceived achieved implementation of the four foundational HFrEF therapies (RASi/ARNi, beta-blockers, MRA, and SGLT2i), (3) preferred strategies to sequence and initiate GDMT in HFrEF, (4) perceived barriers to implementation, and (5) potential strategies to overcome barriers to implementation. The survey was published on the SurveyMonkey platform, and disseminated online via the HFA bulletin, HFA social media channels, and a dedicated e-campaign targeted to HFA members and ESC contacts with interest in acute HF, chronic HF or valvular heart disease. Responses were collected in March–April 2022 (online supplementary e-methods 1).

Statistical analysis

Descriptive analyses of the responses to each item in the questionnaire were provided. Categorical responses were presented as frequencies (percentages) and numerical responses as medians (interquartile range [IQR]). Summary estimates were calculated for the overall cohort as well as according to respondent characteristics (main setting [in-hospital vs. outpatient]; main area of practice [HF vs. other cardiology vs. non-cardiology]; HFrEF patients evaluated per month [<10 patients vs. 11–20 patients vs. 21–40 patients vs. >40 patients]; and years of practice [1–5 years vs. 6–10 years vs. >10 years]). Comparisons were performed across the strata of respondent characteristics by Chi-squared tests for categorical variables and analysis of variance (ANOVA) for continuous variables.

Data management, statistical analyses, and graphical representations were performed by the statistical software R, version 4.0.2. A p-value <0.05 (two-tailed) was considered statistically significant.

Results

Respondent characteristics

Of 432 survey respondents, 36% were female, 52% were aged <50 years, and 70% had >10 years' experience as clinical practitioners (*Table 1*). The main area of practice was HF for 31%

Table 1 Characteristics of survey participants

Level	Overall	Missing
n	432	
Age, years		0.5%
20–29	14 (3.3%)	
30–39	84 (19.5%)	
40–49	124 (28.8%)	
50–59	118 (27.4%)	
60–69	70 (16.3%)	
≥70	20 (4.7%)	
Sex		1.6%
Female	153 (36.0%)	
Male	272 (64.0%)	
Main area		0.7%
Heart failure	131 (30.5%)	
General cardiology	218 (50.8%)	
Interventional cardiology	36 (8.4%)	
Imaging	14 (3.3%)	
General medicine	19 (4.4%)	
Primary care	4 (0.9%)	
Other	7 (1.6%)	
Main cardiology area		0.7%
Heart failure	131 (30.5%)	
Other cardiology	254 (59.2%)	
Non-cardiology	44 (10.3%)	
Years in practice		0.2%
1–5	59 (13.7%)	
6–10	69 (16.0%)	
>10	303 (70.3%)	
Main setting		0.2%
In-hospital	305 (70.8%)	
Outpatient	126 (29.2%)	
HFrEF patients evaluated per month		0.5%
<10	49 (11.4%)	
10–20	160 (37.2%)	
21–40	115 (26.7%)	
>40	106 (24.7%)	

HFrEF, heart failure with reduced ejection fraction.

