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**Global Representation of Heart Failure Clinical Trial Leaders, Collaborators, and  
Enrolled Participants:  
A Bibliometric Review 2000-2020**

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**Data availability statement**

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

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## ABSTRACT

**Background:** The geographic representation of investigators and participants in heart failure (HF) randomized clinical trials (RCTs) may not reflect the global burden of disease.

**Aims:** 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  $\geq 10$  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% CI: 7.8% to 11.8%), and 453 of 4656 collaborators (9.7%; 95% CI: 8.8% to 10.6%) were from outside Europe and North America, with no change in temporal trends and greater disparities in large RCTs. The adjusted odds of trial leadership outside Europe and North America were lower with industry funding (aOR: 0.33; 95% CI: 0.15 to 0.75;  $P = 0.008$ ). Among 157,416 participants in whom geography was reported, only 14.5% (95% CI: 14.3% to 14.7%) were enrolled outside Europe and North America, but odds of enrolment were ten-fold greater with trial leadership outside Europe and North America (aOR: 10.0; 95% CI 5.6-19.0;  $P < 0.001$ ).

**Conclusions:** 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.

**Keywords:** Randomized Controlled Trials, Authorship, Collaboration, Diversity, Geography

**Abbreviations:**

HF = heart failure

LMIC = low- and middle- income countries

PPR Participation-to-Prevalence ratios

RCT = randomized control trial

## Introduction

Heart failure (HF) is a global epidemic with a disproportionate burden in low and middle income countries (LMIC).<sup>1,2</sup> 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.<sup>3</sup> 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,<sup>4-6</sup> with little discussion about geographic diversity. Clinical trials led by women are associated with enrolment of more diverse participants.<sup>4,5,7</sup> 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.<sup>8-10</sup> 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.<sup>11-13</sup>

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-factor 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 Supplemental 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 (PROSPERO).

### *Study selection*

The authors independently screened all titles and abstracts against pre-determined eligibility criteria in duplicate (J.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 January 1, 2000 and June 17, 2020, ii) included adults aged 18 years or older with HF and iii) were 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.<sup>14</sup> 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.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.<sup>15</sup>

### *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 >500 participants. Temporal trends in geographic representation of lead, senior, and any author between 2000 and 2020 were analyzed using the Jonckheere-Terpstra proportion trend test. We used multivariable logistic regression to determine 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 versus international), type of funding (industry versus public), type of intervention (drug, surgical or device versus other), trial size (<500 versus > 500 participants).

We assessed country of enrolment among those participants in whom geography data were reported. We estimated trial participant-to-prevalence ratio in regions across the world using the Global Health Data Exchange registry.<sup>16</sup> Participant-to-Prevalence ratios (PPR) 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 (ORs) with corresponding 95% confidence interval (CI) and associated P values. All P values were 2-tailed, and the level of significance

was set at  $\alpha = 0.05$ . Data were analyzed using SPSS version 27.0 (IBM Corporation, Armonk, New York).

## 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 RCTs*

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 ischemic etiology of heart failure (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% to 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 to 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% to 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 2A). Low- and middle-income countries were particularly underrepresented 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 to 11) in 2001-2003 to 15 (IQR: 12 to 19) in 2016-2020. 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 2A), there was no significant change in the 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 2B).

### *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% to 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% to 7.0%]) and Oceania ( $n = 1$  [1.3%; 95% CI: 0.3% to 7.0%]), respectively. Among the 79 RCTs, 57 (72.2%; 95% CI: 60.9% to 81.7%) were international and 22 (27.8%; 95% CI: 18.4% to 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% to 81.2%) (Table 2). The most

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

#### *Multivariable analysis of RCT 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 to public funding (OR: 0.33; 95% CI: 0.15 to 0.75; P = 0.008) (Table 3). Scope of trial (national versus international), intervention type (drug or device / surgery versus other), and size of trial (> 500 participants versus < 500 participants) had no significant 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 was available for 157,416 (67.2%; 95% CI: 67.0% to 67.4%) trial participants. Among these participants, 54.9% (95% CI: 54.7% to 55.2%) were enrolled in Europe; 30.6% (95% CI: 30.4% to 30.8%) in North American; 5.8% (95% CI: 5.7% to 5.9%) in Asia; 5.8% (95% CI: 5.7% to 5.9%) in Central and South America; 1.94% (95% CI: 1.9% to 2.0%) in Oceania; and 0.95% (95% CI: 0.9% to 1.0%) in Africa (Figure 3). The trial participant-

to-prevalence ratio was highest in North America (3.3) and Europe (2.8) and lowest in Asia (0.1) and Africa (0.1) (Figure 3).

