

Personalized care of patients with heart failure: are we ready for a REWOLUTION? Insights from two international surveys on healthcare professionals' needs and patients' perceptions

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Aims

Guidelines for the management of heart failure (HF) are evolving, and increasing emphasis is placed on patient-centred care. As part of the REWOLUTION HF (REal WORld EdUcATION in HF) programme, we conducted two international surveys aimed at assessing healthcare professionals' (HCPs) educational needs and patients' perspectives on the care of HF.

Methods and results

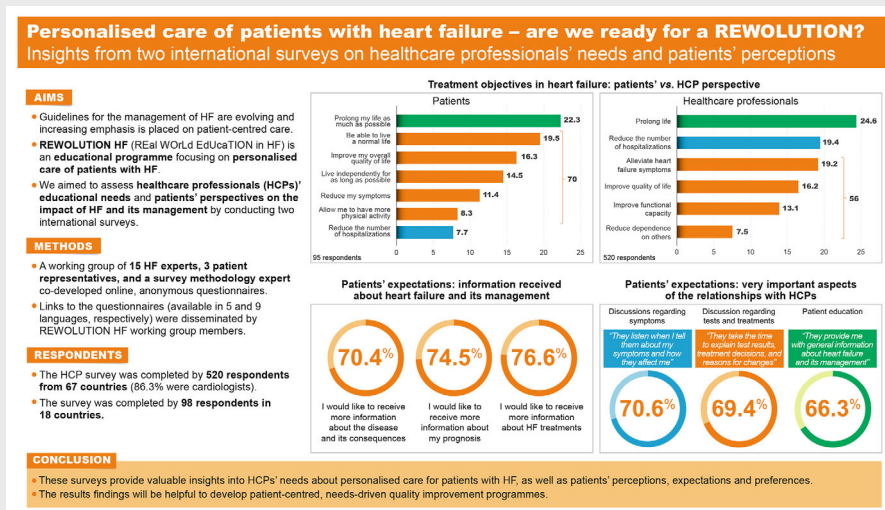
Anonymous online questionnaires co-developed by HF experts and patients assessed HCPs' educational needs (520 respondents, mostly cardiologists, in 67 countries) and patients' perceptions on HF impact and management (98 respondents in 18 countries). Among HCPs, 62.7% prioritized rapid initiation of all guideline-mandated medications over up-titration of some medications, and 87.7% always or frequently discussed treatment goals with patients. There was good agreement between HCPs and patients on key treatment goals, except for a greater emphasis on reducing hospitalizations among HCPs. The most frequently cited barriers to the provision of guideline-recommended pharmacological therapy were treatment side effects/intolerance, complex treatment regimens, low blood pressure, cost/reimbursement issues, and low estimated glomerular filtration rate. Most patients (81.6%) reported no difficulties taking medications as prescribed, although 21.4% felt they were taking too many pills. Patients wanted more information about HF and its consequences, prognosis, and treatments (70.4%, 74.5% and 76.6%, respectively). Cardiologists were the preferred source of information about HF, followed by general practitioners and HF nurses.

Conclusions

These surveys provide valuable insights into HCPs' needs about personalized care for patients with HF, as well as patients' perceptions, expectations and preferences. These findings will be helpful to develop patient-centred, needs-driven quality improvement programmes.

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Graphical Abstract



Personalized care of patients with heart failure (HF) – are we ready for a REVOLUTION? Insights from two international surveys on healthcare professionals' (HCP) needs and patients' perceptions.