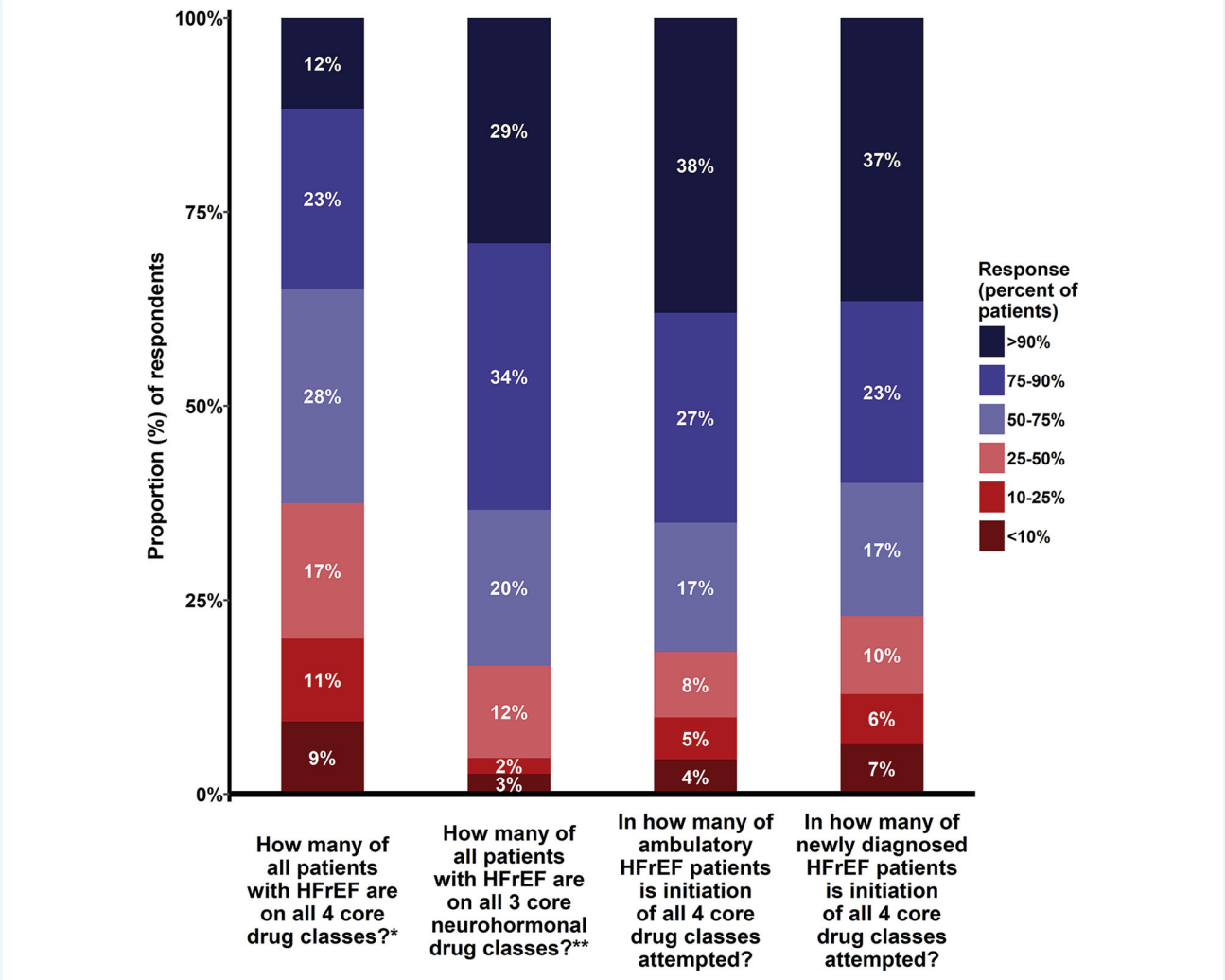


Figure 1 Overall implementation and initiation of core heart failure medications. ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor. *RASi/ARNi, BB, MRA, SGLT2i. **RASi/ARNi, BB, MRA (if SGLT2i was not available for non-diabetes patients in the past 6 months).

of respondents, other cardiology for 59% and non-cardiology for 10%. Approximately 25% of respondents treated >40 patients with HFrEF in a month, and 71% primarily worked in an in-hospital setting. In total, 91 countries were represented among survey respondents (online supplementary *Figure S1*), with the most represented being Spain (9% of respondents), Italy (9%) and the United Kingdom (5%).

Estimated extent of guideline-directed medical therapy implementation

Quadruple HFrEF therapy (RASi/ARNi, beta-blockers, MRA, and SGLT2i) was attempted to be initiated in >90% of ambulatory HFrEF patients according to 38% of respondents, in 75–90% according to 27%, in 50–75% according to 17%, in 25–50% according to 8%, in 10–25% according to 5% and in <10% according to 4% (*Figure 1*). Overall similar estimates were reported for *de novo* HFrEF patients.

When asked to estimate the proportion of HFrEF patients on quadruple therapy, 12% responded >90%, 23% responded 75–90%, 28% responded 50–75%, 17% responded 25–50%, 11% responded 10–25%, and 9% responded <10%. When instead considering triple therapy with RASi/ARNi, beta-blockers and MRA, estimates were higher, with treatment in >90% reported by 29% of respondents, and in 75–90% of patients by 34% of respondents.

Survey participants having HF as their main area of practice and evaluating a greater number of patients with HFrEF per month provided overall higher estimates for treatment and attempted initiation (online supplementary *Figures S2–S5*; *Tables S2* and *S3*). Participant responses did not differ according to years of experience or in-hospital vs. outpatient setting (online supplementary *Tables S4* and *S5*).

