PATIENT-REPORTED OUTCOMES IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE: FROM INCLUSION TO QUALITY OF REPORTING

PATIENT-REPORTED OUTCOMES IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE: FROM INCLUSION TO QUALITY OF REPORTING

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LAY ABSTRACT

Patient-reported outcomes (PROs) produce meaningful information about patient-perceived health status reported directly by patients. Routine collection of PROs data is particularly important in chronic conditions, such as heart failure (HF). Major cardiovascular societies and regulatory agencies encouraged PRO inclusion in randomized controlled trials (RCTs), but PROs remain underutilized as a key outcome in these studies.

In this systematic review, we aimed to evaluate temporal trends and explore trial characteristics associated with PRO inclusion in HF RCTs published in high-impact medical journals. We also assessed the quality of PRO reporting against the Consolidated Standards of Reporting Trials PRO extension.

We found that over half of HF RCTs included a PRO. The proportion of RCTs with PROs increased significantly since 2000. A number of RCT characteristics such as multicentre; medium-sized (n = 51-250 participants); trials coordinated in Central and South America; and that tested health services, devices or surgery, exercise and rehabilitation interventions were independently associated with higher odds of PRO inclusion. The quality of PRO reporting was modest, with better reporting in RCTs with PROs a primary or co-primary endpoint.

Consistent PRO inclusion and high-quality reporting are necessary to increase the utility of these findings by patients, clinicians, and health care policy makers.

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LIST OF ABBREVIATIONS

AHA	American Heart Association
CONSORT	Consolidated Standards of Reporting Trials
CHF	Chronic Heart Failure
ESC	European Society of Cardiology
EQ-5D	EuroQol Five Dimensions Questionnaire
FACT-B	Functional Assessment of Cancer Therapy-Breast Cancer
FDA	Food and Drug Administration
HAQ	Health Assessment Questionnaire
HF	Heart Failure
HFScBs	Heart Failure Self-Care Behaviour Scale
LV-36	Left Ventricle Dysfunction Questionnaire
MCID	Minimal Clinically Important Difference
MLHFQ	Minnesota Living with Heart Failure Questionnaire
MPFH	Medical Psychological Questionnaire for Heart Patients
KCCQ	Kansas City Cardiomyopathy Questionnaire
PCORI	Patient-Centered Outcomes Research
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta- Analyses
PROSPERO	Prospectively Registered Systematic Reviews in Health and Social Care
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure
PROMIS	Patient-Reported Outcomes Measurement Information System
PGA	Patient Global Assessment

QoL	Quality of Life
RCT	Randomized Controlled Trial
ROC	Receiver Operating Characteristic
SF-36	Short Form Survey
VAS	Visual Analogue Scale

DECLARATION OF ACADEMIC ACHIEVEMENT AND COPYRIGHT

The submitted document represents collaborative work under the guidance and involvement of Dr. Harriette Van Spall, with contributions from the students and committee members on this team. The manuscript (Chapter 2) was co-authored by team members, with order of authorship reflecting the roles. I was involved during the article screening stages, data extraction, data analysis, and drafting of the initial manuscript document. I would like to acknowledge the contribution of other team members and collaborators, Dr. Tauben Averbuch, NhatChinh Le, for their extensive help in data extraction, multiple review/editing of the manuscript, auditing of data analysis. Dr. Feng Xie, Dr.Lehana Thabane, and Prof. Mamas A Mamas for their expert feedback and generous review of the manuscript.

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CHAPTER One: Introduction

Patient-oriented research in heart failure clinical trials

Randomized controlled trials (RCTs) are the gold standard for assessing the effectiveness of therapeutics in medical research, including heart failure (HF).[1–4] The standard selected outcomes in HF research have traditionally focused on measuring mortality, hospitalization, and major clinical events.[5,6] The shift toward patient-centered research in HF aimed to maximize survival, prevent hospitalization, and improve health status including symptom burden, functional limitations, social, emotional, and psychological wellbeing commonly referred to as health-related quality of life (HR-QoL).[7–11]

HF, a global epidemic, is a progressive and widely prevalent condition affecting 6.2 million Americans[12] and 64 million people worldwide.[13]As one of the leading causes of hospitalization and mortality, heart failure patients also suffer from decreased quality of life[10,11,14] due to the chronic condition. One of the major treatment goals for HF patients is to improve both quality and quantity of life.[11]

Patient-reported outcomes in heart failure research

Patient-reported outcomes (PROs) are outcomes reported directly by patients without further interpretations by clinicians or study personnel.[15] PROs measure patient's health status and represent outcomes most meaningful to them.[10,11] Instruments used to measure PROs are known as patient-reported outcome measures (PROMs).[9] Several HF-specific PROMs such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ)[16] and Kansas City Cardiomyopathy questionnaire (KCCQ)[17] were developed to reliability measure patients' perspectives on their health status.

The availability of PRO data from RCTs could facilitate patient- and policy-level decision making. In HF RCTs that test the effectiveness of device / surgery, PRO could quantify the symptoms burden associated with the tested therapies, highlighting the trade-off between clinical efficacy and quality of life.[10,11] For example, using implantable cardioverter defibrillator therapy for HF patients may be associated with anxiety and depression.[18] As a result, quantifying quality of life using PROs can yield tangible recommendations about patients' psychological evaluation and can ultimately improve the quality and quantity of life for HF patients.

PROs remain underutilized in cardiovascular RCTs, including HF[19], and they are not often selected as a key study outcome. In a review of 17,704 registered clinical trials between 2004 and 2007, only 14.0% used a PRO.[20] Moreover, many clinical trials include PROs as a secondary outcome. In certain trial intervention such as those assessing healthcare delivery programs, PROs could be included as a primary or co-primary outcome, given that improving patients' health status may be the primary goal of this intervention.[6,21]

The position of the American Heart Association and the European Society of Cardiology toward PROs

Major cardiovascular societies such as the American Heart Association (AHA),[10] the European Society of Cardiology (ESC),[11] and regulatory approval agencies[22] published official statements encouraging the collection of PROs in cardiovascular RCTs. Regulatory agencies such as The United States Food and Drug Administration (FDA) published a guidance report in 2007, titled, *Guidance for Industry, Patient Reported Outcome Measure: Use in Medical Product Development to Support Labeling Claims*, aimed to support PRO implementation in RCTs

seeking approval for medical product labelling claims.[22] Other initiatives such as the NIH-sponsored Patient-reported Outcomes Measurement Information Systems (PROMIS)[23], along with the Patient-Cantered Outcomes Research Institute (PCORI)[24], developed various PRO instruments for RCTs and supported patient-oriented research. These efforts improved the integration of PROs in clinical research.

Reporting standards for patient-reported outcomes data

Consistent and high-quality reporting of PROs is needed to increase the effective uptake of PRO findings from HF RCTs. Major reporting guidelines such as The Consolidated Standards Of Reporting Trials (CONSORT) developed PRO extension in 2013 in order to improve PRO reporting.[7] CONSORT-PRO checklist aimed to increase research transparency, trustworthiness and interpretations of PRO data.[25] CONSORT-2010 checklist had a prominent impact on the quality trial reporting[26]; however, it is not clear if these trials also adhered to PRO extension when reporting their findings. Evidence from non-HF studies suggest that PRO information is poorly reported in trial publications[27,28], and PRO data may be collected but not frequently reported.[29] Consistent, transparent, and high-quality reporting is required to improve the use of PRO findings by decision makers.

