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Review Article

Role of Sex on the Clinical Outcomes of Coronary Artery Diseases Treated with Drug-Eluting Stents

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Abstract

Background: *With consideration of differing cardiac characteristics between women and men, such as coronary vessel sizes, this study was constructed to investigate if sex-based differences are present following drug-eluting stent implantation.*

Methods: *Using PubMed and MeSH search tags, published data analyzing the potential sex differences in clinical outcomes following drug-eluting stent implantation was collected.*

Results: *As compared to male patients, women had similar incidences of major adverse cardiac events and stent thrombosis at long-term follow-up despite being found to consistently have smaller vessels, higher incidences of advanced age, diabetes mellitus, and hypertension at hospital admission. At short-term follow-up, however, women had an increase of major adverse cardiac events as compared to men with complex lesions. Furthermore, height may play a role in clinical outcomes following treatment with a drug-eluting stent. Additionally, women may have superior healing responses with lower neointimal obstruction and lower maximum cross-sectional narrowing following drug-eluting stent implantation.*

Conclusions: *When differing baseline characteristics were corrected for with multivariate analysis, drug-eluting stents demonstrate similar clinical outcomes in women and men at long-term follow-up.*

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Introduction

In the United States, heart disease is the leading cause of death among women.[1] 301,280 women in the United States died of heart disease in 2019.[2] Although almost as many women as men die each year in the U.S. due to heart disease,[3] multiple studies have found women have worse clinical outcomes than men following treatment for acute coronary syndromes and myocardial infarction.[4-6] Specifically, women have been found to experience worse clinical outcomes than men undergoing percutaneous coronary interventions.[7-9] Percutaneous coronary interventions (PCI) are nonsurgical procedures used to improve blood flow to cardiac tissue at the site of vessel narrowing via maneuvers performed through a catheter which may include balloon inflation or stent placement.[10] Balloon angioplasty was a common PCI used to treat coronary artery diseases.[11] During this time, a number of studies indicated female sex was a strong independent predictor of in-hospital morbidity and mortality.[11,12] Female patients were associated with a higher incidence of procedural complications and worse long-term clinical outcomes.[12,13] While there is no scientific consensus as to why women have had worse clinical outcomes after balloon angioplasty, some explanations have been proposed. When compared to men, women have smaller coronary vessels[14] which may result in vessels that are more likely to become re-obstructed after treatment. Differences in vessel architecture may also cause differing onset symptoms between sexes. Women have been found to have longer symptom-onset to

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hospital admission times during heart failure, likely due to less awareness of their atypical symptoms as compared to men.[14] Furthermore, other physiological differences between sexes, such as concentrations of hormones and inflammatory biomarkers, may play a role but are not well understood partly due to the historical practice of excluding women from clinical research.[15]

Currently, drug-eluting stents are widely used for the treatment of coronary artery diseases.[16.17] Drug-eluting stents (DES) are scaffolds implanted into narrowed vessels and gradually release immunosuppressive and/or anti-proliferative drugs. While the implanted scaffolding supports the vessel to stay open, the drugs inhibit smooth muscle cell proliferation, also referred to as neointimal growth, to prevent repeat blockage of the vessel.[17] DES evolved from bare-metal stents (BMS) which were commonly utilized in the treatment of coronary artery diseases, specifically after ST-segment myocardial infarctions (STEMI).[16] Somewhat similarly to balloon angioplasty, BMS have been associated with potential sex-associated difference. One study demonstrated higher rates of death and urgent revascularization in women than in men within 30 days post-procedure.[18] Another study, however, demonstrated no clinical outcome differences between women and men at any follow-up time after a BMS implantation.[19]

DES have been found to have better safety outcomes than their predecessors of balloon angioplasty and BMS.[17] Nonetheless, these stents are still associated with adverse outcomes such as stent thrombosis and restenosis requiring revascularization. When considering over 3 million DES are implanted annually,[20] and the history of sex-based differences with previous PCIs, it is important to investigate any possible clinical outcome differences of DES with respect to sex.

Methods:

The database used for this study was the U.S. National Library of Medicine's database PubMed where the most recent search was performed on April 11, 2021. The keywords used in PubMed included: ((((((sex [Title]) OR female [Title]) OR women [Title]) OR gender [Title]) AND coronary stent) AND drug eluting stents) AND treatment. This initial search returned 138 results.

