**Strategies to Enhance Recruitment of Female Participants to Cardiovascular Research: A Joint British Cardiovascular Societies’ Consensus Document in Collaboration with the British Heart Foundation Clinical Research Collaborative**

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**ABSTRACT**

Despite significant progress in cardiovascular pharmacotherapy and interventional strategies, cardiovascular disease (CVD) remains the lead cause of morbidity and mortality among females in the UK and worldwide. This might be due to lack of robust evidence in the best care of females with CVD related to underrepresentation of females in clinical trials (females accounting for <30% of trial participants). Recently, the British Cardiovascular Society (BCS) together with the affiliated societies put together a consensus document specifically describing the current status on the sex differences in each of the major disease areas and proposed strategies/actionable points to overcome the barriers in access to diagnosis and treatment of CVD among females.

In order to address the disparities, several research organisations including the UK National Institute for Health and Social Care Research (NIHR) have produced guidance to diversify research participation and representation. The UK government has developed a women’s health strategy for England. In the present consensus, we evaluate the barriers to research participation of female participants across the CVD spectrum and describe specific strategies/actionable points to enhance female involvement in clinical cardiovascular research. It is hoped that this document will stimulate a multifaceted approach to address disparities, including raising awareness and undertaking sex/gender-based research. We aim to improve the current status of management in various disease areas among females by collaboration across different affiliations within the BCS, British Heart Foundation Clinical Research Collaborative and the NIHR to collectively work towards improving the health and well-being of females with CVD.

**INTRODUCTION**

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among females in the UK and worldwide. Females are underrepresented in clinical cardiovascular research, constituting approximately 25-30% of research participants1. There is an urgent need for randomised clinical trials (RCTs) to include a mandated number of female participants in all clinical trials. Recently, the British Cardiovascular Society (BCS) together with the affiliated societies put together a consensus document specifically describing the current status on the sex differences in each of the major disease areas and propose strategies to overcome the barriers in access to diagnosis and treatment of CVD among females raising awareness worldwide2.

The present consensus aims to evaluate the current status of research participation of female participants in each of the CVD areas, identify barriers to research participation of female participants across the CVD spectrum and describe specific strategies to enhance female participation in clinical cardiovascular research. It is hoped that this document will stimulate a multifaceted approach to address disparities, including raising awareness, undertaking sex and gender-based research to improve the current status of management of females in various disease areas by collaboration across different affiliations within the British Cardiovascular Society (BCS), British Heart Foundation Clinical Research Collaborative (BHF CRC) and the National Institute for Health and Social Care Research (NIHR) to collectively work towards improving outcomes for females with CVD. The unique aspect of this document compared to other documents3 4 discussing this topic includes the contributions from primary care, patient, nursing, and trainee representatives which strengthens our document further and also its reach to all involved in cardiovascular clinical care and research of female patients emphasising the need for a collective effort (**Figure 1**).

**Female representation in cardiovascular risk factor** **studies**

Landmark randomised controlled trials (RCTs) on CVD prevention have demonstrated underrepresentation of females as shown in **Table S1**. None of these trials, however, have targeted recruitment in females specifically and neither have they specified subgroup analyses of female outcomes. The Dietary Approaches to Stop Hypertension (DASH) trial recruited 459 adults, of whom 49% were females and 66% were black or minority ethnicity. It assessed the effects of a diet rich in fruits, vegetables, low-fat dairy products with reduced saturated and total fat (DASH diet) in comparison to a diet rich in fruits and vegetables and a standard American control diet5. The DASH intervention substantially lowered blood pressure and DASH based dietary advice6 7. The recruitment strategy incorporated workplace and community-based screening and mass mailing to potential participants showing that targeted recruitment to trials works and should serve as an exemplar for further studies.

In the RADIANCE-HTN SOLO and RADIANCE II trials, females accounted for around 29% of the study populations, in the EnligHTN III trial for 38%, and most recently in the TARGET BP I RCT for 26% 8-10. The trials reported modest blood pressure lowering effects, but the limited female participation raises questions about why females are not represented in higher technology interventions for hypertension and subsequently regarding the generalisability of outcomes for this type of intervention in females. Newer trials in blood pressure monitoring innovations, fixed dose drug combinations and personalised medicines approaches to CVD risk reduction all need to learn from the past failures of CVD outcome trials to address the needs of females with CVD risk factors.

Nonadherence to antihypertensive medications is one of the key drivers of suboptimal BP control. A meta-analysis of 25 studies, conducted between 2009-2016 in adult hypertensive patients, using the 8-item Morisky medication adherence scale to assess medication adherence and including 12,603 subjects, reported 45% of the hypertensive patients were non-adherent, with a higher percentage (54%) of nonadherence in females11. These sex differences in adherence appear to be influenced by psychosocial and demographic factors, with lower adherence rates more common among younger females and those with fewer socioeconomic resources12. Strategies to enhance recruitment of female participants to cardiovascular risk prevention studies are shown in **Table 1.**

