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

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ABSTRACT: Background. The TITAX-AMI trial demonstrated a better clinical outcome of titanium-nitride-oxide-coated bioactive stents (BAS) as compared with paclitaxel-eluting stents (PES) in patients with acute myocardial infarction (MI) undergoing early percutaneous coronary intervention (PCI). We explored the gender-based 3-year outcome of BAS as compared with PES in a subgroup analysis of the TITAX-AMI trial. **Methods.** A total of 214 patients (52 women) with acute MI were randomly assigned to BAS, and 211 patients (54 women) to PES. The primary endpoint was major adverse cardiac events (MACE) including cardiac death, recurrent MI, and target lesion revascularization (TLR). Secondary endpoints were all-cause death, a composite of cardiac death or recurrent MI, and stent thrombosis (ST). **Results.** Women were older and had smaller reference vessel diameter (P<.001 for both) as compared with men. At 3-year follow-up, both MACE and TLR showed a trend to be higher in women as compared with men (24.5% versus 16.3% [P=.059] and 15.1% versus 8.8% [P=.065], respectively). The rate of all-cause death was significantly higher in women as compared with men (13.2% versus 6.0%, respectively; P=.02). Among female patients, MACE, cardiac death, recurrent MI, TLR, and ST were all statistically similar between the two stent groups (P>.05 for all). **Conclusions.** In the current *post hoc* gender-based analysis of the TITAX-AMI trial, the 3-year outcome of patients undergoing PCI for acute MI was slightly worse in female patients as compared with their male counterparts, as reflected by a trend toward a higher primary composite endpoint of MACE and TLR.

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Interventional cardiology has come a long way since the introduction of coronary stents in the 1990s provided a safer approach for percutaneous coronary interventions (PCI).[1,2] Overall, women undergoing PCI have more comorbidities, and more often have multivessel disease in predominantly smaller coronaries.[3,4] There is some uncertainty, however, as to whether — and how — gender would influence the outcome of coronary stent implantation.

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Indeed, the arrival of drug-eluting stents (DES) on the scene has dramatically reshaped the landscape of coronary intervention, resulting in a marked reduction of restenosis rates by one-half to two-thirds at 5-year follow-up.[5,6] In patients with stable coronary artery disease, long-term benefit was observed following DES implantation in men and women, alike.[4,7] In fact, most randomized trials comparing DES with bare-metal stents (BMS) in the setting of primary PCI for ST-elevation myocardial infarction (MI) showed a reduction of target lesion revascularization (TLR) with DES, without an increase in the incidence of stent thrombosis (ST).[8-12] Yet, after years 'in duty,' worrisome reports have raised concern about a small, but definite, increase of late and very late ST with the use of DES.[13]

A further step forward was taken with the design of bioactive stents (BAS). The safety of titanium-nitride-oxide-coated BAS has been established in several reports from real-life unselected populations.[14,15] Surprisingly, in the highly challenging realm of acute MI, BAS did achieve a better outcome as compared with the Food and Drug Administration-approved paclitaxel-eluting stent (PES) at 2-year follow-up.[16] A lingering question remains as to whether these results will remain consistent in female patients. So far, we explored the gender-based 3-year outcome of BAS as compared with PES in patients presenting with acute MI as evaluated in a subgroup analysis of the Titanium-Nitride-Oxide-Coated Stents versus Paclitaxel-Eluting Stents in Acute Myocardial Infarction (TITAX-AMI) trial.

Methods

Patient selection and study design. The design of the original trial has been previously reported.[16,17] Briefly, the TITAX-AMI trial is a prospective randomized multicenter trial in which 425 patients presenting with acute MI were randomized in a 1:1 fashion to receive either Titan-2 BAS (Hexacath) or TAXUS Liberte PES (Boston Scientific). Predilatation of culprit lesion, PCI technique, selection of access site, administration of intravenous heparin, low-molecular-weight heparin, bivalirudin, and glycoprotein IIb/IIIa receptor inhibitors were left to the discretion of the operator. In patients not maintained on aspirin, the study protocol recommended premedication with aspirin at a loading dose of 100-500 mg orally, or 250-500 mg intravenously. Clopidogrel was administered at a loading dose of 300-600 mg orally immediately after the index procedure, if the patient was not already maintained on clopidogrel. At discharge, aspirin was prescribed at a dose of 100 mg daily orally, indefinitely, and clopidogrel at a dose of 75 mg daily orally, for at least 6 months. Clinical follow-up was planned at 1, 6, 12, 24, and 36 months.

