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SYSTEMATIC REVIEW

Revascularization versus optimal medical therapy in chronic coronary syndrome in women: A systematic review

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KEYWORDS
Chronic coronary syndrome;
Revascularization;
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Women

Abstract
Aim: We performed a systematic review to compare revascularization to optimal medical therapy (OMT) alone in reducing mortality and improving cardiovascular outcomes in women with chronic coronary syndrome, due to obstructive coronary artery disease.
Methods: PUBMED/EMBASE and CINAHL were searched for randomized trials comparing routine revascularization versus OMT alone in patients with chronic coronary syndrome. We extracted data regarding cardiovascular death, myocardial infarction, heart failure and relief of angina in women. Published data from sub-group analysis in women were the primary sources.
Results: Four randomized clinical trials that enrolled 10 722 patients followed for a mean 4.5 years of follow-up fulfilled our inclusion criteria. Two thousand four hundred one women were included in these trials. Male patients with preserved left ventricular systolic function and without left-main disease, formed the majority of trial participants. Compared with medical therapy alone, revascularization was not associated with a reduced risk of death or myocardial infarction, among women. Greater relief from angina and reduction in heart failure hospitalization was observed with revascularization in women in some studies.
Conclusions: Routine revascularization was not associated with improved survival or decreased rates of myocardial infarction in women when compared to OMT as an initial approach. Better relief from angina, and decreased hospitalizations due to heart failure were noted.

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Women continue to be underrepresented in clinical trials which limits our ability to draw robust conclusions.

PALAVRAS-CHAVE
Doença coronária crónica;
Revascularização;
Terapêutica médica otimizada;
Mulheres

Revascularização *versus* terapêutica médica otimizada na doença coronária crónica nas mulheres: uma revisão sistemática

Resumo
Objetivo: Realizamos uma revisão sistemática a comparar a revascularização com a terapêutica médica otimizada na redução da mortalidade e na melhoria do prognóstico cardiovascular em mulheres com doença coronária crónica.
Métodos: Foram realizadas pesquisas nas bases de dados da PUBMED/EMBASE e CINAHL a comparar a revascularização com a terapêutica médica otimizada em mulheres com doença coronária crónica. Extraímos dados sobre morte cardiovascular, isquemia miocárdica, insuficiência cardíaca e melhoria da angina. Os dados foram colhidos com base nas subanálises das mulheres incluídas nos estudos.
Resultados: Quatro ensaios clínicos randomizados, que incluíram 10 722 doentes, seguidos por uma média de 4,5 anos, foram incluídos nesta revisão sistemática, onde 2401 eram mulheres. Os homens constituíram a maioria dos participantes dos ensaios. Comparada com a terapêutica médica, a revascularização não reduziu o risco de morte ou isquemia do miocárdio entre as mulheres. Observou-se uma melhoria da angina e uma redução nas hospitalizações por insuficiência cardíaca com a revascularização das mesmas.
Conclusões: A revascularização não foi associada a uma melhora na sobrevida ou na redução do risco de isquemia do miocárdio nas mulheres quando comparada com a terapêutica médica otimizada. Em algumas mulheres observou-se melhoria da angina e diminuição das hospitalizações por insuficiência cardíaca. As mulheres continuam subrepresentadas nos ensaios clínicos limitando a capacidade de tirar conclusões robustas.

