Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-23-294

Reviewer A

I think this paper was well reviewed. The conclusion was not yet, but this reviewer agreed some information and is necessary further study Preoperative coronary artery disease risk factors (CADRFs) distribution and pattern may have an important role in determining major adverse cardiovascular events (MACEs). Women undergoing CABG were also older, had a lower body surface area (BSA), and a higher incidence of diabetes, obesity, and hypertension. These associated comorbidities are known to contribute to a significantly higher perioperative mortality following CABG. Women generally receive fewer arterial grafts and less extensive revascularization. It is well known that the use of arterial conduits in itself affects both short- and long-term survival regardless of gender. Sex Differences in Coronary Artery Bypass Grafting Techniques: A Society of Thoracic Surgeons Database Analysis was reported female sex was associated with 14% to 22% lower odds of undergoing guideline-concordant revascularization including left internal mammary artery to left anterior descending artery grafting, multiarterial graft ing, and complete revascularization. So further investigation is needed to determine why revascularization approaches differ by sex and to what degree sex disparities in coronary artery disease outcomes are due to surgical approach.

Reply: Thank you for your comments and the summary of our work. We agree that more study is needed specifically in women in order better understand the driver(s) of higher operative mortality in women after CABG.
Changes in the text: None.

Reviewer B

I have some comments:
1. **The references should be updated as the more recent publications are available (including JTD).**

Reply: Thank you for your comment. We have updated the references by adding more current articles to support our work. A list of the added references is provided below.
Changes in the text: Addition of the updated references includes, but is not limited to, the following:

10. Dixon LK, Di Tommaso E, Dimagli A, Sinha S, Sandhu M, Benedetto U, et al. Impact of sex on outcomes
after cardiac surgery: A systematic review and meta-analysis. Int J Cardiol. 2021 Nov; 343:27–34.
13. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC, et al. The Society of Thoracic
Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1—Background, Design Considerations, and Model
Development. Ann Thorac Surg. 2018 May;105(5):1411–8
17. Gaudino M, Chadow D, Rahouma M, Soletti GJ, Sandner S, Perezgrovas-Olaria R, et al. Operative
Outcomes of Women Undergoing Coronary Artery Bypass Surgery in the US, 2011 to 2020. JAMA Surg

[Internet]. 2023 Mar 1 [cited 2023 Mar 17]; Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2802105
20. Fink N, Nikolsky E, Assali A, Shapira O, Kassif Y, Barac YD, et al. Revascularization Strategies and Survival in Patients With Multivessel Coronary Artery Disease. Ann Thorac Surg. 2019 Jan;107(1):106–11.
37. Taqueti VR. Sex Differences in the Coronary System. In: Kerkhof PLM, Miller VM, editors. Sex-Specific Analysis of Cardiovascular Function [Internet]. Cham: Springer International Publishing; 2018 [cited 2023 May 4]. p. 257–78. (Advances in Experimental Medicine and Biology; vol. 1065). Available from: http://link.springer.com/10.1007/978-3-319-77932-4_17
38. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS, et al. Gender Differences in Coronary Artery Diameter Are Not Related to Body Habitus or Left Ventricular Mass: Gender differences in coronary diameter. Clin Cardiol. 2014 Oct;37(10):605–9.
39. Kim SG, Apple S, Mintz GS, McMillan T, Caños DA, Maehara A, et al. The importance of gender on coronary artery size: In-vivo assessment by intravascular ultrasound: IVUS assessment of coronary size. Clin Cardiol. 2004 May;27(5):291–4.
40. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, Haneya A, Straburzyńska-Migaj E, Bociański M, et al. Gender differences in coronary artery diameters and survival results after off-pump coronary artery bypass (OPCAB) procedures. J Thorac Dis. 2021 May;13(5):2867–73.
54. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87–165.

2. The sex differences in survival regarding surgical revascularisation may vary regarding technique - please include that.

Reply: Thank you for your comment. We respectfully direct the reviewer to our discussion of operative techniques used in women in lines 261-268 where we discuss the limited use of LITA to LAD grafting in women, the overall lower use of arterial, multiple-arterial, and all-arterial grafting in women when compared to men. We also discuss the the impact of arterial grafting on outcomes in women: "After propensity-matching based on preoperative risk profiles as well as extent of CAD and surgeon experience, there were 9,512 male pairs and 1,860 female pairs who receiving single versus multiple arterial grafting. Men who received multiple arterial grafting were found to derive a mortality benefit (adjusted HR 0.60, 95% CI 0.73-0.87; p<0.001), whereas women did not (adjusted HR 0.99, 95% CI 0.84-1.15; p=0.85) (**Figure 3**).[45] However, when patients were stratified into high-risk and low-risk groups, low-risk patients of both sexes were found to derive a mortality and morbidity benefit from arterial grafting (men: adjusted HR 0.80, 95% CI 0.73-0.89; p<0.001 and women: adjusted HR 0.80, 95% CI 0.65-0.97; p=0.02), but the high-risk patients of both sexes did not (men: adjusted HR 0.95, 95% CI 0.82-1.10; p=0.47 and women: adjusted HR 1.14, 95% CI 0.91-1.42; p=0.26) (**Figure 4**). The apparent lack of benefit of multiple arterial grafting in women overall may have been a reflection of the greater proportion of women who were high risk compared to men (13.0% versus 6.0%). Ultimately, a randomized control trial on multiple arterial grafting in women is needed to provide the prospective data on this topic that will better guide surgeons and patients in determining the best operative plan." (lines 272-286)
Changes in the text: None.

