Frequency of Stent Thrombosis Risk at 5 Years in Women Versus Men With Zotarolimus-Eluting Compared With Sirolimus-Eluting Stent

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The prevalence of factors that are associated with an increased risk of stent thrombosis (ST), including smoking, diabetes mellitus, and small stent size, is different in women and men who underwent percutaneous coronary intervention. Thus, gender may potentially modify the relation between stent type and the incidence of ST during long-term follow-up. We explored the data of Patient Related Outcomes With Endeavor Versus Cypher stenting Trial (PROTECT) to evaluate this hypothesis. PROTECT randomized 2,061 women and 6,648 men who underwent percutaneous coronary intervention for various indications to Endeavor zotarolimus-eluting stenting (E-ZES) or Cypher sirolimus-eluting stenting (C-SES). Dual antiplatelet therapy was prescribed for at least 3 months. Data on study end points were collected until 5 years after randomization, including ST, death, and cardiovascular events. We analyzed end points and treatment effect (E-ZES vs C-SES) in relation to gender. Women were on average 4.7 years older (65.8 vs 61.1), had a higher prevalence of insulin-dependent diabetes mellitus, were less often smokers, and had a shorter total stent length than men. At discharge and throughout follow-up, a slightly lower fraction of women were using dual antiplatelet therapy. During 5-year follow-up, definite or probable ST was observed in 36 women (1.8%) and 152 men (2.4%; log-rank p = 0.15). E-ZES reduced the incidence of ST compared with C-SES in women (hazard ratio 0.58) and men (hazard ratio 0.61), with no evidence of heterogeneity (p = 0.89). In conclusion, in PROTECT, women and men had similar cumulative incidence of ST at 5 years after stent placement. The favorable effect of the study stent E-ZES over C-SES was not modified by gender. **(Am J Cardiol 2016;118:1178−1186)**

Recently, a meta-analysis of randomized trials of patients who underwent percutaneous coronary intervention (PCI) showed that the use of newer generation drug-eluting stent (DES) is effective and safe in women during 3-year follow-up.[1] However, the modifying effect of gender on clinical outcome after DES implantation, including stent thrombosis (ST), was not analyzed. Consequently, the interplay between gender, established risk factors for ST, dual antiplatelet therapy (DAPT) use, and patient outcome remains unclear. Against this background, we explored the data of the large (8,709 patients) Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial (PROTECT)[2−4] to evaluate the influence of gender on the incidence of ST (among other clinical end points) and on the relation between DES stent type and these end points during 5-year follow-up.

Methods

PROTECT is a prospective, open-label, multicenter, randomized, superiority trial, powered to study differences in long-term clinical effectiveness and safety in a broad group of coronary artery disease (CAD) patients with an indication for PCI. Details of the trial design and the main results have been published previously (ClinicalTrials.gov, number NCT00476957).[2−4] In short, 8,709 patients from 196 centers in 36 countries were randomized 1:1 to receive either an Endeavor zotarolimus-eluting stent (E-ZES; Medtronic CardioVascular, Santa Rosa, California) or a Cypher sirolimus-eluting stent (C-SES; Cordis, Johnson & Johnson, Warren, New Jersey) and otherwise were treated

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Table 1
Patient characteristics by gender

Variable	Women (n=2061)	Men (n=6648)	P-value
Age (years)	65.8 (10.0), 67 (59-73)	61.1 (10.6), 61 (54-69)	<0.001
Body-mass index (kg/m^2)	28.0 (5.1), 27.5 (24.2-31.2)	27.8 (4.3), 27.4 924.8-30.1)	0.049
Hypertension	1506 (73.1%)	4069 (61.2%)	<0.001
Hyperlipidemia	1373 (66.6%)	4056 (61.0%)	<0.001
Insulin dependent diabetes mellitus	199 (9.7%)	407 (6.1%)	<0.001
Non-insulin dependent diabetes mellitus	445 (21.6%)	1360 (20.5%)	0.28
History of smoking	778 (37.7%)	4237 (63.7%)	<0.001
Current smoker	362 (17.6%)	1820 (27.4%)	<0.001
Family history premature coronary artery disease in first degree relative	682 (38.3%)	1918 (33.3%)	<0.001
Prior myocardial infarction	353 (17.1%)	1439 (21.6%)	<0.001
Prior percutaneous coronary intervention	227 (11.0%)	863 (13.0%)	0.018
Prior CABG	71 (3.4%)	352 (5.3%)	<0.001
Prior heart failure	71 (3.4%)	194 (2.9%)	0.24
Prior peripheral vascular disease	102 (4.9%)	318 (4.8%)	0.77
Prior of stroke	70 (3.4%)	200 (3.0%)	0.38
Glomerular filtration rate (ml/min)	79 (40%), 73 (56-93)	96 (47%), 91 (73-113)	<0.001

according to clinical practice. Patients aged ≥18 years who underwent elective, unplanned, or emergency procedures in native coronary arteries were eligible for enrollment if they provided written informed consent. The main exclusion criteria were a previous DES implantation at any time or a previous bare-metal stent implantation in the preceding 12 months, treatment with warfarin, or similar anticoagulant therapy. Enrollment started May 21, 2007, and was completed on December 22, 2008. The ethical committee of each participating center approved the study in accordance with local regulations.

