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Review Article

Gender-based disparities in outcomes of coronary bifurcation stenting in patients undergoing percutaneous coronary intervention: a systematic review and meta-analysis

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Abstract: Introduction: Around 15-20% of lesions necessitating percutaneous coronary interventions (PCI) are attributed to coronary bifurcation lesions. We aim to study gender-based differences in PCI outcomes among bifurcation stents. Methods: 3 studies were included after thorough systematic search using MEDLINE (EMBASE and PubMed). CRAN-R software using the Metabin module was used for statistical analysis. Pooled odds ratios (OR) were calculated using the random effect model and the Mantel-Haenszel method, with a 95% confidence interval (CI) used to determine statistical significance. Heterogeneity was assessed using Higgins I^2. Result: Women exhibited a higher risk of in-hospital mortality (OR 0.67, 95% CI 0.58-0.76, I^2 = 0%, P < 0.0001), post-procedural bleeding (OR 0.53, 95% CI 0.47-0.6, I^2 = 0%, P < 0.0001) and post-procedure stroke (OR 0.72, 95% CI 0.52-1.0, I^2 = 0%, P < 0.06) as compared to men. However, there were no significant differences in terms of myocardial infarction (OR 0.84, 95% CI 0.22-3.27, I^2 = 49.4%, P < 0.80) and cardiac tamponade (OR 0.63, 95% CI 0.06; 5.72, I^2 = 0%, P < 0.6821) in both groups. Conclusion: Our study reveals a noteworthy increase in in-hospital mortality in women, which could be attributed to a higher rate of major bleeding, advanced age, increased co-morbidities, and complex pathophysiology of the lesion in comparison to men. Further studies are required to gain a better understanding of the precise mechanisms thus enhancing procedural outcomes.

Keywords: Female, male, bifurcation stenting, PCI

Introduction

Cardiovascular disease remains a leading cause of mortality in the United States. Among various treatment modalities for coronary artery disease (CAD), percutaneous coronary intervention (PCI) has evolved as a major therapeutic intervention for obstructive coronary pathologies. PCI was introduced in 1977 and has played a vital role in reducing mortality and overall survival outcomes in patients with CAD [1]. Over time, with an increasing prevalence of CAD, it is imperative to understand the effectiveness of PCI for intricate lesions and advanced CAD such as coronary bifurcation lesions to improve patients' quality of life.

Advanced coronary lesions with complex anatomy are a unique challenge for adverse outcomes during stent placement [2]. The growth of interventional cardiology has led to better success rates and decreased incidence of in-

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Table 1. Characteristics of included studies

Author	Pravda et al.	Osman et al.	Nicolas et al.
Year	2021	2021	2020
Country	Israel	United States	United States
Duration of study	3 years	30 days	3 years
Type of the study	Observational	National Inpatient Data	Observational
Primary outcomes	In-hospital mortality. MACE	In-hospital mortality. Major bleeding, 30-day readmission	MACE
Secondary outcomes	Stent thrombosis, in-stent restenosis, CABG, target lesions revascularization	In-hospital mortality, vascular complications, major bleeding, post-procedural bleeding, need for blood transfusion, AKI, AKI requiring dialysis, stroke, severe disability, length of stay and cost of hospitalization, 30-day readmission	Stent thrombosis, major bleeding, minor bleeding

stent restenosis particularly in the subset of bifurcating coronary stents which approximately accounts for 15-20% of all coronary lesions requiring PCI [3]. There are notable studies that focus on outcomes of PCI in bifurcating lesions focusing on major adverse cardiac events (MACE) eg: bleeding, stent thrombosis, target lesion revascularization (TLR), and mortality, but the impact of patient factors, especially the effect of gender, is currently limited and still an area of ongoing research and a subject of interest in recent medical research [4].

Recent studies exploring gender disparities indicate that women experience far much worse outcomes compared to men undergoing PCI for coronary bifurcation lesions [5]. Recognizing the knowledge gap, this meta-analysis aims to review the currently existing literature in detail and to summarize and give valuable insight on gender-specific influences, thereby contributing towards further understanding and refinement of management strategies in men and women, leading to the ultimate goal of better patient care, clinical decision making while managing coronary artery disease, future research, and optimization of resources in health.

