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**REVIEW**
*Miscellaneous*

# Management of cardiac emergencies in women: a clinical consensus statement of the Association for Acute CardioVascular Care (ACVC), the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the Heart Failure Association (HFA), and the European Heart Rhythm Association (EHRA) of the ESC, and the ESC Working Group on Cardiovascular Pharmacotherapy

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Cardiac emergencies in women, such as acute coronary syndromes, acute heart failure, and cardiac arrest, are associated with a high risk of adverse outcomes and mortality. Although women historically have been significantly underrepresented in clinical studies of these diseases, the guideline-recommended treatment for these emergencies is generally the same for both sexes. Still, women are less likely to receive evidence-based treatment compared to men. Furthermore, specific diseases affecting predominantly or exclusively women, such as spontaneous coronary dissection,

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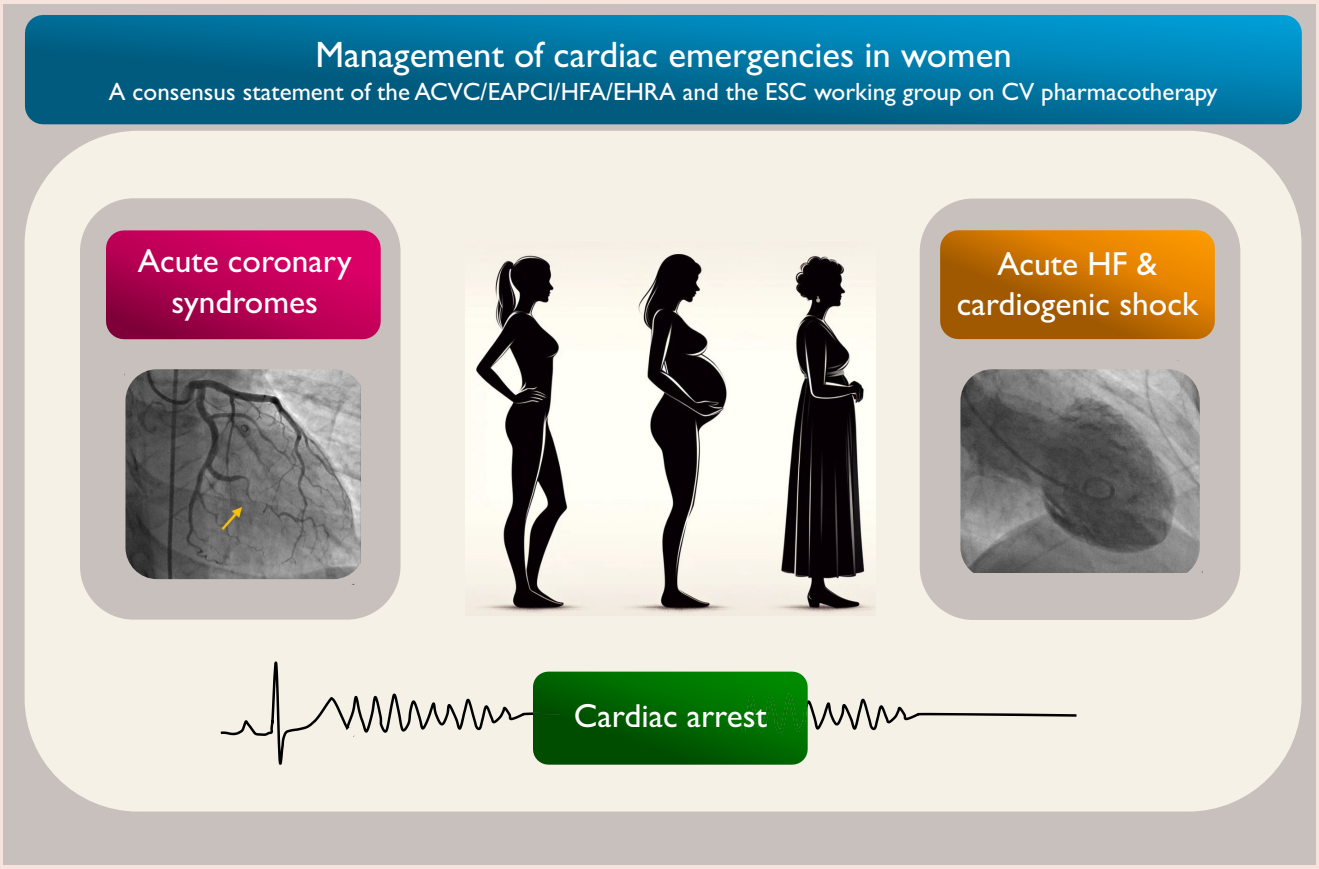
myocardial infarction with non-obstructive coronary arteries, takotsubo cardiomyopathy, and peripartum cardiomyopathy, require specialized attention in terms of both diagnosis and management. In this clinical consensus statement, we summarize current knowledge on therapeutic management of these emergencies in women. Key statements and specific quality indicators are suggested to achieve equal and specific care for both sexes. Finally, we discuss several gaps in evidence and encourage further studies designed and powered with adequate attention for sex-specific analysis.

## Graphical Abstract




**Keywords** Acute coronary syndromes • Acute heart failure • Cardiogenic shock • Cardiac arrest • Women • Sex differences

# Introduction

Cardiovascular (CV) disease is the leading cause of death in women in Europe and USA; still women are affected 5–7 years later than men.[1–3] Multiple studies have demonstrated important sex differences in pathophysiological mechanisms, risk factors, management and outcomes of acute cardiac emergencies such as acute coronary syndromes (ACS), acute heart failure (HF), and cardiac arrest (CA).[4–8] Furthermore, women have been underrepresented in randomized clinical trials (RCTs) on optimal treatment of these emergencies, and there is a paucity of knowledge regarding sex-specific dosing and metabolism of various drugs.[9]

This clinical consensus statement from the Association for Acute CardioVascular Care (ACVC) of the European Society of Cardiology (ESC) in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI), the Heart Failure Association (HFA), the European Heart Rhythm Association (EHRA), and the ESC Working Group on Cardiovascular Pharmacotherapy (WG CVP) was written with the aim to present current knowledge on the management of these emergencies in women. Areas of uncertainty and controversy are discussed, and specific quality indicators (QI) for measuring the attainment of guideline-indicated care are proposed to ensure optimal care for women with acute cardiac disease. This clinical consensus statement from ESC associations and working group is included in a focused article collection in *European Heart Journal Open* on Women in Cardiology.