**Female representation in female specific condition** **studies**

There are many barriers to females of reproductive age being involved in research or even worse, they are excluded, however, the lack of data limits the clinical management options for females of child-bearing age. Following the thalidomide disaster in the late 1950s, early 60s where 10,000 females who were pregnant or conceived whilst taking the drug, licensed for morning sickness, sleep disturbance or anxiety, developed birth defects in their children, understandably led to tougher rules for the testing and licensing of drugs. Pharmaceutical companies are therefore reluctant to invest due to the potential harm of medicines/procedures leading to a further paucity of data due to the fear of litigation, even if the real risk is unknown. This leads to concern amongst clinicians to use medicines which have not been proven to be safe. Females are also understandably reluctant to participate in clinical trials if there is any potential risk their baby may be affected. Therefore, females are usually excluded from clinical trials, even if appropriate contraception is being used, and are increasingly reliant on registry data which has its own confounding bias. Strategies to enhance recruitment of female participants in the context of female specific conditions are shown in **Table 1.**

**Female representation in atherosclerosis and coronary artery disease studies**

Many of the RCTs evaluating treatment strategies for the management of acute coronary syndrome (ACS) are dated, and females constitute a small minority of participants. A meta-analysis of randomised controlled trials (RCTs) of ACS trials conducted between 1990 and 2000 found that, on average, females comprised 25% of the study population (**Table S2**), and subsequent attempts at making cardiovascular RCTs more inclusive have had limited success13-16. Much of the RCT evidence referenced so far precedes current techniques and technologies. Even without the controversy of results, the use of outdated techniques in the studies we rely on to inform our guidelines warrants adequately powered up-to-date clinical trials of the best management approach for females with non-ST segment elevation ACS (NSTEACS). The requirement for “adequately powered RCTs to identify potential sex differences in treatment strategies in patients presenting with ACS” has been highlighted as a gap in the evidence in the latest European Society of Cardiology (ESC) 2023 ACS guidelines17. Of note, a recent UK wide ACS trial led by a female investigator (VK) had 45% female participants18 emphasising the importance of female leadership in clinical research. Strategies to enhance recruitment of female participants with coronary artery disease (CAD) are shown in **Table 1.**

**Female representation in valvular heart disease studies**

Sex differences are also apparent in transcatheter aortic valve replacement (TAVR) trials, where females make up almost half of the study populations19 20. However, females in these trials are typically older and have fewer comorbidities than men, which may influence the outcomes. Despite this, there are no significant sex differences in procedural success rates21 22. However, females are often less likely to receive timely intervention, and when they do undergo procedures, they tend to be older and at a more advanced stage of disease, resulting in higher mortality rates23 24. Pulmonary vascular disease, a known risk factor, is particularly significant in older females with advanced aortic stenosis25. Moreover, studies have shown that females are 20% less likely than men to undergo aortic valve replacement23, a disparity that may be partially attributed to the inclusion of female sex as a risk factor in the EuroSCORE, a surgical risk assessment tool.

Tricuspid regurgitation is more common in females26, with a faster progression of severity than observed in men27. There may be structural differences in tricuspid valve anatomy between the sexes that contribute to these variations in disease progression28. Although isolated tricuspid valve surgery is rarely performed, emerging transcatheter therapies for the tricuspid valve hold promise but have not yet been extensively explored in clinical practice.

Despite the growing recognition of sex differences in heart valve disease (HVD), significant gaps remain in our understanding of the underlying pathophysiology and genetic factors that contribute to these disparities. Current clinical trials and guidelines have been largely based on male-dominated cohorts, leading to the underrepresentation of females in HVD research. This underrepresentation may be influenced by socioeconomic, psychological, and biological factors, all of which require further investigation. Strategies to enhance recruitment of female participants to heart valve intervention studies are shown in **Table 1.**

**Female representation in heart failure studies**

In landmark trials of heart failure (HF) medical therapy between 1980-2000, around 20% of participants were females29. Despite recognition that this fell below HF population prevalence30, there was little increase over subsequent decades: in 118 HF RCTs between 2001-2016, females comprised 27% of participants31. HF RCTs perform worse than other CVDs for enrolment of females. Among 740 cardiovascular RCTs completed between 2010-2017, female prevalence-adjusted participation was lowest for HF RCTs (participant-prevalence ratio 0.4832; ratio >0.8 indicates adequate representation)33.

Potential reasons include sex-related eligibility criteria concerning childbearing, lactation or menopausal status, used without explicit rationale, in a quarter of RCTs between 2000-201934 35. Criteria excluding patients with multimorbidity or poor functional status limit enrolment of older adults, and indirectly females, since females are frequently older at HF presentation. However, recent HF with reduced ejection fraction (HFrEF) RCTs evaluating sacubitril-valsartan reported that similar percentages of females and men failed screening33, suggesting other factors have greater impact.

Limited available data on patient-related factors suggest no significant differences in the reasons females and males with HF decline trial participation, nor higher refusal rates36. However, clinical referral bias is a recognised problem; females with HF are less frequently referred to cardiology clinics than males37, or onward to tertiary HF programmes38, or for device therapy39 likely reducing numbers available for trial screening.