The utility of PRO data by clinicians, regulatory agencies, and knowledge consumers help inform clinical decision making and health care policy in HF.[10,11] To guide investigators when reporting PROs results, it is necessary to identify contemporary trends and limitations that may restrict effective uptake of these findings. We organized the chapters of this report to evaluate temporal trends of PRO inclusion in HF RCTs, explore RCT characteristics associated with PRO inclusion, and assess the quality of PRO reporting. We analyzed HF RCTs published in high-

impact medical journals, and we evaluated the quality of PRO reporting against the CONSORT-PRO extension.[7]

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CHAPTER Two: Temporal trends and trial characteristics associated with patient-reported outcomes inclusion in heart failure clinical trials published in high-impact medical journals: a systematic review

(Edited version submitted for publication)

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Abstract

Objectives: To assess temporal trends of patient-reported outcomes (PROs) inclusion in heart failure (HF) randomized controlled trials (RCTs) published in high-impact medical journals, explore RCT characteristics associated with PRO inclusion and describe the quality of PRO reporting following the Consolidated Standards of Reporting Trials (CONSORT-PRO) extension statements.

Methods: We searched MEDLINE, EMBASE and CINAHL for studies published between January 1, 2000 and July 17, 2020. We included RCTs published in journals with impact factor ≥ 10. We assessed temporal trends of PRO inclusion and conducted multivariable logistic regression analysis to explore trial characteristics independently associated with PRO inclusion. We described the quality of PRO reporting against the international standards for trial reporting (CONSORT-PRO) checklist.

Results: We identified 12,342 unique articles, of which 417 RCTs met inclusion criteria. PROs were included in 224 (53.7%, 95% confidence interval [CI]: 48.8%-58.6%) RCTs, of which 44 (19.6%) RCTs reported PROs as primary or co-primary endpoint. The proportion of RCTs with PROs increased significantly between 2000-2020 ($p < 0.001$). PROs had higher odds of inclusion in RCTs that were multicenter (odds ratio [OR]: 1.95; 95% CI: 1.05-3.64; $p = 0.036$); medium-sized (n = 51-250) (OR: 2.29; 95% CI: 1.24-4.23; $p = 0.008$); coordinated in Central and South America (OR: 6.79; 95% CI: 1.34-34.36; $p = 0.021$); and that assessed health services (OR: 4.21; 1.97-8.98; $p < 0.001$), device / surgical (OR: 6.24; 95% CI 3.05-12.80; $p < 0.001$), or exercise and rehabilitation interventions (OR: 3.98; 95% CI 1.59-9.97; $p = 0.003$). Majority of the 224

RCTs reported four of eleven CONSORT-PRO items (54.9%), and no trial reported all eleven items. The median number of CONSORT-PRO items reported was 4 (IQR 3-6 items per trial), with improved reporting in trials with PROs as primary or co-primary endpoint.

Conclusions: PROs are included in over half of HF RCTs, with a significantly increased trend since 2000. PROs had higher odds of inclusion in multicenter, medium-sized, coordinated in Central America, and tested health services, device/surgery, and exercise or rehabilitation interventions. PROs are moderately reported in HF RCTs with frequent omission of CONSORT-PRO items.

Key words: Heart Failure, Randomized Controlled Trials, Patient-Reported Outcomes

Introduction

Patient-reported outcomes (PROs) are study outcomes reported directly by patients without further interpretation by the health provider or outcome assessor.[1,2] Common selected outcomes in heart failure (HF) randomized controlled trials (RCTs) include hospitalization, mortality and recent emphasis on patient perceived health status.[3,4] Although not routinely collected as a key outcome, patient-reported outcomes measures (PROMs) are used to evaluate health status[5] Ascertaining health status from HF patients supplement other clinical outcomes by providing information about symptoms burden, functional limitations, and social and emotional wellbeing reported directly by patients.[5–7]

Given the importance of PROs in measuring health status, scientific statements from the American Heart Association (AHA),[3] the European Society of Cardiology (ESC),[4]and regulatory agency[1] have encouraged the routine collection of PROs in clinical trials involving cardiovascular conditions, including HF. However, PROs remain underutilized in cardiovascular RCTs.[8] In a systematic review of 413 cardiovascular trials published between 2005 to 2008, only 16% (SE 2%) used at least one instrument to measure PRO.[8] In the same review, 174 trials were judged to have important implications in clinical practice, of which 70% did not use PROs.[8] The clinical trial design may influence the use of PROs as study outcomes, but this has not been investigated in HF research.

The revolutionary impact of HF RCTs on patient management programs, therapeutics and treatment advancements[9–11] warrant the routine use of PROs in clinical trials. To improve PRO interpretation, applicability and transparency in HF research, clinical leaders are encouraged to adhere to international standards for PRO reporting in HF RCTs. However, to our knowledge, no studies investigated the quality of PRO reporting in general cardiovascular research or HF RCTs.

The balance between selecting study outcomes and PROs has not been investigated within contemporary HF RCTs. Without knowledge of current trends in the PRO reporting; clinicians, regulatory agencies, and knowledge consumers may offer suboptimal recommendations based on non-patient-centered outcomes. In this study, we aim to evaluate temporal trends and variation in the inclusion of PROs in HF RCTs published in high-impact medical journals, explore RCT characteristics associated with PRO use, and describe the quality of PRO reporting in HF RCTs following the Consolidated Standards of Reporting Trials (CONSORT-PRO) extension statements.[6] We hypothesized that the reporting of PROs in HF RCTs will have increasing temporal trends between 2000 to 2020 with higher trends in recent years.

Methods

Study registration

We prospectively submitted the study protocol for registration in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42020198676). The conduct and the reporting of this study will follow the Preferred Reposting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

Information sources and search strategy

We conducted a systematic search of the literature for articles published in three online databases, MEDLINE, EMBASE and CINAHL. The preliminary search strategy for MEDLINE was developed and performed by the study reviewer (S.W.), guided by the senior author (H.V.), and an experienced information specialist. We modified and applied the MEDLINE search strategy in the other subsequent databases using database-specific search terms. Two reviewers (S.W. and K.S.) completed a full reference list search once the included studies were identified.

Our search strategy included medical subject headings (MeSH) and keywords such as *heart failure* and *randomized controlled trials*. A full list of included terms for MEDLINE search strategy is available in supplementary appendix 1.

Eligibility criteria

The conduct and the selection of study eligibility criteria followed the Population, Intervention, Comparison, Outcome (PICO) framework.[13] We included RCTs with adult patients (≥ 18 years old) who have heart failure. We included primary RCTs, published in the English language, between January 1, 2000 and July 17, 2020. We searched for secondary RCTs reports with PRO data up-to six months after the final search date. We included studies published in journals with an impact factor of ≥10 based on the Web of Science 2019 classification report.[14] We excluded studies with methodological designs other than RCTs, such as observational cohort studies, viewpoints or commentaries, systematic reviews, and conference abstracts.

Study selection

Four reviewers (S.W., Y.E., K.S., and M.A.) independently screened the titles and abstracts from the original search to determine eligibility for inclusion. Studies identified as potentially relevant were further screened during the full-text evaluation, in duplicates, by the four reviewers (S.W., Y.E., K.S., and M.A.) We recorded reasons for the exclusion of articles evaluated at the full-text stage. Disagreements between reviewers were resolved through discussion, and when required, by consulting the third author.

Patient-reported outcomes (PROs) and reporting standards

We included PROs from HF RCTs that were reported directly by patients and not by clinicians or proxy personnel (i.e., caregivers). We used items reported within the Consolidated Standards of Reporting Trials (CONSORT-PRO) extension[6] to evaluate the quality of PRO reporting. The CONSORT-PRO extension items were based on the methodological framework for guidelines development organized by Enhancing the QUAlity and Transparency Of health Research (EQUATOR)[15], a systematic review of literature[6,16] and a survey of key stakeholders.[6,16] Five primary (P1b, P2b, P6a$_1$, P12a, and P21) CONSORT-PRO checklist items, and six sub-items (2a, 6a$_2$, 13a, 15, 17a, and 22) were recommended for the reporting of PROs in RCTs; we added two more recommendations including: (1) *a priori* statistical analysis plan for the PROs used in the trial; (2) If the study-specific PRO has not been published previously, a copy of the instrument should be attached in the supplementary file.

