

Optimizing outcomes in heart failure: 2022 and beyond

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Abstract

Although the development of therapies and tools for the improved management of heart failure (HF) continues apace, day-to-day management in clinical practice is often far from ideal. A Cardiovascular Round Table workshop was convened by the European Society of Cardiology (ESC) to identify barriers to the optimal implementation of therapies and guidelines and to consider mitigation strategies to improve patient outcomes in the future. Key challenges identified included the complexity of HF itself and its treatment, financial constraints and the perception of HF treatments as costly, failure to meet the needs of patients, suboptimal outpatient management, and the fragmented nature of healthcare systems. It was discussed that ongoing initiatives may help to address some of these barriers, such as changes incorporated into the 2021 ESC HF guideline, ESC Heart Failure Association quality indicators, quality improvement registries (e.g. EuroHeart), new ESC guidelines for patients, and the universal definition of HF. Additional priority action points discussed to promote further improvements included revised definitions of HF 'phenotypes' based on trial data, the development of implementation strategies, improved affordability, greater regulator/payer involvement, increased patient education, further development of patient-reported outcomes, better incorporation of guidelines into primary care systems, and targeted education for primary care practitioners. Finally, it was concluded that overarching changes are needed to improve current HF care models, such as the development of a standardized pathway, with a common adaptable digital backbone, decision-making support, and data integration, to ensure that the model 'learns' as the management of HF continues to evolve.

Keywords Heart failure; Medical decision making; Quality improvement; Clinical practice guidelines; Multidisciplinary management; Pharmacotherapy; Health technology assessment

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Introduction

Following important advances, a range of effective treatments for heart failure (HF) have been developed, which have been integrated into clinical guidelines published by the European

Society of Cardiology (ESC)¹ and the American Heart Association/American College of Cardiology/Heart Failure Society of America.² However, the management of HF is far from ideal in day-to-day clinical practice. In September 2021, key stakeholders in HF management attended an ESC Cardio-

vascular Round Table workshop that aimed to identify barriers to the optimal use of therapies and guideline implementation (Appendix A). The workshop also discussed mitigation strategies to optimize patient outcomes in the future. The key challenges and mitigation strategies discussed in the workshop are summarized below and in *Figures 1* and *2*, respectively.

Therapies for heart failure with reduced ejection fraction

Over time, as new effective therapies have been proven to improve survival and reduce the risk of hospitalization for

patients with HF with reduced ejection fraction (HFrEF), the foundations of guideline-recommended treatment have expanded from an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II type 1 receptor blocker (ARB) if ACEi are not tolerated, to include a beta-blocker and a mineralocorticoid receptor antagonist (MRA). This was followed by the option to replace an ACEi with the angiotensin receptor–neprilysin inhibitor (ARNi), sacubitril/valsartan, and subsequently with the recommendation to add a sodium–glucose co-transporter 2 inhibitor (SGLT2i; dapagliflozin or empagliflozin).¹ In addition to these core life-saving pharmacological therapies, other drug therapies may be prescribed, such as diuretics, digoxin, ivabradine, vericiguat, and the combination of hydralazine plus isosorbide dinitrate.

Figure 1 Key challenges to the optimal management of heart failure.