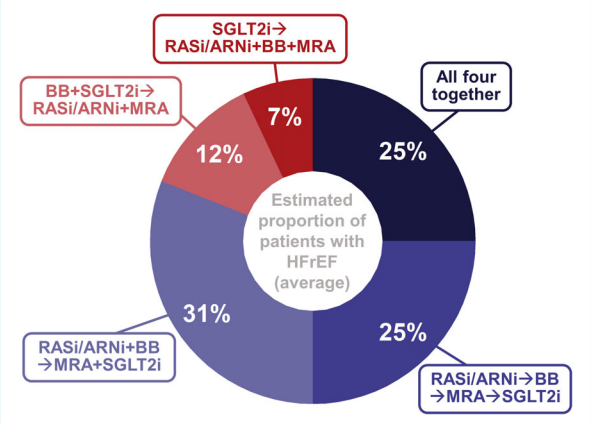


Figure 2 Estimated use of each sequencing strategy when initiating quadruple therapy in patients with newly diagnosed heart failure with reduced ejection fraction (HFrEF). Averaged across surveyed physicians. ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Sequencing approaches and implementation strategies

According to the respondents, a simultaneous initiation of all four drug classes was attempted in average in 25% of patients with newly diagnosed HFrEF (*Figure 2*), the traditional sequential approach (first RASi/ARNi, then a beta-blocker, then an MRA, and last an SGLT2i) again in 25% of patients, whereas the most favoured strategy estimated to be applied in average to 31% of patients included RASi/ARNi + beta-blocker, followed by MRA + SGLT2i. Less common strategies were those that employed an SGLT2i-first approach, i.e. a beta-blocker with an SGLT2i followed by a RASi/ARNi with an MRA (12% of patients), and SGLT2i followed by a RASi/ARNi, a beta-blocker, and an MRA (7% of patients).

The time required to initiate all four foundational treatments was estimated to be 1–2 weeks by 34% of respondents, 1 month by 36%, 3 months by 24%, and ≥6 months by 6% (online supplementary *Figure S6*). The best setting to establish quadruple therapy was in-hospital upon clinical stabilization according to 41% of respondents, in-hospital before discharge according to 45%, outpatient setting shortly following discharge according to 6%, and out of hospital in stable conditions according to 8% (online supplementary *Figure S7*). A majority of respondents were comfortable with following the 2021 ESC HF guideline recommendations regarding the implementation of all four HFrEF drug classes, with 87% of respondents being at least somewhat comfortable (online supplementary *Figure S8*), and higher estimates whether the main area of practice was HF (93%) versus other cardiology (86%) versus non-cardiology (79%) and whether the respondents evaluated more HFrEF patients per month, but not in those with more versus less years of experience. Of non-cardiologists, 21% reported that they were not at least somewhat comfortable with the recommendations (2% uncomfortable, 19% neutral).

Clinical barriers to implementation

The factors that were most frequently listed as a major clinical barrier to the implementation of HFrEF GDMT were, in descending order of frequency, hypotension (selected by 70% of survey respondents), creatinine increase (47%), hyperkalaemia (45%), patient adherence (42%), mild but symptomatic hypotension (33%), and bradycardia (19%) (*Figure 3*).

A majority of respondents were comfortable with managing any listed clinical barrier to implementation; discomfort was most frequently reported for handling patient limited adherence (16% of participants), followed by creatinine increase (13%), hypotension (10%), hyperkalaemia (9%), hypoglycaemia/ketoacidosis (7%), and bradycardia (4%) (online supplementary *Figure S9*).

The most frequently reported primary strategy to manage hypotension was to lower/withdraw diuretic treatment (55% of participants) followed by lower/withdraw ARNi (20%) or RASi (14%) (*Figure 4*; online supplementary *Figure S10*). The primary strategy to manage creatinine increase was to lower/withdraw diuretic treatment (38%), followed by lower/withdraw MRA (22%) or RASi (21%) (online supplementary *Figure S11*). The potassium threshold that warranted therapeutic action was >5.0, >5.5, and >6.0 mmol/L according to 25%, 64%, and 11% of respondents, respectively (online supplementary *Figure S12*), with higher thresholds reported by HF practitioners versus other cardiology versus non-cardiology, but no significant differences according to number of HFrEF patients per month, years of experience, or in-hospital versus outpatient setting. As a first action in managing hyperkalaemia, 54% of respondents would lower/withdraw MRA, 18% would add a novel potassium binder and 10% a resin potassium binder, and 9% would lower/withdraw RASi and 5% ARNi (online supplementary *Figure S13*). The majority of participants (66%) responded that SGLT2i would be the first drug class to initiate in a patient at risk of hyperkalaemia (online supplementary *Figure S14*).