3. **The long-term prognostic scores were proposed after surgical revascularisation that were not including sex disparities. It could be mentioned to present the subject.**

Reply: Thank you for your comments. We have added relevant discussion of both the EuroSCORE I, EuroSCORE II, and the STS Adult Cardiac Surgery Risk Models (lines 67-72).

Changes in the text: "The higher operative mortality in women is sufficiently well-demonstrated such that both the European risk prediction models for operative mortality after cardiac surgery, the 1999 EuroSCORE I and the 2012 EuroSCORE II, which are based on a multi-national, multi-center database, and the 2018 STS Adult Cardiac Surgery Risk Model, include female sex as a variable that is predictive of operative mortality." (lines 67-72)

4. **Sex discrepancies regarding number of male and females procedures should be pointed out**.

Reply: Thank you for your comment. Women make up a smaller proportion of the CABG population, which is noted in the introduction: "…and women comprise 20-30% of the CABG population" (lines 49-51). Women are less likely to be referred for diagnostic testing, which may also contribute to their higher age and greater burden of comorbidity at the time of CABG. Relevant text to this effect has been added to the manuscript (lines 133-136).

Changes in the text: "Said differences may be due, in part, to delayed diagnosis of CAD or lack of referral for surgical revascularization.[18–20] For instance, in a retrospective, multi-center study of 1,064 patients (215 women) with multivessel CAD, Fink et al. demonstrated that male sex was associated with referral to CABG (OR 2.27; $p<0.001$).[19]" (lines 133-136).

19. Gaudino M, Di Franco A, Cao D, Giustino G, Bairey Merz CN, Fremes SE, et al. Sex-Related Outcomes of Medical, Percutaneous, and Surgical Interventions for Coronary Artery Disease. J Am Coll Cardiol. 2022 Apr;79(14):1407– .

20. Fink N, Nikolsky E, Assali A, Shapira O, Kassif Y, Barac YD, et al. Revascularization Strategies and Survival in Patients With Multivessel Coronary Artery Disease. Ann Thorac Surg. 2019 Jan;107(1):106–11.

21. Hansen KW, Soerensen R, Madsen M, Madsen JK, Jensen JS, von Kappelgaard LM, et al. Developments in the invasive diagnostic-therapeutic cascade of women and men with acute coronary syndromes from 2005 to 2011: a nationwide cohort study. BMJ Open. 2015 Jun 10;5(6):e007785–e007785.

5. **The perioperative inflammatory activation as possible risk factor (especially in OPCAB) for long-term prognosis that is pointed out in publications within recent 2-4 years in pubmed may be found. I mentioned this topic as possible factors that may interfere with morbidity and mortality was the subject of the analysis.**

Reply: The question of differences in systemic inflammatory response between on-pump and off-pump CABG has been raised as a possible benefit of off-pump CABG.[1] However, to date, there is no conclusive evidence that demonstrates a significant decrease in the postoperative systemic inflammatory response in off-pump CABG compared with on-pump CABG, as studies evaluating the circulating levels of proinflammatory cytokines after off-pump versus on-pump CABG have had conflicting results.[1,2] In addition, while observational data have

suggested a survival benefit for women with off-pump CABG,[3,4] randomized data comparing on-pump and off-pump CABG have not.[5,6]

1. Gaudino M, Angelini GD, Antoniades C, Bakaeen F, Benedetto U, Calafiore AM, et al. Off-Pump Coronary Artery Bypass Grafting: 30 Years of Debate. J Am Heart Assoc. 2018 Aug 21;7(16):e009934.
2. Wan IYP, Arifi AA, Wan S, Yip JHY, Sihoe ADL, Thung KH, et al. Beating heart revascularization with or without cardiopulmonary bypass: evaluation of inflammatory response in a prospective randomized study. J Thorac Cardiovasc Surg. 2004 Jun;127(6):1624–31.
3. Puskas JD, Kilgo PD, Kutner M, Pusca SV, Lattouf O, Guyton RA. Off-Pump Techniques Disproportionately Benefit Women and Narrow the Gender Disparity in Outcomes After Coronary Artery Bypass Surgery. Circulation [Internet]. 2007 Sep 11 [cited 2023 May 10];116(11_supplement). Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.678979
4. Puskas JD, Edwards FH, Pappas PA, O'Brien S, Peterson ED, Kilgo P, et al. Off-Pump Techniques Benefit Men and Women and Narrow the Disparity in Mortality After Coronary Bypass Grafting. Ann Thorac Surg. 2007 Nov;84(5):1447–56.
5. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, et al. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. N Engl J Med. 2016 Dec 15;375(24):2359–68.
6. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-Pump or On-Pump Coronary-Artery Bypass Grafting at 30 Days. N Engl J Med. 2012 Apr 19;366(16):1489–97.

Changes in the text: None.

I found the manuscript interesting but not updated with recent publications and topics that one may find in pubmed.

Reply: Thank you for your comment. We have updated the references and discussion with more current literature (see below).

