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ORIGINAL RESEARCH

Sex- and Gender-Based Reporting in Antihypertensive Medication Literature Informing Hypertension Guidelines

Nabilah Gulamhusein, BSc; Keila Turino Miranda, MSc; Sandra M. Dumanski, MD, MSc; María Carlota González Bedat, MD; Ifeoma Ulasi, MBBS, MSc; Arvind Conjeevaram, MBBS; Sofia B. Ahmed, MD, MMSc

BACKGROUND: Hypertension is the leading modifiable cardiovascular risk factor with recognized sex- and gender-based differences. We assessed the incorporation of sex and gender reporting in the antihypertensive medication literature informing hypertension guidelines.

METHODS AND RESULTS: Literature cited in the International Society of Hypertension (2020), European Society of Cardiology/European Society of Hypertension (2018), American College of Cardiology/American Heart Association (2017), Latin American Society of Hypertension (2017), Pan-African Society of Cardiology (2020), and Hypertension Canada (2020) guidelines was systematically reviewed. Observational studies, randomized controlled trials, and systematic reviews involving antihypertensive medications were included. Studies with participants of a single sex, guidelines, and commentaries were excluded. Data on study participation-to-prevalence ratio by sex, analysis of baseline demographics and study outcomes by sex, and stratification of adverse events by sex were extracted. Of 1659 unique citations, 331 studies met inclusion criteria. Of those, 81% reported the sex of participants, and 22% reported a male-to-female participation-to-prevalence ratio of 0.8 to 1.2. Three percent of studies stratified baseline characteristics by sex, and 20% considered sex during analysis through statistical adjustment or stratification. Although 32% of studies reported adverse events, only 0.6% stratified adverse events by sex. Most (58%) studies reporting sex/gender used sex and gender terms interchangeably.

CONCLUSIONS: Incorporation of sex- and gender-based considerations in study population, analysis, or reporting of results and adverse events is not common in the antihypertensive medication literature informing international hypertension guidelines. Greater attention to sex- and gender-based factors in research is required to optimally inform management of hypertension.

Key Words: adverse events ■ gender ■ guidelines ■ hypertension ■ sex

Globally, hypertension is the leading modifiable risk factor for cardiovascular mortality in men and women.[1-4] Although the number of adults living with hypertension doubled between 1990 and 2019 to 1.3 billion, 4 of 5 individuals are not adequately treated.[5] Underscoring blood pressure control as 1 of the most important determinants of cardiovascular and kidney health, the World Health Organization has recently set a global target of a 25% relative reduction in the prevalence of increased blood pressure by 2025.[5]

However, despite increasingly recognized sex (biological) and gender (sociocultural) differences in the prevalence, cause, and control of hypertension as well as antihypertensive effects of interventions,[6,7] clinical recommendations for hypertension management endorse a 1-size-fits-all approach. We assessed the

Correspondence to: Sofia B. Ahmed, MD, MMSc, University of Alberta, 11-135 Clinical Sciences Bldg, 11220 83 Ave NW, Edmonton, Alberta, Canada T6G 2B7. Email: sofia.ahmed@albertahealthservices.ca

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CLINICAL PERSPECTIVE

What Is New?

- Approximately 1 in 5 antihypertensive medication studies informing hypertension guidelines do not incorporate any sex- and gender-based reporting or analysis.
- Fewer than 1 in 4 antihypertensive medication studies have appropriate sex-based representation in study participants, and sex-stratified analysis of results is not common.
- Sex-stratified adverse events are rarely reported.

What Are the Clinical Implications?

- Despite an emphasis on precision medicine and mandates from journals and funding agencies, antihypertensive medication studies informing hypertension guidelines rarely incorporate sex- and gender-based reporting and analysis.
- Greater attention to sex- and gender-based factors in research is required to optimally inform clinical practice and improve management of hypertension in all individuals.

