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# Participation in a clinical trial is associated with lower mortality but not lower risk of HF hospitalization in patients with heart failure: observations from the ESC EORP Heart Failure Long-Term Registry

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Randomized controlled trials (RCTs) form the basis for guidelines, regulatory approval, and reimbursement.<sup>1</sup> They are commonly industry-funded and apply selective eligibility criteria,<sup>2</sup> potentially limiting generalizability. A few older cardiovascular studies suggested that factors like renal insufficiency, hyperlipidaemia, male sex, and active smoking were associated with RCT participation.<sup>3</sup> Associations between RCT participation and outcomes are available only for patients with coronary artery disease and are inconclusive.<sup>3,4</sup> In heart failure

(HF), a single centre study suggested that willingness to participate in an RCT at index outpatient visit was associated with lower ejection fraction (EF), more comorbidities, lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) and better survival.<sup>5</sup>

The ESC-EORP Heart Failure Long-Term (ESC-HF-LT) registry was a prospective registry of patients with HF conducted across 337 cardiology centres in 33 countries.<sup>6</sup> Local ethical review boards gave approval for participation in accordance with the regulatory requirements of

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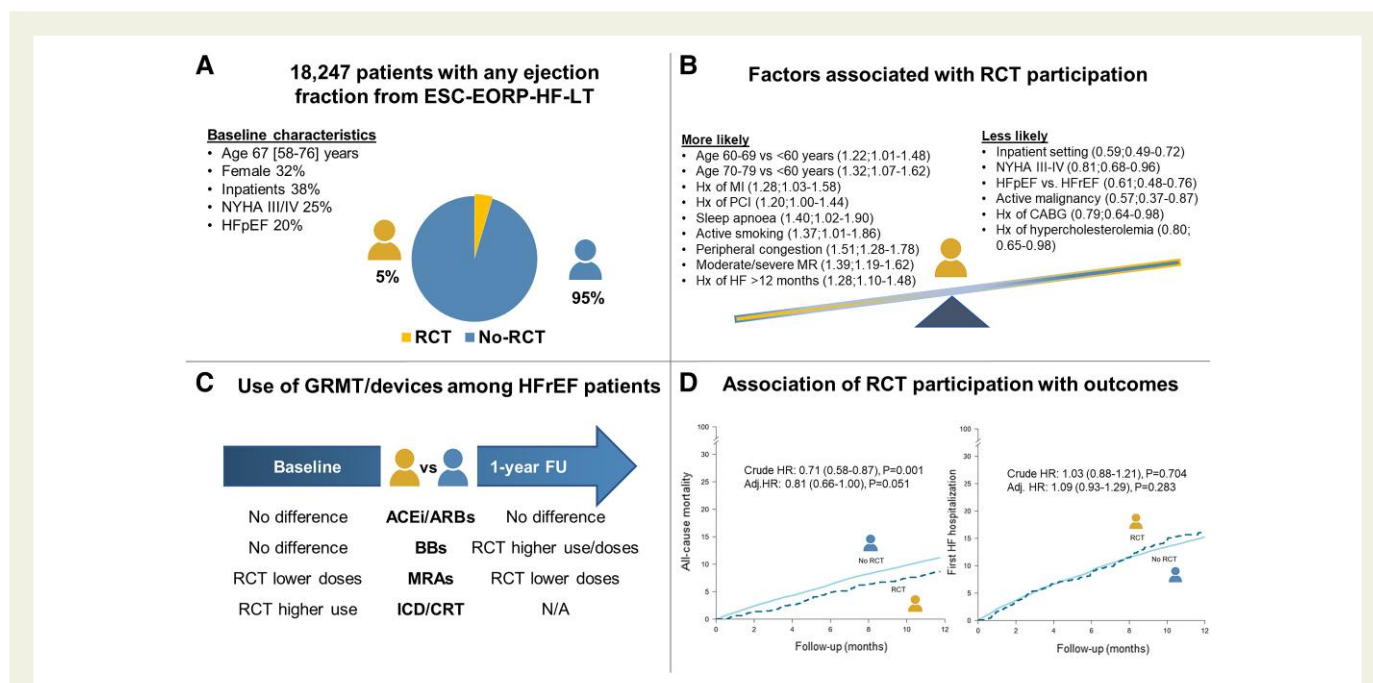
each country. All patients enrolled in the survey signed an informed consent, unless exempt by the local ethics committee. In the ESC-HF-LT registry, we assessed rates of participation in an RCT (for any intervention/arm), association between patient characteristics and participation in RCTs, use and doses of guideline-recommended medical treatment (GRMT) according to RCT participation, and associations between RCT participation and outcomes.

