

Representation of women in cardiovascular disease management: a systematic analysis of ESC guidelines

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ABSTRACT

Objective Sex differences play a critical role in the presentation, progression and treatment outcomes of cardiac diseases. However, historical male predominance in clinical studies has led to disparities in evidence supporting care for both sexes. Clinical guidelines are essential for cardiovascular care, shaping practice and influencing patient outcomes. In this study, we reviewed 34 European Society of Cardiology (ESC) guidelines between 2002 and 2024 to evaluate the representation of women and the inclusion of female-specific recommendations.

Methods We compiled 136 gender-related keywords, validated by six clinicians, and quantified their occurrence across guidelines. While our primary analysis focused on female-specific keywords, we also identified male-specific terms as a comparison point to help quantitatively interpret the representation of female-specific terminology in the guidelines. Each guideline underwent independent review by two auditors who used structured questions to assess its sensitivity to female-specific differences in disease presentation, diagnosis, management and treatment.

Results The most frequent terms were ‘pregnancy’, ‘women’ and ‘sex’, with 1768 (17.9%), 1573 (15.9%) and 676 (6.8%) overall repetitions, respectively, contrasted against ‘cardiac’ (6932 occurrences) as a baseline. Results showed inconsistency in addressing female-specific factors and health considerations in ESC guidelines. We were able to assess the relative frequency of female-specific language and highlight in contrast areas where female representation in cardiovascular guidelines may be insufficient. Most guidelines (24/34) mentioned pregnancy and provided related recommendations, with one of the guidelines entirely dedicated to cardiovascular disease (CVD) in pregnancy (2018) and a new one planned for 2025. Only 10/30 guidelines acknowledged menopause as a CVD risk factor and offered recommendations for clinical practice.

Conclusions These findings highlight the need for systematic integration of female-specific considerations across all guidelines. In the wider context, there is also a need for improved representation of women in clinical trials and for making the available evidence on which the guidelines are based less biased toward men.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Cardiovascular disease research and clinical guidelines have historically been male-dominated, leading to disparities in evidence-based care for women.
- ⇒ Sex differences significantly impact disease presentation, risk factors, treatment responses and outcomes, yet these differences are not consistently incorporated into clinical guidelines.

WHAT THIS STUDY ADDS

- ⇒ A systematic review of 34 ESC (European Society of Cardiology) guidelines from 2002 to 2024 highlights inconsistencies in the integration of sex-specific recommendations.
- ⇒ While pregnancy is frequently addressed, menopause is largely overlooked, despite its significant impact on cardiovascular risk.
- ⇒ There is a critical need for systematic inclusion of sex-specific considerations in future guidelines to ensure equitable cardiovascular care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This study calls for more inclusive cardiovascular guidelines, highlighting gaps in addressing female-specific health issues, to ensure more equitable healthcare for women.

INTRODUCTION

Robust sex-specific evidence forms the ground floor of personalised medicine, providing the essential baseline for truly individualised cardiovascular prevention and treatment. Inclusive and comprehensive clinical guidelines have become a crucial priority within the medical community. These essential guidelines inform clinical practice, guide healthcare professionals in decision-making and ultimately influence patient outcomes. A critical area of examination is how these

guidelines may address sex and gender differences and consider women's unique healthcare needs (In line with the Royal College of Obstetricians and Gynaecologists, we use the terms 'women' and 'maternal' throughout this article to refer to people who may give birth and be pregnant. However, we recognise that research, policy and practice must be inclusive and sensitive to the rights of all birthing people, regardless of birth-assigned sex.¹). While our primary focus is on sex-specific factors, we recognise that gender, encompassing sociocultural influences, also plays a role in shaping healthcare access and outcomes. Later, in the Discussion section, we explore how both sex and gender considerations are relevant in clinical practice and future guideline development.

Sex and gender differences significantly impact the presentation, progression and treatment outcomes of many cardiovascular diseases (CVDs). Historically, CVD medical research and subsequent guidelines have predominantly focused on male populations, resulting in sex bias in evidence-based recommendations. Significant gaps have been identified in the inclusion of women in cardiovascular clinical trials, leading to less robust evidence to inform inclusive guidelines.² Critically, studies have shown that women present with different symptoms, have sex-specific risk factors and may respond differently to treatment as compared with men.³ With a lack of evidence for the latter, however, care must assume that treatment beneficial to men will also benefit female patients, unless proven otherwise. Failure to do so can lead to the underuse of drugs on the basis of sex, such as statins in women.⁴ There is also an inherent misconception that CVD is a 'male disease' leading to underdiagnosis, under treatment and delayed treatment of CVD in women.⁵ Sex-specific research and subsequent guideline adjustment is essential for advancing health equity and ensuring that all patients receive the highest standard of care.

Several studies underscore the importance of incorporating sex-specific data into clinical guidelines. Bairey Merz *et al*⁶ discuss the unique aspects of acute myocardial infarction (MI) and ischaemic heart conditions in women. A later study by Shah *et al*⁷ found that sex-specific troponin thresholds doubled the diagnosis of MI in women, emphasising the criticality of sex-sensitive approaches. Garcia *et al*⁸ highlight the differential impact of cardiovascular risk factors, such as hypertension and diabetes, in women as compared with men. Mosca *et al*⁹ comprehensively review sex differences in CVD prevention, advocating for research focused on women and the inclusion of findings in clinical practice guidelines. Wenger *et al*¹⁰ discuss how cardiovascular risks, particularly hypertension, vary across a woman's life cycle, from teenage years to pregnancy and menopause. Considering sex-based physiology is key: risk, prognosis and care profiles may change drastically over time. Möller-Leimkühler¹¹ noted depression as both a cause and a consequence of CVD with higher prevalence in women. Higher rates of mortality associated with this comorbidity

disproportionately affect women. These studies all highlight the need for guidelines to reflect differences in the presentation, prevention, diagnosis and treatment of CVDs in women.

