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Representation of Females in Atrial Fibrillation Clinical Practice Guidelines

Running Title:
Representation of Females in AF Guidelines

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Summary

Atrial fibrillation is one of the most common cardiac arrythmias which carries a significant risk of stroke and mortality. Various national and international guidelines have been developed aiming to provide evidence-based approaches to treatment. In this study, we investigated the literature that informed such recommendations and determined sex representation in such studies. By examining the 2020 Canadian AF guidelines as an example, we found that females are grossly underrepresented, especially in study designs which guide the strongest recommendations.

Abstract

Background: Atrial fibrillation (AF) is the most common arrhythmia in males and females worldwide, and its prevalence is increasing. Management of AF is guided by evidence-based clinical practice guidelines which provide recommendations based on available evidence. The extent of sex-specific data in the AF literature used to provide guideline recommendations has not been investigated. Therefore, using the 2020 Canadian Cardiovascular Society (CCS) Atrial Fibrillation Management Guidelines as example, the purpose of this study was to review female representation and the reporting of sex-disaggregated data in the studies referenced in AF guidelines.

Methods: Randomized controlled trials (RCTs), prospective and retrospective cohorts, were screened to calculate the proportion of study participants who were female and to establish whether studies provided sex disaggregated analyses. The participant prevalence ratio (PPR), a quotient of the female participant rate and the prevalence of females in the AF population, was calculated for each study.

Results: A total of 885 studies included in the CCS guidelines were considered. Of those, 467 met the inclusion criteria. Overall, females represented 39.1% of the population in all studies and RCTs had the lowest proportions of females (33.8%, PPR: 0.70). Of studies with sex-disaggregated analyses (n=140 (29.9%)), single centered RCTs, and retrospective cohorts had the lowest and highest rate of sex-specific analyses respectively (11.5% vs 32.5%).

Conclusion: The evidence used to derive guideline recommendations may be inadequate for sex-specific recommendations. Until enough data can support female specific guidelines, increased inclusion of females in AF studies, may aid in the precision of recommendations.

Word Count: 250

Introduction

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide. Recent studies and developments have demonstrated significant sex differences in etiology, manifestation, and outcome of CVD[1,2]. Atrial fibrillation (AF), the most common type of sustained arrhythmia, affects over 500,000 Canadians. The prevalence of AF is 1%-2% in the general population with a proportional increase in risk with aging[3,4]. Individuals diagnosed with AF are three to five times more likely to have ischemic stroke and increased morbidity burden and mortality as a result.

Like other cardiovascular diseases, sex differences have been reported in the outcomes of patients with AF. While the onset of AF is typically later in life, the severity of symptoms and likelihood of being undertreated is higher in females than in males[4]. Risk factors for AF also differ between males and females. For instance, while congestive heart failure and valvular disease are more important predictors of AF in females, hypertension and obesity play greater roles in disease manifestation amongst males.[2]

Despite a growing literature supporting or refuting sex differences in therapies for AF, published studies often fail to include a representative population or perform sex disaggregated analyses. As a result, the 2020 Canadian Cardiovascular Society (CCS) Atrial Fibrillation Management Guidelines[5], as other international guidelines[6,7], may be limited in providing recommendations that pertain to males and females[8].

Using the 2020 CCS Atrial Fibrillation Management Guidelines[5] as an example of a major guideline compendium, we investigated whether the evidence utilized for the formulation of guidelines included female participants and incorporated sex disaggregated analyses.

Methods

A comprehensive review of all cited studies by the expert panel of the 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines[5] for the Management of Atrial Fibrillation was performed. We screened and evaluated each study for representation of females, sex-disaggregated reporting and testing of sex differences for the main outcomes.

Inclusion and Exclusion Criteria

The inclusion criteria comprised of randomized controlled trials (RCTs), prospective and retrospective cohorts, surveys, and registries investigating clinical risk factors, treatment and outcomes of AF and its various complications. Systematic or narrative reviews, letter to editors or editorials, basic molecular and cell biology studies, as well as various case series were excluded.

Data Extraction

Using a previously published methodology [9], we extracted the study design, sample size, percentage of females included, and testing of a treatment/intervention (if applicable). Furthermore, we evaluated the methods and results sections for any sex disaggregated analyses and/or outcome reporting. For studies that reported differences between males and females, the findings were evaluated to determine if the evidence supported conclusions for both sexes and whether sex differences were highlighted.