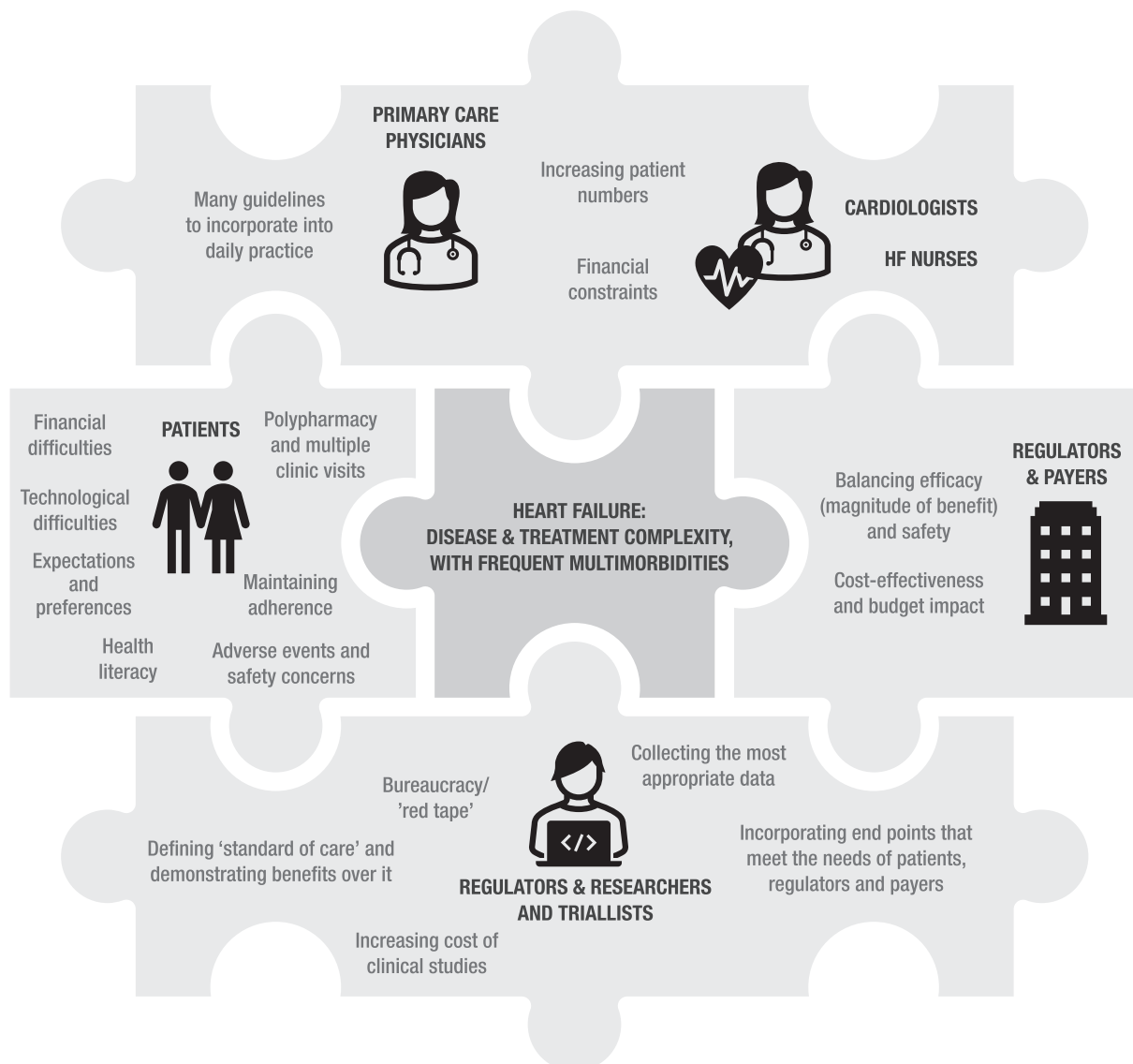
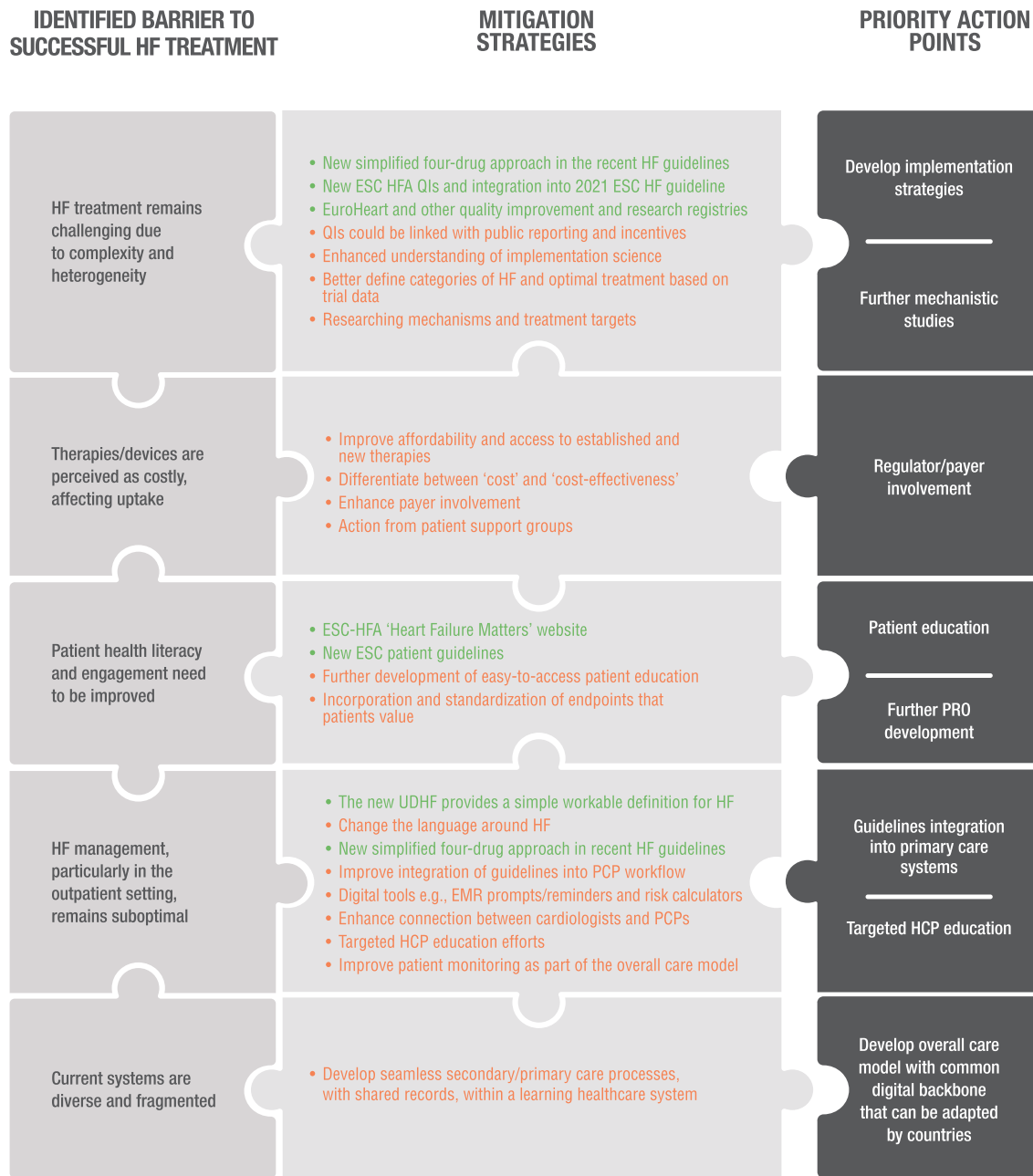


Figure 2 Summary of identified barriers, mitigation strategies, and priority action points. Mitigation strategies in green are recent or ongoing developments. Mitigation strategies in orange as proposed for future implementation. EMR, electronic medical record; ESC, European Society of Cardiology; HCP, healthcare professional; HF, heart failure; HFA, Heart Failure Association; PCP, primary care physician; PRO, patient-reported outcome; QIs, quality indicators; UDHF, universal definition of heart failure.