Females are better represented in HF with preserved EF (HFpEF) RCTs, but enrolment remains below population prevalence. In PARAGON-HF trial (52% females), sacubitril-valsartan significantly reduced hospitalisations in females with HFpEF versus no effect in males40, demonstrating the importance of adequate sample size and power to elicit treatment efficacy in females, and a potential rationale for females-only RCTs. Strategies to enhance recruitment of female participants to HF studies are shown in **Table 1.**

**Table 1. Actionable points to enhance recruitment of female participants to research on disease conditions contributing to CVD.**

|  |  |
| --- | --- |
| DISEASE CONDITION | ACTIONABLE POINTS |
| Cardiovascular risk factors | * Targeted outreach efforts through public health campaigns to educate potential participants. * Partnerships with community organizations and healthcare providers who serve high-risk female populations. * Support with caregiving responsibilities. * Offer flexible participation options and address sex-specific concerns around safety and side effects. * Improved reporting on sex disparities in trial demographics and encourage accountability. |
| Female specific conditions | * Supporting registries to ensure full data acquisition on the impacts of medications/procedures in pregnancy. * Need to educate females on the importance of participating in clinical trials. * Having female only studies to see how that compares to current perceived outcomes across the world literature. |
| Coronary artery disease | * Patient-facing documentation should be tailored to females and PPI tested. * Utilise audio, video, and written platforms for providing patient information. * Provide family-specific information as an important part of the decision-making process. * Provide reimbursement for travel when required, as well as childcare/caring commitments. * Ensure follow-up is flexible and fits around participant’s commitments and needs. * Address any cultural barriers particularly associated with females from the underserved communities. * Ensure a diverse research team consisting of male and female principal investigators. * Improving the level of comfort and the overall clinical trial experience. * Provide females with extra reassurance of their significant value to participate in clinical research. * Educating males so they can help advocate for female family members. |
| Heart valve disease | * Enhance patient education and awareness about HVD. * Improve patient counselling in valve clinics and incorporating multidisciplinary teams to optimize care. * Healthcare professionals must be aware of the sex-specific nuances of HVD. |
| Heart failure | * Trials with females as first or last authors have significantly higher proportions of female participants. * Including females in leadership roles throughout the lifecycle of the clinical trial. * Reconsidering and justifying exclusion criteria for females of child-bearing age. * Individualised approach to contraception, involving obstetrician-gynaecologists. * Supporting participation of older females. * Setting minimum quotas, implementing adaptive trial design and modifying recruitment processes. * Pre-specified sex-based stratification analyses with interaction for sex, powering of trials to detect significant sex differences in safety and efficacy endpoints, and mandating sex-specific reporting of results. * Involving trusted clinicians can enhance females' decisions to participate. * Use of remote follow-up, flexible scheduling, and location of trial sites in community settings. * Fair compensation for inconvenience, transportation, loss of income and childcare costs are essential. * Translation services are needed for those with limited English. * Set trial standards to mandate the representation of females in RCTs as a requirement for funding. |

*Abbreviations: PPI, Patient public involvement; CVD, cardiovascular disease; HVD, heart valve disease.*

**Female representation in cardio-oncology studies**

Cancer survival in the UK has doubled over the past 50 years, with 50% of patients surviving >10 years after diagnosis41. Alongside this, there has been an increase in the burden of CVD in cancer survivors. Cancer survivors are more likely to develop CVD, particularly HF, than people without cancer, independent of traditional cardiovascular risk factors42. There is emerging data, albeit limited, demonstrating sex disparities in the cardiovascular outcomes of patients with cancer. Acute cardiovascular toxicity can infrequently occur and includes acute myocarditis, pericarditis, heart failure and arrhythmias. Female representation in clinical trials has historically been lower than men, although data suggest an increased risk of severe symptomatic adverse events in females following immunotherapy treatment43.

The prevention of adverse cardiac events following cancer treatment has been an area of research interest over recent years, particularly in the context of anthracyclines and HER-2 inhibitors induced cardiotoxicity for breast cancer, however despite this, there remains a lack of evidence-based cardio-protective therapies available. Additional female specific considerations for patients with cancer include the use of the oral contraceptive pill or hormone replacement therapy and associated thromboembolic risk, fertility preservation prior to receiving cancer treatments and the management of cancer during pregnancy. Strategies to enhance recruitment of female participants to cardio-oncology studies are shown in **Table 2.**

**Female representation in heart rhythm studies**

Strategies in addressing underrepresentation of females in arrhythmia research should include increasing awareness of sex-specific differences in arrhythmia pathophysiology, risk factors and clinical outcomes. For example, females with atrial fibrillation (AF) have different risk profiles compared to men, including older age at onset, higher rates of stroke and different responses to antiarrhythmic treatments. Educational campaigns aimed at healthcare providers and public health boards about the importance of including females in arrhythmia research could increase interest in research participation. This might be achieved by disseminating findings on sex differences in arrhythmia outcomes through public health campaigns; training clinicians and researchers to recognise the importance of female inclusion in arrhythmia studies. Understanding the reluctance of females to participate in arrhythmia clinical trials can enable a targeted approach to encourage participation. Reasons for declining participation in research include personal illness, transportation issues, caregiving responsibilities, reluctance to increase medication, and concern about adverse health effects44. It has been documented that a lack of information and understanding of the arrhythmia research, trial related procedures and the perceived health status of the patient limits female participation. Strategies to enhance recruitment of female participants to heart rhythm disorder studies are shown in **Table 2.**

**Female representation in congenital heart disease studies**

Congenital heart diseases (CHD) exhibit asymmetrical sex distributions, with certain types of CHD occurring more commonly in either females or males. Sex-based differences observed in CHD research inclusion may therefore reflect the distributions inherent to the underlying CHD, rather than biased recruitment.45 The heterogeneity of CHDs, characterised by diverse diagnoses, variable surgical treatments, combined with a rapidly evolving care delivery has led to a research landscape strongly reliant on observational cohort studies. Disease specific RCTs are small and limited in number, however no sex-based recruitment bias is conspicuous in published studies (**Table S3**), instead reflecting the underlying prevalence distribution.

