

GENDER DIFFERENCES IN LONG-TERM PROGNOSIS AFTER NSTEACS:

NOW YOU SEE ME, NOW YOU DON'T !

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It is known that women are often under-represented, or even excluded, in randomized clinical trials, the results of which consequently may not be entirely reproduced in the general population. At the same time, however, sex-based differences in various manifestations of cardiovascular disease are increasingly recognized. Consequently, registries and/or retrospective analyses focusing on sex-related diversity have been widely employed in the last years^{1,3}.

In a recent analysis of cardiovascular outcomes after non-ST elevation acute coronary syndrome (NSTEMACS) in 68,730 patients across trials of TIMI Group, women were found to be at lower risk of major adverse cardiovascular events (MACE) and all-cause death than men². In contrast, after ST elevation myocardial infarction (STEMI), in a recent paper on 10,443 patients recruited in the International Survey of Acute Coronary Syndrome in Transitional Countries registry¹, compared with men, women were at increased risk of death and of developing de novo HF; furthermore, women with de novo HF had worse survival than men, indicating a different scenario than NSTEMACS. As for chronic heart failure (HF), sex-related differences are significant in terms of etiology, epidemiology, clinical presentation, prognosis, comorbidities and response to treatment³. In particular, women show more frequently non-ischemic etiology and worse symptoms and quality of life, but better prognosis than men with respect to all-cause death, cardiovascular death and HF hospitalizations in several studies^{3,4}, whereas other studies have shown no sex-specific differences in outcomes^{5,6}. In the ESC HFA EORP HF Long-term registry, analysis of sex-related differences in outcome of chronic HF demonstrated lower crude rates of all-cause mortality and all-cause HF hospitalization in female compared to male patients⁴. However, sex was not an independent predictor of all-cause mortality, suggesting instead a crucial role of baseline characteristics and baseline comorbidities in determining outcome⁴.

Thus, whether female gender intrinsically confers different prognosis in major cardiovascular conditions remains debated. In the present issue of the Journal, Alvarez Alvarez et al.⁷ report on sex-related differences on outcomes in a fairly large contemporary real-world registry

of patients with NSTEMI. Of 5,686 patients, 1,572 (27.6%) were women. Mean follow-up was 60.0 months. Results of overall “crude” analysis revealed that women scored substantially worse than men on all parameters, as they showed higher risk of cardiovascular mortality (OR (Odds ratio) 1.27, CI (confidence interval) 95% 1.08-1.49), heart failure (HF) hospitalization (OR 1.39, CI 95% 1.18-1.63), and all-cause death (OR 1.10, CI 95% 1.08-1.49).

However, when taking into account several major background differences between male and female cohorts (age, hypertension, diabetes, dyslipidemia, history of vascular disease, smoking status, GRACE score, treatments), a substantially different picture emerged. Careful propensity score matching yielded a subset of 3,120 patients, well-balanced with respect to those clinical characteristics. After this propensity score matching, female gender was associated with a similar risk of cardiovascular mortality (OR 0.86, CI 0.71-1.03) and HF hospitalization (OR 0.92, CI 95% 0.68-1.23), compared to males, and with a significant reduction in the risk of total mortality (OR 0.77, CI 95% 0.65-0.90). Thus, re-assessing data after baseline shows that women had better prognosis compared with men in terms of all-cause mortality or cardiovascular mortality, and a similar (not higher) risk of HF.

The paper of Alvarez Alvarez et al.⁷, reminds us that women and men are indeed different, in many a factor, which need to be accurately taken into account. . In fact, in the post-NSTEMI outcomes analysis of TIMI trials², women apparently were at similar risk of MACE than men, and at higher risk of all-cause death before considering relevant confounders; however, after adjustment for baseline differences, risks of MACE and all-cause death were actually lower among women compared to men. On the other hand, analyzing sex profile and risk assessment of HF patients in the MECKI score data-base⁸, female patients with HF showed better outcome, with an independent impact of female sex on prognosis. However, after propensity score matching harmonization, the outcome advantage of female sex vanished.

Collectively, these findings point to the potential fallacy of comparing “crude” event rates of different populations, and underline the importance of adjusting for sex-related characteristics. It is therefore evident that, in analyzing outcome data aiming at detecting sex-related differences, multivariate risk adjustment models or, better still, propensity score matching, are crucial to achieve a solid final message, avoiding confounding variables. Of special interest is a commentary on what these “variables” -other than sex itself- could be that mark “additional” differences between women and men. Some of them are rather intuitive (e.g., greater age), or well described (e.g., greater prevalence of coronary microvascular disease⁹), and pertain to intrinsic differences in pathophysiology. Other differences, however, while real and significant, actually have more to do with how we practice medicine, not with biology.