Introduction

In recent decades, numerous clinical trials and registries have provided valuable insights into the differences in the presentation, management, and outcomes of ischemic heart disease (IHD) in women and men.[1–4] The treatment of coronary artery disease (CAD) aims to improve symptoms, quality of life, and outcomes. Symptomatic women often experience persistent and refractory chest pain, leading to more frequent hospitalizations, lower well-being, and increased limitations in daily activities.[5] Additionally, women tend to have worse prognostic outcomes in various clinical scenarios related to IHD. Furthermore, a significant proportion of women with chronic coronary syndrome (CCS) have non-obstructive coronary artery lesions, for which optimal management has not yet been defined, and are less aggressively treated compared to men.[6–10]

Including women in high-quality randomized controlled clinical trials (RCTs) comparing revascularization with optimal medical therapy (OMT) in patients with obstructive CAD has been challenging. This is primarily due to the exclusion of women with non-obstructive CAD, despite their eligibility based on symptoms. The landmark International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial made a significant effort to enroll a high percentage of women.[11–17] However, women accounted for only 23% of the randomized participants, falling short of the target enrollment of at least 35%. An interesting finding in ISCHEMIA was that despite having less ischemia on stress imaging and less extensive or non-obstructive CAD detected by coronary computed tomography angiography (CCTA), women reported more anginal symptoms assessed by the Seattle Angina Questionnaire.[15]

Publication of the ISCHEMIA and ORBITA trials have maintained the debate about the appropriate management of CCS with obstructive CAD.[18] The ''conservative'' approach involves OMT, including antianginal drugs for symptom relief and disease-modifying agents such as cholesterol-lowering, antithrombotic, and antihypertensive medications. In this approach, disease-modifying agents improve prognosis, while antianginal therapy provides symptom relief. The invasive approach incorporates coronary angiography and revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), always accompanied by OMT.[19] The evolving components within these two strategies have ensured some form of equipoise, as they appear to be clinically equivalent in most outcome measures for patients with CCS.

Despite the wealth of evidence highlighting adverse outcomes for women with CCS, there is a knowledge gap regarding the optimal treatment approach for women.[20–25] This systematic review aims to evaluate the extensive data on OMT and revascularization and compare their efficacy specifically in the treatment of women with CCS.

Methods

Eligibility criteria

The inclusion criteria for this study were RCTs comparing routine revascularization therapy, in combination with current standard OMT, versus initial OMT alone in patients with CCS defined by coronary angiography or a positive functional study consisting of exercise or pharmacologic stress testing. To be eligible for analysis, the patients in the trials should have received a stent, regardless of whether it was a bare-metal stent (BMS) or drug-eluting stent (DES). OMT was defined as a medical regimen consisting of at least an antiplatelet, antianginal, antihypertensive and lipid-lowering therapy. Additionally, only trials where more than half of the patients in the medical therapy group received a statin were included. Trials sponsored primarily by a pharmaceutical company were considered eligible. Trials that compared intervention to other strategies, such as lifestyle changes, were excluded, and only those directly comparing intervention to medical therapy in CCS were included.

Outcomes of interest were death mainly cardiovascular; myocardial infarction (MI) including procedural and nonprocedural MI; heart failure; and angina relief. The events reported at the longest follow-up time point were abstracted from each of the trials. There were some differences in the definitions of acute myocardial infarction and procedure-related myocardial infarction, as noted in the Supplementary Appendix.

Search strategy

Databases including PUBMED/Medline, EMBASE, and CINAHL were systematically searched. These databases were searched between 2000 and 2024 and yielded 51 results. The search strategy combined the two concepts of intervention, revascularization and OMT, investigating the impact on outcomes of interest.

Study selection, data retrieval, data management

Studies were selected and the PRISMA flow diagram sequence (Figure 1) was followed for the inclusion of the RCTs that were to be evaluated. A summary of the literature review, including the reasons for exclusion, is shown in Figure 1. The literature search identified 51 articles or abstracts using the MeSH terms Stable Ischemic Heart Disease, Revascularization, Optimal Medical Therapy, Cardiovascular Disease in women and using only English-language articles as a constraint for the research. The four studies included were COURAGE,[26] BARI-2D,[27] FAME-2[28] and ISCHEMIA[13] and the study characteristics are described in Table 1.