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 (Supplemental Table 1). 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% to 78.7%]) and Journal of the American College of Cardiology (n = 5 [33.3%; 95% CI: 11.8% to 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<sup>16</sup> – 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 was 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 ten-fold greater in trials with leaders outside Europe and North America (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 LMIC. Barriers beyond what can be addressed by the research community in some LMIC 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 centers, advanced research education, research infrastructure, grant funds, and human capacity for research.<sup>17</sup> In addition, ethical and regulatory challenges may hinder the efficient implementation of multicentre trials in Africa, Asia, South America and the Caribbean.<sup>17</sup> 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 rigor; 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 1 first author, 0 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. Prior studies have demonstrated a substantial predominance of non-African co-authors in cardiovascular research,<sup>20</sup> 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.<sup>21</sup> Although we found that the proportion of RCTs with African authors has increased in recent years (Figure 2A), there will need to be marked global funding investment and collaboration efforts to improve capacity and realize the research potential that lies in African countries.<sup>22</sup> 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.<sup>23</sup> African academic institutions continue to have limited research resources, fewer research institutes, and little government support.<sup>22</sup>

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.<sup>24</sup> There are no open processes by which leaders and executive committees are selected in industry-initiated trials, which likely disadvantages women<sup>4</sup> and those from LMIC. 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.<sup>24</sup> 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 LMIC,<sup>25</sup> and the geographic composition of trial leaders has not changed.

Trial enrolment was largely in North American and Europe, and the HF participant-prevalence ratio was highest in these regions, suggesting geographic over-representation in trials. The participant-prevalence ratio was lowest in Asia and Africa, consistent with marked

underrepresentation of participants in these regions. LMIC include a majority of the global population living with HF, and the etiology, access to care, and burden of HF in these countries differ from those of high-income countries.<sup>26</sup> HF patients from countries with greater income inequality, including LMIC, have the highest mortality rates,<sup>25</sup> and income inequality of countries has a prognostic impact similar to those of major HF comorbidities.<sup>27</sup> 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.<sup>28,29</sup> 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.<sup>30,31</sup> 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,<sup>32</sup> and expedite knowledge translation – including drug commercialization - in LMIC.

The adjusted odds of trial recruitment outside Europe and North America were ten-fold greater in trials led outside Europe and North America. The benefits of trial leadership from LMIC extend beyond devising research questions, designing trial protocols, and recruiting trial populations to meet the health care 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.<sup>33,34</sup> Several trials led in the USA and Europe have outsourced their research to LMIC to manage costs and regulatory requirements, which may result not only in

greater research capacity but also more collaborator roles for researchers in these countries.<sup>18,19</sup>

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.<sup>35</sup> Industry and grant funding agencies such as the National Heart, Lung, and Blood Institute (NHLBI) and Global Alliance for Chronic Disease (GACD) can stipulate that studies conducted in LMIC include researchers from these countries as collaborators. GACD can also broaden the current scope of funding for implementation science to heart failure, which would be an important opportunity to reduce the gap in HF research output from LMICs.<sup>32</sup> Increasing emphasis should also be placed on adequate early research training, fellowships, exchange programs, and visiting professorships to foster the growth and development of future human capital, which is key to scientific success. Increasing effort by both low- and high-income countries 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.<sup>36</sup>

#### *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 factor journals. Limitations should be noted. First, we focussed on English language studies published in high impact factor 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.<sup>37</sup> 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.<sup>38</sup> 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.

## **Conclusion**

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 ten-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.

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## References

- [1] Callender T, Woodward M, Roth G, Farzadfar F, Lemarie JC, et al. (2014) Heart Failure Care in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis. *PLOS Medicine* 11(8): e1001699. <https://doi.org/10.1371/journal.pmed.1001699>
- [2] Harikrishnan S, Sanjay G, Anees T, et al. Clinical presentation, management, in-hospital and 90-day outcomes of heart failure patients in Trivandrum, Kerala, India: the Trivandrum Heart Failure Registry. *Eur J Heart Fail.* 2015;17(8):794-800. doi:10.1002/ejhf.283
- [3] Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA.* 2007;297(11):1233-40. doi: 10.1001/jama.297.11.1233. PMID: 17374817.
- [4] Denby KJ, Szpakowski N, Silver J, Walsh MN, Nissen S, Cho L. Representation of Women in Cardiovascular Clinical Trial Leadership. *JAMA Intern Med.* 2020;180(10):1382-1383. doi:10.1001/jamainternmed.2020.2485
- [5] Whitelaw S, Sullivan K, Eliya Y, et al. Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review [published online ahead of print, 2020 Oct 29]. *Eur J Heart Fail.* 2020;10.1002/ejhf.2034. doi:10.1002/ejhf.2034
- [6] Whitelaw S, Thabane L, Mamas MA, et al. Characteristics of Heart Failure Trials Associated With Under-Representation of Women as Lead Authors. *J Am Coll Cardiol.* 2020;76(17):1919-1930. doi:10.1016/j.jacc.2020.08.062
- [7] Wei S, Le N, Zhu, J, et al. Racial reporting and diversity among heart failure clinical trial participants 2000-2020: a systematic review. Manuscript under review.
- [8] Sliwa K, Azibani F, Baard J, et al. Reducing late maternal death due to cardiovascular disease - A pragmatic pilot study. *Int J Cardiol.* 2018;272:70-76. doi:10.1016/j.ijcard.2018.07.140
- [9] Van Spall HGC, Lee SF, Xie F, et al. Effect of Patient-Centered Transitional Care Services on Clinical Outcomes in Patients Hospitalized for Heart Failure: The PACT-HF Randomized Clinical Trial. *JAMA.* 2019;321(8):753-761. doi:10.1001/jama.2019.0710
- [10] Bernabe-Ortiz A, Sal Y Rosas VG, Ponce-Lucero V, et al. Effect of salt substitution on community-wide blood pressure and hypertension incidence. *Nat Med.* 2020;26(3):374-378. doi:10.1038/s41591-020-0754-2