The PCI and stent implantation technique was in accordance with the common clinical standards and the manufacturers' instructions. Direct stenting was at the discretion of the operator. Staging of the procedures within 6 weeks of the initial procedure was allowed. DAPT therapy with aspirin and clopidogrel (75 mg) or ticlopidine was started 3 days before the procedure or through a loading dose for patients not yet taking these medications. Post-procedure, aspirin was to be given indefinitely and clopidogrel or ticlopidine therapy for a minimum of 3 months or up to 12 months, according to device instructions for use or guidelines.[5] In accordance with clinical trial standards, investigators were allowed to extend the duration of DAPT or to restart thienopyridine therapy during the follow-up period if clinically indicated.

Study end points included the incidence of ST (definite or probable and definite), death (all-cause and cardiac), myocardial infarction (MI; major Q-wave MI and all nonfatal MI), and repeat coronary revascularization. ST was defined according to the Academic Research Consortium criteria[6] and was subdivided in early (0- to 30-day post-stent implantation), late (>30 days), and very late (>12 months) ST. An independent Clinical Events Committee adjudicated ST, death, and MI after review of the original data sources. Revascularizations were site reported. For this analysis, we included end points up to 5-year follow-up.

Continuous variables are presented as both means ± SD and medians with interquartile ranges. Categorical variables are presented as counts and percentages. The distribution of baseline characteristics and clinical course variables were compared by gender using the Wilcoxon 2-sample test for continuous variables and the chi-square or Fisher's exact test (in case an expected value in the corresponding contingency table was <5) for categorical data.

The incidences of the study end points are reported as Kaplan-Meier estimates. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Differences between women and men were evaluated using 2-sided log-rank tests.

Multivariate Cox proportional hazards models were used to obtain estimates of the relation between gender and study end points (and E-ZES vs C-SES treatment effect) that are adjusted for the broad range of clinical and angiographic factors that are listed in Tables 1 and 2 and assigned treatment, DAPT, gender × assigned treatment, and DAPT × assigned treatment (as applicable). Because the number of patients with possible or definite ST was limited, only factors with p <0.5 for that end point in univariate analysis were selected for multivariate adjustment. We report adjusted hazard ratios with corresponding 95% confidence intervals.

The age distribution was considerably different between women and men, whereas age was—not unexpectedly—related with the incidence of study end points. Hence, age was a major confounder of gender-outcome relations. Therefore, apart from applying multivariate analyses, we decided to report various results in 5 (clinically relevant) strata according to age.

A 2-sided p value <0.05 was considered statistically significant. Analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, North Carolina).

Results

PROTECT enrolled 2,061 (23.7%) women and 6,648 men who underwent PCI (Table 1). Women and men had a different age distribution (Figure 1). Women were on

Table 2
Angiographic and procedural characteristics

	Women (n=2061)	Men (n=6648)	P-value
Indication*			<0.001
Stable angina pectoris	1014 (49.2%)	3243 (48.8%)	
Unstable angina pectoris	438 (21.3%)	1200 (18.1%)	
ST-elevation myocardial infarction	148 (7.2%)	592 (8.9%)	
Non ST-elevation myocardial infarction	364 (17.7%)	1149 (17.3%)	
Silent ischemia	97 (4.7%)	464 (7.0%)	
Lesion location†			<0.001
Left anterior descending coronary artery	47.9%	46.2%	
Right coronary artery	31.6%	28.9%	
Circumflex artery	19.5%	23.7%	
Lesion length (mm)†‡	17.07 (8.94), 15 (10-20)	17.88 (9.23), 15 (12-22)	<0.001
Stenosis pre procedure (%)†‡	81.98 (13.15), 74 (83-92)	83.02 (12.76), 75 (85-92)	<0.001
Minimal lumen diameter (mm)†‡	0.52 (0.38), 0.5 (0.2-0.8)	0.50 (0.38), 0.5 (0.2-0.7)	0.038
Reference vessel diameter (mm)†‡	2.90 (0.46), 3.0 (2.5-3.1)	2.99 (0.47), 3.0 (2.7-3.5)	<0.001
Bifurcation†	441 (15.6%)	1574 (16.6)	0.20
Calcification			0.25
Non/mild	2033 (72.0%)	6695 (70.8%)	
Moderate	616 (21.8%)	2179 (23.0%)	
Severe	176 (6.2%)	588 (6.2%)	
Tortuosity			0.16
Non	2207 (78.2%)	7270 (76.8%)	
Moderate	549 (19.4%)	1964 (20.8%)	
Severe	68 (6.2%)	226 (2.4%)	
Number of lesions treated per patient*			0.032
0-1	1468 (72.1%)	4585 (69.0%)	
2	434 (21.1%)	1508 (22.7%)	
3	112 (5.4%)	422 (6.3%)	
≥4	29 (1.4%)	130 (2.0%)	
Number of vessels treated per patient*			0.015
0-1	1705 (82.7%)	5357 (80.6%)	
2	333 (16.2%)	1160 (17.5%)	
≥3	23 (1.1%)	128 (1.9%)	
Number of stents per patient*			0.032
0-1	1287 (62.4%)	3927 (59.1%)	
2	492 (23.9%)	1733 (26.1%)	
3	188 (9.1%)	617 (9.3%)	
≥4	94 (4.6%)	368 (5.5%)	
Stent diameter (mm)§‡	2.91 (0.40), 3.0 (2.5-3.0)	3.00 (0.52), 3.0 (2.75-3.5)	<0.001
Minimal stent diameter per patient (mm)*‡	2.86 (0.40), (2.75-2.50-3.00)	2.93 (0.41), 3.00 (2.50-3.00)	<0.001
Total stent length per patient (mm)*‡	29.52 (19.42), 24 (18-36)	31.77 (21.15), 24 (18-41)	<0.001
Staged procedure*	77 (3.7%)	289 (4.3%)	0.23
Lesion success¶†	2772 (99.5%)	9265 (99.5%)	0.99
Procedure success‖*	1951 (96.3%)	6328 (97.2%)	0.038

