Interventional Treatment of Acute Coronary Syndrome (ACS): Non-ST Elevation ACS (NSTE-ACS)

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Piera Capranzano

4.1 Introduction

Cardiovascular disease, of which coronary artery disease (CAD) is the prevalent manifestation, is the most common cause of death for both genders in industrialized countries; women develop CAD nearly a decade later in life. Across the entire spectrum of CAD, acute coronary syndromes (ACSs), characterized by acute plaque rupture or erosion with sudden coronary blood flow impairment, are associated with the highest rates of adverse clinical events. Among ACSs, the non-ST elevation ACS (NSTE-ACS), including non-ST elevation MI (NSTEMI) or unstable angina, is more frequent than ST elevation acute myocardial infarction (STEMI). While hospital mortality is higher in patients with STEMI than among those with NSTE-ACS, at 6 months, the mortality rates are similarly high in both clinical conditions and are higher among patients with NSTE-ACS at longer-term follow-up, most likely due to the more widely heterogeneous and worse overall risk profile of patients with NSTE-ACS. These latter epidemiological data suggest the need for defining optimal acute and chronic treatment strategies for NSTE-ACS.

Recent temporal trends show declining of short- and long-term mortality after an ACS, but some reports suggest less effective reduction in women [1]. In addition, previous studies demonstrated that women with ACSs have higher mortality compared with men. Ongoing debates are focusing on whether gender-specific differences exist in diagnosis, clinical course, management, and response to treatment of all spectrums of CAD presentations and the extent to which these differences can impact on overall clinical approach and on the relative prognosis of both genders.

P. Capranzano, MD
Cardiovascular Department, Ferrarotto Hospital, University of Catania, Catania, Italy
e-mail: pcapranzano@gmail.com

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This chapter describes current recommended treatments for NSTE-ACS, with a special focus on issues regarding specific disease features, outcomes, and management of women.

4.2 Specific Features of Women with NSTE-ACS

Women present more frequently with NSTE-ACS and less frequently with STEMI compared with men. Atypical chest pain or presentations, including dyspnea, vasovagal symptoms, or symptoms of heart failure (HF), are more common in women presenting with NSTE-ACS. Absent or atypical chest pain leads to underrecognition and undertreatment of the disease [1], especially when the ECG is normal or nearly normal or when the ECG is abnormal at baseline. Of note, women around 55 years of age are an important subset with missed ACS diagnosis in the emergency department. Several studies have reported that men with ACS are more likely to have ruptured plaques, whereas women were more likely to present with plaque erosion, suggesting that the mechanism of ACS development in men and women may differ. Patients presenting with plaque erosions are more likely to have a longer indolent period of ischemia as opposed to those with ruptured plaques who present more suddenly. This may partly explain why women with ACS present later than men and with typical or atypical angina symptoms rather than a clear-cut ACS.

Women presenting with NSTE-ACS are older than men and have a higher frequency of diabetes, hypertension, HF, and other comorbidities. Despite being older and having higher prevalence of most CAD risk factors than men, women with NSTE-ACS are more likely than men to have nonobstructive CAD on angiography. There are many potential explanations for NSTEMI without evidence of obstructive CAD at angiography, including plaque rupture with angiographic underestimation of the true burden of CAD, microvascular dysfunction, or coronary spasm. Additional explanations may include noncoronary causes leading to symptoms and/or troponin elevation that may be confused with ACS, such as HF, uncontrolled hypertension, arrhythmias, and pulmonary embolism.

A sex-based analysis from the PROSPECT study demonstrated that women presenting with ACS have less extensive CAD by both angiographic and IVUS assessments, as evidenced by fewer and more focal non-culprit lesions and fewer vessels with angiographic non-culprit lesions compared with men even after multivariable adjustment for age and risk factors [2]. Moreover, this latter analysis showed that non-culprit lesions in women who have less necrotic core volume are less prone to rupture and have similar plaque burden per lesion; however, other observed higher-risk plaque characteristics of women including less calcium, smaller lumen areas, greater proportion of minimal lumen area ≤ 4 mm^2, and significantly less total fibrous volume may explain the similar cardiovascular event rates during 3 years of follow-up, despite women having

less extensive coronary atherosclerosis. Of note, the between-sexes differences in the ACS pathophysiology, which were observed in the PROSPECT subanalysis, appeared to balance out with no impact on culprit- or non-culprit-related clinical outcomes [2].

