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**ORIGINAL ARTICLE**

# Global representation of heart failure clinical trial leaders, collaborators, and enrolled participants: a bibliometric review 2000–20

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**Aims** The geographic representation of investigators and participants in heart failure (HF) randomized controlled trials (RCTs) may not reflect the global distribution of disease. We assessed the geographic diversity of RCT leaders and explored associations with geographic representation of enrolled participants among impactful HF RCTs.

**Methods and results** We searched MEDLINE, EMBASE, and CINAHL for HF RCTs published in journals with impact factor ≥ 10 between January 2000 and June 2020. We used the Jonckheere–Terpstra test to assess temporal trends and multivariable logistic regression models to explore associations between predictors and outcomes. There were 414 eligible RCTs. Only 80 of 828 trial leaders [9.7%; 95% confidence interval (CI): 7.8–11.8%] and 453 of 4656 collaborators (9.7%; 95% CI: 8.8–10.6%) were from outside Europe and North America, with no change in temporal trends and with greater disparities in large RCTs. The adjusted odds of trial leadership outside Europe and North America were lower with industry funding [adjusted odds ratio (aOR): 0.33; 95% CI: 0.15–0.75; $P = 0.008$]. Among 157 416 participants for whom geography was reported, only 14.5% (95% CI: 14.3–14.7%) were enrolled outside Europe and North America, but odds of enrolment were 10-fold greater with trial leadership outside Europe and North America (aOR: 10.0; 95% CI: 5.6–19.0; $P < 0.001$).

**Conclusion** Regions disproportionately burdened with HF are under-represented in HF trial leadership, collaboration, and enrolment. RCT leadership outside Europe and North America is independently associated with participant enrolment in under-represented regions. Increasing research capacity outside Europe and North America could enhance trial diversity and generalizability.



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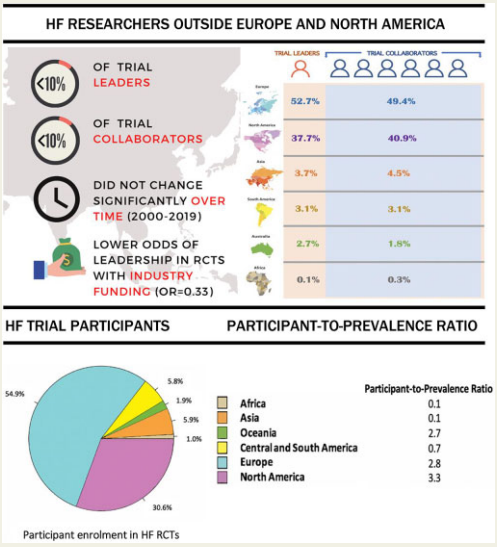
**Graphical Abstract** Temporal trends and factors associated with geographic representation among leaders and collaborators of heart failure (top) and participant-to-prevalence ratio from each region (bottom) for randomized controlled trials published in high-impact journals between 2000 and 2020.




**Keywords** Randomized controlled trials • Authorship • Collaboration • Diversity • Geography

# Introduction

Heart failure (HF) is a global epidemic with a disproportionate burden in low- and middle-income countries (LMICs).[1,2] Clinical trials have the potential to impact practice, but when trial populations do not include regions of the world in which a majority of patients are suffering from the disease, generalizability is limited.[3] While geographic representation of patients is important to ensure external validity of trial results, geographic representation of researchers can ensure that HF is tackled with insight into the local epidemiology and the context that influence outcomes.

Primary research on diversity among cardiovascular clinical trial leaders has focused almost exclusively on gender,[4–6] with little discussion about geographic diversity. Clinical trials led by women are associated with enrolment of more diverse participants.[4,5,7] Indeed, leadership diversity—in its many forms—may broaden the focus of research questions, employ novel trial designs matched to the needs of patients and local healthcare systems, and address unique concerns of participants who may be historically under-represented in clinical trials.[8–10] On a global level, geographic diversity of clinical trial leaders may enhance geographic diversity among trial participants, build research capacity in under-represented regions, and increase academic output and research impact in research-poor settings. For example, international collaborations are associated with a greater number of publications and a higher citation count than single-country authorship teams.[11–13]

In this bibliometric review, we evaluated temporal trends in the geographic representation of leaders and collaborators of HF trials published in high-impact medical journals, defining trial leaders as first and last authors, and collaborators as authors in any other position. We focused on high-impact journals to capture trials with the potential to inform practice on a global scale. We explored trial characteristics independently associated with trial leadership in countries outside Europe and North America and assessed whether geographic representation of trial leaders was independently associated with geographic representation of participants enrolled in the trial.

# Methods

## Search strategy and data sources

We conducted a systematic search of EMBASE, MEDLINE, and CINAHL with the assistance of a professional information specialist. Our search strategy comprised variations of the key terms *heart failure* and *randomized controlled trial* (see Supplementary material online, *Appendix*). Our search was limited to human studies published in English up until June 2020. We manually searched citations of included studies and relevant review articles for additional studies not included in our original search. The study protocol was registered in the International Prospective Register of Systematic Reviews.

## Study selection

The authors independently screened all titles and abstracts against predetermined eligibility criteria in duplicate (J.W.Z., N.L., and S.W.). Discrepancies between reviewers were resolved via consensus. Studies were included if they satisfied the following criteria: (i) published in English between 1 January 2000 and 17 June 2020, (ii) included adults aged 18 years or older with HF, and (iii) published in a medical journal with an impact factor of $\geq 10$ in 2020. The impact factor of 10 was chosen empirically to include publications with highest likelihood of impacting clinical practice.[14] The year 2000 was arbitrarily chosen to include a representative sample of contemporary clinical trials. Full-text manuscripts reporting primary outcomes were included, while protocols and publications following the initial manuscript that reported primary outcomes were excluded. As such, we excluded post-hoc, intermediate, or secondary analyses.