Three independent authors (Y.E., T.A., N.C.L.), following extraction meeting and discussion, scored studies that included PROs against the recommendations, examples and explanations provided by the CONSORT-PRO working group.[6] Each item received one point if reported, or zero point if not reported. For trials without study flow chart, we did not score CONSORT-PRO item (13a), rather the item did not receive a score. We divided CONSORT-PRO item (P6a) into (P6a$_1$) that require study authors to cite evidence of PRO validity, reliability and responsiveness and (6a$_2$) that report 'when', 'how' or ‘who’ completed the PRO measurement (e.g., self-administered versus proxy administered). We evaluated item (P6a$_1$) as ‘yes’ if evidence of PRO validity, reliability and responsiveness was cited for at least one instrument. We scored item (6a$_2$) based on ‘when’ or ‘how’ the PRO was measured and one reviewer (Y.E.) noted if the method of data collection involved a potential observer bias. For example, collecting PRO data

by telephone or face-to-face interviews that may influence participant response. For CONSORT-PRO items (17a), with PRO explanation, "for multidimensional PROs, results from each domain and time point specified for analysis" we considered the item to be adequately reported if one or several domains were reported by the authors.

Data abstraction and management

Four reviewers (S.W., Y.E., K.S., and M.A.) independently extracted the following information induplicate: year of publication, journal impact factor, region of coordinating center (North America, Europe, South America, Australia, Asia), scope of the trial (national, international), location of recruitment (inpatient, ambulatory), sample size, type of consent (informed consent, other), type of intervention (health service, drug, device, surgery, exercise / rehabilitation), level of randomization (individual, cluster), number of centers (single center, multicenter), funding type (public, industry), gender of the lead or senior author (male, female). Two authors (Y.E., and H.V.) selected new variables for extraction. Prior to commencing data extraction for the new variables, all authors attended extraction sessions in which two articles were extracted and thoroughly discussed to ensure consistency and accuracy. Three authors (Y.E., T.A., N.C.L.) independently extracted following information in duplicate: inclusion of PROs (yes/no), PROs types and instrument names, reporting of PROs as primary or co-primary endpoint (yes/no), primary outcome results (positive, neutral), reporting of minimal clinically important difference (MCID) for PROs (yes/no), trial registration (yes/no) and CONSORT-PRO items. We classified trials that received partial or full industry funding as industry funded trials. We classified the gender of the authors using the Web of Science author search engine, institutional websites, and public social media profiles.[17]

Statistical analysis

We summarized data descriptively and present continuous variables using medians and interquartile ranges (IQRs) and categorical variables using numbers and percentages.

Proportions trend test. We used the Jonckheere-Terpstra trend test to assess temporal trends of PRO inclusion in HF RCTs over interval times.

Multivariable logistic regression. We conducted multivariable logistic regression analysis. The regression model aimed to explore RCT characteristics associated with PRO inclusion in HF RCTs. The selection of independent variables for the regression analysis was informed by literature that assessed trial characteristics associated with PRO use in general cardiovascular trials[8]. A list of pre-specified hypotheses for any included independent variables was also constructed. We used patient-reported outcomes (PROs) inclusion (yes/no) as the dependent variable, and the following independent variables: sample size, region, type of intervention, number of centers, location of recruitment, scope of the trial, type of funding, and gender of the lead or senior author. We assessed model fit using Hosmer and Lemeshow test. We tested model discrimination using area under the receiver operating characteristic (ROC) curve. We calculated odds ratios (ORs) from the logistic regression model and presented values with 95% confidence intervals (CIs).

Sensitivity analysis. We described the quality of PRO reporting for RCTs published before and after introducing CONSORT-PRO extension in 2013 and reported the corresponding medians and IQRs.

All p values were two-tailed, and $p<0.05$ was considered statistically significant. Data were analyzed using SPSS (version 23; IBM Corporation).

Results

Our systematic literature search yielded 12,342 unique articles, of which 8,932 were excluded based on title and/or abstract review. We assessed 3,410 full-text articles and included 417 RCTs against the eligibility criteria (Figure 1).

Characteristics of included studies

We included 417 RCTs, representing 237,032 participants (median: 120, IQR 30-406 participants per trial). Of these trials, 224 (53.7%, 95% CI: 48.8%-58.6%) included at least one PRO. Of which, 221 (98.7%) included PRO findings in the primary publications, and 3 (1.3%) included PRO findings in secondary publications. Most of the 224 RCTs were coordinated in Europe (49.1%), were multicenter (67.4%), had a positive primary outcome (59.8%), and assessed drug interventions (51.3%). All RCTs (100.0%) used informed consent forms. Most of the 417 RCTs were recruited in ambulatory settings (76.3%), led by men authors (84.2%), and reported trial registration number (42.9%) (Table 1).

PRO types and temporal trends

Of the 224 RCTs with PROs, 44 (19.6%) were primary or co-primary endpoint, 96 (42.9%) used HF-specific instruments, 65 (29.0%) were generic, and 63 (28.1%) used both HF-specific and generic instruments. Most of the 224 RCTs used the Minnesota living with heart failure questionnaire (MLHFQ) (49.1%), Kansas City cardiomyopathy questionnaire (KCCQ) (22.3%) for HF-specific instruments and self-reported dyspnea scale (12.9%) and EQ-5D (10.7%) for genetic instruments (Table 2). The median number of PRO instruments remained stable from 1 (IQR 1-2) in 2000-2003 to 1 (IQR 1-3) in 2016-2020. The proportion of RCTs with PROs have significantly increased from 37.4% in 2000-2003 to 65.1% in 2016-2020 (difference 27.7%, 95% CI: 21.9%-34.0%, p (trend) < 0.001) (Figure 2).

Multivariable analysis of clinical trial characteristics associated with PRO inclusion

The odds of PRO inclusion were significantly greater in RCTs that were multicenter (OR: 1.95; 95% CI: 1.05-3.64; p = 0.036) relative to single center; medium-sized (n = 51-250) (OR: 2.29; 95% CI: 1.24-4.23; p = 0.008) relative to small (n $\leq$ 50) trials; coordinated in Central and South America (OR: 6.79; 95% CI: 1.34-34.36; p = 0.021) relative to Asia and Australia; and that assessed health services (OR: 4.21; 95% CI: 1.97-8.98; p < 0.001), devices or surgery (OR: 6.24; 95% CI: 3.05-12.80; p < 0.001), or exercise and rehabilitation (OR: 3.98; 95% CI: 1.59-9.97; p = 0.003) relative to drug interventions. There were no significant association between PRO inclusion and other trial characteristics such as: large sample size (n >250) (OR: 1.41; 95%CI: 0.65-3.05; p = 0.381) relative to small trials; ambulatory recruitment (OR: 1.07; 95% CI: 0.64-1.79; p = 0.799) relative to inpatient; international trials (OR: 1.15; 95% CI: 0.62-2.15; p = 0.662) relative to national; industry funded (OR: 1.04; 95% CI: 0.62-1.76; p = 0.879) relative to publicly funded trials, and with women in the lead or senior authorship position (OR: 0.99; 95% CI: 0.60-1.65; p = 0.976) relative to men in the lead or senior authorship position (Table 3).