Research shows that life context (social health determinants, life stage-specific risks and short- and long-term hormone cycles) must be considered to develop more effective care strategies for women. Female sex hormones, predominantly progesterone and oestrogen, fluctuate with reproductive age and significantly during the menstrual cycle. It is known that these hormone fluctuations affect the density and function of cardiomyocyte ion channels.¹² The downstream consequence is that hormone interactions alter the heart's electrical activity and may potentially increase the risk of arrhythmias and the pathophysiology of MI and heart failure in women.^{12 13} Other studies have examined cardiovascular risk in transgender people undergoing hormone therapy,¹⁴ the cardiovascular effects of contraception,¹⁵ and the impact of oestrogen on vascular disease.¹⁶

CVD risk has also been associated with the timing of reproductive milestones and gynaecological conditions in women. Pre-eclampsia during pregnancy is associated with a twofold to fourfold increase in the long-term risk of CVD, including heart failure, coronary artery disease, hypertension and stroke.^{17 18} This risk is raised in the first year post partum and remains elevated throughout women's lifetime. Early-onset and late-onset menopause, premature menarche and irregular menstrual cycles are all associated with increased CVD risk.^{5 17 18} Wayne and Mukherjee¹⁹ reported that the mortality risk of coronary heart disease increases post-menopause.

Female sex hormones affect heart physiology and pathophysiology. A relative scarcity of studies emphasises the critical need for additional data so that female life context, including reproductive history, can be included in CVD risk evaluation. While some guidelines for CVD prevention in women have also been updated to reflect these nuances,²⁰ this is not always the case. For example, despite robust evidence linking pre-eclampsia to adverse outcomes, this condition has yet to be incorporated into risk stratification models or CVD guidelines, unlike non-sex specific factors (eg, smoking or hyperlipidaemia). Other pregnancy-related conditions (ie, gestational diabetes and gestational hypertension) are also associated with increased long-term cardiometabolic risk, but they are similarly absent from current guidance. Translation of these existing data to guidelines for CVD diagnosis and treatment may lead to better prevention and management strategies for women at risk.

Women are also under-represented in cardiology leadership roles, the authorship of guidelines and the research on which recommendations are made.^{21 22} The importance of women's representation in this context was highlighted by Bastian-Pétreil *et al*,²¹ who found that having a female first or last author was significantly correlated with more women study participants. The systemic imbalance in female representation from leadership

and key investigators to study participants is recognised as an ongoing issue, with steps taken to address bias. Between 2020 and 2022, the European Society of Cardiology (ESC) developed a gender policy to align with the European Institute for Gender Equality, aiming to boost female representation and to integrate gender-specific medicine in all ESC publications, including guidelines. However, ESC guidelines still do not wholly account for this mandate.²³

Assessing the scope of the challenge is the first step towards addressing the lack of sex equality in CVD guidelines. We aim to provide an in-depth systematic analysis of 34 ESC clinical guidelines issued between 2002 and 2024, widely used and highly influential in shaping cardiovascular care across Europe and beyond. We evaluate these guidelines across multiple dimensions, including variations in terminology, awareness of sex differences, use of inclusive language, context of mentions, sensitivity to different life stages and conditions (eg, menopause and pregnancy), practical implications for healthcare practitioners and suggestions for future research. Through this comprehensive evaluation, we aim to provide actionable insights to inform the development of more inclusive clinical guidelines for CVD diagnosis, prevention and treatment. We hope to contribute to the ongoing efforts to enhance the quality of healthcare delivery and promote better outcomes for all individuals, independent of sex or gender. The ultimate objective is to ensure that CVD guidelines are reflective of the latest evidence, inclusive of all patient populations and capable of guiding clinicians in providing equitable and effective care.

METHODS

This study conducted a detailed audit of ESC guidelines to assess how well these incorporate female-specific factors in prevention, diagnosis, management and treatment of CVD. Our approach combined both qualitative and quantitative methods to ensure a comprehensive review. First, we selected 34 ESC clinical practice guidelines released between 2002 and 2024 (table 1) relevant to CVDs team of auditors, SSL, AWCL, TMGB, RKB, CPS, CR, MMM and MS, all of whom are researchers with expertise in cardiovascular medicine and engineering.

To guide the review process (figure 1), we compiled an initial list of gender-related keywords based on a literature review of sex-specific and gender-specific terms relevant to cardiovascular health. This draft list included terms related to physiological differences, disease prevalence, risk factors, diagnostic criteria, treatment protocols and life stage conditions, such as pregnancy and menopause. The list was then reviewed and validated by six clinicians with expertise in cardiology, reproductive endocrinology and obstetric medicine (UT, AdM, NP, CW, CB-L and KH). Based on their feedback, several additions were made (eg, 'Turner syndrome', 'amenorrhea') and potentially ambiguous or non-specific terms were removed (eg, 'cycle', 'period') to reduce false positives. Some

