The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials

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Patient-reported outcomes (PROs), such as symptoms, health-related quality of life (HRQOL), or patient perceived health status, are reported directly by the patient and are powerful tools to inform patients, clinicians, and policy-makers about morbidity and ‘patient suffering’, especially in chronic diseases. Patient-reported outcomes provide information on the patient experience and can be the target of therapeutic intervention. Patient-reported outcomes can improve the quality of patient care by creating a holistic approach to clinical decision-making; however, PROs are not routinely used as key outcome measures in major cardiovascular clinical trials. Thus, limited information is available on the impact of cardiovascular therapeutic on PROs to guide patient-level clinical decision-making or policy-level decision-making. Cardiovascular clinical research should shift its focus to include PROs when evaluating the efficacy of therapeutic interventions, and PRO assessments should be scientifically rigorous. The European Society of Cardiology and other professional societies can take action to influence the uptake of PRO data in the research and clinical communities. This process of integrating PRO data into comprehensive efficacy evaluations will ultimately improve the quality of care for patients across the spectrum of cardiovascular disease.

Keywords
- Cardiovascular clinical trials
- Patient-reported outcomes
- Health-related quality of life

Introduction

Patient-reported outcomes (PROs), such as symptoms, health-related quality of life (HRQOL), or satisfaction with care, are reported directly by the patient without interpretation by the clinician or other caregiver.¹ These outcomes inform about morbidity and ‘patient suffering’, especially in chronic diseases, and they provide information that supplements clinical outcomes such as mortality, myocardial infarction, or acute heart failure. Patient-reported outcome data are valued by patients, clinicians, and policy-makers. They inform therapeutic choices, disease management practices, reimbursement decisions, and health policy.

Patient-reported outcomes are not routinely used as key outcomes in major cardiovascular clinical trials, but assessing PRO measures in at least a subset of patients enrolled in cardiovascular mega-trials should be encouraged because of an increased focus on reducing the burden of disease and improving overall well-being, in addition to prolonging life. The increasing role of cost-effectiveness assessment and its ‘currency’, the quality-adjusted life year, has further amplified the need for valid, robust PRO data to facilitate health technology assessments. These data are often unavailable to inform these emerging goals.²,³

Uncertainty about the quality and appropriate application of existing tools for assessing PROs may discourage clinicians from using...
PROs in both research and clinical practice. Some efforts have been made to encourage PRO assessment in specific patient groups and should be considered more broadly in patients with cardiovascular disease.

The European Society of Cardiology (ESC) recognizes the importance of advancing PRO research to inform patients, clinicians, payers, and policy-makers and held a workshop with international experts in cardiovascular medicine and PRO research to discuss the challenges associated with PRO research in cardiovascular clinical trials and to identify strategies to increase the prominence of PROs in these trials. The purpose of this paper is to raise awareness of these issues among researchers to facilitate the advancement of PRO research as it applies to cardiovascular clinical trials.

Nomenclature of outcome assessments in clinical trials

Patient-reported outcomes measure a specific concept [or construct(s)] from the patient perspective, including HRQOL, symptoms, functioning, utility, and knowledge of or adherence to therapy. Patient-reported outcomes and clinician-reported functional outcomes measure different components of perceived patient well-being. Both may be useful to assess a patient and to decide on treatment. Clinician-reported outcomes that inform on patient well-being are commonly used to guide treatment decisions, clinical trial eligibility, and develop consensus recommendations, and they have been used and are available in many existing data sets.

Quality of life

Quality of life is defined by the Food and Drug Administration (FDA) as a ‘general concept that implies an evaluation of the effect of all aspects of life on general well-being’. It reflects physical, functional, psychological, cognitive, or symptomatic impairment.

Health-related quality of life

Obviously, factors unrelated to a patient’s medical condition may influence quality of life. Thus, HRQOL focuses on aspects of quality of life that are related to health, but it can be difficult for patients to delineate health related from other aspects of quality of life. Health-related quality of life is composed of multiple domains that comprehensively measure the patient’s experience of symptoms, functional status, and psychosocial elements against the patient’s expectations to quantify the extent to which the burden of disease impacts a patient’s quality of life (Figures 1 and 2).