Patients enrolled between 22 March 2011 and 29 September 2018 were included. Randomized controlled trial participation was a tick-box in the baseline case report form. Patients were excluded if they had missing data on RCT participation, died during index hospitalization, or were lost to follow-up. One centre exhibited extreme patterns regarding HF hospitalization (HFH) outcomes and was excluded. Data on first HFH and all-cause mortality were obtained over 12-month follow-up. Guideline-recommended medical treatment included renin-angiotensin system inhibitors, beta-blockers, and mineralocorticoid receptor antagonists.

To identify independent predictors of RCT participation, a generalized linear mixed-effects model with a binomial distribution was performed using RCT participation as the dependent variable. The country was included as a random effect in the model. The independent variables included were inpatient setting, age per strata (<60, 60–69, 70–79, ≥80 years), female sex, home situation, body mass index ≥25 kg/m<sup>2</sup>, blood pressure ≥100 mmHg, heart rate ≥70 b.p.m., peripheral and pulmonary congestion, hypoperfusion, HF history >12 months, ischaemic aetiology, prior myocardial infarction (MI),

percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, previous valve surgery, stroke/transient ischaemic attack, venous thromboembolism, current smoking, hypertension, peripheral vascular disease, diabetes, sleep apnoea, obstructive pulmonary disease, hypercholesterolaemia, hepatic dysfunction, depression, current malignancy, atrial fibrillation/flutter, New York Heart Association Classes III and IV, EF per strata (≤40%, 41%–49%, ≥50%), moderate–severe mitral regurgitation, estimated glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup> and NT-proBNP >1,000 pg/mL. Rates of all-cause mortality and first HFH are presented as cases/100 patient-years and visualized with cumulative incidence curves. To identify the association between participation in an RCT and outcomes, univariable and multivariable Cox regression analyses were performed with the same independent variables as above and country as a strata variable. Patients were censored at 12-month follow-up visit if they had not yet experienced an event or on the date of death in the analyses assessing first HFH as outcome. Missing data were imputed with multiple imputation (R-package mice; 10 imputed datasets),<sup>7</sup> including the same variables as the regression models. For patients with missing information on the date of hospitalization, time to hospitalization was imputed with half the time to last follow-up. A two-sided *P*-value of <0.05 was considered statistically significant. Analyses were performed using R version 4.2.1.<sup>8</sup>

Of 25,621 patients in the registry, 7,374 met exclusion criteria and 18,247 patients were analysed. Among these, 938 (5%) participated in an RCT at index visit (Figure 1A).



**Figure 1** (A) Baseline characteristics and rates of participation in randomized controlled trials among 18,247 patients with any ejection fraction from the ESC-EORP-HF-LT registry. (B) Independent predictors of participation in a randomized controlled trial. Odds ratios and 95% confidence intervals derived from multivariable logistic regression analyses using randomized controlled trial participation as the dependent variable are shown. (C) Use of guideline-recommended medical therapy and devices among patients with heart failure and reduced ejection fraction. (D) Cumulative incidence curves for all-cause mortality (left) and for first heart failure hospitalization (right) according to randomized controlled trial participation. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CABG, coronary artery bypass graft surgery; CRT, cardiac resynchronization therapy; HFpEF, heart failure with preserved ejection fraction; Hx, history; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; MR, mitral valve regurgitation; MRA, mineralocorticoid receptor antagonist; N/A, not applicable; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Patient characteristics independently associated with a higher likelihood of RCT participation were outpatient setting, age, less severe HF symptoms and lower EF, absence of active malignancy, history of MI or PCI but no history of CABG or hypercholesterolaemia, history of sleep apnoea, active smoking, peripheral congestion, moderate–severe mitral regurgitation and HF history >12 months (Figure 1B).

Patterns of GRMT and device use among patients with EF  $\leq$ 40% stratified by RCT participation are depicted in Figure 1C. Median (interquartile range) follow-up was 12.2 (11.6–13.7) months. Mortality rates were 9.7 (7.9–11.9) vs. 12.9 (12.3–13.4) deaths/100 patient-years for those enrolled vs. not in RCTs, respectively [crude hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.58–0.87,  $P = 0.001$ ; adjusted HR 0.81; 95% CI 0.66–1.00,  $P = 0.051$ ], while the respective rates for first HFH were 18.4 (15.7–21.4) vs. 16.4 (15.8–17.0) events/100 patient-years (crude HR 1.03; 95% CI 0.88–1.21,  $P = 0.704$ ; adjusted HR 1.09; 95% CI 0.93–1.29,  $P = 0.283$ ; Figure 1D).

