ROMA: Women - a trial dedicated to women to improve coronary bypass outcomes.

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**Glossary of Abbreviations**

- **CABG**: coronary artery bypass grafting
- **MAG**: multiple arterial grafting
- **QOL**: quality of life
- **RA**: radial artery
- **RITA**: right internal thoracic artery
- **ROMA**: Randomized comparison of the Outcome of Single versus Multiple Arterial grafts
- **SAG**: single arterial grafting
- **SV**: saphenous vein
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.
Perspective Statement

ROMA: Women will inform sex-specific CABG guidelines regarding the use of multiple arterial grafts in women to reduce existing outcome disparities and gaps in evidence for women due to underrepresentation in prior trials. Further, the trial will be an example for cardiovascular trialists to design trials specific to women and other minority groups.

Keywords: coronary artery bypass grafting, multiple arterial grafts, single arterial grafts, sex differences in coronary artery disease, sex differences in cardiac surgery, women’s health
Introduction

In the United States every year approximately 240,000 patients undergo coronary artery bypass grafting (CABG), and of them approximately 25% are women.\(^1\,^2\) Data suggests that the use of more than one arterial graft for CABG (multiple arterial grafting [MAG]) may be associated with improved outcomes compared to 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 multiple arterial grafting hypothesis

At least nine 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.\(^3\)\textsuperscript{–}\textsuperscript{11}\) All have reported longer postoperative survival in the MAG group, with hazard ratios (HR) 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).\(^3\) 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% CI 0.63-0.87).\(^11\) 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.\(^12\) 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 two groups.\(^13\) In ART, however, the
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 to 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 six 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 five years of follow-up in favor of the RA (HR 0.67, 95% CI 0.49-0.90),\textsuperscript{14} 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).\textsuperscript{15}

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 that received a RA, had a lower incidence of the composite outcome of all-cause death, myocardial infarction, and repeat revascularization compared to those that received a SV (HR 0.71, 95% CI 0.52-0.98).\textsuperscript{16}

Current guidelines generally support the use of MAG in patients with long life expectancy with Level of Evidence B.\textsuperscript{17,18} However, the uptake in the cardiac surgical community has been limited, with less than 15% of CABG patients receiving MAG in the United States, and 20-30% receiving MAG in Europe, even when patients meet guideline criteria for MAG.\textsuperscript{19–21} Several reports have indicated that the key reason for the underutilization of MAG by cardiac surgeons is the limited available randomized data in support of its clinical benefits.\textsuperscript{22,23}
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 (4,370 patients in >80 international centers) in April 2023 and the primary outcome results will available in 4 or 5 years (the trial analysis is event-driven). As there is evidence that surgeons’ experience with MAG may significantly affect its outcomes, 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 to men. In a meta-analysis of 84 studies and 903,346 patients, women undergoing CABG were at higher 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 to men. Similar results were reported in a patient-level meta-analysis of the largest CABG trials. 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. 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 towards the presentation of myocardial ischemia in men, leading to substantial delay in diagnosis and referral for treatment in women. 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 higher risk of post-operative complications,
including sternal wound infections.\textsuperscript{31–33} Women are also more likely to present for surgery with heart failure or under emergency situations such as cardiogenic shock or acute myocardial infarction.\textsuperscript{31–33 34}

Physiologically, women also have smaller coronary arteries than men, independent of body size, which increases the technical complexity of CABG\textsuperscript{35,36} 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.\textsuperscript{37–39}

Women report also lower quality of life (QOL) after CABG compared to men.\textsuperscript{40,41} Differences in reported QOL between sexes could be due to the difference in symptoms that women experience (including more frequent dyspnea),\textsuperscript{42} differences in the mechanism of angina (microvascular versus epicardial disease), and differences in coronary disease and comorbidities at the time of referral for CABG.\textsuperscript{41} In a meta-analysis of QOL after CABG including 14 randomized trials and 13,595 participants from 15 countries,\textsuperscript{43} there was a significant increase in QOL scores from before surgery to one 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 versus SAG).

Evidence that the MAG treatment effect may be different in women compared to 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 versus 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 versus 1.16\% per year, respectively, p<0.001).\textsuperscript{20} In another study including more than 1.2 million CABG patients, women had significantly lower rates of RITA
(2.9% versus 5.6%, P<0.001) and RA use (3.2% versus 5.6%, p<0.001), and lower odds than men of receiving MAG (adjusted OR 0.78, 95% CI 0.75 to 0.81, p<0.001). Women have higher risk of sternal wound complications after CABG, and this risk is increased with the use of the RITA; this may be one of the reasons for the lower RITA use in women.

In a meta-analysis of six propensity-matched studies, women who received MAG had lower long-term mortality (IRR 0.86, 95% CI 0.76-0.96) compared to women who received SAG. 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.

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 0.84-1.18 for men versus 0.78, 0.53-1.13 for women, but women represented only 14% of the enrolled population and the interaction p was not significant (0.23). In all RADIAL analyses, sex was a significant treatment effect modifier (interaction p=0.01 and 0.004 at five and 10 years, respectively) suggesting that women derived greater benefit than men from the use of MAG. 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 versus 0.37, 95% CI 0.17-0.79 for women, interaction p=0.07), but only 43/225 (19.1%) of the patients included were women. Finally, in the only trial that did not find a beneficial effect for the RA compared to the saphenous vein, >99% of the enrolled patients (751/757) were men.