Methods

Study design

Our approach to searching and conducting the meta-analysis aligns with the recommendations outlined in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews-2) guidelines [6, 7]. The checklists of these guidelines are presented in Supplementary Files 1 and 2 respectively.

Inclusion and exclusion criteria

We conducted a literature search on MEDLINE (Pubmed and Scopus) for trials or observational studies using a systematic search strategy as per PRISMA guidelines. We included studies that investigated disparities related to gender in patients aged 18 or older with stable coronary artery disease or acute coronary syndrome and underwent any form of percutaneous coronary intervention (PCI) involving stent placement at the bifurcation of coronary arteries (**Table 1**). Case reports, clinical spotlights, and review articles were excluded.

Screening

We utilized Medical Subject Heading (MeSH) terms and keywords, employing Boolean operators “OR” and “AND”, to construct our search queries for terms including “bifurcation stent”, “percutaneous coronary intervention at the branch”, “bifurcation lesion”, “gender”, “male”, “female” (Supplementary File 3). Three authors conducted independent screening of the articles. Full-text articles that passed the initial screening were subsequently subjected to a second phase of evaluation to assess outcomes of interest. The backward snowballing method was utilized to identify and include additional studies that matched our specific outcomes of interest.

Study characteristics

Data was collected for: 1. Baseline characteristics including age, sex, and co-morbidities (**Table 2**). 2. In-hospital mortality. 3. Periprocedural bleeding, stroke, target lesion revascularization, cardiac tamponade, myocardial infarction.

Table 2. Baseline demographics and co-morbidities of included studies

Variables	Gender	Pravda et al.	Osman et al.	Nicolas et al.
Number of patients	Male	948	17,570	316
	Female	261	7480	251
Age (mean/SD)	Male	63.12/11.8	63	68/9.13
	Female	69.67/11.7	69	69/10
Hypertension	Male	618	13441	130
	Female	208	6156	140
Diabetes	Male	315	5693	66
	Female	108	3216	71
Obesity	Male	382	3338	35
	Female	126	1735	36
Dyslipedemia	Male	701		96
	Female	208		108
Stroke	Male	72		65
	Female	23		68
Peripheral vascular disease	Male	72	1792	55
	Female	28	1002	53
Previous PCI	Male	403	7379	
	Female	91	3037	
Previous CABG	Male	78		
	Female	23		
History of Smoking	Male	265	4656	41
	Female	23	1818	41
Renal Failure	Male	105	2811	
	Female	30	1421	

Statistical analysis of the data

CRAN-R software (The R Foundation for Statistical Computing, Vienna, Austria) was used to calculate pooled effect sizes. The statistical analysis was performed using the Mantel-Haenszel random-effects model to calculate the unadjusted odds ratio (OR) with a probability value of $P < 0.05$ considered to be statistically significant. Higgins I-squared (I^2) was used to assess statistical heterogeneity, with values of 50% or less indicating low to moderate heterogeneity, and values of 75% or more indicating high heterogeneity [8]. The quality assessment of the included articles was performed using the Newcastle-Ottawa Scale for observational studies [9].

Result

Study characteristics

There were 1199 articles in our dataset following the initial screening. During the first phase of our investigation, all 1199 records underwent a vetting process, resulting in the removal of 1043 of them. In the second phase, the remaining 153 articles underwent further scrutiny, and ultimately, only 3 studies were deemed suitable for our final analysis (**Table 1**).

Baseline patient demographics

A total of 26,826 patients undergoing percutaneous coronary intervention (PCI) for bifurcation stent were studied, out of which 18,834 (70%) were males and 7992 (30%) were females. The mean age of male patients was 63 ± 3 years and female patients was 69 ± 3 years. The study and baseline characteristics of the male and female patients in the included studies are shown in detail in **Tables 1** and **2** respectively.

