An extensive body of research has reported that women experience worse outcomes compared with men when the full spectrum of acute coronary syndromes (ACS) are included (1-4). Compared with men, women are more likely to experience major bleeding (1,2) and vascular access complications (2) post-percutaneous coronary intervention, as well as a higher rate of major adverse cardiovascular events (1) and death (4) within 1 year post-ACS and beyond. Although the “high-risk” profile of women is well established, the degree to which this disparity is explained by differences in age and comorbidities remains an area of debate (1,3). This picture is complicated by the observation that the risk associated with female sex may differ by age strata and ACS subtype. An age-sex interaction has been described (4) whereby younger women, but not older women, experience worse outcomes than their age-matched male counterparts. In addition, a sex-ACS subtype interaction was found in a large sample of clinical trial participants (5), whereby women with ST-segment elevation acute coronary syndromes (STEACS) fared worse, and women with non-ST-segment elevation acute coronary syndromes (NSTEACS) fared better, than men with similar clinical presentations.

Changing demographics have created an imperative to study outcomes in older adults with ACS, and understanding differences between older women and older men undergoing revascularization is one important area for exploration. To date, comparative effectiveness studies are limited because both women (3,6) and older adults (age ≥75 years) (6) have been historically underrepresented in ACS clinical trials. Among ACS subtypes in older adults, NSTEACS is more common than STEACS (7), and a key question among older NSTEACS patients involves whether routine early invasive management is warranted. The mean patient age was only 62 years in a meta-analysis of 7 studies that demonstrated that routine early invasive management for high-risk NSTEACS reduced rates of death or reinfarction, over a mean follow-up of 17 months (8).

One particular topic of uncertainty concerning older adults with NSTEACS centers on whether older women benefit less than older men from an early invasive approach (9). Observational studies of older women in clinical practice show that they are less likely to undergo revascularization at time of hospitalization than older men, although whether this pattern represents appropriate case selection or bias has been an area of debate. In a meta-analysis of patients enrolled in the randomized FRISC II (Fast Revascularization during InStability in Coronary artery disease), ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes), and RITA-3 (Randomized Intervention Trial of unstable Angina) trials comparing a routine invasive strategy with selective invasive strategy in NSTEACS, there was a larger early hazard and less long-term benefit in women than men regardless of age (9). The degree of benefit in women may vary based on the status of myonecrosis markers; a meta-analysis of 8 trials comparing an invasive versus conservative approach found that women with biomarker-positive NSTEACS had a significant reduction in death, myocardial infarction (MI), or rehospitalization for ACS, whereas the same benefit was not seen in women with biomarker negative ACS (10).

In this context, De Carlo et al. (11), in this issue of JACC: Cardiovascular Interventions, further investigated the relationship between sex, age, and outcomes in NSTEACS by analyzing data from the Italian...
Elderly ACS study, which pooled data from NSTEACS patients age ≥75 years enrolled across 23 centers. Patients were enrolled in a randomized controlled trial (n = 313) or a prospective cohort if they met ≥1 exclusion criteria (n = 332) (creatinine >2.5 mg/dl, severe lung disease, malignancy, or recent bleeding, stroke, percutaneous coronary intervention, or coronary artery bypass graft surgery). The original randomized trial (12) reported that NSTEACS patients randomized to an early aggressive strategy, compared with an initial conservative strategy, had no significant reduction in the combined endpoint of death, MI, stroke, and cardiovascular or bleeding readmission within 1 year. In the current study, the authors compared characteristics between the 301 women and 344 men in the pooled randomized and observational cohorts to analyze sex-related differences in revascularization and outcomes.