* 2061 Women, 6648 men.
† Per lesion; 2825 lesions in women, 9465 lesions in men.
‡ Mean (SD), median (interquartile range).
§ 3219 stents in women, 10,832 stents in men.
¶ Attainment of less than 50% residual stenosis of the target lesion with any percutaneous method.
‖ Attainment of less than 50% residual stenosis of all the target lesions and no inhospital major adverse cardiac events.

average 4.7 years older (mean age 65.8 vs 61.1 year, p <0.001) and had a higher prevalence of traditional CAD risk factors, including hypertension (73.1% vs 61.2%, p <0.001), hyperlipidemia (66.6% vs 61.0%, p <0.001), and insulin-dependent diabetes mellitus (9.7% vs 6.1%, p <0.001) but a lower prevalence of smoking (37.8% vs 63.7%, p <0.001) and history of MI, PCI, or CABG. Likewise, women had a lower mean glomerular filtration rate (79 vs 96 ml/min, p <0.001) than men. A total of 53.9% women and 55.8% men underwent the index PCI for stable or silent angina, whereas the remaining patients were treated for acute coronary syndromes.

Women had slightly fewer lesions requiring intervention than men: on average, 1.37 lesions in women versus 1.42 in men (Table 2). Most lesions were located in the left anterior descending coronary artery (47.9% in women and 46.2% in men). There were no significant differences in the degree of calcification of lesions and tortuosity. Women had shorter (17.1 vs 17.9 mm, p <0.001) and less constricted lesions (82% vs 83%, p <0.001), and the average stent

