

# Randomized Comparison of the Outcome of Single Versus Multiple Arterial Grafts trial (ROMA):Women—a trial dedicated to women to improve coronary bypass outcomes

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In the United States every year approximately 240,000 patients undergo coronary artery bypass grafting (CABG), and of them approximately 25% are women.<sup>1,2</sup> Data suggest that the use of more than 1 arterial graft for CABG (multiple arterial grafting [MAG]) may be associated with improved outcomes compared with the use of only one arterial graft (single arterial grafting [SAG]), but the evidence is mixed, and there are reasons to believe that the MAG treatment effect may differ by sex. Herein, we summarize the current evidence on MAG and highlight the need for a trial testing the MAG hypothesis in women.

## THE CABG MAG HYPOTHESIS

At least 9 meta-analyses have pooled data from observational studies comparing the use of the right internal thoracic artery (RITA) or the radial artery (RA) versus the saphenous vein (SV) for CABG.<sup>3-11</sup> All have reported longer postoperative survival in the MAG group, with hazard ratios (HRs) for mortality ranging from 0.65 to 0.81. In the most recent meta-analysis of 32 propensity-score matched studies and 31,688 patients, RITA use was associated with a significant reduction in long-term mortality (HR, 0.78; 95% confidence interval [CI], 0.71-0.86).<sup>3</sup> Similarly, in a meta-analysis of 14 studies and 20,931 patients at 6.6 years of follow-up, mortality was 24.5% in patients who received the RA versus 34.2% in patients who received the SV (incidence rate ratio [IRR], 0.74, 95%

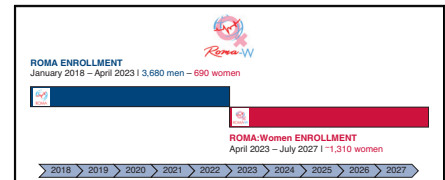
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Rationale and design of the ROMA:Women trial.

## CENTRAL MESSAGE

ROMA:Women is the first cardiac surgery trial dedicated to women and will inform sex-specific CABG guidelines regarding the use of multiple arterial grafts in women.

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CI, 0.63-0.87).<sup>11</sup> However, comparative observational studies are open to treatment allocation bias, and it has been suggested that unmeasured confounders, and not true treatment effect, may be the reason for the reported differences.<sup>12</sup> The randomized evidence in support of the MAG hypothesis is limited. In the Arterial Revascularization Trial (ART), the only adequately powered randomized trial comparing MAG with SAG, no difference in survival or event-free survival at 10 years was found between the 2 groups.<sup>13</sup> In ART, however, the crossover rate was high (single internal thoracic artery to bilateral internal thoracic artery: 38/1554 = 2.4%, bilateral internal thoracic artery to single internal thoracic artery: 215/1548 = 13.9%) and the RA was used in almost 22% of the patients in the single internal thoracic artery group; in a post-hoc analysis comparing SAG with MAG, a significant benefit in both outcomes was found in the MAG group.

In the Radial Artery Database International Alliance (RADIAL), a pooled analysis of individual data from 6 randomized trials comparing the use of the RA versus the SV for CABG, there was a significant reduction in the incidence of the composite outcome of death, myocardial infarction, or repeat revascularization at 5 years of follow-up in favor of the RA (HR, 0.67; 95% CI, 0.49-0.90),<sup>14</sup> and when

follow-up was extended to 10 years, patients who received the RA also had a lower incidence of the composite of death and myocardial infarction (HR, 0.77; 95% CI, 0.63-0.94) and lower mortality (HR, 0.73; 95% CI, 0.57-0.93).<sup>15</sup>

In the Radial Artery Patency and Clinical Outcomes (RAPCO) trial at 15 years, in a cohort of patients older than 70 years of age, those who received a RA, had a lower incidence of the composite outcome of all-cause death, myocardial infarction, and repeat revascularization compared with those that received a SV (HR, 0.71; 95% CI, 0.52-0.98).<sup>16</sup>

Current guidelines generally support the use of MAG in patients with long life expectancy with Level of Evidence B.<sup>17,18</sup> However, the uptake in the cardiac surgical community has been limited, with less than 15% of patients with CABG receiving MAG in the United States, and 20% to 30% receiving MAG in Europe, even when patients meet guideline criteria for MAG.<sup>19-21</sup> Several reports have indicated that the key reason for the underuse of MAG by cardiac surgeons is the limited available randomized data in support of its clinical benefits.<sup>22,23</sup>

The Randomized comparison of the Outcome of single versus Multiple Arterial grafts trial (ROMA; NCT03217006) was designed to provide a definitive answer to the MAG question. ROMA has completed enrollment (4370 patients in >80 international centers) in April 2023, and the primary outcome results will be available in 4 or 5 years (the trial analysis is event-driven).<sup>24</sup> As there is evidence that surgeons' experience with MAG may significantly affect its outcomes,<sup>12,25</sup> surgeons participating in ROMA were selected based on a minimum number of MAG cases (n = 250) or expert vetting by the trial's principle investigators. In ROMA, only 16% of the enrolled patients (approximately 690) are women.