Two reviewers (M.C.C. and I.H.) independently assessed the titles and abstracts of the identified citations to select eligible studies. The full texts of the selected citations were also screened independently by these two reviewers. Any disagreements were resolved through discussion and consensus and after discussion with a third reviewer (B.T.). The final data from the accepted articles were extracted by both reviewers, who cross-checked each other's work to ensure accuracy and resolve inconsistencies.

Study quality was assessed based on the design including randomization method, success of enrolment, data management, blinding of participants and personnel, follow-up and reporting of outcomes, funding, publications that included both the data and editorial and critical reviews of the study in question.

Risk of bias assessment

Following the COCHRANE tool, the risk of bias was assessed. These studies differ due to their chronological separation, reflecting advancements in strategies and standard-of-care at the time. Revascularization methods varied: COURAGE and FAME-2 used only PCI, while BARI-2D and ISCHEMIA used either PCI or CABG. Stents used were BMS in COURAGE, DES and BMS in 35% and 56% of PCI in BARI-2D, and DES in over 97% of PCI subjects in FAME-2 and ISCHEMIA.

In BARI-2D and ISCHEMIA, there was no standardized CABG strategy, but ISCHEMIA specifically encouraged the use of a left internal mammary graft (LIMA). CABG strategies varied, including on-pump and off-pump CABG, hybrid revascularization combining CABG and PCI, and total arterial revascularization using arterial grafts instead of saphenous vein grafts.

Except for ISCHEMIA, participants were enrolled and randomized after coronary angiography, introducing enrollment bias. Clinician bias, assuming revascularization is superior to OMT, may have led to the exclusion of participants. Some patients may have been considered unsafe in the OMT arm alone without evidence that revascularization is superior. ISCHEMIA randomized patients before angiography, which was performed only for those in the revascularization arm. Patients in the OMT arm did not undergo routine angiography; non-invasive testing was used to demonstrate ischemia. To avoid including patients with left-main (LM) disease in the OMT arm, all patients underwent a protocol-mandated CCTA to ensure LM patients were not mistakenly included.

The risk of bias pertaining to sequence generation was low in all the four trials. The risk of bias related to allocation concealment was high in all the trials because both the investigator and the patient knew in which arm of the trial the patient was entered.

Outcomes were assessed by independent board members in each trial, and the risk of bias was low in all four. Data reporting was complete, with very low attrition and exclusions, all of which were reported. There was no evidence of selective outcome reporting in any of the trials.

Results

The baseline characteristics of the included trials and clinical characteristics of the participants are summarized in Table 1.

Table 1 Study characteristics.