Instruments that assess patient-reported outcomes

The content validity of the selected instrument must be demonstrated based on qualitative evidence that the instrument comprehensively measures the concept of interest (e.g. symptoms and...
Use of patient-reported outcome data to support a label claim

Patient-reported outcomes data may be used to support claims that a therapy improves symptoms, functional ability, or HRQOL. The concepts measured by a PRO instrument must support these claims.\textsuperscript{1,8,13} Select instruments that are available for evaluating PROs in cardiovascular trials are shown in Table 1 (www.proqolid.org). The choice of instruments for either general or disease-specific indications is extensive, which introduces challenges for interpretation and evaluating the totality of evidence. Researchers seeking a label claim should interact with regulatory authorities early during the trial planning process.

Both the FDA and the European Medicines Agency evaluate PRO data in the context of the instruments used for data collection.\textsuperscript{1,8,13} It is important to note that not all studies that evaluate PROs are sufficient to support PRO claims.\textsuperscript{1,8,13} In an analysis of 116 new molecular entities or biological license applications reviewed by the FDA between 2006 and 2010, 44.8% reported PROs as part of the pivotal studies, but only 24.1% received a PRO label claim.\textsuperscript{3} These data suggest that there is either (i) limited interest in pursuing PRO claims for cardiovascular therapies; (ii) underutilization of PRO assessments in clinical trials; and/or (iii) that there are few instruments adequate to support label claims.

Use of patient-reported outcome data to support reimbursement decisions

To evaluate whether coverage of an intervention is warranted at the proposed price, decision-makers assess its benefits and risks compared with those of existing interventions and aim to quantify the effect of a therapy from all perspectives.\textsuperscript{14} Efficacy on a primary clinical endpoint is important but not sufficient; the patient’s well-being, functional status, or productivity are also considered. In the UK, the National Institute for Health and Clinical Excellence advocates the use of EQ-5D to generate quality-adjusted life years to inform reimbursement (Supplementary material online, Appendix S1). Some countries focus healthcare coverage and reimbursement decisions on the comparative health effects, whereas others depend on the cost per quality-adjusted life years (Figure 3). Health utility measures

Application of patient-reported outcome data

Use of patient-reported outcome data from clinical trials to inform routine clinical care

Patients are key stakeholders in healthcare decisions.\textsuperscript{9,10} Patient-reported outcomes may provide quantitative information for patients regarding the ‘impact on daily life’. This information may support discussions between a patient and healthcare provider regarding their health status and the net clinical benefit of a new therapy, or when making a choice about alternative therapies.\textsuperscript{1,8,13} Patient-reported outcomes may be particularly applicable for therapies associated with trade-offs between the potential for clinical efficacy and the potential for adverse effects (e.g. antithrombotic agents that reduce the risk of recurrent cardiovascular events such as myocardial infarction or revascularization procedures but increase the risk of bleeding; or mechanical circulatory support devices in advanced heart failure that prolong survival but may be burdensome or associated with significant morbidity), or when patient attitudes and perceptions might influence the outcome of the therapy (e.g. adherence to follow-up visits and immunosuppression post-transplant). Patients may view the balance between such benefits and risks differently from clinicians, and PROs provide applicable data in this regard.

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Design considerations for integrating patient-reported outcomes in clinical trials

The patient-reported outcome hypothesis

The underlying PRO hypothesis should be stated in the protocol with a well-developed rationale and clear statement of the key PRO that will be analysed. Pre-specifying these aspects avoids problems related to multiple statistical testing, Type I error, and selective reporting.15 The process required for instrument development and research documenting content validity should generally be completed prior to selecting a PRO as an endpoint in a clinical trial, although in some circumstances researchers may pilot a new instrument in a trial along with other established instruments. Including PRO experts on the steering committee should be considered to ensure optimal study design, implementation, and reporting.