In-hospital mortality

The meta-analysis revealed a significant difference in in-hospital mortality rates between males and females with post-procedural bleeding and post-procedural stroke are shown in

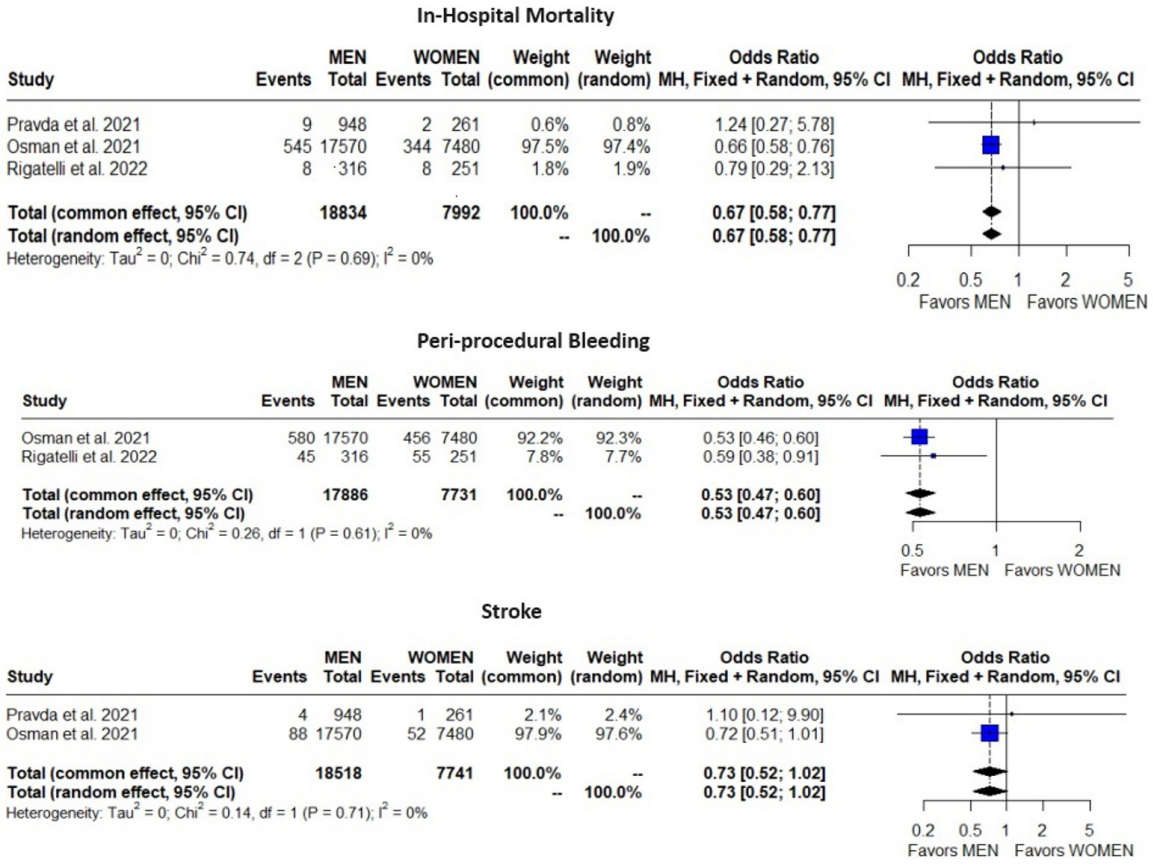

Figure 1. Forest plot of primary outcome. In-hospital mortality and secondary outcomes: peri-procedural bleeding and stroke between males and females undergoing PCI for bifurcation stents.

Figures 1 and **2**. Females exhibited a higher risk of in-hospital mortality with an odds ratio (OR) of 0.67 (95% CI 0.58-0.76, I^2 = 0%, P < 0.0001) as compared to males (**Figure 1**). The results suggest that males have a decreased likelihood of mortality during their hospital stay compared to females (Supplementary File 4).

Periprocedural bleeding

The meta-analysis found a significant difference in peri-procedural bleeding between male and female patients. Females were more likely to have peri-procedural bleeding as compared to males with OR of 0.53 (95% CI 0.47-0.6, I^2 = 0%, P < 0.0001) (**Figure 1**; Supplementary File 4).

Stroke

The meta-analysis also showed no significant difference in stroke between males and females with increased post-procedural stroke in females with OR of 0.72 (95% CI 0.52-1.0, I^2 = 0%, P = 0.06) (**Figure 1**; Supplementary File 4).