Table 1 List of reviewed guidelines

No.	Guideline	Year	Reference
Cardiovascular diseases			
1	Aortic diseases	2014	Erbel <i>et al</i> ⁸⁰
2	Pericardial diseases	2015	Adler <i>et al</i> ⁸⁵
3	Peripheral arterial disease	2017	Aboyans <i>et al</i> ⁸⁷
4	Arterial hypertension	2018	Williams <i>et al</i> ⁸⁴
5	Fourth universal definition of myocardial infarction	2018	Thygesen <i>et al</i> ⁶¹
6	Chronic coronary syndromes	2019	Knuuti <i>et al</i> ⁸⁴
7	Acute pulmonary embolism	2019	Kostantinides <i>et al</i> ⁶²
8	Valvular heart disease	2021	Vahanian <i>et al</i> ⁸⁷
9	Heart failure	2021	McDonagh <i>et al</i> ⁸⁵
10	Pulmonary hypertension	2022	Humbert <i>et al</i> ⁸¹
11	Endocarditis	2023	Delgado <i>et al</i> ⁸⁹
12	Acute coronary syndrome	2023	Byrne <i>et al</i> ⁸³
13	Focused update on heart failure	2023	McDonagh <i>et al</i> ⁸⁴
14	Elevated blood pressure and hypertension	2024	McEvoy J <i>et al</i> ⁸²
15	Peripheral arterial and aortic diseases	2024	Lucia Mazzolai <i>et al</i> ⁴²
16	Updated chronic coronary syndromes	2024	Vrints <i>et al</i> ⁴³
Arrhythmias			
17	Syncope	2018	Brignole <i>et al</i> ²⁸
18	Supraventricular tachycardia	2019	Brugada <i>et al</i> ⁴⁰
19	Atrial fibrillation	2020	Hindricks <i>et al</i> ⁶⁵
20	Ventricular arrhythmia and the prevention of sudden cardiac death	2022	Zeppenfeld <i>et al</i> ⁶⁶
21	Updated atrial fibrillation	2024	Gelder <i>et al</i> ⁴¹
Congenital diseases			
22	Adult congenital heart disease	2020	Baumgartner <i>et al</i> ⁸⁸
23	Cardiomyopathies	2023	Arbelo <i>et al</i> ⁶⁷
Comorbidities			
24	Dyslipidaemias	2019	Mach <i>et al</i> ⁸⁶
25	Cardio-oncology	2022	Lyon <i>et al</i> ⁶⁸
26	CVD and diabetes	2023	Cosentino <i>et al</i> ⁶⁹
Prevention, management and treatment of cardiovascular diseases			
27	The role of endomyocardial biopsy in the management of CVD	2007	Cooper <i>et al</i> ²⁶
28	Myocardial revascularisation	2018	Neumann <i>et al</i> ⁷⁰

Continued

Table 1 Continued

No.	Guideline	Year	Reference
29	Cardiac pacing and cardiac resynchronisation therapy	2021	Glikson <i>et al</i> ⁶⁶
30	CVD prevention in clinical practice	2021	Visseren <i>et al</i> ³³
31	Patients undergoing non-cardiac surgery	2022	Halvorsen <i>et al</i> ⁷¹
Special conditions			
32	Neonatal ECG	2002	Schwartz <i>et al</i> ⁷²
33	Cardiovascular diseases during pregnancy	2018	Regitz-Zagrosek <i>et al</i> ²⁹
34	Sports cardiology and exercise in patients with cardiovascular disease	2020	Pelliccia <i>et al</i> ⁷³

CVD, cardiovascular disease.

context-sensitive but clinically important terms (eg, ‘post-partum’, ‘hormone’) were retained, with instructions to reviewers to manually disregard unrelated mentions during qualitative review. This process enhanced both the clinical specificity and contextual accuracy of the keyword analysis. We automatically highlighted these keywords within the guidelines using pymupdf and pandas python libraries to make it easier for the auditors to spot and assess the presence and context of gender-specific information. Alongside the highlighted guidelines, we provided lists with preliminary keyword counts for each guideline (online supplemental material 1) to offer a quantitative snapshot that supported the qualitative analysis. In addition, the occurrences of gender-neutral keyword ‘cardiac’ were similarly calculated in the guidelines to provide a reference to the relative frequency of the sex/gender-related keywords.

To gather detailed qualitative insights, auditors responded to a series of structured questions (see online supplemental material 2) designed to elicit comprehensive analyses of the guidelines across a broad range of

gender-related aspects. These included topics such as disease presentation, diagnosis, management and treatment, as well as consideration of different life stages (eg, menopause) and special conditions (eg, pregnancy), with the goal of highlighting implications and actionable guidance for healthcare practitioners. Auditors consolidated their responses to subsections into coherent paragraphs, ensuring thorough and reflective evaluations of each guideline’s strengths and areas needing improvement regarding sex-specific considerations. In addition, they categorised the information provided by each guideline on these topics as ‘detailed information’, ‘generic information’, ‘no mention or recommendations’ or ‘has recommendations’ (see online supplemental material 4).

Although we provided highlighted keywords and auto-counted data to assist the auditors, they were not required to verify every individual count. Instead, the primary focus of the review was on evaluating the depth and clinical relevance of how sex-related and gender-related topics were addressed in each guideline. The keyword lists served as a guide, but reviewers concentrated on the extent and substance of content related to these topics, rather than performing a systematic check of term presence. Therefore, a count of zero in the summary tables indicates that the term was not extensively or meaningfully discussed in the guideline, rather than confirming its absolute absence. Moreover, to ensure the accuracy and reliability of our findings, each guideline was reviewed twice, independently by two assigned auditors. This double-review process helped to identify any discrepancies and ensure a robust and unbiased evaluation of the guidelines. Any discrepancies between reviewers were resolved through consensus discussion.

RESULTS

Our analysis of 34 ESC guidelines revealed varying degrees of attention to female-specific factors in the diagnosis, management and treatment of CVDs. To assess this, we examined the frequency of gender-related keywords (figure 2; online supplemental material 1). The three most frequent terms were ‘pregnancy’ (1768 mentions,

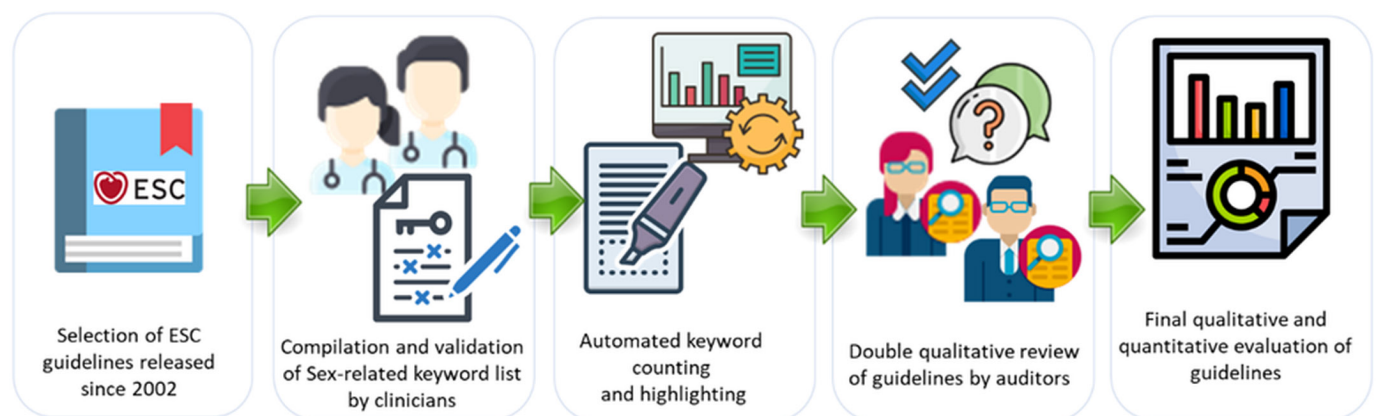


Figure 1 Workflow illustrating our systematic review of ESC guidelines, from guideline selection to the consolidation of findings. ESC, European Society of Cardiology.

