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PERSPECTIVE

ROMA-Women: Innovative Approaches for the First Cardiac Surgery Trial in Women

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The effect of the use of multiple arterial grafts (MAG) for coronary artery bypass grafting (CABG) has been debated for more than 4 decades. The results from observational studies and the only large, randomized trial have been discordant. The adoption of MAG in current practice is very low (≈12%) and significantly lower in women (≈6%).[1] The ongoing Randomized Comparison of the Outcomes of Single vs Multiple Arterial Grafts ([ROMA] URL: https://www.clinicaltrials.gov; Unique Identifier: NCT03217006) was designed to definitively test the MAG hypothesis.[2]

Women are underrepresented in cardiac surgery trials and the majority of the evidence on MAG is derived from studies conducted predominantly in men. Coronary artery disease in women is different than in men and is more often characterized by coronary microvascular dysfunction and coronary vasospasm, 2 conditions for which CABG is a suboptimal treatment.[3] Coronary arteries and bypass grafts are smaller and more prone to spasm in women, making the operation more technically complex.[3] Women referred for CABG are older, with different and more frequent comorbidities compared with men, and studies consistently show that women have higher postoperative mortality and worse long-term outcomes after CABG when compared with men.[3] The risk–benefit ratio of using MAG in women is likely different than in men: women are at higher risk of MAG harvesting site complications (in particular sternal wound infections) and arterial conduits are smaller and more technically complex to use in women. However, women often have diseased or varicose saphenous veins, and it is possible that the better patency rate and lower tendency for arterial graft atherosclerosis may result in better myocardial microperfusion, cardiac function, and ultimately, better outcomes compared with vein grafts. In a pooled analysis of 6 small randomized trials, women (309 of 1036 [29.8%]) had significantly greater reductions in cardiovascular events compared with men when the radial artery, rather than the saphenous vein was used.[4] In a meta-analysis of 6 adjusted, observational CABG studies in women, those receiving MAG had significantly longer postoperative survival times compared with those receiving a single arterial graft (incidence rate ratio, 0.86 [95% CI, 0.76–0.96]).[5] While suggestive, these analyses fail to rigorously assess the risk–benefit of MAG in women.

Currently, ROMA enrollment is ≈15% women and will not be sufficiently powered to provide meaningful data on the risk–benefit of MAG in women. However, ROMA does provide a unique opportunity to leverage the existing trial infrastructure and enrolled population of women to realize the first cardiac surgery trial dedicated to women (ie, ROMA-Women; URL: https://www.clinicaltrials.gov; Unique Identifier: NCT04124120) and to rigorously test the MAG hypothesis in women.

ROMA-Women will use a nested design that has not previously been used in cardiovascular trials (Figure 1) by leveraging the ROMA infrastructure, including clinical trial unit, database, case report forms, randomization system, site training resources, informed consent forms, regulatory approvals, Central Events Review Committee

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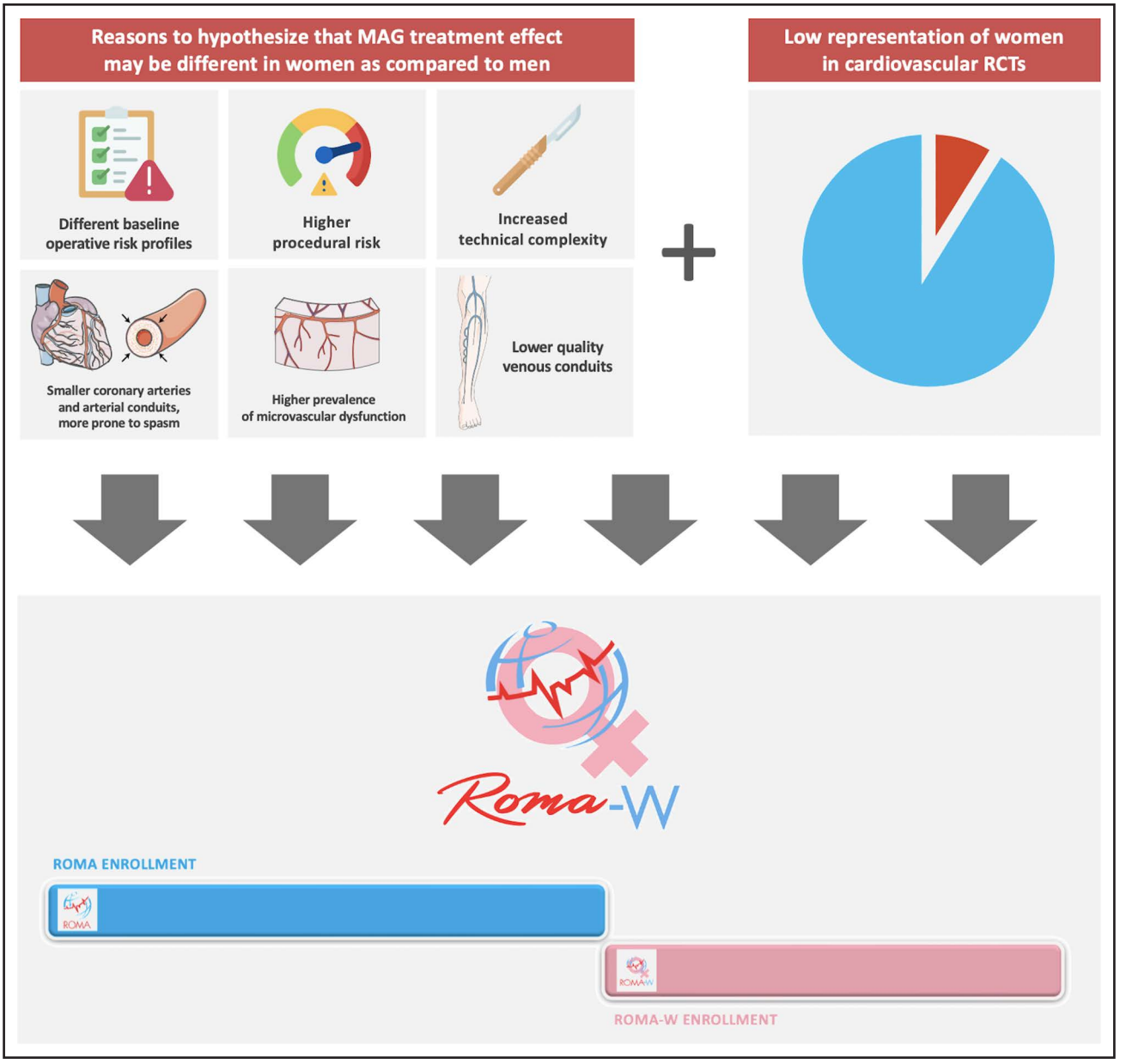