Myocardial infarction

There was no significant difference in myocardial infarction between females and males. The study showed no differences in MI between men and women with OR of 0.84 (95% CI 0.22-3.27, I^2 = 49.4%, P = 0.80) (**Figure 2**; Supplementary File 4).

Cardiac tamponade

There was no significant difference in myocardial infarction between females and males. The study showed no differences in cardiac tamponade between both groups with OR of 0.63 (95% CI 0.06-5.72, I^2 = 0%, P = 0.68) (**Figure 2**; Supplementary File 4).

Target lesion revascularization

There were statistically insignificant increased rates of target lesion revascularization in

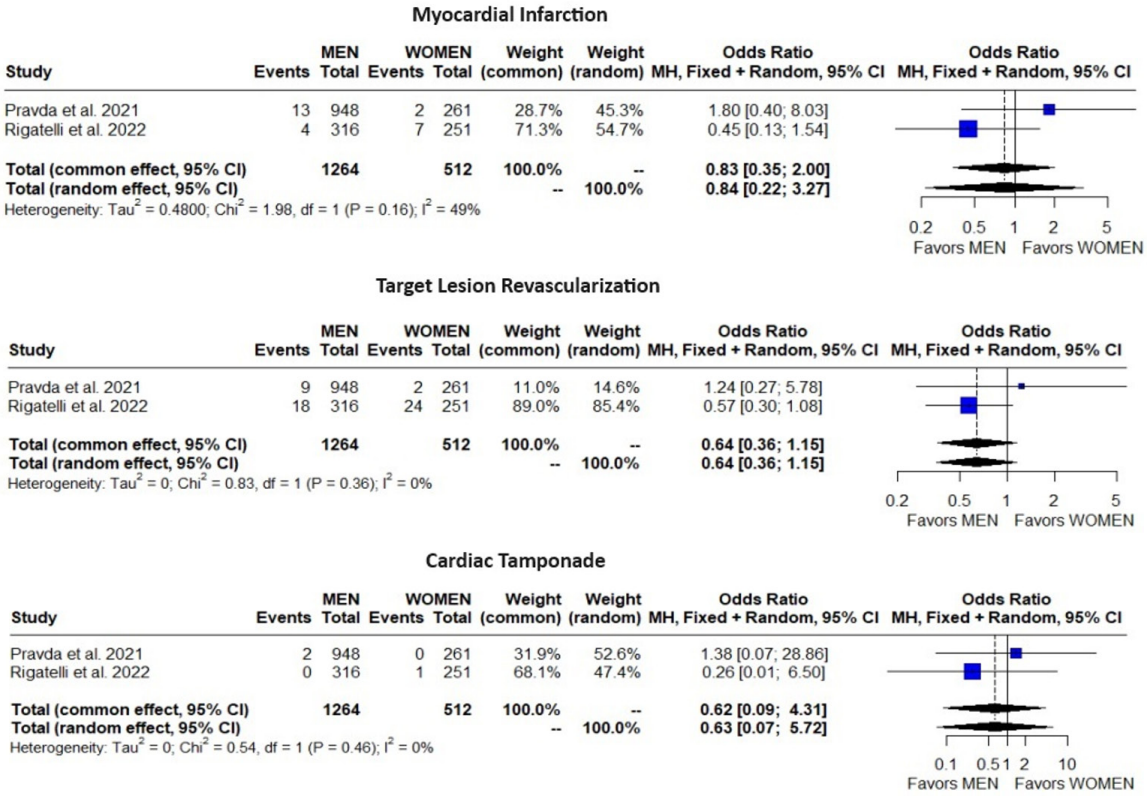

Figure 2. Forest plot of secondary outcomes. Myocardial infarction, target lesions revascularization, and cardiac tamponade between males and females undergoing PCI for bifurcation stents.

females as compared to males with OR of 0.64 (95% CI 0.35-1.15, I^2 = 0%, P = 0.135) (**Figure 2**; Supplementary File 4).

Heterogeneity and quality check

A heterogeneity test assesses the null hypothesis that all studies are investigating the same effect. However, when the number of included studies is less than 10, it becomes difficult to discern true heterogeneity from outcomes that may occur by chance. The heterogeneity observed in secondary outcome MI in our study can be attributed to the inclusion of a low number of studies [10].