Amongst potential non-clinical/organizational barriers to the implementation of HFrEF GDMT, those most categorized as 'very important' were, in descending order, price of treatment (very important according to 54% of survey respondents), reimbursement limitations (46%), clinician inertia (38%), and polypharmacy (33%) (*Figure 5*). The most favoured strategies to address patient adherence were ambulatory follow-up (83%), patient support programmes (44%), remote monitoring (34%), and patient apps (17%) (online supplementary *Figure S15*).

Discussion

In this international survey, we collected information from >400 physicians regarding their beliefs on the current state of, barriers to, and strategies for the implementation of GDMT in patients with HFrEF. This survey predominantly reflected the views of cardiologists with an interest in HF; 31% reported HF as their main area of practice, and 59% other cardiology. According to our findings: (i) there was a considerable discrepancy between the perceived 'attempted initiation' of GDMT (which nearly 40% of respondents estimated they performed in >90% of patients with HFrEF) and

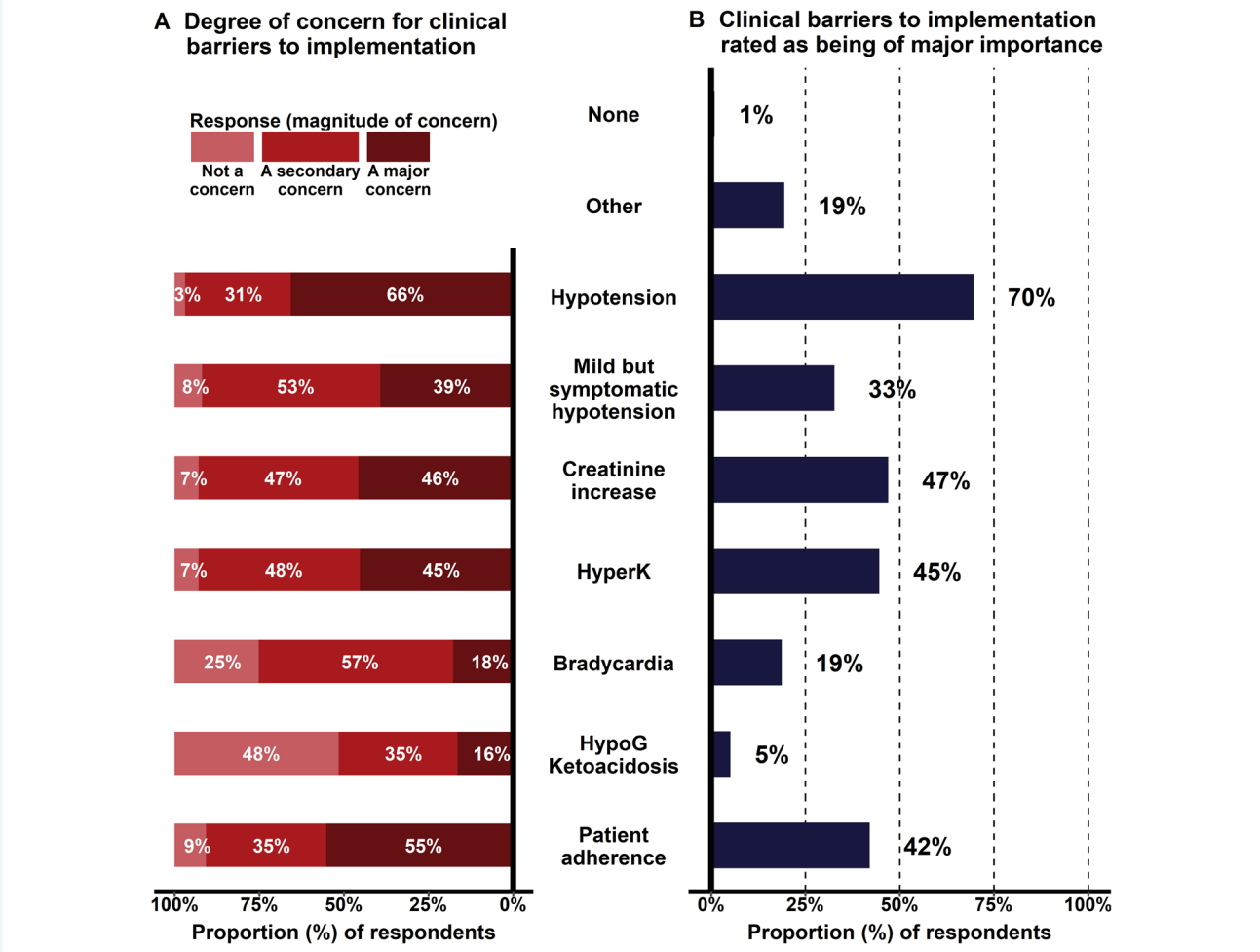


Figure 3 (*A*) Level of concern for each barrier to simultaneous implementation for all core drug classes in heart failure with reduced ejection fraction patients. (*B*) Major clinical barriers/concerns to simultaneous implementation of all four core drug classes in heart failure with reduced ejection fraction patients. HyperK, hyperkalaemia; HypoG, hypoglycaemia.