Inclusion criteria involved primary literature that utilized randomized controlled trials and clinical trials. Additionally, the articles included were published within 2010 to April 2021 and utilized human subjects.

Exclusion criteria involved studies that only had female subjects, only compared post-procedure antithrombotic therapy, and studies that grouped BMS and DES findings together. Any form of secondary or tertiary literature; such as meta-analysis or review articles, case series and non-English literature were excluded. Studies that compared sex differences of DES to other stents, mostly BMS, were allowed but with a focus on the results concerning DES performance between sexes only. After implementing the exclusion criteria, a total of 10 studies were reviewed.

Results

Conducting the search method and applying the exclusion and inclusion criteria resulted in 10 studies for analysis. Each study utilized data obtained from randomized controlled trials or clinical trials. All studies reviewed compared male and female patients with respect to clinical outcomes after DES implantation. Two studies matched men and women with respect to a predetermined factor, one age and another propensity scores, to establish if that factor acts as a confounder. Four studies compared the use of BMS to DES between sexes and one compared bioactive stents to DES. This review focused on the findings these five studies presented about sex differences among DES subgroup only. The first eight articles focus on potential sex-differences in MACE following DES implantation and are organized based on increasing follow-up time. The final two articles concentrate on neointimal obstruction and strut coverage related to DES placement between sexes. A summary of each study's demographics can be found in Table I.

Major Adverse Cardiac Events

Yang et al.[21] investigated real-world patients from the FOCUS registry in order to assess possible sex-based differences in clinical outcomes after DES implantation in patients with severe complications and complex lesions that are often excluded from randomized control trials. This prospective non-randomized study included 4720 patients (3365 males and 1355 females) that underwent sirolimus-eluting stent (SES) implantation. Yang et al.[21] found the incidence of major adverse cardiac events (MACE) (as defined in Table II), differed among sexes with respect to the time of follow-up. Within the first 6 months following implantation, female

Table-I

Demographics of Selected Studies.

No.	Selected Study	Type of Study	Title	Countries	Patient Population (M/F)
1	Yang et al. 2016	Post-hoc analysis of a prospective non-randomized study	Sex-based influence on clinical outcomes after drug-eluting stent implantation in real-world patients: insight from the FOCUS registry	China, Indonesia, & Thailand	3365 M & 1355 F that received SES; included patients with severe complications & complex lesions
2	Fath-Ordoubadi et al. 2012	Post-hoc analysis of a prospective observational study	Gender Impact on Prognosis of Acute Coronary Syndrome Patients Treated with Drug-Eluting Stents	Europe, Asia, Africa, & New Zealand	1268 M & 372 F that received a BES for acute coronary syndrome
3	Lee et al. 2017	Retrospective cohort study from 3 randomized controlled trials	The Effect of Sex and Anthropometry on Clinical Outcomes in Patients Undergoing Percutaneous Coronary Intervention for Complex Coronary Lesions	South Korea	333 M & 333 F that underwent IVUS-guided DES implantation for complex lesions
4	Regueiro et al. 2015	Post-hoc analysis of a randomized control trial	Sex-related Impact on Clinical Outcome of Everolimus-eluting Versus Bare-metal Stents in ST-segment Myocardial Infarction. Insights From the EXAMINATION Trial.	Italy, Netherlands, & Spain	634 M & 117 F that received an EES following STEMI
5	Hansen et al. 2013	Post-hoc analysis of a prospective randomized trial	Improved two-year outcomes after drug-eluting versus bare-metal stent implantation in women and men with large coronary arteries: Importance of vessel size	Austria, Denmark, Italy, & Switzerland	1163 M & 386 F with large coronary arteries that received either a SES or EES
6	Ferrante et al. 2012	Post-hoc analysis of a randomized trial	Sex-specific benefits of sirolimus-eluting stent on long-term outcomes in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: Insights from the Multicenter Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab with Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study trial	Italy	281 M & 91 F that received a SES following STEMI

table continued

Table-I (cont'd)