Patient-reported outcome data collection

Study personnel should be adequately trained on administration of PRO instruments. Whenever possible, the PRO should be completed by the patient. The protocol should specify who may serve as a proxy for instrument completion, in the event the patient is unable to perform this task, and it should be documented and reported if it occurs, but study personnel should not serve as the proxy. The baseline assessment should usually be completed prior to randomization, although in some circumstances researchers may pilot a new instrument in a trial along with other established instruments. Including

Table 1  Select examples of patient-reported outcomes used in heart failure trials

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Domains</th>
<th>Time to complete</th>
<th>Instrument strengths and weaknesses</th>
<th>Comments on validity, reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea Likert Scale</td>
<td>Shortness of breath/dyspnoea</td>
<td>&lt;1 min</td>
<td>Can be biased by patient recall of symptoms, baseline symptom severity, or patient perception of administered treatment if study is unblinded; intermediate levels of change (e.g. mild vs. moderate) may be difficult to differentiate because of large spontaneous variability in the measurement.16 More easily understood by patients than the VAS. High degree of agreement between 5-point Likert and VAS for baseline measures and for assessing change from baseline</td>
<td>Regulatory authorities may grant a label claim for an improvement in dyspnoea if safety is also established. However, improvements in dyspnoea have been challenging to demonstrate in clinical trials because the majority of patients report improvements in dyspnoea with standard therapy over a relatively short timeframe. Interpretation of data from dyspnoea instruments requires knowledge of the timing of dyspnoea assessments and the therapies that have been administered.16</td>
</tr>
<tr>
<td>Dyspnoea Visual Analog Scale (VAS)</td>
<td>Shortness of breath/dyspnoea</td>
<td>&lt;1 min</td>
<td>Visual Analog Scale have detected treatment effects better than Likert in several clinical trials25,49–51</td>
<td>Reliability and validity established (internally consistent and reproducible), instrument is sensitive to change; not accepted by FDA since new guidance in 2007</td>
</tr>
<tr>
<td>Minnesota Living With Heart Failure (MLWHF)</td>
<td>21 items covering signs and symptoms of HF, physical activity, social interaction, sexual activity, work, and emotions</td>
<td>4–6 min</td>
<td>Performs well, widely used in clinical trials</td>
<td>Internally consistent and reproducible</td>
</tr>
<tr>
<td>Kansas City Cardiomyopathy Questionnaire (KCCQ)</td>
<td>Physical limitations, symptoms, self-efficacy, social limitations, quality of life</td>
<td>4–6 min</td>
<td>Documented construct validity (strong associations between SF-36 physical and social functioning domains and with NYHA class).47</td>
<td>Internally consistent and reproducible</td>
</tr>
<tr>
<td>Quality of Life Questionnaire for Severe Heart Failure</td>
<td>Psychological, physical activity, life dissatisfaction, Somatic symptoms</td>
<td>5–7 min</td>
<td>Some data suggest that it is the least responsive47</td>
<td></td>
</tr>
</tbody>
</table>

*Heart failure chosen as an example of a cardiovascular disease where valid and reliable instruments are available.
of activity from which patients are to judge their symptoms (e.g., walking a certain distance on flat ground vs. walking up a certain number of stairs). This approach will yield consistency across the study. The protocol should define time intervals for follow-up assessments and the acceptable window for these assessments.

Some investigators may be concerned about the time involved to collect PROs and the impact that it may have on patient adherence in a study. The literature does not suggest that excessive time is required for instrument completion; average completion time is <10 min for many instruments. Clinicians should consider the potential burden to participants when selecting the questionnaire. Patients may contribute to decisions around the choice of instrument (particularly when several options are available) since they can inform which are most acceptable and relevant. This practice is advocated in some countries, and in our opinion, should be expanded.