Even in the absence of recruitment bias, asymmetrical sex distributions can still be problematic in CHD research, because the magnitude of effect sizes or even the direction of the effects can be different between the sexes. Unbalanced representation makes it difficult to generalize the findings to the overall population, as the results may be skewed towards the overrepresented sex. Without sufficient data on both sexes, studies may fail to capture important sex-specific differences in the outcome of interest. For example, cardiac volumetric thresholds for intervention based on aggregate data could disadvantage females by delayed treatment or expose men to unnecessary early treatment.46 Strategies to enhance recruitment of female participants in CHD studies are shown in **Table 2.**

**Female representation in inherited cardiac conditions studies**

Inherited cardiac conditions (ICCs) comprise a broad range of familial diseases primarily affecting the heart47 48. These conditions represent a broad range of phenotypes, inheritance patterns and outcomes and the influence of biological sex is both complex and widely recognised47.

Studies observing sex-specific differences across a wide range of ICC diagnoses are growing in number49-52 and are an important research priority recognised by international guidelines47. Understanding the complex interplay between sex, genetic susceptibility, protein expression, and environmental modifying factors remains a challenge. Most data from ICC cohorts come from observational longitudinal or cross-sectional registries. The widespread paucity of randomised data in this field is particularly problematic, and the role of biological sex on treatment effectiveness in ICCs is largely unknown.

Since biological sex plays such an important part in phenotypic expression, ensuring that females are adequately represented in registries is crucial. ICC diagnoses often affect relatively younger patients, and socioeconomic factors may influence female’s behaviour in seeking medical attention and participation in research studies (for example, younger females with families, working patterns and having insufficient time to participate in research studies may be relevant). The influence of cultural differences in healthcare behaviour, especially affecting females from ethnic minorities, may also lead to their underrepresentation in ICC registries. Strategies to enhance recruitment of female participants in ICC studies are shown in **Table 2.**

**Female representation in cardiac surgical studies**

Females undergoing cardiac surgery have been identified to have a higher risk of mortality than males as reflected by the EuroScore I and II53. The cause for this is not fully understood or delineated although some factors have been suggested54 55. Every year ~32,000 people undergo heart surgery in the UK (5,6), however the numbers enrolled in clinical trials are only but a fraction. There is ample evidence of inequality in the access to and outcomes of cardiac surgery and poor inclusion of under-served groups in cardiovascular trials56 57, especially females34 58. However, there are efforts to address this in female targeted studies such as Randomized comparison of the Outcomes of single vs Multiple Arterial grafts trial in Women (ROMA-Women)59.

Cardiac surgery is localised in 35 specialist NHS centres with varying populations size and constitution as well as variations in their resources and participation in research. Female participation in cardiothoracic trials remains low, presenting challenges for creating treatments tailored to both sexes. The fact that research in CVD predominantly involved male participants leads to a data gap that impacts treatment accuracy for females. This disparity can result in females experiencing adverse effects or suboptimal results from treatments based on male data alone.

Barriers to participation include logistical issues, lack of awareness, and a perception of higher trial-related risk among females. Many females report transportation difficulties, time constraints, and concerns about child or carer responsibilities as reasons for non-participation. Additionally, fewer females than men are referred to specialists, which reduces opportunities to be informed about trials. Distrust and concerns over the experimental nature of trials also play a role in discouraging females from joining34 58.

The Society for Cardiothoracic Surgery in Great Britain & Ireland (SCTS) Research led National Cardiac Surgery Clinical Trials Initiative is a UK-wide strategy which aims to address research priorities and deliver “a trial for every patient”. It was set up following a James Lind Alliance Priority Setting Partnership that identified the top 10 research priorities and supported by Heart Research UK, BHF, SCTS and the Royal College of Surgeons. One of the current projects relate to equitable access for all minorities including females to participate in research. A major challenge in engaging females in research is a lack of comprehensive understanding about the issues that affect their participation. Equally, there is a need to identify modifiable factors to increase their participation in research. Strategies to enhance recruitment of female participants in cardiac surgical studies are shown in **Table 2.**

**Female representation in cardiac rehabilitation studies**

Females are persistently under-represented in research of cardiovascular prevention and rehabilitation programmes (CPRPs). Whilst there is a robust evidence base demonstrating positive outcomes from rehabilitation in coronary artery disease (CAD)60, HF61, AF62 and following valve surgery, implantable cardioverter defibrillator (ICD) or transplant63-65, the research populations forming this evidence base are typically 30% female (15% in CAD trials60).

Across the CVD spectrum, there is also a lack of rehabilitation research which includes older adults60-65. This may in part explain the low proportions of females in these trials, given that the overall incidence and prevalence of heart and circulatory diseases is lower in females than in men until the age or 85 years or more66. However, perhaps with an ageing population, in some aspects of the evidence base, this may be changing. In the most recent Cochrane systematic review of rehabilitation in HF, newer trials included a wider range of participants (i.e. those with HFpEF) who are more likely to be older and female61.