# Methods

Authors with expertise in acute cardiac care were selected to contribute to this consensus statement. The participants volunteered to write sections relevant to their expertise and experience. Relevant literature was identified by each writing group, and a first draft of the document was prepared and sent to all co-authors. On the basis of feedback from all co-authors and

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discussions within the full group, the sections were edited, and a final version of the document was produced. The final document was circulated among all contributors, and consensus was achieved.

The methodology used for development of the sex-specific QIs for measuring the attainment of guideline-indicated care is described in the Supplementary material online, *Supplementary Material*.

# Acute coronary syndromes

## Epidemiology and risk factors

The incidence of ACS is lower in women compared to men in all age groups, but the sex difference declines with age.[10,11] At all ages, women are more likely to present with non-ST-elevation-ACS, and less likely to present with ST-elevation myocardial infarction (STEMI).[4,7]

Risk factors for ACS in women are the traditional risk factors, such as hypertension, dyslipidaemia, diabetes, obesity, smoking, but also less recognized factors such as psychosocial and socioeconomic factors.[6,7] Sex-specific risk factors also need to be taken into consideration[5–7] (*Figure 1*). Hypertension, diabetes, obesity, and smoking seem to have more impact on the risk for ACS in women compared to men.[5–8] Of note, the prevalence and impact of risk factors seem to vary by age and the differences compared with men are less pronounced in the elderly.[8] After menopause, the prevalence of CV risk factors in women increases,[5] and more than 50% of women with ACS have three or more CV risk factors.[6,12] Although the risk of atherosclerotic ACS is significantly lower in women compared to men, ACS should be the initial working diagnosis when women with a clustering of risk factors present with chest pain.

## Pathophysiology

Obstructive atherosclerotic coronary artery disease (CAD) is the most frequent cause of ACS in women.[13] However, the pathophysiology includes a broader spectrum of aetiologies such as non-obstructive atherosclerotic disease, coronary microvascular dysfunction, coronary spasm, and spontaneous coronary artery dissection (SCAD), requiring different diagnostic and therapeutic strategies.

## Clinical presentation and initial diagnostic management

Chest pain is the dominant and most frequent symptom in women diagnosed with ACS, but women often present with additional symptoms such as pain between the shoulder blades, nausea or vomiting, and shortness of breath.[14–16] Substantial evidence suggests that women present to the hospital for ACS treatment later than men.[7] The reasons for the delay in presentation include lack of awareness, misinterpretation of symptoms, barriers to accessing care, and fear.

A 12-lead electrocardiogram (ECG) and cardiac troponins are important in the initial triage and diagnosis of women with ACS, guiding the initial management strategy (*Figure 2*).[17] High-sensitivity cardiac troponin levels are on average lower in women than in men, and a lower threshold for troponin concentrations in women have been proposed for clinical decisions in women with ACS.[18,19] However, the use of uniform cut-off concentrations remains the standard of care in the 2023 ESC guidelines for the management of ACS.[17]

## Treatment

### Reperfusion strategies

The 2023 ESC guidelines for management of ACS recommend treating both sexes equally concerning reperfusion.[17] Despite clear guideline recommendations, global data report that women are less likely to receive percutaneous coronary intervention (PCI) after admission for ACS, even in the setting of STEMI.[7] This may be linked to the fact that obstructive CAD is less frequent in women, although the lack of utilization of angiography and consequently a lower use of primary PCI in female patients, as well as lower transfer of female patients by network systems, have been shown in several studies.[20–22] Despite clear guideline recommendations, early invasive management of women with NSTEMI is even more underused.[17,23,24]

Risk scores, such as the Global Registry of Acute Coronary Events (GRACE) 2.0 score, may be used to select ACS patients for *early* invasive treatment.[17] The GRACE 2.0 risk score for in-hospital mortality does not include sex as a variable, and it was recently shown that the GRACE 2.0 score underestimated in-hospital mortality risk in women.[25] Moreover, an updated version of GRACE 3.0 score performed better in women compared to GRACE 2.0 and led to a clinically relevant reclassification of female patients to the high-risk group.[25]

### Pharmacological treatment

The ESC guidelines recommend the same pharmacological treatment for women with atherosclerotic ACS as for men.[4,17,26,27] The use of aspirin at the time of ACS is of clear benefit,[26,27] and $P_2Y_{12}$ inhibitors have been shown to reduce adverse outcomes.[27,28] The benefit of antiplatelet drugs must however be weighed carefully against the risk of bleeding, which is higher in women than in men.[29] The Academic Research Consortium on High Bleeding risk (ARC-HBR) definition represents a useful tool for bleeding risk assessment both in women and men undergoing PCI.[29] Use of radial access as well as careful consideration of age, weight, and renal function when selecting antithrombotic therapy may reduce the risk of bleeding.[17,27,30] De-escalation or shortening of dual antiplatelet therapy (DAPT) are alternative antiplatelet strategies which may be considered in those with HBR.[17] The ESC guidelines also recommend adding a proton pump inhibitor to DAPT for patients with HBR.[17] Statins, beta-blockers and angiotensin-converting enzyme (ACE) inhibitors are recommended as secondary prophylaxis after ACS in the same way as in men.[4,26,27]

## Prognosis of women with acute coronary syndrome

Sex-related outcomes after ACS vary by age. Younger women appear to have worse short-term and long-term outcomes compared to younger men, but older women have similar outcomes to those of older men.[31,32] The reason for these differences are not quite clear, and this and other gaps in evidence are discussed at the end of this article.

## Myocardial infarction with non-obstructive coronary arteries

Myocardial infarction with non-obstructive coronary arteries (MINOCA) encompasses a heterogeneous group of underlying causes, both atherosclerotic and non-atherosclerotic.[33–35] Myocardial infarction with non-obstructive coronary artery is a working diagnosis, not a final diagnosis, and it is of utmost importance to identify the underlying cause, e.g. non-obstructive atherosclerotic CAD, coronary microvascular dysfunction, coronary spasm, or spontaneous coronary artery dissection (SCAD).[34,35] The most recent definition of MINOCA excluded non-ischaemic causes of myocardial injury from the MINOCA definition.[33–35] Henceforth, non-ischaemic conditions such as takotsubo cardiomyopathy, myocarditis and non-ischaemic cardiomyopathy are no longer encompassed within the MINOCA definition, but labelled MINOCA mimickers.[33–35]