- [11] Abramo G, D'Angelo CA, Solazzi M. The relationship between scientists' research performance and the degree of internationalization of their research. *Scientometrics* [Internet]. 2011 Mar 29. Available at: <http://link.springer.com/10.1007/s11192-010-0284-7>. Accessed Oct 26, 2020.
- [12] F. Narin and E.S. Whitlow, 1990, Measurement of Scientific Cooperation and Coauthorship in CEC-related Areas of Science (Report EUR 12900, Office for Official Publications of the European Communities, Luxembourg).
- [13] Gal D, Glänzel W, Sipido KR. Mapping cross-border collaboration and communication in cardiovascular research from 1992 to 2012. *Eur Heart J*. 2017;38(16):1249-1258. doi:10.1093/eurheartj/ehw459
- [14] Collier C. Announcing the 2019 journal citation reports. Available at: <https://clarivate.com/webofsciencegroup/article/announcing-the-2019-journal-citation-reports/>. Accessed Jan 20, 2021.
- [15] Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries; Fuster V, Kelly BB, editors. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington (DC): National Academies Press (US); 2010. E, World Bank Income Classifications July 2009. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK45682/>
- [16] GHDx - Global Health Data Exchange (Institute for Health Metrics and Evaluation – IHME). Available at: <http://www.healthdata.org/gbd/2019>. Accessed April 27, 2021.
- [17] Ndebele P, Blanchard-Horan C, Shahkolahi A, et al. Regulatory challenges associated with conducting multi-country clinical trials in resource-limited settings. *J. Acquir. Immune Defic. Syndr.* (1999) 2014;65:S29. doi: 10.1097/QAI.0000000000000037
- [18] Homedes N, Ugalde A. Health and Ethical Consequences of Outsourcing Pivotal Clinical Trials to Latin America: A Cross-Sectional, Descriptive Study. *PLOS One*. 2016;11(6):e0157756. doi:10.1371/journal.pone.0157756
- [19] Belforti RK, Wall MS, Lindenauer PK, et al. International outsourcing of medical research by high-income countries: changes from 1995 to 2005. *J Investig Med*. 2010;58(2):287-294. doi:10.2310/JIM.0b013e3181ca72e2
- [20] Adams J, Gurney K, Hook D. et al. International collaboration clusters in Africa. *Scientometrics*. 2014;98(1):547–556.

- [21] Adams J, Gurney K, Hook D. et al. International collaboration clusters in Africa. *Scientometrics*. 2014;98(1):547–556.
- [22] Zannad, F., Sobhy, M., Almahmeed, W., et al. Clinical research in Africa and middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development. *Journal of Global Health Reports*. 2019. 3, p.e2019082.
- [23] Gaziano TA, Bitton A, Anand S, et al. Growing epidemic of coronary heart disease in low- and middle-income countries. *Curr Probl Cardiol*. 2010;35(2):72-115. doi:10.1016/j.cpcardiol.2009.10.002
- [24] Chopra SS. Industry Funding of Clinical Trials: Benefit or Bias? *JAMA*. 2003;290(1):113–114. doi:10.1001/jama.290.1.113
- [25] Marzouk D, Abd El Aal W, Saleh A, et al. Overview on health research ethics in Egypt and North Africa. *The European Journal of Public Health*. 2014;24(suppl 1):87-91. doi:10.1093/eurpub/cku110
- [26] Gaziano TA, Bitton A, Anand S, et al. Growing epidemic of coronary heart disease in lowandmiddle-income countries. *Curr Probl Cardiol*. 2010;35(2):72-115. doi:10.1016/j.cpcardiol.2009.10.002
- [27] Ferreira JP, Rossignol P, Dewan P, Lamiral Z, White WB, Pitt B, McMurray JJV, Zannad F. Income level and inequality as complement to geographical differences in cardiovascular trials. *Am Heart J*. 2019 Dec;218:66-74. doi:10.1016/j.ahj.2019.08.019
- [28] Nye J, D'Souza MP, Hu D, Ghosh D. Research productivity and collaboration of the NIHfunded HIV vaccine trials network: A bibliometric analysis. *Heliyon*. 2021;7(1):e06005. Published 2021 Jan 22. doi:10.1016/j.heliyon.2021.e06005
- [29] Sweileh WM. Bibliometric analysis of literature in AIDS-related stigma and discrimination. *Transl Behav Med*. 2019;9(4):617-628. doi:10.1093/tbm/iby072
- [30] Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. *Int J Equity Health*. 2018;17(1):37. Published 2018 Mar 22. doi:10.1186/s12939-018-0748-6
- [31] Murray CJ, Lopez AD. Global comparative assessments in the health sector: disease burden, expenditures and intervention packages. 1994.