Changes in the text: Addition of the updated references includes, but is not limited to, the following:

10. Dixon LK, Di Tommaso E, Dimagli A, Sinha S, Sandhu M, Benedetto U, et al. Impact of sex on outcomes after cardiac surgery: A systematic review and meta-analysis. Int J Cardiol. 2021 Nov; 343:27–34.
13. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1—Background, Design Considerations, and Model Development. Ann Thorac Surg. 2018 May;105(5):1411–8
17. Gaudino M, Chadow D, Rahouma M, Soletti GJ, Sandner S, Perezgrovas-Olaria R, et al. Operative Outcomes of Women Undergoing Coronary Artery Bypass Surgery in the US, 2011 to 2020. JAMA Surg [Internet]. 2023 Mar 1 [cited 2023 Mar 17]; Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2802105
21. Fink N, Nikolsky E, Assali A, Shapira O, Kassif Y, Barac YD, et al. Revascularization Strategies and Survival in Patients With Multivessel Coronary Artery Disease. Ann Thorac Surg. 2019 Jan;107(1):106–11.
37. Taqueti VR. Sex Differences in the Coronary System. In: Kerkhof PLM, Miller VM, editors. Sex-Specific Analysis of Cardiovascular Function [Internet]. Cham: Springer International Publishing; 2018

[cited 2023 May 4]. p. 257–78. (Advances in Experimental Medicine and Biology; vol. 1065). Available from: http://link.springer.com/10.1007/978-3-319-77932-4_17
38. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS, et al. Gender Differences in Coronary Artery Diameter Are Not Related to Body Habitus or Left Ventricular Mass: Gender differences in coronary diameter. Clin Cardiol. 2014 Oct;37(10):605–9.
39. Kim SG, Apple S, Mintz GS, McMillan T, Caños DA, Maehara A, et al. The importance of gender on coronary artery size: In-vivo assessment by intravascular ultrasound: IVUS assessment of coronary size. Clin Cardiol. 2004 May;27(5):291–4.
40. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, Haneya A, Straburzyńska-Migaj E, Bociański M, et al. Gender differences in coronary artery diameters and survival results after off-pump coronary artery bypass (OPCAB) procedures. J Thorac Dis. 2021 May;13(5):2867–73.
54. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87–165.

Reviewer C

The authors mentioned several known factors contributing to these differences, supported by literature. The review is limited to these factors only, and does not address how to cope with these differences in the future, or shed a new light on these factors. The scientific relevance and impact to the field of this review may therefore be limited. I would like to comment as follows:

1. A substantial amount of plagiarism was found (37%, TurnItIn). Please use own wording, even when citing your own work.

Reply: We can attest that there was absolutely no copying or plagiarism in this work, however, the reporting of results and outcomes of published studies may have contributed to this finding. We have re-phrased in order to decrease the amount of similar text.
Changes in the text: Throughout, marked with tracked changes.

2. If the search strategy was performed with the quoted phrasing, I can imagine that many articles were missed in this review. Please comment on your search strategy. Your study was done with PubMed, thus leaving out i.e. Scopus, Scholar? What is the impact of that on the papers found? Please comment.

Reply: Thank you for your comment. Our search is described in our methods and in **Table 1** as requested by the Journal of Thoracic Disease editorial team. As we have conducted a narrative review rather than a systematic review, we did not include all articles that our search yielded. The relevant author instructions for a narrative review, as stated by Journal of Thoracic Disease, are provided here: "A narrative review is less methodologically demanding than a systematic review, as it does not require a search of all literature in a field, nor does it necessarily require a rigorous appraisal on the included literature." We have also added a section on limitations of utilizing a narrative review (lines 379-387).
Changes in the text: "The limitations of this work must be acknowledged. We have conducted a narrative review, which is intended to provide an overview and discussion of the evidence regarding sex differences in CABG outcomes. Due to both space limitations and the nature of a narrative review, factors contributing to sex

differences in CABG outcomes that have limited supporting evidence or for which the evidence is mixed may have been excluded from the discussion. In addition, the vast majority of randomized cardiac surgery trials have been conducted in overwhelmingly male populations, limiting the availability of high-quality prospective data on outcomes in women after cardiac surgery." (lines 791-387)

3. A limitations section is missing. Please add. (see e.g. point 2)

Reply: A limitations section has been added (lines 379-387).
Changes in text: "The limitations of this work must be acknowledged. We have conducted a narrative review, which is intended to provide an overview and discussion of the evidence regarding sex differences in CABG outcomes. Due to both space limitations and the nature of a narrative review, factors contributing to sex differences in CABG outcomes that have limited supporting evidence or for which the evidence is mixed may have been excluded from the discussion. In addition, the vast majority of randomized cardiac surgery trials have been conducted in overwhelmingly male populations, limiting the availability of high-quality prospective data on outcomes in women after cardiac surgery." (lines 379-387)

4. It seems that the majority of data and papers are about USA. What about Europe, Asia, etc?

Reply: Thank you for your comment. We agree that the majority of our references are from American publications, however, several report on international trends and data,[1] were published in European or international journals,[2,3] or include multi-national authorship.[4,5] In addition, both trials[6] and meta-analyses[7] that are cited include evaluation of multi-national studies or patient populations. The examples provided below are not exhaustive:

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019. J Am Coll Cardiol. 2020 Dec;76(25):2982–3021
2. Alam M, Lee VV, Elayda MA, Shahzad SA, Yang EY, Nambi V, et al. Association of gender with morbidity and mortality after isolated coronary artery bypass grafting. A propensity score matched analysis. Int J Cardiol. 2013 Jul;167(1):180–4
3. Gaudino M, Di Franco A, Alexander JH, Bakaeen F, Egorova N, Kurlansky P, et al. Sex differences in outcomes after coronary artery bypass grafting: a pooled analysis of individual patient data. Eur Heart J. 2021 Dec 28;43(1):18–28
4. Kosmidou I, Leon MB, Zhang Y, Serruys PW, von Birgelen C, Smits PC, et al. Long-Term Outcomes in Women and Men Following Percutaneous Coronary Intervention. J Am Coll Cardiol. 2020 Apr;75(14):1631–40
5. Reynolds HR, Picard MH, Spertus JA, Peteiro J, Lopez Sendon JL, Senior R, et al. Natural History of Patients With Ischemia and No Obstructive Coronary Artery Disease: The CIAO-ISCHEMIA Study. Circulation. 2021 Sep 28;144(13):1008–23.).
6. Buxton BF, Hayward PA, Raman J, Moten SC, Rosalion A, Gordon I, et al. Long-Term Results of the RAPCO Trials. Circulation. 2020 Oct 6;142(14):1330–8)
7. Shi D, Zhang B, Motamed M, Lee S, Wang P, McLaren C, et al. Higher Mortality in Women After Coronary Artery Bypass: Meta-analysis and Bias Analysis of Confounding. Ann Thorac Surg. 2022 Feb;113(2):674–80.)