Keywords

Heart failure • Guideline-directed medical therapy • Personalized care • Patient engagement • Treatment objectives

Introduction

Guidelines for the management of heart failure (HF) are evolving, with a move away from traditional sequential initiation and up-titration of core disease-modifying agents^{1,2} towards rapid, concurrent initiation of foundational therapies^{3–5} as well as a growing emphasis on personalized treatment^{6,7} and patient engagement.⁸ These changes are being driven by the wealth of evidence supporting the beneficial effects of the four 'pillars' of foundational therapies, namely angiotensin-converting enzyme inhibitors/angiotensin receptor–neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter 2 inhibitors, on outcomes in patients with HF with reduced ejection fraction (HFrEF), with the greatest benefit observed in patients receiving all four classes of drugs.⁹ The former stepwise approach to HFrEF treatment is thought to have contributed to treatment underutilization.⁷ Research has consistently shown that a significant proportion of patients with HFrEF do not receive one or more classes of the recommended core therapies and/or drug doses are not titrated to recommended levels when the sequential approach to treatment initiation is used.^{10–13} This is particularly true in older patients and those with comorbidities,¹⁴ and in those living in low- and middle-income countries.¹⁵ Underutilization of guideline-recommended HF therapies results in worse outcomes with respect to mortality and HF-related hospitalization.^{16,17}

At the same time, intelligent application of guideline-directed medical therapy (GDMT) also needs to take into account the

patients' profiles, their perspective, and opportunity for shared decision-making to achieve greater efficacy and adherence. Following the release of the latest European Society of Cardiology (ESC) guidelines for the management of HF³ supporting rapid, concurrent initiation of foundational therapies and the publication of the Heart Failure Association (HFA) of the ESC consensus paper on individualized patient profiling⁶ for tailoring GDMT, the REVOLUTION HF (REal WORld EdUcation in HF) educational programme was initiated. REVOLUTION HF is a needs-driven, targeted educational initiative with the aim of optimizing implementation of personalized HF treatment and accelerating adoption of this important new approach into clinical practice. To inform the development of the REVOLUTION HF programme and maximize its impact, international surveys were carried out to assess both healthcare professionals' (HCPs) educational needs and patients' perspectives on the impact of HF and its management.

Methods

Open science statement

We were guided by the CHERRIES reporting guideline when reporting our study.¹⁸ The full survey can be accessed in online supplementary Appendix S1 and Appendix S2.

Survey design

Purpose-built surveys of HCPs' educational needs and patients' perspectives were designed by a working group of 15 HF experts, three

patient representatives, and a survey methodology expert. The Global Heart Hub (GHH), an international coalition of patient associations, involved the patient representatives on co-creation of the surveys, discussion of the results and manuscript preparation and/or review. The questionnaires were developed during preparation meetings by three working group members (EAJ, PL, AJSC) with support from a qualitative research design expert (KC) and a medical education company (MedEd Global Solutions, Paris, France), discussed during a plenary working group meeting held in July 2021, revised and circulated by email in August 2021, and finalized in September 2021.

The HCP survey encompassed 11 questions about the respondent and 12 survey questions, and the patient survey included seven questions about the respondent and 11 survey questions. For most questions, respondents were asked to choose between a range of possible answers. However, there were a few exceptions: respondents were sometimes asked to allocate a total of 100 points across the possible answers or to select five answers and to rank them from 1 to 5 (the resulting cumulative score was calculated by assigning 5 points to each 'rank 1' response, 4 points to each 'rank 2' response, 3 points to each 'rank 3' response, 2 points to each 'rank 4' response, and 1 point to each 'rank 5' response).

The English version of the surveys on HCPs' educational needs was translated into Chinese, Portuguese (Brazil), Russian and Spanish, whereas the English version of the survey on patients' needs and perceptions was translated into Chinese, Dutch, French, German, Polish, Portuguese (Brazil), Russian and Spanish. Online versions of each questionnaire were set up using QuestionPro, a software for online surveys (<https://www.questionpro.com>). Pilot testing was conducted to evaluate readability of the questionnaires and functionality of the online system. HCPs and patients participated in the surveys by clicking on the QuestionPro links. The average time taken to complete the online survey was 13.7 min for HCPs and 15.3 min for patients. No personal information was collected during the process.