## Data extraction

We independently extracted the following data in duplicate (J.W.Z., N.L., and S.W.) from individual studies using a standardized form: trial characteristics (publication year, journal of publication, journal impact factor, funding, level of randomization, type of intervention, national or international trial, and number of centres); bibliometric characteristics (journal of publication, total number of authors, gender and geography of authors in lead/first, middle, senior/last, and corresponding positions, and location of the trial coordinating centre); and participant characteristics, including geographic region of enrolment.

We included individual authors listed in the paper and documented shared authorship roles in the first or last positions, where applicable. We defined trial leaders as first or last authors and collaborators as authors in any position. We did not include individuals in trial investigator committees or consortia groups. We regarded trials as having international collaborations when two or more authors had primary institutional affiliations in different countries. Geographic information for authors was established using the address of the primary institutional affiliation of each author in the paper. We used World Bank data to classify countries by income.[15]

## Outcomes

The primary outcome was trial leadership outside Europe and North America. The secondary outcome was the enrolment of trial patients outside Europe and North America.

## Analytic plan

We performed a descriptive analysis on the characteristics of trials and the geography and gender of authors, with continuous variables presented as median and interquartile range (IQR) and categorical variables as numbers and percentages. We conducted a sensitivity analysis, repeating this descriptive analysis in trials that included $\geq 500$ participants. Temporal trends in geographic representation of lead, senior, and any author between 2000 and 2020 were analysed using the Jonckheere–Terpstra proportion trend test. We used multivariable logistic regression to determine randomized controlled trial (RCT) characteristics independently associated with trial leadership outside Europe and North America. Trial characteristics under consideration as predictor variables included scope of the trial (national vs. international), type of funding (industry vs. public), type of intervention (drug, surgical, or device vs. other), and trial size ($<500$ participants vs. $\geq 500$ participants).

We assessed country of enrolment among those participants for whom geography data were reported. We estimated trial participant-to-prevalence ratio (PPR) in regions across the world using the Global Health Data Exchange registry.[16] PPRs were calculated from the regional contribution of participants to the total RCTs divided by the regional contribution of patients with HF relative to the global population with HF. In secondary analysis, we used multivariable logistic regression to determine the independent association between trial leadership outside Europe and North America and enrolment of patients outside Europe and North America. Results were reported as odds ratio (OR) with corresponding 95% confidence interval (CI) and associated *P*-values. All *P*-values were two-tailed, and the level of significance was set at $\alpha = 0.05$. Data were analysed using SPSS version 27.0 (IBM Corporation, Armonk, NY).

# Results

Our systematic search yielded a total of 10 596 articles, of which 8278 were excluded following title and abstract screening. Among the remaining 2318 full-text articles that were assessed, 414 satisfied eligibility criteria and were included (*Figure 1*).

## Baseline characteristics of patients and randomized controlled trials

A total of 234 287 participants with a mean age of 66.3 years were enrolled across all studies (median 120 participants; IQR: 40–389). Most trial participants were male (71.7%) and had an ischaemic aetiology of HF (53.4%).

A majority of the 414 RCTs had trial coordinating centres located in Europe or North America (53.1% and 37.4%, respectively, for a total of 90.5%), tested a drug intervention (65.5%), were conducted in a single country (74.9%), and involved multiple centres (58.7%) (*Table 1*). Informed consent was obtained in all trials.

## Geographic representation of trial leaders and collaborators

Only 80 of 828 trial leaders (9.7%; 95% CI: 7.8–11.8%) were from regions outside Europe and North America. The United Kingdom (10.2%) and United States (34.4%) were the most frequently represented countries among trial leaders. The trials included a total of 4656 collaborators (median 10 authors; IQR: 7–14 authors per trial), most (90.1%) of whom had primary institutional affiliations in Europe (49.2%) and North America (40.9%). Among the 4656 trial collaborators, 453 (9.7%; 95% CI: 8.8–10.6%) were from countries outside Europe and North America. Africa was the least represented continent among trial leaders (0.1%) and all collaborators (0.3%) (*Figure 2*A). LMICs were particularly under-represented among trial leaders and collaborators. A breakdown of trial leaders and collaborators by country is provided in *Table 2*.

The median number of collaborators per trial increased from 8 (IQR: 5–11) in 2001–03 to 15 (IQR: 12–19) in 2016–20. While there was a numeric decrease in the proportion of European collaborators and an increase in North American, Central/South American, and African collaborators since 2012 (*Figure 2*A), there was no significant change in the proportion of trial leaders (first author, $P = 0.75$; last author, $P = 0.64$) or trial collaborators from countries outside Europe and North America between 2000 and 2020 ($P = 0.17$) (*Figure 2*B).

## Sensitivity analysis

Among international trials conducted in two or more countries, there were no significant temporal changes in trial leadership outside Europe and North America ($P = 0.65$). Among the 79 RCTs that included $>500$ participants, 77 (97.5%; 95% CI: 91.2–99.7%) were led by authors from Europe or North America and 2 were led by authors from Asia ($n = 1$; 1.3%; 95% CI: 0.3–7.0%) and Oceania ($n = 1$; 1.3%; 95% CI: 0.3–7.0%), respectively. Among the 79 RCTs, 57 (72.2%; 95% CI: 60.9–81.7%) were international and 22 (27.8%; 95% CI: 18.4–39.1%) were national.