- [32] Davies J. Collaborative funding for NCDs—a model of research funding. *Lancet Diabetes Endocrinol.* 2016;4(9):725-727. doi:10.1016/S2213-8587(16)30184-X
- [33] Lopes RD, Macedo AVS, de Barros E Silva PGM, et al. Continuing versus suspending angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: Impact on adverse outcomes in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARSCoV-2)—The BRACE CORONA Trial. *Am Heart J.* 2020;226:49-59. doi:10.1016/j.ahj.2020.05.002
- [34] Ettarh R. Patterns of international collaboration in cardiovascular research in sub-Saharan Africa. *Cardiovasc J Afr.* 2016;27(3):194-200. doi:10.5830/CVJA-2015-082
- [35] Kyvik S. Changing trends in publishing behaviour among university faculty, 1980–2000. *Scientometrics.* 2003;58:35–48.
- [36] The African Network for Drugs and Diagnostics Innovation. Mboya-Okeyo T, Ridley RG, Nwaka S, ANDI Task Force. *Lancet.* 2009 May 2; 373(9674):1507-8.
- [37] Huffman MD, Baldrige A, Bloomfield GS, et al. Global cardiovascular research output, citations, and collaborations: a time-trend, bibliometric analysis (1999-2008). *PLoS One.* 2013;8(12):e83440. Published 2013 Dec 31. doi:10.1371/journal.pone.0083440\
- [38] Ferreira JP, Kraus S, Mitchell S, Perel P, et al. World Heart Federation Roadmap for Heart Failure. *Glob Heart.* 2019 Sep;14(3):197-214. doi: 10.1016/j.gheart.2019.07.004

## Figure Legends

### Figure 1. PRISMA Flow Diagram

Systematic search strategy conducted in MEDLINE, EMBASE, and CINAHL to identify all randomized controlled trials (RCTs) published in medical journals with an impact factor  $\geq 10$  and recruited adults with heart failure (HF).

### Figure 2. Geographic representation of Heart Failure Randomized Controlled Trial participants compared to world prevalence of Heart Failure

Prevalence of adults from each region enrolled in HF RCTs between 2000-2020 (left) and worldwide adult prevalence of HF 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 HF from the Global Health Data Exchange registry.

### Figure 3. Geographic representation of trial leaders and collaborators among 414 Heart Failure Randomized Controlled Trials published in high impact factor journals 2000-2020.

(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 analyzed using the Jonckheere-Terpstra proportion trend test (2-tailed test,  $\alpha = 0.05$ ). Error bars represent 95% CI.

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

**Table 1.** Baseline Characteristics of Heart Failure Randomized Controlled Trials Published in High Impact Factor Journals Between 2000 and 2020

<b>Clinical Trial Characteristics</b>	<b>No. of trials (%)</b>
	<b>N = 414</b>
<hr/>	
Trials on HF 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)
<b>Type of Intervention</b>	
Health Service	57 (13.8)
Drug	271 (65.5)
Device	47 (11.4)
Surgery	10 (2.4)
Exercise/Rehabilitation	30 (7.2)
<b>Number of Centres</b>	
Single Centre	171 (41.3)
Multicentre	243 (58.7)
<b>Type of Funding</b>	
Any Public Funding	196 (47.3)
Industry Funding	218 (52.7)
<b>Number of Participants</b>	
<100	192 (46.4)
100-500	143 (34.5)
>500	79 (19.1)
<b>Year of Publication</b>	
2000-2003	122 (29.5)
2004-2007	106 (25.6)
2008-2011	48 (11.6)
2012-2015	52 (12.6)

2016-2020

85 (20.5)

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Table 2. Geographic Representation of Authors of HF RCTs Published in High Impact Factor Journals Between 2000 and 2020

	<b>Middle</b>	<b>First</b>	<b>Last</b>	<b>No. Total, N (%)</b>
	<b>Authors (N)</b>	<b>Authors (N)</b>	<b>Authors (N)</b>	
	<b>N = 3828</b>	<b>N=414</b>	<b>N=414</b>	<b>N = 4656</b>
<b>Africa</b>	<b>13</b>	<b>1</b>	<b>0</b>	<b>14 (0.3)</b>
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)
<b>Asia</b>	<b>177</b>	<b>17</b>	<b>14</b>	<b>208 (4.5)</b>
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)