Responses were collected between August and December 2022. Links to the questionnaires were disseminated by REVOLUTION HF working group members (15 HF experts in 11 countries) by email via their professional networks, with support from the Optimize Heart Failure Care programme¹⁹ national coordinators (72 coordinators in 42 countries). Patients diagnosed with HF were invited to take part in the survey on an individual basis, either by an HCP or by a patient representative. In China, the HCP survey link was also disseminated via MedLive, a platform that provides professional medical information services for doctors. Given the wide dissemination of the questionnaire in China, the number of responses for the Chinese version of the HCP survey was limited to a maximum of 250. Compilation and analysis of the fully anonymous raw data were performed by MedEd Global Solutions.

Data analysis

We report basic descriptive statistics for all items (e.g. counts and percentages).

Results

Demographics

The HCP survey was completed by 520 respondents from 67 countries (information about respondents is described in Table 1). Geographic representation was as follows: Americas, 12.5%; Asia-Pacific, 59.8%; Europe and Central Asia, 16.9%; and Middle

Table 1 International surveys on healthcare professionals' educational needs: information about respondents (*n* = 520)

Age (years), <i>n</i> (%)	
25–34	64 (12.3)
35–44	231 (44.4)
45–54	148 (28.5)
55–64	59 (11.3)
65–74	17 (3.3)
≥75	1 (0.2)
Birth sex, <i>n</i> (%)	
Male	337 (64.8)
Female	180 (34.6)
Prefers not to specify	3 (0.6)
Profession, <i>n</i> (%)	
Physician	509 (97.9)
Nurse	11 (2.1)
Speciality (physicians), <i>n</i> (%) (<i>n</i> = 509)	
Cardiology	449 (88.2)
Internal medicine	34 (6.7)
Other	26 (5.1)
Stage in professional career (cardiologists), <i>n</i> (%) (<i>n</i> = 449)	
Cardiologist in training	29 (6.5)
Certified cardiologist with ≤5 years of practice	46 (10.2)
Certified cardiologist with >5 years of practice	374 (83.3)
Main practice setting – level of care, <i>n</i> (%)	
Primary care	46 (8.9)
Secondary care	123 (23.6)
Tertiary care	351 (67.5)
Main practice setting – type of institution, <i>n</i> (%)	
Public hospital (teaching)	322 (61.9)
Public hospital (non-teaching)	85 (16.3)
Public outpatient clinic	16 (3.1)
Private hospital	68 (13.1)
Private outpatient practice	21 (4)
Other	8 (1.6)
Proportion of working time spent in clinical practice, <i>n</i> (%)	
0–20%	16 (3.1)
>20–40%	29 (5.6)
>40–60%	70 (13.5)
>60–80%	213 (40.9)
>80–100%	192 (36.9)
Proportion of clinical practice time dedicated to heart failure, <i>n</i> (%)	
0–20%	39 (7.5)
>20–40%	118 (22.7)
>40–60%	202 (38.9)
>60–80%	123 (23.6)
>80–100%	38 (7.3)

East and Africa, 10.8%. Ten countries had 10 or more respondents: China (*n* = 250), Argentina, (*n* = 19), United Arab Emirates (*n* = 18), Brazil (*n* = 17), Italy (*n* = 15), Malaysia (*n* = 15), Russia (*n* = 11), Colombia (*n* = 10), Indonesia (*n* = 10), and Saudi Arabia (*n* = 10). The majority of respondents worked in tertiary care (67.5%) and secondary care (23.6%), mainly in a public teaching

hospital (61.9%) or a public non-teaching hospital (16.3%). Most respondents were cardiologists (86.3%), of whom 83.3% had over 5 years of practice.

The patient survey was completed by 98 respondents in 18 countries (information about respondents is described in Table 2). The proportion of female patients was 61.2%, and 56.1% of respondents were between 55 and 74 years old. Geographic representation was as follows: Americas, 25.5%; Asia-Pacific, 24.5%; and Europe and Central Asia, 50%. The majority (61.5%) lived in cities with over 50 000 inhabitants, and 66.7% had a post-secondary

Table 2 International surveys on patients' needs and perceptions: information about respondents ($n = 98$)