Study	Participants	Study design	Aim	Intervention	Comparator	Follow-up (years)	Outcomes in woman
COURAGE (Boden et al., 2007)[26]	2287 (15% female)	Randomized clinical trial	PCI to OMT in patients with CCS	PCI in one arm+OMT	OMT	4.6 (IQR 3.8–5.2)	There was no difference in treatment effect by sex for the primary endpoint (death or MI; hazard ratio [HR] 0.89; 95% confidence interval [CI], 0.77–1.03 for women and HR 1.02, 95% CI 0.96–1.10 for men; P for interaction=0.07). Although the event rate was low, a trend for interaction by sex was nonetheless noted for hospitalization for heart failure, with only women, but not men, assigned to PCI experiencing significantly fewer events as compared to their counterparts receiving OMT alone (HR 0.59; 95% CI 0.40–0.84; p<0.001 for women and HR 0.86; 95% CI 0.74–1.01; p=0.47 for men; P for interaction=0.02). Both sexes randomized to PCI experienced significantly reduced need for subsequent revascularization (HR 0.72; 95% CI 0.62–0.83; p<0.001 for women; HR 0.84; 95% CI 0.79–0.89; p<0.001 for men).
BARI-2D (Boden et al., 2007)[27]	2368 (29.6% female)	Randomized clinical trials	Revascularization to OMT in patients with CCS and DM	PCI or CABG+OMT	OMT and protocolized control of DM	5	No sex differences were observed in BARI-2D study outcomes after adjustment for difference in baseline variables (death/myocardial infarction/cerebrovascular accident: hazard ratio: 1.11, 99% confidence interval [CI]: 0.85–1.44). However, women reported more angina than men (adjusted odds ratio: 1.51, 99% CI: 1.21–1.89, p=0.0001).
FAME-2 (De Bruyne et al., 2012)[28]	888 (22% female)	Randomized clinical trial	FFR-guided PCI versus OMT in patients with CCS	FFR (<0.80)+OMT	OMT	5	There were no differences in myocardial infarction, stroke, all-cause mortality and target vessel revascularization (20.3% versus 20.2%, p=0.923) and its individual components at 2 years. FFR values were significantly higher in women than in men (0.75±0.18 versus 0.71±0.17, p=0.001). The proportion of functionally significant lesions (FFR ≤0.80) was lower in women than in men for lesions with 50–70% stenosis (21.1% versus 39.5%, p<0.001) and for lesions with 70–90% stenosis (71.9% versus 82.0%, p=0.019). An FFR-guided strategy resulted in similar relative risk reductions for death, myocardial infarction, and repeat revascularization in men and in women.
ISCHEMIA (Reynolds et al., 2024)[13]	5179 (23% female)	Randomized clinical trial	Revascularization to OMT in patients with CCS	PCI and CABG+OMT	OMT	3.2 (IQR, 2.2–4.3)	No difference between men and women in the primary outcome (cardiovascular death, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest) (HR 0.93; 95% CI 0.77–1.13; p=0.47) or the major secondary outcome of cardiovascular death/myocardial infarction (adjusted HR 0.93; 95% CI 0.76–1.14; p=0.49).

CABG: coronary artery bypass grafting; CCS: chronic coronary syndrome; DM: diabetes; FFR: fractional flow reserve; IHD: ischemic heart disease; OMT: optimal medical therapy; PCI: percutaneous coronary intervention.