The participation rate captured in our study (5%) may have been too low for optimal power, but may also have been greater than in unselected HF populations, given that the ESC-HF-LT registry was conducted at cardiology centres with potentially greater research interest.<sup>6</sup> Several studies have evaluated differences in baseline characteristics between HF registry patients eligible and ineligible for enrolment in specific HF RCTs.<sup>9</sup> Our study is the first to report associations between clinical characteristics and RCT participation, rather than RCT eligibility, after extensive adjustment for confounders.

Data demonstrating a higher proportion of GRMT use among patients enrolled vs. not in RCTs, even when the latter are eligible for RCT participation, are present in the literature.<sup>10</sup> However, these comparisons were performed between different populations rather than within a single cohort such as ours. A key novel finding was that enrolment in an RCT was associated with a strong trend towards a 19% lower all-cause mortality, after adjustment for all measured confounders, including those commonly used for trial selection. The unique design of our study (direct comparisons between RCT vs. non-RCT participants within the same registry) and the lower risk for all-cause mortality after extensive adjustment potentially reflects, at least in part, actual benefits of participating in an RCT, regardless of background therapy and treatment assignment in that RCT. The statistically neutral and numerically higher incidence rates of HFH among patients participating in RCTs, despite lower mortality, may represent, in part, the selection of patients with higher risk for presumably modifiable cardiovascular and HF events, but may also reflect more follow-up contacts during the conduct of the RCT and increased vigilance, which may prompt hospitalization in patients who would not otherwise seek care (until after further deterioration).

The ESC-HF-LT registry is more selective than many real-world cohorts and registries,<sup>6</sup> and GRMT was used more than in less selective registries.<sup>11</sup> This might have minimized the differences in characteristics and outcomes between trial participants and non-participants, potentially blunting the beneficial 'effect' that RCT participation may exert in unselected HF patients.

In summary, 5% of patients in the ESC-HF-LT registry who participated in an RCT had characteristics associated with higher risk of HF events but lower risk of competing events, had greater use of background GRMT, and indeed had lower risk of all-cause mortality but not HFH.

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## Data availability statement

The R code, the project-specific data handling and statistical analyses can be found online at: <https://github.com/KIHeartFailure/esctrilparticipation>.

## Conflict of interest statement

A.J.S.C.: none related to the present work. Outside the present work: consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Edwards, Menarini, Novartis, Nutricia, Servier, Vifor, Abbott, Actimed, Arena, Cardiac Dimensions, Corvia, CVRx, Enopace, ESN Cleer, Faraday, Gore, Impulse Dynamics, Respicardia. A.P.M.: none related to the present work. Outside the present work: personal fees from Novartis, Bayer, AstraZeneca for participation in study committees. L.H.L.: none related to the present work. Outside the present work: grants: AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis, MSD; Consulting: Vifor, AstraZeneca, Bayer, Pharmacosmos, MSD, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier, Edwards Life Sciences, Alleviant; Speaker's honoraria: Abbott, OrionPharma, MedScape, Radcliffe, AstraZeneca, Novartis, Boehringer Ingelheim, Bayer; Patent: AnaCardio. M.F.P.: none related to the present work. Outside the present work: Consultancy, speaker's, institutional fees from AstraZeneca, Boehringer Ingelheim, CHF solution, Menarini, Novartis, Servier. M.G.C.-L.: none related to the present work. Outside the present work: Speakers honorary and/or consultancy fees from AstraZeneca, Boehringer Ingelheim, Novartis, Rovi, Vifor, Bayer, CareDx, Pfizer, Abbott and Medtronic. M.L.: none related to the present work. Outside the present work: speakers honoraria: AstraZeneca, Vifor, Boehringer Ingelheim, Novartis, Bayer, Sanofi; Consulting: Vifor, Boehringer Ingelheim. P.M.S.: honoraria for lectures from Servier, AstraZeneca, Respicardia, Menarini. Consultancy agreement and honoraria from Boehringer Ingelheim, Novartis, Vifor Pharma and Roche diagnostic. S.D.A.: grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards, Farraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious, and V-Wave. T.M.: none related to current work. Outside of current work, speaker honoraria; Boehringer Ingelheim, AstraZeneca, Edwards and Abbott. All other authors declare no conflict of interest for this contribution.

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