Age (years), n (%)	
25–34	0 (0)
35–44	13 (13.3)
45–54	20 (20.4)
55–64	30 (30.6)
65–74	25 (25.5)
≥75	10 (10.2)
Birth sex, n (%)	
Male	38 (38.8)
Female	60 (61.2)
Prefers not to specify	0 (0)
Place of life, n (%) ($n = 96$)	
Rural area or town with less than 1000 inhabitants	19 (19.8)
Town/city with 1000–50 000 inhabitants	18 (18.7)
City with 50 000–1 000 000 inhabitants	28 (29.2)
City with more than 1 000 000 inhabitants	31 (32.3)
Highest level of schooling completed, n (%) ($n = 96$)	
Primary education (typically up to 11 years of age)	7 (7.3)
Secondary education (typically up to 18 years of age)	25 (26)
Post-secondary education (typically over 18 years of age)	64 (66.7)
Time since heart failure diagnosis (years), n (%) ($n = 95$)	
<1	7 (7.4)
1–5	37 (38.9)
6–10	24 (25.3)
11–15	14 (14.7)
16–20	7 (7.4)
>20	6 (6.3)
Concomitant chronic diseases, n (%)	
High blood pressure	45 (45.9)
Blood vessel disease	19 (19.4)
Heart rhythm disturbances	48 (49)
Heart valve disease	13 (13.3)
Kidney disease	12 (12.2)
Lung disease	6 (6.1)
Diabetes	26 (26.5)

education. Time since HF diagnosis was 1–5 years for 38.9%, 6–10 years for 25.3%, and 11–15 years for 14.7%. The most common self-reported concomitant diseases were heart rhythm disturbances (49%), hypertension (45.9%) and diabetes (26.5%).

Treatment objectives: healthcare professionals' versus patients' perspective

Respondents to the HCP survey rated prolonging life (mean 24.6/100 points), reducing the number of hospitalizations (mean 19.4/100 points), alleviating HF symptoms (mean 19.2/100 points), and improving quality of life (mean 16.2/100 points) as the main objectives of HF management (Figure 1). The number of points assigned to the objective of prolonging life was highest among cardiologists in training (mean 30.3/100 points), followed by certified cardiologists with ≤5 years of practice (mean 24.4/100 points), and certified cardiologists with >5 years of practice (mean 23.5/100 points). Most respondents reported discussing treatment goals with their patients either always (33.3%) or frequently (54.4%).

Patients rated prolonging life (mean 22.3/100 points), being able to live a normal life (mean 19.5/100 points), improving overall quality of life (mean 16.3/100 points) and living independently for as long as possible (mean 14.5/100 points) as the most important objectives of treatment, whereas they assigned the lowest number of points to reducing the number of hospitalizations (mean 7.7/100 points) (Figure 1). Overall, patients assigned a total of 70/100 points to treatment objectives related to symptoms, functional capacity and quality of life, compared with 56/100 points for HCPs.

Influences on clinical practice and adherence to guidelines

Amongst participants taking part in the HCP survey, guidelines and position papers were reported to have the strongest impact on clinical practice (mean 38.2/100 points). This ranged from a mean 31.6/100 points in Asia-Pacific respondents to a mean 68.9/100 points in respondents from the Americas. Cardiologist respondents said they referred most frequently to ESC HF guidelines (mean 39.3/100 points), local national guidelines (mean 24.1/100 points) and US (ACC/AHA/HFSA) guidelines (mean 22.7/100 points). Other significant influences on clinical practice were reports from randomized controlled trials (mean 15.8/100 points), reports from observational studies and registries (mean 13.8/100 points), hospital protocols and quality improvement programmes (mean 12/100 points), international and national congresses (mean 11.9/100 points), guidance from experts, mentors or respected colleagues (mean 10.8/100 points), online educational initiatives (mean 10.1/100 points), and discussions with patients and their relatives (mean 8.5/100 points).