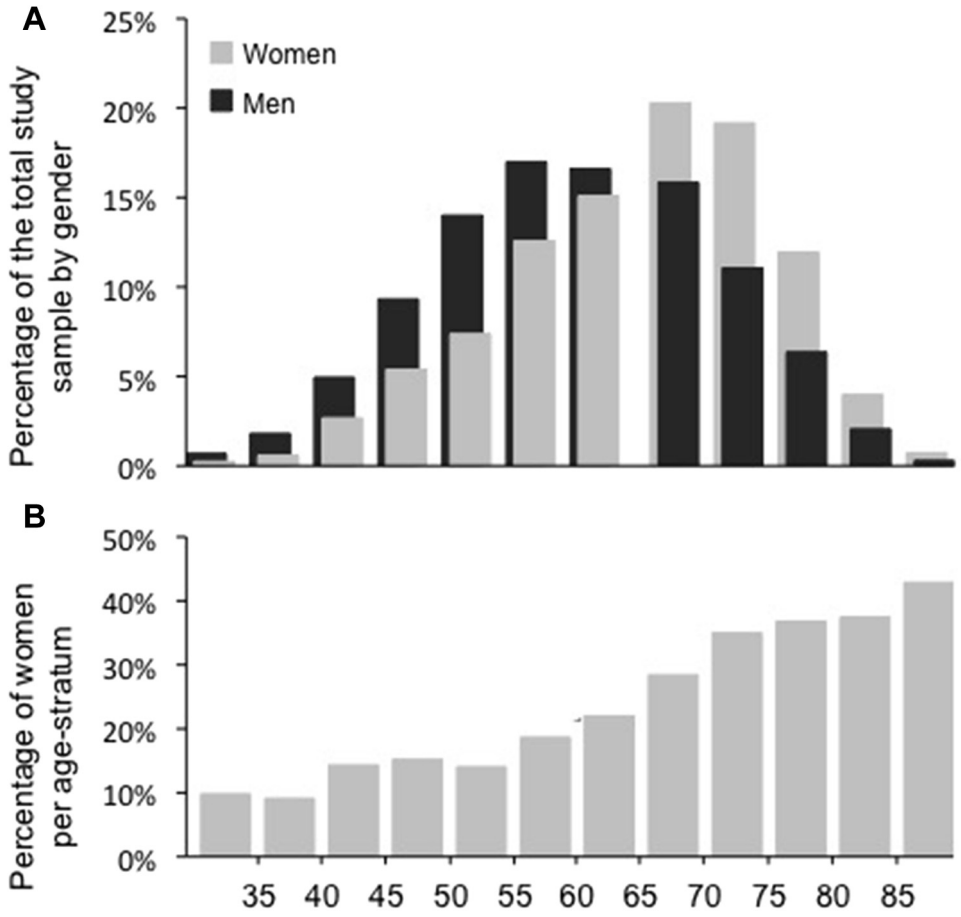

Figure 1. PROTECT study patients by gender and age. *(A)* Percentage of the total study sample by gender. *(B)* Percentage of women per age stratum.

diameter (2.9 vs 3.0 mm, p <0.001) and the minimal stent diameter (2.86 vs 2.93, p <0.001) were smaller and total stent length (29.5 vs 31.8 mm, p <0.001) shorter than in men. There were no differences in predilation. In women, less often a multivessel treatment was performed (17.3% vs 19.4%, p = 0.033), and fewer stents were implanted. The success rate per lesion was similar in women and men, although procedural success was somewhat lower in women (96.3% vs 97.2%, p = 0.038).

During the PCI procedure, combined antithrombin therapy with heparin or low−molecular weight heparin (95.0% vs 96.1%, p = 0.019) was less often given to women than men. Women received more often direct thrombin inhibitors like bivalirudin (4.6% vs 3.8%, p = 0.15), although this difference was nonsignificant. Glycoprotein IIb/IIIa inhibitors (15.7% vs 18.9%, p <0.001) were less often administered to women than to men.

At discharge up to 3 years, the use of aspirin was similar in women and men. Thereafter, fewer women than men used aspirin, especially in patients >80 years (Figure 2). DAPT was applied (slightly) less frequent in women than in men at the time of discharge (95.7% vs 96.6%, p = 0.042). The fraction of women on DAPT remained systematically lower during follow-up, in particular in patients <50 years.

Table 3 and Figure 3 show the end points in women and men. At 5 years, the end point of definite or probable ST was reached in 1.8% of women and 2.4% of men. In all age strata, women had slightly lower incidence of definite or probable ST (Figure 4). There were no differences in the incidence of early, late, and very late ST between women and men. The same was observed for definite ST. During follow-up, there were significantly more revascularizations in men, largely explained by a higher number of target vessel revascularizations. Target lesion revascularization was performed in 5.8% of men and 5.3% of women. Most revascularizations happened in the first 2 years after the initial procedure. No differences were found between women and men with respect to the other end points including all-cause death, cardiac death, MI, and composed end points. After multivariate adjustment for age and other risk factors, women had significant lower incidence of death during 5-year follow-up than men, but the incidences of other end points were similar (Figure 3).

As a result of the randomization process, 1,017 (49.3%) women and 3,340 (50.2%) men were allocated to treatment with E-ZES. In women and men, E-ZES was consistently associated with lower risk of definite or probable ST, death, MI, the composite of death and MI, and the composite of death, MI, and ST (Figure 5). In particular, the incidence of definite or probable ST was reduced by 42% in women and by 39% in men, with no evidence whatsoever of treatment heterogeneity. The gender × allocated