the perceived population of patients 'on-treatment' with GDMT (which only 12% of respondents estimated was achieved in >90% of patients); (ii) an estimated 25% of patients were initiated with quadruple therapy, 56% with some version of the traditional drug sequence (RASi/ARNi with/followed by beta-blocker, and then MRA with/followed by SGLT2i) and only 19% with a sequence involving an SGLT2i-first approach; (iii) an overwhelming majority of physicians reported being comfortable with the recent guideline recommendations on GDMT in HFrEF, and in dealing with the potential barriers to implementation; (iv) hypotension, renal function impairment, hyperkalaemia, and limited patient adherence were rated as the major barriers to implementation, with hyperkalaemia managed by 54% of treating physicians with lowering/withdrawing of MRA as first choice (*Graphical Abstract*).

Given the profound benefit in terms of patient outcomes achieved by the use of GDMT,[1,2] timely and opportunistic initiation is central. The parallel approach to initiation recommended by the current ESC and American Heart Association/American College of Cardiology guidelines on HF replacing the traditional sequential approach is an attempt to avoid delay deriving from the time-consuming drug up-titration required before the initiation of the following treatment in the algorithm.[9,10,15] However, in this survey, only 63% of respondents estimated that most patients with HFrEF and without contraindications were treated with all four foundational treatments, and 77% that initiation is attempted in most patients with newly diagnosed HFrEF. The low estimate of implemented GDMT could be explained by a perceived limited use of SGLT2i, which had not yet been extensively introduced at the time of the survey.[16] Recent real-word data suggest that implementation of SGLT2i in daily clinical practice might not be challenging,[16] since they have few tolerability issues and interactions with other major drugs. We observed that physicians with HF as their main area of practice reported overall higher estimated GDMT implementation and greater comfort with guidelines. This might suggest that better knowledge dissemination and referral pathways