Nonstandard Abbreviations and Acronyms

AE	adverse event
PPR	participation-to-prevalence ratio

incorporation of sex and gender reporting in the antihypertensive medication literature informing hypertension guidelines.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files. We systematically reviewed all literature cited in the International Society of Hypertension (2020),[8] Latin American Society of Hypertension (2017),[9] European Society of Cardiology/European Society of Hypertension (2018),[10] Pan-African Society of Cardiology (2020),[11] American College of Cardiology/American Heart Association (2017),[12] and Hypertension Canada (2020)[13] guidelines (Table S1). The terms sex and gender are not synonymous. However, recognizing these terms are often used interchangeably in studies, we assumed women to mean female sex and men to mean male sex. The inclusion criteria were observational studies, randomized controlled trials, and systematic reviews involving antihypertensive medications. The exclusion criteria were single-sex studies, guidelines, and commentaries (Table S2). Two reviewers (N.G. and K.T.M.) independently extracted data using a standardized data abstraction form, with data items including ratio of male-to-female participants, analysis of baseline demographics and study outcomes by sex, reporting of adverse events (AEs), and stratification of AEs by sex. Any event reported using terminology such as "adverse effects, side effects, adverse outcomes, or safety outcomes" was defined an "AE." The participation-to-prevalence ratio (PPR) is a measure of the representation of a specific group in the study population relative to the prevalence of the condition of interest in the same group. In the context of sex and hypertension, this metric can be calculated by dividing the proportion of men or women in the study population by the proportion of men or women, respectively, with hypertension in the general population,[14] which, given that the global prevalence of hypertension is roughly equal in men and women,[3,6,15] is 0.5. As a PPR approximating 1 suggests a representative study population composition, a PPR <0.8 and >1.2 indicates the underrepresentation and overrepresentation of male or female participants. Calculation of the PPR is an important metric in the development of sex-specific guidelines.[14,16] Institutional review board approval and informed consent were not required for this study as all data were publicly available.

RESULTS

Of 1659 unique articles cited in the 6 guidelines, 331 studies met inclusion criteria (Figure 1). Of the 331 studies that met the inclusion criteria, 267 (81%) reported the sex of participants (Table S3), with only 73 (22%) reporting a male-to-female PPR of 0.8 to 1.2, 140 (42%) with a PPR of >1.2 (overrepresentation of men), and 40 (12%) with a PPR of <0.8 (overrepresentation of women), whereas the PPR could not be determined for 14 studies (4%) (Figures 2 and 3). Baseline characteristics were stratified by sex in 11 studies (3%), and 67 (20%) considered sex in analysis through statistical adjustment (n=18 [5%]) or stratification (n=49 [15%]). Although 105 studies (32%) reported AEs, only 2 (0.6%) stratified AEs by sex. Of the 267 studies that reported the sex or gender of participants, 87 (33%) used sex-based terms (eg, male or female) to describe their participants, 24 (9%) studies used gender-based terms (eg, men or women), and 156 (58%) used sex- and gender-based terms interchangeably. No study reported how the sex or gender of participants was determined.[17]

DISCUSSION

Our key findings were as follows: (1) approximately 1 in 5 antihypertensive medication studies informing