Figure 1. Rationale and design of the ROMA-Women trial.
The sites participating in ROMA will continue enrollment of women after the completion of the ROMA trial and additional sites will also be opened to reach the target sample size for ROMA-Women. MAG indicates multiple arterial grafting; RCT, randomized clinical trial; ROMA, Randomized Comparison of the Outcomes of Single vs Multiple Arterial Grafts; and ROMA-W, Randomized Comparison of the Outcomes of Single vs Multiple Arterial Grafts in Women. Parts of the figure were drawn by using pictures from Flaticon.com and Servier Medical Art (servier.com). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported license (http://creativecommons.org/licenses/by/3.0).

processes and personnel, and the network of participating sites. The randomization procedure, interventions, and follow-up protocol of ROMA-Women will be identical to those of the parent ROMA trial. More importantly, ROMA-Women will include all of the women enrolled in ROMA, increasing efficiency and reducing enrollment time, which are key considerations because of challenges associated with enrolling an all-women population. Dedicated analytic strategies will be used to minimize any cohort effect from inclusion of the ROMA patients.

The American Heart Association, American College of Cardiology, Society of Thoracic Surgeons, European Association of Cardio-Thoracic Surgery, Society for Cardiovascular Angiography and Intervention, Society of Cardiac Anesthesiologists, Women in Thoracic Surgery, and Women as One, as well as the patient-centered WomenHeart organization, have all endorsed the trial, a testament to the support for trials dedicated to women by the cardiovascular community.

The funding strategy is also innovative: the trial has received endorsement from the Global Cardiovascular

Research Funders Forum Multinational Clinical Trials Initiative, and currently, national agencies are evaluating individual funding proposals. The Starr Foundation (https://starrfoundation.org/) has provided philanthropic bridge funding, so that ROMA sites will transition to ROMA-Women without interruption once recruitment in the parent trial is complete.

Patient representatives have been involved in ROMA-Women from its inception. WomenHeart: The National Coalition for Women with Heart Disease has been critical in highlighting the priorities for women facing treatment decisions about coronary artery disease. Patient representatives will serve on the Steering Committee and participate in ROMA-Women oversight, and patient-reported outcomes will be powered secondary end points of the trial.

ROMA-Women will adopt innovative recruitment strategies designed specifically for women. It is expected that selective screening of women will result in a higher enrollment rate compared with mixed-population trials. Higher-enrollment sites will be surveyed by the study team and the results will be used to develop best practices to support sites with lower enrollment. The Steering Committee of the trial comprises a majority of women (>75%) and identification of women as principal investigators and study personnel will be strongly encouraged locally; this has facilitated the enrollment of women in other clinical trials. In addition, the study team will interview women who were screened and eligible but declined to participate in ROMA or ROMA-Women, in order to obtain qualitative perspectives on why they chose not to participate. This information will be used for modifying future recruitment approaches to better engage women. Last, through the support of professional societies and associations dedicated to women's health, the trial will be actively promoted in the cardiovascular community through presentation at meetings, newsletters, social media, and email outreach.

If successful, ROMA-Women will not only inform sex-specific cardiovascular guidelines regarding the best coronary bypass strategy for women, but also will be a model for cardiovascular trialists to design trials specific to women and other groups are underrepresented in traditional clinical trials.

ARTICLE INFORMATION

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