Contextual influence can also impact PRO data. Long waiting times, stressful environments (e.g. busy, noisy, disorganized waiting areas), or other factors (e.g. difficult travel to the appointment) may negatively influence results, although the impact should be minimal in a randomized, controlled trial. Completing questionnaires using the same mechanism (e.g. electronic, paper, or telephone interview) and in the same setting (e.g. hospital, clinic, home) throughout the study should minimize the impact of such influences.

Tablet computers and smart phones are user-friendly and can be used in the clinic or provided to patients for extended use during longitudinal follow-up. These devices provide exact information on the time of the evaluation, which enables information to be captured on changes in the severity and frequency of symptoms. Evidence indicates that equivalent data are captured regardless of whether paper or electronic methods are used.

Computerized adaptive testing is an approach that tailors assessment questions according to item responses. The approach is interesting, but it requires further validation. Close collaboration with regulatory agencies should be undertaken in the study planning phase to ensure that the methods for electronic data capture will produce valid and reliable data, and satisfy regulatory requirements.

Patient-reported outcomes data integrity

Patient-reported outcomes must meet the same level of scientific rigour as other outcomes, in terms of monitoring, auditing, and statistical analyses. Statistical power should be allocated to the PRO endpoint if it is a primary, co-primary, or key secondary endpoint. Study procedures should be planned to minimize missing data (e.g. reminders, postage supplies to facilitate return of completed instruments, assistance with transportation for visits if applicable). Items missing at random (i.e. patients overlooked an item unintentionally) are not a major analytic concern unless they are very common, whereas systematically missing data fields (i.e. patients omit responses to items that are unclear, not applicable, or address sensitive topics) are problematic. Patient input during instrument development may reduce the chance of systematically missing data.

Missing data rates are relatively high for PROs. Bias will be introduced if data are absent because of a change in clinical status (e.g. death or deterioration) and the analysis only includes patients who completed all assessments. A treatment that prolongs life may perform worse on PRO or HRQOL outcomes than a treatment.
without a survival benefit because the patients survive to report PROs but still experience disease progression that results in recurrent events or multiple hospitalizations. Reasons for missing data should be captured on the case report form. Statistical procedures for handling missing data should be established a priori and specified in the analysis plan. Many imputation methods are available (e.g. imputation of worst score, last value carried forward, or multiple imputation techniques), but they are limited by the accuracy of the assumptions used in the imputation.5,24

Interpretation of patient-reported outcome data

Determining an evidence-based level of meaningful change in a PRO measure is a major challenge for cardiovascular clinical trials and clinical practice, and consensus has not been reached on what constitutes a clinically meaningful change. Further research efforts are needed to resolve this major issue. The RELAXin in Acute Heart Failure (RELAX-AHF) trial is a recent example of this problem. The study was designed with PROs as co-primary endpoints: change in patient-reported dyspnoea [quantified by the area under the curve (AUC) of the visual analogue scale (VAS) scores from baseline to Day 5] and moderate or marked improvement in patient reported dyspnoea using a 7-point Likert scale at 6, 12, and 24 h after the start of study drug.25 The clinical meaning of AUC in a VAS is not readily apparent to either investigators or clinicians.

Anchor-based methods are among the preferred approaches for establishing the clinically meaningful change for a given PRO.5 Using this approach, the clinically meaningful change is quantified by evaluating the association between change in the PRO and the accepted clinically relevant change in a known variable (e.g. 6-minute walk distance, peak VO₂, NYHA class).26–29 This process helps to provide context for the PRO change.

Patients can also be categorized according to self-report of whether they experienced no change or small, moderate, or large improvements, or worsening. The clinically relevant change would be the observed change within the group that self-identified as improved (either any improvement or limited to small or moderate improvements, depending on the specific study and population).5,28 This approach would not be appropriate in an unblinded trial. Other limitations of this approach include problems of patient recall and whether or not such ratings reflect the change in a patient’s health status or their current health state.26 Using global patient ratings to establish a clinically important difference is strengthened if other clinical anchors are available to aid in the determination.

