**Global Representation of Heart Failure Clinical Trial Leaders, Collaborators, and**

**Enrolled Participants:**

**A Bibliometric Review 2000-2020**

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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 ≥ 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).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-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 ≥ 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.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 >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.16 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

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 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 scale16 – 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.17 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 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,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 will 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

women4 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.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 LMIC,25 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.26 HF patients from countries with greater income inequality, including LMIC, 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 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.33,34 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.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 (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.32 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.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 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.37 Furthermore, this may contribute to reinforcing the researchcenteredness 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.

**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 Americal

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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**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 ≥10 and

recruited adults with heart failure (HF).

**Figure 2. Geographic representation of Heart Failure Randomzied 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, α = 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

Table

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Table 2. Geographic Representation of Authors of HF RCTs Published in High Impact Factor

Journals Between 2000 and 2020

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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)

Graphical user interface, application

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

Text

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**Figure 1**

Diagram

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**Figure 2**

**AChart, bar chart

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**BChart, histogram

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**Figure 3**

**Chart, pie chart

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**Graphical Abstract**

Chart, application, pie chart

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**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)

**Table

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