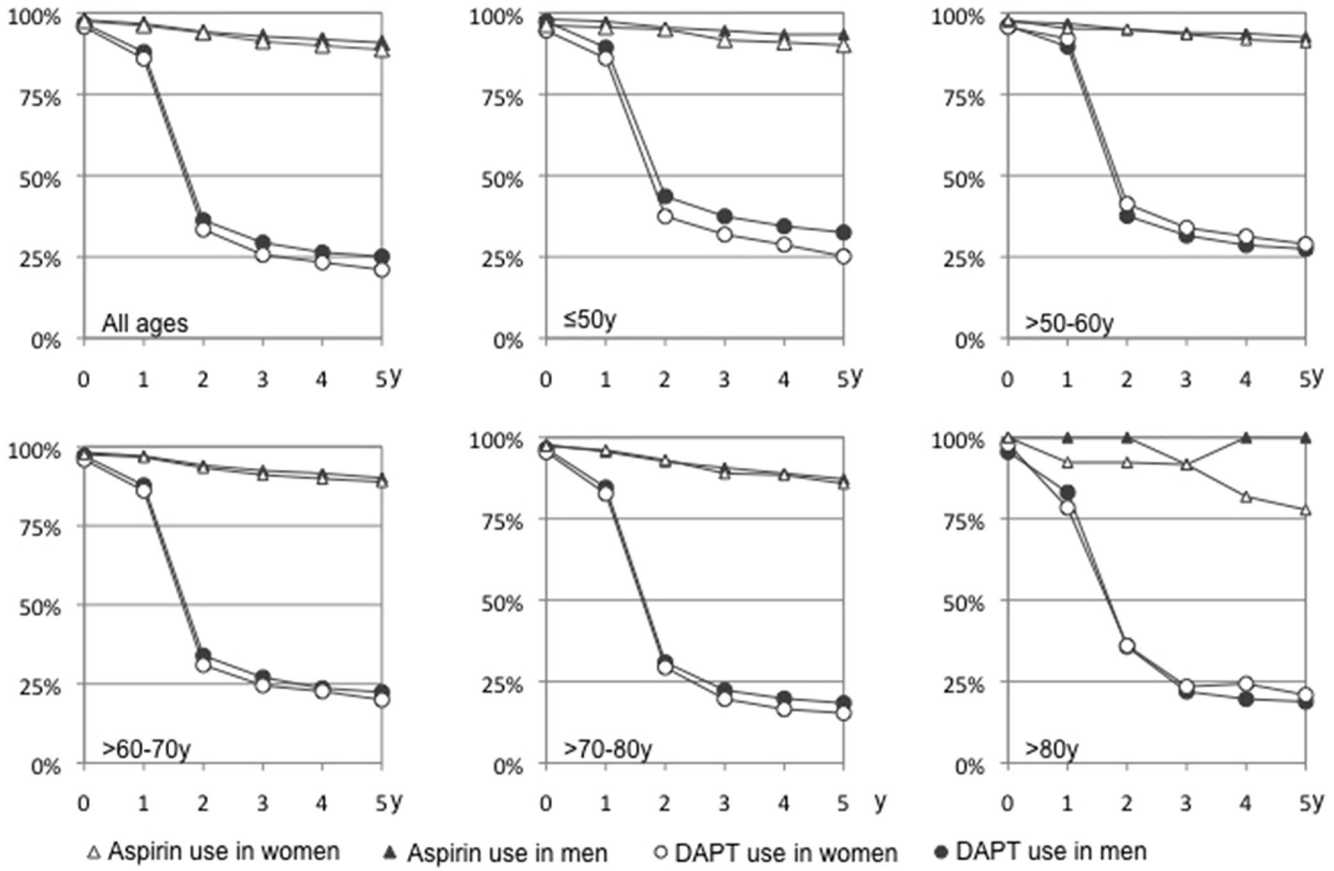

Figure 2. Aspirin and DAPT by gender at different age strata. The thin and thick lines represent women and men, respectively, and the *triangular* and *circular* markers represent aspirin and DAPT, respectively.

treatment (E-ZES vs C-SES) interaction was nonsignificant for all end points.

Discussion

The present study performed on the data of PROTECT, a large prospective international randomized trial comparing 2 DES types with different vascular healing characteristics, did not reveal gender differences in the incidence of ST and other major clinical cardiovascular end points over a follow-up period of 5 years after stent placement. The favorable long-term effect of E-ZES over C-SES, which we reported earlier,[3,4] was consistently found in women and men of all ages.

The age distribution differed markedly between the genders, and women were on average almost 5 years older than men. This observation underscores epidemiologic studies reporting that CAD will become manifest later in life in women than in men.[7] Because (advanced) age is one of the determinants of (an increased risk of) the incidence of ST among other cardiovascular outcomes, age must be considered a confounder of the gender-outcome relations, and therefore, it is expedient to perform stratified analyses according to age.[8]

In PROTECT, per age class, women had consistently slightly better outcomes than men, although we may consider the small observed differences as possible statistical artifacts. Still, the >2-fold lower ST incidence in women <50 years is remarkable—in particular, because the DAPT use was also lower—and warrants further investigations in larger series with detailed information on women-specific factors. It is a well-accepted knowledge that premenopausal women are (relatively) protected against CAD progression because of higher estrogen levels.[9] We do not exclude the possibility that thrombogenicity in women with established CAD might also be age dependent because of hormonal influences.

Women not only were older but also had a higher prevalence of "classical" CAD risk factors including hypertension, hyperlipidemia, and diabetes. Furthermore, women had somewhat less well-preserved kidney function as their glomerular filtration rate was lower than men, albeit largely in the normal range. These findings concur with previous studies in CAD patients.[10,11] Also, we found a relatively high number of women with a history of PCI and CABG, suggesting that PROTECT enrolled a sample of women with a very high cardiovascular risk profile compared with previous observational studies with unselected real-world CAD patients.[10–12]

In particular, diabetes and impaired kidney function are known prothrombotic factors for late and very late ST with the subsequent risk of MI and death.[13,14] In addition, the