Table 1. Baseline clinical characteristics of the 2 individual subgroups.

Variable	Female Subgroup (N = 106)	Male Subgroup (N = 319)	*P*-Value
Age (years)	68 ± 10	62 ± 11	<.001
Risk factors			
Family history of CAD	47 (44%)	151 (47%)	.65
Diabetes	21 (20%)	60 (19%)	.89
Hypertension	57 (54%)	171 (54%)	1.0
Hypercholesterolemia	77 (73%)	215 (67%)	.34
History of smoking	35 (33%)	175 (55%)	.001
Medical history			
Myocardial infarction	11 (10%)	42 (13%)	.50
PCI	6 (6%)	26 (8%)	.53
CABG	3 (3%)	26 (8%)	.074
Medication			
Thrombolysis	19 (18%)	47 (15%)	.44
Bivalirudin	1 (0.9%)	10 (3.1%)	.22
GP IIb/IIIa inhibitors	51 (48%)	161 (50%)	.74
Indication for PCI			
NSTEMI	63 (59%)	182 (57%)	.73
STEMI	43 (41%)	137 (43%)	.73

Continuous variables are presented as means ± standard deviations, while categorical variables are presented as frequencies and percentages.
CAD = coronary artery disease; PCI = percutaneous coronary revascularization; CABG = coronary artery bypass grafting; GP = glycoprotein; NSTEMI = non-ST elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

Study endpoints and definitions. Diagnostic criteria for non-ST elevation MI and ST-segment elevation MI have been described in detail previously.[16,17] The primary endpoint was the first occurrence of major adverse cardiac events (MACE), defined as a composite of cardiac death, recurrent MI, or TLR. Secondary endpoints included all-cause death, a composite of cardiac death or recurrent MI, and ST. The 3-year analysis was prespecified per protocol (follow-up data were planned to be collected yearly for 5 years).

Ethical issues. The study was initiated by the investigators and conducted according to the ethical guidelines of the American Physiological Society. Informed written consent was obtained from every patient after full explanation of the study protocol. The study protocol was approved by the Ethics Committees of the coordinating center, Satakunta Central Hospital, and the participating hospitals. The study has been registered at www.clinicaltrials.gov, under the number NCT00495664.

Statistical analysis. Continuous variables were presented as means ± standard deviations, while categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two groups were performed using the unpaired two-tailed t-test for continuous, and the Pearson Chi-square test or Fisher's exact test for categorical variables. Time-to-event curves were constructed using the Kaplan-Meier method and data were compared using the log-rank test. Univariate and multivariable logistic regression analyses were performed to identify the independent predictors of MACE at 3-year follow-up. All tests were two-sided and statistical significance was set at 5%. All data were analyzed with SPSS version 17.0 (SPSS).

Results

Baseline, angiographic and procedural characteristics. Of the 425 randomized patients, 214 were assigned to Titan-2 BAS (including 52 women [24.3%]), and 211 to TAXUS Liberte PES (including 54 women [25.6%]). Baseline clinical characteristics were balanced between female and male patients (Table 1). However, women were significantly older and less commonly smokers as compared with men. Diabetes mellitus was present in one-fifth of patients. Baseline angiographic characteristics were also balanced between genders except for a significantly smaller reference vessel diameter in women (Table 2).

Clinical outcome of the TITAX-AMI at 3-year follow-up. The 3-year cumulative incidence of MACE was significantly lower in patients assigned to BAS as compared with those assigned to PES (13.1% versus 23.7%, respectively; *P*=.006). Similarly, the 3-year rates of cardiac death and recurrent MI were significantly lower in patients assigned to BAS (1.4% versus 5.2% and 6.1% versus 16.6%, *P*=.028 and *P*=.001, respectively). Nevertheless, the rates of TLR were similar between the two study groups (9.8% versus10.9%, respectively; *P*=.75). The rate of ST was again significantly lower in patients assigned to BAS (0.5% versus 6.6%, respectively; *P*<.001).