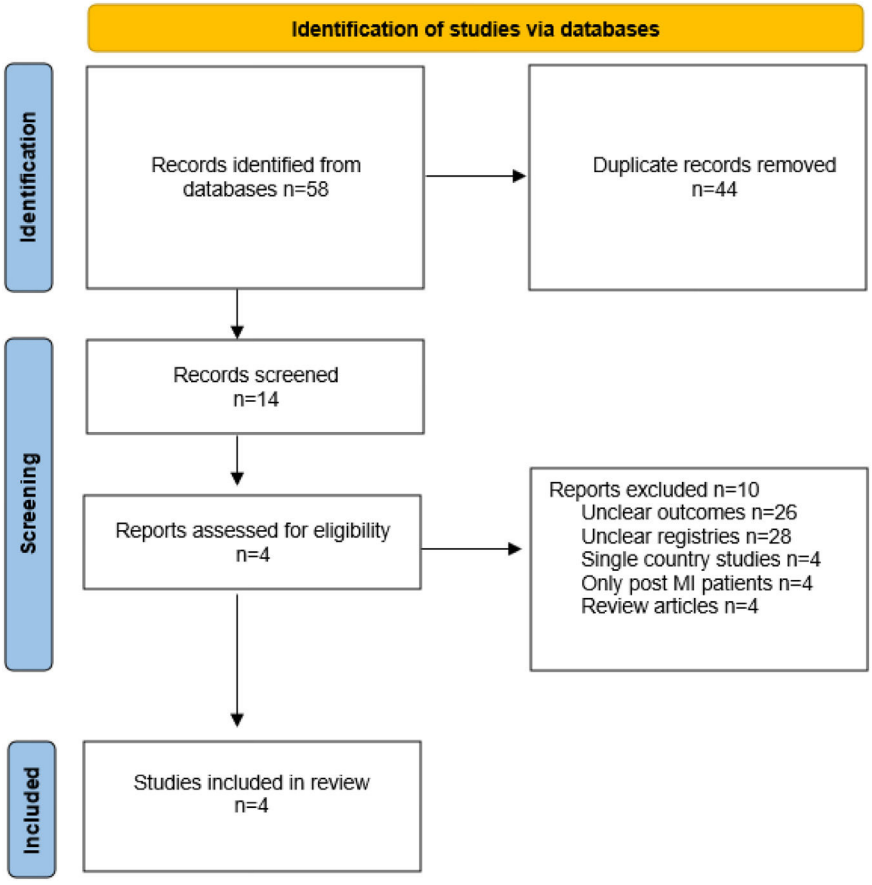

Figure 1 PRISMA flow diagram sequence.

Clinical characteristics of trial participants

Patients enrolled in the four trials had similar age ranges and the presence of comorbidities such as hypertension and diabetes, except for the BARI-2D trial, which specifically enrolled patients with diabetes. They also had comparable left ventricular ejection fraction (LVEF) and history of stroke. The prevalence of smokers was also similar across the trials.

The mean percentage of women enrolled in these studies was 22%. The studies showed that, for the most part, the women were older, had better LVEF, and less extensive CAD compared to men. For example, in the COURAGE trial, 14% of women versus 24% of men had triple-vessel disease.

In the ISCHEMIA trial, which randomized participants before cardiac catheterization to an initial invasive or conservative management strategy, women had less severe ischemia on imaging than men. Fewer women underwent coronary computed tomographic angiography (CCTA) than men (67.4% versus 70.0%; p=0.02), and women were less likely to undergo revascularization (73.4% of invasive-assigned women received revascularization versus 81.2% of invasive-assigned men; p<0.001) because women had less severe CAD on invasive angiography, with more non-obstructive disease (12.3% versus 4.5% with no stenosis ≥50%; p<0.001) and less triple-vessel CAD (29.8% versus 42.7%; p<0.001). In the PCI group, women had fewer coronary stenoses per patient. Even within the subgroup of invasive-assigned patients who underwent CCTA, women still had a higher likelihood of non-obstructive CAD on invasive angiography (10.2% versus 3.9%; p<0.001). Consistently, the most common reason revascularization was not performed was the absence of obstructive CAD, which was the case for 71.7% of women not revascularized versus 53.3% of men. The likelihood of revascularization did not differ by sex in analyses stratified by the number of diseased vessels at coronary angiography. In the invasive strategy group, the first revascularization was more likely to be percutaneous coronary intervention in women compared with men (79.1% versus 72.8%; p=0.008). In those with double or triple-vessel CAD, including severe proximal left anterior descending artery stenosis on CCTA, there was no difference in the rate of revascularization (80.5% in women versus 81.9% in men; p=0.825). There was no difference in the rate of coronary artery bypass grafting by sex (30.3% in women versus 41.4% in men; p=0.223) in those with multivessel disease who underwent revascularization. This contrasted with BARI-2D, where women who underwent CABG received fewer grafts than men, likely due to their less extensive and severe disease.

Optimal medical therapy

A large proportion of women showed elevated baseline levels of LDL and HbA1c. In BARI-2D, women were less likely

than men to achieve the target goal for LDL-C of 100 mg/dL over the five years of follow-up (adjusted OR 0.62, 99% CI: 0.50–0.77, p<0.0001), a result not observed in the COURAGE trial. The adjusted odds for achieving an HbA1c <7% or blood pressure <130/80 mm Hg over five years of follow-up were not significantly different between sexes in both studies. Mirroring BARI-2D, in ISCHEMIA, despite the trial's rigorous design and focus on lifestyle intervention and intensive use of OMT, women were less likely to achieve targets for blood pressure, LDL-C, and HbA1c. The goal of achieving systolic blood pressure (SBP) <140 mm Hg was met by 73.6% of women compared to 77.9% of men (p=0.003) and the LDL-C goal of <70 mg/dL was attained by 50.2% of women versus 61.3% of men (p<0.001). The utilization of OMT in women was unexpectedly lower than in men throughout the study's follow-up period. Women were less likely to be prescribed high-intensity statin therapy (60.7% versus 64.3%; p=0.025), even among those with obstructive CAD identified during cardiac catheterization.