Changes in the text: None.

5. A 2021 systematic review and meta-analysis from the Bristol group on sex-differences for CABG is missing. (https://doi.org/10.1016/j.ijcard.2021.09.011) This might be the result of the narrow search strategy. The fact that that paper is missing, makes the overview questionable. (The reviewer has no conflict of interest regarding the paper mentioned)

Reply: Thank you for your comment. Dixon et al.[1] should be commended on their 2021 systematic review and meta-analysis on sex differences in outcomes after cardiac surgery, and we have added citation of Dixon et al.[1] (reference 10) in our discussion of outcomes in women. Dixon et al.[1] included 17 CABG studies and over three million subjects reporting short-term (operative) mortality. We have also already included a more recent (2022) meta-analysis by Shi et al.[2] of over 112 studies and over five million patients that has demonstrated similar results (lines 83-89). As already discussed, this is not a systematic review and not all relevant references are quoted.

1. Lauren Kari Dixon, Ettorino Di Tommaso, Arnaldo Dimagli, Shubhra Sinha, Manraj Sandhu, Umberto Benedetto, Gianni D. Angelini, Impact of sex on outcomes after cardiac surgery: A systematic review and meta-analysis, International Journal of Cardiology, Volume 343, 2021, Pages 27-34
2. Shi D, Zhang B, Motamed M, Lee S, Wang P, McLaren C, et al. Higher Mortality in Women After Coronary Artery Bypass: Meta-analysis and Bias Analysis of Confounding. The Annals of Thoracic Surgery. 2022 Feb;113(2):674–80.

Changes in the text: Citation of Dixon et al.[1] to support the finding of increased operative mortality in women after CABG (reference 10).

6. Many outcomes for many time points (early, mid and late follow-up) are mentioned. The review might benefit from a table with these outcomes, and the certrain, potential, and no differences in outcomes for all time points for sex.

Reply: Thank you for your comment. We will add a table to this effect, modified from a similar, previously-published table by the authors (permission has been granted). In addition, we added discussion of a new landmark analysis published in JAMA Surgery of sex differences in CABG outcomes in over one million patients from the STS database over the last decade (lines 104-109).

Changes in the text: Please see the new table, **Table 2**, as well as the following text: "Most recently, in a large retrospective analysis of over one million CABG patients (24.5% women) from the STS database from 2010 to 2020,[18] women had a higher unadjusted operative mortality (2.8%, 95% CI 2.8-2.9 versus 1.7%, 95% CI 1.7-1.7; $p<0.001$), and the attributable risk to female sex for operative mortality ranged from 1.28 in 2011 to 1.41 in 2020, with no change over the study period (p for trend=0.38)." (lines 104-109)

17. Gaudino M, Chadow D, Rahouma M, Soletti GJ, Sandner S, Perezgrovas-Olaria R, et al. Operative Outcomes of Women Undergoing Coronary Artery Bypass Surgery in the US, 2011 to 2020. JAMA Surg [Internet]. 2023 Mar 1 [cited 2023 Mar 17]; Available from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2802105

Table 2. Selected studies describing sex differences in operative mortality after CABG. Modified from Gaudino et al.

Author	Year	Study Period	Sample Size (n)	Follow-Up	Mortality Outcomes
Gaudino et al.	2023	2010-2020	1,297,204 Women: 24.5%	30 days	Unadjusted 30-day Mortality 2.8% (95% CI 2.8-29.9) in women versus 1.7% (95% CI 1.7-1.7, p<0.001) in men 30-day Mortality Attributable Risk to Female Sex 2010: 1.28 2020: 1.41, p for trend= 0.38
Enumah et al.	2020	2011-2018	1,042,506 Women: 25.1%	30 days	Unadjusted 30-day Mortality Women: OR 1.68 (95% CI 1.63-1.73) MVA for 30-day Mortality Women: OR 1.26 (95% CI 1.21-1.30)
Shi et al.	2020	N/A	5,008,262 Women: 28.8%	30 days	Unadjusted 30-day Mortality Women: OR 1.81 (95% CI 1.72-1.91) Adjusted 30-day Mortality Women: OR 1.40 (95% CI 1.35-1.45)
Angraal et al.	2018	1999-2014	1,863,719 Women: 33.6%	30 days	30-day mortality 1999: 6.6% (95% CI 5.4-6.6) in women versus 4.3% (95% CI 4.2-4.5) in men 2014: 4.8% in women (95% CI 4.5-5.1) versus 2.7% in men (95% CI 2.6-2.9) Adjusted Annual Decline in 30-day Mortality Women: -2.70% (95% CI -2.97 to -2.44) Men -2.44% (95% CI -2.67 to -2.21)
				1 year	Adjusted Annual Decline in 1-year Mortality Women: -1.67%, 95% CI -1.88% to -1.46% Men: -1.20%, 95% CI -1.37 to -1.03%
Guru et al.	2004	1991-1999	54,425 Women: 22.2%	30 days	Adjusted 30-day Mortality Women: OR 1.45 (95% CI 1.23-1.63)
				1 year	Adjusted 1-year Mortality Women: HR 1.44 (95% CI 1.29-1.61)
				>1 year	Adjusted late (>1-year) Mortality Women: HR 0.89 (95% CI 0.78-1.02)
Johnston et al.	2019	2008-2016	52,546 Women: 20.5%	5 years	Adjusted Mortality Women: HR 1.15 (95% CI 1.08-1.21)

CI: confidence interval, HR: hazard ratio, MVA: multivariable analysis, OR: odds ratio.