Table 3
Clinical outcome at 5 years

Variable	Women (n=2061)	Men (n=6648)	P-value
Definite or probable stent thrombosis	36* (1.8%)	152 (2.4%)	0.16
Early	10 (0.5%)	47 (0.7%)	0.28
Late	7 (0.3%)	16 (0.2%)	0.43
Very late	20 (1.0%)	89 (1.4%)	0.21
Definite stent thrombosis	25 (1.3%)	98 (1.5%)	0.41
Early	7 (0.4%)	27 (0.4%)	0.84
Late	3 (0.2%)	9 (0.1%)	1.00
Very late	16 (0.8%)	62 (1.0%)	0.59
All cause death	151 (7.5%)	458 (7.0%)	0.44
Cardiac death	78 (3.9%)	245 (3.8%)	0.78
Myocardial infarction†	113 (5.6%)	372 (5.8%)	0.92
Death, myocardial infarction	241 (11.9%)	763 (11.7%)	0.67
Death, myocardial infarction, stent thrombosis	246 (12.2%)	781 (12.0%)	0.69
Revascularization‡	304 (15.4%)	1153 (18.0%)	0.011
Major adverse cardiac events§	420 (20.9%)	1481 (22.8%)	0.13

Kaplan-Meier estimates for clinical outcome at 5 years.

* 1 Female patient had both early and very late stent thrombosis.

† According to historical WHO definition, based on total creatine kinase measurements.

‡ Revascularization after initial procedure, including target lesion revascularization, target vessel revascularization and non-target vessel revascularization through percutaneous coronary intervention or coronary artery bypass graft surgery.

§ Including definite or probable stent thrombosis, cardiac death, myocardial infarction (historical definition) and revascularization.

effect of diabetes on the risk of restenosis[10] and clinical outcomes is more deleterious in women than in men.[15] Nevertheless, we found similar outcomes in women and men. Possibly, the clinical trial design with a controlled environment contributed to this result. Another explanation might be that prothrombotic factors and protective factors balanced out in the women and men participating in PROTECT. In this respect, it is important to emphasize that there were differences in the indication for the index PCI. Women presented more often with unstable angina and less often with ST-segment elevation myocardial infarction then men, and it is well known that the thrombogenic state in an STEMI setting is higher than in other acute coronary syndrome phenotypes.[16] Furthermore, in women, a lower number of lesions and coronary arteries were treated than in men. Subsequently, a lower number of stents were implanted, which, obviously, reduces the overall incidence of stent-related complications and in particular thrombosis. Of note, however, is that these results were obtained despite a lower use of DAPT in women than in men, suggesting again a lower thrombogenicity in the studied women collective potentially also because of higher age and lower thrombocyte turnover rate.

The safety and efficacy benefits of DES with strong inhibitory properties—as first-generation DES—with regard to angiographic outcomes and repeat revascularizations were similar in women and men at 1-year follow-up compared with bare-metal stent in previous randomized controlled trials.[17,18]

PROTECT, as well as the SORT OUT (Scandinavian Organization for Randomized Trials With Clinical