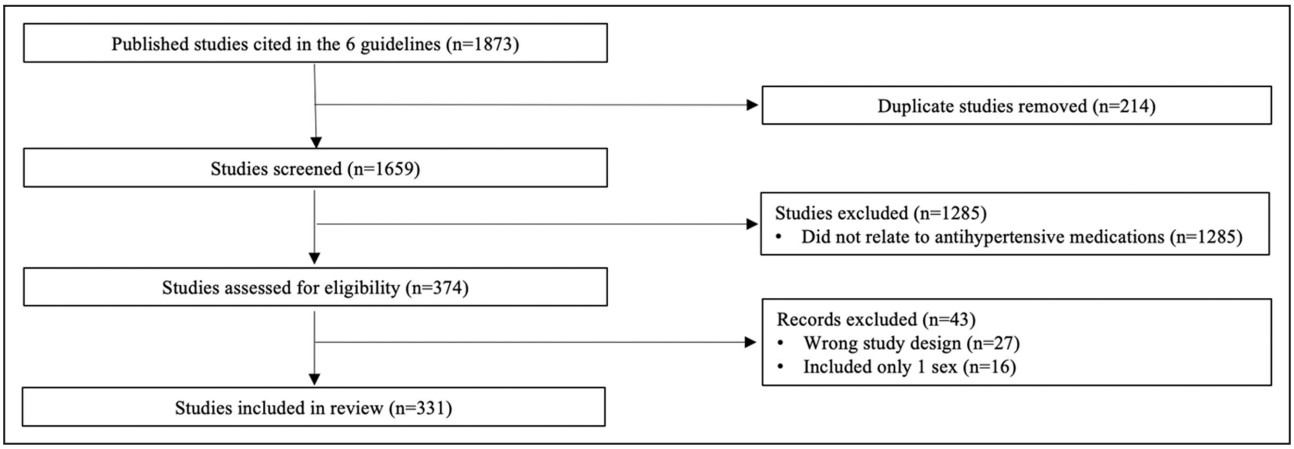

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

hypertension guidelines did not incorporate any sex- and gender-based reporting or analysis; (2) <1 in 4 studies had appropriate sex-based representation in study participants; (3) approximately15% of studies reported sex-stratified outcomes; (4) sex-stratified AEs were rarely reported; and (5) sex- and gender-based terminology was commonly used interchangeably. The results highlight that despite the increasing emphasis on precision health and personalized cardiovascular care,[18-22] few antihypertensive medication studies informing commonly used guidelines for hypertension management incorporated principles of sex- and gender-based analysis, including targeting a study PPR of 0.8 to 1.2, reporting baseline participant demographics by sex and gender, or analyzing or reporting study outcomes and AEs stratified by sex and gender.[23] These findings are concerning given the recognized sex and gender differences in the pathophysiology and cardiovascular and kidney risks of hypertension,[3,6,24-28] as well as access,[29,30] adherence,[31] and AEs[32-35] related to antihypertensive agents.[6]

The National Institutes of Health launched the Precision Medicine Initiative and instituted the Sex as a Biological Variable Policy in 2015[36,37]; and although the guidelines included in this review were published between 2017 and 2020, the design of this study does not capture more recently published research. However, a subanalysis of literature informing the guidelines published during or after 2015 demonstrated a similar pattern to our overall results (Figure S1). Our findings are