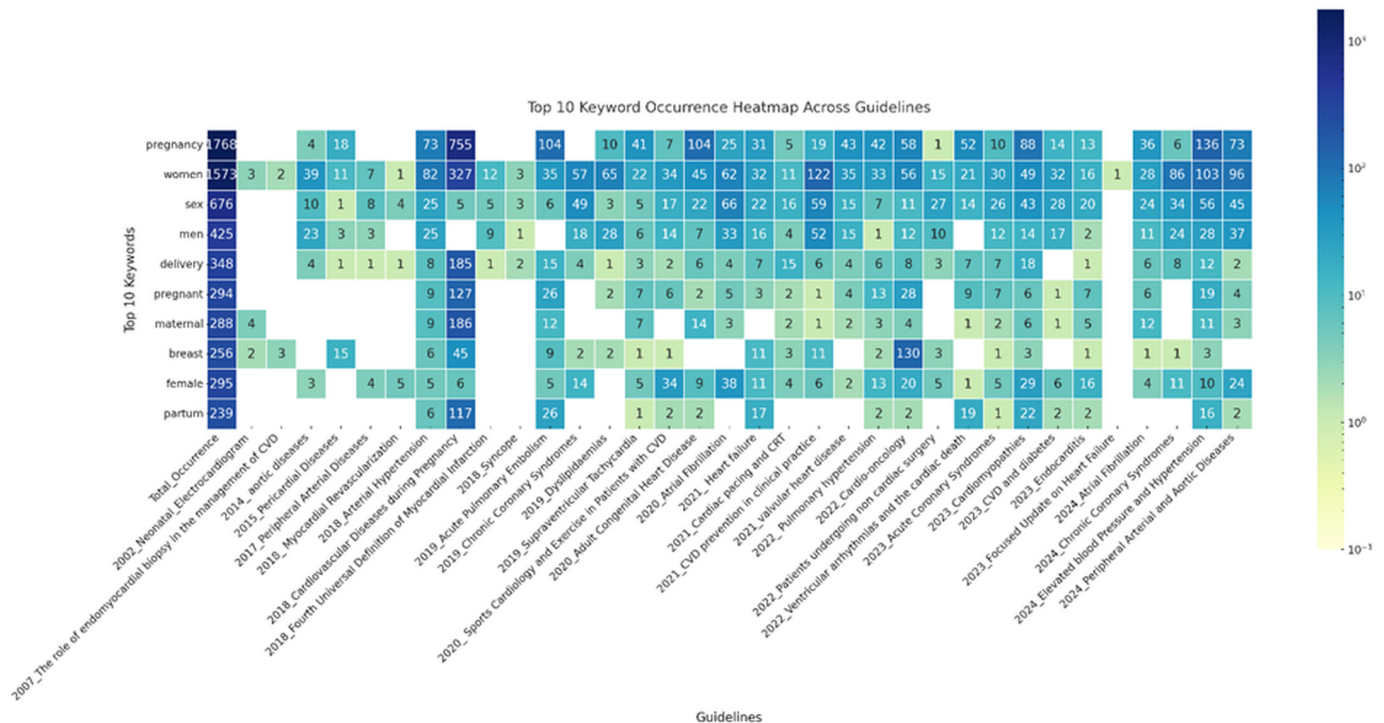


Figure 2 Frequency of gender-related keywords across ESC guidelines over time. Male-specific terms were included as a comparison point to help quantitatively interpret the representation of female-specific terminology. Frequency of the top 10 keyword repetitions across 34 ESC guidelines. The numbers in the cells represent the automatic keyword count. The colour gradient reflects the logarithmic scaling of the frequency of mention, providing a clearer visualisation of both low and high repetition rates. Cells with a value of zero are highlighted with a white background. CRT, cardiac resynchronisation therapy; CVD, cardiovascular disease; ESC, European Society of Cardiology.

17.9%), ‘women’ (1573, 15.9%) and ‘sex’ (676, 6.8%). Several other pregnancy-related terms also appeared among the top 10, including ‘delivery’ (348, 3.5%), ‘pregnant’ (294, 3.0%), ‘maternal’ (288, 2.9%) and ‘partum’ (239, 2.4%), indicating that pregnancy-related content is prominently represented across ESC guidelines. By contrast, ‘men’ accounted for just 425 mentions (4.3%), likely reflecting the traditional assumption of the male patient as default, with sex or gender only highlighted when differing from that baseline. This pattern underscores a greater emphasis on pregnancy-related topics, while other sex-specific health dimensions—such as menopause or hormonal risk—appear less frequently. To put these numbers in context, we also assessed the frequency of the gender-neutral keyword ‘cardiac’, which was found to occur 6932 times across the guidelines. Below, we provide a qualitative summary of each gender-specific aspect considered in our review.

Additional details are provided in the online supplemental materials 1–5. Online supplemental material 1 shows the full keywords count for each guideline. Online supplemental material 2 lists the questions and categories that the auditors were asked to consider for each guideline. Online supplemental material 3 describes keyword mentions in each guideline in detail. Finally, online supplemental material 4 displays a table summarising the level of information provided by each guideline in terms of female-specific CVD prevalence, diagnosis, treatment,

life-stage awareness, special conditions and the awareness of gaps in knowledge. Online supplemental material 5 visualises the occurrence of gender-specific keywords across various CVD guidelines in chronological order.