Quality of PRO reporting following the CONSORT-PRO extension statements

Among 224 RCTs with PROs, no trial reported all CONSORT-PRO items, and majority 123 (54.9%) reported at least four of eleven items. Most of the 224 RCTs (93.3%) failed to report eight or more CONSORT-PRO items. The median number of CONSORT-PRO items reported was 4 (IQR 3-6 items per trial). Of 224 RCTs with PROs, the most commonly reported item included: specifying methods on PRO data collection, including ‘when’ or ‘how’ (70.1%), reporting of PRO baseline value (56.3%), citing evidence for instrument validity and reliability (55.8%), and interpreting PRO findings in relation to clinical outcomes (50.4%). PRO hypotheses, discussion of PRO limitations, and statistical approaches for dealing with PRO

missing data were not commonly reported in HF RCTs (8.9%, 19.2%, 24.1%, respectively). The median number of CONSORT-PRO items reported in trials with PRO as primary endpoint was 7 (IQR 5-8 items per trial) and 4 (IQR 2-5 items per trial) in trials with PRO as secondary endpoint. Of the 44 RCTs with PRO as primary endpoint, the most commonly reported CONSORT-PRO items included: specifying methods on PRO data collection, including 'when' or 'how' (86.4%), identifying PRO as primary outcome in the abstract (84.1%), assessing rationale for PRO inclusion in RCTs (75.0%), and interpreting PRO findings in relation to clinical outcomes (72.7%). Most of 224 RCTs reported *a priori* statistical analysis plan for PROs (68.3%). Only 8 RCTs used study-based instruments, of which 3 (37.5%) attached a copy of the tool in the appendix (Table 4).

Sensitivity analysis. The median number of CONSORT-PRO items reported was 4 (IQR 3-5 items per trial) in trials published before the introduction of CONSORT-PRO extension in 2013 and 5 (IQR 3-7 items per trial) in trials published after the introduction of CONSORT-PRO extension.

Discussion

In this systematic review of 417 RCTs published in high-impact medical journals between 2000 and 2020, 224 (53.7%) included at least one PRO. Among the 224 RCTs that included PROs, only 44 (19.6%) reported PROs as a primary or co-primary endpoint. The proportion of RCTs with PROs increased significantly since 2000. PROs had a greater odds of inclusion in RCTs that were multicenter; medium-sized trials (n= 51-250); coordinated in Central and South America; and tested health services, device/surgery, and exercise/ rehabilitation interventions. Location of recruitment, scope of trial, type of funding, and gender of lead or senior author were not associated with PRO inclusion. Among 224 RCTs with PROs, adherence to CONSORT-PRO

extension was modest with majority of the trial (54.9%) reported at least 4 of 11 items (Central illustrator).

Half of HF RCTs included at least one PRO with increasing trends over the study period. In a similar study of 413 cardiovascular trials published between 2005 and 2008, only 16% included PROs.[8] This study described the increasing prevalence of PROs but did not assess trial characteristics associated with PRO inclusion nor evaluated the quality of PRO reporting. Similar studies that focused on HF PROs summarized psychometric properties of these instruments to ease the selection of available tools for clinical trials.[18–25] To our knowledge, our study is the first to describe the temporal trends of PROs in HF RCTs.

Although we found an increasing trend of PRO inclusion in HF trials, less than 10.6% were primary or co-primary endpoints. It is possible that the majority of the included trials were not adequately powered to detect meaningful treatment effect for PROs.[26–28] The use of PROs as part of composite outcomes could be improved for trials that incorporate outcomes of different importance to the patients. It is critical to adhere to the best methodological frameworks for selecting outcomes within a composite.[29–31] It can be problematic to have certain composite outcomes – of less relevance to the patients – to dominate treatment effect.[30–33] Exploring PROs as a secondary endpoints amplify power estimation challenges and highlight that outcomes reported by patients are inferior to other study outcomes.[27] In this case, PRO estimates provided in these trials may be of less relevance to clinical decision making, health care policy and regulatory approval claims.[34]

The odds of PRO inclusion was higher in medium-sized trials (n=51-250 participants) and multicenter trials. The implementation of PROs in clinical trials is logistically complex and requires site personnel training on data collection, management and follow-up.[4,35,36] The inclusion of PROs in medium-sized trials may be influenced by the manageable participant size, simple data collection process and lack of PRO missing data for analysis. Number of centers is also a reflection of resources utilized to complete the study. These resources may include purchasing copyrighted PRO instruments, hiring an expert statistician for analysis and training site staff to maximize PRO data collection.[37]

PROs had higher odds of inclusion in RCTs coordinated in Central and South America. While we found that European sites coordinated the highest number of trials, these sites appear to use PROs less frequently. The role of coordinating centers and the use of PROs may be multifactorial. It is possible that if one or more PROs were to be translated, culturally adapted and validated to the Spanish language, the majority of participating sites in Central America (i.e., Brazil, Mexico, Colombia, and others) will have access to these questionnaires.[38] Other reasons for higher odds of PRO inclusion in Central and South America include government and funding agencies' mandate to prioritize health care intervention based on cost-effectiveness and cost-utility analysis.[39] To perform a cost-utility analysis, health evaluation using quality-adjusted life-years will require the use of various PROs.[40] It is possible that other coordinating regions did not include PROs due to linguistic and cultural barriers often presented by a lack of research capacity to translate PRO instruments into native languages.

We found RCTs that tested health services, device/surgery and exercise/rehabilitation interventions to have higher odds of PRO inclusion. One of the goals of PRO inclusion in cardiovascular clinical trials is to support approval for medical product labelling claims.[1,41,42] Major approval agencies, such as the United States Food and Drug Administration (FDA), published a guidance report in 2009 to support the routine collection of PROs in clinical trials.[1] Since then, the acceptance by cardiovascular societies such as the AHA and ECS propelled PRO inclusion in HF RCTs.[3,4] However, current HF PRO instruments appear to lack one or more items recommended by the FDA for product labelling approval.[42] Such limitations included inadequate content validity evaluation, longer recall periods, and lack of responder definition.[42] It is critical that FDA criteria, and other regulatory approval recommendations, guide the development and evaluation of future PRO instruments for HF.

More than 93.3% of HF RCTs failed to adequately report eight or more CONSORT-PRO items in published reports. We found that rudimentary design elements — such as reporting of PRO hypotheses, statistical approaches for dealing with PRO missing data, discussing PRO limitations and interpreting results in relation to other clinical outcomes — were not commonly reported. These omissions may reduce data quality, research transparency and threaten PRO interpretability.[28,43,44] Suboptimal reporting of PRO data may also reduce the validity and impact of patient perception on their health status as a trial outcome. It is also possible that valuable information omitted during PRO reporting may reduce the use of PROs by clinicians or health care policymakers, patients, and knowledge consumers.[4,45] More importantly, low quality of PRO reporting devalues trial participants' time and energy needed to complete PRO questionnaires. For example, in one study with 1,376 patients, researchers noted the use of

multiple quality-of-life questionnaires within the published protocol[46], but results of only one instrument were published as a secondary report.[47] It may be unethical to neglect publishing this important patient data.

Quality of PRO reporting improved when selected as a primary or co-primary endpoint, which represented only 10.6% of RCTs included in our study. We also found that trials with a secondary PRO publication adequately report most of the CONSORT-PRO extension items. It is possible that when PROs are treated as a secondary endpoint, suboptimal reporting may be supplemented by a lack of journal space to provide additional details of PRO design and conduct. We also found that trials published after the introduction of the CONSORT-PRO extension reported a greater number of CONSORT-PRO items compared to trials published before the introduction of the CONSORT-PRO extension. It is likely that leaders of recent HF RCTs utilized the available reporting guidelines, such as CONSORT-PRO, to describe PROs in their trials. However, our findings coincide with previous non-heart failure studies concluding persistent poor quality of PRO reporting and adherence to CONSORT-PRO statements in published reports.[48,49]

To our knowledge, this is the first systematic review that identified gaps in the quality of PRO reporting in HF RCTs published in high-impact medical journals. Existing resources such as the international reporting guidelines published by CONSORT-PRO working group[6] should be routinely used to guide investigators on best reporting practices for PROs in clinical trials. Other reporting guidelines could be incorporated at the protocol formation stages using the SPIRIT-PRO extensions.[50] Although medical journal editorial policies vary on ‘how’ to implement PRO

data, consistent standards following international reporting guidelines should be encouraged.[51] By endorsing the available reporting guidelines, transparent and accurate PRO data will be easily accessible to clinicians, health care policy makers and other stakeholders to further inform patient-centered care in heart failure.