7	Tuomainen et al. 2012	Post-hoc analysis of a prospective randomized trial	Gender-based analysis of the 3-year outcome of bioactive stents versus paclitaxel-eluting stents in patients with acute myocardial infarction: an insight from the TITAX-AMI trial	Finland	157 M & 54 F that received a PES following acute MI
8	Ten Haaf et al. 2016	Post-hoc analysis of a prospective randomized trial	Frequency of Stent Thrombosis Risk at 5 Years in Women Versus Men with Zotarolimus-Eluting Compared with Sirolimus-Eluting Stent	Netherlands	6648 M & 2061F that received either a ZES or SES
9	Nakatani et al. 2011	Post-hoc analysis of 3 randomized controlled trials	Sex Differences in Neointimal Hyperplasia Following Endeavor Zotarolimus-Eluting Stent Implantation	France & USA	281 M & 110 F that received a ZES
10	Guagliumi et al. 2014	Prospective cohort study	Mechanisms of Atherothrombosis and Vascular Response to Primary Percutaneous Coronary Intervention in Women Versus Men with Acute Myocardial Infarction	Italy	140 M & 140 F that received an EES for STEMI treatment

Abbreviations:

F: Female, M: Male, BES: Biolimus-eluting stent, DES: Drug-eluting stent, EES: Everolimus-eluting stent, IVUS: Intravascular ultrasound, MI: Myocardial infarction, PES: Paclitaxel-eluting stents, SES: Sirolimus-eluting stent, STEMI: ST-segment elevation myocardial infarction, ZES: Zotarolimus-eluting Stent

Table-II

Summary of Results of Selected Studies

N	Selected Study	Outcome
1	Yang et al.	Female patients had a higher risk of MACE at <6m; no difference between sexes >6m & 3y after adjustment
2	Fath-Ordoubadi et al.	MACE was not significantly different between sexes at in-hospital, 1y, and 2y follow-up
3	Lee et al.	Incidence of MACE was similar between sexes in patients with complex lesions at 1y follow-up
4	Regueiro et al.	Incidence of MACE was similar between sexes in STEMI patients at 2y follow-up
5	Hansen et al.	No difference in relative risk of MACE between sexes with large coronary arteries at 2y follow-up after adjustment
6	Ferrante et al.	No difference in relative risk of MACE between sexes at 3y follow-up after adjustment
7	Tuomainen et al.	Incidence of MACE was statistically matched between sexes at 3y follow-up
8	Ten Haaf et al.	No difference in relative risk of definite or probable stent thrombosis, cardiac death, and MI between sexes at 5y post-stent placement after adjustment
9	Nakatani et al.	Female sex was associated with lower neointimal obstruction and lower maximum CSN
10	Guagliumi et al.	Men had a higher frequency of MACCE at 1m after stent placement; statistically similar MACCE rates between sexes at 1y

* aHR does not include revascularizations
Abbreviations:
M: Months, Y: Years, MACE: Major adverse cardiac events

patients had a higher cumulative incidence of MACE as compared to male patients, (2.4% vs. 1.5% respectively with unadjusted HR of male sex (95% CI) = 0.6 (0.4-0.9), p=0.03). After implementation of a multivariate analysis (Table II), female patients remained to have a higher risk of MACE, with an adjusted HR of male sex (95% CI) as 0.5(0.3-0.9), (p=0.01). Inversely, follow-up beyond 6 months found males had a higher cumulative incidence of MACE as compared to female patients, (5.4% vs. 4.8% with an unadjusted HR (95% CI) = 1.4 (1.1-1.9), p=0.04). This increased risk of MACE in males became insignificant after applying the multivariate analysis, (HR (95% CI) = 1.4 (0.9-2.0), p=0.10). After multivariate analysis, males were found to have a higher risk of cardiovascular death with follow-up beyond 6 months (adjusted HR (95% CI) = 1.9 (1.1-3.6), p=0.03). When analyzing the data of the entire 3-year follow-up, the risk of MACE was not statistically different among sexes (adjusted HR (95% CI) = 1.0 (0.7-1.3), p=0.95).