In summary, there is evidence that suggests that MAG may be beneficial in CABG patients 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 outcome in women (a 
crucial need due to the current outcomes disparity) may be lost. This constitutes a strong 
rationale for a 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 1,310 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 2).

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.\textsuperscript{50} The trial has been endorsed by the Expert Advisory Panel of the Global Cardiovascular 
Research Funders Forum (GCRFF) 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 (see 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, 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 one of two groups: MAG or SAG (Figure 1). In all patients, the left internal thoracic artery will be anastomosed to the left anterior descending coronary artery. For patients 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,\textsuperscript{51,52} 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
underutilization 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, and to higher 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 15th 2023 and is actively recruiting patients.
References:


389 Dec 5];109(6):722–5. Available from:
390 https://www.ahajournals.org/doi/10.1161/01.CIR.0000115525.92645.16
391 38. Burke AP, Virmani R, Galis Z, Haudenschild CC, Muller JE. Task force #2—what is the
392 pathologic basis for new atherosclerosis imaging techniques? J Am Coll Cardiol [Internet].
393 2003 Jun [cited 2022 Dec 5];41(11):1874–86. Available from:
394 https://linkinghub.elsevier.com/retrieve/pii/S0735109703003590
396 Myocardial Infarction in Women Without Angiographically Obstructive Coronary Artery
398 https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.111.026542
400 Gender differences in health-related quality of life in patients undergoing coronary
403 quality of life after coronary artery bypass grafting surgery and the role of gender.
406 Differences in Health-Related Quality of Life After Coronary Bypass Surgery: Results
407 From a 1-Year Follow-Up in Propensity-Matched Men and Women. Psychosom Med
408 [Internet]. 2011 Apr [cited 2022 Dec 5];73(3):280–5. Available from:
409 https://journals.lww.com/00006842-201104000-00010
411 coronary artery bypass grafting on quality of life: a meta-analysis of randomized trials. Eur
412 Heart J - Qual Care Clin Outcomes [Internet]. 2022 May 5 [cited 2022 Oct 17];8(3):259–
415 Differences in Coronary Artery Bypass Grafting Techniques: A Society of Thoracic
420 [Internet]. 2016 Dec [cited 2022 Sep 13];102(6):2109–17. Available from:
421 https://linkinghub.elsevier.com/retrieve/pii/S0003497516305422
423 Association between sternal wound complications and 10-year mortality following
429 Jan 11];S0022522321018122. Available from:
430 https://linkinghub.elsevier.com/retrieve/pii/S0022522321018122
431
433 artery bypass with single versus multiple arterial grafts in women: A meta-analysis. J
435 Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022522321011478
436
437 48. Gaudino M, Samadashvili Z, Hameed I, Chikwe J, Girardi LN, Hannan EL. Differences in
438 Long-term Outcomes After Coronary Artery Bypass Grafting Using Single vs Multiple
439 Arterial Grafts and the Association With Sex. JAMA Cardiol [Internet]. 2021 Apr 1 [cited
441
443 Term Mortality Follow-Up of Radial Artery Versus Saphenous Vein in Coronary Artery
446
448 Gender Disparities in Cardiac Surgery Trials: Leadership, Authorship, and Patient
450 Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003497523000401
451
453 predictors of 3-year patency of bypass grafts implanted on the right coronary artery system:
454 a prospective randomized comparison of gastroepiploic artery, saphenous vein, and right
456
457 52. Schmidt SE, Jones JW, Thornby JI, Miller CC, Beall AC. Improved Survival With Multiple
458 Left-Sided Bilateral Internal Thoracic Artery Grafts. Ann Thorac Surg [Internet]. 1997 Jul 1
459 [cited 2022 May 3];64(1):9–15. Available from:
461
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Table 1. Inclusion and exclusion criteria for ROMA:Women.

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<th>Inclusion criteria:</th>
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<tr>
<td>1. Isolated CABG</td>
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<td>2. Primary (first time) cardiac surgery procedure</td>
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<td>3. Significant disease of the left main coronary artery or of the left anterior</td>
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<td>descending and the circumflex coronary system with or without disease of the right</td>
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<td>coronary artery</td>
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<th>Exclusion criteria:</th>
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<tr>
<td>1. Planned single graft CABG</td>
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<td>2. Emergency operation</td>
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<td>3. Left ventricular ejection fraction &lt; 35%</td>
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<td>4. Preoperative ST elevation myocardial infarction within 48 hours</td>
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<td>5. Any concomitant cardiac or non-cardiac procedure</td>
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<td>6. Any previous cardiac operation</td>
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<td>7. Preoperative severe end-organ dysfunction, cancer or any co-morbidity that</td>
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<td>reduces life expectancy to less than 5 years</td>
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<td>8. Inability to use either the saphenous vein or both the right internal thoracic</td>
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<td>artery and the radial artery as grafts</td>
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CABG: coronary artery bypass grafting.
Central Picture Legend: Rationale and design of the ROMA:Women trial.

Figure 1. 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, while only the use of SVG is allowed in the SAG group. LAD: left anterior descending artery, LITA: left internal thoracic artery, MAG: multiple arterial grafting, RA: radial artery, RITA: right internal thoracic artery, SAG: single arterial grafting, SVG: saphenous vein graft.

Figure 2. Rationale and design of the ROMA:Women trial. ROMA: Randomized comparison of the Outcome of Single versus Multiple Arterial grafts.