In a newly diagnosed patient, 62.7% of respondents stated they would give priority to initiating all guideline-recommended medications versus achieving target doses for some medications if both objectives could not be achieved. However, 29.2% of respondents reported that they still followed the conventional sequencing of drug treatment, as opposed to a more personalized approach, in

Treatment objectives in heart failure: patients' vs. healthcare professionals' perspective

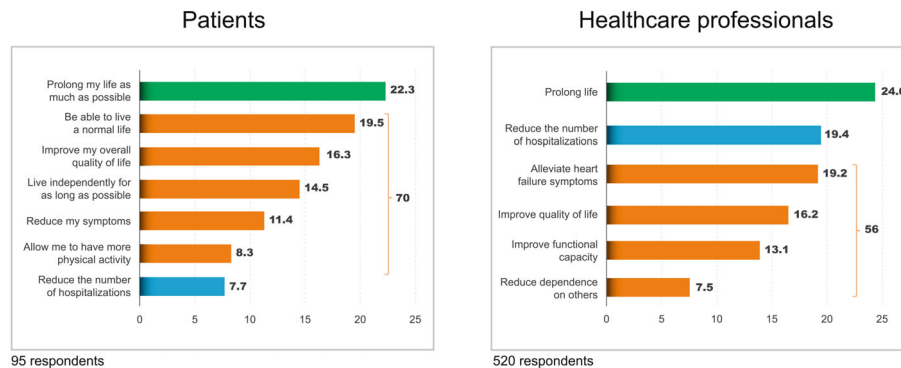


Figure 1 Treatment objectives in heart failure: patients' versus healthcare professionals' perspective. Respondents were asked to allocate a total of 100 points across the proposed answers.

Table 3 Relative importance of barriers to the provision of guideline-recommended pharmacological therapy (healthcare professional survey, 520 respondents)

Rank	Barrier to guideline-recommended pharmacological therapy	Cumulative score
1	Treatment side effects/intolerance	1556
2	Complex treatment regimen requiring administration of numerous drugs	1228
3	Low blood pressure	1150
4	Cost/reimbursement issues	1104
5	Low estimated glomerular filtration rate	853
6	Older age	517
7	Low heart rate	393
8	Frailty	360
9	Hyperkalemia	316
10	Cognitive impairment	156
11	Social isolation	84
12	Depressive symptoms	56

over 60% of their patients with HF. The relative importance of selected barriers to the provision of guideline-recommended pharmacological therapy is described in *Table 3*. Treatment side effects/intolerance (cumulative score [CS] 1556), a complex treatment regimen requiring administration of numerous drugs (CS 1228), a low blood pressure (CS 1150), cost/reimbursement issues (CS 1104) and a low estimated glomerular filtration rate (CS 853) were considered the greatest barriers to the implementation of GDMT.

Interventions to improve quality of care

The interventions most frequently recommended by HCP survey respondents to improve quality of care were increasing patient follow-up frequency (mean 21/100 points), setting up a