Fath-Ordoubadi et al.[22] utilized the prospective NOBORI-2 trial to investigate the impact of sex on clinical outcomes following DES placement for treatment of acute coronary syndrome (ACS) in-hospital and at 1- and 2-years post-procedure. Investigators analyzed 1,268 men and 372 women that received a Nobori DES between 2008 to 2009 and compared target lesion failure, cardiac death, myocardial infarction (MI), target lesion revascularization (TLR), and MACE (Table II). In-hospital results found no differences in death (0.2% vs 0.3%, p=0.54), MI (0.6% vs. 0.8%, p=0.70), or need for revascularization (0.2% vs. 0.3%, p=0.54). There was no sex-associated difference in total in-hospital MACE (0.7% vs 1.1%, p=0.51). Additionally,

there was no difference in in-hospital bleeding or vascular complications (0.7% vs. 0.5%, p=1). At 12 months, investigators found no sex-based differences in cardiac death (1.3% vs 2.7%, p=0.10), MI (2.1% vs. 3.2%, p=0.24), or target lesion failure (4.5% vs. 5.9%, p=0.27) between sexes. MACE was also found to be similar between sexes (5.7% vs 7.3%, p=0.27). At 24 months, investigators found the same trends as at 12 months with no significant differences in cardiac death (2.0% vs. 3.2%, p=0.16), MI (2.5% vs. 3.5%, p=0.37), or target lesion failure (5.7% vs. 7.3%, p=0.27). Additionally, MACE was not significantly different between men and women at 24 months (7.5% vs 8.9%, p=0.38). Furthermore, investigators applied a multivariate analysis (Table II) to their data for 24-month follow-up, and found gender was not a predictor of MACE, (HR (95% CI) of 0.921 (0.63-1.35), p=0.67). Multivariate analysis found the worse outcomes were related to age (HR (95% CI) of 1.031 (1.01-1.05), p=0.0002), diabetes mellitus (HR (95% CI) of 1.540 (1.11-2.213), p=0.009), and presence of 3-vessel disease (HR (95% CI) of 1.801 (1.22-2.85), p=0.003).

In order to study the effect of sex on clinical outcomes in patients after DES implantation at 12-months, Lee et al. [23] performed a retrospective cohort study using data from three randomized trials. Researchers formed 333 pairs of women and men matched by propensity scores (Table II). By matching for differences in clinical and vessel characteristics, investigators could study if sex or other lesser studied factors are independent risk factors for MACE after PCI. Interestingly, all patients received intravascular ultrasound (IVUS)-guided PCI for complex lesions with implantation of either an everolimus-, zotarolimus-, or biolimus-eluting stent at 12-month follow-up. Incidence of MACE (Table II) was similar between sexes in patients with complex lesions, with a rate of 2.4% in both sexes (p=0.939) and an HR (95% CI) of 1.039 (0.390-2.769). Unlike female sex, post-intervention minimum lumen area (MLA) as determined by IVUS was found to be a predictor of MACE, with a HR (95% CI) of 0.620 (0.423-0.909). Relatedly, investigators implemented a multivariable linear regression analysis and found post-intervention MLA to have an association with height (R^2=0.040), weight (R^2=0.030), body surface area (R^2=0.038), and lean body mass (R^2=0.039), but not with BMI (R^2=0.002) or fat mass (R^2=0.002). Post-intervention MLA as assessed by IVUS was found to be independently associated with height, (regression coefficient=0.041, 95% CI=0.025 to 0.057, p<0.001) and chronic total occlusion (CTO) lesions (regression coefficient=-0.622, 95% CI=1.077 to -0.167, p=0.008). Patients within the lowest percentile of height displayed the greatest risk for MACE at 12 months than those in higher percentiles after an adjusted age and sex model, with a HR (95% CI) of 6.391 (1.160-35.206) and p-value of 0.033.

A study by Regueiro et al.[24] utilized data from the EXAMINATION trial to evaluate the role of sex on clinical outcomes of Everolimus-eluting stent (EES) versus BMS in ST-segment elevation myocardial infarction (STEMI) at 2-year follow-up. In this study, 117 women and 634 male patients received EES implantation. This study found women treated with EES had similar rates of MACE (Table II) when compared to men (6.8% vs. 8.2%, p-value not published). Definitive/probable stent thrombosis with EES at 2-year follow-up was also similar between women and men (0.0% vs. 1.6%, p-value not published). In addition, major bleeding with EES at 2-year follow-up was similar (0.9% vs. 1.3%, p-value not published). EES was found to have a superior effect in women as compared to men with respect to a lower rate of revascularization. Specifically, women had lower percentages of TVR (1.7% vs. 4.6%, p-value not published) and non-TVR (1.7% vs 6.9%, p-value not published) after EES implantation at 2-year follow-up as compared to male patients.