Furthermore, implantable devices that have been demonstrated to reduce mortality are indicated in selected patients, including implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT). After medical and device therapy, there are now multiple effective medical, catheter-based, and surgical interventions for specific structural, functional, or electrical abnormalities for advanced

HF, where palliative care is also an important component. Additionally, palliative care and specialized therapies, such as mechanical circulatory support and cardiac transplantation, should be considered for selected patients with advanced HF according to the guidelines, when consistent with the patient's goals of care. Combining multiple therapeutic options has resulted in complex treatment algorithms, which are

further complicated by the fact that most patients with HF have multiple cardiovascular and non-cardiovascular comorbidities³ and are on many medications.

There has been inertia and hesitancy towards initiating and titrating medical therapies, resulting in many patients not being prescribed proven therapies or not receiving the drugs promptly or at sufficient doses.^{4–9} This may be partially due to perceived or actual intolerance related to low blood pressure, slow heart rate, impaired kidney function or hyperkalaemia, or the presence of perceived contraindications when non-cardiovascular comorbidities coexist. The implementation of ICDs and CRT devices is also suboptimal, which may be due to lack of access to specialist cardiology care.^{4,10} Up to two-thirds of eligible patients are not referred for CRT and, when implanted, experience inadequate follow-up and monitoring, hampering CRT optimization.¹⁰ There is also wide geographical variation in usage of therapies across Europe,¹¹ which reflects wide global differences.

Unlike other conditions, such as cancer, the risk of mortality and morbidity is often underappreciated in patients with HF, and treatment is not escalated in the setting of apparently stable symptoms in clinical practice.⁵ Furthermore, the historically driven sequential approach to medical therapy of HF could take as long as 6 months to achieve optimal treatment dosages, and often, this prolonged approach was not completed.¹²

It was thought that moving away from the sequential approach based on the chronology of clinical trials and complex algorithms may help to simplify HF treatment and improve timely initiation and titration. The updated 2021 ESC guideline advocates that patients with HF should receive an ACEi/ARNi, a beta-blocker, an MRA, and an SGLT2i,¹ and rapid sequencing strategies have been proposed.¹² The new guideline also provides scope for individualization based on patient phenotypes and comorbidities, emphasizing a new philosophy towards management. Recently, the Heart Failure Association (HFA) of the ESC suggested a personalized patient approach, adjusting guideline-recommended treatment to the patient's haemodynamic profile (blood pressure, heart rate, and congestion), electrical substrate [atrial fibrillation (AF) or no AF], and kidney function, with the aim of achieving the best and most comprehensive therapy for each individual patient.¹³

The 2022 US guideline states that more than one of the core quadruple therapies for HFrEF can be started simultaneously at initial (low) doses or, alternatively, started sequentially, with the sequence guided by clinical or other factors, without the need to achieve target dosing before initiating the next medication.² Medication doses are recommended to be increased to target as tolerated. Since the guidelines were published, results from the STRONG-HF trial demonstrated that an intensive strategy of rapid up-titration and close follow-up reduced symptoms, improved quality of life (QoL), and reduced 180 day death or HF readmission compared with usual care in patients with acute HF.¹⁴

The role of quality indicators (QIs) is being increasingly recognized and attracts interest from healthcare authorities, professional organizations, health technology assessment bodies, payers, and the public as a way of driving improvement. By stimulating the delivery of evidence-based medicine,¹⁵ QIs may serve as mechanisms for benchmarking of care providers, for accountability purposes, and to provide a backbone of pay-for-performance programmes. The lack of widely agreed definitions for data variables has hampered the development of QIs and their integration with clinical registries; however, following new ESC methodology for QI development,¹⁵ the ESC and HFA have recently published 12 main and 4 secondary QIs for care and outcomes of adult patients with HF.¹⁶ It is hoped that these ESC HFA QIs will serve as a catalyst for quality improvement by highlighting areas with suboptimal guideline implementation, which could then be linked with public reporting and incentives. ESC HFA QIs have been incorporated into the 2021 ESC HF guideline¹ and are also integrated into the ESC's European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) project.¹⁷ EuroHeart aims to harmonize data standards for cardiovascular disease and establish a platform for continuous data collection, which will facilitate evaluating cardiovascular care through QIs.

Heart failure with preserved or mildly reduced ejection fraction

Treatment options for HF with preserved ejection fraction [HFpEF; left ventricular ejection fraction (LVEF) $\geq 50\%$] are limited, but progress is being made. Results from the CHARM programme, TOPCAT, and a recent analysis of PARAGON-HF indicate that treatment with an ARB, MRA, or ARNi may be of benefit beyond the upper limit of LVEF eligibility used in contemporary HFrEF clinical trials (40%) and may extend to HF with mildly reduced ejection fraction (HFmrEF; LVEF 41–49%) and even to the lower end of the normal range for LVEF.^{18,19} Expansion of the US Food and Drug Administration (FDA) labelling for sacubitril/valsartan for use in individuals with HF with LVEF lower than normal has the potential to increase the potential HF population eligible for an ARNi,²⁰ although this indication has not been approved by the European Commission (EC).

After the 2021 ESC guideline was prepared, empagliflozin met its primary endpoint in the EMPEROR-Preserved trial in patients with HFpEF,²¹ and after the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) issued a positive opinion, the EC has approved an expanded indication for empagliflozin to include patients with HFrEF, HFmrEF, and HFpEF. The US FDA has made a similar approval. In the 2022 US guideline, SGLT2is have a Class IIa recommendation in HFmrEF, whereas weaker recommendations

(Class IIb) are made for ARNis, ACEis, ARBs, MRAs, and beta-blockers in this population.² Since the US guideline was published, dapagliflozin met its primary endpoint in patients with HFmrEF and HFpEF (LVEF > 40%) in the DELIVER trial,²² and it is hoped that guidelines will be updated promptly.

The diagnosis of HFpEF remains challenging. Two score-based algorithms (H2FPEF and HFA-PEFF) have been proposed to aid diagnosis^{23,24}; however, physicians may not have access to all the specialized tests recommended by these diagnostic algorithms. To allow broader clinical application, the 2021 ESC HF guideline provides a simplified approach to the HFA-PEFF algorithm, which may be used as an alternative.^{1,25} Furthermore, based on the results of EMPEROR-Preserved and DELIVER, diagnosis of HFmrEF and HFpEF may now be determined by the relatively simple trial criteria than by more complex algorithms.

