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Short communication

Effect of stent diameter in women undergoing percutaneous coronary intervention with early- and new-generation drug-eluting stents: From the WIN-DES collaboration

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ABSTRACT

Background: The risk of stent thrombosis (ST) or target lesion revascularization (TLR) is increased with smaller stent diameters (SD). Whether SD has a deleterious effect in women treated with early- vs. new-generation drug-eluting stents (DES) is unknown.
Methods: We pooled patient-level data from 26 randomized control trials of DES. Only women treated with DES were included. Subjects were stratified according to SD: small, SD ≤ 2.75 mm; intermediate, 2.75 mm < SD ≤ 3.25 mm; and large, SD ≥ 3.25 mm. Endpoints of interest were 3-year definite ST, TLR, major adverse cardiac events (MACE: the composite of death, myocardial infarction or TLR) and death.
Results: Of 6413 women, 2274 (35.0%) had a small SD, 2448 (38.0%) had an intermediate SD, and 1691 (26.0%) had a large SD. By multivariable analysis, stent diameter (per 0.25 mm decrease) was associated with an increased risk of TLR and ST, which was uniform in terms of magnitude and direction between early- and new-generation DES. There were no differences in MACE or death across groups.
Conclusion: Small SD in women undergoing PCI is associated with an increased risk of definite ST and TLR, consistently with both early- and new-generation DES.

1. Introduction

In patients undergoing percutaneous coronary intervention (PCI) with stent implantation, an inverse relationship has been shown between stent diameter (SD) and device-oriented outcomes including stent thrombosis (ST) and target lesion revascularization (TLR) [1]. Compared to men, women are more likely to have smaller and more tortuous vessels, more clinical comorbidities and subsequent periprocedural complications [2,3]. However, the impact of nominal SD on outcomes in women undergoing PCI with drug-eluting stents (DES) has not been well defined as women have historically been underrepresented in randomized control trials (RCTs) investigating the safety and efficacy of cardiovascular devices. In the 2011 FDA guidance document, sex disparities in RCTs investigating medical devices were recognized [4]. In response, the Women in Innovation (WIN) initiative led the creation of a collaborative international patient-level dataset of RCTs to evaluate the safety and efficacy of DES in women. Therefore, in the current analysis from the WIN-DES collaboration we investigated the effect of SD on ischemic outcomes in women undergoing PCI with DES overall and by DES generation.

2. Methods

2.1. Study design

We pooled patient-level data of female participants from 26 RCTs between 2000 and 2013 evaluating the safety and efficacy of DES. The rationale of the present patient-level pooled database, list of trials, analytic strategies and pre-specified endpoints have been previously reported [5]. Briefly, female participants from 26 RCTs evaluating safety and efficacy of DES were pooled. Every study included in our analysis complied with the provisions of the Declaration of Helsinki, and was approved by the institutional review board at each study center.

2.2. Study population, definitions and endpoints

Only women treated with DES and for whom information regarding nominal SD was available were included in this analysis. The present study population was stratified into 3 categories based on SD: small, defined as SD ≤ 2.75 mm; intermediate, SD between

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2.75 and 3.25 mm; and large, SD ≥ 3.25 mm. Women randomized to bare-metal stent treatment were excluded from the present analysis. Our primary endpoints of interest were 3-year TLR and definite ST. Our secondary endpoints were 3-year major adverse cardiac events (MACE; defined as the composite of death, myocardial infarction or TLR) and death.

2.3. Statistical analysis

Patient-level data were aggregated and combined as one structured dataset on a pre-specified extraction sheet. Adjusted hazard ratios (HR) and 95% confidence intervals (CI) were generated using a Cox proportional hazard model. We included a frailty term (γ) within our Cox model to account for random effects across trials and for inter-trial heterogeneity. For these analyses, the total follow-up was defined as the time from index procedure until death, last follow-up date, or 3 years, whichever came first. The consistency of the effect of DES generation across SD sizes was evaluated with a formal interaction test. A p-value <0.05 was considered statistically significant. Analyses were performed using Stata version 14.0.