Hansen et al. [25] investigated the 2-year clinical outcomes after DES versus BMS in women and men with large coronary arteries to study the importance of vessel size within stent implantation outcomes. Investigators utilized data from the BASKET-PROVE trial where, through randomization, 775 patients received a SES and 774 patients received an EES. Among patients with large coronary arteries treated with a DES (EES or SES), MACE (as defined in Table II) at 2 years was reported less in women as compared to men (4% vs. 6%, p=0.17) but with an unadjusted HR (95% CI) of 0.67 (0.39-1.13). After a multivariate analysis (Table II), HR was similar at 0.73 (0.42-1.28). In the aforementioned study, Hansen et al. [25] found that the rate of cardiac death or non-fatal

MI after DES implantation did not differ between sexes (3% vs. 3%; p=0.92) with an adjusted HR (95% CI) of 0.88 (0.42-1.85). TVR was also found to be similar in women and men (2% vs. 4%, p=0.10) with an adjusted HR (95% CI) of 0.67 (0.32-1.39).

Moreover, Ferrante et al. [26] utilized the MULTISTRATEGY trial to investigate sex-specific differences in long-term benefit of SES use compared with BMS at 3 years (1,080 days) post-procedure. 372 patients were randomized to SES with 91 female and 281 male patients. Interestingly, women were found to have a higher incidence of death (10.99% vs. 5.69%, p=0.085), reinfarction (7.69% vs. 5.69%, p=0.491) and MACE (21.98% vs. 13.88%, p=0.066) with MACE as defined in Table II. TVR was found to have no statistically significant sex-based difference (6.6% vs. 6.1%, p=0.85). After adjustment for confounders with regression models (Table II), however, sex-specific differences in death (adjusted HR 0.72, 95% CI 0.19-2.71, p=0.63), reinfarction (adjusted HR 3.54, 95% CI 1.01-12.32, p=0.047) and MACE (adjusted HR 1.53, 95% CI 0.69-3.31, p=0.29) failed to remain significant between sexes.

Tuomainen et al. [27] investigated sex-based outcomes between bioactive stents (BAS) and paclitaxel-eluting stents (PES) in patients with acute MI at 3-year follow-up from the prospective randomized TITAX-AMI multicenter trial. 211 patients were assigned to the PES arm of the study, specifically 54 women and 157 men. Primary endpoint was a first occurrence of a MACE (as defined in Table II). Secondary endpoints included all-cause death, a composite of cardiac death or recurrent MI, and stent thrombosis (ST). Tuomainen et al. [27] found all primary and secondary endpoints were statistically matched between male and female patients within the PES arm of the study (MACE 22.9% vs. 25.9%, cardiac death 5.1% vs. 5.6%, TLR 10.8% vs. 11.1%, MI 16.6% vs. 16.7%, and definite ST 7.1% vs. 5.6% with p>0.05 for all).

On the other hand, Ten Haaf et al.[28] investigated the frequency of stent thrombosis, an adverse clinical outcome after DES implantation, up to 5 years after implantation of either a zotarolimus-eluting stent (ZES) or a SES. Researchers used data from the prospective multicenter randomized PROTECT trial which included 2,061 (23.7%) women and 6,648 (76.3%) men. Ten Haaf et al.[28] found at 5 years, definite or probable stent thrombosis occurred in 1.8% of women and 2.4% of men, (p=0.16). In all age strata, women had slightly less incidence of definite or probable stent thrombosis. Furthermore, the data found no statistically significant differences among women and men with respect to cardiac death (3.9% vs. 3.8%, p=0.78), MI (5.6% vs. 5.8%, p=0.92), or the composite of death, myocardial infarction, or stent thrombosis (12.2% vs. 12.0%, p=0.69). Overall, however, male patients experienced slightly more MACE (Table II) than female patients (22.8% vs. 20.9%, p=0.13), primarily due to higher rates of revascularizations (18.0% vs. 15.4%, p=0.011). The majority of clinical outcome differences between sexes became statistically insignificant after applying a multivariate adjustment for age and other risk factors (that were not specified in the article). The singular difference that remained after multivariate adjustment was women had a significantly lower incidence of death during 5-year follow-up than men (adjusted HR (95% CI) = 0.81 (0.66-0.99), $p_{log\text{-}rank}$=0.043).