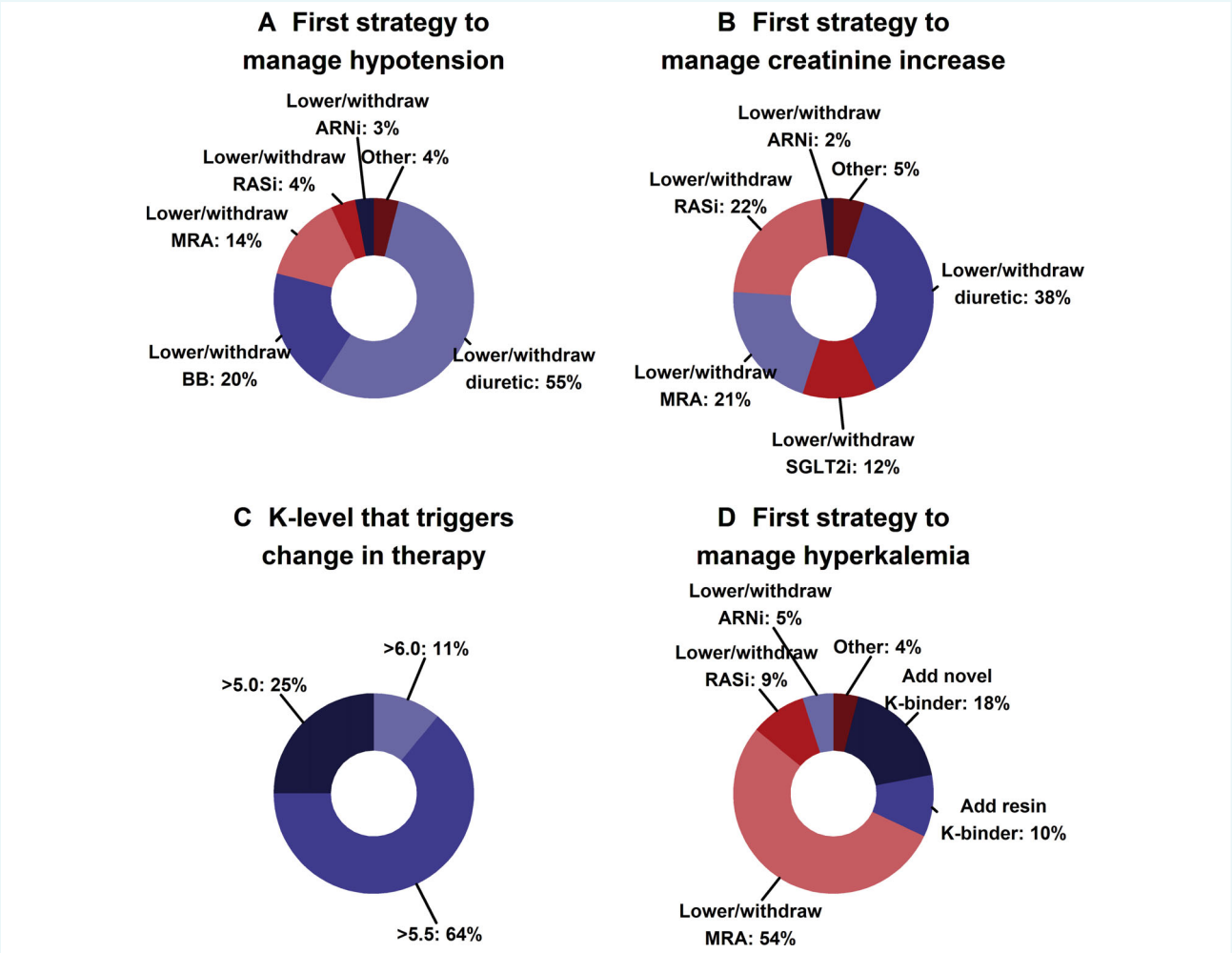


Figure 4 Strategies to manage clinical barriers hypotension (*A*), creatinine increase (*B*), and hyperkalaemia (*C*,*D*). ARNi, angiotensin receptor–neprilysin inhibitor; BB, beta-blocker; K, potassium; MRA, mineralocorticoid receptor antagonist; RASi, renin–angiotensin system inhibitor; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

could be potential targets to improve implementation. The deployment of such efforts has been linked with better treatments and outcomes in HF.[17] The results of the current survey highlight that efforts targeting underuse are still needed to improve outcomes in HFrEF, as also shown by numerous reports from real-world settings.[3,4,18–20]

Approximately 34% of participants estimated that initiation of all four HFrEF foundational medications is feasible within 1–2 weeks, 36% within 1 month, 24% within 3 months, and 6% ≥6 months. This wide range of estimated time-to-initiation amongst physicians might partially be explained by differences in respondents' characteristics including setting and country of care. Prioritizing titration over adding another drug class might also lead some physicians still using a sequential approach to perceive that a longer time is required, although more drug classes at a lower dose might be superior to fewer drug classes at target dose beyond being a faster and more feasible approach.[21] Respondents might also have differing access to transitional care support such as nurse-led HF clinics which are associated with better implementation of HF treatments.[22] The STRONG-HF trial demonstrated the feasibility of rapid initiation and up-titration of GDMT provided dedicated transitional care programmes following a HF hospitalization.[23] This stands in strong contrast to what has been observed in clinical practice, prior to the publication of STRONG-HF, where the average time to initiation of a GDMT (at any dose) was delayed for weeks or more after incident HF as well as after HF hospitalization.[19] In this survey, a majority of respondents stated that GDMT should be initiated during an in-hospital stay. This observation might reflect physicians' real-world experiences that if initiation is not done in-hospital, significant delay often follows.

According to the average respondent in this survey, most (56%) patients are initiated on HF drugs in a sequence that mimics the traditional approach (i.e. RASi/ARNi with/followed by beta-blocker, and then MRA with/followed by SGLT2i). This is consistent with a recent European survey, where the most common responses for

