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Quality of inclusion criteria in the registered clinical trials of heart failure with preserved ejection fraction: Is it time for a change?

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ABSTRACT

Background: No uniform diagnostic criteria have been developed for heart failure with preserved ejection fraction (HFpEF), resulting in huge discrepancies in the patient recruitments of HFpEF trials. This study aims to assess the quality of inclusion criteria in HFpEF trials.
Methods: We systematically searched the International Clinical Trials Registry Platform for HFpEF trials and extracted the basic characteristics and inclusion criteria. We then scored and compared the quality of inclusion criteria using an adapted 5-point scoring system of ejection fraction (EF), symptoms, signs, natriuretic peptides and other tests.
Results: A total of 121 trials and 19,494 patients were finally included for statistical analyses. More than half (67/121, 55.4%) of the trials employed 50% as the cut-off value for diagnosing HFpEF. Symptoms (102/121, 84.3%) are mostly provided by trial registrars, followed by natriuretic peptides (46/121, 38.0%) and signs (32/121, 26.4%). Average total scores of inclusion criteria wavily increased from 2.00 in 2002 to 3.00 in 2016 ($P = 0.04$). Interventional trials were not significantly different from observational trials (3.00 ± 1.18 *vs.* 2.75 ± 1.53, $P = 0.45$), but ongoing trials were higher in total score than completed trials (3.28 ± 1.24 *vs.* 2.72 ± 1.17, $P = 0.01$). Published trials were not significantly different from the unpublished trials at registration (2.76 ± 1.13 *vs.* 2.69 ± 1.20, $P = 0.82$), but their total scores significantly increased to 3.48 ± 0.96 at publication ($P < 0.01$).
Conclusions: The qualities of inclusion criteria are heterogeneous and significantly improved with time in registered HFpEF clinical trials. EF, symptoms and signs should be specified at trial registration to make a more reliable diagnosis and to recruit a more homogenous population.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF, also diastolic heart failure [DHF] or heart failure with normal ejection fraction [HFNEF]) is a complex clinical syndrome caused by the impairment of ventricular filling or blood ejection [1]. The prevalence of HFpEF is on the rise and higher than heart failure with reduced ejection fraction (HFrEF) in the population aged over 60 years [2,3]. Recent understandings of HFpEF have greatly benefited from the results of clinical trials, although little progress has been made for the therapy [4]. Clinical trials are mandatory to register on a publicly accessible platform, and patient recruitments based on specific inclusion criteria are commonly the first step of a trial [5]. The quality of inclusion criteria therefore greatly affects the quality of a clinical trial, yet it has not been systematically studied [6].

In this study, we aim to appraise the quality of inclusion criteria of ongoing and completed clinical trials with a 5-point scoring system developed from a widely-used heart failure guideline [7]. We also compare the quality of inclusion criteria between different types of trials.

2. Methods

2.1. Database search and reference download

On July 3, 2016, two researchers (F.Y.Y. and C.C.) independently searched the International Clinical Trials Registry Platform Search Portal (ICTRP Search Portal, http://apps.who.int/trialsearch/Default.aspx) in a standard search strategy for the trials containing the following terms: "heart failure with preserved ejection fraction OR HFpEF OR HF-PEF OR heart failure with normal ejection fraction OR HFNEF OR diastolic heart failure OR DHF" [8]. The standard search looks for words or phrases in trial title, primary sponsor, health condition and intervention, and thus is sensitive in finding as many records as possible. The following databases are updated on ICTRP every week: Australian New Zealand Clinical Trials Registry, Chinese Clinical Trial Registry, ClinicalTrials.gov, EU Clinical Trials Register, ISRCTN, The Netherlands

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National Trial Register. The search results were downloaded in .xml format and exchanged between two researchers for confirmation of the consistency.

The trials with a recruitment status of 'completed' were also checked for their reference lists. Only the most recently published original articles were downloaded for analyses. For those not giving any reference, a manual search was conducted on PubMed using their universal trial numbers and the searched articles were downloaded.

2.2. Trial selection and data extraction

Clinical trials were selected by their recruitment status, sample size and description. A trial was eligible for inclusion if it had a sample size, was ongoing or completed, and was related to HFpEF. To include as many trials as possible for statistical analyses and minimize selection bias, we did not limit the study type, phase, registration date, or target sample size.

Two reviewers (H.X.L. and C.Z.) independently extracted the following information from the .xml file with a standardized extraction form: recruitment status, primary sponsor, year of registration, study type, phase, target sample size, country of recruitment, inclusion criteria, intervention, and primary outcomes. Then the third reviewer (Y.X.) compared the two extraction forms and any difference would be resolved by a discussion with two primary extractors (H.X.L. and C.Z.). For published trials, the full texts were read and inclusion criteria were extracted.