"This implies that studies in which authors observed differences (be it clinical or statistical) between males and females and did not reflect on such difference in the final conclusions were not applicable to females."

The average proportion of females in all studies and the proportion of studies reporting sex disaggregated analyses were computed. The participation to prevalence ratio (PPR), a value determining the degree of sex-specific representation in each study relative to the population prevalence of females with AF was utilized to assess female representation in each study. This value is the quotient of percent females in a study and the proportion of females with AF in the Canadian population which has been previously reported at 48% [9,10]. A PPR value PPR≤ 0.9 or PPR≥1.1 reflects under or over representation of females respectively relative to the disease in the population[9,11].

Results

Representation of Females

Of 885 studies included in the 2020 CCS Guidelines for AF management, 467 met the inclusion criteria including: 100 (21.4%) multicenter RCTs; 26 (5.5%) single-center RCTs; 26 (5.5%) sub-study RCTs; 103 (22.1%) prospective cohorts; 175 (37.5%) retrospective cohort; 34 (7.3%) registries; and 3 (0.6%) surveys (**Figure 1**).

Overall, females made up 39.1% of the population across studies (RCTs: 33.8%, prospective cohorts: 42.9%, retrospective cohorts: 40.4%, registries: 44.6%, and surveys: 47.2%) Retrospective studies had the highest proportion of females (37.4%) followed by RCTs (33.4%) and prospective studies (22.1%).

The PPR revealed underrepresentation of females in all study types except for registries and surveys (RCT: 0.70, prospective cohorts: 0.89, retrospective studies: 0.84, registries: 0.93, and surveys: 0.98) (Table 1). The RCTs, specifically single center studies, were the least representative of females amongst the studies investigated (PPR:0.67). (Table 1)

Consideration of Sex Differences

Of all studies reviewed, 30% reported sex-disaggregated results, including Forest plots, or text within the results section, with observed sex differences in the main study outcome. Registries (33.3%) and retrospective (33.1%) cohorts had the highest proportion of studies that performed sex disaggregated analyses, while RCTs fared the poorest with just over a quarter of studies undertaking sex disaggregated analyses (25.6%).

Within RCTs, multicenter RCTs had the highest percentage of reporting on sex disaggregated results as compared with single-center RCTs (32.0% vs 11%). Considering the conclusions drawn by these studies, overall findings were reported as applicable to both sexes.

Amongst studies that reported sex-disaggregated results, a total of 126 (26.9%) studies had conclusions which were applicable to both males and females. Within each study category, findings from retrospective cohorts were most generalizable to both sexes, while the conclusions for RCTs were less likely to be generalizable to both sexes (31.4% vs 23%). (Table 2)

Discussion

The purpose of the current study was to utilize the 2020 CCS AF guidelines as a framework to evaluate the integration and reporting of sex-specific data in the development of clinical practice guidelines. Sex-specific evidence and recommendations are a very much unmet need, though we acknowledge that some guidelines committees including the European Society of Cardiology are starting to address the issue much more is needed. Among the evidence guiding the 2020 CCS AF guidelines, an underrepresentation of females in clinical studies across the spectrum of AF management emerged, particularly for RCTs and prospective cohort studies.

It is important to note that the low representation of females in the studies used for guideline development relates to the low enrolment of females in various trials rather than study selection by the Guidelines. Since the publication of these guidelines, there have been several studies which follow similarly low inclusion of females as the studies cited in the guidelines. For instance, CIRCA-DOSE trial consisted of nearly 70.6% male participants[12]. This study published a female sex specific analysis to assess the outcomes in females[13]. As such higher female enrolment in clinical trials may be the most effective path forward.

A low PPR was observed in conjunction with the lack of sex disaggregated analyses in most studies. It is important to note that PPR value is dependent on the prevalence of females in the population with the disease and hence may differ based on variable sources reporting prevalence of females in AF population. Surprisingly, very few data exist on atrial fibrillation prevalence in the population in males and females.

