

# Sex and mortality associated with coronary artery bypass graft

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A consistent finding among individuals undergoing coronary artery bypass graft (CABG) surgery is that mortality after CABG surgery is considerably higher in women as compared to men. As early as 1980 reports from clinical trials and registries demonstrated a significant risk of short-term mortality among women. The disparity between genders has persisted despite of a remarkable decrease in mortality for patients undergoing CABG surgery over the last 20 years mainly due to the improved surgical technique, the largest use of IMA even in the women, the adequate postoperative treatment and the diffusion of antithrombotic drugs and statins (1-6). The early-postoperative worse outcomes in women have been attributed over the time to the more urgent or emergent CABG, the smaller body surface area (BSA) with relatively smaller coronary artery and the more advanced and diffuse stage of coronary artery disease (CAD) compared with the male counterpart (7,8). In addition, women undergoing CABG have more associated comorbid conditions than men which include older age, diabetes mellitus, hypertension, dyslipidaemia, renal insufficiency, chronic obstructive pulmonary disease (9).

This body of evidence led to the inclusion of female sex as significant factors in the most important risk models such as Euro Score II, modified Parsonnet's score, Northern New England Cardiovascular Disease Study Group score, Society of Thoracic Surgeons score and New York's Cardiac Surgery Reporting System score. As a consequence of the significant weight of the variable "female sex" in these risk models, surgeons have often been directed toward a more conservative approach to CAD in women especially when

additive risk are present.

The evidence of early worse results in woman after CABG surgery has been also confirmed in the results of long-term analysis published over the time by a number of studies (10-15). However, some recent studies challenged this literature reporting that long-term survival (from 5 to 10 years) was similar between the sexes after risk variable adjustment (7-9). Among these, the study by Piña *et al.*, from the STICH trial, suggests that, in spite of the higher cardiovascular risk and the poorer hemodynamic conditions at baseline, women who underwent CABG had not higher rate of surgical deaths either as cardiovascular mortality or all-cause mortality (16). Authors concluded that that female sex should not influence the choice of CABG surgery in women with CAD. This point is very important because it challenges the risk factor conventionally considered among the most important for open-heart surgery. Hence, according with the conclusion from the STICH trial and some other studies, a revision of the traditional risk scores could be indicated. However, in our opinion, before a similar revolutionary correction, a preliminary critical analysis of these studies is mandatory in terms of number of women included, selection criteria, the representativeness compared with male counterpart, and so on. In addition, in these studies mainly of retrospective nature, protocols did not include the specific analysis of the characteristics of the female sex. Likely the indications to CABG surgery were not equally aggressive and extensive in both sexes. Furthermore, no studies took into account that women show the onset of CAD later than male sex, generally

during menopause, in a metabolic situation deeply different. Data items should take into account all potentially relevant characteristics of female sex, including hormonal imbalance, use of oral contraceptive and post-menopausal replacement therapy by estrogens.

Indeed, intrinsic differences between sexes exist and support that it might not be rational to expect similar outcomes after identical treatment strategies in women and men. Among women, the specific features of the conduits for CABG themselves, which probably depend on age and hormonal status, could be factors related to early and late surgical results. Several recent studies, which analysed the relationships between early and long-term patency of conduit for CABG and endothelial metabolism, evidenced that the higher endothelial nitric oxide (NO) expression was related with the higher patency rate of internal mammary artery (IMA) (17,18). Indeed, endothelial function is affected by aging process and is due to impaired expression of NO in the endothelium, increased concentration of endogenous peroxides and imbalanced peroxidase activity (19,20). In Aged women the impaired production of endothelial NO related to postmenopausal status is likely one of the most important determinant of increased cardiovascular risk and could be ascribed to the loss of protective antiaging effect of estrogens. A recent study evidenced that endothelial cells of the IMA collected from postmenopausal women undergoing surgery have reduced expression of messenger RNA for enzyme endothelium derived nitric oxide synthase (eNOS) and, consequently, lower eNOS levels. Reduced concentration and activity of NO results in impaired endothelial metabolism that could contribute to less favorable surgical results in postmenopausal women (21).

Indeed, women have a lower risk of cardiovascular disease likely due to the protective effect estrogens on the vascular endothelium. However, this protection of gender diminishes rapidly after menopause and with advancing age, particularly in obese women.

Whether substitutive therapy with estrogens in menopausal women improves the endothelial function and exerts antiatherosclerotic benefits in these women is not clearly addressed at the present. In this regard, the Heart and Estrogen/progestin Replacement Study (HERS), the most extensive randomized controlled trial with associated placebo published until now, reported that hormone replacement therapy can decrease cardiovascular (CV) mortality in postmenopausal women (22). By contrast, in the Women's Health Initiative, authors found that estrogens alone offered no significant protection for healthy

postmenopausal women who were followed for 7–10 years. Nonetheless, this study provided also the interesting conclusion that CAD risk was reduced in women aged 50–59 years at onset of replacement therapy (23).

In conclusion, the current body of literature suggests that we could now be able to provide better surgical revascularization to women. Nonetheless, the highest quality of surgical results need a more extensive use of non-invasive diagnostic tools for the early assessment of CAD in postmenopausal women and timely indications for surgery, taking also into account that postmenopausal women could have atypical onset of ischemic symptoms (24).

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### Footnote

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

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