Gender-based 3-year clinical outcome. The 3-year cumulative incidence of MACE trended higher in women as compared with men (24.5% versus 16.3%, respectively; *P*=.059) (Table 3 and Figure 1). Likewise, TLR rates trended higher in women (15.1% versus 8.8%, respectively; *P*=.065). Otherwise, the 3-year rates of cardiac death, recurrent MI, and ST were statistically matched between genders. However, the rate of all-cause death was significantly higher in women as compared with men (13.2% versus 6.0%, respectively; *P*=.02) (Table 3).

Stent-based analysis of the two gender subgroups. Among male patients, the primary composite endpoint of MACE was significantly lower in those assigned to receive BAS as compared with those assigned to receive PES (9.9% versus 22.9%, respectively; *P*=.002). Similarly, the rates of cardiac death, recurrent MI, and ST were significantly lower in those assigned to receive BAS (0.6% versus 5.1% [*P*=.02], 5.6% versus 15.6% [*P*=.002], and 0.0% versus 7.1% [*P*<.001], respectively). The rates of TLR, however, were statistically similar between the two stent groups (*P*=.22) (Figure 2A). On the other hand, among female patients, the primary composite endpoint of MACE was statistically similar between the two stent groups (*P*=.82). Similarly, the rates of cardiac death, recurrent MI, TLR, and ST were statistically similar between the two stent groups (*P*>.05 for all) (Figure 2B).

Gender-based analysis of the two stent treatment arms. Among patients assigned to receive BAS, the primary composite endpoint of MACE was significantly higher in women as compared with men (23.1% versus 9.9%, respectively; *P*=.02) (Figure 3A). Similarly, TLR was significantly higher in women (19.2% versus 6.8%, respectively; *P*=.01). Both cardiac death and ST showed a trend to be higher in women as compared with men (3.8% versus

Table 2. Angiographic and procedural characteristics of the 2 individual subgroups.

Variable	Female Subgroup (N = 106)	Male Subgroup (N = 319)	*P*-Value
Lesion characteristics			
Left anterior descending artery	44 (42%)	140 (44%)	.74
Bifurcated lesion	28 (26%)	75 (24%)	.60
Reference diameter (mm)	2.98 ± 0.44	3.19 ± 0.48	<.001
Lesion length (mm)	13.44 ± 6.99	13.36 ± 5.64	.91
TIMI flow grade			
0	21 (20%)	70 (22%)	.68
1	5 (5%)	19 (6%)	.81
2	24 (23%)	75 (24%)	.90
3	56 (53%)	155 (49%)	.50
Procedural characteristics			
Direct stenting	11 (10%)	41 (13%)	.61
Postdilatation	41 (39%)	121 (38%)	.91
Paclitaxel-eluting stent	54 (51%)	157 (49%)	.82
Nominal stent size (mm)	3.10 ± 1.05	3.18 ± 0.44	.30
Stent length (mm)	17.06 ± 5.21	17.67 ± 4.80	.26
Total stent length (mm)	18.91 ± 7.88	18.79 ± 6.42	.88
Duration of clopidogrel use (mo.)	8.72 ± 3.27	8.80 ± 3.24	.83

Continuous variables are presented as mean ± standard deviation, while categorical variables are presented as frequency (percentage).

Table 3. Clinical outcome in the 2 individual subgroups at 3-year follow-up.

Variable	Female Subgroup (N = 106)	Male Subgroup (N = 319)	Hazard Ratio	95% Confidence Interval	*P*-Value
Cardiac death	5 (4.7%)	9 (2.8%)	1.71	0.56-5.21	.34
MI	13 (12.3%)	35 (11.0%)	1.13	0.58-2.24	.72
TLR	16 (15.1%)	28 (8.8%)	1.85	0.96-3.57	.065
MACE	26 (24.5%)	52 (16.3%)	1.67	0.98-2.84	.059
ST	4 (3.8%)	11 (3.4%)	1.09	0.34-3.51	.88
Cardiac death or MI	14 (13.2%)	38 (11.9%)	1.13	0.58-2.17	.73

Variables are presented as frequency (percentage). MI = myocardial infarction; TLR = target lesion revascularization; MACE = major adverse cardiac events; ST = stent thrombosis.