Clinical trials have used varying definitions for HFpEF, and the heterogeneous use of terminology in trials has implications for indications, payers, and prescribing.^{26,27} Given the complexity, it is important to decide which patient populations should be treated with which drugs based on the trials and then refine categories (or 'phenotypes') and nomenclature based on those. In addition, a better understanding of the mechanisms involved in HF aetiology at normal and higher ejection fractions may help in the development of new treatments for patient groups sub-divided by phenotype.

Health economics

HF management is perceived as costly, and HF treatments may have a significant impact on healthcare budgets due to the large absolute number of patients who are eligible for lifelong therapy. However, a major impact of HF on healthcare budgets is due to the very substantial costs of hospitalizations and its morbidity and associated healthcare resource utilization. Therefore, economic evaluations should be based on systematic and transparent decision analyses²⁸ including all relevant health states and transitions.²⁹ They should follow the key principles of health technology assessments such as adopting a full societal perspective and a sufficiently long time horizon and linking evidence from diagnostic studies, clinical trials, and real-world observational data and registries using appropriate causal inference methods.^{30,31} The foundational treatments for HF have all been shown to substantially reduce these long-term events and are considered highly cost-effective from a holistic societal health-economic perspective.^{2,32} Nevertheless, health-economic considerations are thought to be responsible, at least partly, for the underuse of implantable devices such as CRT. These interventions often undergo undue scrutiny by regulators, health technology assessment agencies, and payers as a result of their high upfront costs and related short-term

budget impact; however, they are still within accepted cost-effectiveness boundaries.¹⁰

There is considerable heterogeneity in the resources available for HF management and reimbursement policies across ESC member countries as shown by the ESC HFA Atlas survey.³³ Nearly all ESC member countries reported full or partial reimbursement of standard guideline-recommended treatment, except for ivabradine and sacubitril/valsartan. Indeed, high costs and partial reimbursement may help to explain why uptake of novel agents such as sacubitril/valsartan has been slow.^{34–36} Once the treatment is prescribed, high costs may also affect patient adherence and persistence. Ongoing efforts are needed to promote high-value care while improving affordability and access to established and emerging HF therapies.

Further discussions between stakeholders, with greater engagement of regulators, national health technology assessment agencies, and payers, may help to address the cost-related barriers to HF medications and devices and provide greater clarity on issues of cost-effectiveness and long-term budget impact. In addition, as observed with cancer, medical societies and patient groups could advocate for approval/reimbursement of new therapies. Moreover, causal per-protocol analysis adjusting for non-adherence in pragmatic trials³⁷ can provide important evidence on the full potential of treatments and should therefore be used to inform patients, providers, and payers.

Patient engagement and advocacy

Patient engagement and patient-shared decision making is fundamental to the optimal effectiveness of guideline-recommended treatment and adherence. Discussions should centre on the disease itself, its clinical trajectory, treatments (including information on potential side effects), and the importance of adherence/persistence, physical activity, symptom monitoring, and symptom self-management.¹ An 'announcement consultation' has been proposed, whereby the care plan is presented to patients and carers using a standardized guide to ensure that key topics related to diagnosis, prognosis, and treatment are covered and that patients are aware of how they can self-manage.³⁸ In the end-of-life setting, it is particularly important to have frank conversations to understand the expectations of the patient and family and to develop mutually agreed-on goals.³⁹

The educational website, heartfailurematters.org, has been developed by the HFA to provide advice for patients living with HF and their carers⁴⁰ and is available in 10 languages. New ESC patient guidelines are now available, which will provide another source of useful information.⁴¹ Other easy-to-access approaches may be explored to increase patient engagement, for example, simple infographics and

patient education videos on video-sharing websites, which may help to empower patients to know what good care is, to advocate for their own optimal therapy, and to self-manage more effectively. Digital health applications create the opportunity to educate patients with HF to enhance adherence and modify healthy behaviours,⁴² and further research may provide better insight into the long-term effects of such applications. Patient advocacy may also be useful to help improve guideline-recommended treatment implementation in general, for example, via QI benchmarking of local institutions.

Patient-reported outcomes

Patient-reported outcomes (PROs)—tools that directly measure a patient's perception of health status (symptoms, functional limitation, and QoL)—are endpoints considered in drug development when assessing the clinical relevance of an effect and when performing health technology assessments.³⁰ The majority of HF drugs are approved based on studies investigating an impact on clinical endpoints such as HF hospitalizations and mortality, and in the regulatory context, PROs are usually measured as secondary endpoints. They may be relevant in support of the effect on exercise capacity in selected patient populations or even as a primary endpoint in cases where patients are unable to undergo exercise testing.⁴³ In the latter scenarios, demonstration of cardiovascular safety of a medicinal product is essential. Patients themselves appear to value QoL improvements. In fact, in a survey of patient preferences among 1000 outpatients at an HF clinic in the Netherlands, 61% of the patients indicated that they attach more weight to QoL over longevity.⁴⁴

Many PRO instruments have limitations and/or are not validated in HF at all or in specific forms of HF, which may hinder their acceptability by regulators. Standardization, expert consensus, and regulatory agreement on the validation of PROs are needed, which may be achieved within the framework of an EMA qualification procedure.⁴⁵ Issues include the most appropriate instruments, content and construct validity, reproducibility, internal consistency, sensitivity to detect change, and the magnitude of a meaningful effect.⁴⁵ The possibility of using new technologies in functional assessment, for example, activity monitors, should also be explored. Analysing PRO data from trials of new treatments/devices may help to identify those patients who benefit most in terms of QoL and functional activity, providing important mechanistic information. In clinical practice, routine collection of data on QoL and functional capacity should be promoted as this could provide valuable information to support healthcare professionals (HCPs) in the monitoring of patients and provide another tool for advocacy efforts.