The reported prevalence of MINOCA varies widely across studies (1–15%)[35] but is significantly higher in women than in men, and higher in younger compared to elderly women.[34,35] When the diagnosis is not clear after invasive coronary angiography, echocardiography, cardiac magnetic resonance, intra-coronary imaging, and provocative spasm testing, are useful tools to establish the underlying cause.[17,34,36,37] Determining the cause of MINOCA and excluding other possible causes for cardiac troponin elevation have important implications for tailoring

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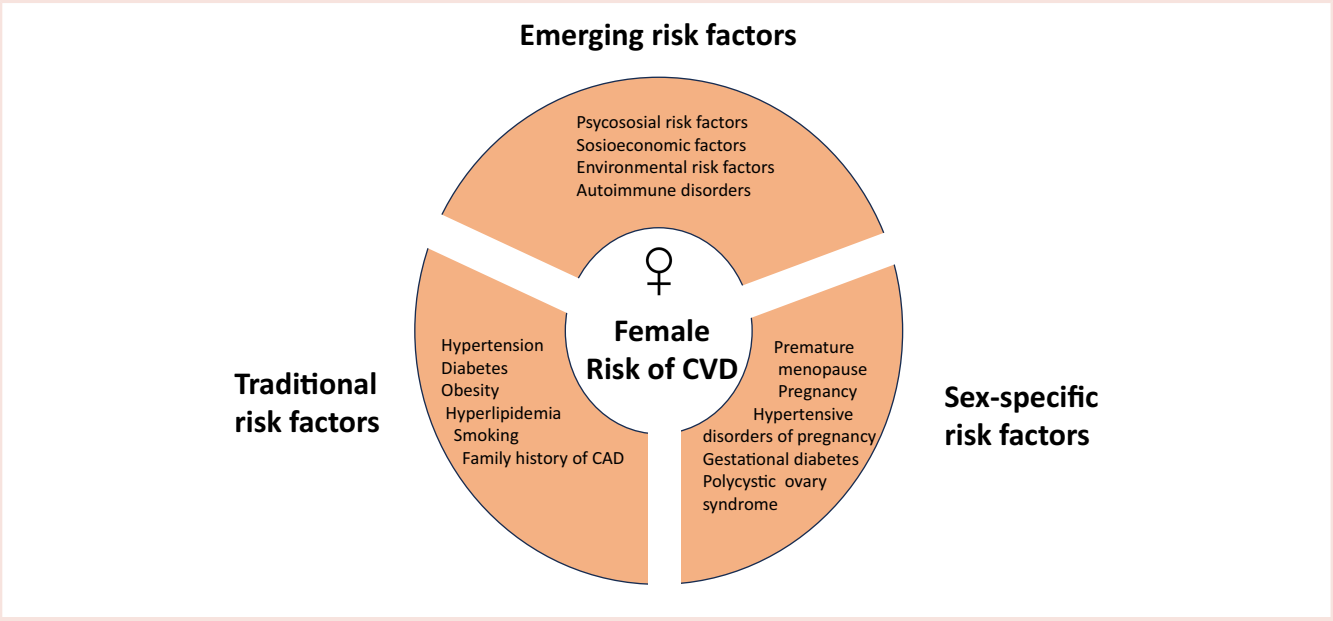


**Figure 1** Risk factors for cardiovascular disease in women.[6,7] CAD, coronary artery disease; CVD, cardiovascular disease.

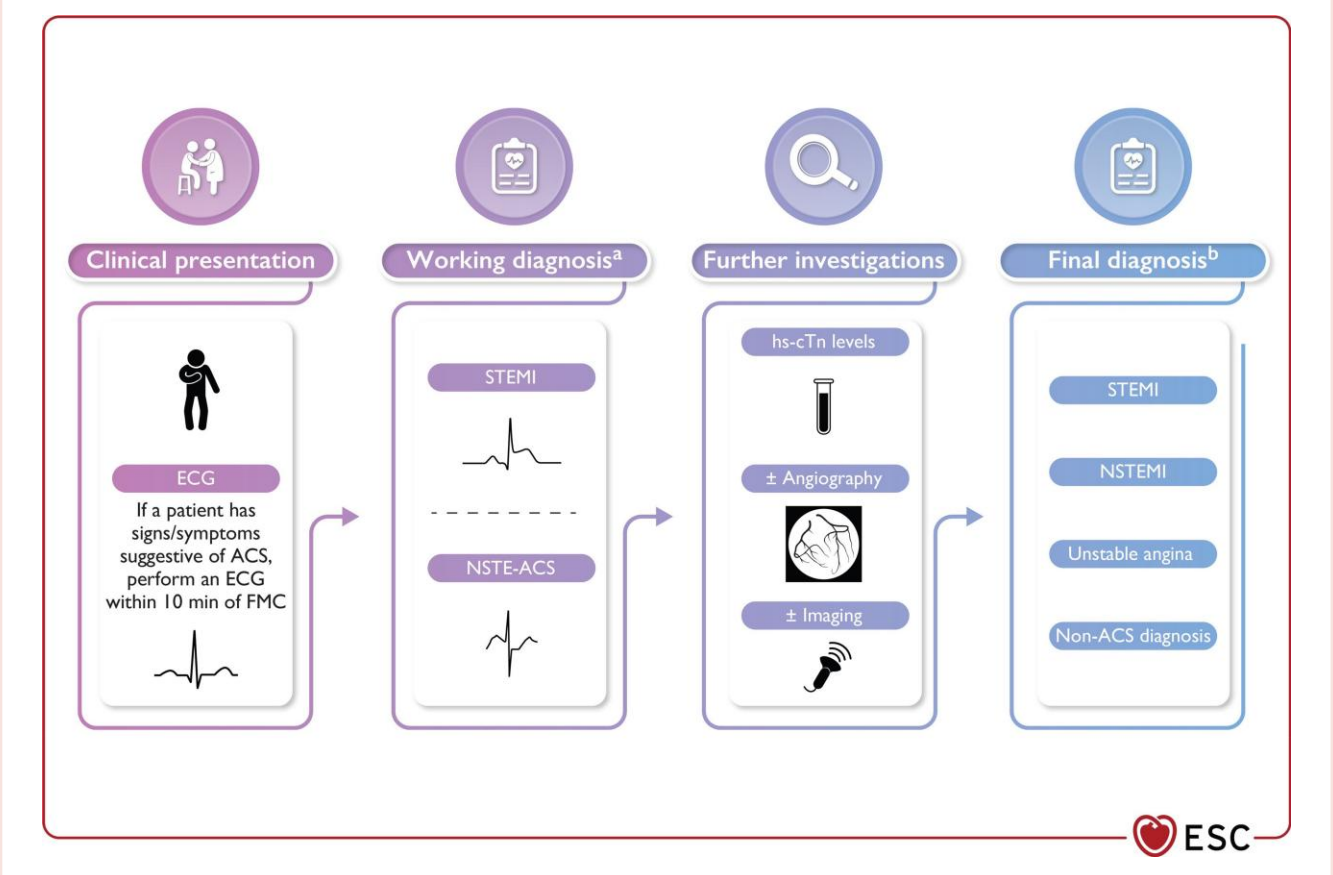


**Figure 2** Classification and diagnosis of patients presenting with suspected acute coronary syndrome. Reprinted with permission from Byrne *et al.*[17] ACS, acute coronary syndrome; ECG, electrocardiogram; FMC, first medical contact; hs-cTn, high-sensitivity cardiac troponin; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction.