7. Was the study protocol approved by an ethics committee? Was the search strategy pre-defined?

Reply: The search strategy was defined as described in Table 1 and in the methods section, lines 58-63. Ethics approval was not required given the nature of the study (narrative review, without use of any identifying patient information or data), and the articles cited and discussed had obtained ethics approval for their studies.
Changes in the text: None.

8. Women might benefit more from OPCAB than men, as stated by the senior author before (DOI: 10.1161/JAHA.118.009934). Why was this omitted from this review?

Reply: Thank you for your comment. While observational studies, such as large-scale retrospective studies by Puskas et al.[1,2] have found that in women, off-pump CABG is associated with fewer major adverse events including mortality, stroke, and myocardial infarction when compared with on-pump CABG, randomized studies have not replicated these results.[3-6] For example, at mean 4.8-year follow-up of the CABG Off or On Pump Revascularization (CORONARY) trial,[6] on prespecified subgroup analysis, female sex was not a significant effect modifier of the composite outcome of death, stroke, myocardial infarction, renal failure, or repeat revascularization (hazard ratio 0.89, 95% confidence interval 0.70-1.15). Given the conflict between retrospectively-derived, and randomized, prospectively-derived data, unforeseen confounders may have influenced reported results, and the benefit of off-pump CABG in women remains unclear.

1. Puskas JD, Kilgo PD, Kutner M, Pusca SV, Lattouf O, Guyton RA. Off-Pump Techniques Disproportionately Benefit Women and Narrow the Gender Disparity in Outcomes After Coronary Artery Bypass Surgery. Circulation [Internet]. 2007 Sep 11 [cited 2023 May 10];116(11_supplement). Available from: https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.678979
2. Puskas JD, Edwards FH, Pappas PA, O'Brien S, Peterson ED, Kilgo P, et al. Off-Pump Techniques Benefit Men and Women and Narrow the Disparity in Mortality After Coronary Bypass Grafting. Ann Thorac Surg. 2007 Nov;84(5):1447–56.
3. Faerber G, Zacher M, Reents W, Boergermann J, Kappert U, Boening A, et al. Female sex is not a risk factor for post procedural mortality in coronary bypass surgery in the elderly: A secondary analysis of the GOPCABE trial. Ngo DTM, editor. PLOS ONE. 2017 Aug 30;12(8):e0184038.
4. Diegeler A, Börgermann J, Kappert U, Hilker M, Doenst T, Böning A, et al. Five-Year Outcome After Off-Pump or On-Pump Coronary Artery Bypass Grafting in Elderly Patients. Circulation. 2019 Apr 16;139(16):1865–71.
5. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al. Off-Pump or On-Pump Coronary-Artery Bypass Grafting at 30 Days. N Engl J Med. 2012 Apr 19;366(16):1489–97.
6. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Straka Z, et al. Five-Year Outcomes after Off-Pump or On-Pump Coronary-Artery Bypass Grafting. N Engl J Med. 2016 Dec 15;375(24):2359–68.

Changes in the text: None.

9. Though the factors/subsection headings are known, it is unclear why these, and exactly these and no others, were selected. i.e. off-pump CABG, potential differences in TTFM, etc. Please comment.

Reply: Thank you for your comments. We discussed the most relevant preoperative and intraoperative factors contributing to sex differences in CABG outcomes with consistent evidence to support them. The evidence supporting a sex difference in outcomes between on-pump and off-pump CABG has been mixed (please see response to previous comment). The authors are unaware of high-quality evidence on sex differences in TTFM. Most recently, D'Alessio et al.[1] found lower mean graft flow in women and found that mean graft flow was a predictor of early graft failure; however, these findings were from a single-center, single-surgeon, prospective study, and of the 148 participants, only 17 were women. While sex differences in TTFM may prove to be a driver of sex differences in outcomes, further research is still needed.

1. Andrea D'Alessio, Ioannis Akoumianakis, Andrew Kelion, Dimitrios Terentes-Printzios, Andrew Lucking, Sheena Thomas, Danilo Verdichizzo, Amar Keiralla, Charalambos Antoniades, George Krasopoulos, Graft flow assessment and early coronary artery bypass graft failure: a computed tomography analysis, Interactive CardioVascular and Thoracic Surgery, Volume 34, Issue 6, June 2022, Pages 974–981, https://doi.org/10.1093/icvts/ivab298

Changes in the text: None.

10. The fact that sex is a variable in EuroSCORE I and II as a predictor for operative mortality is not mentioned. Please comment.

Reply: Thank you for your comment. Text regarding EuroSCORE I,[1] EuroSCORE II,[2] and the STS risk prediction model[3] have been added to the discussion of higher operative mortality in women undergoing CABG (lines 67-72).

1. Nashef SAM, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999 Jul;16(1):9–13.
2. Nashef SAM, Roques F, Sharples LD, Nilsson J, Smith C, Goldstone AR, et al. EuroSCORE II. Eur J Cardiothorac Surg. 2012 Apr 1;41(4):734–45.
3. Shahian DM, Jacobs JP, Badhwar V, Kurlansky PA, Furnary AP, Cleveland JC, et al. The Society of Thoracic Surgeons 2018 Adult Cardiac Surgery Risk Models: Part 1—Background, Design Considerations, and Model Development. Ann Thorac Surg. 2018 May;105(5):1411–8.

