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Mismatch between heart failure patients in clinical trials and the real world ☆

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ABSTRACT

Background: Evidence-based medicine urges physicians to translate results from clinical trials to their patients. This, however, can only work, if real world patients are represented in clinical trials.
Methods: We searched the literature on chronic heart failure (1950-2/2011) for studies designed to detect effects on mortality (mortality studies, MS) and exercise training studies (ETS) as the leading non-pharmaceutical/non-surgical treatment option in order to compare their characteristics with European (Euro Heart Survey on Heart Failure, EHSHF) and North American (Framingham Heart Study, FHS) epidemiological studies.
Results: After an extensive literature search, we identified 207 ETS and 59 MS. Subjects enrolled in ETS were younger (ETS: 62.5 ± 6.6; MS: 63.9 ± 4.6; EHSHF: 71.0 ± 3.5; FHS: 78.0 years), more often male (ETS: 80.9%; MS: 77.3%; EHSHF: 53.0%; FHS: 49.6%; $p<0.001$), and had substantially less comorbidities such as diabetes mellitus (ETS: 13.6%; MS: 22.5%; EHSHF: 27.0%; FHS: 25.3%; $p<0.001$), or hypertension (ETS: 26.3%; MS: 39.1%; EHSHF: 53.0%; FHS: 46.9%; $p<0.001$). Angiotensin converting enzyme-inhibitors, beta-blockers, and angiotensin-receptor-blockers were more commonly used in ETS than in EHSHF (all $p<0.001$). Only 16 (10.6%) ETS and 20 (62.5%) MS reported ethnic background.
Conclusion: Heart failure patients in exercise training studies and mortality studies do not represent real world patients. In order to extrapolate data to the general population future exercise training studies as well as mortality studies need to include representative patients. Otherwise, knowledge gained can only be translated to a minority of our patients.

1. Introduction

Evidence based medicine urges physicians to implement findings of clinical trials into everyday practice. As a consequence, patients in clinical trials need to be a representative sample of everyday patients. Van Spall et al. [1] analyzed eligibility criteria of randomized controlled trials published in high-impact general medical journals and found that women, children, elderly, and even those with common medical conditions are frequently excluded from clinical trials. It has been reported that multi-center trials and those involving drug interventions are most likely to have extensive and medically unjustified exclusion criteria, which may impair the generalizability of the results. Also, Masoudi et al. [2] applied the inclusion and exclusion criteria of three major chronic heart failure (CHF) trials to 20,388 representative patients in the US. Only 18%, 13%, and 25% met the enrollment criteria of the SOLVD, MERIT-HF, and RALES trials, respectively. A similar result was reported by Lenzen et al. [3] who applied the inclusion and exclusion criteria of the same three trials to the population of the Euro Heart Survey on Heart Failure (EHSHF). Of 10,701 patients, only 13% would have been eligible to participate in at least one of the three studies. Besides studies that aim to detect differences on so called "hard end points" such as mortality (mortality studies, MS), other investigations try to elucidate effects on surrogate parameters such as left ventricular ejection fraction, weight, and blood pressure. According to the recent guidelines of the ESC [4] and AHA/ACC [5,6], exercise training is the leading non-pharmacological/non surgical interventions in CHF.

It was the aim of our study to compare patient characteristics of ETS and MS with epidemiological data of the EHSHF and Framingham Heart Study (FHS). We postulated that characteristics of real world

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patients differed substantially from those enrolled in clinical trials questioning the generalizability of the study findings.

2. Methods

2.1. Literature search

We searched MEDLINE, EMBASE, the Cochrane Collaboration Central Register of Controlled Clinical Trials (CENTRAL), and CINAHL (1950-2/2011) in order to locate publications on clinical heart failure trials implementing exercise training. Only adult human subjects (aged >19 years) suffering from chronic heart failure (CHF) were included. No language restrictions were applied; and clinical heart failure trials aiming at a reduction in mortality through various treatment options other than exercise training (see Table 1).

For ETS we applied the search strategy used by Davies et al. [7] in their systematic Cochrane review on the same topic. Briefly, synonyms for heart failure and exercise training were combined using the operator OR; the results were then combined using the operator AND. Searches were limited to prospective clinical trials investigating the effects of any form of exercise training with the exception of electrical muscle stimulation and investigations on heart transplant recipients. We further systematically studied review articles and meta-analyses published between 2003 and 2011 and searched the references of all included exercise training studies in order to identify further publications relevant to our study.

For MS we used medical subject headings (MeSH) for heart failure and mortality. Searches were limited to prospective randomized controlled CHF trials with mortality as their primary or secondary endpoint.

Titles and abstracts of 5095 (for ETS) and 2057 (for MS) potentially relevant references were identified through our literature search and reviewed independently by 2 investigators (D.N., C.T.) to determine whether they met eligibility criteria for inclusion provided in Table 1. Discrepancies regarding whether or not to include a reference were resolved by consensus with another investigator (J.N.). A flow chart of the literature search is provided in Fig. 1.