There are number of possible factors that contribute to lower enrolment of females in clinical trials of atrial fibrillation. One such factor may be the later onset of atrial fibrillation in

females compared to males, Indeed, the mean age of atrial fibrillation has been reported to be 66.8 years in males and 74.6 years in females[14]

Indeed, of the 152 RCTs and their sub-studies, only a quarter of the RCTs presented either a sensitivity analysis by sex or demonstrated sex-specific results. This observation is concerning given that these trials are considered gold-standard for recommendations, and typically guide healthcare professionals' medical practice. Such a phenomenon, in conjunction with underrepresentation of females in most studies, results in conclusions and recommendations that may not apply to females and is of particular importance given sex differences in risk, diagnosis, and prognosis of AF [4]. Consequently, larger sample sizes with higher proportion of females ideally closer to population prevalence with adequate statistical power to make definitive conclusions, along with sex disaggregated analyses, might mitigate sex-disparity and male-oriented recommendations in guidelines.

Sex differences in Atrial Fibrillation

Though the exact mechanism and etiology of AF is still poorly understood, previous studies have shown significant differences in symptomatology, pathophysiology, risk factors, and outcome between males and females suffering from this arrythmia. Specifically, males have a 50% higher chance of developing AF after adjusting for age and other comorbidities[15]. Similarly, age-adjusted prevalence of AF is typically higher in males compared to females (10.3% vs 7.4%)[16]. The risk factor profile for disease manifestation also differs between males and females[17]. While valvular heart disease, and congestive heart failure are important risk factors for AF in females, coronary artery disease, and chronic obstructive pulmonary disease play a more significant role in disease development in males[4,15,18–21]. In addition, there are number of pathophysiological

characteristics in AF manifestation mechanism which differ between males and females. For instance, estrogen and progesterone impact conduction delay and duration of action potential respectively[22–25]. The exact mechanism of action has been previously discussed in detail, but briefly, estrogen has been shown to prolong atrial and atrioventricular nodal conduction time and effective refractory period[2,4,23], while progesterone lengthens action potential duration[2,4]. In addition to the role that estrogen plays on action potential duration, it has a significant effect on atrial effective refractory period by downregulating cardiac potassium channels which further protect against atrial fibrillation onset[4]. The cumulative effects of estrogen and progesterone on cardiac electrophysiology increase the likelihood of circuit re-entry and atrial fibrillation onset in females. Furthermore, studies have demonstrated female sex to be more commonly associated with non-pulmonary vein originating foci for AF[26,27]. Such phenomenon may be partially responsible for sex differences observed in AF catheter ablation outcomes[28].

A study be Grecu et al investigating the differences between males and females in catheter ablation of AF concluded that females suffering from the disease are likely to have more significant comorbidities including obesity, diabetes mellitus and hypertension and they are typically older[29]. At the same time, a population level study conducted by Samuel et al. demonstrated that females were much less likely to undergo catheter ablation compared to males[30]. Though females have a lower incidence of AF compared to their male counterparts, they typically have more severe symptoms upon onset and are less likely to have asymptomatic AF[31,32]. Additionally females are more likely to present with "atypical" symptoms including weakness, dyspnea, and anxiety[33]. Since females are more likely to exhibit symptoms secondary to AF, quality of life measures report poorer outcomes for females compared to males[34], which can result in higher degree of depression and anxiety in this population[35].

Perhaps the most striking sex differences observed in patients with AF concern treatment and management. A study by Tsadok, et al investigating the risk of stroke in patients over the age of 65 with new onset of AF concluded that females are at significantly higher risk of having stroke than males[3]. Other large studies including the Framingham and Copenhagen heart studies have confirmed this finding by estimating that females are at 92% and 260% increased risk of thromboembolic event compared to males respectively [36–38]. While such risk is well studied, females with indication for oral anticoagulation (OAC) therapy are still significantly less likely to be treated with OAC compared to their male counterparts[39–41]. In other words, female are either not prescribed anticoagulation, and are rather treated with antiplatelet therapy, or for those who are anticoagulated, they may not be on the target dose, or be receiving proper regimen[41]. In fact, a recent study by Thompson et al. investigating the sex differences in use of OAC agents in AF using the cardiovascular registry found that women are much less likely to be properly anticoagulated at all levels of CHA_2DS_2- VASc score[42].

