

Gender and surgical revascularization: there is a light at the end of the tunnel?

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Provenance: This is an invited Editorial commissioned by the Section Editor Raffaele Giordano (Department of Advanced Biomedical Sciences, Adult and Pediatric Cardiac Surgery, University of Naples Federico II, Naples, Italy).

Comment on: Piña IL, Zheng Q, She L, *et al.* Sex Difference in Patients With Ischemic Heart Failure Undergoing Surgical Revascularization: Results From the STICH Trial (Surgical Treatment for Ischemic Heart Failure). *Circulation* 2018;137:771-80.

Submitted Jun 13, 2018. Accepted for publication Jun 22, 2018.

doi: 10.21037/jtd.2018.06.145

View this article at: <http://dx.doi.org/10.21037/jtd.2018.06.145>

Female sex is perceived as an important risk factor for surgery and is included in the most diffused operative risk scores, as EuroSCORE II (1) and STS score (2). In a recent paper, it was again emphasized that in a 'real world' unselected cohort of patients who underwent myocardial revascularization, survival was superior as well as the rate of major adverse cardiovascular events (MACE) was inferior with coronary artery bypass grafting (CABG) rather than with percutaneous coronary intervention (PCI) in men, but not in women. Outcomes of women were worse than men and were equivalent with both procedure (3).

Differences in biology between female and male gender can account for differences in outcome when the same therapy is delivered. Biological factors are at the basis of the differences associated with gender-specific coronary disease progression. Estrogen have been postulated to be protective toward atherosclerotic plaque formation, inducing a favorable lipid profile (4). Moreover, estrogen has been reported to upregulate nitric oxide synthetase, which appears to be important in protection observed in females (5). All these factors cause a delay in atherosclerotic plaque formation, which, in males, can start since the youth. The estrogenic decreased concentration after menopause accompanies to a worsening lipid profiles, with increased insulin resistance. The reduced protective effect on vascular endothelium can favor microvascular dysfunction, making the microcirculation more susceptible to the effect of

smoking. Then the history of coronary atherosclerosis starts later in women than in men, but with increased pathologic changes in microcirculation due to diabetes and estrogen level reduction. However, if estrogen deficiency in young women increases the risk of coronary disease by 7-fold (6), estrogen supplementation has not demonstrated a clear benefit after menopause (7,8).

However, the negative perception of the impact of female gender on the results of surgical myocardial revascularization seems to be reduced. Piña *et al.* (9), in a paper focused on the long-term results of patients with ischemic heart failure undergoing medical therapy or surgical revascularization (9), reported that women who underwent surgical revascularization had lower, even if not statistically significant, events rate than women who had medical treatment related to all-cause mortality (32/73, 43.8%, *vs.* 41/75, 54.7%, $P=0.1891$) and to cardiovascular mortality (19/73, 26%, *vs.* 29/75, 38.7%, $P=0.1017$). Interestingly, when receiving surgical revascularization, women, compared to men, had lower all-cause mortality rate (32/73, 43.8%, *vs.* 327/537, 60.9%, $P=0.0055$) and cardiovascular mortality (19/73, 26%, *vs.* 228/537, 42.5%, $P=0.0073$). The baseline risk profile was worse in women, who were older, had higher BMI, higher incidence of diabetes mellitus, higher prevalence of advanced heart failure, lower estimated glomerular filtration rate. Men were more frequently current smokers, had previous

surgical myocardial revascularization and lower ejection fraction. This study, as acknowledged by the Authors, has several limitations, as the small numbers of women, the possibility that more symptomatic patients (angina class III or IV) could be excluded and that, being women considered a priori bad candidates to surgery, many of them could be not enrolled in the study. Nevertheless, the results of this analysis, even if the trial was not targeted to find a difference between genders, provide an information we have to take into due account: decision making between medical therapy and surgery has no anymore influenced by gender differences.