### SEX-RELATED CABG DIFFERENCES

CABG outcomes have consistently been reported to be worse in women compared with men. In a meta-analysis of 84 studies and 903,346 patients, women undergoing CABG were at greater risk for operative (odds ratio [OR], 1.77; 95% CI, 1.64-1.92) and late mortality (IRR, 1.16; 95% CI, 1.06-1.26) compared with men.<sup>26</sup> Similar results were reported in a patient-level meta-analysis of the largest CABG trials.<sup>27</sup> In a study including more than 1.2 million patients and based on the United States Adult Cardiac Surgery Database of the Society of Thoracic Surgeons, the sex-related gap in early CABG outcomes did not improve from 2011 to 2020.<sup>28</sup>

Reasons for differences in outcomes are likely multifactorial. Current diagnostic and treatment algorithms for coronary artery disease are based on data from a predominantly male population and are biased toward the presentation of myocardial ischemia in men, leading to substantial delay in diagnosis and referral for treatment in women.<sup>29</sup> On

average, women present with coronary artery disease at older ages than men. Due to delays in referral for CABG, they also present with more cardiovascular risk factors, including diabetes, hypertension, peripheral vascular disease, and dyslipidemia, which put them at greater risk of postoperative complications, including sternal wound infections.<sup>30-32</sup> Women are also more likely to present for surgery with heart failure or under emergency situations such as cardiogenic shock or acute myocardial infarction.<sup>30-33</sup>

Physiologically, women also have smaller coronary arteries than men, independent of body size, which increases the technical complexity of CABG.<sup>34,35</sup> In addition, the pathophysiology of myocardial ischemia in women is more often related to coronary hyperreactivity, microvascular dysfunction, and distal microembolization, which may be only partially relieved by CABG.<sup>36-38</sup>

Women report also lower quality of life (QOL) after CABG compared with men.<sup>39,40</sup> Differences in reported QOL between sexes could be due to the difference in symptoms that women experience (including more frequent dyspnea),<sup>41</sup> differences in the mechanism of angina (microvascular vs epicardial disease), and differences in coronary disease and comorbidities at the time of referral for CABG.<sup>40</sup> In a meta-analysis of QOL after CABG including 14 randomized trials and 13,595 participants from 15 countries,<sup>42</sup> there was a significant increase in QOL scores from before surgery to 1-year postoperatively in both sexes, but women had significantly lower QOL improvement than men. However, 78% of the study participants were men and these limited data are inadequate to address the issue of sex differences in QOL relative to more durable revascularization (MAG vs SAG).

### EVIDENCE THAT THE MAG TREATMENT EFFECT MAY BE DIFFERENT IN WOMEN COMPARED WITH MEN

Women are significantly less likely to receive MAG than men. A study on 19,557 patients reported that RITA is underused in women (OR for RITA use in men vs women 1.68, 95% CI, 1.16-2.39) and that the annual increase in RITA use among women was significantly lower than in men (0.73% per year vs 1.16% per year, respectively,  $P < .001$ ).<sup>20</sup> In another study including more than 1.2 million patients with CABG, women had significantly lower rates of RITA (2.9% vs 5.6%,  $P < .001$ ) and RA use (3.2% vs 5.6%,  $P < .001$ ), and lower odds than men of receiving MAG (adjusted OR, 0.78; 95% CI, 0.75-0.81,  $P < .001$ ).<sup>43</sup> Women have greater risk of sternal wound complications after CABG, and this risk is increased with the use of the RITA<sup>44,45</sup>; this may be one of the reasons for the lower RITA use in women.

In a meta-analysis of 6 propensity-matched studies, women who received MAG had lower long-term mortality (IRR, 0.86; 95% CI, 0.76-0.96) compared with women who received SAG.<sup>46</sup> In another study of >63,000 patients

based on the New York State Database, the benefit of MAG varied significantly between men and women, highlighting the need for MAG studies dedicated to women.<sup>47</sup>