0.6% [*P*=.09] and 1.9% versus 0.0% [*P*=.08], respectively). Otherwise, the rates of recurrent MI and all-cause death were statistically matched between genders (*P*>.05 for both). On the other hand, among patients assigned to receive PES, all primary and secondary endpoints were statistically matched between genders (*P*>.05 for all) (Figure 3B).

Independent predictors of MACE at 3-year follow-up. By multivariable logistic regression analysis, the independent predictors of MACE at 3-year follow-up were smaller stent diameter (*P*=.007; hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.22-3.46), previous coronary bypass surgery (*P*=.007; HR, 3.22; 95% CI, 1.37-7.53), and assignment to the PES group (*P*=.003; HR, 2.06; 95% CI, 1.24-3.43).

Discussion

Main findings. The current *post hoc* gender-based analysis of the TITAX-AMI trial demonstrated that the 3-year outcome of patients undergoing PCI for acute MI (irrespective of stent type) was slightly worse in female patients as compared with their male counterparts, as reflected by a trend toward a higher primary composite endpoint of MACE and a similar trend toward a higher TLR rate. Moreover, among female patients, those who received BAS had a 3-year outcome similar to those who received PES (*P*>.05 for all). However, among patients who received BAS, female patients had significantly higher rates of MACE and TLR, with trends toward higher rates of cardiac death and ST as compared with their male counterparts.

Cardiovascular disease in women. The rates of coronary artery disease in women increase by two- to three-fold after menopause.[18] Moreover, it has recently been recognized that significant differences exist between men and women as regards coronary artery disease.[19] Atypical presentation of angina and MI in women may eventually result in some delay in seeking medical care, a possible delay in diagnosis, and underuse of aggressive therapeutic approaches. Furthermore, women have been mostly under-represented in large clinical trials.[19] Rather controversial results drawn from these trials underscoring a probably worse long-term clinical outcome in women undergoing PCI, as compared with men, may have, in a way, conditioned the referral process so that fewer women were subsequently referred to invasive procedures.[20-22]

Clinical outcome in females: TITAX-AMI trial. Despite the fact that females fared quite non-inferiorly as compared with their male counterparts as far as the long-term clinical outcome was concerned, all-cause death was significantly higher in the female subgroup. Although both genders were almost similar regarding the classic cardiovascular risk factors, substantially older age in the female subgroup may well have contributed to the overall mortality difference. Older age at presentation might in turn bring another variable into account: reduced creatinine clearance, a well-known predictor of worse outcome. Weighted evidence from literature similarly demonstrated higher-risk demographic and angiographic characteristics in females undergoing PCI, as compared with males.[3,4,23,24] However, due to the retrospective nature of this *post hoc* analysis, some data relevant to outcome of PCI, such as body mass index, creatinine clearance, and time from symptom onset to intervention, have been overlooked.

Indeed, the trend toward a higher primary composite endpoint of MACE in the female subgroup was fundamentally driven by

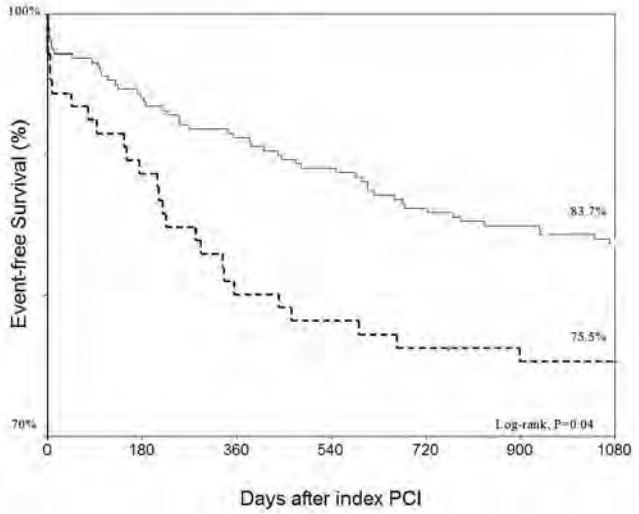

Figure 1. *Event-free survival curves for the 2 gender subgroups. Dashed line indicates survival curve for women; solid line indicates survival curve for men.*

