**Management of cardiac emergencies in women. A clinical consensus statement of the Association for Acute CardioVascular Care (ACVC) of the ESC, 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**

***Supplementary material***

**Methodology for the development of sex-specific quality indicators**

The methodology for the construction of the ESC Quality Indicators (QI) has been defined previously.**1** The QIs are defined for different domains of care where quality should be assessed. For each domain, “main” and “secondary” QIs are selected. The main QIs are considered as the most appropriate indicators for capturing quality, or an essential element that is mandatory for basic assessment. Secondary QIs may be used either to perform complementary measurements, or as a substitute in case of missing variables.

We based our selection of QIs for detection of sex equality on the previously developed QIs for ACS,1 and selected domains and QIs where sex differences have been observed. For example, in the management of acute myocardial infarction (AMI), sex differences have been reported in time-to-reperfusion, bleeding and secondary prevention treatment at discharge. Thus, the QIs related to reperfusion, antithrombotics, and secondary prevention could be used to measure sex equity. Since the advice is that women should be treated in the same way as men with respect to reperfusion and secondary preventive therapy, a “significant” imbalance in the rates of QI attainment between women and men could be interpreted as sex inequality in the quality of care.

We based the acceptable margin of non-inferiority for sex differences in times to reperfusion on the results of a study assessing the relation between time to treatment and mortality in primary angioplasty for AMI.2 In this study, time to reperfusion was on average 12% longer in women than in men (233±137 versus 208±139 minutes), and a 30 minute delay was associated with a relative risk for 1-year mortality of 1.075 (95% CI 1.008 to 1.15; P=0.041). Thus, a difference of >10% in time to reperfusion may be considered as unacceptable, and this threshold was selected. The same threshold of 10% was chosen for all the selected QIs.

The QIs for sex equality and women specificity in the management of ACS and how to assess them are listed in Supplemental table 1.

**Supplemental table 1.** Quality Indicators for sex equality and women specificity in the management of ACS

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| ***Delayed management*** | | **Assessment** | **ACP\*\* Measure criteria** |
| Main QI (1) | Sex ratio\* of the median times between first medical contact and ECG + troponin assess ment; ratio women vs men should not be higher than 110% for both QIs. | ***Numerator:*** *Sex ratio of the median times* | ***Importance***: high impact  ***Appropriate care***: underuse  ***Evidence base***: it is advised,  low level of evidence  ***Measure specification***: uncertain reliabil- ity, no denominator (for the center) ***Measure feasibility***: under physicians’  control, usable, data collection feasible, high complexity, time dependent variable |
| Secondary QI (1) | Sex ratio of the median times between onset of symptoms and call; ratio should not be higher than 110% | ***Numerator:*** *Sex ratio of the median times* | ***Importance***: high impact  ***Appropriate care***: underuse  ***Evidence base***: is advised, low level of evidence  ***Measure specification***: uncertain reliabil- ity, no denominator (for the center) ***Measure feasibility***: under patients’ con- trol, usable, data collection feasible, high complexity, time dependent variable |
| ***Lower Reperfusion/Invasive strategy rate and speed*** | | **Assessment** | **ACP Measure criteria** |
| Main (2) | Sex ratio of the rate of reperfusion in pa- tients with STEMI\*\*\*, eligible for PCI: onset of symptoms<12h and anatomy suitable for angioplasty; ratio should not be lower than 90%. | ***Sex ratio***  ***Numerator:*** *Number of eli- gible patients with STEMI*  *<12 hours undergoing reperfusion*  ***Denominator:*** *number of* patients with *STEMI eligible for reperfusion and without contraindications* | ***Importance***: high impact  ***Appropriate care***: underuse  ***Evidence base***: is advised, high level of evidence  ***Measure specification***: measure reliable, numerator-denominator clearly defined ***Measure feasibility***: under physicians’ control, usable, high burden of patients (STEMI), data collection feasible, low  complexity, variable recorded in most cur- rent registries. |