2.2. Data extraction

All data were extracted by one investigator (D.N.) and then checked and rechecked by another investigator (C.T.). The extracted data comprised name of first author, year of publication, journal, trial design, number of participants both in total and per group, age, gender distribution, ethnicity, socioeconomic variables, body mass index (BMI), New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), primary cause of heart failure, diabetes mellitus, and hypertension. For ETS we further extracted dropouts both in total and per group, maximal oxygen consumption, and medication (beta-blockers, Angiotensin converting enzyme [ACE]-inhibitors, angiotensin receptor blocker). We did not extract medication in MS because most of the included studies investigated one of these pharmacological agents or had inclusion or exclusion criteria based on the medication of the subjects. The definition of heart failure differed among studies; however all included studies provided compelling reports on how they made sure to only include patients suffering from CHF. If a separate publication on the methods of a study had been published previously, we looked for further details in these manuscripts. No restrictions were made to whether systolic or diastolic heart failure was investigated nor did we limit the result to certain etiologies of heart failure.

Only the mean values were extracted. Mostly means were provided separately for the control group and the intervention group. If the desired variable was not provided, we contacted corresponding authors of the studies, and if unsuccessful we left the space in our database blank.

Epidemiological data were obtained from publications of the EHSHF [8–10] and the FHS [11,12] since they are universally accepted as the most comprehensive epidemiologic assessments of CHF in the respective continents. We extracted the same characteristics as in ETS and MS.

In some ETS, baseline characteristics were only provided for those patients who completed the study; accordingly a per-protocol-analysis was employed in these studies. Thus, baseline variables of dropouts were not reported in these papers. The author(s) of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

Table 1
Inclusion criteria of exercise training studies and mortality studies of our literature search.

Inclusion criteria for exercise training studies:
1) Prospective study design
2) Human adult subjects suffering from any form of chronic heart failure
3) Any form of exercise training as intervention
Inclusion criteria for mortality studies:
1) Prospective randomized study
2) Human adult subjects suffering from any form of chronic heart failure
3) Any report on mortality as a primary or secondary end-point

2.3. Statistical analysis

Extracted mean values of each variable were used to calculate weighted means for ETS and MS, in order to avoid misrepresentation of smaller and larger studies. All data are presented in mean ± standard deviation (SD) or percentages. We could only extract means of each included study (e.g. age) and were therefore unable to test our data on normal distribution. Because it is impossible to test properties of "studies" vs. "patients" as in EHSHF and FHS we did not test any statistical differences in continuous variables such as age, body mass index (BMI), NYHA functional class, and LVEF. In categorical variables (gender, diabetes mellitus, hypertension, and pharmacological treatment) we employed two-sided χ^2-tests with Yate's continuity correction or Fisher's exact test to evaluate statistically significant differences between baseline characteristics of ETS, MS and ES. Statistical significance was defined as $p<0.05$. Data were analyzed using Graph Pad InStat 3 for Windows (InStat Software, California, USA) and PASW Statistics 18, Release Version 18.0.0 (SPSS, Inc. 2009, Chicago, IL, USA).

3. Results

Our abovementioned search strategy revealed 207 ETS and 59 MS studies (see Fig. 2).

3.1. Exercise training studies in heart failure

Of the 207 studies analyzed, three (1.5%) studies were conducted before 1990, 53 (25.6%) between 1990 and 1999 and 152 (73.4%) between 2000 and 2011 (see Fig. 1). Publications were written in English (n = 197/95.2%), Chinese (n = 3/1.5%), Polish (n = 3/1.5%), German (n = 2/1.0%), French (n = 1/0.5%), or Lithuanian (n = 1/0.5%). Studies were designed as randomized controlled studies (n = 123/59.4%), controlled studies (n = 27/13.0%), non-controlled studies (n = 42/20.3%) and cross-over trials (n = 15/7.2%). 134 (64.7%) publications reported 829 drop-outs. Diabetics were excluded in 17 publications, two studies excluded uncontrolled and one decompensated diabetes. Patients suffering from hypertension were excluded in eight investigations, uncontrolled hypertension in 13 studies (see Table 2).

3.2. Mortality studies

Of the 59 studies analyzed, two (3.4%) studies were conducted before 1990, 25 (42.4%) between 1990 and 1999 and 32 (54.2%) between 2000 and 2011 (see Fig. 1). All publications were written in English and designed as randomized controlled trials. Patient characteristics of subjects included in MS in heart failure are shown in Table 2.

3.3. Patient characteristics

Comparison of patient characteristics of ETS, MS, and ES is shown in Table 2 and Fig. 3. Subjects enrolled in ETS were younger (ETS: 62.5 [SD 6.6]; MS: 63.9 [SD 4.6]; EHSHF: 71.0 [SD 3.5]; FHS: 78.0 years), more often male (ETS: 80.9%; MS: 77.3%; EHSHF: 53.0%; FHS: 49.6%; $p<0.001$), had substantially less comorbidities such as diabetes mellitus (ETS: 13.6%; MS: 22.5%; EHSHF: 27.0%; FHS: 25.3%; $p<0.001$), or hypertension (ETS: 26.3%; MS: 39.1%; EHSHF: 53.0%; FHS: 46.9%; $p<0.001$), and were better treated with pharmacological agents known to reduce mortality such as Angiotensin converting enzyme-inhibitors/Angiotensin receptor blockers ($p<0.001$), and beta-blockers ($p<0.001$) as compared to MS and ES, respectively. Furthermore, ETS predominantly enrolled patients with a higher NYHA functional class, but a lower LVEF. Also BMI was higher in these subjects.

In MS, patients differed significantly from epidemiological studies in terms of gender distribution, and comorbidities such as diabetes and hypertension (all $p<0.001$). Also, age, etiology of heart failure, LVEF, NYHA functional class, and BMI differed considerably.

Ethnicity was reported only in a minority of ETS, but in about half of MS, whereas socioeconomical variables were only available in 9 (4.3%) ETS, but not in MS.