2.3. Quality assessment

A 5-item scale was developed with reference to the "4.3.2 Diagnosis of heart failure with preserved ejection fraction" section in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (see Table 1) [7]. The 5-item scoring system includes ejection fraction (EF), symptoms, signs, natriuretic peptides and other tests. Each trial was evaluated according to its provision of the assessment items rather than according to its specific values. Two reviewers (H.X.L. and C.Z.) independently scored all trials, and then the third reviewer (F.Y.Y.) rechecked the two scoring tables for potential inconsistencies and discussed them with H.X.L and C.Z. for consensus.

2.4. Statistical analyses

All analyses were performed with the SPSS software 22.0 (IBM Corporation, Armonk, New York). Categorical data were expressed as number (percentage) and continuous data as mean ± standard deviation or median (25th quartile to 75th quartile). Categorical data were compared with independent-samples Mann–Whitney *U* test and continuous data with independent samples *t*-test. Spearman's rank correlation test was employed to reveal the relationship between time and total score. A P value <0.05 was defined as significant difference.

Table 1
Five scoring items for the inclusion criteria of HFpEF trials.

Items	Description	Score
Ejection fraction	40–55%	1
Symptoms	Dyspnea, fatigue, chest pain, anorexia, palpitations, syncope, disordered breathing at night, functional scores (New York Heart Association class)	1
Signs	Heart murmurs, displaced point of maximal impulse, right ventricular heave, hepatomegaly/ascites, peripheral edema	1
Natriuretic peptides	NT-proBNP, BNP	1
Other tests	Chest X-ray, Doppler echocardiography, electrocardiogram, cardiac magnetic resonance, coronary arteriography	1
Total score		5

NT-proBNP = N-terminal pro-brain natriuretic peptide, BNP = brain natriuretic peptide.

3. Results

3.1. Search results and selection of trials

Fig. 1A shows the procedures of trial search and selection. A total of 262 records of 204 trials were identified by a standard search. They were first screened by the recruitment status, so 29 trials not stating current status, 14 prematurely terminated, and 14 not starting enrolments were excluded. Prematurely terminated trials were excluded from our analyses because in general, they are unlikely to have an important impact on clinical decision making. Five trials not giving a sample size were excluded. Trials were checked for their description, thus 21 trials unrelated to HFpEF were excluded. As a result, 121 trials of 19,494 patients were finally included for statistical analyses (see Supplement 1). Of 67 completed trials, 24 trials listed references on the registration website, and 1 trial was added by manually searching the universal trial number on the PubMed database. Supplement 2 shows the quality of inclusion criteria of registered HFpEF studies at publication. Of note, a study might show different scores between Supplement 1 (at registration) and Supplement 2 (at publication).

Table 2 shows most interventional and observational HFpEF trials were registered on the ClinicalTrials.gov website. There were more trials primarily sponsored by nonindustry organizations, registered after the year 2010 and recruited in the non-United States countries. Sample sizes were similar between interventional trials and observational trials (52 [29–121] *vs.* 145 [46–359], $P = 0.07$). The top 3 interventions were drug (61.0%), behavior (18.1%) and procedure (10.5%). Composite primary outcomes were employed in 44 (41.9%) interventional trials.

3.2. Quality assessment

Table 3 shows that HFpEF is the most frequently used name in all trials (66/121, 54.5%) and ongoing trials (38/54, 70.4%), while DHF in completed trials (34/67, 50.7%). However, most published trials preferred HFpEF at publication (24/25, 96.0%). Overall, more than a half (67/121, 55.4%) of total trials employed 50% as the LVEF cut-off value for diagnosing HFpEF. Extreme LVEF cut-off values were rarely adopted, with 40% and 55% for 5 (4.1%) and 1 (0.8%) trials, respectively. Symptoms (102/121, 84.3%) were the most common information provided by trial registrars, followed by brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels (46/121, 38.0%) and signs (32/121, 26.4%). Interventional trials were not significantly different from observational trials in total scores (3.00 ± 1.18 *vs.* 2.75 ± 1.53, $P = 0.45$). Ongoing trials had significantly higher total scores than completed trials (3.28 ± 1.24 *vs.* 2.72 ± 1.17, $P = 0.01$). Since more ongoing trials were registered in the recent 5 years (42/54, 77.8% *vs.* 25/67, 37.3%), we further examined how the year of registration influenced the total score and found that the total scores significantly increased with time ($P = 0.04$).

Fig. 1B shows the wavy increase of the average total score of inclusion criteria from 2.00 in 2002 to 3.00 in 2016. Among completed trials, the published ones were not significantly different from the unpublished ones at registration (2.76 ± 1.13 *vs.* 2.69 ± 1.20, $P = 0.82$), but their scores increased significantly to 3.48 ± 0.96 at publication ($P = 0.003$).

4. Discussion

HFpEF is heterogeneous in terms of etiology and pathophysiology, rather than being a single disease [9]. Different subgroups of patients significantly vary in mortality and treatment response [10]. Molecular and cellular studies also demonstrate complex yet poorly understood pathophysiological mechanisms underlying HFpEF [11,12]. Symptoms and signs are always the first reasons for an HFpEF patient turning to a doctor. In fact, no symptoms or signs predict heart failure at 0%

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