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| Secondary (2) | Sex ratio of the rate of patients with STEMI who receive timely reperfusion. Ratio should not be lower than 90%. Timely is defined as:   1. *For patients treated with primary PCI and* ***admitted directly*** *to centres with PCI facilities*: <60 min from initial STEMI di- agnosis to infarct-related artery wire crossing 2. *For patients treated with primary PCI and* ***transferred*** *to centres with PCI facil- ities:* <90 min from initial STEMI diag-   nosis to infarct-related artery wire cross- ing. | ***Sex ratio***  ***Numerator:*** *number of pa- tients with STEMI undergo- ing timely reperfusion with Primary PCI or fibrinolysis* ***Denominator:*** *all patients with STEMI eligible for reperfusion* | ***Importance***: high impact  ***Appropriate care***: underuse  ***Evidence base***: is advised, high level of evidence  ***Measure specification***: uncertain reliabil- ity, numerator-denominator clearly de- fined  ***Measure feasibility***: under physicians’ control, usable, high burden of patients (STEMI), data collection feasible, low complexity, but variables not recorded in all current registries. |
| Secondary (3) | Sex ratio of the rate of NSTEMI\*\*\*\* pa- tients who receive invasive coronary an- giography within 24h of their diagnosis; ratio should not be lower than 90%. | ***Sex ratio***  ***Numerator:*** *number of NSTEMI patients who re- ceive invasive coronary an- giography within 24h of their diagnosis.*  ***Denominator:*** *all NSTEMI patients without contraindi- cations* | ***Importance***: high impact  ***Appropriate care***: underuse  ***Evidence base***: is advised, high level of evidence  ***Measure specification***: measure reliable, numerator-denominator clearly defined ***Measure feasibility***: under physicians’ control, usable, high burden of patients (NSTEMI), data collection feasible, low  complexity, variable recorded in most cur- rent registries. |
| Secondary (4) | Sex ratio of the median time between the initial STEMI diagnosis and arterial ac-  cess (absolute value) for primary PCI. Ratio should not be higher than 110%. | ***Sex ratio***  ***Numerator*** *median time be- tween initial STEMI diagno- sis and arterial access* | ***Importance***: high impact  ***Appropriate care***: underuse  ***Evidence base***: is advised, high level of evidence |

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| --- | --- | --- | --- |
|  |  | *among STEMI patients un- dergoing reperfusion* | ***Measure specification***: uncertain reliabil- ity, numerator-denominator clearly de- fined  ***Measure feasibility***: under physicians’ control, usable, high burden of patients (STEMI), data collection feasible, low complexity, variable recorded in most cur- rent registries. |
| ***Higher bleeding risk*** | | **Assessment** | **ACP measure criteria** |
| Main (4) | Ischaemic and haemorrhagic risk assess- ment should be performed using a validated risk score. | ***Numerator:*** *number of patients who have been stratified according to a validated risk score* ***Denominator:*** *Total number of patients with a diagnosis of AMI* | ***Importance***: performance gap  ***Appropriate care***: underuse  ***Evidence base***: is advised, low level of evidence  ***Measure specification***: measure reliable, numerator-denominator clearly defined ***Measure feasibility***: uncertain, usable, high burden of patients, data collection  feasible, low complexity, but variable not recorded in all current registries. |
| Secondary (5) | Sex ratio of the proportion of patients with “adequate P2Y12 inhibition” defined as: (number of patients discharged with P2Y12 inhibitor) / (eligible patients). Ratio should not be lower than 90%.  Eligible is defined as follows:   * For ticagrelor: AMI patients without previ- ous haemorrhagic stroke, high bleeding risk, fibrinolysis or oral anticoagulation. | ***Sex ratio*** | Proportion of patients with “adequate P2Y12 inhibition” defined as: (number of patients discharged with prasugrel, ticagrelor, or clopidogrel)/(patients eligi- ble). |