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**Table 1 Suggested diagnostic and therapeutic management of SCAD**

| Clinical management | Suggested approach |
|---|---|
| Diagnosis | |
| Invasive angiography | Angiographic appearances diagnostic in most cases (*Figure 3*). Careful technique due to increased risk of iatrogenic dissection |
| Optical coherence tomography (OCT) | Useful and low risk in cases where angiographic appearances are non-diagnostic or to guide PCI |
| Intravascular ultrasound | Lower spatial resolution than OCT. Alternative when OCT unavailable |
| Computed tomography | Lower spatial resolution than angiography. May be helpful where non-invasive follow-up is required of proximal or mid-vessel disease |
| Revascularization | |
| PCI | Reserved for cases with high myocardial jeopardy at presentation (e.g. occlusive SCAD). Long segments of small calibre stents often needed |
| CABG | Reserved as bail-out for high-risk scenarios. Increased risk of early graft failure over time. |
| Conservative | Good outcomes with healing, restoration of coronary architecture and small myocardial injuries in most non-occlusive cases |
| Thrombolysis | Isolated reports of complications. Not the preferred management option in SCAD |
| Medical management | |
| Clopidogrel/P2Y12 inhibitors | In cases managed with PCI, manage according to guidelines. In conservatively managed SCAD, limited observational data suggest increased risk of dual over monotherapy. Clinical trial data awaited |
| Aspirin | Use as long-term prophylaxis is controversial. Clinical trial data awaited |
| Statin | No current evidence to suggest a benefit of statins after SCAD outside primary prevention guidelines |
| Beta-blockers | Use according to guidelines in patients with LVSD after SCAD. Use of beta-blockers and control of hypertension may reduce the risk of recurrent SCAD. Clinical trial data awaited |
| ACE inhibitors/ARB | Use according to guidelines in patients with LVSD post-SCAD or to control hypertension |

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; LVSD, left ventricular systolic dysfunction; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.

secondary prevention measures. Notably, women with non-obstructive CAD are advised aggressive risk factor management.[17] The prognosis of MINOCA depends on the underlying cause and comorbidities, may vary. A recent study utilizing data from a nationwide registry found that patients diagnosed with MINOCA and those suffering from myocardial infarction with obstructive CAD had comparable clinical outcomes.[38]

## Spontaneous coronary artery dissection

Spontaneous coronary artery dissection is an important cause of ACS in women, with the peak incidence at 50 years and accounting for 23–36% of ACS events in women under 50–60 years.[39–42] Spontaneous coronary artery dissection is also a cause of pregnancy-associated MI occurring primarily in the first few months postpartum and accounting for 23–67% of ACS in this context.[43,44]

Accurate diagnosis of SCAD is critical, as the management is different to atherosclerotic ACS (*Table 1*).[39,40] Angiographic appearances are often diagnostic[39] but in ambiguous cases, intra-coronary imaging with optical coherence tomography (OCT) is useful (*Figure 3*, *Table 1*).[45]

Percutaneous coronary intervention in SCAD is associated with an increased risk of complications, particularly iatrogenic dissection and haematoma extension.[46] For this reason, a conservative approach to revascularisation is advised where possible.[39,40] However, where PCI is essential (e.g. proximal or mid-vessel occlusive SCAD), improvements in flow are achievable but at the expense of long-stented segments. Following SCAD, optimal medical management is unknown but is now the subject of an ongoing clinical trial.[47] Limited observational data suggest that beta-blockers and control of hypertension may be associated with a lower risk of recurrent SCAD.[48,49] The role of antiplatelet therapies in conservatively managed SCAD has been questioned, as the pathophysiology of SCAD is thought to relate to the development of a spontaneous intramural haematoma, and it is unclear how medications that prolong bleeding time would reduce future risk in this context.[39]

Chest pain after SCAD is common and leads to frequent hospital readmissions (27.6% ACS). It is usually non-ischaemic and generally slowly improves but can be challenging to manage. Around 10% of SCAD survivors will have a recurrent event over a 5- to 10-year follow-up.[39–42] Despite this, the prognosis from SCAD is good due to the small infarct sizes, as most SCAD is non-occlusive and affects more distal coronary territories.[50] Suggested diagnostic strategies and therapeutic management of SCAD are summarized in *Table 1*.

## Acute coronary syndrome during pregnancy

Acute coronary syndromes are overall rare during pregnancy (1.7–6.2/100 000 pregnancies) but is responsible for approximately 20% of maternal CV deaths during this period.[51,52] As the birth rate in women >40 years increases, ACS in pregnancy may become more common. The underlying pathophysiological mechanism is most often non-atherosclerotic mechanisms, and SCAD is the most frequent cause.[43] The clinical presentation and management of ACS during pregnancy are similar to ACS in non-pregnant women and are detailed in the 2018 ESC Guidelines for the management of cardiovascular diseases (CVD) during pregnancy.[52] Foetal monitoring and a multidisciplinary approach are essential. The guidelines recommend primary PCI as the preferred reperfusion therapy for STEMI.[52] Intravenous unfractionated heparin and low-dose aspirin appear to be safe.[43,52,53] If DAPT is required, clopidogrel is considered safe, but should be maintained for the shortest time possible.[52,53] There are very limited safety and efficacy data on bivalirudin, prasugrel, ticagrelor, and glycoprotein IIb/IIIa inhibitors.[52,53] Beta-blockers are considered safe (except for atenolol