Strengths and limitations

This is the first systematic review to assess trends of PRO inclusion and quality of reporting in HF RCTs. The strengths of this study include a systematic search strategy and the inclusion of RCTs published over a two-decade time span. We incorporated best practices for systematic reviews[12] ranging from protocol registration, independent and duplicate review processes including data extractions, and consultations with other reviewers to resolve discrepancies. We also utilized international standards for RCTs reporting, such as the Consolidated Standards of Reporting Trials (CONSORT-PRO) extension[6] to evaluate the quality of PRO reporting.

This study has several limitations. First, we restricted this review to English language articles published in medical journals with impact factor of $\geq$ 10. It is possible that articles published in high-impact medical journals may be subjected to potential publication bias, as trials with neutral outcomes get rejected.[52] Second, recent trials included in our review may publish their PRO data as secondary reports after our last search date; this limitation should be considered when interpreting our results. Third, most included studies were published before the development of the CONSORT-PRO extension.[6] However, major cardiovascular scientific societies and regulatory agencies, such as the FDA, AHA, and ECS endorsed the inclusion of PRO in early 2009[1]. Fourth, our results focused on HF RCTs and may not be generalizable to other specialties,

trials, and/or populations. Fifth, despite selecting model predictors based on literature and testing of assumptions, we acknowledge that our multivariable analysis is exploratory and results should be interpreted with caution. Sample size was selected based on established standards of 10 events per independent variable[53]; however, the risk of overfitting may appear due to low ratio of events to the degrees of freedom.[54]

Conclusions

Among 417 HF RCTs published between 2000-2020, 224 (53.7%) reported having a PRO. Of which, 44 (19.6%) were primary or co-primary endpoints. The proportion of PROs in HF RCTs has changed significantly since 2000. PROs had a greater odds of inclusion in RCTs that were multicenter; medium-sized trials (n= 51-250); coordinated in Central and South America; and tested health services, device/surgery, and exercise/ rehabilitation interventions. Among 224 RCTs with PROs data, no trial reported all CONSORT-PRO items. Majority of the included trial reported at least 4 of 11 CONSORT-PRO items. Valuable patient-centered information is frequently omitted in heart failure trials due to modest reporting. These deficiencies may reduce the use of patient-reported outcomes by clinicians, health care policy makers, and knowledge consumers.

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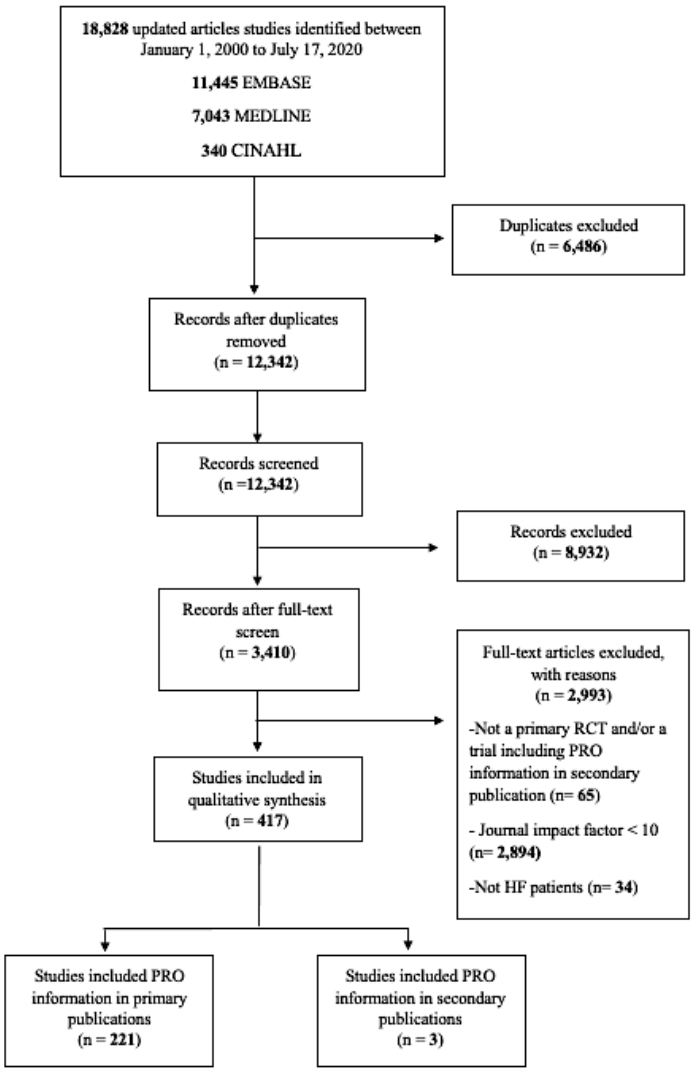


Figure 1. PRISMA flow diagram of the study selected in this systematic review.

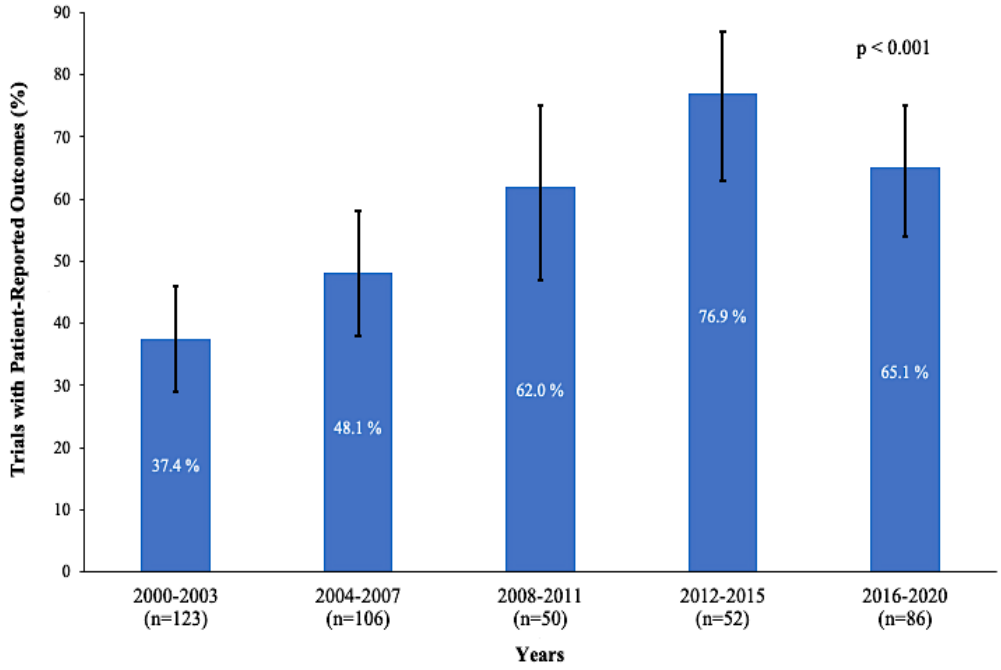
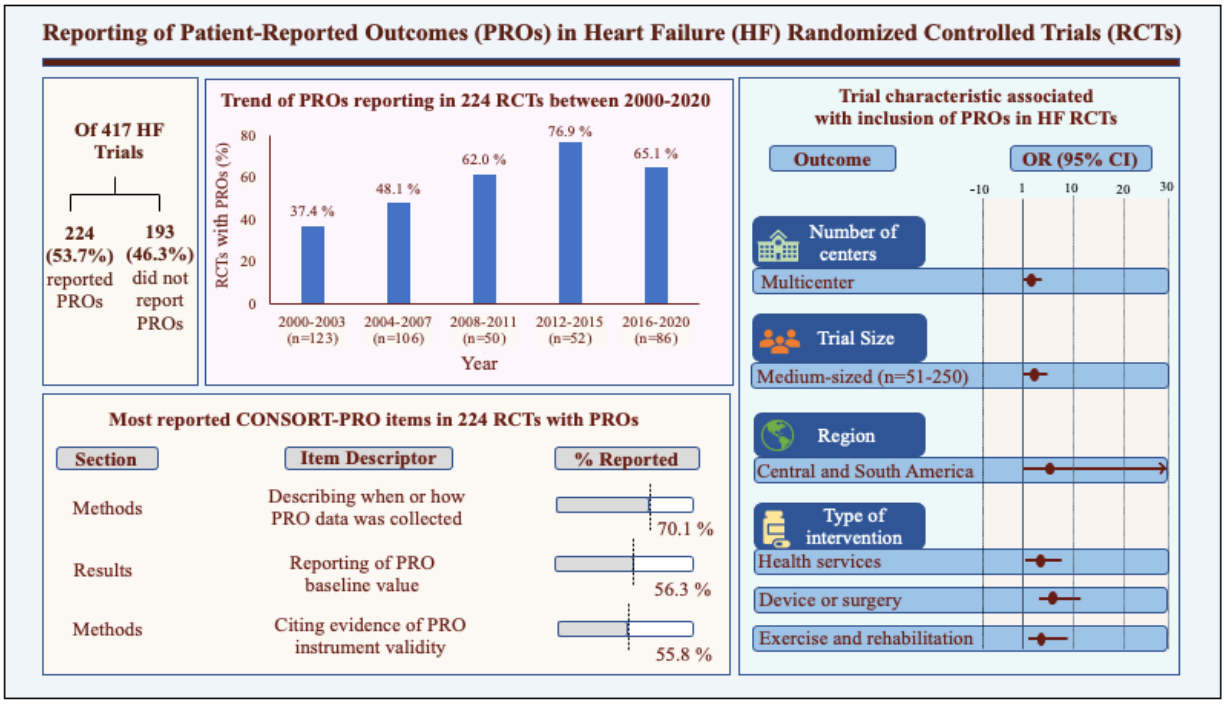