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|  | * For prasugrel: PCI-treated AMI patients without previous haemorrhagic or is- chaemic stroke, high bleeding risk (patients   ⩾75 years and/or <60 kg body weight are also considered as high bleeding risk fea- tures), fibrinolysis or oral anticoagulation.   * For clopidogrel: no indication for prasugrel   or ticagrelor and no high bleeding risk. |  |  |  |

\*Ratio corresponds to the proportion of values for women/men. \*\*ACP Measure criteria: criteria to assess the validity of performance measures as defined by the American College of Physicians. *\*\*\*STEMI= ST segment elevation acute myocardial infarction; \*\*\*\*NSTEMI=Non-ST elevation acute myocardial infarc- tion; GL=guidelines; NSTEMI=Non-ST elevation myocardial infarction; \*\*\*\*\*LDL=low-density lipoprotein; DAPT=dual antiplatelet therapy;*

Heart failure

Supplemental Table 2. Female participation and sex-specific effects of pharmacotherapy for heart failure in some landmark trials.

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| **Study/year** | **Patient group** | **N** | **Women %** | **Results** |
| **Beta-blocker** | | |  | |
| CIBIS II 19993 | Chronic HF,  LVEF ≤0.35 | 2647 | 20% | The effect of bisoprolol on mortality in patients with chronic HF was not analysed separately in women |
| COPERNICUS 20014,5 | Chronic HF,  LVEF <0.25 | 2289 | 20% | Carvedilol showed similar benefits on cardiovascular death or admission for HF in patients with severe HF, irrespective of sex |
| **Angiotensin-converting-enzyme inhibitors** | | | | |
| SOLVD 19916 | Chronic HF, LVEF ≤0.35 | 2569 | 20% | The effect of enalapril on mortality was not ana lysed in the subgroup of women |
| **Angiotensin receptor blocker** | | |  | |
| Val-HEFT 20017 | Chronic HF,  LVEF <0.40 | 5010 | 20% | Valsartan showed a significant reduction in the combined mortality-morbidity endpoint in patients with HF irrespective of sex. |
| CHARM-Overall programme 20038 | Chronic HF,  LVEF >0.40 | 7599 | 32% | Candesartan showed similar benefit on cardiovascular death or admission for HF in both sexes |
| **Mineralocorticoid receptor antagonist** | | | | |
| RALES 19999 | Chronic HF,  LVEF ≤0.35 | 1663 | 27% | Spironolactone in addition to standard therapy substantially reduced the risk of both morbidity and death among men and women |
| EMPHASIS-HF 201110 | Chronic HF,  LVEF ≤0.35 | 2737 | 22% | Eplerenone showed similar benefits on cardiovascular death or admission for HF among women and men |
| **Sacubitril/valsartan** | | | | |
| PARADIGM-HF 201411 | Chronic HF,  LVEF<40% | 8442 | 22% | Sacubitril/valsartan showed similar benefits on cardiovascular death or admission for HF in both women and men |
| **Sodium-glucose-transporter-2 inhibitors (SGLT2i)** | | | | |
| EMPEROR Reduced 202012 | Chronic HF,  LVEF <40% | 3730 | 24% | Empagliflozin showed comparable clinical benefits on cardio- vascular death or admission for HF in both women and men |
| DAPA-HF 201913,14 | Chronic HF,  LVEF <40% | 4744 | 24% | Dapagliflozin reduced the risk of worsening HF, cardiovascular death, and all-cause death similarly in men and women. In addition, dapagliflozin was safe and well-tolerated irrespective of sex. |
| EMPULSE 202215 | Acute HF irrespective of LVEF | 530 | 34% | Initiation of empagliflozin in patients hospitalized for *acute heart failure* was well tolerated and associated with clinical benefit in both women and men |

*HF=heart failure; LVEF=left ventricular ejection fraction*

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