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Research Letter | Diversity, Equity, and Inclusion

Evaluation of Representation of Women as Authors in Pivotal Trials Supporting US Food and Drug Administration Approval of Novel Cardiovascular Drugs

Izza Shahid, MBBS; Muhammad Shahzeb Khan, MD, MSc; Aruba Sohail, MBBS; Safi U. Khan, MD, MS; Stephen J. Greene, MD; Marat Fudim, MD, MHS; Erin D. Michos, MD, MHS

Introduction

Pivotal efficacy trials provide foundational evidence supporting US Food and Drug Administration (FDA) approval of novel drugs. It is well documented that women are underrepresented as authors in cardiovascular clinical trials, among trial leadership committees,[1-3] and as participants in trials of cardiovascular drugs. However, gender inequity in authorship across pivotal trials of FDA-approved novel cardiovascular drugs remains unknown.[4] Therefore, we sought to investigate the representation of women as authors of these pivotal trials.

+ Invited Commentary

+ Supplemental content

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Table 1. Characteristics of Novel Cardiovascular Drugs Approved by the US Food and Drug Administration Between 2008 and 2020

Drug	Approval year[a]	Disease indication	No. of trials	No. of publications	Women authors, No. (%)
Regadenoson	2008	Other	2	2	3 (17.6)
Clevidipine	2008	Hypertension	6	4[b]	3 (10.3)
Dronedarone	2009	AF	4	4	0
Prasugrel	2009	ACS	1	1	2 (14.3)
Pitvastatin	2009	Hypercholesterolemia	5	5	2 (10.5)
Dabigatran	2010	AF	1	1	4 (20.0)
Azilsartan	2011	Hypertension	7	3	0
Rivaroxaban	2011	AF	3	3	4 (13.8)
Ticagrelor	2011	ACS	1	1	0
Lomitapide mesylate	2012	Hypercholesterolemia	1	1	6 (35.3)
Apixaban	2012	AF	2	2	4 (6.3)
Mipomersen	2013	Hypercholesterolemia	1	1	3 (23.1)
Riociguat	2013	PAH	2	2	1 (4.0)
Macitentan	2013	PAH	1	1	2 (10.5)
Vorapaxar sulfate	2014	CHD	1	1	3 (17.6)
Edoxaban	2015	AF	2	2	5 (15.6)
Ivabradine hydrochloride	2015	HF	3	3	1 (5.3)
Cangrelor	2015	ACS	1	1	4 (16.7)
Sacubitril/valsartan	2015	HF	1	1	0
Selexipag	2015	PAH	1	1	6 (31.6)
Alirocumab	2015	Hypercholesterolemia	5	4[c]	10 (21.3)
Evolocumab	2015	Hypercholesterolemia	4	4	8 (14.8)
Betrixaban	2017	AF	1	1	0
Angiotensin II acetate	2017	Other	1	1	5 (16.7)
Tafamidis meglumine	2019	Other	1	1	7 (33.3)
Bempedoic acid	2020	Hypercholesterolemia	2	2	6 (33.3)

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CHD, coronary heart disease; HF, heart failure; PAH, pulmonary arterial hypertension.

[a] Years 2016 and 2018 were not included because of a lack of approval of any novel cardiovascular drugs.

[b] Results of 3 trials were mentioned in 1 publication.

[c] Results of 2 trials were mentioned in 1 publication.

Methods

Because publicly available data that did not involve patients were used in this cross-sectional study, institutional review board approval was not required. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Methods related to study sources and data abstraction were reported previously.[4] We searched the Drugs@FDA portal for novel cardiovascular drugs approved between 2008 and 2020. Drug approval labels were searched to identify all pivotal trials listed in Section 14 under "Clinical Studies." Only pivotal trials with corresponding trial publications were included in this study. Details regarding trial selection are provided in the eMethods in the Supplement. The gender of trial authors was captured as binary (women and men) and was identified by using Genderize software (Demografix ApS) or by verifying personal pronouns on authors' institutional profiles or other sources. Study-level estimates for the proportion of women authors were pooled using the DerSimonian and Laird random-effects meta-analysis of proportions model. Analyses were conducted with OpenMeta[Analyst] software version 10.12.

Table 2. Representation of Women Authors in Pivotal Efficacy Trials of Novel Cardiovascular Drugs

Category	No. of drugs	No. of trial publications	Women authors, % (95% CI)	*P* value of heterogeneity[a]
Overall	26	53	10.0 (7.8 to 12.2)	.64
Year[b]				
2008	2	6	11.8 (2.7 to 20.9)	.94
2009	3	10	7.9 (1.8 to 14.0)	.99
2010	1	1	20.0 (2.5 to 37.5)[c]	NA
2011	3	7	6.0 (0.6 to 11.4)	.91
2012	2	3	11.5 (−1.1 to 24.1)	.02
2013	3	4	7.8 (1.1 to 14.6)	.46
2014	1	1	17.6 (0.0 to 35.8)[c]	NA
2015	7	16	13.7 (9.1 to 18.2)	.73
2017	2	2	11.7 (0.8 to 22.5)	.28
2019	1	1	33.3 (13.2 to 53.5)[c]	NA
2020	1	2	33.1 (11.5 to 54.8)	.74
Approval pathway				
Expedited	9	15	7.6 (4.3 to 10.9)	.47
Standard	17	38	11.8 (8.9 to 14.8)	.76
Orphan drug				
Yes	7	11	15.9 (9.2 to 22.6)	.08
No	19	42	9.0 (6.6 to 11.5)	.94
Funding[d]				
Within US	14	26	14.1 (10.3 to 17.9)	.21
Outside US	12	27	8.0 (4.9 to 11.1)	.97
Disease indication				
ACS	3	3	9.0 (−0.5 to 18.5)	.20
AF	6	13	7.2 (3.6 to 10.8)	.84
HF	2	4	6.4 (−1.9 to 14.7)	.93
Hypertension	2	7	7.7 (0.7 to 14.7)	.99
Hypercholesterolemia	6	17	18.0 (12.5 to 23.6)	.84
PAH	3	4	10.9 (1.0 to 20.8)	.13
CHD	1	1	17.6 (0.0 to 35.8)[c]	NA
Other	3	4	20.6 (11.1 to 30.1)	.57
Women participants, %				
≥45	12	20	11.0 (6.9 to 15.1)	.86
<45	19	33	10.3 (7.4 to 13.1)	.33

Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; CHD, coronary heart disease; HF, heart failure; NA, not applicable; PAH, pulmonary arterial hypertension.

[a] Shows significance of heterogeneity of the observed pooled meta-analysis of proportions. The significantly increased heterogeneity in 2012 suggests that the proportion of women authors varied substantially across the 3 trial publications.

[b] Years 2016 and 2018 were not included because of a lack of approval of any novel cardiovascular drugs.

[c] Proportional meta-analysis could not be conducted because only 1 trial was available.

[d] Funding was recording as US-based industry or non–US-based industry depending on the location of the company headquarters from the industry sponsor's website.

Results

From 2008 to 2020, the FDA approved a total of 26 novel cardiovascular drugs, corresponding to 60 trials. Of these, 53 trial publications (235 331 participants) were included in this study (**Table 1**). One publication included the results of 2 trials, 1 publication included the results of 3 trials, and 4 trials were excluded because the corresponding publications could not be found. A total of 641 authors were screened, and 8 were excluded because of the inability to assign author gender. Genderize was used to identify the gender of 593 authors; 552 were further confirmed by checking personal pronouns. Of the 48 authors with a prediction probability estimate less than 90.0% on Genderize, author gender was identified for 40 by using personal pronouns listed in institutional profiles or other sources.

The median number of men and women authors of trial publications was 9 (IQR, 7-13) and 1 (IQR, 0-3), respectively. The overall proportion of women authors was 10.0% (95% CI, 7.8%-12.2%). The proportion of women as first and senior authors was 7.5% (95% CI, 0.4%-14.7%) and 11.3% (95% CI, 2.8%-19.9%), respectively. **Table 2** lists potential sources of heterogeneity according to different subgroups.

Discussion

The results of this cross-sectional study suggest that women comprised only 10.0% of authorship in pivotal efficacy trials of novel cardiovascular drugs approved by the FDA between 2008 and 2020, with similarly low representation as first and senior authors. Although these findings may be attributed to a lower proportion of women cardiologists, reasons for persistent gender disparities are multifactorial and may be attributed to decreased funding, fewer opportunities for multicenter collaborations, and fewer leadership roles.[5]

Previous studies have reported that women comprise 10.0% to 20.0% of authors in heart failure trials.[1,2] Although our results are consistent with these prior estimates, this study expands these findings across cardiovascular therapeutic areas and suggests marked gender disparities in authorship that extend to pivotal clinical trials for drug approval. The results of this study also suggest that the underrepresentation of women persists across 8 different cardiovascular indications (including acute coronary syndrome, atrial fibrillation, coronary heart disease, heart failure, hypertension, hypercholesterolemia, pulmonary arterial hypertension, and other indications), the majority of which have not previously been associated with reports of authorship disparity.

An increased focus on women as clinical trial leaders could improve the representativeness of women trial participants, attract more junior female investigators, and strengthen the quality of the research. Such attention toward women authorship may be particularly relevant to pivotal drug approval trials, given the potential direct effect on clinical practice and heightened importance of ensuring representative trial cohorts.

This study has some limitations. First, gender was only captured as binary, hence there could be error in identifying gender. Second, we were unable to record coauthorship among first and senior authors. Concerted efforts are required to increase the number of women in cardiovascular trial leadership by ensuring diversity while choosing site-based principal investigators, requiring diversity information when submitting a trial publication, and sponsoring female faculty to start serving as ad hoc members of trial committees.

ARTICLE INFORMATION

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Corresponding Author: Erin D. Michos, MD, MHS, Division of Cardiology, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Blalock 524-B, 600 N Wolfe St, Baltimore, MD 21287 (edonnell@jhmi.edu).

Author Affiliations: Department of Medicine, Ziauddin Medical University, Karachi, Pakistan (Shahid); Division of Cardiology, Duke University School of Medicine, Durham, North Carolina (M. S. Khan, Greene, Fudim); Department of Medicine, Dow University of Health Sciences, Karachi, Pakistan (Sohail); Department of Cardiology, Methodist DeBakey Heart and Vascular Center, Houston, Texas (S. U. Khan); Division of Cardiology, Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, Maryland (Michos).

Author Contributions: Dr Shahid had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Shahid, M.S. Khan, Fudim, Michos.

Acquisition, analysis, or interpretation of data: Shahid, M.S. Khan, Sohail, S.U. Khan, Greene, Michos.

Drafting of the manuscript: Shahid, Sohail.

Critical revision of the manuscript for important intellectual content: M.S. Khan, S.U. Khan, Greene, Fudim, Michos.

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Supervision: Shahid, M.S. Khan, Fudim, Michos.

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SUPPLEMENT.

eMethods.
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