<b>CSA</b>	<b>120</b>	<b>13</b>	<b>13</b>	<b>146 (3.1)</b>
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)
<b>Europe</b>	<b>1863</b>	<b>218</b>	<b>218</b>	<b>2299 (49.4)</b>
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)
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)
<b>NA</b>	<b>1592</b>	<b>156</b>	<b>156</b>	<b>1904 (40.9)</b>
Canada	162	15	11	188 (4.0)
United States	1425	140	145	1710 (36.7)
Mexico	5	1		6 (0.1)
<b>Oceania</b>	<b>63</b>	<b>9</b>	<b>13</b>	<b>85 (1.8)</b>
Australia	40	4	9	53 (1.1)
New Zealand	23	5	4	32 (0.7)
<b>Total</b>	<b>3828</b>	<b>414</b>	<b>414</b>	<b>4656 (100)</b>

Legend: **red** represents low income; **orange** represents lower-middle income; **blue** represents upper-middle; **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)

<b>Clinical Trial Characteristics</b>	<b>OR (95% CI)</b>	<b>p-value</b>
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

**Table 4.** Recommendations to Close Geographic Gaps in RCT Leadership and Collaborations**Recommendations for LMIC**

- 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
- Incentivise 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 programs.
- Create a favorable environment for local Contract Research Organizations (CRO) and academic CRO operations

**Recommendations for professional societies**

- Include researchers from LMIC in position statements, guidelines, 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 programs high income countries
- Waive publication and conference fees for trialists from LMIC who present results

**Recommendations for industry sponsors**

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

**Recommendations for research teams in Europe and North America**

- Engage in more frequent international collaborations on research
- Expand recruitment sites to enroll 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 low- and middle-income countries (LMIC) through
  - Local training programs
  - Advanced degree programs that favour applicants from LMIC
  - Research fellowships for visiting scholars
  - Web-based research education programs