3. Results

Out of 11,577 women included in the database, 6413 (55.4%) had nominal SD data available with a median follow-up time of 2.28 years (IQR: 1.09–3.53). Of these, 2274 (35.0%) had a small SD, 2448 (38.0%) had an intermediate SD and 1691 (26.0%) had a large SD. Women treated with smaller stents had lower BMIs and a higher prevalence of diabetes mellitus, previous PCI, lower left ventricular ejection fraction, multivessel disease, ACC/AHA type B2 or C lesions, number of lesions treated and stents implanted (Table 1). There were 309 total TLR events, 42 ST, 753 MACE and 266 deaths. There was a step-wise increase in the risk of TLR and definite ST at 3 years in the transition from large to intermediate to small SD (Table 1). By multivariable analysis, SD per 0.25 mm decrease was associated with an increased risk of TLR (adjusted HR 1.12; 95% CI 1.04–1.23; $p = 0.006$) and definite ST (adjusted HR 1.37; 95% CI 1.06–1.77; $p = 0.016$). These findings were consistent in both magnitude and direction when stratified by generation of DES without evidence of interaction between SD and generation of DES (Fig. 1). There were no significant differences in MACE (early-generation DES Adjusted HR: 1.04, 95% CI: 0.96–1.12; new-generation DES adjusted HR: 1.01, 95% CI: 0.94–1.09; $p_{\text{interaction}} = 0.68$) or death (early-generation DES adjusted HR: 1.01, 95% CI: 0.89–1.15; new-generation DES Adjusted HR: 0.90, 95% CI: 0.80–1.02; $p_{\text{interaction}} = 0.22$) across groups.

4. Discussion

In the present manuscript we elucidated the effect of nominal SD on 3-year outcomes in women, overall and by DES generation. The main findings of this large-scale study that included patient-level data from >6400 women undergoing PCI with DES suggest that an inverse relationship between SD and ischemic outcomes following PCI exists, with smaller stents being associated with a significantly higher risk of TLR and definite ST at 3 years. Of note, the effect of smaller SD on ischemic outcomes was consistent between DES generations. To our knowledge, this is the first study to report the effect of SD overall and by DES generation, based on data from a large, female-only cohort. Our findings are consistent with results from a pooled-analysis of 14 RCTs of DES ($N = 2808$ patients and 2931 lesions) in which the incidence of definite/probable ST was significantly higher in smaller vessels and there was a progressive decrease in the TLR rate across increasing vessel size [1]. In addition, SD is one of only three procedural characteristics used in calculating the DAPT Score, a risk prediction tool to estimate the risk and benefits of extended duration dual antiplatelet therapy (DAPT) after PCI [6]. Reasons for the increased risk of thrombotic events associated with smaller SD are multifactorial. First, within small stents, the same proportion of neointimal hyperplasia may lead to luminal occlusion in comparison to vessels with a larger diameter. Second, blood flow at the level of smaller stents may be associated with greater thrombogenic flow abnormalities predisposing to ST. Finally, patients with smaller vessels (requiring smaller nominal SD) display a greater prevalence of comorbidities which may influence future residual atherothrombotic risk. In aggregate, our findings support that SD is a strong determinant of future ischemic risk and should be considered at the time of clinical-decision making upon DAPT intensity and duration even after implantation of new-generation DES.

Table 1
Baseline characteristics and 3-year cumulative incidence of adverse events according to stent diameter.

	Small SD ($N = 2274$)	Intermediate SD ($N = 2448$)	Large SD ($N = 1691$)	p_{trend}
Baseline characteristics				
Age, years	67.50 ± 10.46	67.21 ± 10.55	66.79 ± 10.69	0.11
BMI (kg/m^2)	27.32 ± 5.38	27.60 ± 5.51	27.76 ± 5.65	0.05
Diabetes mellitus	827 (36.4)	760 (31.0)	451 (26.7)	<0.0001
Hypertension	1700 (74.8)	1840 (75.2)	1241 (73.4)	0.42
Hypercholesterolemia	1581 (69.5)	1652 (67.5)	1144 (67.7)	0.27
Serum creatinine, mg/dl	0.91 ± 0.56	0.95 ± 0.83	0.93 ± 0.77	0.18
Current or former smoker	694 (30.5)	718 (29.3)	532 (31.5)	0.33
Previous MI	424 (18.7)	458 (18.7)	276 (16.3)	0.10
Previous PCI	404 (18.3)	416 (17.9)	250 (15.4)	0.04
Previous CABG	107 (4.7)	102 (4.2)	77 (4.6)	0.66
LVEF (%)	53.92 ± 20.01	55.90 ± 18.33	56.16 ± 18.03	0.003
Multivessel disease	711 (32.2)	751 (32.3)	423 (26.0)	<0.0001
Number of lesions treated	1.32 ± 0.66	1.34 ± 0.70	1.21 ± 0.50	<0.0001
Number of stents implanted	1.64 ± 1.01	1.60 ± 1.01	1.44 ± 0.77	<0.0001
Mean stent diameter (mm)	2.57 ± 0.14	3.00 ± 0.06	3.51 ± 0.19	<0.0001
Total stent length (mm)	31.64 ± 21.65	30.92 ± 21.10	27.30 ± 16.15	<0.0001
3-year adverse events				
Definite stent thrombosis	$n = 25$ [1.22% (0.82%–1.82%)]	$n = 11$ [0.54% (0.29%–0.99%)]	$n = 6$ [0.47% (0.20%–1.08%)]	0.005
Target lesion revascularization	$n = 129$ [6.42% (5.41%–7.62%)]	$n = 120$ [5.93% (4.95%–7.11%)]	$n = 60$ [4.21% (3.25%–5.45%)]	0.009
Major adverse cardiac events[a]	$n = 277$ [13.73% (12.26%–15.37%)]	$n = 304$ [14.55% (13.05%–16.21%)]	$n = 172$ [12.26% (10.58%–14.19%)]	0.08
All-cause death	$n = 89$ [4.84% (3.93%–5.97%)]	$n = 108$ [5.50% (4.55%–6.65%)]	$n = 69$ [5.55% (4.37%–7.04%)]	0.74