Similar trends are observed when comparing cardioversion, and catheter ablation therapies. Females are consistently less likely to undergo pulmonary vein antrum isolation, or be cardioverted back to sinus rhythm, compared to males[43–45]. Following catheter ablation risk of recurrence and complications are more pronounced for females[43,46,47]. Finally, studies have suggested that females are at a 12% increased risk of overall mortality compared to males, after taking into consideration age, and other comorbidities[48]. Therefore, there are numerous significant differences between sexes, from pathophysiology, diagnosis, to treatment and outcome. As we move towards a more precise model of medical practice and individualized care, it is imperative for investigators and practitioners to consider sex differences in study design and treatment regimens[49].

Clinical Significance and Future Directions

The underrepresentation of females in the AF studies supporting the recommendations of major society guidelines which aim to provide a framework for AF treatment, introduces numerous challenges for practitioners. By basing clinical guidelines on the outcomes of studies for which males are the predominant participants, the clinical and physiological variations that exist between sexes are often neglected. As a result of such omissions, prognosis for females may not be as favorable as their male counterparts as the treatment regimen may not be ideally curated. Such deficiencies might be the underlying cause for increased risk of stroke in females with AF, and worse prognosis amongst those with stroke. Furthermore, while some studies did incorporate sex-specific analyses and did not identify sex differences, there is evidence that these results may have been due to a lack of power and warrant further investigation. Until enough of females are enrolled in clinical trials with sufficient sample sizes, sex disaggregated data may provide some indication and guidance for sex-specific treatment regimens.

To address this gap in care, guideline recommendations must assess sex differences of the evidence used to create clinical practice guidelines. Such a paradigm shift will require concurrent efforts to increase the enrolment of females in clinical trials and consistent sex disaggregated analyses and results. Though we acknowledge that the evidence currently available to form recommendations is limited in sex-specific data, it may be beneficial to address such issue in "Gap in Knowledge" section of guidelines. Though data obtained from each study was not correlated to its corresponding component of the guidelines, the proportion of females included was relatively consistent throughout the various components. As modern frameworks of medicine strive to implement a more inclusive approach to treatment aimed at providing evidenced base precision

health care, implementing such changes may well be the first step in particularly in patients with AF.

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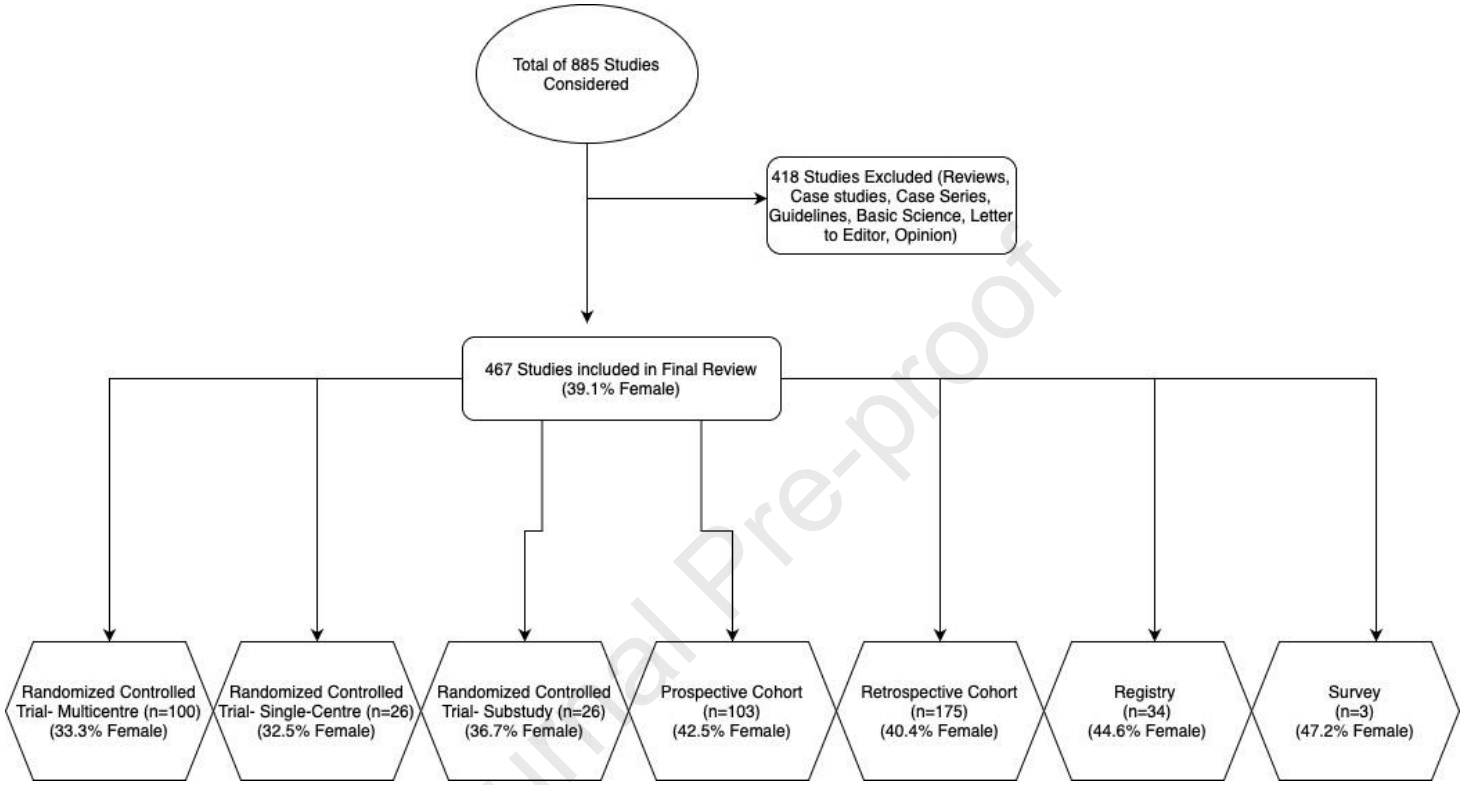