Changes in the text: "The higher operative mortality in women is sufficiently well-demonstrated such that both the European risk prediction models for operative mortality after cardiac surgery, the 1999 EuroSCORE I and the 2012 EuroSCORE II, which are based on a multi-national, multi-center database, and the 2018 STS Adult Cardiac Surgery Risk Model, include female sex as a variable that is predictive of operative mortality." (lines 67-72)

11. Section on "anemia and hemodilution", last paragraph: Most likely, the difference is about teams of perfusionists, anesthesists, and cardiac surgeons not working as a team to provide adequate CPB for patients with lower BSA, i.e. women. Please comment.

Reply: Thank you for your comment. The issue is multifactorial and there may be many areas for intervention. For instance, women are likely more anemic preoperatively, so there may be room for intervention before the patient reaches the operating room. Alternatively, smaller perfusion machines, smaller tubing, or a change in priming strategy may also decrease the degree of hemodilution and intraoperative anemia. However, prior to taking these interventions, it is important to identify an acceptable intraoperative nadir hematocrit in men and women (i.e., at what hematocrit does operative mortality increase), thus further research is still needed.
Changes in the text: None.

12. Only the disparities are mentioned, but there is no clear view on the future. What to do with these findings? The added value of this manuscript is therefore limited; what does it truly add to the field?

Reply: Thank you for your comment. We respectfully believe that we have proposed areas for future study. In our discussion on the question of arterial grafting in women, we mention the first cardiac surgery trial in women

that will test single versus multiple arterial grafting in women (ROMA:Women), which will help answer the question raised in this manuscript on the benefits of the technique of arterial grafting in women: "Ultimately, a randomized control trial on multiple arterial grafting in women is needed to provide the prospective data on this topic that will better guide surgeons and patients in determining the best operative plan. The results of the ongoing ROMA:Women trial (ClinicalTrials.gov: NCT04124120) will hopefully bring clarity to this issue" (lines 287-288). In the section entitled "Future Directions" (lines 336-378) we propose areas for future research that may elucidate and subsequently help address sex differences in CABG outcomes. The first topic is further study on the relationship between hemodilution, anemia, and sex (lines 337-341), the second is on the relationship between graft failure, clinical outcomes, and sex (342-363), the next is on the question of patient-surgeon sex concordance and outcomes in women (364-378). The need for more high-quality data in women undergoing CABG (384-387) has been added to the manuscript.
Changes in the text: Addition of lines on the need for more high-quality data in women: "In addition, the vast majority of cardiac randomized trials have been conducted in overwhelmingly white, male populations, limiting the availability of high-quality prospective data on outcomes in women after cardiac surgery" (lines 384-387).

Minor comments:

1. **Suboptimal keywords were provided. Consider MeSH terms other than title + abstract for improved findability.**

Reply: We have replaced or edited keywords to correspond with MeSH terms when able. (lines 42-44)
Changes in the text: "Key Words: coronary artery bypass, sex characteristics, sex differences, sex differences in coronary artery bypass, women and coronary artery bypass, women's health" (lines 42-44)

2. Line 56: "This manuscript is written following the narrative review checklist." Please specify, a checklist according to whom?

Reply: Thank you for your comment. This verbiage is requested and specified by the Journal of Thoracic Disease when submitting a manuscript for a narrative review. It is provided in the **Supplementary Appendix** as **Figure 1**. **Narrative Review Checklist**, also as requested and specified by the Journal of Thoracic Disease.
Changes in text: None.

3. Line 110: BSA (as calculated by Du Bois) is indeed often missing. Consider to add that to body size.

Reply: Thank you for your comment. BSA has been added to line 123-124: "…differences in surgical technique employed, and differences in body size (including body surface area [BSA])…"A more fulsome discussion of BSA and its relation to sex differences in CABG is discussed more fulsomely in the sections "Anemia and Hemodilution", line 300, and "Coronary Artery Size," line 176.
Changes in text: "…differences in surgical technique employed, and differences in body size (including body surface area [BSA])…"(lines 123-124)

4. Line 146. Reference 20 is about PCI. Please add that context. Furthermore: Is it anticipated that PCI OR CABG is better for women related to any endpoint?

Reply: The relevant context has been added to the text (lines 165-166). There is limited evidence on outcomes of CABG versus PCI in women, and the evidence that does exist has been mixed. For instance, in a meta-analysis of six randomized trials, Gul et al.[1] found that women had a significantly higher risk of adverse cardiac events with PCI compared to CABG (adjusted HR=1.31, 95% CI: 1.05, 1.63). In the SYNTAX (Synergy Between PCI with TAXUS and Cardiac Surgery) trial five-year follow-up,[2] women had significantly lower mortality after CABG than PCI (HR=0.38, 95% CI: 0.17, 0.87), yet this difference was not sustained at ten-year follow-up.[3] The EXCEL (Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization)[4] and NOBLE (Nordic Baltic British Left Main Revascularization Study)[5] trials found that women had higher risks of MACE after PCI, but also found that the interaction between sex and PCI vs. CABG on outcomes was not statistically significant.