Death, myocardial infarction, heart failure and revascularization

Revascularization did not demonstrate a statistically significant difference in benefit over OMT alone in terms of the primary composite endpoint, with no significant interaction by sex. In the COURAGE trial, PCI did not show additional benefit over OMT in reducing death and non-fatal MI (HR 0.89; 95% CI 0.77–1.03; p=0.10 for women; HR 1.02; 95% CI 0.96–1.10; p=0.52 for men) over 4.5 years. Similarly, in the BARI-2D trial, revascularization showed no significant benefit (HR 1.11; 99% CI 0.85–1.44).

In the FAME-2 trial, it was hypothesized that fractional flow reserve (FFR)-guided PCI could provide better outcomes compared to medical therapy in patients with stable CAD, which was not seen (HR 0.70; 95% CI 0.48–1.04). There was no significant difference in incidence of death or MI (HR: 0.86; 95% CI: 0.36–2.09) between men and women.[29]

In ISCHEMIA, no significant difference was found (HR 0.93; 95% CI 0.77–1.13; p=0.47). The rate of periprocedural MI was lower among women (adjusted HR 0.40; 95% CI 0.21–0.76; p=0.005), consistent with lower rates of revascularization among women. When considering only those in the invasive strategy group who underwent revascularization, there was no difference in the four-year rate of procedural MI between women and men.

However, the COURAGE trial showed a significantly reduced need for subsequent revascularization in the PCI plus OMT group compared to OMT alone (p<0.001 for both), which was also observed in the BARI-2D trial. It was noted that women were more likely than men to have CHF. Furthermore, in the COURAGE trial, fewer women in the PCI plus OMT arm were subsequently hospitalized for heart failure compared to those who did not undergo PCI and remained on OMT.

Angina relief

Women exhibited a longer duration of angina, increased angina frequency, and more angina-related physical limitations, indicating poorer angina-related health status. This was reflected by a higher proportion of women in the more unfavorable Canadian Cardiovascular Society functional classes (classes 3 and 4), despite having less extensive CAD.

In these studies, freedom from angina was similar between men and women, regardless of treatment assignment. However, in the COURAGE trial, patients in the OMT arm showed less improvement compared to those in the PCI plus OMT arm (p=0.002). This disparity might explain the lower rate of subsequent revascularizations in the OMT subgroup. In contrast, in the BARI-2D study, women remained more symptomatic than men (adjusted OR 1.51, 99% CI 1.21–1.89, p<0.0001), experiencing more angina and a lower functional status as measured by the Duke Activity Status Index. Women who underwent PCI in FAME-2 were significantly less likely to undergo urgent revascularization compared with women treated medically (HR 0.26; 95% CI 0.1–0.68; p=0.007). Persistence of angina was reported in 18.6% of women in the OMT group and 8.9% of women in the PCI group (p=0.04) at one year, and 10.3% versus 4.5%, respectively, at three-year follow-up (p=0.15).[30]

Interestingly, in ISCHEMIA women had more emergency room admissions for noncardiac chest pain than men (3.3% versus 1.8%, p=0.004) but no increased admissions for the same reason.

Discussion

The studies showed that women were generally older and had less severe CAD than men. Women had fewer instances of triple-vessel disease and less severe ischemia. They were also less likely to undergo coronary procedures like CCTA and revascularization due to less severe CAD. The main reason for not performing revascularization in women was the absence of obstructive CAD. Women had more non-obstructive disease and fewer coronary stenoses. In procedures, women received fewer grafts in CABG. Despite these differences, the rate of revascularization did not significantly differ by sex in severe CAD cases.