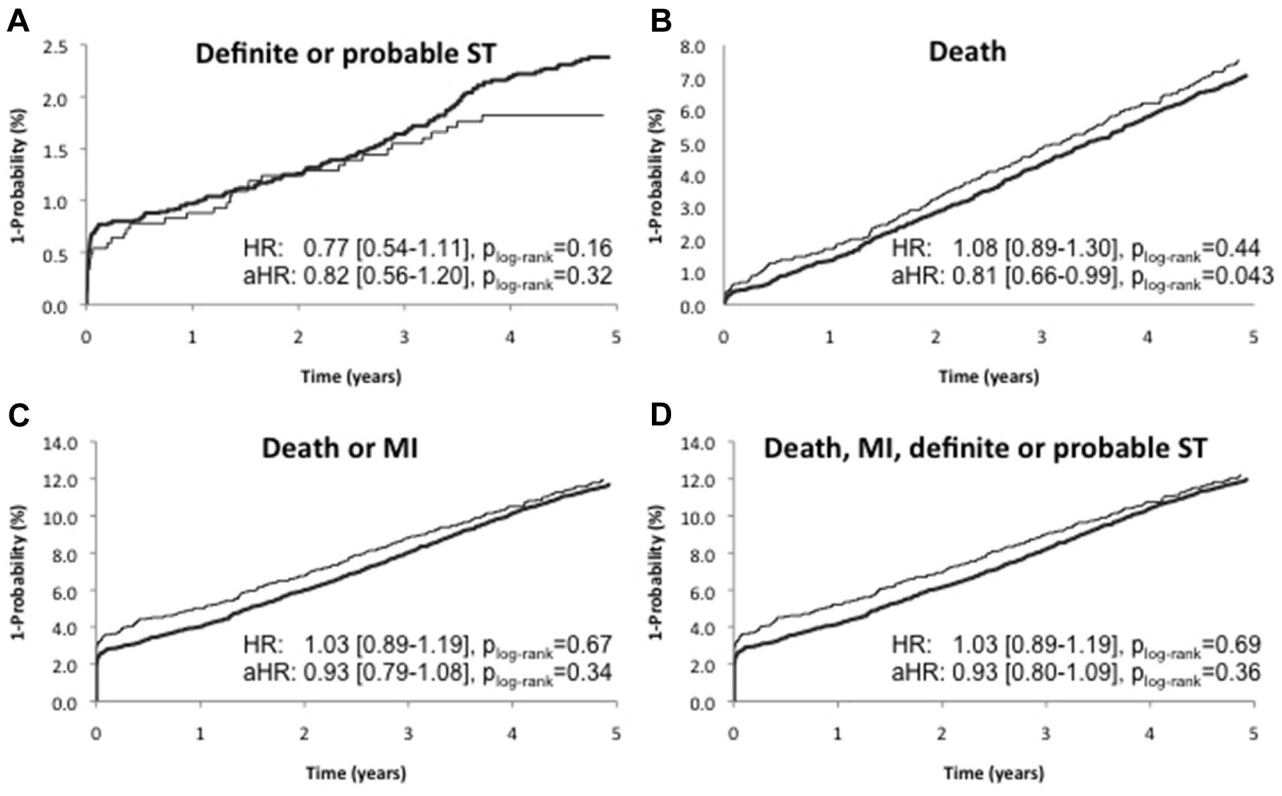

Figure 3. Kaplan-Meier estimates, crude and adjusted hazard ratios with corresponding 95% confidence intervals for outcome according to gender. *(A)* Definite or probable ST; *(B)* death; *(C)* death and MI; *(D)* death, MI, and definite or probable ST. The black and gray lines represent women and men, respectively.

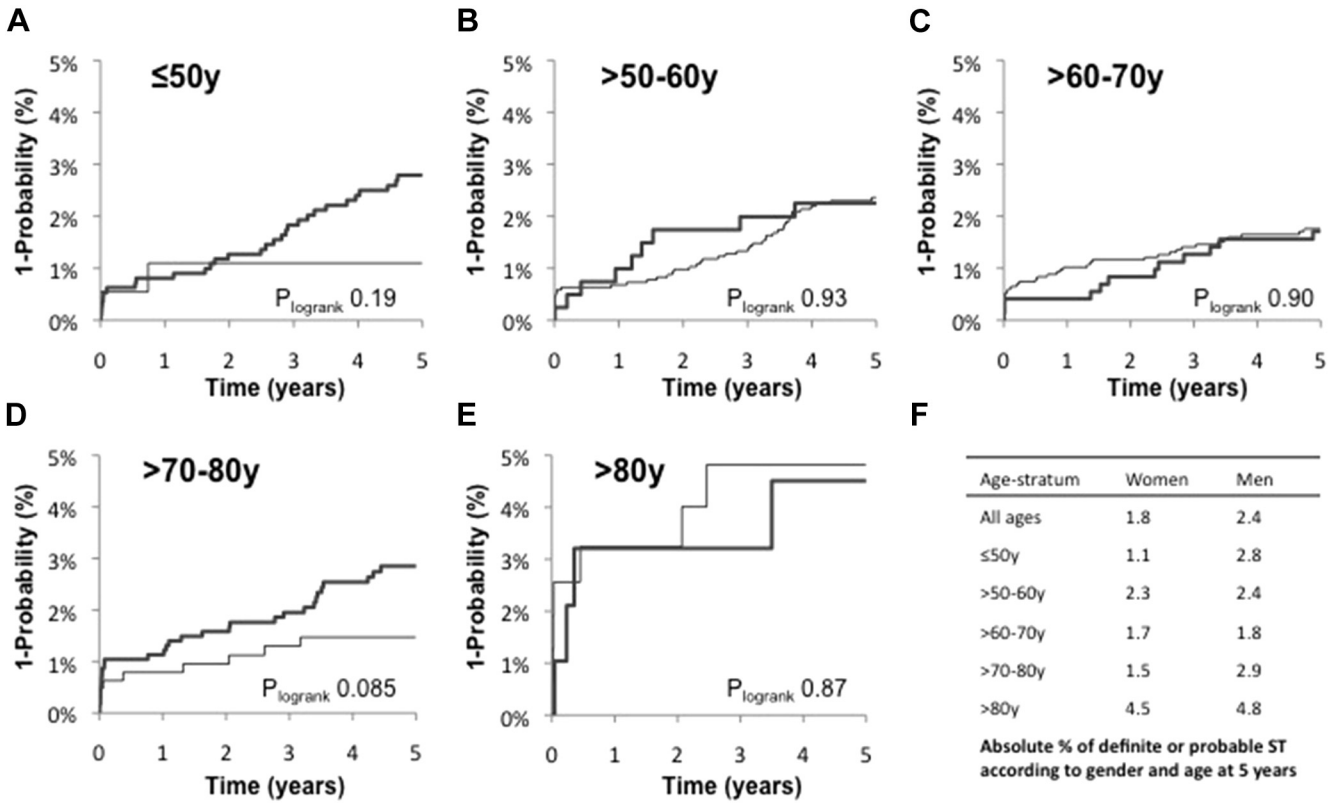

Figure 4. Kaplan-Meier estimates for definite or probable ST according to gender and age stratum up to 5 years after randomization. *(A−E)* Definite or probable ST according to age stratum. The thin and thick lines represent women and men, respectively. *(F)* Absolute % of definite or probable ST according to gender and age stratum at 5 years.