In cardiac conditions that affect higher proportion of females (e.g. spontaneous coronary artery dissection, ischaemia with non-obstructive coronary arteries, and CHD), females are better represented in research trials. Unfortunately for these groups, the evidence base for CPRPs is small and more research is needed67-70. Age and cardiac diagnostic specifics aside, reasons for females not taking part in rehabilitation research are largely unexamined, and therefore unclear. They may mirror the complex barriers to CPRP participation identified for females in the clinical setting, and overcoming these barriers may enhance recruitment of females in research. Furthermore, if female engagement with CPRPs can be improved in practice, this may subsequently improve their research engagement in this field. Strategies to enhance recruitment of female participants in CPRP studies are shown in **Table 2.**

**Table 2. Actionable points to enhance recruitment of female participants to research on disease conditions contributing to CVD.**

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| --- | --- |
| DISEASE CONDITION | ACTIONABLE POINTS |
| Cardio-oncology | * Early collaboration with oncology colleagues is key to align with the oncology clinic visit schedules. * Minimise and simplify cardio-oncology trial protocols to address childcare or caring responsibilities. * Use of telephone/video visits, visits outside of normal working hours, or in community centres with childcare facilities, or the patient’s own home. * Travel reimbursement for research visits. * Use longer investigational echocardiographic protocols for cardio-oncology trials or use of cardiac MRI. * Avoid cardiovascular imaging modalities that use radiation, e.g., CT/PET, during cardio-oncology trials. |
| Heart rhythm | * Implementing targeted recruitment strategies, creating inclusive study designs, and fostering partnerships with advocacy organizations (arrhythmia alliance). * Provide flexible participation options, to include virtual or home-based recruitment or data collection. * Partner with female health organisations to increase trust and engagement in arrhythmia studies. * Implementing sex-stratified analyses in arrhythmia clinical trials and observational studies. * Designing studies to assess the effects of sex hormones and reproductive health on arrhythmic outcomes in females (e.g., how menopause or oral contraceptive use influences arrhythmic risk). * Organize information sessions and community outreach events in collaboration with female health organizations, female support groups. * Encourage female researchers to take leadership roles in research trials to improve trust and foster female-specific considerations. * Ensure recruitment considers all cultural backgrounds, uses gender sensitive language, and transparent. |
| Congenital heart disease | * Patients are usually well known to their clinical team, with the multi-disciplinary relationship spanning the life course. * Recruiting through virtual approach or using survey as the primary data collection tool. * Incorporating specialist nursing teams into research recruitment. * Sex specific topics for research are important to females with CHD, but remain relatively understudied. * Addressing the issue of asymmetrical sex distribution in CHD research is crucial. |
| Inherited cardiac conditions | * Offering flexible study appointments and childcare support. * Improving engagement with partners and public health campaigns. * Ensuring that well-designed observational studies examine research questions specific to females. * Examine female-only cohorts of patients (e.g., optimal diagnosis/management of female Duchenne carriers). |
| Cardiac surgery | * Identify and quantify capability and capacity for females in cardiac surgery research. * Explore the facilitators and barriers to optimising participation of females in cardiac surgery trials. * Develop a logic model for improving research engagement and develop guiding principles. * Provision of logistical support, like transportation assistance and childcare. * Expanding leadership roles for females in cardiac surgery trials. * Partnerships with community groups to build awareness and trust. |
| Rehabilitation | * Conducting research activities in social care or community settings. * Offering flexible timings/locations and financial reimbursement. * Providing clear, impactful healthcare messages as part of the research invitation. * Need to develop and examine alternative, innovative CPRP formats (e.g. virtual). |

*Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; CHD, congenital heart disease; CPRP, cardiovascular prevention and rehabilitation programme; HCP, Healthcare professionals.*

**Female representation in cardiovascular imaging studies**

***Cardiac CT studies***

Of the recent major cardiac imaging trials, the PROMISE trial had an increased representation of females (53%) compared to men. In other trials such as the SCOT-HEART, female representation was 44%, and 47% in the CONFIRM trial71-73. In the ISCHEMIA trial, which incorporated computed tomography coronary angiography (CTCA) to exclude left main disease, female representation was only 22%74.

There has been extensive development in the field of artificial intelligence (AI) and data diversity included sex related data, is important to ensure performance is robust when applied to clinical practice75. There remain challenges in recruiting females to imaging trials. Imaging plays a vital role in establishing CAD as well as assessing the response to treatment. CT imaging involves radiation dose, and this may be a concern to females. However, use of prospective ECG gating with ECG dose modulation, high pitch helical scanning and adjusting scanning parameters can substantially reduce radiation dose. The mean effective dose was 1.7 mSv in females and 2.6 mSv in men in the Crescent trial76. Radiation dose in CT is lower than in single positron emission computed tomography (SPECT) where the mean effective dose is approximately 8-10 mSv. CT is the gold standard imaging modality to assess aortic annulus measurements and peripheral access in assessment for TAVI. More research regarding sex-based differences in aortic valve disease using imaging modalities is required.

***Cardiac nuclear studies***

Females have a higher prevalence of microvascular disease. Positron emission tomography myocardial perfusion imaging (PET MPI) allows for assessment of myocardial blood flow and coronary flow reserve. PET has a higher spatial resolution compared to SPECT and is also associated with a lower radiation dose. 18F-Sodium Fluoride PET MPI has been shown to assess microcalcification in the coronary arteries and also has a role in assessing plaque progression in females77. More studies in females are required to assess for features of plaque progression in females with PET imaging. Sarcoidosis is a systemic disease which can involve the heart and has a slightly higher prevalence in females. Whilst cardiac magnetic resonance (CMR) can be used for investigation, 18F–FDG PET allows for assessment of myocardial inflammation related to sarcoidosis78 and is useful for assessing response to treatment. Further studies are required to assess the timing of follow up in these patients.