Figure 1

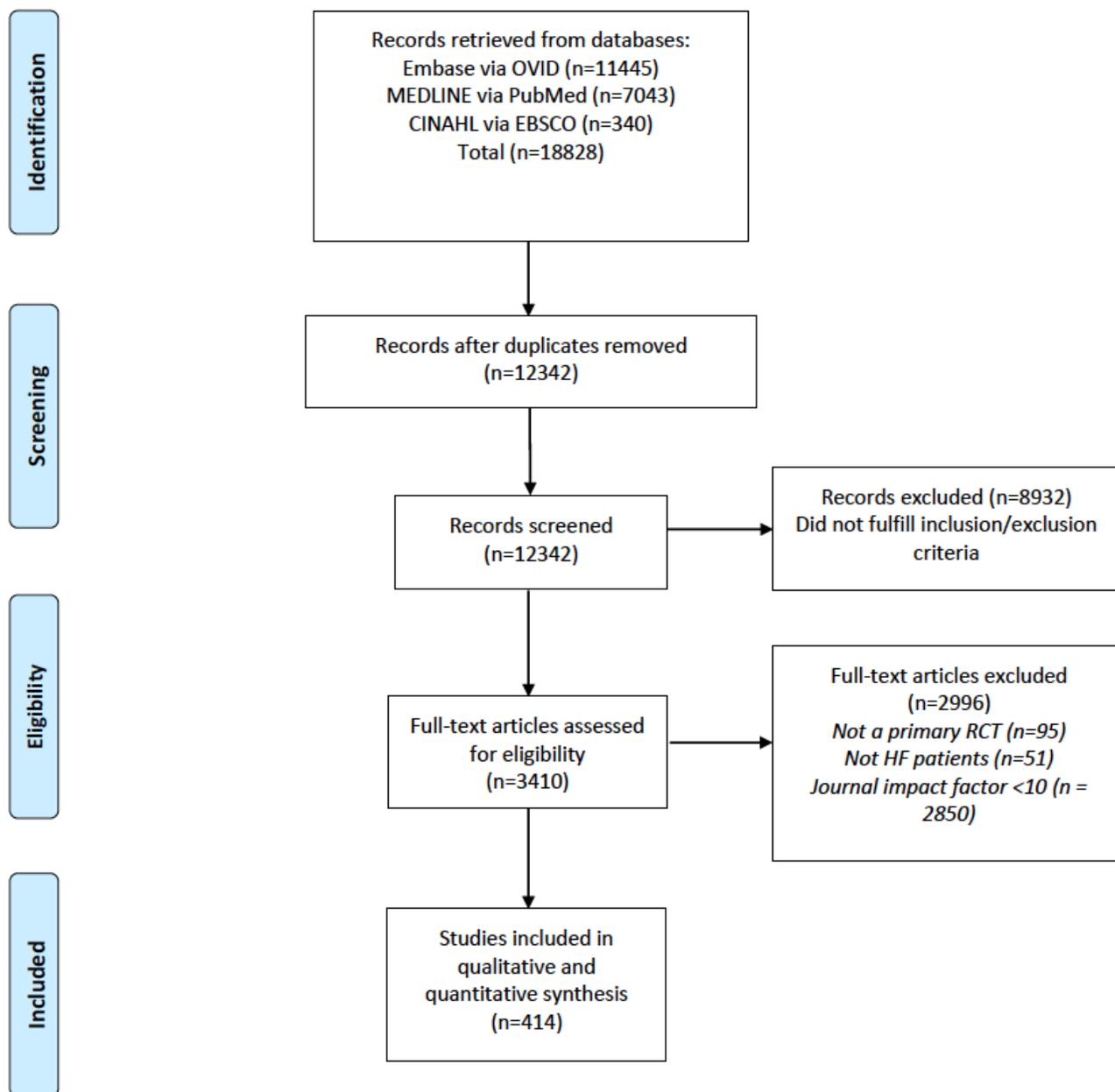