4.3 Prognosis of Women with NSTE-ACS

A significant gender by type of ACS interaction has been demonstrated. Indeed, in STEMI, the 30-day mortality was higher among women, whereas in NSTEMI, mortality was lower among women [3]. In a recent analysis of trends in gender differences in cardiac care and outcome after an acute myocardial infarction (MI) from the RIKS-HIA (Register of Information and Knowledge About Swedish Heart Intensive Care Admissions) registry, women as a group have better-adjusted prognosis than men after acute MI; however, younger women and women with STEMI have disproportionately poor prognosis [1]. The lower mortality risk of women with NSTEMI may be due to the higher proportion of women with nonobstructive CAD regardless of ACS type, as demonstrated in a cohort of 35,128 patients with angiographic data. In this latter analysis, after additional adjustment for angiographic disease severity, 30-day mortality among women was not significantly different than men, regardless of ACS type [3]. Moreover, the relationship between sex and 30-day mortality was similar across the levels of angiographic disease severity [3].

Despite presenting with higher-risk characteristics and having higher in-hospital risk and similar mortality than men when adjusting for risk profile, women with NSTE-ACS are treated less aggressively than men [4]. One perceived obstacle in treating women, especially those older, might be related to an increased incidence of bleeding [5]. Indeed, despite reductions in bleeding events over time, female sex remained a strong independent predictor of bleeding and vascular complications. The risk of bleeding complications can be assessed using integer scoring systems involving clinical variables associated with a heightened risk. Although the use of scores goes beyond sex in providing an overall estimation of bleeding risk, common to all scores is the independent association between female sex and risk of bleeding complications. Clinical factors, such as older age, renal failure, cardiogenic shock, and use of larger sheaths, have been specifically identified as predictors of risk in women. However, the female propensity for bleeding persists beyond these risk factors. Indeed, while the sex-specific risk of increased cardiovascular events persists after adjustment for comorbidities, the association between bleeding and female sex persists after adjustment for confounding clinical factors. Sex-specific mechanisms surrounding body mass index, access vessel anatomy, platelet-vessel biology, and percutaneous coronary intervention (PCI)-related pharmacotherapy may play a role [5].

The observed higher rates of access site bleeding among women set the rationale for the Study of Access Site for Enhancement of PCI for Women (SAFE-PCI) trial, in which women were randomized to undergoing radial or femoral access coronary angiography and if required PCI [6]. The study was stopped early due to a lower-than-expected event rate. Among the 1787 women enrolled (>50 % presented with NSTE-ACS) and 691 undergoing PCI, there was no significant difference in bleeding or vascular complications (primary endpoint) between radial and femoral access among those undergoing PCI (radial 1.2 % vs. 2.9 % femoral, $p=0.12$), while in the overall cohort of women undergoing coronary angiography, a benefit associated with the radial access was detected (0.6 % radial vs. 1.7 % femoral; $p=0.03$).

4.4 Management of NSTE-ACS

The first step of NSTE-ACS management is assessment of acute risk, which drives the selection of the site of care and treatment, including antithrombotic treatment and timing of coronary angiography. The indication and optimal timing for an invasive approach are mostly based on overall clinical presentation and several risk factors. Indeed, a routine invasive strategy compared with a selective invasive strategy in NSTE-ACS has been shown to decrease mortality, recurrent ACS episodes, subsequent rehospitalization, and revascularization. Moreover, large meta-analyses have shown that the benefit of a routine invasive strategy was confined to biomarker-positive patients and was more pronounced in high-risk patients. Thus, the results of trials and meta-analyses support the broad implementation of a routine invasive strategy and highlight the role of risk stratification in the decision process. With regard to the optimal timing of the invasive approach in NSTE-ACS patients, available data indicate that an early as opposed to a delayed invasive strategy is safe and associated with a lower risk of refractory symptoms and a shorter hospitalization. Also the optimal timing of coronary angiography and revascularization should be guided by individualized risk stratification. Recommended indications for the invasive (urgent, early, or delayed) and conservative strategies for the treatment of NSTE-ACS according to risk stratification are illustrated in Fig. 4.1. It is recommended that patients at very high risk with at least one very high-risk criterion undergo an urgent invasive strategy (within 2 h). In patients at high risk with at least one high-risk criterion, an early invasive strategy (within 24 h) is recommended. In patients with at least one intermediate-risk criterion, the coronary angiography may be delayed up to 72 h from admission [7, 8]. Finally, in low-risk patients, a conservative is recommended, and decision for an invasive strategy is guided by a noninvasive stress test (preferably with imaging) for inducible ischemia. Besides risk factors indicated in Fig. 4.1, also comorbidities, frailty, cognitive status, and estimated life expectancy have to be assessed when deciding the invasive approach for NSTE-ACS.