Figure 2: Proportions of heart failure (HF) randomized controlled trials (RCTs) that reported a patient-reported outcome (PRO) between 2000 to 2020. The proportion of HF RCTs with PROs increased significantly since 2000 ($p < 0.001$). Bars represent 95% confidence intervals (CIs).



Central Illustration. Of 417 HF RCTs, 224 (53.7%) included at least one PRO. The proportion of RCTs with PROs increased significantly between 2000-2020 ($p < 0.001$). Number of centers, trial size, region of coordinating center, and type of intervention were independently associated with higher odds of PRO inclusion in HF RCTs. Among 224 RCTs with PROs, most reported CONSORT-PRO item included: describing when or how PRO data was collected (70.1%), reporting of PRO baseline value (56.3%), and citing evidence of PRO instrument validity, reliability, and responsiveness (55.8%).

Table 1. Characteristics of randomized controlled trials (RCTs) included according to reporting of patient-reported outcomes (PROs) (n=417).

Clinical trial characteristic	No. (%) of RCTs with PROs (n=224)	No. (%) of RCTs without PROs (n=193)	No. (%) of total RCTs (n=417)
Trial size			
Small (≤ 50)	52 (23.2)	82 (42.5)	134 (32.1)
Medium (51-250)	88 (39.3)	52 (26.9)	140 (33.6)
Large (> 250)	84 (37.5)	59 (30.6)	143 (34.3)
Analysis of PRO			
Primary outcome	17 (7.6)	N/A	17 (4.1)
Co-primary	27 (12.1)	N/A	27 (6.5)
Secondary outcome	180 (80.4)	N/A	182 (43.6)
Report minimal clinically important difference (MCID)			
Yes	36 (16.1)	N/A	36 (8.6)
Type of PRO			
HF-specific	96 (42.9)	N/A	96 (23.0)
Generic	65 (29.0)	N/A	65 (15.9)
Both	63 (28.1)	N/A	63 (15.1)
Primary outcome results			
Positive	134 (59.8)	139 (72.0)	273 (65.5)
Neutral	90 (40.2)	54 (28.0)	144 (34.5)
Unit of randomization			
Individual	220 (98.2)	193 (100.0)	413 (99.0)
Cluster	4 (1.8)	0 (0.0)	4 (1.0)
Type of consent			
Informed consent	224 (100.0)	193 (100.0)	417 (100.0)
Region of coordinating center			
Europe	110 (49.1)	110 (57.0)	220 (52.8)
North America	93 (41.5)	64 (33.2)	157 (37.6)
Asia	4 (1.8)	13 (6.7)	17 (4.1)
Australia	6 (2.7)	3 (1.6)	9 (2.2)
South America	11 (4.9)	3 (1.6)	14 (3.4)
Recruitment			
Inpatient	54 (24.1)	45 (23.3)	99 (23.7)
Ambulatory	170 (75.9)	148 (76.7)	318 (76.3)
Type of intervention			
Health service	42 (18.8)	13 (6.7)	55 (13.2)
Exercise/ rehabilitation	19 (8.5)	10 (5.2)	29 (7.0)
Drug	115 (51.3)	158 (81.9)	273 (65.5)
Device	40 (17.9)	10 (5.2)	50 (12.0)
Surgery/procedure	8 (3.6)	2 (1.0)	10 (2.4)
Scope of trial			
National	155 (69.2)	142 (73.6)	297 (71.2)

International	69 (30.8)	51 (26.4)	120 (28.8)
Type of funding			
Industry*	121 (54.0)	101 (52.3)	222 (53.2)
Public	103 (46.0)	92 (47.7)	195 (46.8)
Number of centers			
Multicenter	151 (67.4)	94 (48.7)	245 (58.8)
Single center	73 (32.6)	99 (51.3)	173 (41.2)
Gender of the lead author			
Male	187 (83.5)	164 (85.0)	351 (84.2)
Female	37 (16.5)	29 (15.0)	66 (15.8)
Gender of the senior author			
Male	200 (89.3)	171 (88.6)	371 (89.0)
Female	24 (10.7)	22 (11.4)	46 (11.0)
Year of publication			
2000-2003	46 (20.5)	77 (39.9)	123 (29.5)
2004-2007	51 (22.8)	55 (28.5)	106 (25.4)
2008-2011	31 (13.8)	19 (9.8)	50 (12.0)
2012-2015	40 (17.9)	12 (6.2)	52 (12.5)
2016-2020	56 (25.0)	30 (15.5)	86 (20.6)
Trial registration			
Yes	123 (54.9)	56 (29.0)	179 (42.9)

*We classified trials that received partial or full industry funding as industry funded trials.
Abbreviation: CONSORT, Consolidated Standards of Reporting Trials; HF, heart failure; PROs, patient-reported outcomes; MCID, minimal clinically important difference.

Table 2. Types of patient-reported outcome (PRO) instruments reported in heart failure (HF) randomized controlled trials (RCTs) (n=224).

