



# HHS Public Access

Author manuscript

*JACC Cardiovasc Interv.* Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

*JACC Cardiovasc Interv.* 2015 May ; 8(6): 797–799. doi:10.1016/j.jcin.2015.02.006.

## **Editorial: Improving outcomes in older women?:**

**In response to: Gender-related outcomes in elderly patients presenting with acute coronary syndrome: Insights from the Italian Elderly ACS study**

**John A. Dodson, MD, MPH\*** and **Judith S. Hochman, MD\***

\*Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY

An extensive body of research has reported that women experience worse outcomes compared with men when the full spectrum of acute coronary syndromes (ACSs) are included<sup>1-4</sup>. Compared with men, women are more likely to experience major bleeding<sup>1,2</sup> and vascular access complications<sup>2</sup> post-percutaneous coronary intervention (PCI), as well as a higher rate of major adverse cardiovascular events<sup>1</sup> and death<sup>4</sup> within 1 year post-ACS and beyond. While 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<sup>1,3</sup>. 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<sup>4</sup> 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<sup>5</sup>, whereby women with ST elevation ACS (STEACS) fared worse, and women with non-ST elevation ACS (NSTEMACS) 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, as both women<sup>3,6</sup> and older adults (age  $\geq 75$ )<sup>6</sup> have been historically under-represented in ACS clinical trials. Among ACS subtypes in older adults, NSTEMACS is more common than STEACS<sup>7</sup>, and a key question among older NSTEMACS 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 NSTEMACS reduced rates of death or reinfarction, over a mean follow-up of 17 months<sup>8</sup>.

One particular topic of uncertainty concerning older adults with NSTEMACS centers on whether older women benefit less than older men from an early invasive approach<sup>9</sup>. Observational studies of older women in clinical practice show that they are less likely to

---

Corresponding Author: Judith S. Hochman, MD, Division of Cardiology, Department of Medicine, New York University School of Medicine, 530 First Avenue, Skirball 9R, New York, NY 10016, Tel. 212-263-6927, Fax. 212-263-7129, Judith.Hochman@nyumc.org.

Disclosures: The authors have no conflicts of interest relevant to the contents of this paper to disclose

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, ICTUS, and RITA-3 trials comparing a routine invasive strategy with selective invasive strategy in NSTEMI, there was a larger early hazard and less long-term benefit in women than men regardless of age<sup>9</sup>. 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 NSTEMI had a significant reduction in death, MI, or rehospitalization for ACS, while the same benefit was not seen in women with biomarker negative ACS.<sup>10</sup>

In this context, De Carlo et al. further investigated the relationship between sex, age, and outcomes in NSTEMI by analyzing data from the Italian Elderly ACS study, which pooled data from NSTEMI patients age  $\geq 75$  enrolled across 23 centers.

Patients were enrolled in a randomized controlled trial (N=313) or a prospective cohort if they met  $\leq 1$  exclusion criteria (N=332) (creatinine  $>2.5$  mg/dl, severe lung disease, malignancy, or recent bleeding, stroke, PCI, or CABG). The original randomized trial<sup>11</sup> reported that NSTEMI patients randomized to an early aggressive strategy, compared with an initial conservative strategy, had no significant reduction in the combined endpoint of death, myocardial infarction (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, in order to analyze sex-related differences in revascularization and outcomes.

Notably, despite the age restriction, there were still sex differences between women and men; women were slightly older, had a higher ejection fraction, and lower hemoglobin. Fifty-five percent of women underwent coronary angiography vs. 61.6% of men (P=0.11) with significantly lower rates of revascularization for women compared with men (37% vs. 45%, P=0.04). While 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 GFR) 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 has several strengths. Older adults with ACS are historically under-represented 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 NSTEMI “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 non-revascularized group was significantly older and had worse renal function, which likely influenced treatment. The practically threefold 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,<sup>10</sup> 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.

While the low reported complication rate reflects progress in interventional procedures, the external validity of the Italian Elderly ACS Study 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, as it occurred in no older patients who underwent revascularization, and only 1 patient (0.5%) who did not undergo revascularization. High rates of radial access (70%) may be partially accountable; however, in the RIVAL study, the rate of major bleeding with radial access for NSTEMI (N=2,552) was 1.8%, in a population whose mean age was 63 years<sup>12</sup>. 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 prior data demonstrate similar risk-adjusted outcomes for men and women with NSTEMI. The worse outcomes for this cohort of older women compared to men, although potentially due to residual between-group differences as potential confounders, suggests the need for further assessment of this excess risk and understanding mechanisms. The conclusion that older women with NSTEMI 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 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.

## References

1. Hess CN, McCoy LA, Duggirala HJ, et al. Sex-based differences in outcomes after percutaneous coronary intervention for acute myocardial infarction: A report from TRANSLATE-ACS. *J Am Heart Assoc.* 2014; 3:e000523. [PubMed: 24510115]

2. Lichtman JH, Wang Y, Jones SB, et al. Age and sex differences in in-hospital complication rates and mortality after percutaneous coronary intervention procedures: Evidence from the NCDR®. *Am Heart J*. 2014; 167:376–383. [PubMed: 24576523]
3. Buchholz EM, Butala NM, Rathore SS, Dreyer RP, Lansky AJ, Krumholz HM. Sex differences in long-term mortality after myocardial infarction: A systematic review. *Circulation*. 2014; 130:757–767. [PubMed: 25052403]
4. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. *N Engl J Med*. 1999; 341:217–225. [PubMed: 10413733]
5. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. *J Am Med Assoc*. 2009; 302:874–882.
6. Dodd KS, Saczynski JS, Zhao Y, Goldberg RJ, Gurwitz JH. Exclusion of older adults and women from recent trials of acute coronary syndromes. *J Am Geriatr Soc*. 2011; 59:506–511. [PubMed: 21361882]
7. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med*. 2011; 124:40–47. [PubMed: 21187184]
8. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: A collaborative meta-analysis of randomized trials. *J Am Med Assoc*. 2005; 293:2908–2917.
9. Damman P, Clayton T, Wallentin L, et al. Effects of age on long-term outcomes after a routine invasive or selective invasive strategy in patients presenting with non-ST segment elevation acute coronary syndromes: A collaborative analysis of individual data from the FRISC II - ICTUS - RITA-3 (FIR) trials. *Heart*. 2012; 98:207–213. [PubMed: 21930723]
10. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. *J Am Med Assoc*. 2008; 300:71–80.
11. Savonitto S, Cavallini C, Petronio AS, et al. Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: A randomized controlled trial. *JACC Cardiovasc Interv*. 2012; 5:906–916. [PubMed: 22995877]
12. Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol*. 2012; 60:2490–2499. [PubMed: 23103036]