NOTEABLY, DESPITE THE AGE RESTRICTION, THERE WERE STILL SEX DIFFERENCES BETWEEN WOMEN AND MEN; WOMEN WERE SLIGHTLY OLDER, HAD A HIGHER EJECTION FRACTION, AND HAD LOWER HEMOGLOBIN. FIFTY-FIVE PERCENT OF WOMEN UNDERWENT CORONARY ANGIOGRAPHY Versus 61.6% of men (p = 0.11) with significantly lower rates of revascularization for women compared with men (37% vs. 45%, p = 0.04). Although in-hospital outcomes did not differ, at 1-year follow-up, women experienced a significantly higher rate of the combined endpoint (death, MI, cardiac rehospitalization, severe bleeding, stroke). Among women, those who were revascularized had a better risk profile (younger age, higher glomerular filtration rate) and a significantly lower rate of the 1-year endpoint compared with women who were not revascularized (17.0% vs. 33.9%, p = 0.002), including a lower rate of death (8.1% vs. 21.6%, p = 0.002).

The study (11) has several strengths. Older adults with ACS are historically underrepresented in outcome studies, and enrollment is challenging; the authors made an admirable effort to randomize those who were appropriate and also to follow those who met exclusion criteria in a prospective registry. The sample size for this age group was larger than many reports, and follow-up data were available on all patients. The very low rate of complications in women undergoing an invasive strategy, despite their age, is encouraging and suggests that in the contemporary era of revascularization, concerns over adverse treatment effects may be exaggerated.

However, there are several factors that should be considered in interpreting the conclusion that older women with NSTEACS “should always be considered for early revascularization.” First, in older adults, individual factors, including cognitive impairment and patient/family goals of care, are critical components in determining treatment. Second, the observation that women who were revascularized fared better than women who were not revascularized was contributed to by measured or unmeasured confounders in the observational cohort; for example, the nonrevascularized group was significantly older and had worse renal function, which likely influenced treatment. The practically 3-fold difference in 1-year mortality between women who did versus did not undergo revascularization is far outside the benefit reported with an invasive strategy in randomized trials (10) and suggests that other variables that may influence decision making in older patients, but are frequently unreported (such as frailty or disability), played a role.

Although the low reported complication rate reflects progress in interventional procedures, the external validity of the Italian Elderly ACS study (11) is unclear; it was underpowered to detect infrequent events and had a stringent definition of severe bleeding that required rehospitalization. The rate of severe bleeding was negligible; it occurred in no older patients who underwent revascularization and in only 1 patient (0.5%) who did not undergo revascularization. High rates of radial access (70%) may be partially accountable; however, in the RIVAL (RadIal Vs femorAL access for coronary intervention trial) study, the rate of major bleeding with radial access for NSTEACS (n = 2,552) was 1.8%, in a population whose mean age was 63 years (13). Site-specific attention to management of anticoagulant or antiplatelet agents, or other factors such as a healthier than average population, may account for the very low observed bleeding rate. Nonetheless, it is unclear whether these results apply to more “typical” older adults with ACS in practice and when systematic complete capture of events is ensured. It is also worthy of mention that women in the current study underwent invasive angiography at the same rate as men but were revascularized less, which suggests that anatomic differences between the groups (e.g., higher rate of chronic total occlusions, distal vessel disease, or nonobstructive disease) were a factor in decision making.

In conclusion, robust previous data demonstrate similar risk-adjusted outcomes for men and women with NSTEACS. The worse outcomes for this cohort of older women compared with men, although potentially a result of residual between-group differences as potential confounders, suggest the need for further assessment of this excess risk and understanding
mechanisms. The conclusion that older women with NSTEACS undergoing revascularization can fare well both in-hospital and after 1 year suggests that older women should not be denied consideration of an invasive strategy. The extremely low rate of revascularization-related complications in the current report (11) is encouraging and points to the need for more robust data on the risk-benefit ratio across the spectrum of older women in order to better inform patients.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Judith S. Hochman, Division of Cardiology, Department of Medicine, New York University School of Medicine, 530 First Avenue, Skirball 9R, New York, New York 10016. E-mail: Judith.Hochman@nyumc.org.

---

**REFERENCES**


**KEY WORDS** acute myocardial infarction, coronary revascularization, elderly, women