Quality assessment of the 3 non-randomized trials was done using the NewCastle-Ottawa Scale as shown in Supplementary File 5. Our quality check shows that all the included studies were of sufficiently high quality.

Discussion

We performed a meta-analysis on gender-based differences in men and women undergoing PCI on bifurcation lesions. Our studies have several significant findings. Firstly, women had a significantly higher risk of in-hospital mortality after undergoing PCI for bifurcation lesions as compared to men. Secondly, women had a significantly higher risk of post-procedural bleeding as compared to men. Thirdly, women were also found to have higher odds of stroke and target lesion revascularization, however it did not reach statistical significance. Finally, there were no significant differences in post-procedural myocardial infarction and cardiac tamponade.

The female population was notably underrepresented in our study, comprising only 30% of the total participants. This trend is consistent with previous studies, which typically reported female representation ranging from 21% to 29% [2, 5, 11].

Similar to our study, the study by Pradaxa et al. revealed a higher mean age among women undergoing bifurcation lesion stenting or complex PCI compared to men, with women averag-

ing 69.7 ± 11 years and men 63.1 ± 11 years [2]. This was consistent with a higher mean age of women in the other studies by Osman et al. (women 69 years vs. men 63 years) and Nicholas et al. (women 68.4 ± 11.8 years vs. men 64.5 ± 11.5 years) [5, 11]. In comparison to men, women exhibited a greater prevalence of comorbidities such as diabetes, hypertension, hyperlipidemia, peripheral artery disease, chronic kidney disease, chronic heart failure, and chronic lung disease in all three studies [2, 5, 11].

Our study showed a higher risk of in-hospital mortality in females compared to males. In line with our findings, the study conducted by Osman et al. showed increased rates of in-hospital major adverse events, which included a composite of in-hospital mortality, vascular complications, and major bleeding even after propensity score matching suggesting elevated risk in females [5]. Female sex was found to be an independent risk factor for all-cause mortality [2]. These were attributed to higher age, increased coronary calcification, and comorbidities in female patients as compared to males [2].

Similar to our study, periprocedural bleeding was higher in women as compared to men regardless of the complexity of PCI [5, 11]. Multiple previous research studies have established that the female gender is associated with an increased risk of bleeding [11, 12]. One such study, the CRUSADE trial, examining gender-based differences in non-ST elevation coronary artery disease, reported a higher incidence of red blood cell transfusion requirement in women (17.2% versus 13.2% adjusted OR 1.17 (1.09-1.25) suggesting an increased incidence of bleeding [12]. Another study by Daughtery et al. stated that women had twice the risk of bleeding as compared to male after PCI. They also suggested higher bleeding events in women when bleeding avoidance strategies (BAS) were not used (crude rates of 12.6% vs. 6.2%, $P < 0.01$). Overall the bleeding risks were lower in both genders with the bleeding avoidance strategy, however, absolute risk differences continued to be comparatively higher in women even with BAS (6.3% vs. 3.2%, $P < 0.01$) [4]. Interestingly, it has been found that women exhibit significantly smaller sizes of iliofemoral arterial systems as compared to men, even after adjusting height, weight, and other comorbidities that are known to impact vascular anatomy [13]. In light of the increased risk of bleeding in the female population, implementing measures such as employing the radial access site, administering bivalirudin, and utilizing vascular closure devices can prove beneficial [11, 12].

We found no significant differences in the post-procedural myocardial infarctions and cardiac tamponade between female and male patients comparable to previous studies. These findings suggest this association was not attributed to the bifurcation PCI procedure itself but related to advanced age and comorbidities [2].

We observed a higher risk of target lesion revascularization among females as compared to males, although it is important to note that these findings did not reach statistical significance. Interestingly, follow-up studies have reported no discernible differences in outcomes during a follow-up period of up to 3 years [2, 14].