PRO Types	No. (%) of RCTs with PROs (n=224)
Heart failure specific	
Minnesota living with heart failure questionnaire (MLHFQ)	110 (49.1)
Kansas city cardiomyopathy questionnaire (KCCQ)	50 (22.3)
Chronic heart failure (CHF)	7 (3.1)
Heart failure self-care behaviour scale (HFScBs)	6 (2.7)
Heart failure knowledge score	5 (2.2)
LV dysfunction questionnaire (LV-36)	2 (0.9)
Medical psychological questionnaire for heart patients (MPFH)	1 (0.4)
Generic questionnaires	
Self-reported dyspnea scale	29 (12.9)
Short form survey (SF-36 or SF-12)	24 (10.7)
EQ-5D	24 (10.7)
Patient global assessment (PGA)	21 (9.4)
General quality of life (QoL) †	6 (2.7)
Study-based scale	8 (3.6)
Other*	74 (33.0)

*Other included: Visual Analogue Scale (VAS) such as Global status VAS (7 trials), Sedation VAS (1 trial), Fatigue VAS (4 trials), Thirst VAS (1 trial), Fear of movement VAS (1 trial), Daily satisfaction VAS (2 trials), Respiratory status VAS (2 trials), Solicited sedation events questionnaire (1 trial), McMaster overall treatment (2 trials), Ware satisfaction with care scale (1 trial), The Guyatt respiratory scale (1 trial), Beck Depression Inventory (BDII) (3 trials), Beck Anxiety Inventory (BAII) (1 trial), WHO nausea and vomiting (PONV) (1 trial), Epworth sleepiness scale (ESS) (6 trials), Duke activity status index (DASI) (2 trials), International index of erectile function (IIEF) (1 trial), Hospital anxiety and depression scale (HAD) (4 trials), Zung self-rating depression scale (SDS) (2 trials), Health-related quality of life questionnaire (MacNew) (2 trials), Health complaints scale (HCS) (1 trial), Specific activity scale (SAS) (1 trial), Patient health questionnaire (PHQ) (5 trials), Hamilton rating for depression (HDRS) (1 trial), Validated national institute of health PROMs (1 trial), The Seattle angina questionnaire (SAQ) (2 trials), The functional assessment of chronic illness therapy (FACIT) (4 trials), Generalized anxiety disorder questionnaire (GAD) (2 trials), Decisional conflict scale (DCS) (1 trial), Decision regret scale (DRS) (1 trial), Validated measures of control preferences (1 trial), Peace, equanimity, and acceptance (PEA) (1 trial), Perceived stress scale (PSS) (1 trial), Borg rating of perceived exertion scale (RPE) (1 trial), General symptom distress scale (GSDS) (1 trial), The memorial symptom assessment scale (MSAS) (1 trial), The preparedness for hospital discharge to home (B-PREPARED) (1 trial), The care transitions measure (CTM-3) (1 trial), Measurement system global health (1 trial), Measurement system pain intensity and interference (1 trial).

†This category included Likert-based QoL questionnaire, trials using the term QoL without reference to a tool, Iceland QoL questionnaire, and VAS QoL.

Abbreviation: QoL, quality of life; VAS, visual analogue scale.

Table 3. Multivariable analysis of trials characteristics associated with patient-reported outcome (PROs) inclusion in randomized controlled trials (RCTs) of heart failure (n=417).

Variable	Multivariable model§	
	OR (95% CI)	***P* value**
Trial size		
Small (≤ 50)	1.00 (Reference)	-
Medium (51-250)	2.29 (1.24- 4.23)	0.008
Large (> 250)	1.41 (0.65- 3.05)	0.381
Region		
Other*	1.00 (Reference)	-
Europe	1.45 (0.58- 3.63)	0.428
North America	1.77 (0.69-4.54)	0.233
Central and South America	6.79 (1.34- 34.36)	0.021
Type of intervention		
Other†	1.00 (Reference)	-
Health services	4.21 (1.97- 8.98)	<0.001
Device / Surgery	6.24 (3.05- 12.80)	<0.001
Exercise and rehabilitation	3.98 (1.59- 9.97)	0.003
Number of centers		
Single center	1.00 (Reference)	-
Multicenter	1.95 (1.05- 3.64)	0.036
Location of recruitment		
Inpatient	1.00 (Reference)	-
Ambulatory	1.07 (0.64- 1.79)	0.799
Scope of trial		
National	1.00 (Reference)	-
International	1.15 (0.62- 2.15)	0.662
Type of funding		
Public	1.00 (Reference)	-
Industry‡	1.04 (0.62- 1.76)	0.879
Gender of author		
Man lead and senior author	1.00 (Reference)	-
Woman lead or senior author	0.99 (0.60- 1.65)	0.976

*Region 'other 'category included Asia and Australia.
†Intervention category 'other' included drug interventions.
‡We classified trials that received partial or full industry funding as industry funded trials.
§We assessed model fit using the Hosmer-Lemeshow test (p=0.296). Non-significant findings indicating that the model is not a poor fit.
We also assessed model discrimination using Area under the Curve (AUC) value of ROC curves. AUC was (0.75,95% CI 0.70-0.79, p<0.001), indicating acceptable level of discrimination according to Hosmer et al. (2013)[55].

Table 4. Recommendations for the reporting of randomized controlled trials with patient-reported outcomes (PROs) using the Consolidated Standards of Reporting Trials (CONSORT-PRO)[6] guidelines and findings from this study (n=224).

Section	Item	Descriptor of PRO-specific statement	No. (%) RCTs with PRO as primary or co-primary endpoint (n=44)	No. (%) RCTs with PRO as secondary endpoint (n=180)	Total, No. (%) RCTs with PROs (n=224)
Title and Abstract	P1b*	"The PRO should be identified in the abstract as a primary or secondary outcome."	37 (84.1)	62 (34.4)	99 (44.2)
Introduction					
	2a	"The relevant background and rationale for why PROs were assessed in the RCT should be briefly described."	33 (75.0)	77 (42.8)	110 (49.1)
	P2b	"The PROs hypothesis should be stated, and relevant domains identified, if applicable."	10 (22.7)	10 (5.6)	20 (8.9)
Methods					
	$P6a_1$†	"Evidence of [any] PRO instrument validity and reliability should be provided or cited, if available."	32 (72.7)	93 (51.7)	125 (55.8)
	$P6a_2$‡	"Details of the method [how or when] of data collection (paper, telephone, electronic, other) should also ideally provided particularly when the PRO is the primary outcome."	38 (86.4)	119 (66.1)	157 (70.1)
	P12a	"Statistical approaches for dealing with missing data should be explicitly stated for PROs prespecified as primary or important secondary outcomes."	21 (47.7)	33 (18.3)	54 (24.1)
	13a§	For CONSORT flow chart, "The number of participants reporting PRO data at baseline and at subsequent	6/34 (17.6)	6/120 (5.0)	12/154 (7.8)

		time points should be made transparent."			
Results					
	15	For table showing baseline characteristics, "Including baseline PRO data when collected."	31 (70.5)	95 (53.8)	126 (56.3)
	17a	"For multidimensional PROs, results from [one or several] domain and time point [could be] specified for analysis."	26 (59.1)	83 (46.1)	109 (48.7)
Discussion					
	P20/21	"PRO specific limitations and implications for generalizability of study findings and clinical practice."	20 (45.5)	23 (12.8)	43 (19.2)
	22	"PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant."	32 (72.7)	81 (45.0)	113 (50.4)
Extension					
	-	*a priori* statistical analysis plan for the PROs used in the trial.	43 (97.7)	110 (61.1)	153 (68.3)
	-	If the study-specific PRO tool has not been published previously, a copy of the instrument should be attached in the supplementary file.	1/3 (33.3)	2/5 (40.0)	3/8 (37.5)

*Primary CONSORT-PRO items were prefixed with the letter P. Selected items not denoted with the letter P were adapted from the CONSORT-2010 statement based on CONSORT-PRO group suggestions.
†We scored this item if evidence of at least one instrument psychometric properties was cited.
‡We scored this item based on when or how the PRO data was measured. We found 15 trials that collected PRO data via face-to-face interview or telephone call.
§Of the 70 trials that did not publish their study flowchart, 10 and 60 trials reported PRO as a primary and secondary endpoint respectively.
Abbreviation: PROs, patient-reported outcomes; RCT, randomized controlled trial.