## International collaboration between trial leaders

Of 167 trials with international collaboration between trial leaders, 125 represented European or North American countries (74.9%; 95% CI: 67.6–81.2%) (*Table 2*). The most frequent type of

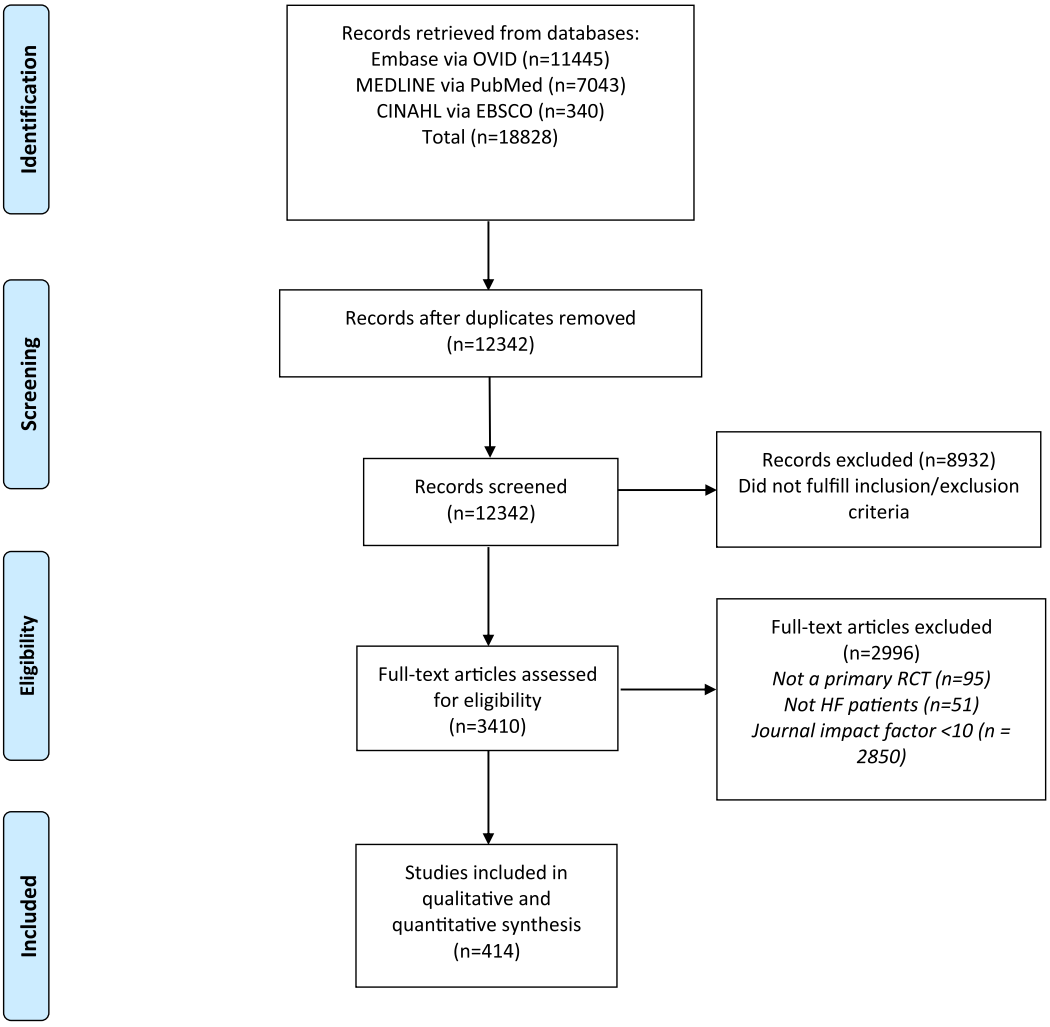



**Figure 1** PRISMA flow diagram. Systematic search strategy conducted in MEDLINE, EMBASE, and CINAHL to identify all randomized controlled trials published in medical journals with an impact factor ≥ 10 and recruited adults with heart failure.

international collaboration was between countries in Europe ($n = 79$; 47.3%; 95% CI: 39.5–55.2%); then between countries in North America ($n = 42$; 25.1%; 95% CI: 18.8–32.4%); and finally, between countries in Europe and North America ($n = 31$; 18.6%; 95% CI: 13.0–25.3%). Only 15 of 167 trials (9.0%; 95% CI: 5.1–14.4%) with international collaborations between trial leaders involved a country outside Europe and North America.

## Multivariable analysis of randomized controlled trial characteristics associated with trial leadership outside Europe and North America

The odds of trial leadership outside Europe and North America were significantly lower in trials with industry funding compared with public funding (OR: 0.33; 95% CI: 0.15–0.75; $P = 0.008$) (*Table 3*). Scope of trial (national vs. international), intervention type (drug or device/surgery vs. other), and size of trial (≥500 participants vs. <500 participants) had no signification association with trial leadership outside Europe and North America (*Table 3*).