Distribution-based methods may also be used to support the clinically meaningful change determined by anchor-based methods. This approach yields information on effect size or magnitude of change within the population based on the distribution of the PRO instrument scores, but it does not quantify a threshold for the clinically relevant change.27,29

Clinician interpretation of PRO endpoints can be helped by the way data are presented. Reporting mean change from baseline is not fully informative since it lacks details on the distribution of responses within a treatment group unless some measure of variance is also provided. The mean can be driven by a small proportion of patients who exhibit a large change, thereby failing to reflect the larger proportion of patients who did not respond or who responded to a lesser extent. Some data suggest that patients prefer and more accurately interpret HRQOL data presented as mean values.30

Reporting the proportion of patients achieving each level of change (i.e. the cumulative distribution of response) may be more informative and valid (Figure 4).21 Results can also be presented as the proportion of patients who improve, worsen, or experience no change, although this requires that these categories be defined and it introduces analytic challenges (e.g. loss of statistical power with analysis of categorical vs. continuous data). It can be recommended that mean values and distributions should be used for analysis, and if significant, the data can be presented as proportions to aid in interpretability.31 Until a common approach to such analyses has been adopted, we suggest that the analysis plan for PROs should be discussed with regulatory agencies and with stakeholders (patients, PRO experts) early in the trial planning process.21

No single threshold of clinically important change would be accurate for all patients with a specific cardiovascular disease. One major aspect is identifying anchors with close associations to the PRO of interest. This process is less mature in cardiovascular disease than in other areas of medicine, since cardiovascular research has largely focused on clinical outcomes rather than surrogate markers that can serve as anchors. Although work has been done in several studies, it is an important area that needs to be further developed if PROs are to become prominent in cardiovascular clinical trials.

Incorporating PROs into composite endpoints introduces unique analytic challenges: what is the relative contribution of each component in the analysis (e.g. should the PRO score should carry equivalent, more, or less weight than a clinical event), how are issues of divergence addressed (e.g. clinical events and the PRO differ directionally) (Table 2), how are competing outcomes handled (e.g. a patient who dies cannot provide PROs)? Additional research is warranted to refine the optimal analytic approaches to deal with these issues (Table 3).

**Table 3**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Clinical endpoint of primary interest</td>
</tr>
<tr>
<td>Secondary</td>
<td>Clinical endpoints of secondary interest</td>
</tr>
<tr>
<td>Controlled</td>
<td>Clinical endpoints controlled for in the analysis</td>
</tr>
</tbody>
</table>

**Figure 4** Example of a cumulative distribution curve. Reprinted with permission from Patrick et al.21 (Elsevier, copyright 2007).
and the CONSORT executive have recently developed a CONSORT PRO Extension that aims to promote the transparent reporting of PROs in trials. This guidance is to be used by authors, reviewers, and editors in conjunction with other CONSORT guidance as appropriate for the trial design (http://www.consort-statement.org/).

The position of the European Society of Cardiology towards patient-reported outcomes

The ESC has a unique opportunity to advance initiatives aimed at increasing the prominence of PROs in cardiovascular research and translating the findings to clinical practice. Placing an emphasis on publication of high-quality research papers that describe the development and validation of PRO instruments or that report results of studies where PRO measures were key endpoints will enhance the visibility and reinforce the importance of PROs among cardiovascular clinicians. Cardiovascular therapies are becoming more complex. For example, mechanical circulatory support devices prolong survival but have the potential to be highly burdensome for patients and caregivers. Anxiety and depression are common in these patients and are associated with an increased risk of mortality and hospitalization. Similarly, implantable cardioverter defibrillator therapy is associated with anxiety, depression, and device concerns. The availability of PRO data to quantify these issues increases physician awareness of the potential problem and may facilitate early referral for psychosocial evaluation or care. How these PROs may influence clinical outcomes is currently being studied. Such results would provide valuable resources for the generation of future practice guidelines.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Challenges of divergent patient-reported outcomes and clinical outcomes in composite endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of a new treatment on either clinical outcome or PRO</td>
<td>Approvability/acceptability of new treatment</td>
</tr>
<tr>
<td><strong>Clinical outcome</strong> (e.g. survival or other endpoints)</td>
<td><strong>Physician perspective</strong></td>
</tr>
<tr>
<td>Improve</td>
<td>Improve</td>
</tr>
<tr>
<td>Improve</td>
<td>Neutral</td>
</tr>
<tr>
<td>Improve</td>
<td>Worsen</td>
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<tr>
<td>Neutral</td>
<td>Improve</td>
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<tr>
<td>Neutral</td>
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<tr>
<td>Worsen</td>
<td>Improve</td>
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<tr>
<td>Worsen</td>
<td>Neutral</td>
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<tr>
<td>Worsen</td>
<td>Worsen</td>
</tr>
</tbody>
</table>