Awareness of sex differences

The ESC guidelines exhibit a range of awareness of sex differences in CVD. For example, the 2018 arterial hypertension²⁴ and 2021 heart failure²⁵ guidelines are particularly attentive to sex-specific nuances. The 2018 arterial hypertension guideline sets distinct criteria for defining left ventricular hypertrophy from ECGs, with different thresholds for men and women. It also includes separate echocardiographic definitions and waist circumference criteria, recognising the higher prevalence of fibromuscular dysplasia and the impact of early-onset menopause in women. Additionally, it addresses differences in systolic blood pressure response during exercise in women. It also recommends a lower alcohol consumption limit for women and includes comprehensive sections on managing hypertension during pregnancy, eclampsia and pre-eclampsia. Similarly, the 2021 heart failure guideline emphasises sex differences in prognosis and comorbidities, recommending the CHA₂DS₂-VASc [Congestive heart failure (1 pt), Hypertension (1 pt), Age ≥75 (2 pts), Diabetes (1 pt), Stroke/TIA (2 pts), Vascular disease (1 pt), Age 65–74 (1 pt), and Sc (Sex category, female) (1 pt)] score, which includes a point

for female sex, to manage heart failure and atrial fibrillation (AF). The 2021 heart failure guideline also advises caution in using digoxin in women due to higher adverse effects and provides detailed sections on managing heart failure during pregnancy, from prepregnancy counselling to postpartum care. These guidelines reflect an understanding of the importance of tailored diagnostic and therapeutic strategies to address female-specific risks and responses to treatment.

Conversely, some guidelines demonstrate limited awareness of sex differences. The 2007 role of endomyocardial biopsy (EMB)²⁶ in the management of CVD, the 2017 peripheral arterial diseases²⁷ and the 2018 syncope²⁸ guidelines, for instance, lack comprehensive sex-specific data and recommendations. The 2007 EMB guideline only mentions iron staining practices for men and postmenopausal women, without delving into broader sex-related diagnostic or therapeutic considerations. The 2017 peripheral arterial diseases guideline notes the sex differences in benefits of carotid endarterectomy and in clinical presentations of peripheral arterial diseases, but it makes no sex-specific recommendations. The 2018 syncope guideline notes the higher prevalence of drop attacks and orthostatic vasovagal syncope in women, but it fails to provide comprehensive diagnostic and management strategies tailored to these differences. Such gaps highlight the need for more inclusive research and guideline development to fully address sex differences, ensuring that both male and female patients receive optimal care.

Sensitivity to different life stages and special conditions

Most of the guidelines consider pregnancy as a unique condition in the context of CVD management and treatment, with recommendations pertaining to 'pregnancy' presented in 24/34 guidelines. Guidelines such as the 2018 CVDs during pregnancy²⁹ offer comprehensive recommendations for the management of a wide range of CVDs during pregnancy, recognising the unique risks and physiological changes women experience while pregnant. The 2020 adult congenital heart disease (CHD) showed sensitivity towards pregnancy, providing information about maternal mortality and underlying the impact of CHDs on pregnancy. Similarly, the 2014 aortic diseases guideline³⁰ details how pregnancy and conditions such as Turner syndrome influence diagnosis and intervention strategies, emphasising the importance of tailored management during critical life stages. Similarly, the 2022 pulmonary hypertension³¹ guideline emphasises the increased risks associated with pregnancy in women with pulmonary hypertension and gives guidance about disease management from the early stages of pregnancy to postpartum follow-up.

The guidelines exhibit inconsistent consideration of the implications of menopause on CVDs, with specific recommendations pertaining to menopause only found in 10/34 of the assessed guidelines. The 2018 arterial hypertension,²⁴ 2024 elevated blood pressure and hypertension³²

and 2021 CVD prevention in clinical practice³³ guidelines identify early-onset menopause as a risk factor for hypertension and CVD, respectively, underscoring the need for targeted management strategies in postmenopausal women. Similarly, the 2019 chronic coronary syndromes (CCS) guideline³⁴ notes that hormone replacement therapy (HRT) increases the risk of CVD in women aged 60 or above and recommends that HRT not be given for risk reduction in postmenopausal women. The singular mention of 'menopause/menopausal' in the 2015 pericardial diseases guideline³⁵ is for the recommendation of the concurrent use of bisphosphonates in postmenopausal women for osteoporosis prevention in patients given corticosteroids as a second-line treatment of recurrent pericarditis. The 2019 guideline on dyslipidaemias³⁶ discusses the importance of screening and managing lipid profiles in postmenopausal women, emphasising the need for aggressive risk management due to the increased CVD risk associated with menopause. Specific recommendations are provided in the 2021 valvular heart disease guideline³⁷ for postmenopausal women with severe valvular heart disease, who are recommended to undergo coronary angiography prior to valve surgery. In the 2020 adult CHD,³⁸ 2021 valvular heart disease³⁷ and 2023 endocarditis³⁹ guidelines, postmenopausal women are recommended to undergo preoperative coronary angiography due to their increased CAD risk. Similarly, the 2019 supraventricular tachycardia⁴⁰ recommends myocardial ischaemia testing in postmenopausal women due to the increased CAD risk. Despite these references, the other guidelines do not have specific recommendations pertaining to menopause, rather frequently noting gaps in research and the need for more female-specific data, particularly concerning how menopause influences the presentation, diagnosis and treatment of CVDs. Overall, however, many guidelines fall short in comprehensively or partially addressing life stage-specific risks and management strategies.

Our analysis revealed that female-specific risk factors beyond pregnancy and menopause, such as polycystic ovary syndrome (PCOS) and endometriosis, were infrequently mentioned across the ESC guidelines. Keyword analysis showed that these terms appeared only a few times in the entire dataset (polycystic ovary syndrome or PCOS seven times and endometriosis only once), indicating a lack of detailed recommendations for these conditions despite their established association with increased cardiovascular risk.