## Geographic representation of trial participants

Of the 414 RCTs, a total of 97 (23.4%) recruited participants outside Europe and North America, and only 2.9% recruited participants from Africa (*Table 1*). Participant-level data on region of enrolment were available for 157 416 (67.2%; 95% CI: 67.0–67.4%) trial participants. Among these participants, 54.9% (95% CI: 54.7–55.2%) were enrolled in Europe, 30.6% (95% CI: 30.4–30.8%) in North America, 5.8% (95% CI: 5.7–5.9%) in Asia, 5.8% (95% CI: 5.7–5.9%) in Central and South America, 1.94% (95% CI: 1.9–2.0%) in Oceania, and 0.95% (95% CI: 0.9–1.0%) in Africa (*Figure 3*). The trial PPR was highest in North America (3.3) and Europe (2.8) and lowest in Asia (0.1) and Africa (0.1) (*Figure 3*).

**Table 1 Baseline characteristics of heart failure randomized controlled trials published in high-impact journals between 2000 and 2020**

| Clinical trial characteristics | No. of trials (%) (*N* = 414) |
|---|---|
| Trials on heart failure with reduced ejection fraction | 347 (83.8) |
| Scope of trial | |
| National | 302 (74.9) |
| International | 101 (25.1) |
| Continent of coordinating centre | |
| Africa | 0 (0.0) |
| Asia | 17 (4.1) |
| Oceania | 9 (2.2) |
| Central and South America | 12 (2.9) |
| Europe | 219 (52.9) |
| North America | 156 (37.7) |
| Continent of patient recruitment | |
| Africa | 12 (2.9) |
| Asia | 35 (8.5) |
| Oceania | 24 (5.8) |
| Central and South America | 26 (6.3) |
| Europe | 229 (55.3) |
| North America | 151 (36.5) |
| Recruitment location | |
| Inpatient | 98 (23.7) |
| Ambulatory | 316 (76.3) |
| Type of intervention | |
| Health service | 57 (13.8) |
| Drug | 271 (65.5) |
| Device | 47 (11.4) |
| Surgery | 10 (2.4) |
| Exercise/rehabilitation | 30 (7.2) |
| Number of centres | |
| Single centre | 171 (41.3) |
| Multicentre | 243 (58.7) |
| Type of funding | |
| Any public funding | 196 (47.3) |
| Industry funding | 218 (52.7) |
| Number of participants | |
| <100 | 192 (46.4) |
| 100–500 | 143 (34.5) |
| >500 | 79 (19.1) |
| Year of publication | |
| 2000–03 | 122 (29.5) |
| 2004–07 | 106 (25.6) |
| 2008–11 | 48 (11.6) |
| 2012–15 | 52 (12.6) |
| 2016–20 | 85 (20.5) |

Trial leadership outside Europe and North America was independently associated with recruitment of patients outside Europe and North America (OR: 10.0; 95% CI: 5.6–19.0; $P < 0.001$).

## Trial leadership and journal of publication

The studies included in this analysis were published in 14 medical journals (Supplementary material online, *Table S1*). Most of the 414 trials were published in the *European Journal of Heart Failure* (*n* = 109; 26.3%), followed by *Journal of the American College of Cardiology* (*n* = 87; 21.0) and *Circulation* (*n* = 63; 15.2%). Among trials with first or last study authors outside Europe and North America, most were published in the *European Journal of Heart Failure* (*n* = 8; 53.3%; 95% CI: 26.6–78.7%) and *Journal of the American College of Cardiology* (*n* = 5; 33.3%; 95% CI: 11.8–61.6%).

# Discussion

This bibliometric review of 414 HF RCTs published between 2000 and 2020 in high-impact medical journals is the first to rigorously examine the geographic representation of HF clinical trial leaders, collaborators, and participants. We found that countries outside Europe and North America—which bear the greatest burden of HF on a global scale[16]—were under-represented among trial leaders (9.7%), collaborators (9.7%), and participants (14.5%), with no change in temporal trends over the past 20 years. The gaps in geographic representation of trial leaders and collaborators were even more pronounced in large trials. International collaborations were primarily between or within Europe and North America, and Africa was the least represented continent. Industry funding was independently associated with lower odds of trial leadership outside Europe or North America. The geographic location of trial enrolment reflected that of trial leadership, with the adjusted odds of enrolling trial participants outside Europe and North America 10-fold greater in trials with leaders outside Europe and North America (see Graphical abstract).

The under-representation of clinical trial leaders and collaborators from regions outside Europe and North America was even more marked in large trials, and may reflect systemic barriers to trial coordination in these regions, particularly in LMICs. Barriers beyond what can be addressed by the research community in some LMICs include social and political instability, economic deprivation, and suboptimal healthcare systems for the reliable delivery of an intervention. Research-specific barriers include limited trial coordination centres, advanced research education, research infrastructure, grant funds, and human capacity for research.[17–19] In addition, ethical and regulatory challenges may hinder the efficient implementation of multicentre trials in Africa, Asia, South America, and the Caribbean.[17] Thus, while the global maldistribution of trial activity decreases the generalizability of results, it can increase efficiency by concentrating resources in regions with established research capacity and rigour; however, without broadening this capacity across regions, the cycle is expected to self-perpetuate.

Our findings that African researchers were the least represented globally in HF RCT authorship—comprising one first author, zero last authors, and 0.3% of middle authors—highlight the potential that the cardiovascular research community has lost in harnessing research ideas, answering research questions, and designing pragmatic trials to respond to the healthcare needs of African patients.