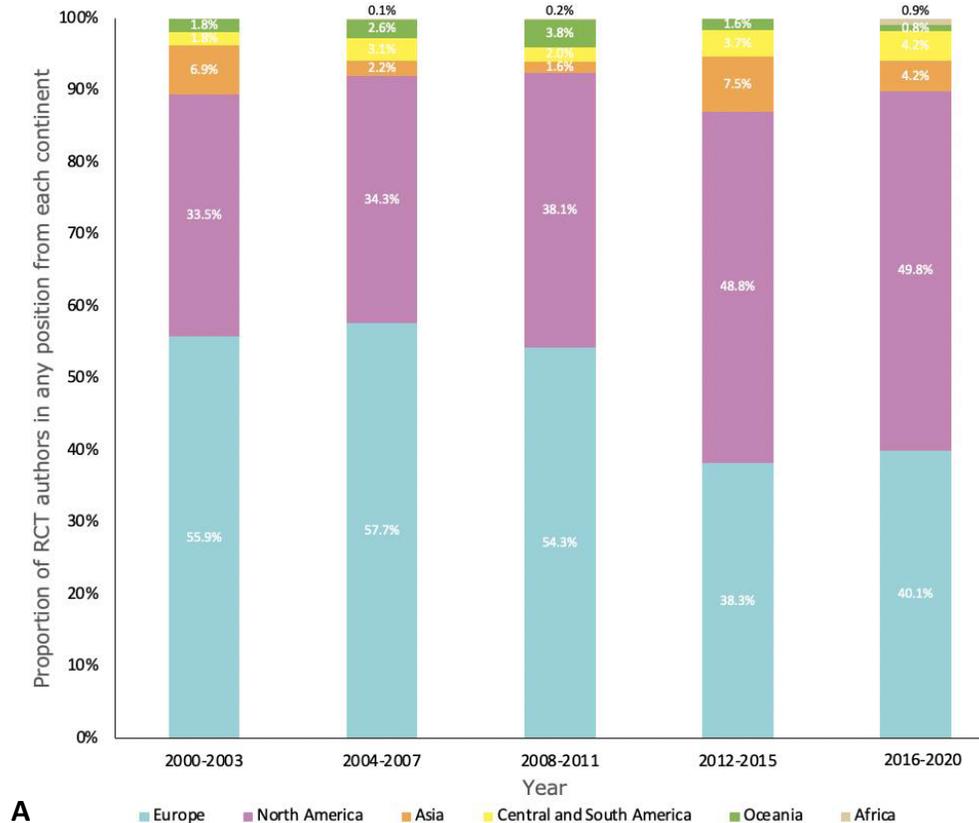
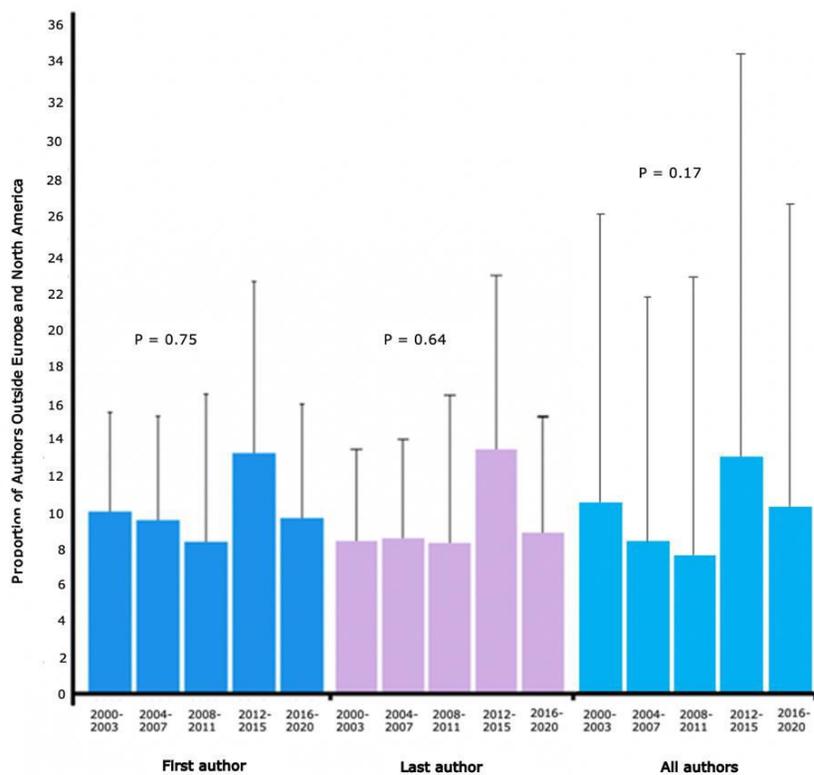