Gender-specific advancements in the ESC cardiovascular guidelines

The analysis of gender-related keyword occurrences in ESC guidelines from 2002 to 2024 reveals a fluctuating but generally increasing trend in the recognition of sex and gender differences (online supplemental material 5). Before 2010, there were limited references to sex (roughly 8–77 keyword mentions). This transitioned by 2018, where there appears to have been consistent

representation, particularly in accounting for pregnancy (see online supplemental material 1). In the last decade, a more sustained increase is evident, particularly in the 2018–2024 period, where pregnancy-related terms dominated the content. Broader female-specific considerations, such as menopause and hormonal influences, still lagged behind. Notably, the 2024 guidelines introduced specific refinements for women, including lowered intervention thresholds and female-specific diagnostic criteria, indicating a shift toward more comprehensive gender-sensitive recommendations.

Specifically, in the recently published 2024 AF guideline,⁴¹ a notable change was made by replacing the CHA₂DS₂-VASc score, previously used in the 2020 AF guidelines, with the CHA₂DS₂-VA score, making it more inclusive for non-binary and transgender people. Similarly, the 2024 combined peripheral arterial and aortic diseases guideline⁴² introduces female-specific refinements, improving on the 2014 aortic diseases and 2017 peripheral arterial diseases guidelines. The new guideline lowers the intervention threshold for abdominal aortic aneurysms (AAA) in women to 50 mm (compared with 55 mm for men), acknowledging their higher rupture risk at smaller sizes. Additionally, it incorporates sex-specific high-sensitivity cardiac troponin cut-offs, which enhance MI diagnosis in women. The 2024 ESC CCS guideline⁴³ also introduces updates regarding female-specific cardiovascular risk factors that were either absent or minimally addressed in the 2019 guidelines. The latest version places a stronger emphasis on the different symptom presentation of women, particularly highlighting the prevalence of microvascular angina and ischaemia with non-obstructive coronary arteries (INOCA), which often lead to delayed or missed diagnoses in female patients. Moreover, the guidelines now explicitly recognise pregnancy-related cardiovascular risks, noting that conditions such as hypertensive disorders of pregnancy, gestational diabetes and pre-eclampsia significantly increase a woman's long-term risk of developing CCS. Another important update is the inclusion of personalised risk stratification models incorporating female-specific factors such as premature menopause, which were largely overlooked in 2019 guideline.

DISCUSSION

The analysis of 34 ESC guidelines carried out in this study reveals a complex landscape in the integration of sex and gender-specific considerations into CVD management, underscoring the need for more systematic inclusion of sex and gender differences in clinical practice. We found that 'pregnancy' was the most mentioned keyword, with most (24/34) guidelines providing specific recommendations relevant to this condition. Conversely, 'menopause/menopausal' was not among the 10 most frequently recurring keywords, with recommendations related to menopause in only 10/34 guidelines. This was reflected in the qualitative analysis, which highlighted a lack of guidance for this life stage, with only a few exceptions providing

information about the additional risk associated with menopause and how to manage them. Our analysis shows that a more systematic and consistent approach to integrating sex-specific factors in clinical guidelines is needed in order to address the specific needs of women and highlight the evidence gaps that need to be addressed.

Our findings indicate that, while some ESC guidelines, particularly those for arterial hypertension,²⁴ elevated blood pressure and hypertension³² and heart failure,²⁵ have made significant strides in recognising and addressing sex-specific differences, there remains substantial inconsistency among other guidelines. This inconsistency is reflected in the limited attention given to sex-specific medicine in many areas, a concern echoed by Piani *et al*²³ in their evaluation of ESC guidelines from 2018 to 2023. Their study found that less than half of the guidelines included dedicated sections on sex/gender-specific medicine, with most mentions related to epidemiology rather than diagnosis or therapy, a trend also observed in our analysis.

The importance of sex-specific considerations in cardiovascular health cannot be overstated. Mensah and Fuster⁴⁴ highlighted the critical roles of both biological sexes, as determined by physical attributes such as chromosomes, reproductive organs and hormone levels, and sociocultural gender, determined by roles, behaviours, expressions and assigned or assumed identities,⁴⁵ in shaping cardiovascular outcomes, emphasising that these factors should be integral to clinical guidelines and practice. Our study supports this view, particularly in identifying the strong sex-specific content in the guidelines for arterial hypertension, recognising the impact of early-onset menopause and other female-specific factors. However, the under-representation of women in clinical trials and the consequent lack of robust female-specific data remain significant challenges. Burgess⁴⁶ pointed out that women are often understudied, under-recognised and undertreated in cardiovascular research, leading to suboptimal outcomes for female patients. This is corroborated by our findings, which show that many ESC guidelines, such as those for pericardial diseases and syncope, still lack comprehensive female-specific recommendations. This gap highlights a broader issue within the clinical research community, where the failure to include adequate female representation in trials leads to guidelines that are less applicable to women. National societies are beginning to tackle these gaps; for example, the consensus document from the British Cardiovascular Society in 2024 on improving women's access to cardiovascular diagnosis and treatment offers practical steps toward equitable care.⁵

Peters *et al*⁴⁷ underscore the importance of monitoring and managing cardiovascular risk factors, noting significant sex differences in the prevalence and control of these factors over time in the USA. Our study found a similar pattern within the ESC guidelines, where sex-specific considerations in the management of risk factors such as hypertension and dyslipidaemia are more robustly

addressed in some guidelines than in others. This variability suggests that, while awareness of sex differences in terms of risk factor management is growing, it is not yet fully integrated across all aspects of cardiovascular care.