In the 2022 US HF guideline, standardized assessment of patient-reported health status using a validated questionnaire is specified as a tool that can be useful to provide incremental information for patient functional status, symptom burden, and prognosis.² Finally, personalized values, preferences, and QoL weights could be used in patient-shared decision making and to guide future clinical guidelines and reimbursement.⁴⁶

Monitoring

Recent technological innovations, such as implantable pulmonary arterial pressure (PAP) monitoring devices, wearable activity monitors, and mobile applications, have the potential to improve monitoring and optimize patient management. However, results are inconsistent and adherence is not always high.^{1,47–53} The ESC and US guidelines both include Class IIb recommendations for non-invasive home telemonitoring and for wireless haemodynamic monitoring of PAP.^{1,2} Results from GUIDE-HF in patients with New York Heart Association Classes II–IV demonstrated that haemodynamic-guided management of HF did not result in a lower composite endpoint rate of mortality and total HF events compared with the control group in the overall study analysis; however, a pre-COVID-19 impact analysis indicated a possible benefit in the pre-COVID-19 period, primarily driven by a lower HF hospitalization rate.^{54,55}

Despite inconsistent results, monitoring tools are evolving. In the future, artificial intelligence (AI) may help to select patients for monitoring and support the development of new tools (e.g. voice or body position analysis for lung congestion). Providing a clear and effective way for care teams to receive, analyse, and act on the information remains an important and costly challenge with medicolegal ramifications.^{3,56} Other challenges to the use of digital monitoring include the accuracy of the technologies, patient adherence, and potential privacy issues.^{3,56} Although digitalization is to be encouraged, it should not fully replace human interactions and patient-shared decision making, but rather be developed further and considered as part of the overall HF care model, which also includes guideline-recommended treatment, direct follow-up, education, and patient empowerment.

Healthcare professionals

Until recently, definitions of HF were ambiguous, which may have hindered the ability of HCPs to diagnose HF and to provide appropriate treatment and care. In 2021, a universal definition of HF (UDHF) was proposed, which is designed to be simple but conceptually comprehensive and clinically relevant.²⁵ The UDHF is accompanied by suggestions to

change the terminology surrounding HF. For example, lack of improvement is a marker of worse prognosis and should be termed as 'persistent' rather than 'stable', thereby prompting clinicians to continue to optimize therapy.²⁵ Following the development of the UDHF, changing the International Classification of Diseases 10th Revision codes could further help to simplify HF management for HCPs.

In addition to cardiologists, specialist HF nurses can play a central role in clinical evaluation, monitoring of laboratory parameters, therapy adaptation (e.g. up-titration), and providing education; however, nurse-led management is not currently available across all of Europe.⁵⁷ Due to the increasing numbers of HF patients seen by primary care physicians (PCPs), there is also a need for further investment and training in this sector. Some patients with HFrEF may not receive cardiology input in hospital, and many others are not followed up early after discharge or are only managed by PCPs. A recent study highlighted that a primary care HF service was able to identify a missed cohort of patients with HFrEF, enabling the optimization of medication and an increase in device therapy.⁵⁸ Given that PCPs have many guidelines to incorporate into their daily practice, HF guidelines should be better integrated into their workflow. Digital tools could be further developed, for example, reminders in electronic medical records (EMRs) to alert clinicians to prescribe guideline-recommended treatment and provide risk calculators/tools to demonstrate how risk is modified by therapy, with auditing and feedback of the effectiveness of these strategies.⁵⁹

Non-cardiologists should be given thorough and repeated training on how to identify and treat patients with, or at risk of, HF and when referral to a cardiologist is needed. As part of this, general availability of N-terminal pro-B-type natriuretic peptide (or B-type natriuretic peptide) measurements may be beneficial in primary care, as well as incorporating basic ultrasound and even AI-assisted diagnostic ultrasound care.⁶⁰ In the area of devices, education for PCPs and also for cardiologists less familiar with devices may help to improve implementation, with open discussions on the myths that contribute to non-referral.

Conclusions: wider changes to heart failure management are needed

A key conclusion from the ESC Cardiovascular Round Table workshop was that in addition to the individual action points identified, there is a need for wider changes to HF management as current systems are diverse and fragmented (*Figure 2*). With so much geographical variation, a 'one-size-fits-all' approach to organizational changes may not succeed. However, a standardized care pathway with a common digital backbone could be developed, which can be adopted in most countries with differing levels of sophistication. The common digital backbone could reduce reliance on specialists, improve evidence-based

decision making, and be supported by an integrated information base. The application of systematic health data and decision science, as well as integrating data domains for individual and community risk (e.g. EMR, social determinants, and environmental factors) with external data (clinical guidelines and policies), could help to inform evidence-based decision analyses and create decision support tools for a broad range of HCPs⁶¹ who can then implement them and also evaluate their effectiveness and cost-effectiveness. 'Learning healthcare systems' could be developed in which research influences practice and practice influences research.⁶¹ Seamless secondary–primary care processes should be encouraged in such a model, with consolidated messaging between sectors. As HF therapies, data collection, and digital tools continue to progress, such an integrated approach could evolve in a dynamic manner to be fit for future advances.