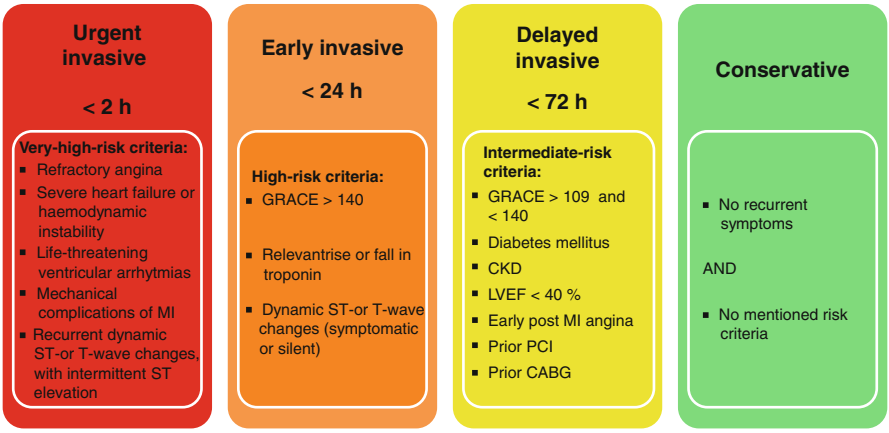

Fig. 4.1 Recommended indications for the invasive and conservative strategies for the treatment of NSTE-ACS according to risk stratification (*MI* myocardial infarction, *CKD* chronic kidney disease, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting)

Coronary angiography has a central role in the management of patients with NSTE-ACS, as it helps clinicians in the diagnosis of ACS related to obstructive epicardial CAD and thus stratifying the patient's short- and long-term risk and guiding the long-term medical treatment, avoiding, for instance, unnecessary exposure to antithrombotic agents. Angiographic patterns of CAD in NSTE-ACS patients are widely heterogeneous, ranging from normal epicardial coronary arteries to a severely and diffusely diseased coronary artery tree. Up to 20 % of patients with NSTE-ACS have no lesions or nonobstructive lesions of epicardial coronary arteries, while among patients with obstructive CAD, half to two thirds of patients have multivessel disease.

The indication and timing of myocardial revascularization are based on the same factors, which drive also the selection of an invasive approach, and on the functional and anatomic severity of CAD. The selection of the revascularization modality, PCI, or coronary artery bypass grafting (CABG) is based on the assessment of risk features specific to each revascularization strategy and on the angiographic pattern of CAD. No contemporary trials comparing PCI with CABG in patients with NSTE-ACS and multivessel CAD are available. Moreover, in NSTE-ACS trials comparing an early with a delayed invasive strategy, or a routine invasive with a selective invasive strategy, the decision to perform PCI or CABG was left to the discretion of the operator. Retrospective subanalysis and meta-analysis comparing CABG versus PCI for the treatment of NSTE-ACS have shown similar long-term mortality, lower stroke, and higher need for repeat revascularization with PCI. To guide the choice of revascularization modality among stabilized patients with NSTE-ACS, including those

undergoing ad hoc PCI of the culprit lesion, it is reasonable to use the criteria applied in patients with stable CAD.

Finally, there is a lack of prospective randomized studies assessing the type, complete versus incomplete, and timing, simultaneous versus staged, of percutaneous revascularization in NSTE-ACS. A complete revascularization of significant lesions should be pursued in multivessel disease patients with NSTE-ACS as multiple PCI and NSTE-ACS trials have shown a detrimental prognostic effect of incomplete revascularization, although unmeasured confounding factors in these retrospective studies cannot be excluded. Nevertheless, the need for complete revascularization has to be tailored to age, overall patient clinical status, and comorbidities. The decision to treat all the significant lesions in the same or staged PCI procedures should be based on clinical presentation, comorbidities, renal function, coronary anatomy complexity, and ventricular function. Indeed, a staged PCI in multivessel disease may be associated to lower periprocedural complications, especially in high-risk settings (i.e., low ejection fraction, chronic renal insufficiency).