*Table is simplification of decision process; assumes that there are no other areas of safety concerns (e.g. liver or other organ toxicities, new onset diseases, or disease exacerbations).*

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Select topics for future research</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Appropriate methodology to achieve consistency in symptom assessment</td>
<td></td>
</tr>
<tr>
<td>• Accounting for patient avoidance of symptom-producing activities</td>
<td></td>
</tr>
<tr>
<td>• Techniques to impute the effect of missing data</td>
<td></td>
</tr>
<tr>
<td>(2) Floor and ceiling effects of PRO instruments in long-term studies</td>
<td></td>
</tr>
<tr>
<td>(3) Role (if any) of proxy reported outcomes</td>
<td></td>
</tr>
<tr>
<td>(4) Optimizing/adapting PRO measures used in clinical trials for use in clinical practice</td>
<td></td>
</tr>
<tr>
<td>(5) Best practice for protocol writers, PRO data collection, and management</td>
<td></td>
</tr>
<tr>
<td>(6) Adapting PRO instruments to report adverse events</td>
<td></td>
</tr>
<tr>
<td>(7) Analytic techniques for incorporating PROs into a composite secondary endpoint that incorporates information from clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>• Relative weighting of the PRO and clinical outcomes</td>
<td></td>
</tr>
<tr>
<td>• Handling divergent outcomes</td>
<td></td>
</tr>
<tr>
<td>• Dealing with competing outcomes</td>
<td></td>
</tr>
<tr>
<td>(8) Refine methods to define clinically important treatment effects. Develop consistent approaches that can be applied to trial results according to the specific study population and/or therapeutic agent being tested (with modification as necessary to account for severity of disease, baseline values, or other relevant factors)</td>
<td></td>
</tr>
<tr>
<td>(9) Identify optimal clinical parameters to serve as ‘anchors’ for specific cardiovascular conditions</td>
<td></td>
</tr>
</tbody>
</table>

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Downloaded from https://academic.oup.com/eurheartj/article-abstract/35/30/2001/2293072 by guest on 08 February 2019
guidelines. Ensuring well-designed studies that include PRO assessments are represented during prominent sessions of international congresses is another mechanism by which the ESC can increase the awareness and knowledge base of practicing cardiologists, nurses, pharmacists, and other healthcare providers. Importantly, the ESC will establish PROs as a relevant factor that should be considered by all of its committees charged with developing guidelines.

The ESC aims to include more patient representation in ESC activities and partner with academic experts, regulatory agencies, industry sponsors, reimbursement/payer groups, and political or grant resources to identify priorities for research, increase funding opportunities for PRO methodological research, and encourage the incorporation of appropriate PRO measures in all pivotal cardiovascular trials and registries (Box 1).

### Box 1 Summary of group recommendations to advance patient-reported outcomes in cardiovascular medicine

- Patient-reported outcomes reflect a key dimension of overall disease burden, and they should be a primary aim of disease management to improve patient well-being.
- Publication of high-quality research papers that describe the development and validation of PRO instruments or that report results of studies where PRO measures were primary or secondary endpoints should be encouraged.
- Patient-reported outcomes measures should be reported in all trials alongside mortality/morbidity outcomes (i.e. as major secondary endpoints) in accordance with the CONSORT PRO Extension.
- Patient-reported outcomes should be available and considered for future practice guidelines.
- Train physicians in the application and interpretation of PROs. Patient-reported outcomes should inform clinical decisions and evidence-based guidelines.