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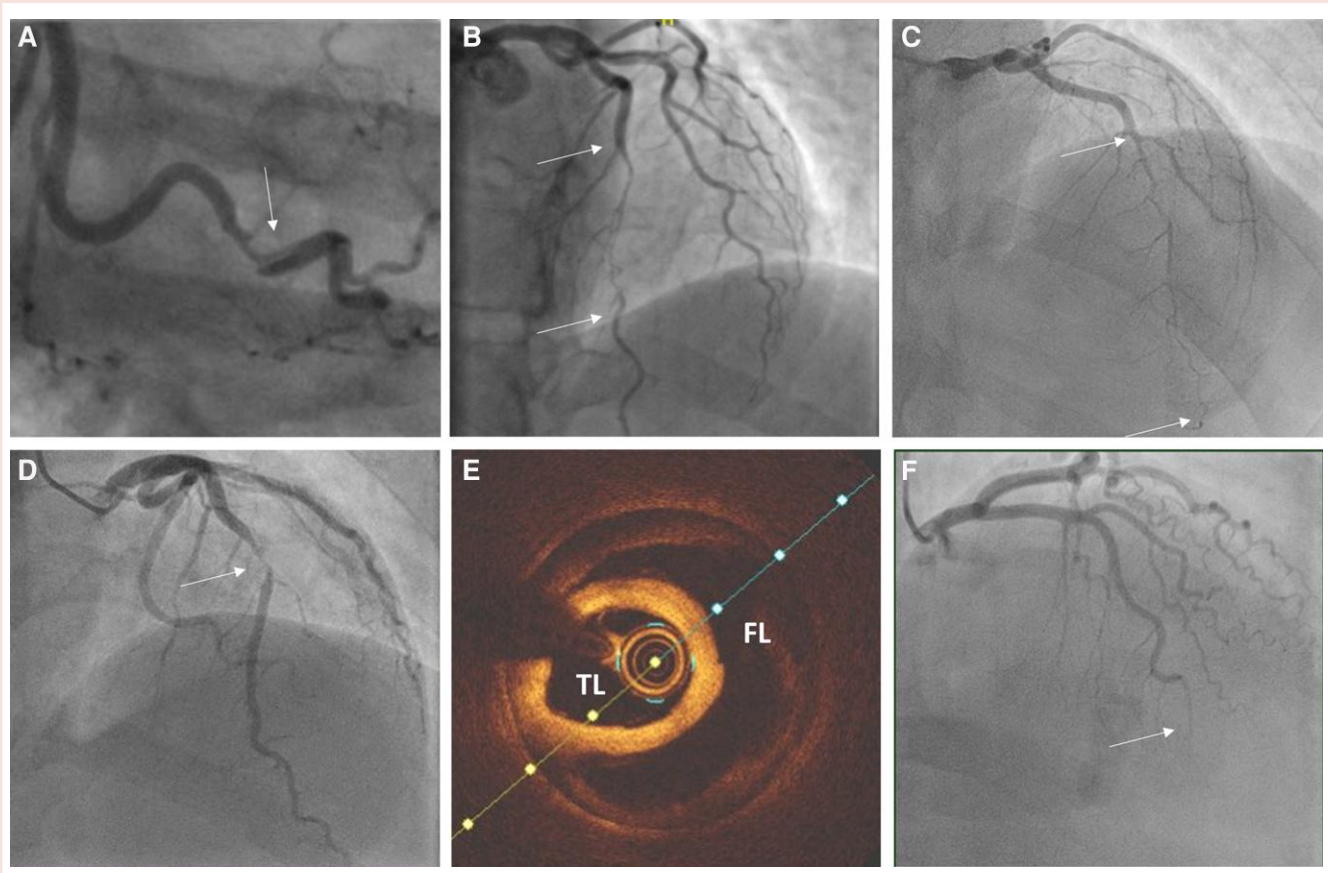


**Figure 3** Angiographic appearances of spontaneous coronary artery dissection: (*A*) Type 1—characterized by dual lumen appearance and contrast hang-up due to contrast penetration of the false lumen. (*B*) Type 2A—long narrowing (arrows) often tapering at the distal extent and with recrudescence of a normal calibre vessel distally. (*C*) Type 2B—long narrowing (arrows) which extends distally with- out restoration of a normal calibre vessel distally. (*D*) Type 3—shorter stenosis (arrow) angiographically difficult to distinguish from focal atherosclerotic plaque without confirmation by intra-coronary imaging. (*E*) Optical coherence tomography (OCT) image from case shown in (*D*). TL, true lumen; FL, false lumen. (*F*) Type 4—Occlusion, often distally. May be difficult to distinguish from coronary embolus but may have upstream tapering to suggest an underlying occlusive intramural haematoma.

and non-selective beta-blockers),[52] although some effects on foetal growth have been observed.[54]

## Targets for equality in the management of acute coronary syndrome

In order to further implement potentially life-saving therapy and procedures, the ESC ACVC established 20 QIs for measuring the attainment of guideline-indicated care.[55] These QIs were defined and intended to be used similarly in both men and women. Since no difference across genders is expected, a 'significant' imbalance in the rates of QIs between men and women might be interpreted as gender inequality in the quality of care. See Supplementary material online, *Table S1* for suggested QIs to measure sex inequality.

### Consensus statements on acute coronary syndromes

- Chest pain is the dominant and most frequent symptom in women with ACS, but additional symptoms as shortness of breath and nausea/vomiting are common.
- Obstructive atherosclerotic CAD is the most frequent cause of ACS in women. The guideline-recommended treatment is the same as in men, both with respect to revascularization and pharmacological therapy.
- Non-obstructive atherosclerotic CAD, microvascular disease, coronary spasm, and SCAD are common causes of ACS in younger women and need specific management.
- Use of radial access during invasive angiography, as well as careful tailoring of antithrombotic drugs in relation to age, weight, renal function, and bleeding risk category, are advised in order to reduce the bleeding risk in women.
- Beta-blockers are suggested treatment in SCAD. The use of antiplatelets is controversial.