It is important to note that in all the published randomized trials, the MAG treatment effect was different by sex and larger in women. In the ART trial, the HR for the MAG treatment effect was 1.00, 95% CI 0.84 to 1.18 for men versus 0.78, 0.53 to 1.13 for women, but women represented only 14% of the enrolled population and the interaction *P* was not significant (.23). In all RADIAL analyses, sex was a significant treatment effect modifier (interaction *P* = .01 and .004 at 5 and 10 years, respectively), suggesting that women derived greater benefit than men from the use of MAG.<sup>14,15</sup> In the RAPCO trial, at subgroup analysis women derived a greater benefit from RA use than men (HR, 0.82; 95% CI, 0.58-1.18 for men vs 0.37, 95% CI, 0.17-0.79 for women, interaction *P* = .07), but only 43 of 225 (19.1%) of the patients included were women. Finally, in the only trial that did not find a beneficial effect for the RA compared with the saphenous vein, >99% of the enrolled patients (751/757) were men.<sup>48</sup>

In summary, there is evidence that suggests that MAG may be beneficial in patients with CABG and that the MAG treatment effect is different by sex and larger in women, but all the CABG trials (including ROMA) have included only a minority of women and are largely underpowered to test the MAG hypothesis in women. It is possible that if the results of the primary analysis of ROMA are neutral in a prevalently male patient population, a signal for the benefit of MAG in women may be diluted and an important opportunity to improve CABG outcomes in women (a crucial need due to the current outcomes disparity) may be lost. This constitutes a strong rationale for an MAG trial dedicated to women.

## OVERVIEW OF THE ROMA:WOMEN STUDY DESIGN

The ROMA:Women trial (NCT04124120, approved by the Weill Cornell Medicine, Institutional Review Board #1703018094, on April 4, 2023) will include all women

enrolled in ROMA and will add 1310 women in order to test the MAG hypothesis in women with adequate statistical power. A dedicated analytic plan will assess and eventually address the presence of a cohort effect from the included ROMA patients.

ROMA:Women will leverage the existing ROMA infrastructure increasing efficiency and minimizing enrollment time. The trial will use a nested trial design that has not been previously used in cardiac surgery trials (Figure 1).

The trial represents a departure from typical cardiovascular and cardiac surgery trials by including a majority of women in its leadership (and also in the Steering Committee [21/27 = 77%]). We will also prioritize identification of women principal investigators and junior faculty at each site to improve the current disparity in female leadership in cardiovascular trials.<sup>49</sup> The trial has been endorsed by the Expert Advisory Panel of the Global Cardiovascular Research Funders Forum Multinational Clinical Trials Initiative and will be funded by an international collaboration that also includes philanthropic and industry partners.

## DETAILS OF ROMA:WOMEN

The patient population consists of women referred for primary isolated CABG. Inclusion and exclusion criteria are identical to those of the ROMA trial (Table 1). The only exception is the 70 year age cut-off that was used in ROMA and will not be used in ROMA:Women. This decision is based on the fact that women are referred for CABG at an older age than men,<sup>29</sup> so that the 70-year age cut-off (that makes sense in the predominantly male ROMA population) would greatly limit the generalizability of the results of ROMA:Women.

The randomization procedure, interventions and treatment arms, outcome assessments, and follow-up protocol of ROMA:Women are identical to those of the parent ROMA trial. As in the ROMA trial, patients will be assigned to 1 of 2 groups: MAG or SAG (Figure 2). In all patients, the left internal thoracic artery will be anastomosed to the left anterior descending coronary artery. For patients

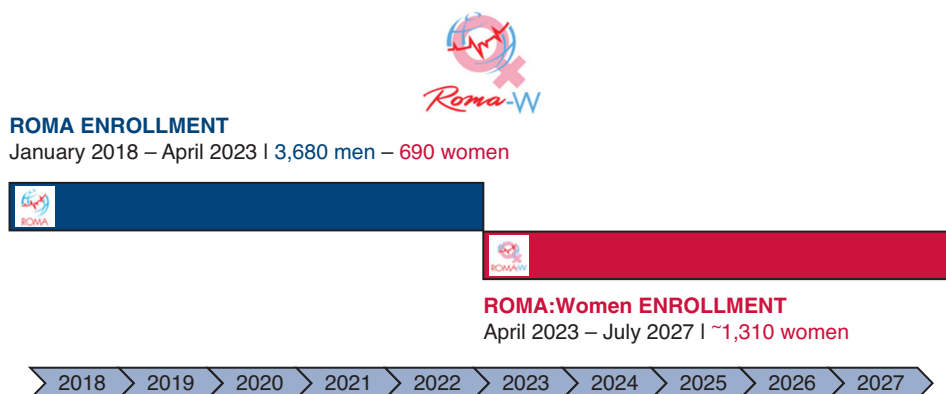


FIGURE 1. Rationale and design of the ROMA:Women trial. ROMA, Randomized comparison of the Outcome of Single versus Multiple Arterial grafts.