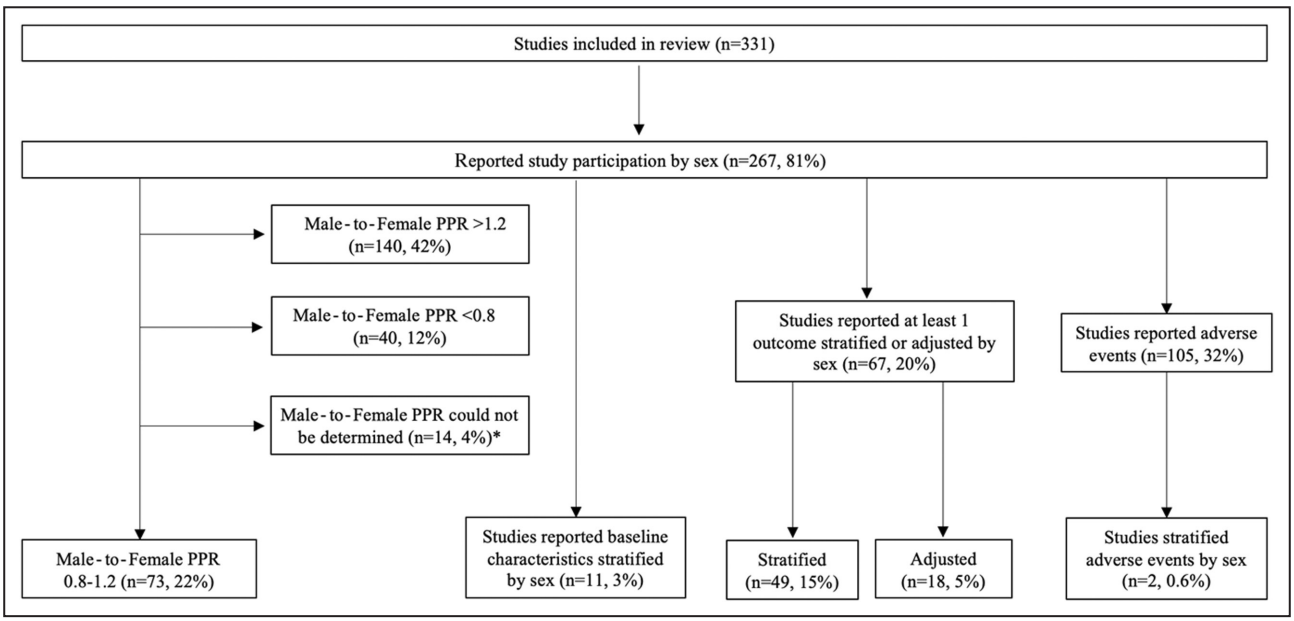

Figure 2. Flowchart of sex-based analysis and reporting in antihypertensive medication studies informing clinical hypertension guidelines.
*Studies that were systematic reviews. PPR indicates population-to-prevalence ratio.