4.5 Management of NSTE-ACS: Gender Issues

There is conflicting evidence regarding the benefit of an early invasive strategy in women with NSTE-ACS [7]. Indeed, while post hoc analysis of the FRISC II and RITA 3 trials showed no benefit of an invasive strategy in women, in contrast to its beneficial effect in men, the TACTICS-TIMI 18 indicated similar benefits of a routine early invasive versus a conservative (ischemia-guided) strategy in men and women. Caution is needed in interpreting the findings of these subgroup analyses, as differences in clinical and angiographic risk profile between women and men, and the markedly lower number of women included in those trials may explain the observed interaction of sex subgroup with the treatment effect of an invasive strategy in NSTE-ACS. Moreover, several important differences between the latter randomized trials may explain the discordant findings and the lack of benefits from a routine invasive strategy compared with a conservative strategy. For instance, in the FRISC II trial, the excess of risk with the invasive strategy group among women was driven by a particularly high CABG-related mortality; the RITA 3 trial included a cohort of women at lower risk, with no or single-vessel disease in the majority of cases (67 %) and lower rates of death and MI at 1 year in women in both the invasive (8.6 %) and conservative groups (5.1 %) than those of patients enrolled in the FRISC II and TACTICS-TIMI 18 trials. Importantly, in the TACTICS-TIMI 18 trial, the benefit of an early invasive therapy, in terms of significant reduction in death and MI at 1 year, was further enhanced in women with elevated troponin T levels [7]. Differently, women with NSTE-ACS and no elevation in troponin who underwent an early invasive strategy had a nonsignificant increase in events, as did women with a low-risk TIMI score. The meta-analysis by the Cochrane Collaboration pointed out that women

derive a significant reduction in death or MI for a routine invasive versus a conservative strategy, although with an early hazard due to an increase in procedure-related events, including periprocedural MI and bleeding, suggesting the adoption of strategies minimizing these events especially in women (i.e., optimization of stenting strategies, staged PCI procedures, accurate selection of upstream and periprocedural medical therapy, and antithrombotic regimens and radial access). It has been shown that when bleeding avoidance strategies are not used, women have significantly higher rates of bleeding than men. Both genders have similar adjusted risk reductions of bleeding when any of those strategies are used. Thus, overall available data suggest that a routine early invasive strategy should be considered in women on the same principles as in men, that is, after careful risk stratification for both ischemic and bleeding risks including clinical and ECG evaluations, analysis of biomarkers, comorbidities, and use of risk scores. Indeed, as stated above in the paragraph on prognosis, sex-based differences in 30-day mortality observed among ACS patients are markedly attenuated after adjustment for baseline characteristics, angiographic disease severity, and treatment strategies in a cohort of 35,128 patients with angiographic data, taken from a pooled analysis of 11 trials [3]. Based on these overall evidences, according to the NSTE-ACS guidelines, both genders should be evaluated and treated in the same way for acute care and for secondary prevention. Women with NSTE-ACS and low-risk features should not undergo early invasive treatment because of the lack of benefit and the possibility of harm. The guidelines point out that particular attention to weight and/or renally calculated doses of antiplatelet and anticoagulant agents has to be placed to reduce bleeding risk among women. Despite the higher number of risk factors, the lack of gender differences in treatment guidelines, and no observed sex-specific treatment effect for most therapeutic agents, women with NSTE-ACS compared with men are less likely to receive evidence-based therapies including both invasive coronary angiography and revascularization [4]. Of interest, even after adjusting for age, cardiovascular risk factors, and extent of disease, myocardial revascularization (PCI or CABG) in patients with significant CAD was less frequently used in women. This has an important prognostic impact as it has been shown that elderly women who are not revascularized have a three-fold higher in-hospital and 1-year mortality rate compared with revascularized women with no increased severe bleeding in this latter group undergoing revascularization [9]. Therefore, elderly women with an NSTEACS should not be denied an evidence-based diagnostic and therapeutic approach because of presumptive excess in risks.

Conclusions

A routine invasive strategy compared with a conservative therapy has been associated with better outcomes for women at higher risk and those with positive biomarkers. Thus, in NSTE-ACS, the choice of an invasive versus a conservative strategy, the optimal timing of catheterization, and the type and completeness of coronary revascularization should be based on objective risk

stratification and not be influenced by the sex of patients, because of a presumption on an increased risk or frailty of women. Strategies to minimize possible complications (i.e., bleeding and periprocedural MI), that could be more frequent among women with NSTE-ACS managed invasively, should be implemented. Moreover, women should receive the guideline-recommended medical therapy as men.

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