The characteristics of PCI bifurcation stenting were observed to be similar in both genders, with an equivalent rate of angiographic success [2]. However, previous studies have shown a worse prognosis with higher mortality in the female population with bifurcation lesion PCI compared to males as observed over a three-year follow-up period [2]. This suggests that factors other than the procedure itself led to higher in-hospital mortality in females. Apart from advanced age, comorbidities, and increased bleeding risk, the underlying pathophysiology of myocardial infarction (MI) can lead to an unfavorable clinical outcome in women undergoing PCI. The occurrence of myocardial infarction (MI) in men is typically associated with plaque rupture, whereas plaque erosion is the predominant mechanism in women [11]. Notably, impaired endothelial functions within the coronary arteries and microvasculature are frequently implicated in MI in women, as opposed to the angiographic changes seen in men. Unfortunately, these differences can result in women being inadequately treated during complex revascularization procedures, leading to residual coronary disease and consequent unfavorable outcomes in the long term [11, 15].

Women are less likely to be referred for cardiac catheterization as compared to men (41.9 vs. 49.6%; P < 0.001) and overall receive fewer evidence-based treatments [5, 16].

Osman et al. further discusses a higher readmission rate in women undergoing PCI for bifurcation stent which is likely due to atypical presentation of MI and lower referral to catheterization leading to treatment delay causing longer periods of ischemia [5].

Limitation

There are some limitations to our meta-analysis. First, there was an overall low representation of female population comparison of only 30% of the population. Second, there were no randomized controlled trial comparing the outcomes between female and male; we only included observational studies which resulted in lack of matching, blinding and the potential introduction of selection bias.

Conclusion

Females undergoing bifurcation PCI exhibit a increased risk of in-hospital mortality, which can be attributed to several factors, including comorbidities, heightened periprocedural bleeding, atypical clinical presentations, and reduced referrals for cardiac catheterization. Nonetheless, it is essential to acknowledge that the overall lower representation of the female population prevents a precise determination of the underlying mechanisms leading to these poorer outcomes. Consequently, there is a clear need for large-scale randomized controlled trials to provide more robust insights and ultimately improve patient outcomes.

Disclosure of conflict of interest

None.

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Supplementary File 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	–
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4

Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	5
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	--
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5-7
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	7

DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9
	23b	Discuss any limitations of the evidence included in the review.	10
	23c	Discuss any limitations of the review processes used.	10
	23d	Discuss implications of the results for practice, policy, and future research.	10
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	--
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	1
Competing interests	26	Declare any competing interests of review authors.	1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	--

Supplementary File 2. AMSTAR-2 (Assessing the methodological quality of systematic reviews-2) guidelines checklist

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
x Population
x Intervention
x Comparator group
x Outcome

Optional (recommended)
• Timeframe for follow-up

x Yes
• No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
x review question(s)
x a search strategy
x inclusion/exclusion criteria a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
• a meta-analysis/synthesis plan, if appropriate, *and*
• a plan for investigating causes of heterogeneity
• justification for any deviations from the protocol

• Yes
x Partial Yes
• No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:
• *Explanation for* including only RCTs
x OR *Explanation for* including only NRSI
• OR *Explanation for* including both RCTs and NRSI

x Yes
• No

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):	For Yes, should also have (all the following):	
x searched at least 2 databases (relevant to research question)	x searched the reference lists/bibliographies of included studies	• Yes
x provided key word and/or search strategy	• searched trial/study registries	x Partial Yes
x justified publication restrictions (e.g. language)	• included/consulted content experts in the field	• No
	• where relevant, searched for grey literature	
	x conducted search within 24 months of completion of the review	

5. Did the review authors perform study selection in duplicate?

For Yes, either ONE of the following:

x at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include	x Yes
• OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	• No

6. Did the review authors perform data extraction in duplicate?

For Yes, either ONE of the following:

x at least two reviewers achieved consensus on which data to extract from included studies	x Yes
• OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.	• No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:	For Yes, must also have:	
• provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	x Justified the exclusion from the review of each potentially relevant study	x Yes • Partial Yes • No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
• described populations	x described population in detail	x Yes
• described interventions	x described intervention in detail (including doses where relevant)	• Partial Yes
• described comparators	x described comparator in detail (including doses where relevant)	• No
• described outcomes	x described study's setting	
• described research designs	x timeframe for follow-up	

9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
• unconcealed allocation, *and*	• allocation sequence that was not truly random, *and*	• Yes
• lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	• selection of the reported result from among multiple measurements or analyses of a specified outcome	• Partial Yes • No x Includes only NRSI