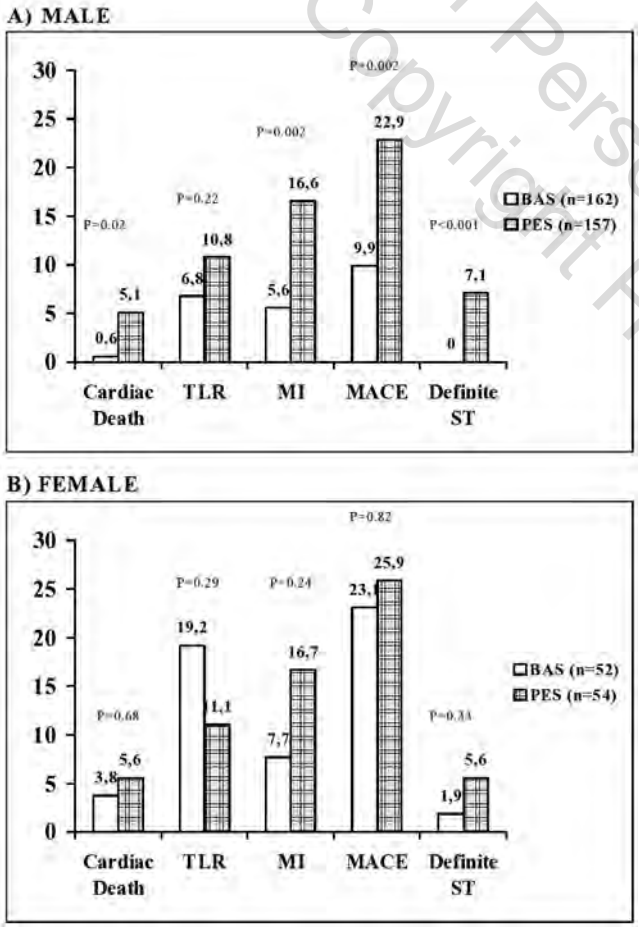

Figure 2. *Stent-based analysis of the 2 gender subgroups.* **(A)** *Male; and* **(B)** *Female subgroup.*

a trend toward higher TLR rates. Higher reintervention rates in female patients may be chiefly attributed to a significantly smaller reference vessel diameter in this subgroup, accounting for higher re-