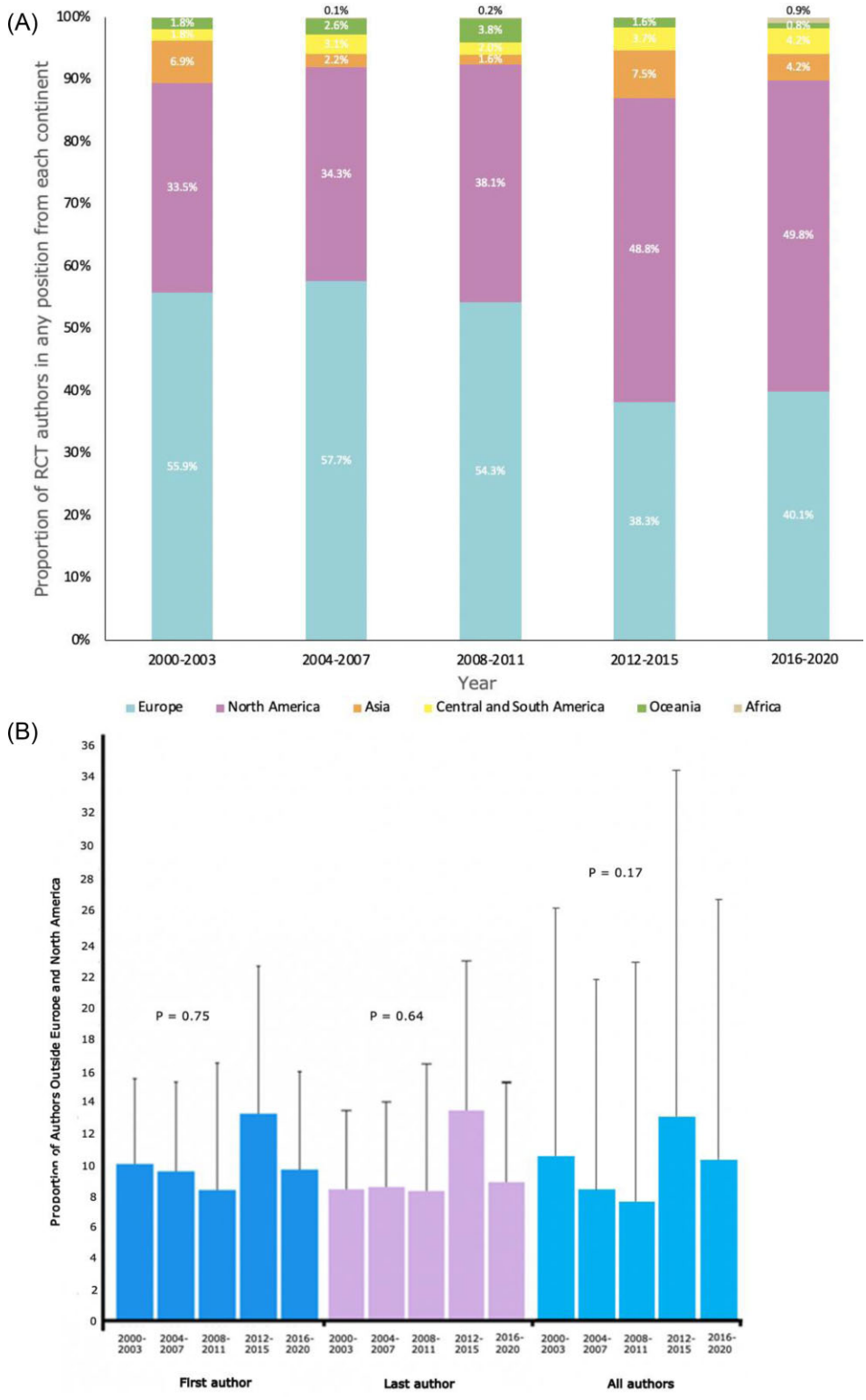



**Figure 2** Geographic representation of trial leaders and collaborators among 414 heart failure randomized controlled trials published in high-impact journals between 2000 and 2020. (*A*) Geographic representation of 4656 collaborators from each continent by year. (*B*) Temporal trends in the proportion of trial leaders (first or last authors) and collaborators (authors in any position) outside Europe and North America. There were 828 trial leaders and 4656 trial collaborators represented in the sample. Trends were analysed using the Jonckheere–Terpstra proportion trend test (two-tailed test, $\alpha = 0.05$). Error bars represent 95% confidence interval.

**Table 2 Geographic representation of authors of heart failure randomized controlled trails published in high-impact journals between 2000 and 2020**

