

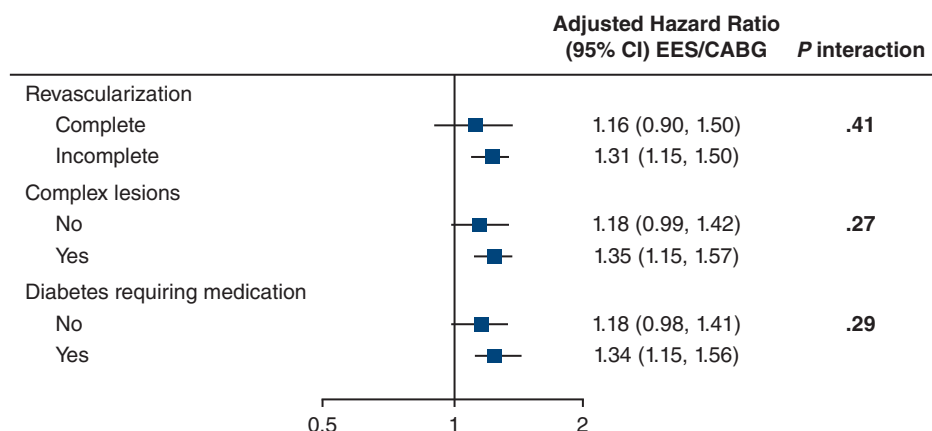


FIGURE 1. Forest plot for adjusted hazard ratios for mortality among subgroups of women with multivessel coronary artery disease undergoing percutaneous interventions with everolimus-eluting stents/coronary artery bypass graft surgery: New York State, 2012–2018. Taken from Hannan and colleagues,¹ and *P* for interaction included. *CI*, Confidence interval; *EES*, everolimus-eluting stents; *CABG*, coronary artery bypass graft.

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REPLY: INTERPRETATION OF SUBGROUP ANALYSES Reply to the Editor:



In our propensity-matched analysis of women with multivessel coronary artery disease who underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in New York State from 2012 to 2018, we found that women who underwent PCI had a greater risk of long-term (6-year) mortality when compared with CABG (15.75% vs 23.57%, adjusted hazard ratio, 1.29; 95% confidence interval, 1.14–1.45). We concluded that “For women with multivessel coronary artery disease, CABG is associated with lower six-year mortality, myocardial infarction, and repeat revascularization rates in comparison to PCI with everolimus-eluting stents.”¹

In response to the publication of our work, Dayan and colleagues² wrote a dissenting letter titled: “CABG is Superior to PCI for All Women Subgroups.” Specifically, the authors take issue with the fact that in our subgroup analysis we did not use interaction testing, a technique used most frequently in randomized trials (the article by Sun and colleagues³ to which they refer discusses in fact subgroup analysis in randomized trials or meta-analyses of randomized trials).

The purpose of testing interactions in subgroup analyses is to determine whether the magnitude of the main effect (in this case degree of superiority of CABG compared with PCI) differs among subgroups (eg, completeness vs incompleteness of PCI revascularization). In other words, they test for homogeneity of the main effect among categories within subgroups. As indicated by Dayan and colleagues, the degree of superiority does not differ in the 3 of many subgroup analyses for which one of the categories showed no statistical mortality difference between CABG and PCI.

The purpose of the subgroup analyses that we conducted was to determine whether the superiority of CABG compared with PCI persisted when the data were examined for various categories of different subgroups, eg, were there significant differences among propensity-matched patients when the patient receiving PCI was completely revascularized and were there significant differences when the patient receiving PCI was not completely revascularized? Our findings were that the significant CABG versus PCI differences generally occurred for all categories of the subgroups, but the differences did not occur among matched pairs where the patients receiving PCI were completely revascularized, or matched pairs without complex lesions, or matched pairs without diabetes. However, there were still significant differences in favor of CABG among the other categories in those matched pairs (where the patients receiving PCI were incompletely revascularized, had complex lesions, and had diabetes).

In conjunction with the interaction analyses suggested by Dayan and colleagues, a reasonable conclusion is that CABG has lower mortality for one category of each subgroup examined (eg, matched pairs with incomplete revascularization among patients receiving PCI) and no demonstrated mortality difference for the other category (matched pairs with complete revascularization among



FIGURE 1. The first cardiac surgery trial in women: ROMA:Women.

patients receiving PCI), yet there is no significant difference in the magnitude of the CABG versus PCI differences between the 2 categories.

It is likely that the fact that some subgroups had categories that were not statistically different was a result of low statistical power. For example, the magnitude of the adjusted hazard ratios for categories within those subgroups were quite large (eg, 1.31 vs 1.16 for completeness of revascularization). This suggests that with more statistical power, a significant CABG versus PCI mortality difference for pairs with PCI having complete revascularization could be identified. It is also possible that with more statistical power, the nonsignificant categories (eg, complete PCI revascularization) could have reached significance despite being statistically different than their companion categories (incomplete PCI revascularization in this example). Thus, we conclude that all subgroup analyses suffer from power limitations and confounders and must be interpreted as hypothesis generating. This is acknowledged very clearly in our manuscript, where the need for more data and in particular randomized studies is highlighted. Although our conclusion that some categories (eg, complete PCI revascularization) show no CABG versus PCI mortality differences may be somewhat overstated because of low statistical power considerations, we also believe that Dayan and colleagues' conclusion that "CABG is superior to PCI for all women subgroups" is also an overstatement.

Furthermore, it is unclear to us to which "guidance" Dayan and colleagues refer that "may harm future patients"—as no guidance for treatment is provided in our

manuscript (that focuses on the description of our findings); our results are in fact consistent with current myocardial revascularization guidelines that recommend surgery in patients with complex coronary anatomy and both PCI and CABG in patients with less-extensive disease (ie, those more likely to receive complete revascularization and less likely to have diabetes).^{4,5}

We thank Dayan and colleagues for their continued efforts to generate debate in scientific journals and on social media. Please also note that we (M.G. and colleagues) are leading the first randomized trial comparing PCI versus CABG in women and the first CABG trial dedicated to women (see Figure 1) and hope to soon provide better data to inform key treatment decisions in this important and neglected patient population.

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Conflict of Interest Statement

The authors reported no conflicts of interest.

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