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Appendix A

A.1 Additional participants

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References

- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group, de Boer RA, Christian Schulze P, Abdelhamid M, Aboyans V, Adamopoulos S, Anker SD, Arbelo E, Asteggiano R, Bauersachs J, Bayes-Genis A, Borger MA, Budts W, Cikes M, Damman K, Delgado V, Dendale P, Dilaveris P, Drexel H, Ezekowitz J, Falk V, Fauchier L, Filippatos G, Fraser A, Frey N, Gale CP, Gustafsson F, Harris J, Jung B, Janssens S, Jessup M, Konradi

- A, Kotecha D, Lambrinou E, Lancellotti P, Landmesser U, Leclercq C, Lewis BS, Leyva F, Linhart A, Løchen M-L, Lund LH, Mancini D, Masip J, Milicic D, Mueller C, Nef H, Nielsen J-C, Neubeck L, Noutsias M, Petersen SE, Sonia Petronio A, Ponikowski P, Prescott E, Rakisheva A, Richter DJ, Schlyakhto E, Seferovic P, Senni M, Sitges M, Sousa-Uva M, Tocchetti CG, Touyz RM, Tschoepe C, Waltenberger J, Adamo M, Baumbach A, Böhm M, Burri H, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gardner RS, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2021; **42**: 3599–3726.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022; **145**: e895–e1032.
 3. Maddox TM, Januzzi JL Jr, Allen LA, Breathett K, Butler J, Davis LL, Fonarow GC, Ibrahim NE, Lindenfeld J, Masoudi FA, Motiwala SR, Oliveros E, Patterson JH, Walsh MN, Wasserman A, Yancy CW, Youmans QR. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021; **77**: 772–810.
 4. Maggioni AP, Anker SD, Dahlström U, Filippatos G, Ponikowski P, Zannad F, Amir O, Chioncel O, Leiro MC, Drozd J, Erglis A, Fazlibegovic E, Fonseca C, Fruhwald F, Gatzov P, Goncalvesova E, Hassanein M, Hradec J, Kavoliumiene A, Lainscak M, Logeart D, Merkely B, Metra M, Persson H, Seferovic P, Temizhan A, Tousoulis D, Tavazzi L, on behalf of the Heart Failure Association of the ESC (HFA). Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2013; **15**: 1173–1184.
 5. Khan MS, Butler J, Greene SJ. Simultaneous or rapid sequence initiation of medical therapies for heart failure: seeking to avoid the case of 'too little, too late'. *Eur J Heart Fail*. 2021; **23**: 1514–1517.
 6. Brunner-La Rocca HP, Linssen GC, Smeele FJ, van Drimmelen AA, Schaafsma HJ, Westendorp PH, Rademaker PC, van de Kamp HJ, Hoes AW, Brugts JJ, CHECK-HF Investigators. Contemporary drug treatment of chronic heart failure with reduced ejection fraction: the CHECK-HF registry. *JACC Heart Fail*. 2019; **7**: 13–21.
 7. Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF, Fonarow GC. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF registry. *J Am Coll Cardiol*. 2018; **72**: 351–366.
 8. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M, Zwinderman AH. Determinants and clinical outcome of up-titration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *Eur Heart J*. 2017; **38**: 1883–1890.
 9. Savarese G, Bodegard J, Norhammar A, Sartipy P, Thuresson M, Cowie MR, Fonarow GC, Vaduganathan M, Coats AJS. Heart failure drug titration, discontinuation, mortality and heart failure hospitalization risk: a multinational observational study (US, UK and Sweden). *Eur J Heart Fail*. 2021; **23**: 1499–1511.
 10. Mullens W, Auricchio A, Martens P, Witte K, Cowie MR, Delgado V, Dickstein K, Linde C, Vernooy K, Leyva F, Bauersachs J, Israel CW, Lund LH, Donal E, Boriani G, Jaarsma T, Berruezo A, Traykov V, Yousef Z, Kalarus Z, Cosedis Nielsen J, Steffel J, Vardas P, Coats A, Seferovic P, Edvardsen T, Heidebuchel H, Ruschitzka F, Leclercq C. Optimized implementation of cardiac resynchronization therapy: a call for action for referral and optimization of care: a joint position statement from the Heart Failure Association (HFA), European Heart Rhythm Association (EHRA), and European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology. *Eur J Heart Fail*. 2020; **22**: 2349–2369.
 11. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D, Gale CP, Maggioni AP, Petersen SE, Huculeci R, Kazakiewicz D, de Benito RV, Ignatiuk B, Raisi-Estabragh Z, Pawlak A, Karagiannis E, Treskes R, Gaita D, Beltrame JF, McConnell A, Bardinet I, Graham I, Flather M, Elliott P, Mossialos EA, Weidinger F, Achenbach S. European Society of Cardiology: cardiovascular disease statistics 2021. *Eur Heart J*. 2022; **43**: 716–799.
 12. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail*. 2021; **23**: 882–894.
 13. Rosano GMC, Moura B, Metra M, Böhm M, Bauersachs J, Ben Gal T, Adamopoulos S, Abdelhamid M, Bistola V, Čelutkienė J, Chioncel O, Farmakis D, Ferrari R, Filippatos G, Hill L, Jankowska EA, Jaarsma T, Jhund P, Lainscak M, Lopatin Y, Lund LH, Milicic D, Mullens W, Pinto F, Ponikowski P, Savarese G, Thum T, Volterrani M, Anker SD, Seferovic PM, Coats AJS. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2021; **23**: 872–881.
 14. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, Metra M, Ponikowski P, Sliwa K, Voors AA, Edwards C, Novosadova M, Takagi K, Damasceno A, Saidu H, Gayat E, Pang PS, Čelutkienė J, Cotter G. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. *Lancet*. 2022; **400**: 1938–1952.
 15. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes*. 2022; **8**: 4–13.
 16. Aktaa S, Polovina M, Rosano G, Abidin A, Anguita M, Lainscak M, Lund LH, McDonagh T, Metra M, Mindham R, Piepoli M, Störk S, Tokmakova MP, Seferović P, Gale CP, Coats AJS. European Society of Cardiology quality indicators for the care and outcomes of adults with heart failure. Developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2022; **24**: 132–142.
 17. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. *Eur Heart J*. 2019; **40**: 2745–2749.
 18. Dewan P, Jackson A, Lam CSP, Pfeiffer MA, Zannad F, Pitt B, Solomon SD, McMurray JJV. Interactions between left ventricular ejection fraction, sex and effect of neurohumoral modulators in heart failure. *Eur J Heart Fail*. 2020; **22**: 898–901.