***Echocardiography***

In addition to sustained underrepresentation in the evidence-base, inherent anatomical sex differences likely cause sex-specific variability in the sensitivity and specificity of non-invasive imaging, such as echocardiography. There are inherent anatomical sex differences including smaller aortic dimensions, left ventricular chamber size and pulmonary arteries, even when adjusted for body size79. Whilst these differences are acknowledged80, their widespread integration in clinical guidance and care continues to be lacking.

Even with a spotlight on these sex-specific differences in diagnostic measurements, a recent review found that only 5 clinical trials focused on cardiovascular imaging in females80. Importantly, women who present requiring echocardiographic assessment are often more symptomatic and at a more advanced stage of disease, and certain disease processes identified primarily through echocardiography are more common in older females, for example diastolic dysfunction81. Also, ventricular remodelling in pressure overload is different in females when compared with men82 and females often have less valvular calcification for a given severity of valvular disease than men83.

Despite all these important sex-based differences, there are disproportionately fewer studies attempting to address this, however recent research has reached more representative sex distributions; the EVAREST study84, documenting real world practice in stress echocardiography, recruited 45% female participants, and the OPT-PACE trial85, evaluating the effectiveness of echocardiographic screening for HF, achieved 40% female participation.

As echocardiography is the primary imaging modality for the assessment of CVD, particularly in those requiring serial assessments, specific strategies to enhance recruitment of female participants in studies involving echocardiography are shown in **Table 3.**

***Cardiovascular magnetic resonance imaging***

CMR imaging is considered the gold-standard for cardiac chamber volumetric and functional quantification, and with the addition of tissue characterisation, it is an ideal surrogate endpoint for both mechanistic studies and trials of intervention. Its higher reproducibility allows lower sample sizes to show meaningful differences. The key CMR studies in the areas of valve disease, IHD, inherited cardiac conditions, heart failure, COVID-19 and population-based studies, are summarised in **Table S4**. Female participants are generally underrepresented in these studies, with the % representation varying with the underlying diagnosis and cohort. CMR studies on VHD and ischaemic heart diseases were particularly male dominated, with female representation in studies of aortic valve disease being 25-35% and 28% for ST-elevation myocardial infarction (STEMI). The study on microvascular angina was the only one with a majority of females (60%). Whilst this likely reflects variation in disease prevalence to some extent, the underrepresentation of females is out of proportion to this, and likely reflects lower recruitment rates in general. For example, the % of male patients presenting with STEMI and non-STEMI was ~73% and 66-69%%, respectively86 87. The participation to prevalence ratio was <0.6 for CAD/ACS studies33.

Some male preponderance in CMR studies is unsurprising – e.g. those in transthyretin (ATTR) amyloidosis (particularly wild-type ATTR), and it is reassuring that in large-scale population studies, such as UK Biobank (largely aged 40-69 years at the time of recruitment) and MESA (aged 45-84 years at baseline), female representation was high (exceeding that of males). Strategies to enhance recruitment of female participants in cardiovascular imaging studies are shown in **Table 3.**

**Table 3: Strategies to enhance recruitment of female participants in cardiovascular imaging studies.**

|  |  |
| --- | --- |
| IMAGING MODALITY | ACTIONABLE POINTS |
| CTCA | * Ensure reassurance as females tend to be risk averse. * Provision of childcare support. * Providing information including leaflets with details regarding the study. * Ensure diversity in leadership positions in clinical trials. * Imaging studies should be performed in the same visit, along with other investigations if possible. * Use of lowest radiation dose, with appropriate ECG gating and acquisition parameter optimisations. * In addition, telephonic consultations regarding the investigation where possible may be useful. |
| Cardiac Nuclear imaging | * Provide information about the study with information leaflets. * Discussion with the patient to answer queries regarding tracer administration and radiation dose. |
| Echocardiography | * Use of safe imaging protocols during pregnancy or when regular serial assessments are mandated, for example with cardio-oncology assessments. * Encouraging, enabling and empowering more female researchers to lead research programmes. * Openly offering female echocardiographer provision, modesty gowns, permitting flexible research appointments and promoting female participant stories. |
| Cardiac MRI | * Offering females flexible research appointments and offering to cover the costs of their travel and time. * Reducing the scan duration, provision of eye mask, mirror or sedation, to improve compliance. * For females with intrauterine devices or requiring transdermal patches for contraception or hormone replacement therapy, misinformation or confusion about the safety of CMR may be another potential factor driving their disengagement with CMR research. |

*Abbreviations: CTCA, computed tomography coronary angiography; PET, positron emission tomography; CMR, cardiac magnetic resonance.*

**Female representation in primary care cardiovascular studies**

Primary care is a challenging healthcare environment typically based around brief patient contacts typically covering more than one clinical area including established CVDs and their associated risk factors. Health care professionals (HCPs) in primary care are “specialists in generalism”, frequently challenged by the nuanced applicability of the relevant evidence base and related guidelines to the person in front of them. HCPs do not have the capacity to systematically appraise the applicability of guidelines and research during each consultation. In addition, the consequences of blindly applying generalised guidelines or sex biased studies may lead to potential harm. Around 2,400 General Practices across the UK contribute to the Clinical Practice Research Datalink (CPRD) database, providing a rich source of real-world observational data for research purposes88. However, the culture, training, contracting, and working environment arguably present significant potential barriers to research curiosity, capability and capacity in primary care. Strategies to enhance recruitment of female participants in primary care studies are shown in **Table 4.**

**Female representation in cardiovascular research: Trainees’ perspective**

Clinical trials led by female principal investigators recruit more female patients than those led by males18 89. However, females continue to be the minority within academic cardiology90, in particular amongst procedural subspecialities including intervention and electrophysiology91. An essential step in pursuing a career in academic cardiology is being awarded a higher degree, most frequently achieved by undertaking a period of out of programme research. However, multiple barriers exist for cardiology trainees wishing to do this, including a lack of flexibility for academic trainees to undertake research alongside clinical work and restrictions on the number of years allowed out of training92. These barriers are further exacerbated for female trainees, who may have periods out of training for maternity leave and feel their training time has already been significantly extended.