| | Middle authors (*n*) (*N* = 3828) | First authors (*n*) (*N* = 414) | Last authors (*n*) (*N* = 414) | Total, *n* (%) (*N* = 4656) |
|---|---|---|---|---|
| **Africa** | **13** | **1** | **0** | **14 (0.3)** |
| Cameroon | 2 | 0 | 0 | 2 (0.04) |
| Kenya | 2 | 0 | 0 | 2 (0.04) |
| Mozambique | 1 | 0 | 0 | 1 (0.02) |
| Nigeria | 3 | 0 | 0 | 3 (0.06) |
| Senegal | 1 | 0 | 0 | 1 (0.02) |
| South Africa | 3 | 1 | 0 | 4 (0.09) |
| Uganda | 1 | 0 | 0 | 1 (0.02) |
| **Asia** | **177** | **17** | **14** | **208 (4.5)** |
| China | 45 | 6 | 5 | 56 (1.2) |
| India | 3 | 0 | 0 | 3 (0.06) |
| Israel | 40 | 0 | 0 | 40 (0.9) |
| Japan | 70 | 10 | 8 | 88 (1.9) |
| Jordan | 1 | 0 | 0 | 1 (0.02) |
| Korea | 8 | 1 | 1 | 10 (0.2) |
| Singapore | 6 | 0 | 0 | 6 (0.1) |
| Taiwan | 3 | 0 | 0 | 3 (0.06) |
| Vietnam | 1 | 0 | 0 | 1 (0.02) |
| **Central and South America** | **120** | **13** | **13** | **146 (3.1)** |
| Argentina | 15 | 1 | 1 | 17 (0.4) |
| Brazil | 87 | 11 | 11 | 109 (2.3) |
| Chile | 16 | 1 | 1 | 18 (0.4) |
| Columbia | 1 | 0 | 0 | 1 (0.02) |
| Peru | 1 | 0 | 0 | 1 (0.02) |
| **Europe** | **1863** | **218** | **218** | **2299 (49.4)** |
| Austria | 36 | 5 | 6 | 47 (1.0) |
| Belgium | 29 | 3 | 3 | 35 (0.8) |
| Bulgaria | 9 | 0 | 0 | 9 (0.2) |
| Cyprus | 1 | 0 | 0 | 1 (0.02) |
| Czech Republic | 15 | 1 | 1 | 17 (0.4) |
| Denmark | 107 | 11 | 10 | 128 (2.7) |
| Estonia | 1 | 0 | 0 | 1 (0.02) |
| France | 159 | 15 | 12 | 186 (4.0) |
| Finland | 37 | 7 | 7 | 51 (1.1) |
| Germany | 282 | 29 | 28 | 339 (7.3) |
| Greece | 70 | 11 | 9 | 90 (2.0) |
| Hungary | 11 | 1 | 0 | 12 (0.3) |
| Iceland | 3 | 2 | 1 | 6 (0.1) |
| Ireland | 17 | 2 | 3 | 22 (0.5) |
| Italy | 250 | 33 | 37 | 320 (6.9) |
| Latvia | 1 | 0 | 0 | 1 (0.02) |
| Lithuania | 1 | 0 | 0 | 1 (0.02) |
| Monaco | 0 | 0 | 1 | 1 (0.02) |
| Netherlands | 103 | 11 | 15 | 129 (2.8) |
| Norway | 67 | 6 | 5 | 78 (1.7) |

**Table 2 Continued**

| | Middle authors (*n*) (*N* = 3828) | First authors (*n*) (*N* = 414) | Last authors (*n*) (*N* = 414) | Total, *n* (%) (*N* = 4656) |
|---|---|---|---|---|
| Poland | 64 | 6 | 7 | 77 (1.7) |
| Portugal | 7 | 1 | 1 | 9 (0.2) |
| Romania | 9 | 0 | 0 | 9 (0.2) |
| Russia | 18 | 1 | 0 | 19 (0.4) |
| Serbia | 6 | 0 | 0 | 6 (0.1) |
| Slovakia | 7 | 0 | 0 | 7 (0.2) |
| Spain | 54 | 5 | 5 | 64 (1.4) |
| Sweden | 72 | 17 | 16 | 105 (2.3) |
| Switzerland | 90 | 6 | 11 | 107 (2.3) |
| Turkey | 7 | 0 | 1 | 8 (0.2) |
| United Kingdom | 328 | 45 | 39 | 412 (8.8) |
| Ukraine | 2 | 0 | 0 | 2 (0.04) |
| **North America** | **1592** | **156** | **156** | **1904 (40.9)** |
| Canada | 162 | 15 | 11 | 188 (4.0) |
| United States | 1425 | 140 | 145 | 1710 (36.7) |
| Mexico | 5 | 1 | | 6 (0.1) |
| **Oceania** | **63** | **9** | **13** | **85 (1.8)** |
| Australia | 40 | 4 | 9 | 53 (1.1) |
| New Zealand | 23 | 5 | 4 | 32 (0.7) |
| **Total** | **3828** | 414 | 414 | **4656 (100)** |

Red represents low income; orange represents lower-middle income; blue represents upper-middle income; green represents high income (World Bank, 2021).

**Table 3 Multivariable analysis of trial characteristics associated with leadership outside Europe and North America among heart failure randomized controlled trials (*n* = 414)**

| Clinical trial characteristics | OR (95% CI) | *P*-value |
|---|---|---|
| Scope of trial | | |
| International | 1.00 (reference) | — |
| National | 1.49 (0.45–4.92) | 0.51 |
| Funding type | | |
| Public | 1.00 (reference) | — |
| Industry | 0.33 (0.15–0.75) | 0.008 |
| Intervention type | | |
| Other (health service, exercise) | 1.00 (reference) | — |
| Surgery and device | 0.26 (0.06–1.23) | 0.09 |
| Drug | 0.98 (0.46–2.09) | 0.96 |
| Size of trial | | |
| ≤500 participants | 1.00 (reference) | — |
| >500 participants | 0.30 (0.07–1.38) | 0.12 |

CI, confidence interval; OR; odds ratio.

Prior studies have demonstrated a substantial predominance of non-African co-authors in cardiovascular research,[20] and reported that Africa produced 0.3% of the total cardiovascular research output from 1995 to 2002 with an average of 27 publications per year.[21] Although we found that the proportion of RCTs with African authors has increased in recent years (*Figure* 2A), there need to be marked global funding investment and collaboration efforts to improve capacity and realize the research potential that lies in African countries.[22] Although there are international initiatives that provide grant funding to African-based organizations, these are not specific to the healthcare sector and funds for cardiovascular research remain limited.[23] African academic institutions continue to have limited research resources, fewer research institutes, and little government support.[22]

Over half the RCTs in this study were industry sponsored and industry funding was associated with lower odds of trial leadership outside Europe or North America. Industry sponsors typically select trial leaders from a small pool of clinician researchers who lend their credentials and scientific influence to the trial.[24] There are no open processes by which leaders and executive committees are selected in industry-initiated trials, which likely disadvantages women[4] and those from LMICs. Indeed, industry-funded trials are not conducted with diversity and inclusion as a goal, but rather for commercial reasons and profit generation in high-income countries.[24] Although there has been a shift towards conducting industry-initiated trials in regions outside Europe and North America, ethical, legislative, and regulatory barriers persist in some LMICs,[25] and the geographic composition of trial leaders has not changed.