**TABLE 1. Inclusion and exclusion criteria for ROMA:Women**

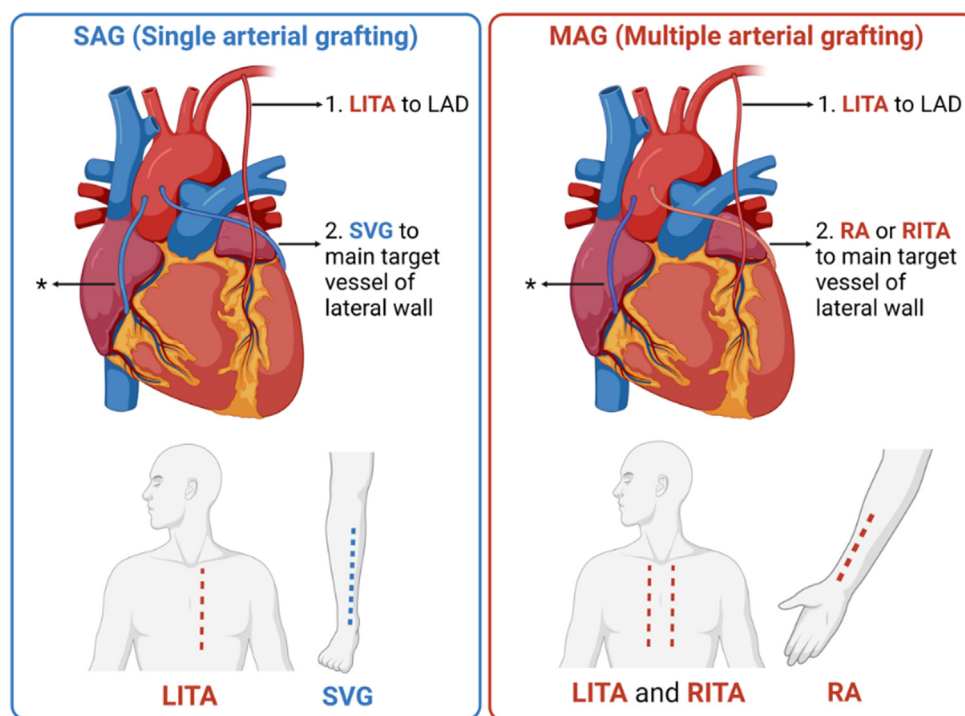
Inclusion and exclusion criteria
<b>Inclusion criteria</b>
1. Isolated CABG
2. Primary (first-time) cardiac surgery procedure
3. Significant disease of the left main coronary artery or of the left anterior descending and the circumflex coronary system with or without disease of the right coronary artery
<b>Exclusion criteria</b>
1. Planned single-graft CABG
2. Emergency operation
3. Left ventricular ejection fraction <35%
4. Preoperative ST-elevation myocardial infarction within 48 h
5. Any concomitant cardiac or noncardiac procedure
6. Any previous cardiac operation
7. Preoperative severe end-organ dysfunction, cancer or any comorbidity that reduces life expectancy to less than 5 y
8. Inability to use either the saphenous vein or both the right internal thoracic artery and the radial artery as grafts

CABG, Coronary artery bypass grafting.

randomized to the MAG group, the RITA or the RA (according to the surgeon's preference) will be used to graft the main target vessel of the circumflex coronary artery. As there is evidence that the efficacy of arterial grafts to the right coronary artery is reduced,<sup>50,51</sup> the second arterial graft in the MAG group should be directed to the circumflex territory and not be used on the right coronary artery. For patients randomized to the SAG group, SV grafts will be used for all non-left anterior descending target vessels. Surgical revascularization will be performed with the current standard technique in use at the local centers.

## CONCLUSIONS

The findings of ROMA:Women will inform guidelines for the practice of CABG in women—a unique and biologically distinct patient population that has been underrepresented and poorly studied. At the moment, women receive significantly less MAG than men and have worse outcomes and QOL after CABG. Multiple studies have reported that a key reason for the underuse of MAG by cardiac surgeons is the limited randomized evidence in support of its clinical benefits. Should ROMA:Women support the MAG hypothesis, the results will lead to the endorsement of the use of MAG in women by guidelines and professional societies



**FIGURE 2.** Treatment arms in ROMA:Women. \*For revascularization of the right coronary artery, the use of additional arterial grafts or SVG is allowed in the MAG group, whereas only the use of SVG is allowed in the SAG group. LITA, Left internal thoracic artery; LAD, left anterior descending artery; SVG, saphenous vein graft; RA, radial artery; RITA, right internal thoracic artery.

and to greater adoption of MAG in women undergoing CABG, improving clinical and patient-reported outcomes. As CABG is the most commonly performed adult cardiac surgery worldwide, the ROMA:Women findings will impact the health of hundreds of thousands of women globally.

Further, the trial will be an example for cardiovascular trialists to design trials specific to women and other minority groups. The ROMA:Women trial started on April 15, 2023, and is actively recruiting patients.

### Conflict of Interest Statement

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