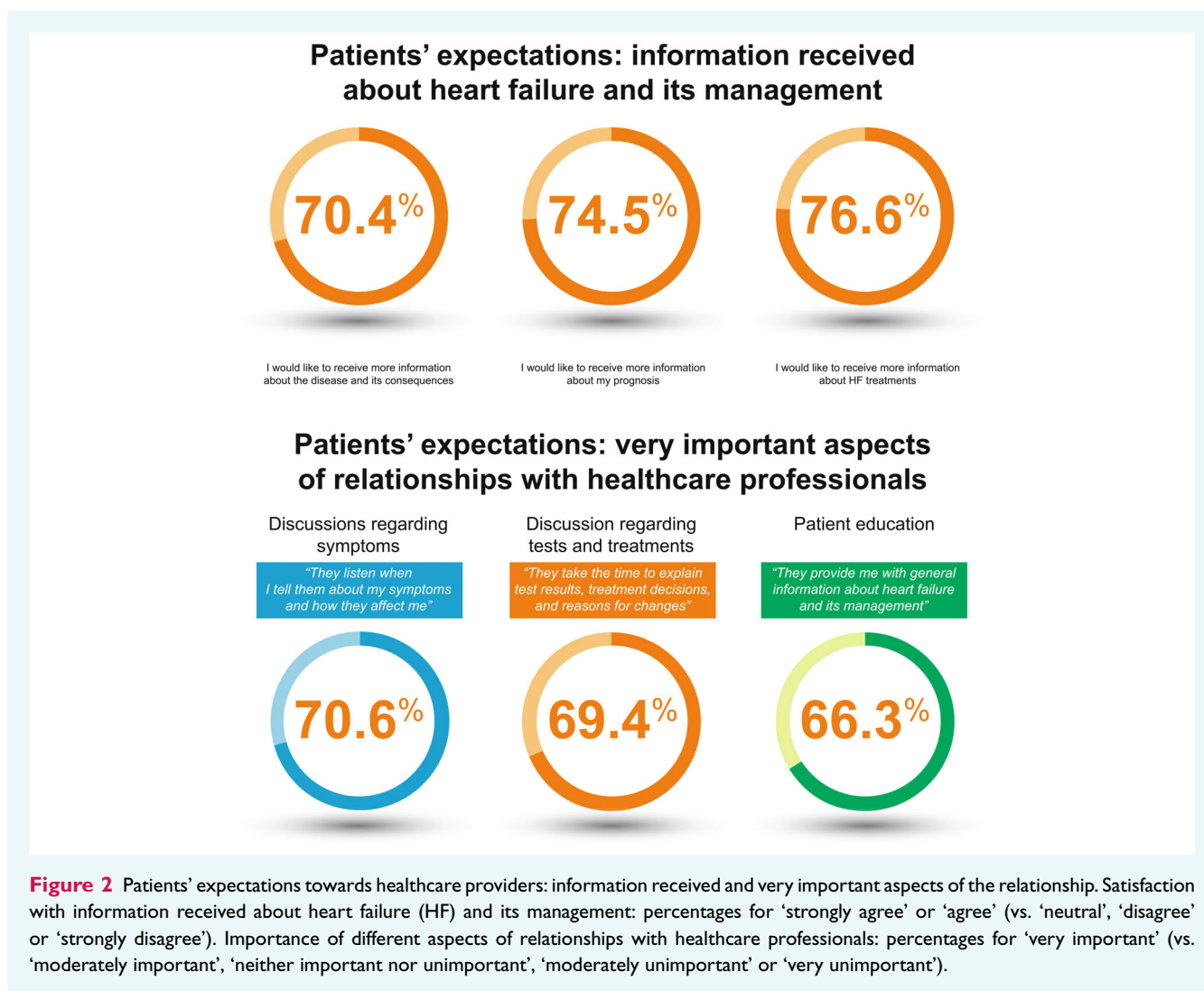
Table 4 Relative impact of selected symptoms on quality of life (patient survey, 98 respondents)

Rank	Impact of symptoms on your quality of life	Cumulative score
1	Fatigue	285
2	Shortness of breath when you exert yourself or when you lie down	267
3	Reduced ability to exercise	230
4	Swelling in your legs, ankles, feet	149
5	Rapid or irregular heartbeat	110
6	Dizziness	104
7	Increased need to urinate at night	65
8	Swelling of your abdomen	65
9	Persistent cough or wheezing	63
10	Rapid weight gain from fluid retention	51
11	Lack of appetite	22
12	Nausea	14

multidisciplinary HF team (mean 19.3/100 points), and improving coordination with primary care physicians (mean 17.3/100 points). Amongst various educational tools, updates and reminders on current clinical practice guidelines were rated as very helpful by the greatest proportion of respondents (64.8%).

Patients' experience: disease and treatment burden

In the patient survey, the symptoms felt to have the greatest impact on quality of life were fatigue (CS 285), shortness of breath (CS 267), reduced ability to exercise (CS 230), swelling legs, ankles, feet (CS 149), and a rapid or irregular heartbeat (CS 110) (*Table 4*).



The median number of prescribed pills taken per day was 8 (range 2–25), including 6 (range 1–25) for heart disease. Most respondents (81.6%) reported they had no difficulties taking their medications as prescribed; however, 28.6% reported they sometimes forgot to take them, and 21.4% felt they had to take too many pills.