19. Kondo T, McMurray JJV. Re-emergence of heart failure with a normal ejection fraction? *Eur Heart J*. 2022; **43**: 427–429.
20. Vaduganathan M, Claggett BL, Greene SJ, Aggarwal R, Bhatt AS, McMurray JJV, Fonarow GC, Solomon SD. Potential implications of expanded labeling for sacubitril/valsartan in the US. *JAMA Cardiol*. 2021; **6**: 1415–1423.
21. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca HP, Choi DJ, Chopra V, Chuquiere-Valenzuela E, Giannetti N, Gomez-Mesa JE, Janssens S, Januzzi JL, Gonzalez-Juanatey JR, Merkely B, Nicholls SJ, Perrone SV, Piña IL, Ponikowski P, Senni M, Sim D, Spinar J, Squire I, Taddei S, Tsutsui H, Verma S, Vinereanu D, Zhang J, Carson P, Lam CSP, Marx N, Zeller C, Sattar N, Jamal W, Schnaidt S, Schnee JM, Brueckmann M, Pocock SJ, Zannad F, Packer M, EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021; **385**: 1451–1461.
22. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Squire AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM, DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022; **387**: 1089–1098.
23. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation*. 2018; **138**: 861–870.
24. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail*. 2020; **22**: 391–412.
25. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa JE, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferovic P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021; **23**: 352–380.
26. Lam CSP, Solomon SD. Classification of heart failure according to ejection fraction: JACC review topic of the week. *J Am Coll Cardiol*. 2021; **77**: 3217–3225.
27. Campbell RT, Petrie MC, McMurray JJV. Redefining heart failure phenotypes based on ejection fraction. *Eur J Heart Fail*. 2018; **20**: 1634–1635.
28. Siebert U. When should decision-analytic modeling be used in the economic evaluation of health care? *Eur J Health Econ*. 2003; **4**: 143–150.
29. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, Kuntz KM. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-3. *Med Decis Making*. 2012; **32**: 690–700.
30. Drummond MF, Schwartz JS, Jönsson B, Luce BR, Neumann PJ, Siebert U, Sullivan SD. Key principles for the improved conduct of health technology assessments for resource allocation decisions. *Int J Technol Assess Health Care*. 2008; **24**: 244–2258.
31. Siebert U. Cost-effectiveness. In King S. P. III, Yeung A. C., eds. *Interventional Cardiology*. New York: McGraw Hill; 2007. p 767–782.
32. Brownell NK, Ziaiean B, Fonarow GC. The gap to fill: rationale for rapid initiation and optimal titration of comprehensive disease-modifying medical therapy for heart failure with reduced ejection fraction. *Card Fail Rev*. 2021; **7**: e18.
33. Seferovic PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinkovic I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R, Kazakiewicz D, Coats AJS, National Heart Failure Societies of the ESC member countries. The Heart Failure Association Atlas: heart failure epidemiology and management statistics 2019. *Eur J Heart Fail*. 2021; **23**: 906–914.
34. Sangaralingham LR, Sangaralingham SJ, Shah ND, Yao X, Dunlay SM. Adoption of sacubitril/valsartan for the management of patients with heart failure. *Circ Heart Fail*. 2018; **11**: e004302.
35. Ozaki AF, Krumholz HM, Mody FV, Tran TT, Le QT, Yokota M, Jackevicius CA. Prior authorization, copayments, and utilization of sacubitril/valsartan in Medicare and commercial plans in patients with heart failure with reduced ejection fraction. *Circ Cardiovasc Qual Outcomes*. 2021; **14**: e007665.
36. Sumarsono A, Vaduganathan M, Ajufu E, Navar AM, Fonarow GC, Das SR, Pandey A. Contemporary patterns of Medicare and Medicaid utilization and associated spending on sacubitril/valsartan and ivabradine in heart failure. *JAMA Cardiol*. 2020; **5**: 336–339.
37. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med*. 2017; **377**: 1391–1398.
38. Berthelot E, Beauvais F, Abassade P, Amiour F, Bendriss A, Guedj D, Yahia A, Baumgaertner I, Gibault Genty G, Belloir E, Bouleti C. Consultation d'annonce dans l'insuffisance cardiaque: quelle place? *Arch Mal Coeur Vaiss Pratique*. 2020; **202**: 22–28.
39. Whellan DJ, Goodlin SJ, Dickinson MG, Heidenreich PA, Jaenicke C, Stough WG, Rich MW, Quality of Care Committee, Heart Failure Society of America. End-of-life care in patients with heart failure. *J Card Fail*. 2014; **20**: 121–134.
40. Wagenaar KP, Rutten FH, Klompstra L, Bhana Y, Sieverink F, Ruschitzka F, Seferovic PM, Lainscak M, Piepoli MF, Broekhuizen BDL, Strömberg A, Jaarsma T, Hoes AW, Dickstein K. 'heartfailurematters.org', an educational website for patients and carers from the Heart Failure Association of the European Society of Cardiology: objectives, use and future directions. *Eur J Heart Fail*. 2017; **19**: 1447–1454.
41. European Society for Cardiology. Guidelines for patients. Available at: www.escardio.org/Guidelines/guidelines-for-patients?utm_source=social&utm_medium=twitter&utm_campaign=Guidelines (accessed 24 May 2022).
42. Farwati M, Riaz H, Tang WHW. Digital health applications in heart failure: a critical appraisal of literature. *Curr Treat Options Cardiovasc Med*. 2021; **23**: 12.
43. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure, 20 July 2017, CPMP/EWP/235/95, Rev.2. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-chronic-heart-failure-revision-2_en.pdf (accessed 24 May 2022).
44. Kraai IH, Vermeulen KM, Luttik ML, Hoekstra T, Jaarsma T, Hillege HL. Preferences of heart failure patients in daily clinical practice: quality of life or longevity? *Eur J Heart Fail*. 2013; **15**: 1113–1121.
45. European Medicines Agency. Qualification of novel methodologies for drug development: guidance to applicants, 10 November 2014, EMA/CHMP/SAWP/72894/2008. Available at: <https://>