Neointimal Obstruction and Stent Strut Apposition

A study by Nakatani et al.[29] investigated the sex differences in neointimal hyperplasia following ZES implantation. Investigators utilized a total of 391 patients from the ENDEAVOR II, ENDEAVOR III, and ENDEAVOR IV randomized trials and studied their volumetric intravascular ultrasound (IVUS) analyses at 8-month follow-up. Investigators found women had significantly lower neointimal obstruction as compared to men receiving ZES (15.5 ± 9.5% vs. 18.2 ± 10.9%, p=0.025). Maximum cross-sectional narrowing (CSN) was also significantly lower in women (30.3 ± 13.2% vs 34.8 ± 15.0%, p=0.007). Similarly, the total change in lumen volume index from follow-up to baseline was lower in women (-0.9 ± 1.0 mm^3/mm vs -1.4 ± 1.1 mm^3/mm, p=0.002). After adjustment with a multivariate linear regression analysis (Table 2), female sex remained an independent factor associated with lower neointimal obstruction (regression coefficient=-3.70, 95% CI=-6.97 to -0.43, p=0.027) and lower maximum CSN (regression coefficient=-6.67, 95% CI=-11.23 to -2.10, p=0.004). Additionally, Nakatani et al.[29] evaluated incomplete stent

apposition at baseline between sexes and defined incomplete stent apposition as a stent strut separated from the vessel wall with evidence of blood flow behind the strut. Women were found to have less incomplete stent apposition as compared to men (11.6% vs. men 19.3%, p=0.091).

Guagliumi et al.[30] also investigated sex-based differences in vascular healing responses, specifically following EES implantation in STEMI patients in a prospective cohort study. Investigators utilized the prospective multi-centre OCTAVIA study, which included 140 age-matched men and women with STEMI receiving an EES. Strut coverage and in-stent volume obstruction were evaluated at 9-month follow-up using optical coherence tomography (OCT). Strut coverage was defined as the percentage of the stent with overlying tissue and is an indicator of adequate stent placement. Women and men had similar EES strut coverage (90.9% vs. 92.5%, p=0.89). Women and men also had a similar amount of in-stent neointimal volume obstruction, (10.3% vs. 10.6%, p=0.76) as measured by OCT. Additionally, investigators evaluated rates of incompletely apposed struts post-procedure and at 9-month follow-up. Rate of acute incomplete stent strut apposition at post-implantation were similar between men and women (5.1% [95% CI: 1.5 to 10.8] vs. 5.0% [95% CI: 1.7 to 10.5], p=1.00) and at 9-months follow-up (0.9% [95% CI: 0.00 to 6.4] vs. 0.3% [95% CI: 0.00 to 3.5], p=0.13).

Additionally, related to the results reported in the first eight articles, Guagliumi et al.[30] also observed clinical outcomes at 1-month and 1-year follow-up after DES implantation. At 30-day follow-up, men had a higher frequency of major adverse cardiac or cerebral events (MACCE) (Table II), (5.7% vs. 1.4%, p=0.37). At 1-year follow-up, men continued to have a slightly higher frequency of MACCE (7.1% vs. 5.7%, p=0.69). Stent thrombosis was also slightly more frequent in men at 30-day follow-up (2.9% vs. 1.4%, p=1.00) and at 1-year follow-up (2.9% vs. 1.4%, p=0.55).

Discussion:

The purpose of this literature review was to determine if there were sex-based differences in clinical outcomes following DES implantation. MACE related to DES implantation between sexes was studied by the majority of studies reviewed. Although these articles had varying degrees of power, used different parameters, and variations in the definition of MACE, they were all consistent with supporting that DES are not associated with worse long-term clinical outcomes in women as compared to men. Short-term outcomes, however, revealed some potential avenues of further study. The unique finding by Yang et al.[21] of women having higher incidence of MACE after multivariate analysis within 6-month follow-up is certainly a source of further research. Of note, this study included patients with complex lesions and severe complications which suggests short-term sex-based differences may exist in the real-world that are overlooked in clinical trials due to selection bias. Additionally, Guagliumi et al.[30] observed MACCE to be more prevalent in men at 1-month and 1-year, but with the addition of cerebral events into this statistic, a small sample size, and no multivariate analysis, this study can be utilized to observe potential relationships but not powered enough to make clinical conclusions.