Over the last 12 months, respondents had had a median of 3 (range 0–20) consultations with a cardiologist, 1 (0–12) with a non-cardiologist specialist physician, 1 (0–20) with a HF nurse, and 2 (0–18) with a general practitioner/family physician; they had also required a median of 1 (0–11) urgent care visit. The proportion of consultations conducted remotely (by phone, video, etc.) was 0–20% for 58.1% of respondents, 20–40% for 14.3%, 40–60% for 13.3%, and over 60% for 14.3%.

Patients' expectations: relationship with healthcare professionals

Three quarters (76.4%) of patient respondents were satisfied with their follow-up appointments. 49% wanted more frequent

appointments with a cardiologist and 43.9% wanted more frequent appointments with a specialized HF nurse. While most patients agreed that they had a clear understanding of HF and its consequences (82.7%), most of them also wanted more information about the disease and its consequences (70.4%), about their prognosis (74.5%), and about HF treatments (76.6%) (Figure 2).

The three aspects of their relationship with HCPs that were rated as very important by the greatest percentage of respondents were: (1) "They listen when I tell them about my symptoms and how they affect me" (70.6%), (2) "They take the time to explain test results, treatment decisions, and reasons for changes" (69.4%), and (3) "They provide me with general information about heart failure and its management" (66.3%) (Figure 2).

The cardiologist was the preferred source of information about HF and its management (CS 461), followed by the general practitioner (CS 270) and the HF nurse (CS 270), patient groups/associations (CS 150), printed books, articles and leaflets (CS 140), internet research (CS100), and mobile health applications (CS79).

Discussion

We conducted a large-scale international cross-sectional survey of HCPs and patients related to personalized care of patients with HF (*Graphical Abstract*). Key findings from these surveys are that: (i) nearly two thirds of respondents to the HCP survey now prioritize early and rapid initiation of all guideline-recommended medications for HF compared with achieving target doses of some medications if both objectives cannot be achieved; (ii) there is good alignment between HCP and patient respondents on treatment goals, except for a greater emphasis on reducing hospitalizations among HCPs; and (iii) there are clear clinical and financial barriers to the provision of guideline-recommended pharmacological therapy, creating inequities which need to be addressed. It is encouraging to see that recent changes in guideline recommendations for rapid initiation of foundational therapies are already being reflected in clinical practice, and that clinicians increasingly recognize the importance of both survival and quality of life for patients with HF.

The HCP survey provides valuable insights into the barriers to the provision of guideline-recommended pharmacological therapy. These demonstrate that suboptimal adherence to recommendations should not be attributed solely to limitations on access to specialist care, organizational deficiencies, or clinical inertia. Treatment side effects and patient characteristics and comorbidities (e.g. a low blood pressure or a low estimated glomerular filtration rate), as well as cost/reimbursement issues, clearly play a significant role in treatment decisions and optimization. Gaps in adherence to guidelines have previously been shown even in specialized HF settings and were related mainly to physiological factors rather than inertia.²⁰ Older age and a history of stroke/transient ischaemic attack – potential markers of frailty – were associated with suboptimal doses of GDMT, and the authors suggested that an individualized rather than a ‘one-size-fits-all’ approach may be required.²⁰

Clinical barriers to treatment such as those reported in our survey were addressed in the recent ESC HFA consensus document on patient profiling for tailoring medical therapy in HF.⁶ For example, the publication acknowledged that most core therapies for HFrEF affect blood pressure, heart rate and potassium levels, and require dose adjustments and gradual dose up-titration.⁶ This consensus document proposed nine phenotypes of patients with individual needs for up-titration. For patients in each profile group, the consensus described a personalized approach involving adjustment of GDMT according to haemodynamic parameters and kidney function. For example, in patients with a heart rate <60 bpm and a blood pressure <90/60 mmHg, but without atrial fibrillation or chronic kidney disease, the document recommends reducing beta-blocker dose and adding vericiguat while, for a patient with a heart rate >70 bpm and a blood pressure >90/60 mmHg, but without atrial fibrillation or chronic kidney disease, the document recommends maintaining the dose of all foundational therapies and adding ivabradine. The authors recognize that, as randomized clinical trials have excluded patients with a low blood pressure, a low heart rate or a low estimated glomerular filtration rate, and used standardized drug titration protocols, there is still a need for randomized clinical trials with more real-life patients, including better

female representation, and testing of different strategies for optimizing medication.⁶