The mechanistic pathways underlying sex differences in CVD, as discussed by Regitz-Zagrosek and Kararigas,⁴⁸ provide a biological foundation for the sex differences observed clinically. They highlight how genetic, hormonal and molecular differences between sexes can lead to distinct disease manifestations and responses to treatment. While at least some biological determinants of differences between the male and female heart are understood, our analysis shows that this insight is not consistently reflected in the ESC guidelines, reflecting an additional need to translate sex-specific research findings to guidelines and clinical practice. This particularly appears to be true in the areas of diagnosis and therapy, where sex-specific recommendations remain limited. The need for a more consistent, research-based and evidence-based approach is further illustrated by the guidelines' disparities in addressing life stage-specific risks.¹⁹

The broader literature highlights the need for sex-specific guidelines in CVD management. DeFilippis and Van Spall⁴⁹ argue that without such guidelines, the health-care system risks disseminating disparities in care and outcomes between men and women. Our findings support the need for more targeted and inclusive guidelines. While some ESC guidelines have begun to incorporate sex-specific recommendations, others would benefit from updates to better align with ESC's guidance on enhancing consideration of sex-based differences. Moreover, a study by Piani *et al*²³ highlights the impact of female authorship on the inclusion of gender medicine in guidelines, noting that guidelines with at least 30% female authors tend to include more gender-specific content. Tong *et al*⁵⁰ found that guidelines authored by more female contributors tend to include greater sex-specific content, suggesting that increasing diversity within guideline-writing committees may improve the integration of sex-sensitive recommendations. However, a major barrier remains the lack of sex-stratified evidence from clinical trials, which influences guideline recommendations. Lam⁵¹ noted that many cardiovascular studies fail to analyse and report sex-based differences, resulting in predominantly male-driven guideline recommendations. Hassan *et al* (2022)⁵² emphasised that female-predominant cardiovascular risk factors, such as pregnancy complications and menopause, remain poorly incorporated into heart failure guidelines, reflecting a broader trend observed in our analysis of ESC guidelines. This highlights the need for more structured inclusion of sex-specific considerations in cardiovascular recommendations.

Computational techniques are increasingly used in clinical practice and can accelerate progress towards more equitable healthcare. Machine learning algorithms have been used to quantify gender bias in clinical trials in the literature⁵³ and to mitigate it⁵⁴ by incorporating a sex weighting on the relative impact of evidence from

clinical trials based on the number of male/female participants. This could serve as a tool for the design of CVD guidelines, in order to provide clear stratification of the evidence used in the guideline according to sex representation. In complement, biophysical computational modelling provides a deterministic representation of the physiological processes underlying cardiac function and can be used to identify and investigate differences between male and female hearts. Simulations of cardiac electrophysiology have shown that sex-specific thresholds for the QRS duration in determining cardiac resynchronisation therapy cut-offs would improve response to pacing in the smaller female heart.⁵⁵ Notably, although this computational study was mentioned in the cardiac pacing and resynchronisation therapy guideline,⁵⁶ there was no accompanying recommendation for sex-specific thresholds for male and female patient selection, potentially indicating an additional opportunity for building trust in complementary computational methods and in their translation to clinical practice. Computational modelling can also improve our understanding of the effect of sex hormones on the function of the heart. Using a model of human cardiomyocytes in combination with experimental data, Yang *et al*⁵⁷ quantified the effects of testosterone, progesterone and oestrogen on the action potential, and how these alter arrhythmia risk. Finally, shape modelling can be used to formally quantify global and local differences between the male and female heart. While it is acknowledged that the female heart is smaller in size compared with the male heart, Pierre *et al*⁵⁸ were additionally able to show that sex differences in heart shape go beyond size. The studies listed above constitute only a few examples of how computational techniques—including machine learning and physiological computational modelling—can contribute to the delivery of better care in patients with CVDs independent of sex or gender.

This review highlights several areas where future research is needed to improve the inclusivity and comprehensiveness of clinical guidelines (table 2). In addition to existing ESC guidance on incorporating sex differences in guidelines, it would be helpful to identify cases where evidence shows no sex differences or where evidence is currently lacking. This approach could highlight areas needing further research. We also suggest that, when reporting on the results from clinical trials, both the number of patients and the percentage male/female in the trial and prevalence of the disease should be stated and it should be indicated if the evidence is for men, women or both. A consistent and systematic implementation of these approaches to future guidelines would highlight where evidence is needed for sex/gender equality in CVD research.

Ongoing research into sex differences in CVD means guidelines are constantly evolving and updated as new evidence emerges. In the recently published 2024 AF guidelines, the CHA2DS2-VASc score, mentioned in the 2020 AF guidelines, was replaced by the CHA2DS2-VA

Table 2 Table of recommendations for areas of improvement

Areas for improvement	Recommendations
Female representation in clinical trials	When reporting on the results from clinical trials, both the number of patients and the percentage male/female in the trial and prevalence of the disease should be stated. Statistical methods are being used to quantify and mitigate gender bias in clinical trials in meta-analysis, and these weighted results should be considered when reporting evidence.
Diagnosis and treatment	Genetic, hormonal and molecular differences between sexes can lead to distinct disease manifestations and responses to treatment; however, there is inconsistent translation of sex-specific research findings to guidelines and clinical practice. Specifically, in the areas of diagnosis and therapy, evidence supporting sex-specific recommendations and diagnostic thresholds remains limited. Guidelines should include a section on sex/gender-specific medicine or a statement highlighting where there is evidence or lack of evidence of no sex differences.
Risk factor management	Female life context, including reproductive history (eg, early menarche or early/late onset of menopause, pre-eclampsia during pregnancy) and age (eg, menopause) should be included in CVD risk evaluation.
Special conditions: menopause and pregnancy	The majority of guidelines have recommendations pertaining to pregnancy reflecting the changes in the physiology and CVDs in this population, while pregnancy advice may also reflect changes in a patient's risk profile. Another major reproductive milestone that is associated with changes in CVD risks, presentation, diagnosis and treatment options in CVD is menopause. A small portion of the guidelines considers the implications of menopause in their recommendations. In guidelines where menopause or pregnancy are not considered, a statement highlighting where evidence shows no sex differences or where evidence is currently lacking for these specific conditions should be included.
Gaps in evidence	Where no sex-specific recommendations are given in a guideline, a statement highlighting where evidence shows no sex differences or where evidence is currently lacking, and what clinical studies could be performed to address these knowledge gaps should be included.
CVD, cardiovascular disease.	

score, which does not account for the sex differences, based on the evidence that female sex is a risk modifier rather than a risk factor for stroke in patients with AF.^{41 59} The 2024 peripheral arterial and aortic diseases guideline⁴² introduces key female-specific updates, lowering the AAA intervention threshold for women due to their higher rupture risk and incorporating sex-specific cut-offs to improve MI diagnosis. These updates reflect an important shift toward more equitable, evidence-based care that better accounts for sex-specific risk factors. By explicitly acknowledging female sex as a risk modifier rather than an independent risk factor, and adjusting intervention thresholds accordingly, these guidelines demonstrate progress in addressing sex differences in CVD management.