Supplementary Material

Supplementary Table 1. The Consolidated Standards of Reporting Trials (CONSORT-PRO) recommendations for the reporting of randomized controlled trials with patient-reported outcomes (PROs). Scores ranged between zero and eleven. Table adapted from Calvert et al., (2013)[6] for the recommended five PRO-specific items (prefixed with the letter 'P'), selected sub-items, and modified items (e.g., P6a).

Section	Item	Descriptor of PRO-specific statement	Scoring criteria
Title and Abstract	P1b	"The PRO should be identified in the abstract as a primary or secondary outcome."	1 point = item reported 0 point= item not reported
Introduction			
	2a	"The relevant background and rationale for why PROs were assessed in the RCT should be briefly described."	1 point = item reported 0 point= item not reported
	P2b	"The PROs hypothesis should be stated, and relevant domains identified, if applicable."	1 point = if hypothesis is stated and/or PRO domains specified in hypothesis
Methods			
	$P6a_1$	"Evidence of [any] PRO instrument validity and reliability should be provided or cited, if available."	1 point = if evidence of PRO validity, reliability and responsiveness was cited for at least one instrument
	$P6a_2$	"Details of the method [how or when] of data collection (paper, telephone, electronic, other) should also ideally be provided particularly when the PRO is the primary outcome."	1 point = if the method of data collection (paper, telephone, electronic, other) and/or when PRO data was collected is described
	P12a	"Statistical approaches for dealing with missing data should be explicitly stated for PROs prespecified as primary or important secondary outcomes."	1 point = item reported 0 point= item not reported
	13a	For CONSORT flow chart, "The number of participants reporting PRO data at baseline and at subsequent	1 point = item reported 0 point= item not reported N/A = trial did not publish study flow chart

		time points should be made transparent."	
Results			
	15	For table showing baseline characteristics, "Including baseline PRO data when collected."	1 point = if stated in the demographics table (i.e., table 1) or reported in the results section
	17a	"For multidimensional PROs, results from [one or several] domain and time point [could be] specified for analysis."	1 point = if PRO findings from one or several domains reported with effect size and precision estimate
Discussion			
	P20/21	"PRO specific limitations and implications for generalizability of study findings and clinical practice."	1 point = if PRO-specific limitations or implications for generalizability and/or use in clinical practice are discussed
	22	"PRO data should be interpreted in relation to clinical outcomes including survival data, where relevant."	1 point = item reported 0 point = item not reported

*Primary CONSORT-PRO items were prefixed with the letter P. Selected items not denoted with the letter P were adapted from the CONSORT-2010 statement based on CONSORT-PRO group suggestions.
Abbreviation: PROs, patient-reported outcomes; RCT, randomized controlled trial.

Supplementary Table 2. Search Strategy

1	Heart failure.mp or Heart Failure/
2	Limit 1 to (English language or humans)
3	Limit 2 to yr=*2000-Current*
4	Limit 3 to randomized controlled trial
5	Limit 4 to (meta-analysis or "review" or systematic reviews)
6	Limit 4 not 5

CHAPTER Three: discussion and summary conclusions

Summary of findings

Among 417 HF RCTs, 224 (53.7%) included a PRO. We found that the proportions of HF RCTs with PROs increased significantly in the past 20 years. PRO was independently associated with greater odds of inclusion in trials that were multicenter relative to single center trials, medium-sized (n=51-250) relative to small (n<50), trials coordinated in Central and South America relative to Asia and Australia, and that assessed health services, device / surgery, and exercise or rehabilitation relative to drug interventions. The quality of PRO reporting, as measured by the adherence to CONSORT-PRO, was modest; with RCTs with PROs as a primary or co-primary endpoint reported greater number of CONSORT-PRO items compared to RCTs with PROs as a secondary endpoint.

Opportunity for future research

In this systematic review, we summarized the contemporary trend of PRO inclusion in HF RCTs published in high-impact medical journals. We also highlighted the quality of PRO reporting using the Consolidated Standards of Reporting Trials PRO extension.[1] Our findings offer multiple areas for future PRO research in HF RCTs, including special considerations for quality of reporting, PRO implementation, and PRO data interpretation.

Given the modest quality of PRO reporting, we suggest that future research should aim to investigate quality of reporting during protocol formation stages. To do that, the SPIRIT-PRO extension[2] should be used to assess design considerations and PRO integration in HF RCTs. We also suggest investigating RCT characteristics associated with higher reporting standards.

Consistent, high-quality PRO reporting is also a reflection of the methodological rigour utilized during the study and may present findings with a lower risk of bias.

We also suggest that future research focuses on barriers of PRO integrations in HF RCTs and offers solutions to ease the use of PROs in clinical trials. The implementation of PRO is logistically complex and requires extensive training in data management and analysis. PROs are also associated with a higher degree of missing data.[3] With the increased use of digital health technologies HF investigators may consider using digital tablets or smartphones for PRO data collection and the association of this data collection method with PRO missing values. Many other digital devices are also user-friendly and may help in collecting PRO data during longitudinal follow-up periods.

Effective interpretation of PRO measures based on a meaningful change to patients-perceived health status is also a major challenge in HF RCTs. The minimal clinically important difference (MCID) – initially defined as the smallest change that patients perceive as beneficial and would influence patient clinical care – is the most common approach that facilitate PRO interpretation.[4,5] The estimation of MCID involves two general approaches: distribution- and anchor-based methods.[6,7] These utilize statistical distribution based on effect size or standardized response mean or compare the selected MCID against an external anchor as a measure of global rating change.[6,7] Over the past decade, MCIDs of major HF PROs have been developed.[8] It is not clear; however, if these thresholds are routinely included in HF RCTs with PROs in order to maximize the utility of PROs by clinicians, or health care decision makers.

We suggest that future research may focus on creating HF PRO inventory of all developed HF-specific instruments with corresponding MCIDs. Such a HF PRO inventory would allow future HF researchers to select appropriate instruments that best fit their study goals, and aid in the inclusion of PROs in their trials. We also recommend that MCID thresholds and development of new PRO tools should incorporate data related to women and vulnerable populations. This will allow for an accessible, tangible improvement in measuring health outcomes of these populations, considering they are underrepresented in HF research.

International cardiovascular research conferences and events should focus on introducing PRO workshops and discussion panels to advance PRO research. These workshops could focus on topics related to challenges and lessons associated with PRO inclusion in trials and promote networking and collaboration among junior researchers interested in PRO research. Organizers of major cardiovascular research events, such as the Global CardioVascular Clinical Trialists Forum,[9] have created expert panel discussions on PROs and patient engagement activities during the 2020 meeting. More of such events are encouraged by other research event organizers.

Finally, we encourage HF researchers to engage patients and the public during the design, execution and dissemination stages of the trial. To improve patient-centered care in HF, investigators should actively select outcomes most meaningful to patients and involve them as research partners. We believe that patients and the public engagement could improve the selection of PROs in HF RCTs and offer valuable insights on methodological designs beyond investigators expertise during RCT execution stages.

PROs offer meaningful information about patient-perceived health status including quality of life, disease burden and symptoms limitations, but are not routinely included as key outcomes in RCTs. We found that the proportion of HF RCTs with a PRO significantly increased since during the study period. The quality of PRO in HF RCTs were modest with greater reporting of CONOSRT-PRO items in trials with PROs as a primary or co-primary outcome. We suggest that PROs should be included and reported with methodological rigor that improves PRO data uptake given their importance to patients, clinicians, regulators, and all other stakeholders. PROs are frequently used during evidence-based clinical and policy decision making, and they can ultimately improve the quality of care for many HF patients.

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