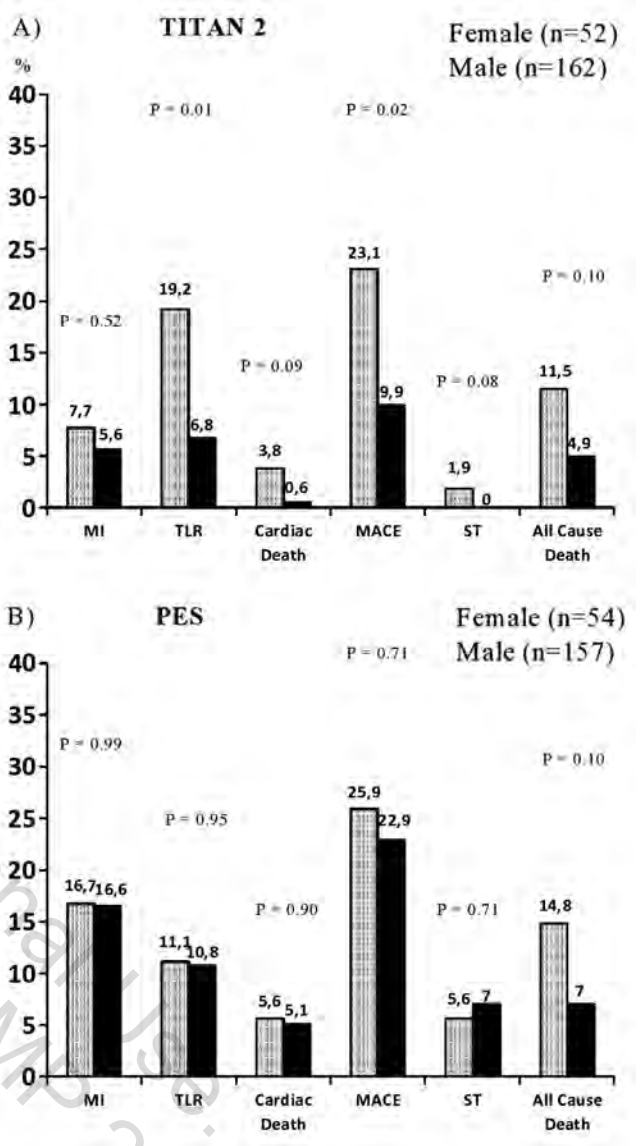

Figure 3. *Gender-based analysis of the 2 stent treatment arms.* **(A)** *Titan-2 bioactive stent;* **(B)** *Taxus Liberte paclitaxel-eluting stent.*

stenosis rates, ultimately causing further symptom-driven coronary angiography. Actually, within the female subgroup, TLR rate was numerically higher — albeit statistically insignificant — in patients assigned to receive BAS versus those assigned to receive PES (*P*=.29). Total MACE, however, and its two other components were better — again although statistically insignificant — in those who received BAS. It is noteworthy that among the male subgroup, total MACE, cardiac death, recurrent MI, and ST rates were all significantly better with BAS (*P*<.05 for all); TLR rate was better, but without meeting statistical significance.

In the trial arm that received BAS, the rate of total MACE was higher in females as compared with their male counterparts, obviously driven by a significantly higher rate of TLR. Once again, this may be viewed in light of the smaller-sized vessels in these patients, rather than any influence of gender, *per se*, on outcomes. Given the nearly similar gender-based rates of MACE and TLR in the arm that received PES, higher TLR in females who received BAS probably underlies the trend toward increased TLR in the female population

as a whole. Albeit lower in the BAS group as compared with the PES group, the rate of cardiac death among patients who received BAS trended to be higher in females versus males, mostly driven by a trend toward a higher rate of ST in this particular subgroup. Although lower stent diameter, and quite possibly BAS undersizing, in the female subgroup might have contributed to the higher ST rates from a hypothetical perspective; the precise mechanisms underlying this surprising outcome are far from clear, and may leave a whole avenue for future research.

Independent predictors of outcome. Multivariable logistic regression analysis did not identify female gender among the independent predictors of MACE at 3-year follow-up. Instead, smaller stent diameter (again speaking of smaller coronary vessels), prior surgical revascularization, and allocation to PES independently predicted outcome. This makes a strong case for the theme that the divergence in outcome between the two gender subgroups most probably reflects differences in the nature of the underlying coronary disease, later presentation in life, and variance of comorbidities, rather than an influence of gender *per se*.

Study limitations. The TITAX-AMI trial was not designed to particularly explore gender-specific differences in outcome, whether as a pooled gender-based analysis or as regards gender and type of stent implanted. Furthermore, as already stated earlier, due to the retrospective nature of this *post-hoc* analysis, some data relevant to the outcome of PCI may have been missed. In addition, the trial may have been underpowered for specific subgroup analysis; therefore, any conclusions drawn from the analysis data should be taken with caution.

Conclusion

In the current *post hoc* gender-based analysis of the TITAX-AMI trial, the 3-year outcome of patients undergoing PCI for acute MI was slightly worse in female patients as compared with their male counterparts, as reflected by a trend toward a higher primary composite endpoint of MACE and a trend toward a higher TLR rate.