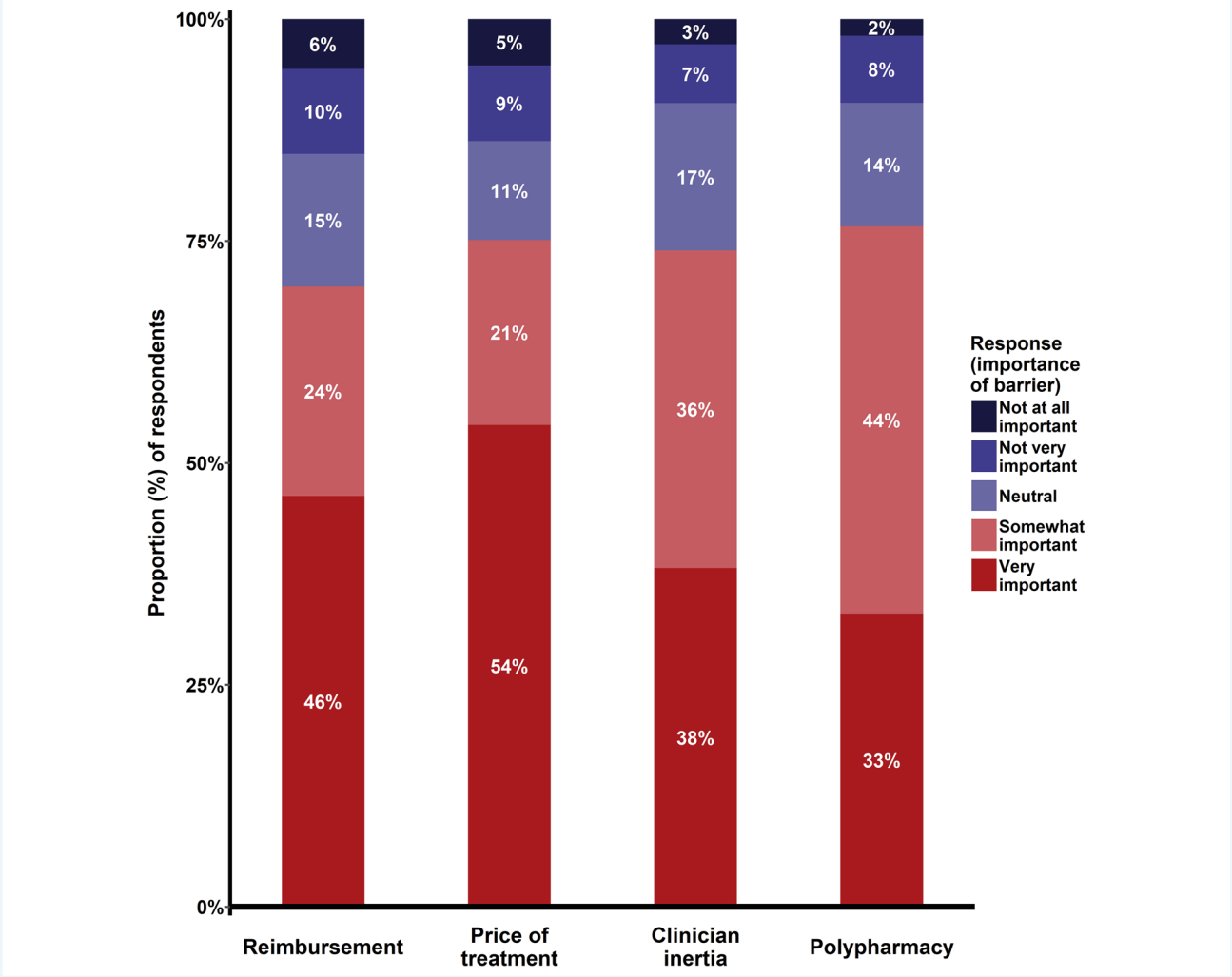


Figure 5 How important are the following non-clinical barriers to implementing treatment based on the 2021 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure?

first, second, third, and fourth initiated HF drugs were RASi/ARNi, beta-blocker, MRA, and SGLT2i, respectively.[24] However, this traditional sequence lacks foundation in biological reasoning or evidence, as treatment effects of the core HF drugs are understood to be independent of background HF therapy.[25] Simultaneous initiation of all four pillars could achieve the fastest implementation of GDMT, but also possibly enhance the risk of tolerability issues. Patient profiling should be considered when approaching treatment initiation and optimization. According to the average participant in this survey, 25% of patients might undergo simultaneous initiation of all four GDMT therapies. Others have suggested that opting for SGLT2i as the first drug might offer rapid initiation without compromising safety, due to renal benefits and limited effects on potassium and blood pressure.[11,12] However, according to the participants in this study, only 19% of HFrEF patients would be allocated to an SGLT2i-first approach. This might be explained by the relatively recent introduction of SGLT2i in HF and more experience amongst clinicians in prescribing the other drug classes at the time of the survey, and is consistent with findings that initiation of novel GDMTs are disproportionately delayed.[19]