- www.ema.europa.eu/en/documents/regulatory-procedural-guideline/qualification-novel-methodologies-drug-development-guidance-applicants_en.pdf (accessed 24 May 2022).
46. Rogowski W, Payne K, Schnell-Inderst P, Manca A, Rochau U, Jahn B, Alagoz O, Leidl R, Siebert U. Concepts of 'personalization' in personalized medicine: implications for economic evaluation. *Pharmacoeconomics*. 2015; **33**: 49–59.
 47. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. *Heart*. 2017; **103**: 255–257.
 48. Lin MH, Yuan WL, Huang TC, Zhang HF, Mai JT, Wang JF. Clinical effectiveness of telemedicine for chronic heart failure: a systematic review and meta-analysis. *J Invest Med*. 2017; **65**: 899–911.
 49. Adamson PB, Ginn G, Anker SD, Bourge RC, Abraham WT. Remote haemodynamic-guided care for patients with chronic heart failure: a meta-analysis of completed trials. *Eur J Heart Fail*. 2017; **19**: 426–433.
 50. Chaudhry SI, Mattera JA, Curtis JP, Spertus JA, Herrin J, Lin Z, Phillips CO, Hodshon BV, Cooper LS, Krumholz HM. Telemonitoring in patients with heart failure. *N Engl J Med*. 2010; **363**: 2301–2309.
 51. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M, Boll H, Baumann G, Honold M, Koehler K, Gelbrich G, Kirwan BA, Anker SD, Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation*. 2011; **123**: 1873–1880.
 52. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Winkler S, Vettorazzi E, Polze A, Stangl K, Hartmann O, Marx A, Neuhaus P, Scherf M, Kirwan BA, Anker SD. Telemedical Interventional Management in Heart Failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: study design and description of the intervention. *Eur J Heart Fail*. 2018; **20**: 1485–1493.
 53. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, Winkler S, Vettorazzi E, Bruch L, Oeff M, Zugck C, Doerr G, Naegele H, Stork S, Butter C, Sechtem U, Angermann C, Gola G, Prondzinsky R, Edelmann F, Spethmann S, Schellong SM, Schulze PC, Bauersachs J, Wellge B, Schoebel C, Tajsic M, Dreger H, Anker SD, Stangl K. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet*. 2018; **392**: 1047–1057.
 54. Lindenfeld J, Zile MR, Desai AS, Bhatt K, Ducharme A, Horstmanshof D, Krim SR, Maisel A, Mehra MR, Paul S, Sears SF, Sauer AJ, Smart F, Zughuib M, Castaneda P, Kelly J, Johnson N, Sood P, Ginn G, Henderson J, Adamson PB, Costanzo MR. Haemodynamic-guided management of heart failure (GUIDE-HF): a randomised controlled trial. *Lancet*. 2021; **398**: 991–1001.
 55. Zile MR, Desai AS, Costanzo MR, Ducharme A, Maisel A, Mehra MR, Paul S, Sears SF, Smart F, Chien C, Guha A, Guichard JL, Hall S, Jonsson O, Johnson N, Sood P, Henderson J, Adamson PB, Lindenfeld J. The GUIDE-HF trial of pulmonary artery pressure monitoring in heart failure: impact of the COVID-19 pandemic. *Eur Heart J*. 2022; **43**: 2603–2618.
 56. Singhal A, Cowie MR. Digital health: implications for heart failure management. *Card Fail Rev*. 2021; **7**: e08.
 57. Girerd N, von Hunolstein JJ, Pellicori P, Bayés-Genís A, Jaarsma T, Lund LH, Bilbault P, Boivin JM, Chouhied T, Costa J, Eicher JC, Fall E, Kenizou D, Maillier B, Nazeyrollas P, Roul G, Zannad N, Rossignol P, Seronde MF, EF-HF Group. Therapeutic inertia in the pharmacological management of heart failure with reduced ejection fraction. *ESC Heart Fail*. 2022; **9**: 2063–2069.
 58. Kahn M, Grayson AD, Chaggar PS, Ng Kam Chuen MJ, Scott A, Hughes C, Campbell NG. Primary care heart failure service identifies a missed cohort of heart failure patients with reduced ejection fraction. *Eur Heart J*. 2022; **43**: 405–412.
 59. Ghazi L, Yamamoto Y, Riello RJ, Coronel-Moreno C, Martin M, O'Connor KD, Simonov M, Huang J, Olufade T, McDermott J, Dhar R, Inzucchi SE, Velazquez EJ, Wilson FP, Desai NR, Ahmad T. Electronic alerts to improve heart failure therapy in outpatient practice: a cluster randomized trial. *J Am Coll Cardiol*. 2022; **79**: 2203–2213.
 60. Tseng AS, Lopez-Jimenez F, Pellikka PA. Future guidelines for artificial intelligence in echocardiography. *J Am Soc Echocardiogr*. 2022; **35**: 878–882.
 61. Pearson TA, Califf RM, Roper R, Engelgau MM, Khoury MJ, Alcantara C, Blakely C, Boyce CA, Brown M, Croxton TL, Fenton K, Green Parker MC, Hamilton A, Helmchen L, Hsu LL, Kent DM, Kind A, Kravitz J, Papanicolaou GJ, Prospero M, Quinn M, Price LN, Shireman PK, Smith SM, Szczesniak R, Goff DC Jr, Mensah GA. Precision health analytics with predictive analytics and implementation research: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020; **76**: 306–320.