Trial enrolment was largely in North American and Europe, and the HF PPR was highest in these regions, suggesting geographic over-representation in trials. The PPR was lowest in Asia and Africa,

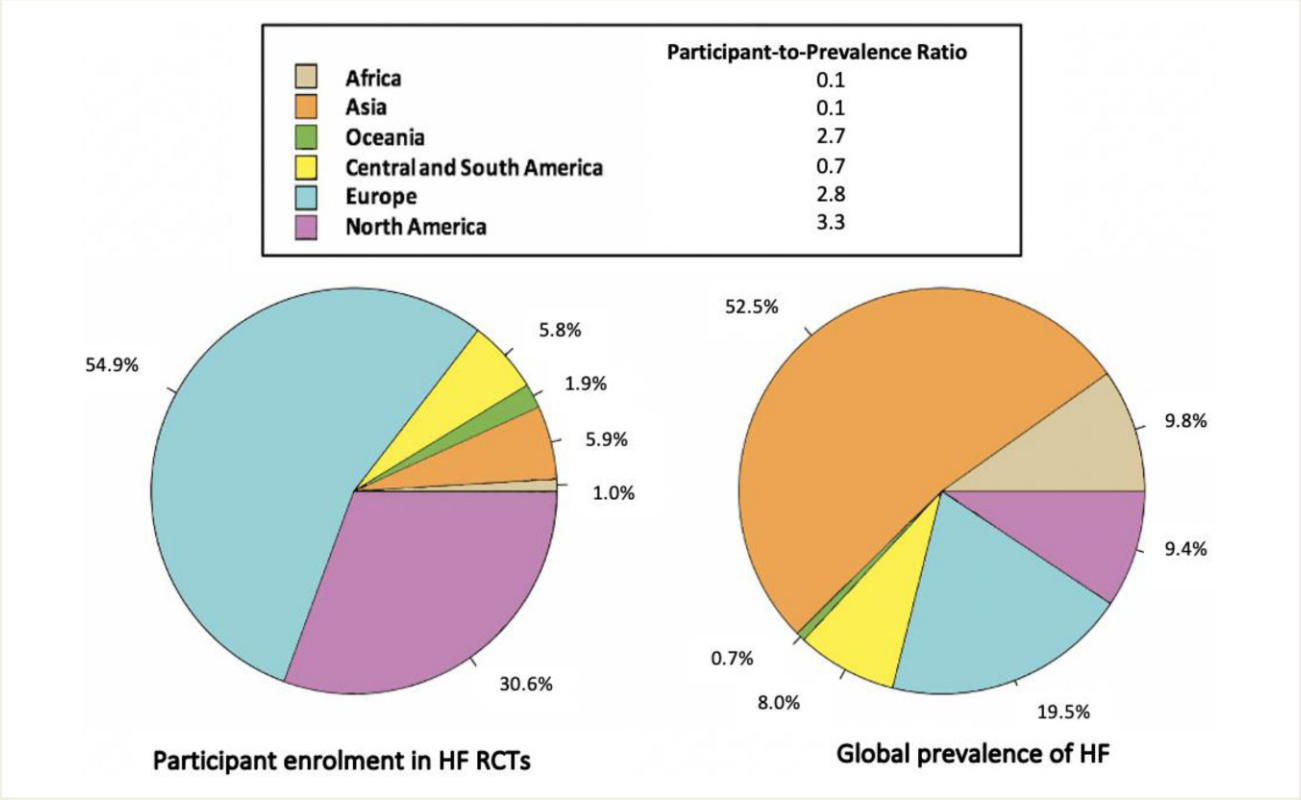



**Figure 3** Geographic representation of heart failure randomized controlled trial participants compared with world prevalence of heart failure. Prevalence of adults from each region enrolled in heart failure randomized controlled trials between 2000 and 2020 (left) and worldwide adult prevalence of heart failure by region (right). Detailed region data not available for 76 871 (32.8%) out of a total 234 287 enrolled participants; they were excluded from the analysis. Adult global prevalence of heart failure from the Global Health Data Exchange registry.

consistent with marked under-representation of participants in these regions. LMICs include a majority of the global population living with HF, and the aetiology, access to care, and burden of HF in these countries differ from those of high-income countries.[26] HF patients from countries with greater income inequality, including LMICs, have the highest mortality rates,[25] and income inequality of countries has a prognostic impact similar to those of major HF comorbidities.[27] Similarly, Africa and other LMICs are underrepresented in authorship of endemic diseases such as HIV, despite the steady temporal increase in international research collaboration and more than two-thirds of HIV-infected individuals living in Africa.[28,29] The impact of research-driven solutions could potentially produce the greatest mortality benefit in the poorest regions of the world that are largely under-represented in research.[30,31] This could come from direct benefits of trial participation—closer monitoring and care for those enrolled—and also from healthcare research investments that could potentially improve healthcare processes and infrastructure,[32] and expedite knowledge translation—including drug commercialization—in LMICs.