Widespread implementation of GDMT in HF is impeded by clinical as well as non-clinical barriers. Two major clinical barriers identified by most participants were hypotension (70%) and creatinine increase (47%) which were most frequently addressed by weaning diuretic therapy. This might reflect that physicians appropriately prioritize evidence-based GDMT over diuretic therapy, which, although important to maintain euvolaemia, lacks evidence of prognostic benefits.[26] It is important to note that mild hypotension does not necessarily require a change in HF therapy.[27] Moreover, small transient increases in creatinine are expected when initiating SGLT2i and RASi/ARNi, but are not associated with less treatment benefit. Hyperkalaemia was perceived as a major barrier by 45% of respondents. Although hyperkalaemia is common and associated with higher mortality in HF,[28] part of this association might be due to hyperkalaemia prompting physicians to withdraw

MRA, RASi and ARNi.[29] Our findings highlight actual/fear for hyperkalaemia as a major reason for MRA underuse in this setting. However, although in patients with/at risk of hyperkalaemia several trials have demonstrated that novel potassium binders facilitate the continuation of MRA treatment,[30–33] among survey respondents only 18% would select a novel potassium binder (and 10% a resin potassium binder), whereas far more (54%) would instead wean MRA treatment. Additionally, although guidelines recommend maintaining MRA dose whether potassium ≤5.5 mmol/L,[10] 25% of participants in this survey would make therapy changes already at potassium levels >5.0 mmol/L. These data clearly highlight that overcaution might cause missed initiation/premature discontinuation of MRA, as has been observed in real-world data,[29] and more awareness on the clinical usefulness of potassium binders in this setting is needed in clinical practice. A certain proportion of barriers might be also overcome by access to stricter follow-up, drug layering according to patient profiles,[8] and use of further 'enablers'—for example, by harnessing the nephroprotective and slight potassium-lowering effects of SGLT2i to enable the initiation of MRA.[34]

Patient adherence was a major barrier to implementation according to 42% of participants in this survey. Previous studies have shown that adherence is an important issue in HF, with the proportion of days covered as low as 42% in patients prescribed a RASi, a beta-blocker and an MRA.[35] Importantly, polypharmacy was associated with poor adherence,[35] and recognized as an important clinical barrier by 77% of survey participants, which might lead to speculation that a single-pill combination might be an option also in HF, as a similar approach has been reported to improve outcomes in primary and secondary cardiovascular prevention.[36,37] An ongoing trial is evaluating a single-pill combination strategy in patients with HFrEF.[38] Ambulatory follow-up was the most favoured strategy to address non-adherence, although benefits of follow-up strategies on long-term adherence specifically have been found to be elusive.[39]

Some limitations of the present study deserve acknowledgment when interpreting its results. First, physicians who participated in the survey were likely to have particular interest in the field of HF and were predominantly cardiologists, with the majority encountering >20 HFrEF patients per month. Therefore, the results might not be generalizable to the broader cohort of physicians who treat patients with HF, and our results might overestimate the quality of the current HF management and likely represent an optimistic view on physician comfort and GDMT implementation. Of note, a large proportion of patients with HF are treated in the primary care setting, and by physicians who see few HFrEF patients per month.[40] The low representation of general practitioners/non-cardiologists to this survey is therefore a limitation. For broader evaluation of HFrEF caregivers in future surveys, directed efforts to reach non-cardiologists (and HF nurse clinics) are encouraged. Second, the survey did not involve any patient group/organization, which could have revealed different perspectives on barriers and strategies to improve implementation. Third, responses to this survey were collected prior to the publication of STRONG-HF,[23] which provided important evidence for rapid titration of HFrEF medications. Fourth, the sample size could not rule out small-to-moderate differences between respondent subgroups.

Conclusion

In this international physician survey, most participants were comfortable with implementing GDMT according to the 2021 ESC HF guidelines, but <40% of participants estimated that >90% of patients with HFrEF without contraindications received all core pillars of HFrEF GDMT. Most physicians favoured traditional drug sequencing strategies over simultaneous initiation or SGLT2i-first sequences. MRA and RASi/ARNi down-titration and discontinuation represented a common approach to hyperkalaemia, despite the guideline recommendation of managing hyperkalaemia with potassium binders instead of reducing GDMT. Our findings highlight the need to further improve implementation of GDMT in HFrEF, and target important perceived clinical and non-clinical barriers to implementation by ad-hoc strategies.

Supplementary Information

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

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