Lee et al.[23] matched male and female patients by propensity scores in a retrospective cohort study and found female sex was not an independent risk for MACE following DES implantation for complex coronary lesions. They did, however, find post-intervention minimum lumen area (MLA) was a significant predictor of MACE and post-intervention MLA itself was found to be impacted by height. Patients in the lowest percentiles of height were found to have the greatest risk of MACE at 1 year with strong statistical power. These findings suggest height may be a confounder given women tend to be shorter than men.[31] The mechanism as to how height affects cardiovascular morbidity and mortality is unclear. Relatedly, a large study found an association between height-associated single nucleotide polymorphisms and adverse lipid profiles.[32] Lee et al.[23] finding of height having a potential relationship to adverse clinical outcomes is unique and provides an avenue of further study with higher powered design models.

Moreover, both Nakatani et al.[29] and Guagliumi et al.[30] examined stent performance and adequate implantation between sexes by studying neointimal obstruction and strut apposition. Nakatani et al.[29] found women had significantly lower neointimal

obstruction and lower maximum CSN as compared to men receiving ZES after adjustment with a multivariate linear regression analysis. Additionally, Nakatani et al.[29] found at baseline women had less incomplete stent apposition. In contrast, Guagliumi et al.[30] found at 9-month follow-up age-matched women and men had a similar amount of in-stent neointimal obstruction and similar EES strut coverage. Relatedly, Guagliumi et al.[30] found the rate of incomplete stent strut apposition was similar between women and men both at post-implantation and at 9-months. The difference these studies found in stent apposition outcomes may be due to both utilizing different imaging modalities (IVUS vs OCT) and different DES (ZES vs EES). Additionally, and importantly, the stents Nakatani et al.[29] compared between sexes for apposition were observed at baseline and not subjected to inclusion or exclusion criteria, such as selection for DES, like Guagliumi et al.[30] Furthermore, with respect to neointimal obstruction, the differences in findings are likely due to Guagliumi et al.[30] limited correction for confounders, selecting for low-risk patients, small sample size, and utilizing a different imaging modality. Ultimately, Nakatani et al.[29] finding of less neointimal obstruction and less maximum CSN in women with strong statistical power is of interest and confirming these results with long-term studies would add value to the overall understanding of sex-related vascular healing following PCI.

Study Limitations

Although the articles in this literature review assess possible sex-based differences in clinical outcomes, neointimal hyperplasia, and strut coverage following DES implantation, this literature review does have limitations. Multiple studies in this review compared BMS and DES and our review only focused on the DES subgroup which limits the data's power. Relatedly, a few studies did not utilize a multivariate analysis to correct for possible confounders. Additionally, studies could not correct for all possible confounders with their multivariate analysis given such information was not collected. These possible confounders include presentation time after symptom onset, post-procedure medication compliance, and sex-based differences in referral rate for revascularization. Furthermore, many studies reviewed were post hoc analyses which are not able to provide clinical conclusions but do provide avenues for further research.

Conclusion:

After review of the relevant literature, a few conclusions can be made with respect to sex-based differences in the clinical outcomes following DES implantation. Despite having smaller vessels and higher incidences of advanced age, diabetes mellitus, and hypertension at hospital admission, women had similar incidences of MACE and stent thrombosis at long-term follow-up. Women may, however, have an increase of MACE within short-term follow-up as compared to men with complex lesions. Additionally, height may play a role in clinical outcomes following treatment with a DES. Lastly, women may have superior healing responses with lower neointimal obstruction and lower maximum CSN following DES implantation.

This field of study can benefit from further research, particularly with higher-powered studies and longer-term follow-up with respect to vascular healing responses. Furthermore, although multivariate analysis was used to correct for differing baseline characteristics, it is important to consider how to effectively reduce cardiac risk factors that were consistently found to be higher among women at hospital admission as compared to men. Lastly, given the physiological differences between sexes, and the history of differing clinical outcomes of previously used PCIs, sex-differences need to continue to be taken into account when imploring new coronary artery disease treatments.

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