Updates also enhance pregnancy-related risk management, recommending prophylactic aortic root surgery for women with Marfan syndrome and favouring beta-blockers over ARBs (Angiotensin II Receptor Blockers), for fetal safety. Additionally, menopause-related lipid and blood pressure changes are now recognised as major cardiovascular risk factors, prompting earlier intervention. The 2024 CCS guideline⁴³ strengthens the recognition of women's atypical symptom presentation, emphasising microvascular angina and INOCA, which often lead to delayed diagnoses. They also explicitly highlight pregnancy-related cardiovascular risks, acknowledging conditions like hypertensive disorders of pregnancy, gestational diabetes and pre-eclampsia as long-term CVD risk factors. While pregnancy is a uniquely

female life event, the physiological effects it imposes are multifaceted. Some pregnancy-related cardiovascular risks such as those associated with pre-eclampsia, gestational hypertension and hormonal fluctuations are tightly linked to female-specific endocrine and reproductive mechanisms. However, other effects, including increased blood volume, elevated cardiac output and vascular remodelling, represent haemodynamic stressors that are not intrinsically female but occur in the context of pregnancy. These latter factors could potentially inform broader cardiovascular research beyond sex-specific populations. Recognising this dual nature of pregnancy both as a hormonal and haemodynamic stress condition may help refine risk stratification and deepen our understanding of cardiovascular adaptations across sexes. Personalised risk stratification models now integrate female-specific factors, including premature menopause. Despite these advancements, gaps persist, particularly in addressing the long-term cardiovascular impact of menopause and ensuring equitable access to coronary interventions for women. ESC guidelines still lack comprehensive consideration of several important female-specific conditions. While pregnancy-related complications such as pre-eclampsia and gestational diabetes are acknowledged, other factors like PCOS and endometriosis, conditions linked to long-term CVD, are rarely mentioned and lack actionable recommendations. Recent changes in clinical guidelines represent meaningful progress toward sex-specific care, yet achieving equitable outcomes for both sexes will require further steps. A key priority is the

inclusion of women across different life stages in clinical trials, which is necessary to generate robust evidence for developing sex-specific guidelines and to advance from a 'one size fits all' model to more personalised and effective care for all patients.

LIMITATIONS

We used an automated keyword count procedure to estimate the frequency of gender-related terms within the ESC guidelines. While this method provides a quantitative estimation of gender-specific content, it was not possible to fully verify the accuracy of these counts. Due to the extensive occurrence of keywords, individually scoring contextual relevance was impractical. Instead, we qualitatively validated keyword mentions through independent manual review, in which two auditors answered structured questions and categorised the mentions into different levels (online supplemental material 4). Although this approach ensures relevance, it limits precise quantitative differentiation, potentially leading to underestimation or overestimation. Future studies could explore advanced computational techniques, such as machine learning, to enable more precise, scalable analyses of context-specific relevance. A further limitation is that zero keyword counts may indicate a lack of substantive discussion, rather than a confirmed absence of the term, as no manual verification was performed. Thus, zeros reflect minimal coverage, not necessarily the complete absence of the word.

The study relied on the content analysis of ESC guidelines between 2002 and 2024, meaning that it reflects the biases and limitations inherent in those guidelines. The focus was primarily on explicit mentions of sex and gender differences, identified through keyword searches and qualitative assessments, which might overlook more subtle or implicit considerations not explicitly labelled as such. Moreover, the study does not evaluate the quality or clinical impact of the sex-specific recommendations provided in the guidelines. While a guideline may mention sex differences, the practical applicability and effectiveness of these recommendations in clinical practice are not assessed.^{41 59}

Future Directions

With the appearance of novel artificial intelligence techniques, it has now become possible to re-examine the existing evidence without the necessity to repeat historical clinical trials. By means of natural language processing pipelines, one can automatically collect participant-level sex information from already published reports and perform wide, sex-stratified meta-analyses of the legacy studies. At the same time, privacy-preserving federated learning that is conducted across different centres may detect the real biological differences between women and men while the raw patient data remain in their local hospitals.

Moreover, advanced machine-learning frameworks that combine anatomical information obtained from imaging, haemodynamic parameters and other clinical variables into sex-specific cardiac atlases could give less biased risk scores and help to adjust diagnostic thresholds.⁶⁰ The employment of these tools has the potential to speed up the transition from general recommendations in guidelines to a more personalised and sex-oriented cardiovascular care.

CONCLUSION

While the ESC guidelines have made commendable progress in incorporating sex differences into clinical practice, there is still much work to be done before men and women receive equal quality of care. The findings of this study, supported by the broader literature, emphasise the need for a more systematic and consistent approach to integrating female-specific medicine into all aspects of cardiovascular care. By addressing these gaps and ensuring that guidelines are based on the latest evidence that includes more diverse and balanced patient cohorts, we can improve the quality of care for all patients, regardless of sex or gender, and move towards a more equitable healthcare system. The ongoing effort to refine and expand these guidelines will be a crucial step in promoting health equity and advancing the standard of care in cardiovascular medicine.

DISSEMINATION

Findings from this study will be disseminated through peer-reviewed publication and presentations at relevant cardiovascular and health equity conferences. The study aims to inform ongoing updates to clinical practice guidelines and support broader efforts to enhance sex-based and gender-based inclusion in CVD management.

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