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Commentary

Outcomes in Contemporary Coronary Interventions with Drug-Eluting Stents for Acute Myocardial Infarction: The Gender Role

Nicolas W. Shammas, MD, MS

In a *post hoc* gender-based analysis of the TITAX-AMI trial,[1] Tuomainen et al noted that at 3-year follow-up, females had a higher trend of major adverse events than males for the composite endpoint of cardiac death, recurrent myocardial infarction (MI), and target lesion revascularization (TLR) (24.5% versus 16.3%; *P*=.059) driven mostly by a trend toward higher TLR. Multivariate analysis, however, showed that female gender *per se* was not a predictor of adverse events when adjusting for important demographic and angiographic variables. Females were older on presentation and with smaller

coronary arteries, which are factors associated with higher adverse events. When these variables and others are adjusted for, predictors of adverse events were smaller stent diameter (*P*=.007), prior coronary bypass surgery (*P*=.007), and receiving the paclitaxel-eluting stent (PES) (*P*=.003) rather than gender. Similarly, data from a Polish registry[2] for acute ST-elevation myocardial infarction (STEMI) that included 8989 females and 17,046 males showed that women were older and had more risk factors. The incidence of in-hospital (11.9% vs 6.9%; *P*<.0001) and 12-month (22% vs 14.1%; *P*<.0001) mortality was significantly higher in women than men. In multivariate analysis, predictors of mortality were pulmonary edema, cardiogenic shock, cardiac arrest, age, diabetes, and anterior infarction. Gender was not an independent predictor of mortality. In addition, similar data were reported from the Korean Acute Myocardial Infarction Registry (KAMIR),[3] which included 4037 patients admitted with STEMI to 41 facilities. In this registry, women had higher rates of in-hospital mortality (8.6% vs 3.2%; *P*<.01) and cardiac death (7.1% vs 2.8%; *P*<.01) than men. Multivariate analysis identified age, prior angina, hypertension, a higher Killip class, reduced LV systolic function, and a Thrombolysis in Myocardial Infarction flow grade <3 after angioplasty as predictors of in-hospital death. Female gender was also not an independent predictor of in-hospital mortality in this registry. Furthermore, recent data from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) PCI registry recently reported that differences in mortality between men and women no longer exist post PCI.[4]

In contrast to the above data, the mandatory Greater Paris Coronary Intervention Registry[5] with 16,760 STEMI patients from 41 centers showed that female gender *per se* was an independent predictor of in-hospital mortality (9.8% vs 4.3%; *P*<.0001). This is also similar to published data on non-STEMI and unstable angina patients from the randomized RITA-3 trial.[6] In this study, 1810 patients (682 women and 1128 men) were randomized to early intervention versus initial conservative treatment. More men than women benefited from an early intervention strategy with fewer deaths or non-fatal myocardial infarctions at 1 year.

In the TITAX-AMI trial,[1] males receiving the bioactive stent (BAS) had better outcomes than males or females receiving the PES, and females receiving the BAS had the same outcome as females receiving the PES stent. The BAS stent was also more effective in males than in females in reducing major adverse events. Also, Nakatani et al[7] showed an interaction between female gender and reduced smooth muscle cell proliferation in patients treated with the zotarolimus-eluting stent (ZES). In their study, restenosis was significantly more reduced in women than men with ZES. In contrast, data from RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital)[8] showed no interaction with the rapamycin and paclitaxel stents and gender. DES reduced revascularization equally in both men and women compared to bare-metal stents in these studies. Similarly, data from the SPIRIT II and SPIRIT III studies[9] indicated that the everolimus-eluting stent was superior to the PES in reducing angiographic late loss, major adverse events and target vessel failure. There was no interaction between gender and stent type in reducing major adverse events at 2 years. Whether an interaction between stent type and gender exists needs to be confirmed in future studies. It is possible that if interaction between stent and gender exists, it is likely to be stent-specific.

In summary, when females present with an acute coronary syndrome (ACS), they are usually older, have more comorbidities, and are hemodynamically more unstable. In addition, they have smaller coronaries and tend to have less successful PCI. Despite our ability to statistically identify predictors of mortality in an ACS patient, these predictors remain inherently present more in women than men, which explains the worse outcomes in women irrespective of whether gender *per se* is or is not an independent predictor of adverse events post PCI. The TITAX-AMI confirms these observations and supports the presence of a stent-specific gender interaction.

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