# Acute heart failure and cardiogenic shock

Acute HF and cardiogenic shock (CS) represent the most extreme manifestations of CV disease, with significant differences in clinical

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characteristics and administered treatment between female and male patients.[3,56,57] With respect to prognosis, however, most studies report similar or better outcomes in women compared to men when adjusted for comorbidities and age. In the EuroHeart Failure Survey II on acute heart failure, both in-hospital and 1-year mortality were similar (6.6% and 20%, respectively).[57]

## Epidemiology and clinical presentation

Women with acute HF tend to be older and present with more hypertension, atrial fibrillation, diabetes, and valvular heart disease than men. They also have a higher incidence of *de novo* HF, especially in the setting of acute myocardial infarction (AMI).[3,56,57] With respect to hypertension, the Framingham study showed that the risk of developing HF was higher in hypertensive women than men, and that hypertension could be causing 59% of HF cases in women.[56,58]

Heart failure with preserved ejection fraction (EF) (HFpEF) is the most frequent phenotype. In a recent cohort study, 55% of women presented with HFpEF, 39% with HF with mildly reduced EF, and 29% with HF with reduced EF.[3]

## Management of acute heart failure

As acute HF is a heterogeneous condition, initial management may differ according to the main clinical presentation. Diagnostic workup and treatment according to the clinical presentation are detailed in the 2021 ESC guidelines for diagnosis and treatment of acute and chronic HF and its 2023 Focused Update.[59,60] Recommendations are the same for women as for men.

In all HF patients, the key for good outcomes is rapid identification and reversal of any potentially treatable underlying condition with institution of supportive therapies where required. Differences between men and women largely do not affect their management on the cardiac intensive care unit except relating to their physical size. Consideration must however be given to anatomical and physiological differences (body weight and composition, gastrointestinal motility, liver metabolism, and glomerular filtration rate) as these significantly affect pharmacokinetics/dynamics of drugs.[27]

In acute HF, intravenous diuretics are the cornerstone of treatment. According to guidelines, intravenous vasodilators may be considered to relieve HF symptoms when SBP is >110 mmHg.[54] In patients with low cardiac output and hypotension, inotropes may be needed.[59,60]

Current ESC guidelines recommend early initiation and rapid uptitration of key HF drugs in patients admitted with acute HF, similar in men and women.[59,60] Data on the therapeutic effect of several agents in women are however limited, with women remaining underrepresented in clinical trials. This has a potentially significant impact on the generalization of observed results on the female population and underscores the need for more evidence and higher female representation in HF trials. Sex-specific results in some of the HF landmark trials are shown in Supplementary material online, *Table S2*.

Recent data suggest that women with HF might need lower doses of key disease-modifying agents than men. In the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF), the relationship of administered dose of ACE inhibitors and angiotensin receptor blockers (ARBs) on all-cause mortality and hospitalization for HF was investigated.[61] As expected, the survival and freedom of hospitalization increased with increasing dose in men. Surprisingly, there was a paradoxical lower risk of death and hospitalization for HF in females that received <50% of the target dose. In addition, women were more likely to have side effects at the same doses. This unexpected finding in available evidence brings into question whether the optimal dose for women may be different to that for men.

## Special situations

Two potentially life-threatening conditions in women which require urgent and specific assessment and management warrant particular consideration; takotsubo syndrome (TTS) and peripartum cardiomyopathy (PPCM).

### Takotsubo syndrome

Commonly known as stress cardiomyopathy, TTS typically presents in postmenopausal woman. Women comprise approximately 90% of the TTS cases reported with a mean age of 65–75 years in most series, and the risk of developing TTS increases five-fold in women after the age of 55 years.[62,63] The presentation may be similar to ACS, and characterized by ECG changes and transient left ventricular (LV) and/or right ventricular wall dysfunction caused by a number of triggers including physical or emotional factors.[62,63]

A diagnostic algorithm has been proposed where patients presenting with ST-elevation should undergo urgent coronary angiography with left ventriculography to exclude acute STEMI. In those with non-ST-segment elevation, the INterTAK Diagnostic Score can be used (*Figure 4*).[64] Patients with low/intermediate probability (score ≤70) are advised to undergo coronary angiography with left ventriculography, while patients with a high probability (score >70) only require transthoracic echocardiography (TTE).[64] Although there are no RCTs to guide therapy, advice includes avoidance of precipitants (including beta-adrenergic agents) and considering the use of levosimendan if haemodynamics indicate.[64] Its reversible nature justifies a supportive medical approach to avoid or treat possible complications including acute LV dysfunction aggravated by mitral regurgitation or LV outflow tract obstruction, until full recovery. Mechanical circulatory support (MCS) has been used as 'bridge to recovery' in selected cases.[65]

### Peripartum cardiomyopathy

Peripartum cardiomyopathy is defined as a new-onset cardiomyopathy during the peripartum episode or up to 6 months postpartum, manifesting as reduced LV ejection fraction without any other cause of HF.[66] The presentation may vary from subtle or asymptomatic to CS. The management strategy considers both mother and foetus and includes urgent hospital admission and transfer to an advanced HF centre where MCS and/or cardiac transplantation can be provided. Where CS is present, urgent delivery by caesarean section (irrespective of gestation) should be considered according to current guidelines, while breastfeeding is currently discouraged.[52,59] Regarding the initial treatment of HF caused by PPCM, management goals are similar to acute HF in non-pregnant women[59,66] whilst avoiding teratogenic agents (see below). Further management of PPCM, including the use of disease-modifying agents and bromocriptine, is detailed in the ESC guidelines for the management of CVD during pregnancy.[52] Levosimendan does not seem to increase myocardial oxygen demand and may be considered in patients with severe PPCM.[52]

## General treatment of acute heart failure during pregnancy

Medical treatment of HF in pregnancy is complex because of the teratogenic effect of many commonly used HF medications, which must be avoided (including ACE inhibitors, ARB, angiotensin receptor/neprilysin inhibitors, aldosterone antagonists, sodium-glucose co-transporter-2 inhibitors, and atenolol).[52] Loop diuretics, such as furosemide, are considered safe.[52] When required, acute vasodilatation may be obtained with nitroglycerine or nitroprusside. According to the 2018 ESC guidelines, hydralazine, in combination with nitrates, may be used after the acute phase.[52] Beta-blockers should be initiated with caution and gradually uptitrated. Beta-1-selective drugs are

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| InterTAK Diagnostic Score | |
|---|---|
| Female sex | 25 points |
| Emotional stress | 24 points |
| Physical stress | 13 points |
| No ST-segment depression | 12 points |
| Psychiatric disorders | 11 points |
| Neurologic disorders | 9 points |
| QTc prolongation | 6 points |
| | |
| **≤70 points**<br>Low/intermediate probability of TTS | **>70 points**<br>High probability of TTS |