These concerns have been augmented by the introduction of mandated dual accreditation in cardiology with general internal medicine (GIM) as part of the new cardiology curriculum in 202293. In the 2024 British Junior Cardiologists’ Association survey, approximately 40% of female trainees stated they were less likely to pursue an academic career given the introduction of the new curriculum and in particular the increased demands from GIM dual accreditation92.

In addition, the age at which female trainees are considering coming out of training programme to study for a higher degree frequently coincides with when they are starting a family. Funding of maternity leave beyond statutory maternity pay during clinical research training fellowships is not guaranteed by all funders and host institutions and is another factor that female trainees must consider94. Strategies to enhance recruitment of female participants in cardiovascular research from a trainee perspective are shown in **Table 4.**

**Female representation in cardiovascular research: Nursing perspective**

Females suffer with underdiagnoses as they present later to seek professional help due to a lack of awareness of their potential risk of developing the disease combined with experiencing atypical signs and symptoms, that even health care professionals do not correlate to heart disease sometimes95 96. In this context, female patients are receptive to misdiagnosis and under treatment as health practitioners usually underestimated female risk factors96 97. On the other hand, t**he Women’s Health Strategy for England (2022)98 reported 84% of females stated that healthcare professionals were not listening to their problem when they came to seek help.** Interestingly, although nurses have a notable role in daily educational practice as they are in close contact with patients99 100, they may not feel competent in providing effective health education101. Strategies to enhance recruitment of female participants in cardiovascular research from a nursing perspective are shown in **Table 4 (see also supplementary file).**

**Female representation in cardiovascular research: Cardiac physiologists’ perspective**

The healthcare science workforce constitutes 5% of the healthcare workforce but is involved in 80% of all diagnoses102, and cardiac scientists are in the unique position of seeing patients across the full range of CVD. Modernising Scientific Careers102 overhauled the education and training of cardiac scientists and recognised the potential contribution of scientists to research and innovation. Those on the Health and Care Professions Council Clinical Scientist register have proven knowledge and skills of research methods and a consequent better appreciation of the role of research in clinical practice. Cardiac clinical scientists are playing leading roles in research in the UK, including but not limited to a recently published RCTs103 104 and long-term prospective study105. Cardiac scientists also play an important role in delivery of diagnostics within research projects. However, many cardiac scientists are still not actively involved in research and more needs to be done to empower them to address the gap in the recruitment of females to research. Strategies to enhance recruitment of female participants in cardiovascular research from a cardiac physiologist perspective are shown in **Table 4.**

**Female representation in cardiovascular research: Patient perspective**

Medicine is the skilful art of applying research based scientific evidence with compassion and empathy, with the aim of improving the length and quality of life of patients. Research in modern medicine is fundamental in ensuring patients are offered safe and effective treatment. There is a growing awareness that female heart patients are not being fully involved and represented in clinical research. The treatments they are being offered are based on what works for men, this may not serve females well. At present, the way clinical research is designed, funded, and promoted is not meeting the needs of female patients living with heart disease34. How females themselves feel about research, how funding bodies make decisions about which research is funded and how researchers may have unconscious biases about females participating in research are all potential barriers to females participating in research. Female heart patients may not want to be involved in research because they feel the research has little or no relevance to them, they may not trust research, or they are concerned that they will be harmed in some way. When, how, by whom and in what circumstances the initial meeting with the person recruiting participants for a study, may influence whether a woman decides to take part. The design of the study will need to consider the different roles females have in their communities and wider society. Strategies to enhance recruitment of female participants in cardiovascular research from a patient perspective are shown in **Table 4.**

**Female representation in cardiovascular research: BHF CRC perspective**

To enable high quality clinical research and improved female participation, researchers must consider sex and gender at every stage of the research process, from designing the study and collecting data to analysing results and reporting findings106. Collaboration between research institutions, regulatory agencies, and funding bodies is critical to creating targeted strategies that promote female inclusion in clinical trials107. Enhancing female participation in cardiovascular research requires a collaborative, multi-faceted approach.

***Improved awareness, empowerment, and communication***

Failing to address the concerns of female patients and empowering them in decision-making can lead to misunderstandings, distrust, and ultimately reduced participation in research108. Involving females early in the research process and ensuring effective communication channels are in place will likely result in more females taking part in the trials. However, this is only part of the equation. A deeper issue lies in the persistent lack of awareness among researchers when it comes to understanding and addressing the unique health needs of females109. As the NIH emphasises, health disparities are closely linked to social, economic, and/or environmental disadvantage, and often affect individuals based on intersecting factors including gender, race, ethnicity, and socioeconomic status108. Therefore, understanding how these factors uniquely impact females is crucial for developing communication strategies that not only increase participation but truly empower them in research settings.