Figure 1: Flowchart diagram of studies included in the review

Tables:

Table 1: Representation of Females in the Studies Referred by 2020 CCS AF Guidelines

Type of study	Studies in the guidelines N (%)	Studies with sex data N (%)	% Female Proportions Mean (SD)	Participation to Prevalence Ratio Mean (SD) (prevalence 48%)
All	467(100)	140 (29.9)	39.1 (13.9)	0.81 (0.28)
RCT – All	156 (33.4)	39 (27.8)	33.8 (10.9)	0.70 (0.23)
Multicenter	100 (21)	32 (32)	33.3 (10.6)	0.69 (0.22)
Single Center	26 (5.56)	3 (11.5)	32.5 (14.1)	0.67 (0.29)
Sub-analysis	26 (5.56)	4 (15.3)	36.7 (16.6)	0.76 (0.35)
Prospective Cohort	103 (22.1)	32 (31.1)	42.9 (13.7)	0.89 (0.28)
Retrospective Cohort	175 (37.4)	57 (32.5)	40.4 (14.8)	0.84 (0.31)
Registry	34 (7.28)	8 (23.5)	44.6 (8.3)	0.93 (0.17)
Survey	3 (1.1)	1 (33.3)	47.2 (3.1)	0.98 (0.1)

Table 2: Sex Disaggregated Analyses by Study Type

Type of study	Number of Studies	Proportion of females	Forest Plots /Text include sex	Conclusions generalizable to both women and men?
All n (%)	467(100)	39.1 (13.9)	140 (30)	126 (26.9)
RCT – All	152 (32.5)	33.8 (10.9)	39 (25.6)	35 (23)
Multicentre	100 (21)	33.3 (10.6)	32 (32)	27 (27)
Single Center	26 (5.6)	32.5 (14.1)	3 (11.5)	2 (7.6)
Sub-analysis	26 (5.56)	36.7 (16.6)	4 (15.3)	4 (15.3)
Prospective Cohort	103 (22.1)	42.9 (13.7)	33 (32)	30 (29.1)
Retrospective Cohort	175 (37.4)	40.4 (14.8)	58 (33.1)	55 (31.4)
Registry	34 (7.3)	44.6 (8.3)	9 (26.4)	7 (20.5)
Survey	3 (1.1)	47.2 (3.1)	1 (33.3)	1 (33.3)