Figure 2

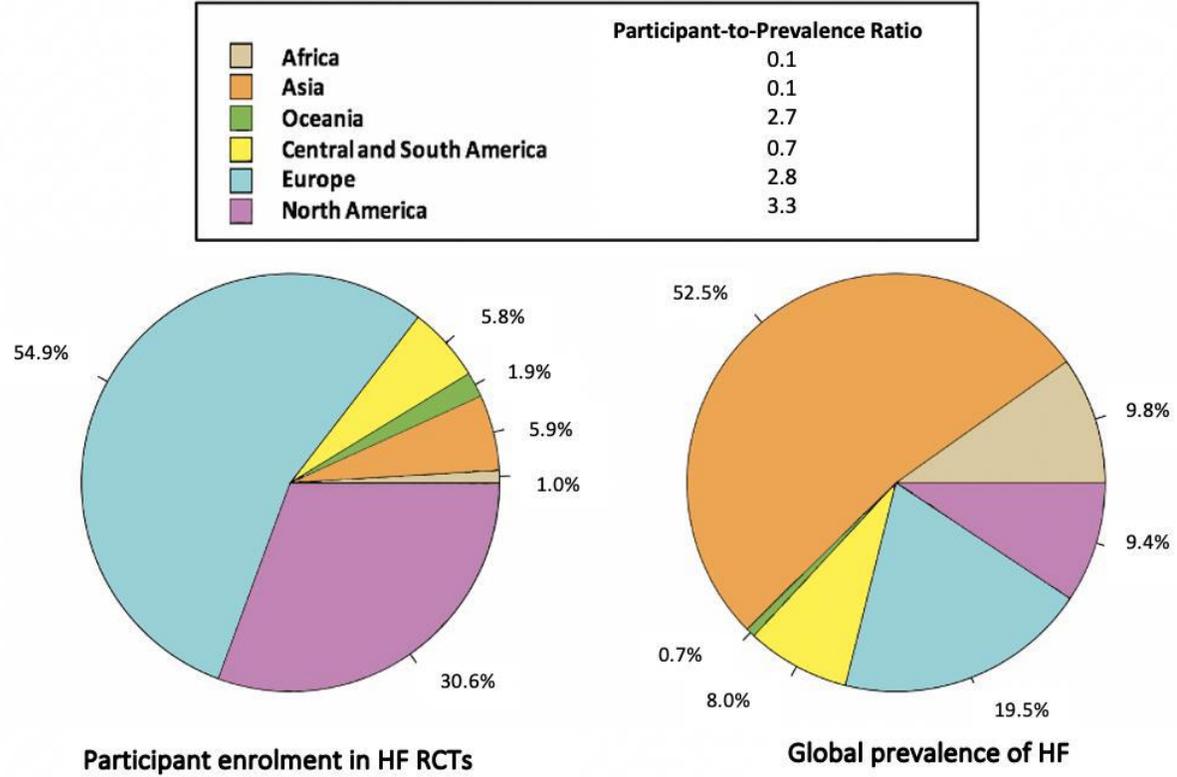


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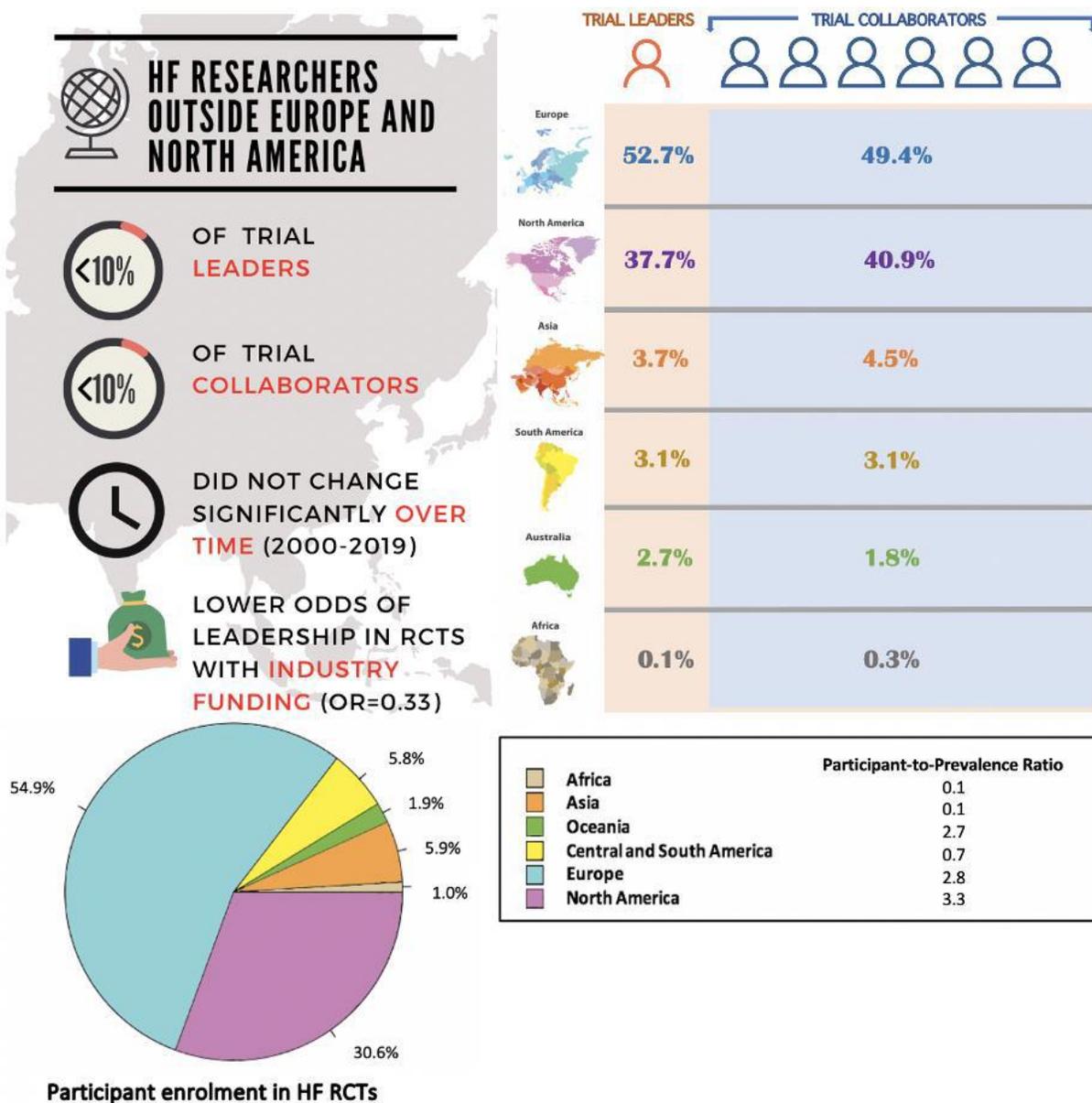


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Figure 3



## Graphical Abstract



**SUPPLEMENTARY MATERIAL****Supplemental Methods:** 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. 4 not 5

**Supplemental Table 1.** Journal of Publication and Geographic Representation of Leaders of Heart Failure Randomized Controlled Trials published in Major Medical Journals (N=414)

<b>Journal</b>	<b>Total RCTs, N (%)</b>	<b>RCTs with International Collaboration Between Trial Leaders, N (%)</b>	<b>RCTs with Trial Leaders Outside Europe and North America, N (%)</b>
American Journal of Respiratory and Critical Care Medicine	2 (0.4)	0	0
Annals of Internal Medicine	1 (0.2)	0	0
British Medical Journal	4 (1.0)	1 (0.6)	0
Circulation	63 (15.2)	22 (13)	0
Circulation Research	5 (1.2)	1 (0.6)	1 (6.7)
European Heart Journal	40 (9.7)	17 (10.2)	1 (6.7)
European Journal of Heart Failure	109 (26.3)	38 (22.8)	8 (53.3)
European Respiratory Journal	1 (0.2)	1 (0.6)	0
Journal of the American Medical Association	29 (7.0)	15 (9.0)	0
Journal of the American Medical Association Cardiology	4 (1.0)	1 (0.6)	0
Journal of the American Medical Association Internal Medicine	7 (1.7)	0	0
Journal of the American College of Cardiology	87 (21.0)	27 (16.2)	5 (33.3)
Lancet	21 (5.1)	18 (10.8)	0
New England Journal of Medicine	41 (9.9)	26 (15.6)	0
<b>Total</b>	<b>414 (100)</b>	<b>167 (100)</b>	<b>15 (100)</b>