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
• from confounding, *and*	x methods used to ascertain exposures and outcomes, *and*	x Yes
• from selection bias	x selection of the reported result from among multiple measurements or analyses of a specified outcome	• Partial Yes • No • Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

•Must have reported on the sources of funding for individual studies included	x Yes. Note: Reporting that the reviewers looked for this information • No was not reported by study authors also qualifies

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs	
For Yes: x The authors justified combining the data in a meta-analysis x AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. x AND investigated the causes of any heterogeneity	x Yes • No • No meta-analysis conducted
For NRSI	
For Yes: x The authors justified combining the data in a meta-analysis x AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present x AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available x AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	x Yes • No • No meta-analysis conducted

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

For Yes: • included only low risk of bias RCTs x OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.	x Yes • No • No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?

For Yes: • included only low risk of bias RCTs x OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results	x Yes • No

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For Yes: x There was no significant heterogeneity in the results • OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review	x Yes • No

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For Yes: x performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	x Yes • No • No meta-analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes: x The authors reported no competing interests OR • The authors described their funding sources and how they managed potential conflicts of interest	x Yes • No

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E and Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017; 358: j4008.

Supplemental File 3. Research question, PICO, MeSH and keywords and search strategy

Research Question:

Gender-Based Disparities in Outcome of Coronary Bifurcation Stenting in patients undergoing Percutaneous Coronary Intervention

PICO:

Population: Patient undergoing Percutaneous Coronary Intervention for Bifurcation Stent

Intervention: Bifurcation Stent

Comparison: Female versus Male

Outcome: 1) in-hospital mortality 2) peri-procedural bleeding 3) stroke 4) target lesion revascularization 5) myocardial infarction 6) Cardiac tamponade

Study type: Odds Ratio to compare binary outcomes and standard mean difference to compare continuous outcomes meta-analyses.

MeSH Terms & Keywords:

bifurcation stent

percutaneous coronary intervention at branch

branch stenting

branch PCI

branch PTCA

lesion at branch

bifurcation lesion

Gender based

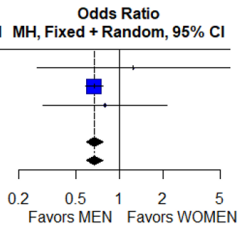
Sex based

(((((((((bifurcation stent) OR (percutaneous coronary intervention at branch)) OR (branch stenting)) OR (branch PCI)) OR (branch PTCA)) OR (lesion at branch)) OR (bifurcation lesion)) OR (double kissing balloon)) OR (culotte stenting) AND (clinicaltrial[Filter] OR clinicaltrialprotocol[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])) AND ((((gender) OR (male)) OR (female)) OR (sex based) AND (clinicaltrial[Filter] OR clinicaltrialprotocol[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR meta-analysis[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))

Primary Outcome: All-cause mortality

Study	MEN Events	MEN Total	WOMEN Events	WOMEN Total	Weight (common)	Weight (random)	Odds Ratio MH, Fixed + Random, 95% CI
Pravda et al. 2021	9	948	2	261	0.6%	0.8%	1.24 [0.27; 5.78]
Osman et al. 2021	545	17570	344	7480	97.5%	97.4%	0.66 [0.58; 0.76]
Rigatelli et al. 2022	8	316	8	251	1.8%	1.9%	0.79 [0.29; 2.13]
Total (common effect, 95% CI)		**18834**		**7992**	**100.0%**	--	**0.67 [0.58; 0.77]**
Total (random effect, 95% CI)					--	**100.0%**	**0.67 [0.58; 0.77]**

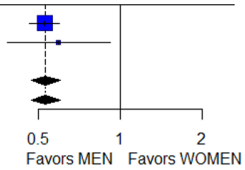
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.74$, df = 2 (P = 0.69); $I^2 = 0\%$



Secondary Outcomes: Post-procedural bleeding

Study	MEN Events	MEN Total	WOMEN Events	WOMEN Total	Weight (common)	Weight (random)	Odds Ratio MH, Fixed + Random, 95% CI
Osman et al. 2021	580	17570	456	7480	92.2%	92.3%	0.53 [0.46; 0.60]
Rigatelli et al. 2022	45	316	55	251	7.8%	7.7%	0.59 [0.38; 0.91]
Total (common effect, 95% CI)		**17886**		**7731**	**100.0%**	--	**0.53 [0.47; 0.60]**
Total (random effect, 95% CI)					--	**100.0%**	**0.53 [0.47; 0.60]**