In taking a personalized approach to optimization of foundational therapies in patients with HFrEF, Sharma *et al.*⁷ recently showed how, by anticipating potential side effects in patients with hypotension, declining renal function or hyperkalaemia, and acting to prevent them, it should be possible for clinicians to start patients with HFrEF on foundational therapies in 4 weeks.

In addition to taking into account patients’ clinical characteristics, their preferences and objectives need to be considered when making decisions about foundational therapies – as highlighted in the recent ESC HF guidelines.³ Research has demonstrated that, although patients express growing trust and optimism with time after their HF diagnosis, some negative emotions such as fear remain, and the emotional rollercoaster that some patients experience needs to be considered when discussing treatment options with patients.²¹ It is encouraging that, in our HCP survey, nearly 90% of respondents said they frequently or always discussed treatment goals with their patients. Healthcare providers need to understand patients’ expectations, their experiences with symptoms and treatment, and their need for knowledge, skills and support. The results of our patient survey provide valuable key insights about what patients regard as priorities in the treatment of HF. For example, it is clear that patients valued their HCPs for discussions about their symptoms, explanations of test results and treatment decisions, and as a source of general information about HF and its management. Many wanted to obtain more information about HF treatments and about their prognosis, and to have more time with HCPs. Our findings are consistent with the current concepts of shared decision-making with patients in complex treatment regimens with the results of some other recent studies of educational needs of patients with HF. In one such study, top educational needs for patients, cited by both patients and HF care providers, included what patients should know to do if their symptoms worsened, and what are the signs and symptoms of worsening HF.²² However, patients were more concerned than HCPs about what to do if problems occur with medications, and what would happen if they could not follow their doctor’s recommendations.

In our survey, the cardiologist remained the preferred source of information about HF and its management. General practitioners and HF nurses were also seen as valued information providers but some traditional sources of information such as books, articles, leaflets, internet sources and mobile health applications were rated quite poorly. This underlines the importance of personalized HF education tailored to individual patient needs, with treatment decisions aligned with patients’ values, goals, and preferences. The introduction of a Patient/Caregiver Charter for HF, as has been carried out in Canada, can support these objectives, with the overall goal of establishing high-quality, consistent care [<https://heartlife.ca/resources/>]. Such charters provide a guide to patients and caregivers about what to expect throughout their HF care, empower them to ask questions that matter to them, and understand their individual responsibilities for their own health. For healthcare providers, they support understanding of the lived experience of HF, recognition of opportunities within systems of care and identification of solutions that fit with local settings. For

policymakers and private payers, they guide the identification of opportunities within their jurisdictions and support development of solutions.

Our survey has several limitations. The sample size of both HCPs and patients was small, and there was an imbalance between HCP and patient participation. There was an over-representation of Chinese HCPs whereas a limited number of European HCPs took part in the survey. Although recommendations are globally accepted, we cannot exclude a bias due to this geographic imbalance. Most of the HCPs participating in the survey were cardiologists who worked in tertiary/secondary care. Therefore, the perception of the objectives of treatment might have been different if a greater number of general practitioners and HF nurses had taking part in the survey. Two-thirds of the patients who participated in the survey had a post-secondary education. The perspectives and expectations of the respondents may differ from those of less educated patients. Finally, participation was made on a voluntary basis and was not based on a random selection of participants.

The results of the REVOLUTION HF international surveys provide valuable insight into HCPs' educational needs with respect to personalized care of patients with HF as well as into patients' perceptions on the impact of HF and its management and their expectations towards healthcare providers. This information will be helpful to develop patient-centred, customized and needs-driven quality improvement programmes.

Supplementary Information

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

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