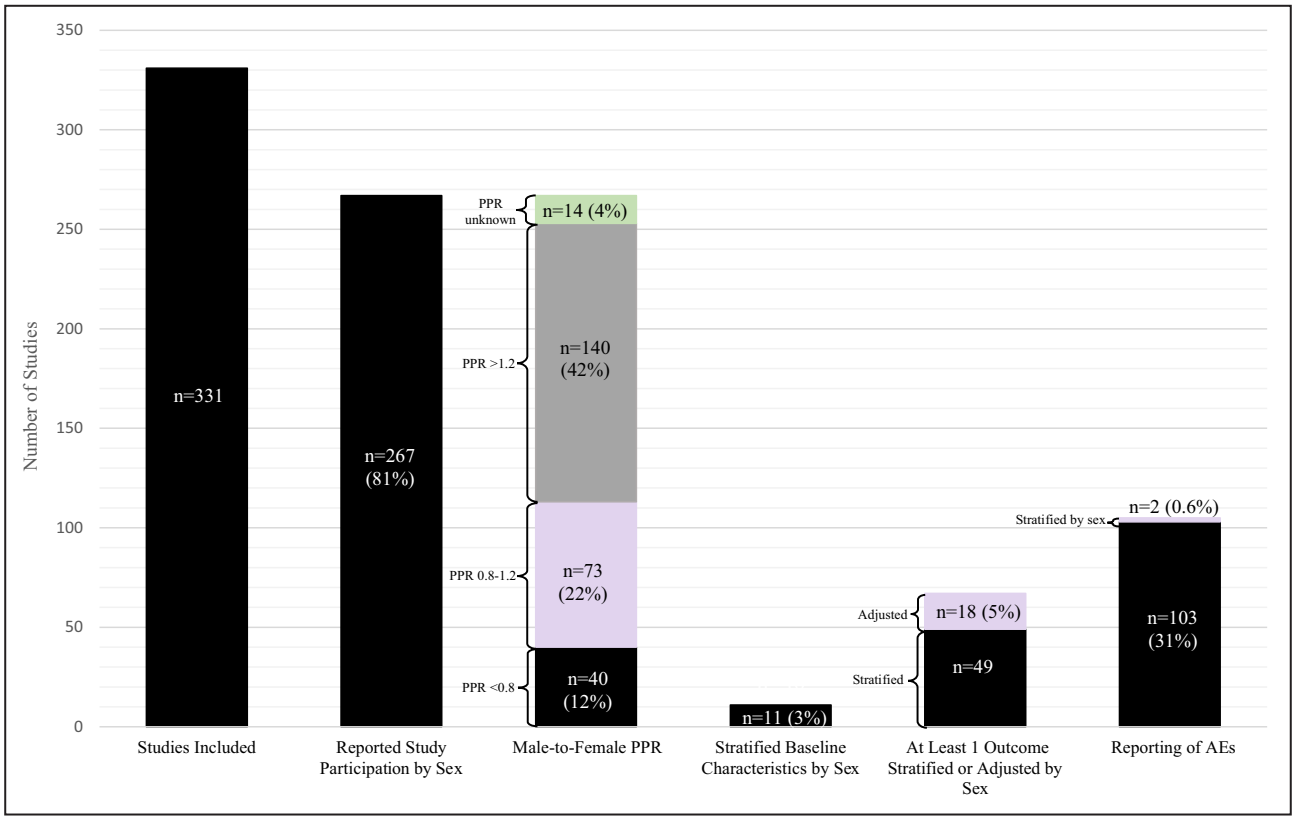

Figure 3. Bar chart displaying the number of studies looking at sex-based analysis and reporting in antihypertensive literature informing clinical hypertension guidelines.
AE indicates adverse event; and PPR, population-to-prevalence ratio.

also consistent with a recent scoping review of antihypertensive medication studies published between 1964 and 2020 that showed substantial underrepresentation of female participants in clinical trials, with only 3.7% of studies stratifying results by sex.[38] Our results are also in keeping with previous work highlighting the underrepresentation of women in cardiovascular and kidney trials.[14,38-41] Pharmacokinetics and pharmacodynamics of drugs differ by sex,[42] which may account for greater AEs and lower adherence in women compared with men using antihypertensive medications,[32-35] underscoring the importance of reporting sex-stratified AEs.

The incomplete reporting of sex and gender and an emphasis on sex rather than gender noted in this study have also been observed in other research settings.[43-45] Similar to our findings showing most studies used the terms sex and gender interchangeably, only 35% of Canadian clinical practice guidelines published between 2013 and 2015 for noncommunicable health conditions that included "sex" and/or "gender" used the terms correctly[46] according to the Sex and Gender Equity in Research guidelines.[47] This may partially reflect a lack of integration of sex, as a biological attribute, and gender, as a socially constructed identity, in health research reporting guidelines. In a systematic review of 407 reporting guidelines listed on the Equator Network registry and published between 1995 and 2018, only 1 reporting guideline met the criteria of the correct use of sex and gender concepts.[48]

The fact that no study reported both the sex *and* the gender of participants deserves mention. The assumption that sex assigned at birth always aligns with gender identity does not take into account the growing global transgender, gender-diverse, and nonbinary populations; moreover, these populations are impacted by disparities across a variety of cardiovascular risk factors compared with their cisgender peers.[49] Most research on hypertension in transgender or nonbinary adults has focused on the impact of gender-affirming hormone therapy on blood pressure, which to date has been overall inconclusive.[50,51] Application of frameworks[52,53] to improve incorporation of sex and gender considerations in blood pressure research has the potential to create new knowledge in the management of hypertension.

Our study provides evidence that literature informing guidelines for management of hypertension poorly incorporates sex and gender considerations in study design, analysis, and reporting despite mandates from funders,[36,54,55] journals,[47] and governments.[56-58] Structured frameworks exist to determine whether

sex-specific recommendations should be made in clinical guidelines.[23] However, research informing guidelines first needs to systematically incorporate sex- and gender-related considerations to achieve the goal of optimizing health outcomes for all.

ARTICLE INFORMATION

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Affiliations

Cumming School of Medicine (N.G., S.M.D., S.B.A.), and Libin Cardiovascular Institute (N.G., S.M.D.), University of Calgary, Calgary, Alberta, Canada; Department of Kinesiology and Physical Education, McGill University, Montreal, Quebec, Canada (K.T.M.); Alberta Kidney Disease Network, Calgary, Alberta, Canada (S.M.D., S.B.A.); O'Brien Institute for Public Health, Calgary, Alberta, Canada (S.M.D.); Uruguayan Dialysis Registry and Latin American Dialysis and Renal Transplantation Registry, Montevideo, Uruguay (M.C.G.B.); University of Nigeria, Nsukka, Enugu State, Nigeria (I.U.); The Bangalore, Sagar and Trustwell Hospitals, Bengaluru, Karnataka, India (A.C.); and Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada (S.B.A.).

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Disclosures

None.

Supplemental Material

Tables S1–S3
Figure S1

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