Results are reported as n (%) or mean ± standard deviation as appropriate. Adverse events at 3 years are reported as Kaplan-Meier estimates and 95% confidence interval. BMI: Body Mass Index; CAD: Coronary Artery Disease; MI: Myocardial Infarction; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; LVEF: Left Ventricular Ejection Fraction; SD: Stent Diameter.

[a] Defined as the composite of all-cause death, myocardial infarction or target lesion revascularization.

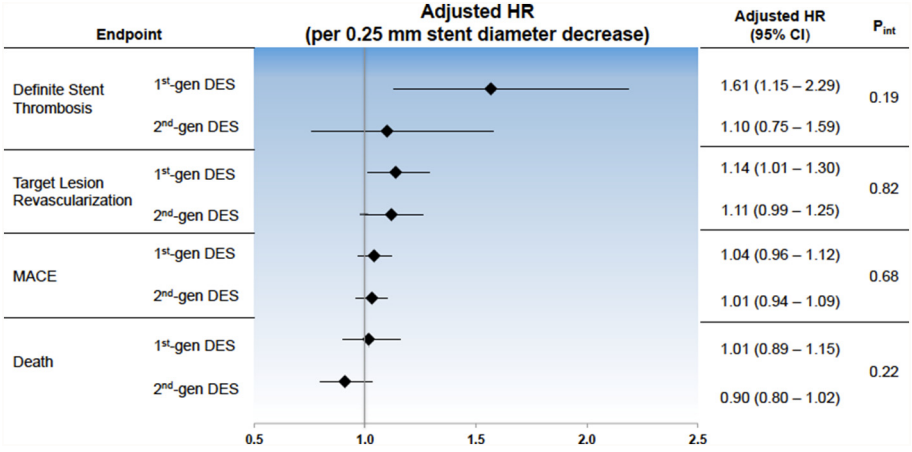

Fig. 1. Impact of stent diameter on ischemic outcomes in women undergoing PCI with early- and new-generation DES. Results adjusted for the following covariates: age, BMI, diabetes, smoking, hypertension, B2C lesions, multivessel disease, mean stent length, previous PCI, number of stents implanted and clinical presentation. HR: Hazard Ratio; CI: Confidence Interval; DES: Drug Eluting Stent; ST: Stent Thrombosis; TLR: Target Lesion Revascularization; MACE: Major Adverse Cardiac Events.

4.1. Limitations

The major limitations of the current report are the lack of data on the duration and intensity of DAPT, the lack of more detailed baseline angiographic data (e.g., reference vessel diameter), and the lack of intracoronary imaging data (e.g., IVUS, OCT). In addition, final SD and residual diameter stenosis were not available in the current dataset, which have also been shown to be associated with increased ischemic risk post-PCI. Finally, the lack of inclusion of male subjects in the WIN-DES dataset precludes the evaluation of the relative effect of SD by sex.

4.2. Conclusions

Smaller SD in women undergoing PCI is associated with increased risk of stent-related complications, including TLR and ST, consistently with both early- and new-generation DES. Intraprocedural and pharmacologic measures to mitigate residual thrombotic risk in patients treated with smaller DES are required.

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References

[1] H. Kitahara, K. Okada, T. Kumura, et al., Impact of stent size on acute and long-term outcomes after drug-eluting stent implantation in de novo coronary lesions, Circ. Cardiovasc. Interv. 10 (10) (2017) (pii:e004795).
[2] P. Genereux, M.V. Madhaven, G.S. Mintz, et al., Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes: pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials, J. Am. Coll. Cardiol. 63 (2014) 1845–1854.
[3] G.D. Dangas, B.E. Claessen, A. Caixeta, E.A. Sanidas, G.S. Mintz, R. Mehran, In-stent restenosis in the drug-eluting stent era, J. Am. Coll. Cardiol. 56 (2010) 1897–1907.
[4] US Food and Drug Administration, Draft guidance for industry and Food and Drug Administration staff: evaluation of sex differences in medical device clinical studies, http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm283453.htm, Accessed date: 7 March 2019.
[5] G.G. Stefanini, U. Baber, S. Windecker, et al., Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomized trials, Lancet 382 (2013) 1879–1888.
[6] R.W. Yeh, E.A. Secemsky, D.J. Kereiakes, et al., Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond year 1 after PCI, JAMA 315 (2016) 1735–1749.