The adjusted odds of trial recruitment outside Europe and North America were 10-fold greater in trials led outside Europe and North America. The benefits of trial leadership from LMICs extend beyond devising research questions, designing trial protocols, and recruiting trial populations to meet the healthcare needs of their local populations. Trial leadership in these countries can provide opportunities to expand institutional capacity, improve infrastructure, train junior researchers, and advance the careers of able scientists through publications, citations, and name recognition. Benefits can also extend to collaborators from high-income countries, as publications involving multinational authorship tend to have greater academic impact than single-country publications.[33,34] Several trials led in the United States and Europe have outsourced their research to LMICs to manage costs and regulatory requirements, which may result in not only greater research capacity but also more collaborator roles for researchers in these countries.[18,19]

There are several multi-level strategies that may address current challenges and promote geographic diversity among leaders of HF RCTs (*Table 4*). Research teams from high-income countries can engage in more frequent international collaborations, relatively easily in the current era of digital communications and virtual meetings.[35] Industry and grant funding agencies such as the National Heart, Lung, and Blood Institute and Global Alliance for Chronic Disease (GACD) can stipulate that studies conducted in LMICs include researchers from these countries as collaborators. GACD can also broaden the current scope of funding for implementation science to HF, which would be an important opportunity to reduce the gap in HF research output from LMICs.[32] Increasing emphasis should also be placed on adequate early research training, fellowships, exchange programmes, and visiting professorships to foster the growth and development of future human capital, which is key to

**Table 4 Recommendations to close geographic gaps in randomized controlled trial leadership and collaborations**

**Recommendations for LMICs**
- Adopt international standards of clinical trial regulatory framework
- Enhance and restructure the medical curriculum in universities to include clinical research syllabus for undergraduate and graduate studies
- Create durable local research capacity, including sustainable research networks—clinical investigation centres, biobanks, and core laboratories
- Implement e-Health, starting with electronic medical records
- Prioritize engagement in trials that have objectives best aligned with local burden of diseases
- Incentivize investments from international pharmaceutical and biotech companies that would develop the clinical research culture and infrastructure
- Earmark funding sources dedicated to clinical research capacity building and granting local priority research programmes
- Create a favourable environment for local contract research organizations (CROs) and academic CRO operations

**Recommendations for professional societies**
- Include researchers from LMICs in position statements, guidelines, and policy documents
- Increase opportunities and research funding allocation to foster the growth and development of future human capital
- Increased participation in research training opportunities and exchange programmes in high-income countries
- Waive publication and conference fees for trialists from LMICs who present results

**Recommendations for industry sponsors**
- Rely on open processes and objective criteria to select trial leaders
- Require that trials conducted in LMICs include local investigators as collaborators and co-authors
- Invest in building research infrastructure in LMICs

**Recommendations for research teams in Europe and North America**
- Engage in more frequent international collaborations on research
- Expand recruitment sites to enrol patients outside Europe and North America
- Include local researchers in meaningful collaboration and authorship when conducting trials outside Europe and North America
- Increase research capacity building activities in LMICs through
  - Local training programmes
  - Advanced degree programmes that favour applicants from LMICs
  - Research fellowships for visiting scholars
  - Web-based research education programmes

LMICs, low- and middle-income countries.

scientific success. Increasing effort by LMICs therefore should be directed towards providing training in an equitable, respectful way to establish long-lasting, sustainable partnerships. Lastly, to address the ethical and regulatory approval system obstacles, capacity strengthening activities initiated through grants from high-income countries (at the level of the World Health Organization, pharmaceutical and device companies, and professional societies) have been previously proposed as a promising strategy.[36]

## Study strengths and limitations

Methodological strengths of our study included the comprehensive search strategy, duplicate extraction, large sample size, and temporal range (20-year time span) of RCTs published in high-impact journals. Limitations should be noted. First, we focused on English-language studies published in high-impact medical journals to capture the most widely read trials with the potential to impact clinical practice. We recognize that the geographic representation of authors and participants reported in this study may not apply to RCTs published in lower-impact non-English journals or adequately capture the growth in cardiovascular research in non-English countries.[37] Furthermore, this may contribute to reinforcing the research-centeredness around English-language publications from North America and Europe. Second, the trials were specific to HF and results may not be generalizable to trials in other cardiovascular diseases. Indeed, HF is a younger discipline and the organization of HF care in low-income countries is less developed than that of other cardiovascular diseases like coronary artery disease.[38] Third, some authors may have had a primary or secondary institution affiliation outside their current country of residence and the institutional addresses may not accurately reflect their geographic location. Fourth, we used first and last authorship status as surrogates for leadership of RCTs, although we acknowledge that some trials are led by industry partners. Fifth, while our geographic classification was continent-based, we recognize the inter-country variation in research contribution, as outlined in *Table 2*. Sixth, our multivariable analysis is exploratory in nature and the results should be interpreted with caution.

# Conclusions

Among the 414 HF RCTs published between 2000 and 2020, researchers outside Europe and North America were under-represented as trial leaders and collaborators in high-impact HF RCTs, with no significant temporal changes in representation over time. Trial participants in regions outside Europe and North America were grossly under-represented relative to HF prevalence, particularly in Africa and Asia. Trial leadership outside Europe and North America was less likely in industry-funded trials, but associated with 10-fold greater odds of participant enrolment outside Europe and North America. Building research capacity in under-represented regions has the potential to increase the diversity and external validity of clinical trials.

# Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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