Differences in outcome, largely described in the literature, were supposed to have at the basis anatomic factors as well. Women have coronary arteries of smaller size (10-12) and more tortuous (13) than men and this can be a limitation to a more complete revascularization. Development of collateral vessels in coronary artery stenosis or complete coronary occlusions is poor in female gender, especially if diabetic or in post-menopausal period (14).

In patients with acute coronary syndrome (ACS), women presented more vulnerable plaques components than man, even if related to higher incidence of diabetes. This finding, even if not a true gender difference, makes women more exposed to worse outcome (15). The PROSPECT study however found that, in ACS patients, despite having more comorbid risk factors than men, women had less extensive coronary artery disease by both angiographic and IVUS measures (similar culprit and lower non-culprit lesions), and that lesions in women compared with men had less plaque rupture, less necrotic core and calcium, similar plaque burden, and smaller minimal lumen area, independently from body mass and other comorbidities. Rates of MACE attributed to culprit and non-culprit lesions till 3-year follow-up were not significantly different between men and women, although women were rehospitalized more frequently due to culprit lesion-related angina (16).

In a computed coronary angiography study Makaryus *et al.* (17) showed that women had lower average calcium scores in each coronary artery than males with a lower tendency to have multiple vessel involvement, with a lower risk of future adverse coronary events. Some of these findings were coherent with the data reported by Nasir *et al.* (18), who found that women tended to have more exclusively non-calcified plaque and were less likely to have calcified or mixed plaques compared to men. These differences were predominantly present in patients aged <65 years and were lost in those aged ≥65 years (19).

The symptoms due to ischemic heart disease can vary as well. Non-chest pain symptoms (occipital pain, jaw pain, neck/throat pain, shoulder pain, upper arm pain, back pain, and nausea) during the 60-second balloon occlusion of the coronary artery during PCI were more common in women than in men, supporting the presence of the gender difference in myocardial ischemic symptoms (20).

Primary PCI mortality rates are higher among young women (<40 years) with ACS, but this difference tends to disappear with age, and long-term prognosis is even better among older women if compared with older men (21). Moreover, the unrestricted use of DES is associated with similar long-term safety and efficacy among women and men with coronary artery disease (22), showing that in the most recent era interventional cardiology eliminated the gender differences.

The role of gender in patients who undergo surgical myocardial revascularization still has to be defined. Female sex was associated with early combined morbidity and long-term cardiac mortality. A greater proportion of concomitant risk factors characterize female patients undergoing CABG (23). The higher prevalence of diabetes in female patients in combination with the older age at presentation might result in the higher overall mortality observed in female patients compared to men (24).

Due to a more unfavorable anatomy, women are more likely to receive, together with a left internal thoracic artery (ITA), saphenous vein grafts (SVGs) rather than other arterial conduits. Patency rates of arterial grafts is not significantly different between the genders; however, those of SVGs are lower in females than those in males (25) When liberally applied, BIMA grafting reduces the perioperative mortality in female patients, effectively reversing the negative influence of gender on both short- and long-term outcomes of CABG surgery (26). However, in patients undergoing totally arterial CABG, late follow-up revealed a higher graft patency in men undergoing the on-pump approach, compared to women (27).

The paper from Piña *et al.* (9), at the basis if this editorial, shows that, in a randomized controlled trial, results of surgery can be similar or superior in females than in males, and that medical treatment can be as well a second option in female patients who have symptoms of heart failure and need of revascularization. It is evident that the gender gap is going to be filled completely both in interventional and in surgical revascularization. Even with a higher risk profile, women have not to be denied any kind of procedure of revascularization, in particular CABG, as still reported in

some studies (28).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Di Mauro M, Totaro A, Foschi M, Calafiore AM. Gender and surgical revascularization: there is a light at the end of the tunnel? *J Thorac Dis* 2018;10(Suppl 18):S2202-S2205. doi: 10.21037/jtd.2018.06.145