### Conclusion

Patient-reported outcomes measure key aspects of disease burden, but they have received limited attention in cardiovascular medicine. Cardiovascular clinical research should shift its focus to more broadly include PROs when evaluating the efficacy of therapeutic interventions. Patient-reported outcomes assessments should be scientifically rigorous so that the data can be confidently applied to evidence-based decision-making among all stakeholders including clinicians, patients, regulators, payers, sponsors, and health policymakers. Professional societies can take action to influence the uptake of PRO data in the research and clinical communities. This process of integrating PRO data into comprehensive efficacy evaluations will ultimately improve the quality of care for patients across the spectrum of cardiovascular disease.

### Supplementary material

Supplementary material is available at European Heart Journal online.

### Acknowledgements

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### Conflict of interest

S.D.A.: Consultant for Bosch GmbH, Impulse Dynamics, BioVentrix, CardioMems, Thermo Fischer GmbH, Vifor International (clinical events committee), Servier (Steering Committee), Jansen (Steering Committee), Medical Sensible, Novartis (Steering Committee), Cardiorenists (Steering Committee), BG Medicine (Steering Committee), Psioxus (Steering Committee), Bayer (Steering Committee); speaker for Servier and Vifor International. S.A.: Advisory board for Sanofi and Astra Zeneca; Speaker for Siemens and Boehringer-Ingelheim.

M.B.: Consultant to Bard, St Jude Medical, Boehringer-Ingelheim, Sanofi Aventis, Impulse Dynamics, Bayer Healthcare, Boston Scientific, Medtronic, Vest; speakers Bureau for Medtronic, Sanofi Aventis, Pfizer, St Jude Medical, Impulse Dynamics, Boehringer-Ingelheim, Vest; Royalties from Wiley-Blackwell (editor of book Cardiac Mapping 2013); M.C.: Travel support for meetings from European Society of Cardiology; Grant from Medical Research Council for development of the CONSORT Extension described in the manuscript; Grant from Canadian Institutes for Health Research for the development of the CONSORT Extension described in the manuscript; Member of the CONSORT PRO Executive group and first author of the CONSORT PRO Extension described in the manuscript. J.J.C.: Travel support from European Society of Cardiology to attend one meeting to discuss this paper; Employment by UBC, a consultancy that does PRO research. M.R.C.: None declared. I.F.: Travel support from European Society of Cardiology to attend one meeting to discuss this paper; Consultant for Servier, RESMED, Biotronik, Medtronic; Grants/grants pending from Servier, Vifor, Biotronik, Medtronic, J.A.P. and J.P.R.: None declared. K.S.: Travel support from European Society of Cardiology to attend one meeting to discuss the content of this paper; Consultant to Amgen, Novartis, Roche, Servier, Vifor. Research support from Amgen, Pfizer, Servier. L.T.: Board membership for Servier, St Jude Medical, Boston Scientific, Medtronic, Vifor Pharma, Cardiorenists; Speakers Bureau for Servier. I.W.: None declared. P.K.: Consulting fees and honoraria from 3M Medica, MEDA Pharma, AstraZeneca, Bayer Healthcare, Biosense Webster, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, German Cardiac Society, Medtronic, Merck, MSD, Otsuka Pharma, Pfizer, Sanofi, Servier, Siemens, Takeda; Research Grants from 3M Medica, MEDA Pharma, Bristol-Myers Squibb, Cardiovascular Therapeutics, Medtronic, OMRON, Sanofi, St Jude Medical, German Federal Ministry for Education and Training of high-quality research papers that describe the development and validation of PRO instruments or that report results of studies where PRO measures were primary or secondary endpoints should be encouraged.
References