Endpoint	Gender	Events E-ZES (n, %)	Events C-SES (n, %)	HR	95% CI	p-value	Interaction p-value
Definite or probable ST	W	13 (1.3)	23 (2.2)	0.58	0.29-1.14	0.11	0.89
	M	58 (1.7)	94 (2.8)	0.61	0.44-0.84	0.003	
Death	W	66 (6.5)	85 (8.1)	0.79	0.57-1.09	0.15	0.31
	M	226 (6.8)	232 (7.0)	0.96	0.80-1.15	0.67	
MI	W	52 (5.1)	61 (5.8)	0.88	0.61-1.27	0.49	0.38
	M	157 (4.7)	215 (6.5)	0.72	0.59-0.88	0.002	
Death, MI	W	111 (10.9)	130 (12.5)	0.88	0.68-1.13	0.31	0.80
	M	351 (10.5)	412 (12.5)	0.84	0.73-0.96	0.014	
Death, MI, definite or probable ST	W	116 (11.4)	130 (12.5)	0.92	0.72-1.18	0.51	0.52
	M	357 (10.7)	424 (12.8)	0.83	0.72-0.95	0.008	

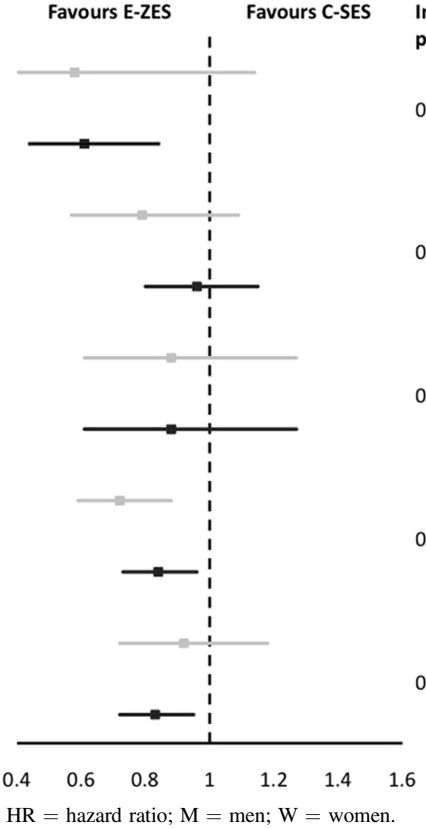

Figure 5. Effect of stent type in women versus men. CI = confidence interval; HR = hazard ratio; M = men; W = women.

Outcome) IV and V trials, did not reveal a gender interaction between women and men independently of the second-generation DES types (E-ZES, C-SES, and everolimus- or biolimus-eluting stent).[19,20] The finding is not self-evident because stent materials might have variable effects in women and men. For example, several studies have suggested enhanced neointimal suppression after E-ZES implantation in women compared with men,[21,22] a finding that is not reported after C-SES. Apparently, these differential effects between 2 DES types do not have impact on clinical end points, including ST.

DAPT, consisting of aspirin plus a P2Y12 receptor antagonist, is recommended after DES implantation for 6 to 12 months by European guidelines, followed by life-long aspirin monotherapy.[5] In PROTECT, ~1 in each 4 patients still used DAPT 5 years after the index stent placement, whereas 9 in each 10 patients used aspirin. Slightly fewer women than men used DAPT or aspirin during long-term follow-up. We may speculate that the observed differences might be a result of aspirin intolerance or active bleeding, which, in other studies, are more often seen in women.[23,24] Especially in women <50, heavy menstrual bleeding may have led to lower DAPT adherence. Also, long-term maintenance of DAPT was according to the protocol physician driven and, thus, more likely to be interrupted in a hemorrhagic-prone elderly with lower BMI subset as in women.[23,24] In an earlier report of PROTECT, based on the 3-year follow-up data, the incidence of ST was lower with E-ZES versus C-SES in the absence of DAPT, whereas no difference was found in the presence of DAPT.[4]

The present study was based on a randomized trial, and consequently, internal validity is high, especially for the estimated treatment effects of E-ZES versus C-SES. External validity, however, very much depends on patient selection. In particular with respect to the relation between gender and clinical outcomes, our data are as good as observational studies, albeit that the data quality can be considered higher than average because data are collected in well-controlled clinical settings and are extensively monitored. We realize that inclusion in PROTECT was targeted to patients who are referred to a cathlab for PCI. Possible gender differences in diagnosis and referral for revascularization could, therefore, not been taken into account, and thus, generalized conclusions in that direction cannot be drawn. Also, importantly, the number of young women and men with clinical end points was low, so that effects could only be estimated with limited precision. Finally, not all predictors of ST were recorded. In particular, no detailed information was available on the PCI procedure, such as, for example, on (under) sizing of the implanted stent, which most likely has been different in women and men.

Disclosures

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