Underuse of guideline-directed medical therapy in women is an important issue in this respect. In the post-NSTEACS outcomes analysis of TIMI trials², women were under-treated with many relevant therapies during hospitalization for NSTEMI: they were less likely than men to receive aspirin, P2Y₁₂ inhibitors, statin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and were less likely than men to undergo coronary angiography or to be treated with percutaneous coronary intervention. Even after STEMI, on average women are less likely to receive antiplatelet and anticoagulant agents and female sex was a predictor for not receiving reperfusion therapy¹. Women are only less likely than men to receive aspirin, beta-blockers or thrombolytic therapy, or to be referred for revascularization procedure, after myocardial infarction¹⁰. Even in patients with stable angina, although women generally present more severe symptoms than men¹¹, female patients are undertreated, with less frequent angiography, percutaneous coronary intervention and coronary artery bypass graft surgery¹². Moreover, women with coronary heart disease are less likely to achieve therapeutic targets in the management of the disease¹³ or of the risk factors, such as dyslipidemia, diabetes and obesity¹¹. Regarding HF population, an analysis of 15,415 patients enrolled in the 2 most recent and largest trials of pharmacological therapy in patients with HF with reduced ejection fraction¹⁴ compared women and

men to evaluate the evolution of therapeutic differences between sex, with particular concern about the under-treatment of women highlighted in the last century. No significant sex-related differences in the prescription of evidence-based drug therapies for HF emerged, except for diuretics³, but, in contrast, device use is much less in women than in men, in particular cardiac resynchronization therapy, which instead might be more effective in female sex (more common left bundle block)³. Looking at the subgroup of HF women with atrial fibrillation, it was demonstrated a higher risk of stroke than men when treated with warfarin but not with novel anticoagulants, prescription of which is significantly suboptimal.

In conclusion, studying sex as a biological variable for a “gender-specific” medicine is an exciting challenge but, to effectively achieve that, careful application of evidence-based therapies in female patients is mandatory, leading to an individually tailored therapeutic approach, rather than a generic “gender-based” one, as the best choice¹⁵.

REFERENCES

1. Cenko E, van der Schaar M, Yoon J et al. Sex-related differences in heart failure after ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2019; 74: 2379-89.
2. Sarma AA, Braunwald E, Cannon CP et al. Outcomes of women compared with men after non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol* 2019; 74: 3013-22.
3. Aimo A, Vergaro G, Barison A et al. Sex-related differences in chronic heart failure. *Int J Cardiol* 2018; 255: 145-51.
4. Lainscak M, Milinkovic I, Polovina M et al. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term registry. *Eur J Heart Fail* 2020; 22: 92-102.
5. Hsich EM, Grau-Sepulveda MV, Hernandez AF et al. Sex differences in in-hospital mortality in acute decompensated heart failure with reduced and preserved ejection fraction. *Am Heart J* 2012; 163: 430-7.
6. Ogah OS, Davison BA, Sliwa K et al. Gender differences in clinical characteristic and outcome of acute heart failure in sub-Saharan Africa: results of the THESUS-HF study. *Clin Res Cardiol* 2015; 104: 481-90.
7. Alvarez Alvarez B, Casas CAJ, Bermejo RA et al. Sex-related differences in long-term mortality and heart failure in a contemporary cohort of patients with NSTEMI. The cardiochus-HSUJ registry. *Eur J Int Med*, <https://doi.org/10.1016/j.ejim.2020.06.011>.
8. Corrà U, Agostoni PG, Giordano A et al. Sex profile and risk assessment with cardiopulmonary exercise testing in heart failure: propensity score matching for sex selection bias. *Can J Cardiol* 2016; 32: 754-9.
9. Zuchi C, Tritto I, Ambrosio G. Angina pectoris in women: focus on microvascular disease. *Int J Cardiol*. 2013 Feb 20;163(2):132-40.
10. Pathak LA, Shirodkar S, Ruparelia R et al. Coronary artery disease in women. *Indian Heart J* 2017; 69: 532-8.

11. Manolis AJ, Ambrosio G, Collins P et al. Impact of stable angina on health status and quality of life perception of currently treated patients. The BRIDGE 2 survey. *Eur J Int Med* 2019; 70: 60-67.
12. Ambrosio G, Collins P, Dechend R et al. Stable angina: perception of needs, quality of life and management of patients (BRIDGE study)- a multinational European Physician Survey. *Angiology* 2019; 70: 397-406.
13. Renda G, Patti G, Lang IM et al. Thrombotic and hemorrhagic burden in women: gender-related issues in the response to antithrombotic therapies. *Int J Cardiol* 2019; 198-207.
14. Dewan P, Rorth R, Jhund PS et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol* 2019; 73: 29-40.
15. Manolis AJ, Poulimenos LE, Ambrosio G et al. Medical treatment of stable angina: a tailored therapeutic approach. *Int J Cardiol* 2016; 220: 445-53.