**Figure 4** InterTak diagnostic score for Takotsubo syndrome.[64]

**Table 2 Female representation and outcomes in landmark RCTs on management of patients in cardiogenic shock**

| Study name | Year | Intervention | Indication | *n* | Women (%) | Main outcomes in women compared to men |
|---|---|---|---|---|---|---|
| IABP-SHOCK II[68] | 2012 | IABP vs. no IABP | AMI-CS | 600 | 31 | Consistent results in men and women with respect to 30-day mortality |
| CULPRIT-SHOCK[66,67] | 2017 | Culprit-lesion-only vs. multivessel PCI | AMI-CS | 686 | 24 | No interaction between sex and coronary revascularization strategy regarding mortality or renal failure (interaction $P = 0.11$) |
| ECLS-SHOCK[69] | 2023 | ECLS vs. no ECLS | AMI-CS | 420 | 19 | Consistent results in men and women with respect to 30-day mortality |

AMI-CS, acute myocardial infarction-cardiogenic shock; ECLS, extracorporeal life support; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention; RCT, randomized controlled trial.

preferred.[52] Management of acute HF during pregnancy requires a multidisciplinary approach and referral to an expert centre with a surgical and MCS/transplant program as a backup option.[52] Foetal monitoring is advised in all cases.

## Cardiogenic shock

The incidence of CS is rising at a higher rate in women compared with men, and several studies suggest that women with AMI are more likely to develop CS than men.[67,68] Women also tend to present with an overall higher risk profile (older age, more comorbidities, haemodynamic derangement, vasopressor requirements, and CA).[69] There are conflicting data regarding outcomes; recent studies suggest similar mortality rates in women and men after adjusting for baseline differences.[67,70]

### Treatment

Relatively few women (19–31%) have been included in RCTs regarding treatment of CS (*Table 2*), limiting the generalizability of observed results for women. In the CULPRIT-SHOCK trial, 686 patients (24% women) with CS-AMI and multivessel CAD were randomly assigned to the culprit-lesion-only PCI vs. multivessel PCI.[71,72] Sex did not influence mortality or renal failure according to revascularisation strategies (interaction $P = 0.11$). Hence, revascularization of the culprit lesion only should be the preferred strategy equally among women and men.

In pivotal RCTs on MCS in AMI-CS (IABP-SHOCK II and the ECLS-SHOCK), the number of included women were again low, but the results were neutral and similar in men and women (*Table 2*).[73,74] Although no convincing evidence exist, acute MCS may be appropriate in selected patients with AMI-CS according to current guidelines as a bridge to recovery/decision/bridge/transplant.[17,59] Published data suggest however that only a minority of MCS recipients are women (33%).[67,69] The reasons for this potential under-utilization remain poorly understood. Data regarding complication rates are conflicting, with some studies reporting MCS use in women is associated with increased complication rates (bleeding, vascular, and readmission) and inferring this might impact

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**Table 3 Female representation and outcomes in recent RCTs on management of out-of-hospital cardiac arrest**

| Study name | Year | Intervention | Indication | *n* | Women (%) | Main outcomes in relation to sex |
|---|---|---|---|---|---|---|
| COACT[86] | 2019 | Immediate vs. delayed angiography | OHCA without ST-segment elevation | 552 | 20% | Similar results in women and men (no benefit of immediate angiography on survival at 90 days) |
| TOMAHAWK[81] | 2021 | Immediate vs. delayed angiography | OHCA without ST-segment elevation | 554 | 30% | Immediate angiography no benefit over delayed with respect to 30-day mortality—no interaction with sex |
| BOX trial[82] | 2022 | Oxygen targets | OHCA | 789 | 19% | Similar results in women and men |
| BOX trial[83] | 2022 | Blood pressure targets | OHCA | 789 | 19% | Similar results in women and men |
| INCEPTION[84] | 2023 | Extracorporeal vs. conventional CPR | Refractory OHCA | 134 | 10% | No subgroup analysis on sex |
| ARREST[87] | 2023 | Immediate transfer to CAC vs. standard care | OHCA without ST-segment elevation | 827 | 32% | Similar results in women and men (no reduction in 30-day mortality) |
| TAME[88] | 2023 | Mild hypercapnia vs. normocapnia | | 1700 | 23% | Similar result in women and men (no effect of hypercapnia on 6 months mortality) |

BOX, Blood Pressure and OXygenation Targets After OHCA; CAC, cardiac arrest centre; COACT, Coronary Angiography After Cardiac Arrest; INCEPTION, Early Initiation of Extracorporeal Life Support in Refractory OHCA; OHCA, out-of-hospital cardiac arrest; RCT, randomized controlled trial; TAME, Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest; TOMAHAWK, Immediate Unselected Coronary Angiography Versus Delayed Triage in Survivors of Out-of-hospital Cardiac Arrest Without ST-segment Elevation.

decision-making to implement MCS, but other studies reporting no difference in complication rates and outcomes.[70] Practical differences due to patient size (normothermic flow indices and cannulae/vessel dimensions) do present physical limitations regarding the opportunities for safe peripheral MCS. However, as access routes and technologies change, the recommendations in 2021 HF guidelines, for their use in selected patients, using a predefined algorithm coupled with close monitoring,[59] could avoid that sex *per se* precludes female patients from consideration.[69,70]

## Consensus statements on acute heart failure

- Heart failure with preserved ejection fraction (HFpEF) is the most frequent phenotype in women with HF.
- Most studies report similar or better outcomes in women compared to men when adjusted for comorbidities and age.
- Takotsubo and peripartum cardiomyopathy are rare causes of HF affecting predominantly or exclusively women and requiring urgent and specific assessment and management.
- ESC guidelines recommend early initiation and target-dosage of key disease-modifying drugs, similar in men and women.
- It is advised to adjust doses of drugs according to age, body weight, and kidney function.
- The therapeutic dose of pharmaceutical agents for treating HF in women is inconclusive and should be re-evaluated in RCTs with equal rates of women vs. men.
- Many commonly used HF medications are teratogenic and must be avoided in pregnant women with HF.
- It is advised that treatment of CS in women follow the same guidelines as for men.