***Female perspective in research development***

Diversifying research teams and actively involving females, both as investigators and patients in shaping research questions and study design is crucial in responding to the needs of female participants110. There are several ways in which diversifying research teams can aid recruitment of females in clinical trials: it can nurture trust between the public and researchers; it can enable development of solutions to barriers specific to this population; and it can improve the access to information through advising targeted communications strategies (**Figure 2**)111. Reducing the gender gap in female leadership may assist in closing the gender gap in recruitment.Research undertaken by female investigators, has been found to achieve higher recruitment rates of females35 112. Strategies to enhance recruitment of female participants in cardiovascular research from BHF CRC perspective are shown in **Table 4.**

**CONCLUSION**

Despite CVD remaining the lead cause of mortality worldwide, females are underrepresented in cardiovascular research. There are several barriers for female participation in research (**Figure 3**). To address this problem, this consensus provides several actionable points in the different disease areas to enhance recruitment of female participants in research (**Figures 4, 5**) and ultimately help reduce the burden of CVD among females in the UK and worldwide.

**Table 4: Actionable points on primary care, trainees, patients, physiologists, and nursing perspectives to enhance recruitment of female participants to research.**

|  |  |
| --- | --- |
| PERSPECTIVES | ACTIONABLE POINTS |
| Primary Care | * Educate primary care around all aspects of research. * Train and enable primary care HCPs to routinely appraise research. * Use digital technology to alert the clinician on the applicability of any given aspect of management. * Improve the contracting arrangements to encourage participation in research * Proactively recruit females to research studies. |
| Trainees’ perspective | * Derogation of specific curriculum requirements for academic cardiology trainees. * Funders and host institutions to support the terms of entitlements for maternity leave. * All trainees should be included in equality, diversity and inclusion training programmes. * Mentorship of trainees is vital and the development of clinical trial networks. * Protected time from service provision to engage in research activity. |
| Nursing perspective | * **Nurses should equip themselves on the knowledge and awareness of CVD in females.** * Nurses feel empowered to address their specific concerns raised by female patients. * Develop trust and build a rapport through effective communication and active listening. * Nurses should continue to be active advocates when reviewing study protocols * Ensure that all patients facing materials are culturally and linguistically appropriate. |
| Physiologist perspective | * Cardiac scientists may have developed a rapport in the catheter laboratory which makes them well-placed to inform patients of potential involvement in research opportunities. * Females healthcare professionals are able to foster an environment where females feel safe to participate. * Help improve communication between research and clinical teams. * Help improve dissemination of active research to ensure the wider team is aware of projects. |
| Patient perspective | * Females may need a period of reflection and wish to discuss with another family member. * A section of frequently asked questions could be created either on an app or in written form. * Patients may feel inhibited to ask some very basic questions about the research, preferring to talk to a fellow patient. * Local NIHR research champions could be utilised after appropriate training to provide this support. * Clinical research should be patients working in equal partnership with researchers. * Patients may have different priorities about what they would like to be research priority. * Involve female heart patients in all the stages of research from the initial concept, design of the study, sitting on trial steering committees, contributing to the publication and dissemination of the findings. * The female patient voice should be heard throughout. |
| BHF CRC | * Inter-disciplinary collaborations allow the sharing of resources and expertise. * Facilitate knowledge sharing and support collaborative efforts. * Communicate to the wider research community and raise awareness about the benefits of clinical research. * Unite resources, expertise, and influence across sectors to gather collaborative efforts to dismantle barriers. |

*Abbreviations: GIM, General internal Medicine; UK, United Kingdom; CVD, cardiovascular disease; BJCA, British Junior Cardiologists’ Association; BHF CRC, British Heart Foundation Clinical Research Collaborative; NIHR, National Institute for health and care research.*

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**Figures legend**

**Figure 1. Rationale of the Joint British Cardiovascular Societies’ Consensus to enhance recruitment of female participants to cardiovascular research.**

Abbreviations: BHF CRC, British Heart Foundation Clinical Research Collaborative; BCS, British Cardiovascular Society; NIHR, National Institute for Health and Care Research; CVD, cardiovascular disease.

**Figure 2. Ways to aid recruitment of females in clinical trials by nurturing trust between the public and researchers.**

Abbreviations: MSc, Master of Science; PhD, Doctor of philosophy; AHPs, Allied Health Professions; NIHR, National Institute for Health and Care Research; NHS, National Health Service; BHF, British Heart Foundation; CRC, Clinical Research Collaborative; GPs, general practitioners.

**Figure 3. Current barriers and gaps to female recruitment in cardiovascular research.**

Abbreviations: RCT, randomised controlled trial; CVD, cardiovascular disease; HRT, hormone replacement therapy; TE, thromboembolic; ACS, acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; AF, atrial fibrillation; CPRCPs, cardiovascular prevention and rehabilitation programmes; HCP, healthcare professional.

**Figure 4.** **Female representation in research.**

Abbreviations: CAD, coronary artery disease; TAVI, transcatheter aortic valve intervention; ANOCA/INOCA, Angina/Ischaemia with non-obstructive coronary arteries; SCAD, spontaneous coronary artery dissection; MI, myocardial infarction; CV, cardiovascular; HVD, heart valve disease; BP, blood pressure; RCT, randomised controlled trials; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; ACS, acute coronary syndrome.

**Figure 5:** **Strategies to enhance recruitment of females in research.**

Abbreviations: RCTs, randomised controlled trials; HCPs, healthcare professionals.

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All authors contributed to the document on behalf of their relevant affiliated society (listed below) and provided critical review of the document.

GP created the Figures, undertook multiple revisions and critical review.

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