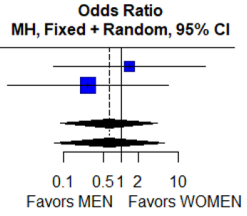
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.26$, df = 1 (P = 0.61); $I^2 = 0\%$



Secondary Outcome: Cardiac Tamponade

Study	MEN Events	MEN Total	WOMEN Events	WOMEN Total	Weight (common)	Weight (random)	Odds Ratio MH, Fixed + Random, 95% CI
Pravda et al. 2021	2	948	0	261	31.9%	52.6%	1.38 [0.07; 28.86]
Rigatelli et al. 2022	0	316	1	251	68.1%	47.4%	0.26 [0.01; 6.50]
Total (common effect, 95% CI)		**1264**		**512**	**100.0%**	--	**0.62 [0.09; 4.31]**
Total (random effect, 95% CI)					--	**100.0%**	**0.63 [0.07; 5.72]**

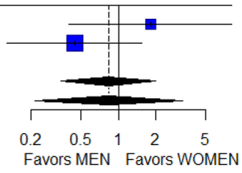
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.54$, df = 1 (P = 0.46); $I^2 = 0\%$



Secondary Outcome: Myocardial Infarction

Study	MEN Events	MEN Total	WOMEN Events	WOMEN Total	Weight (common)	Weight (random)	Odds Ratio MH, Fixed + Random, 95% CI
Pravda et al. 2021	13	948	2	261	28.7%	45.3%	1.80 [0.40; 8.03]
Rigatelli et al. 2022	4	316	7	251	71.3%	54.7%	0.45 [0.13; 1.54]
Total (common effect, 95% CI)		**1264**		**512**	**100.0%**	--	**0.83 [0.35; 2.00]**
Total (random effect, 95% CI)					--	**100.0%**	**0.84 [0.22; 3.27]**

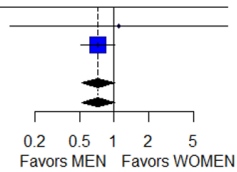
Heterogeneity: $Tau^2 = 0.4800$; $Chi^2 = 1.98$, df = 1 (P = 0.16); $I^2 = 49\%$

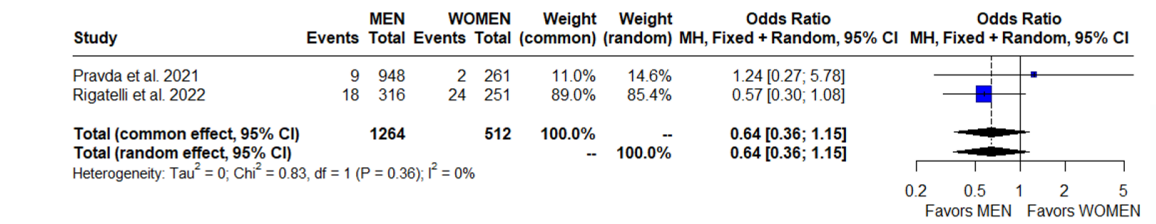


Secondary Outcome: Stroke

Study	MEN Events	MEN Total	WOMEN Events	WOMEN Total	Weight (common)	Weight (random)	Odds Ratio MH, Fixed + Random, 95% CI
Pravda et al. 2021	4	948	1	261	2.1%	2.4%	1.10 [0.12; 9.90]
Osman et al. 2021	88	17570	52	7480	97.9%	97.6%	0.72 [0.51; 1.01]
Total (common effect, 95% CI)		**18518**		**7741**	**100.0%**	--	**0.73 [0.52; 1.02]**
Total (random effect, 95% CI)					--	**100.0%**	**0.73 [0.52; 1.02]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.14$, df = 1 (P = 0.71); $I^2 = 0\%$





Supplemental File 4. Subgroup analysis.

Supplementary File 5. Newcastle-Ottawa Scale (NOS) assessment for included observational studies

Study	NOS
Pravda et al.	8/9
Osman et al.	8/9
Rigatelli et al.	8/9