# Cardiac arrest in women

## Epidemiology and prognosis

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in Europe.[75] Consistent with other reports, only 35% of patients are women.[76,77] Although survival rates have increased in the last decades, mortality after OHCA remains high for both sexes. In Europe, only 8% of all patients with OHCA survive to hospital discharge, but of those admitted with return of spontaneous circulation, up to 50% may be discharged alive.[75] Younger age, witnessed arrest, initiation of resuscitation by bystanders, and an initial shockable rhythm, irrespective of sex, are important factors consistently associated with a higher probability of survival.[78,79]

Female sex is associated with poorer outcomes after OHCA.[77,80,81] Not only is overall survival to hospital discharge lower in women but also survival to hospital admission, survival to hospital discharge of patients successfully resuscitated, and survival with a good neurological outcome.[76,77,80,81] Outcome differences between sexes can be largely explained by patient characteristics and arrest circumstances. Women resuscitated from OHCA are older, more often live alone when they are older and have less frequently witnessed arrests, and present less often with STEMI and more often with non-cardiac causes of arrest.[77,80,81] In a large observational study, 34% of women compared to 52% of men with OHCA presented with an initial shockable rhythm, which is the most important factor associated with survival after OHCA.[80] This finding might partly be explained by a longer evolution of arrest related to later recognition of alarming symptoms by women and OHCA by bystanders.

## Resuscitation care

The steps to perform cardiopulmonary resuscitation (CPR) are the same in women as in men. However, studies indicate that women

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may receive suboptimal resuscitation care with less likelihood of undergoing CPR by bystanders, even when OHCA is witnessed.[77,80] The potential reasons for inhibiting bystander resuscitation of women are complex and include fear by the public regarding inappropriate touching, or accusations of sexual assault.[82] This highlights the importance of the development of focused programs and educational campaigns for the general population.

## Post-resuscitation care

Women less frequently undergo invasive coronary angiography after OHCA compared to men,[83,84] but this might be explained by other factors and does not necessarily represent real undertreatment.[83] Targeted temperature control is also less frequently carried out.[84,85] In addition, women receive 'do-not-resuscitate orders' and 'withdrawal of life-sustaining therapy orders' more often and earlier than men, frequently before the advised 72-h window for neuroprognostication.[77,84] The latter may not only contribute to the overall worse outcome of women but also explain the less frequent use of in-hospital procedures after OHCA.[86]

Women are still significantly underrepresented in recent RCTs on interventions for improving outcomes after OHCA (*Table 3*). Two recent RCTs failed to show a benefit of performing early angiography in patients presenting without STEMI, and to target a specific blood pressure or oxygen saturation during admission at the intensive care, respectively.[87–89] Although there were no differences related to sex, women represented only 19–30% of the included patients (*Table 3*), limiting the generalizability of these results for women. Similarly, a recent trial on the use of e-CPR for refractory OHCA included only 14 women from a total of 134 randomized patients (10%), highlighting again the insufficient representation of women in RCTs.[90]

## Cardiac arrest in pregnancy

Although the basic principles of resuscitation for CA apply to pregnant women, some differences should be kept in mind. If arrest occurs beyond 20 weeks of pregnancy, manual displacement of the uterus to the left or left lateral position of the patient can reduce aortocaval compression and is suggested in a scientific statement from the American Heart Association.[91]

At late stages of pregnancy, emergency caesarean is advised when initial resuscitation fails (within 4 min of CA).[53,91] If this is not feasible, rapid maternal transfer to the appropriate clinical setting with uninterrupted resuscitation is advised.

### Consensus statements on cardiac arrest

- Women resuscitated from OHCA are older, have less frequently witnessed arrest, and present less often with STEMI and more often with non-cardiac causes of arrest compared to men
- In unadjusted analyses, female sex is associated with poorer outcomes after OHCA. In most studies, the sex differences disappear when adjusting for baseline characteristics and treatment
- It is advised that management of CA in women follow the general guideline recommendations
- It is important to increase awareness of OHCA and the importance of bystander resuscitation in both men and women
- Increased representation of women in RCTs on management of OHCA is of urgent importance.

# Gaps in evidence and need for further research

Cardiac emergencies in women are associated with a high risk of adverse outcomes and mortality. Still, women are less likely to receive evidence-based treatment compared to men. Despite the recent encouragement to include more women, there is an alarming underrepresentation of women in most RCTs on optimal management of these emergencies.

The first step to improving outcome in women, is to focus attention on sex-specific characteristics. Understanding sex disparities will likely improve the awareness, prevention, recognition, treatment, and outcomes of CVD in women, especially in potentially life-threatening cardiac emergencies. Closing the sex gap in these pathologies requires sex-specific research on:

- Pathophysiology of CAD (particularly MINOCA), HF, and CA
- Sex-specific clinical risk stratification and decision tools
- Development of approaches to shorten interval to diagnosis and treatment of ACS
- Optimal target dosage of drugs: antithrombotic and HF agents
- Exploration of subpopulations of women who are socially disadvantaged because of race, ethnicity, income level, or education.

We therefore encourage a new era in research, where studies on acute CVD are designed and powered with adequate attention for sex-specific analysis to understand the complex mechanisms of women's biology. We also underline the need for better consideration of sex hormones as effect-modifiers in healthcare delivery and urge the development of optimal treatments to reduce potentially avoidable deaths among women.

# Lead author biography

Professor Sigrun Halvorsen (MD, PhD, FESC) is a clinical cardiologist working as Head of Cardiology at Oslo University Hospital Ullevål, Oslo, Norway, and Professor at the University of Oslo. She is also a member of the Executive Board of the Acute Cardiovascular Care Association of the European Society of Cardiology (ESC), and an associate editor of *European Heart Journal Acute Cardiovascular Care*. Halvorsen has been involved in writing of several of the recent ESC guidelines, including the 2023 ESC guidelines on management of acute coronary syndromes. Her main research interests are acute coronary syndromes, antithrombotic treatment, and cardiovascular disease in women.

Professor Antonia Sambola (MD, PhD, FESC) is a cardiologist specialised in Acute Cardiac Care at University Hospital Vall d'Hebron in Barcelona. She is an associate professor at Autonomous University of Barcelona, where she also coordinates the MSc in translational research in cardiovascular disease. She has formed and led the Working Group of cardiovascular disease in Women of the Spanish Society of Cardiology, and the Task Force on Cardiac emergencies in women of

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Acute Cardiac Care Association-ESC. She is member of the advisory board of the Health Ministry on Government strategies for National Health in cardiovascular disease in women and actively contributes to the National Strategy for Cardiovascular Health in women in Spain.

# Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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## Data availability

No new data were generated or analysed in support of this research.

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American College of Cardiology Foundation; Society of Thoracic Surgeons; American Medical Women's Association; Centers for Disease Control and Prevention; Office of Research on Women's Health; Association of Black Cardiologists; American College of Physicians; World Heart Federation; National Heart, Lung, and Blood Institute; American College of Nurse Practitioners. Evidence-based guidelines for cardiovascular disease prevention in women: 2007 update. *Circulation* 2007;**115**:1481–1501.
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