1. Gul B, Shah T, Head SJ, Chieffo A, Hu X, Li F, et al. Revascularization Options for Females With Multivessel Coronary Artery Disease. JACC Cardiovasc Interv. 2020 Apr;13(8):1009–10.
2. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Five-Year Outcomes in Patients With Left Main Disease Treated With Either Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting in the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery Trial. Circulation. 2014 Jun 10;129(23):2388–94.
3. Thuijs DJFM, Kappetein AP, Serruys PW, Mohr FW, Morice MC, Mack MJ, et al. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. The Lancet. 2019 Oct;394(10206):1325–34.
4.Serruys PW, Cavalcante R, Collet C, Kappetein AP, Sabik JF, Banning AP, et al. Outcomes After Coronary Stenting or Bypass Surgery for Men and Women With Unprotected Left Main Disease. JACC Cardiovasc Interv. 2018 Jul;11(13):1234–43.
5.Holm NR, Mäkikallio T, Lindsay MM, Spence MS, Erglis A, Menown IBA, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in the treatment of unprotected left main stenosis: updated 5-year outcomes from the randomised, non-inferiority NOBLE trial. The Lancet. 2020 Jan;395(10219):191–9.

Changes in the text: "In addition, prior evidence in patients with CAD undergoing percutaneous revascularization has shown that compared to men, women are more likely to have microvascular disease that, like non-obstructive CAD, may not be effectively treated by revascularization." (lines 165-166)

5. Line 164: Gender or sex? Please be consistent. I expect this is sex.

Reply: Thank you for your comment. This has been changed to "sex" for consistency (line 186).
Changes in the text: "…outcomes were not reported by sex." (line 186).

6. Section on "cornary artery size": Is the conclusion that there has been no research after the 1990s investigating this topic?

Reply: Thank you for your comment. The studies cited are landmark studies on the topic. More recent studies, in particular studies on sex differences in coronary artery diameter detected using angiography and computed tomography, have demonstrated sex differences in coronary artery size, and these have been added (lines 196-198, references 37-40).

Changes in the text: "…More recent studies have demonstrated an association between sex and smaller coronary artery size utilizing techniques such as intravascular ultrasound, computed tomography, and measurement with vascular sheaths." (lines 196-198, and addition of the references below)
References 37-40:

37. Taqueti VR. Sex Differences in the Coronary System. In: Kerkhof PLM, Miller VM, editors. Sex-Specific Analysis of Cardiovascular Function [Internet]. Cham: Springer International Publishing; 2018 [cited 2023 May 4]. p. 257–78. (Advances in Experimental Medicine and Biology; vol. 1065). Available from: http://link.springer.com/10.1007/978-3-319-77932-4_17
38. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS, et al. Gender Differences in Coronary Artery Diameter Are Not Related to Body Habitus or Left Ventricular Mass: Gender differences in coronary diameter. Clin Cardiol. 2014 Oct;37(10):605–9.
39. Kim SG, Apple S, Mintz GS, McMillan T, Caños DA, Maehara A, et al. The importance of gender on coronary artery size: In-vivo assessment by intravascular ultrasound: IVUS assessment of coronary size. Clin Cardiol. 2004 May;27(5):291–4.
40. Urbanowicz T, Michalak M, Olasińska-Wiśniewska A, Haneya A, Straburzyńska-Migaj E, Bociański M, et al. Gender differences in coronary artery diameters and survival results after off-pump coronary artery bypass (OPCAB) procedures. J Thorac Dis. 2021 May;13(5):2867–73.

7. Lines 187-188: This is a tricky definition of incomplete revascularization. I would personally go for 70% stenosis, and preferably FFR-guided CABG. Please comment.

Reply: Thank you for your comment. While the utility of preoperative FFR to help guide arterial revascularization has been demonstrated, more data is needed before wide adoption of FFR-guided surgical revascularization.[1] Furthermore, studies examining sex differences in functional completeness of surgical revascularization are very limited, but demonstrate that even when using FFR, women are less likely to be completely revascularized.[2]
We agree that the lack of universal definition of incomplete graft failure may make existing evidence difficult to interpret, thus we have added text to clarify this: "Unfortunately, there is no universal definition of incomplete revascularization, which is a limitation of the existing evidence on this topic" (lines 234-235). We have also provided the definition of incomplete revascularization for each study discussed in the text (lines 215, 224-225, 228-230). The other studies cited, but not explicitly discussed in the text, utilized definitions of incomplete revascularization similar to the aforementioned studies: failure to graft one or more of the three main coronary arteries with 50% or grater stenosis that were identified preoperatively as a surgical target (Mohammadi et al.)[3] and the number of diseased coronary systems exceeding the number of distal anastomoses (Caputo et al.).[4]

1. Spadaccio C, Glineur D, Barbato E, Di Franco A, Oldroyd KG, Biondi-Zoccai G, et al. Fractional Flow Reserve–Based Coronary Artery Bypass Surgery. JACC Cardiovasc Interv. 2020 May;13(9):1086–96.
2. Lakhter V, Alkhouli M, Zack CJ, et al. Sex Differences in Fractional Flow Reserve-Guided Revascularization: A Nationwide Analysis. J Womens Health (Larchmt). 2017;26(2):109-115. doi:10.1089/jwh.2016.5806
3. Mohammadi S, Kalavrouziotis D, Dagenais F, Voisine P, Charbonneau E. Completeness of revascularization and survival among octogenarians with triple-vessel disease. Ann Thorac Surg. 2012;93(5):1432-1437. doi:10.1016/j.athoracsur.2012.02.033

4. Caputo M, Reeves BC, Rajkaruna C, Awair H, Angelini GD. Incomplete revascularization during OPCAB surgery is associated with reduced mid-term event-free survival. Ann Thorac Surg. 2005;80(6):2141-2147. doi:10.1016/j.athoracsur.2005.05.077

Changes in the text: "…defined as a completeness of revascularization index (the difference between the number of coronary grafts and the number of diseased coronary systems) less than or equal to one…" (lines 228-230) "Unfortunately, there is no universal definition of incomplete revascularization, which is a limitation of the existing evidence on this topic" (lines 234-235)