In patients with CCS, revascularization did not provide additional benefits over OMT in terms of reducing major cardiac events among the different studies. The primary composite endpoint of death and non-fatal myocardial infarction (MI) did not differ significantly between men and women. However, women who underwent PCI along with OMT had a lower risk of subsequent hospitalization for heart failure compared to those on OMT alone in COURAGE study. The cumulative event rates at six months and five years showed variations between the invasive and OMT arms, primarily driven by procedure-related MI and spontaneous MI rates. This highlights the importance of long-term follow-up in assessing treatment outcomes. Our findings are similar to recent reports addressing this question although gender-based outcomes were not assessed.[17,29,31]

It is worth mentioning that in all the conducted trials, PCI was the predominant mode of revascularization, performed in approximately 65–75% of patients in the revascularization arm. Therefore, the primary comparison remains between PCI and OMT, rather than the general term ''revascularization'' which encompasses both PCI and CABG.

Recent evidence from RCTs and meta-analyses has influenced professional society guidelines, which now

recommend OMT as the initial treatment approach for symptomatic patients with CCS because the addition of revascularization to OMT has not consistently shown superior cardiovascular outcomes, including reduced mortality, myocardial infarction, or heart failure. This may be attributed to the significant improvement in OMT over the past two decades, including better management of risk factors and implementation of secondary prevention strategies.

Despite having lesser extent of disease angiographically, women tend to be more symptomatic compared to men. The reasons for refractory angina in women are often not related to the extent of epicardial CAD and therefore symptoms are less likely to be ameliorated by revascularization especially PCI alone. Lesser extent of disease suggests that women will generally undergo PCI more often than CABG. Even after revascularization, persistent angina is more prevalent in women, given the multi factorial etiology of angina in these patients. Improvements in angina and reduced rates of hospitalization are seen with revascularization in women compared to OMT. This finding is predominantly found in one trial – COURAGE. It is important to note that despite the lack of consistent cardiovascular outcome benefits, revascularization has been associated with improved angina symptoms and quality of life compared to OMT alone.

Women consistently form a minority of patients enrolled in RCTs comparing the two strategies. The reason seems to be that a significant portion of symptomatic women have non-obstructive CAD and trial designs mandating the need for obstructive CAD are excluded. This analysis therefore includes the 338, 701, 247 and 1168 women included in COURAGE, BARI-2D, FAME-2 and ISCHEMIA. This confirms that less than a quarter of trial participants are women in patients with CCS. It is highly unlikely that a RCT to compare the two strategies that enrolls only women will ever be conducted. Given the general difficulty that RCTs have in recruiting patients comparing the two strategies, these difficulties will be magnified in a potential RCT that includes solely women.

The presence of ischemic changes and elevated biomarkers were not mandatory for admission or the decision to revascularize those patients who had been initially randomized to the OMT arm, as was the case with ISCHEMIA. As patients and physicians were technically unblinded to which arm the patient was in, the subsequent threshold for revascularization may have been lower on the part of the physicians, for those on OMT.

The study highlights significant differences between men and women in reaching cardiovascular health targets. Women were less likely to meet treatment goals for LDL-C, blood pressure, and HbA1c compared to men across multiple trials. Additionally, women were prescribed high-intensity statin therapy less frequently than men, even when diagnosed with obstructive coronary artery disease. These findings suggest the need for more therapeutic vigilance to improve cardiovascular outcomes for women.

Conclusions

In women presenting with symptomatic CCS due to obstructive CAD, the strategy of revascularization added on to OMT is not superior to OMT alone to improve cardiovascular outcomes. OMT alone may be pursued as an initial strategy with revascularization deferred to a later stage if deemed necessary. However, for angina relief, revascularization is a more robust approach and can be offered if OMT is unsuccessful in controlling symptoms. Moreover, limited data suggest that revascularization may decrease hospitalization for heart failure in women.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.repc.2025.01.009.

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