8. Lines 223-225: Again, only USA guidelines were mentioned. Please also cite the ESC/EACTS guidelines.

Reply: Thank you for your comment. The ESC/EACTS guidelines have been added.
Changes in the text: "In patients undergoing CABG, professional society guidelines recommend utilizing the LITA to bypass the LAD, due to decades of observational data that suggest improved patency and outcomes compared with other conduits (American College of Cardiology [ACC]/ American Heart Association [AHA]/ Society for Cardiovascular Angiography and Interventions [SCAI] Class 1, Level of Evidence B-NR; European Society of Cardiology [ESC]/ European Association for Cardio-Thoracic Surgery [EACTS]: Class 1, Level of Evidence B).[42] The RA is recommended as the second arterial conduit in lieu of the SVG to bypass the second most important coronary target after the LAD (ACC/AHA/SCAI Class 1, Level of Evidence B; ESC/EACTS: Class 1, Level of Evidence B)." (lines 251-259)

9. Lines 262-264: Is increased mediastinitis rate after BITA because of mammae sternal traction? Please comment.

Reply: While there is concern that the increased rate of sternal wound infection after BITA may be related to excess sternal traction during surgery,[1] there is no high-quality data to support this, and other possible etiopathologies have been proposed, including a decrease in sternal blood flow with BITA harvesting, in particular with pedicled harvesting, among others.[2]

1. Rupprecht L, Schmid C. Deep Sternal Wound Complications: An Overview of Old and new Therapeutic Options. Open J Cardiovasc Surg. 2013 Jan;6:OJCS.S11199.
2. Gatti G, Dell'Angela L, Barbati G, Benussi B, Forti G, Gabrielli M, et al. A predictive scoring system for deep sternal wound infection after bilateral internal thoracic artery grafting. Eur J Cardiothorac Surg. 2016 Mar;49(3):910–7.

Changes in the text: None.

10. Lines 264: Unfortunately, the authors do not describe why women don't get total arterial revascularization. Please add.

Reply: The reasons underlying why women are less likely than men to receive total arterial revascularization is not clear and is likely multifactorial. A retrospective study of revascularization techniques from the STS database by Jawitz et al.[1] noted that women had a lower rate of BITA and RA grafting throughout the study period (2011-2019) compared with men, despite the existence of STS,[2] ACC/AHA/SCAI,[3] and ESC/EACTS[4] guidelines for RA use in lieu of the SVG as a second conduit. The authors suggest that the infrequent use of the RA in female patients is possibly due to actual or perceived differences in vessel size, flow, and spasticity. The

authors report that the most commonly documented reasons why surgeons did not utilize any ITA grafts for women were case urgency, inadequate ITA size or flow, subclavian stenosis, previous cardiothoracic surgery, and previous mediastinal radiation. However, at this time there is no conclusive data regarding the etiology of the disparity in total arterial grafting technique.

1. Jawitz OK, Lawton JS, Thibault D, O'Brien S, Higgins RSD, Schena S, et al. Sex Differences in Coronary Artery Bypass Grafting Techniques: A Society of Thoracic Surgeons Database Analysis. Ann Thorac Surg 2022;113:1979–1988. doi:10.1016/j.athoracsur.2021.06.039.
2. Aldea GS, Bakaeen FG, Pal J, et al. The Society of Thoracic Surgeons clinical practice guidelines on arterial conduits for coronary artery bypass grafting. Ann Thorac Surg. 2016;101:801-809.
3. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation [Internet]. 2022 Jan 18 [cited 2022 Aug 22];145(3). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001039
4. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019 Jan 7;40(2):87–165.

Changes in the text: None.

11. Line 335: I think "woman" in the second sentence should be "female"

Reply: Thank you for your comment. The requested change has been made (lines 365-366)
Changes in the text: "…by female physicians had lower rates of readmission and mortality when compared with male physicians" (lines 365-366)

Reviewer D

I want to thank the authors for this nice paper. Sex -related differences in outcomes in cardiac surgery are largely discussed in literature. However, to date, no clearer explanation is available, confirming maybe the multifactorial of genesis of this issue.

Reply: Thank you for your supportive comments.
Changes in the text: None.

In my opinion, when we talk about sex differences in cardiac surgery, the factor age must be considered. Mortality and morbidity differences in relation to sex vary in relation of patients age. for example, in a recent analysis regarding sex differences in outcomes in patients undergoing surgical repair for ATAD, young women had a higher rate of mortality and morbidity (Morjan et al, the impact of age and sex on in-hospital outcomes in acute type A aortic dissection surgery. J Thorac Dis. 2022 Jun;14(6):2011-2021), while no difference was found in older age. This effect of age on outcome -differences in relation to sex is also not well elucidated, and possibly hormonal changes could play a role. genetical and biological studies still needed

Reply: Thank you for your comment. Women presenting for CABG are generally approximately ten years older than men presenting for CABG, not younger, and have relatively more cardiovascular risk factors than men at time of presentation for CABG (line 130-133, 137-143). In addition, in propensity-matched studies (which included matching for age between men and women), women still had worse outcomes than men (lines 144-152). We agree that hormonal changes, such as premature menopause, and other pregnancy-related conditions such as gestational diabetes, pre-eclampsia, and eclampsia, among others, are risk factors for cardiovascular disease that are unique to women, but these risk factors do not specifically explain differences in outcomes after surgical revascularization.
Changes in the text: None.

I want just to suggest to replace the word disparities to differences in the title of the paper and among the manuscript.

Reply: Thank you for your comments. The requested change has been made to replace "disparities" with "differences."
Changes in the text: Throughout the text.